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INTERNATIONAL ACADEMIC RESEARCH AND STUDIES IN

DENTISTRY

EDITORS

ASSOC. PROF. DR. NESLİHAN YILMAZ ÇIRAKOĞLU

ASSOC. PROF. DR. TÜRKAN SEZEN ERHAMZA

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CONTENTS

Chapter 1

THE IMPACT OF SYSTEMIC DISEASES AND CONDITIONS ON THE PERIODONTIUM

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The tissue destruction observed in periodontal diseases results from a disruption in the balance between specific pathogenic bacteria present in the periodontal pocket and the host inflammatory response. Due to the defense mechanisms of the host organism, a large proportion of the population is able to prevent these bacteria from damaging the periodontal supporting tissues. However, systemic diseases and conditions present in individuals may alter the host response, leading to either inadequate or excessive immune reactions and thereby increasing susceptibility to more severe forms of periodontal disease. (Klokkevold & Mealey, 2006) Therefore, although the presence of microbial dental plaque is sufficient for the initiation of periodontal disease, the severity of the disease, the extent to which it affects the individual, and its progression rate depend on the individual's immune and inflammatory responses, which are shaped by systemic factors. (Palmer & Soory, 2003) In the classification of periodontal diseases, numerous systemic diseases and conditions have been identified as risk factors or risk indicators for gingivitis and periodontitis.

Hormonal Diseases and Conditions

Diabetes Mellitus (DM)

Diabetes Mellitus is a clinically and genetically heterogeneous metabolic disorder characterized by elevated blood glucose levels. Hyperglycemia arises as a result of dysfunction of pancreatic β-cells leading to insufficient insulin production and/or resistance to insulin action in peripheral tissues. (Mealey & Ocampo, 2007) Today, diabetes is recognized as a syndrome, with well-documented long-term detrimental effects of persistent hyperglycemia on various organs and systems, including the heart, kidneys, eyes, nervous system, and circulatory system. The classification of diabetes is based on the pathogenesis of each specific form. (Table 1)

Type 1 Diabetes	This form of diabetes develops due to the autoimmune destruction of β-cells in the pancreas, leading to a complete cessation of insulin production. Although it typically manifests during childhood and early adulthood, it can also be diagnosed after the age of 30. Individuals with type 1 diabetes require external insulin supplementation to sustain life. Furthermore, there is a significant genetic predisposition in these individuals, notably related to human leukocyte antigens (HLA). (Mealey & Ocampo, 2007)
Type 2 Diabetes	In individuals with type 2 diabetes, there is no destruction of pancreatic β-cells; however, insulin resistance exists, which reduces the effectiveness of the insulin produced in target tissues. Approximately 90 - 95% of diabetes cases are of the type 2 variety. A significant portion of these individuals is obese or has an increased body fat percentage. Excess adipose tissue contributes to insulin resistance by releasing free fatty acids into circulation, which inhibit glucose uptake, glycogen synthesis, and glycolysis. Chronic insulin resistance eventually forces β-cells to produce more insulin, which can lead to a functional decline in these cells over time. (Mealey & Ocampo, 2007)

Table 1. *Classification of Diabetes*

The development of microvascular complications (retinopathy, nephropathy, neuropathy) and macrovascular diseases (hypertension, cardiovascular and cerebrovascular diseases) in diabetic patients over the long term has been associated with alterations in inflammatory mechanisms. (Mealey & Ocampo, 2007) In these individuals, significant reductions in essential immune functions such as neutrophil chemotaxis and phagocytosis have been identified. (Mealey and Ocampo, 2007) At the macrophage level, a hyperinflammatory response has been observed, characterized by increased production of tumor necrosis factor (TNF), interleukin-1 (IL-1), interleukin-8 (IL-8), prostaglandin E2 (PGE2), and adhesion molecules. (Fıratlı, 1997; Mealey & Ocampo, 2007) Additionally, in hyperglycemic individuals, advanced glycation end-products (AGEs), which result from the glycation of body proteins, play a key role in the development of diabetic complications. (Schmidt et al., 1996) AGEs are stable carbohydrate-containing molecules that bind to their receptors (RAGE) on smooth muscle cells, monocytes and macrophages, endothelial cells, and neurons, thereby disrupting cell-cell, cell-matrix, and matrix-matrix interactions, and adversely affecting tissue homeostasis. (Mealey & Ocampo, 2007)

The effects of diabetes on periodontal tissues resemble the pathogenic mechanisms of general microvascular and macrovascular complications. In individuals with diabetes, major periodontal pathogens such as *Capnocytophaga*, *Porphyromonas gingivalis*, and *Prevotella intermedia* are reported to be more prevalent. (Mealey & Ocampo, 2007) Moreover, impaired neutrophil functions (Gürsoy, Marakoğlu, & Öztop, 2008), increased susceptibility to infections (Ünlü et al., 2003), delayed wound healing, and elevated production of inflammatory cytokines have been demonstrated in diabetic individuals. (Kurtiş et al., 1999) Accumulation of AGEs in the gingival connective tissue also leads to collagen degradation and negatively impacts vascular metabolism. (Güneri et al., 2004; Sakallıoğlu et al., 2007)

Currently, diabetes is recognized as a confirmed risk factor for both gingivitis and periodontitis, and periodontitis is considered one of the complications of diabetes. (Löe, 1993) Periodontal differences between individuals with Type 1 and Type 2 diabetes vary depending on several factors, including the level of hyperglycemia, duration of the disease, age, and smoking status. (Aren et al., 2003) Glycemic control is a critical variable in the relationship between diabetes and periodontal diseases; in individuals with poor glycemic control, the frequency and severity of gingival inflammation and periodontal breakdown are significantly increased. Epidemiological and longitudinal studies have reported that, compared to healthy individuals, diabetic patients have approximately a threefold increased risk of alveolar bone loss and periodontal attachment loss; however, in diabetic individuals

with good glycemic control, this risk is comparable to that of non-diabetic individuals. (Mealey & Ocampo, 2007)

Sex Hormones

The impact of sex hormones on the periodontium is a well-known and extensively studied topic. Although these hormones alone are insufficient to initiate gingival reactions, they exert indirect effects by modulating the host response to microbial plaque. The gingiva is one of the target tissues for all sex steroid hormones. Physiological hormonal changes, such as those occurring during puberty, menstruation, and pregnancy, as well as non-physiological hormonal changes like the use of hormonal contraceptives and hormone replacement therapy, can significantly affect the periodontium. (Palmer & Soory, 2003; Klokkevold & Mealey, 2006) These effects are particularly pronounced in gingival diseases already associated with pre-existing plaque. Primary female sex hormones, such as estrogen and progesterone, can influence periodontal tissues through various mechanisms, including reducing the levels of bacterial inhibitory enzymes such as peroxidases in saliva, enhancing the production of growth factors and collagen, and promoting angiogenesis. (Mealey & Moritz, 2003; Mascarenhas, Gapski, Al-Shammari, & Wang, 2003)

Puberty, Menstruation, and Pregnancy

During puberty, the rapid increase in sex hormones is associated with increased inflammation and bleeding in the marginal and interdental gingiva, as observed in some studies; however, this relationship has not been confirmed in other studies. These inconsistencies can be explained by various factors, including differences in oral hygiene levels, the presence of caries, mouth breathing habits, dental malocclusions, and eruption patterns. Additionally, some studies have reported that anaerobic bacteria, particularly *Prevotella intermedia*, can utilize estrogen and progesterone, instead of menadione, which is required for their growth. (Mealey & Moritz, 2003; Güncü, Tözüm, & Cağlayan, 2005)

Similarly, while no significant changes are observed in the gingiva during menstruation in the general population, women with pre-existing gingivitis show increased gingival bleeding and erythema, which have been linked to hormonal fluctuations. (Güncü, Tözüm, & Cağlayan, 2005) During pregnancy, elevated hormone levels lead to distinct gingival findings due to endocrine changes. Estrogen and progesterone, which are continuously secreted by the corpus luteum in the uterus, increase 10 to 30 times in concentration by the end of the third trimester compared to pre-pregnancy levels. (Mascarenhas, Gapski, Al-Shammari, & Wang, 2003; Mealey & Moritz, 2003) Pregnancy gingivitis is highly prevalent, affecting approximately 20 - 30% of pregnant women. The inflammatory changes observed in the gingiva typically begin in the second month of pregnancy and continue with increasing severity

until the eighth month. (Mealey & Moritz, 2003; Güncü, Tözüm, & Cağlayan, 2005) This inflammation is usually concentrated in the anterior teeth and interproximal areas. Numerous studies have shown that, regardless of the level of plaque accumulation, the prevalence and severity of gingival inflammation during pregnancy are significantly higher compared to the postpartum period. (Güncü, Tözüm, & Cağlayan, 2005) Other findings in the gingiva during pregnancy include bleeding upon mechanical stimulation or probing (Yalçın et al., 2002), increased gingival crevicular fluid (GCF) volume, elevated inflammatory cytokine levels (Yalçın et al., 2002), changes in the bacterial microbiota (Buduneli et al., 2005), and increased mobility. However, although pregnancy causes notable gingival inflammation, it has been reported that it does not serve as a risk factor for attachment loss or periodontitis on its own. (Tilakaratne et al., 2000)

In addition to these gingival changes, approximately 1 - 10% of pregnant women may experience localized gingival enlargements. These enlargements, temporarily referred to as "pregnancy tumors," are not neoplastic and cannot be clinically or histologically distinguished from pyogenic granulomas. Typically, they are localized in the interproximal areas of the upper jaw anterior teeth, presenting as pedunculated, painless, red to purple-colored lesions that bleed easily. These lesions should be considered as an exaggerated tissue response to local irritants such as calculus or over-contoured restorations. Although they usually do not exceed 2 cm, in some cases, they may reach the occlusion, affecting chewing and speaking functions. Postpartum, these lesions typically shrink, and in some cases, they disappear completely. (Barak et al., 2003; Suresh & Radfar, 2004) The underlying factors responsible for gingival changes observed during pregnancy are explained by immunological, microbiological, and hormonal mechanisms. These include reduced neutrophil chemotaxis and phagocytosis, decreased antibody production, increased levels of cytokines and growth factors, and changes in CD3, CD4 cells, and B-lymphocyte activity. (Mascarenhas, Gapski, Al-Shammari, & Wang, 2003; Suresh & Buffalo, 2004) Additionally, an increase in anaerobic bacteria, such as *P. intermedia*, which can metabolize estrogen and progesterone, contributes to the microbial aspect, while the hormonal effects are supported by the elevation of vascular endothelial growth factor (VEGF), which triggers neoangiogenesis. (Buduneli et al., 2005; Barak et al., 2003)

Hormonal Medications

The long - term use of oral contraceptives (birth control pills), which mimic the hormonal conditions observed during pregnancy, has been associated with an increase in gingival inflammation. (Zachariasen, 1993) However, the use of newer generation drug combinations, which contain lower levels of hormones, has significantly reduced the frequency of inflammation.

(Preshaw, Knutsen, & Mariotti, 2001) Similarly, in individuals undergoing assisted reproductive therapy, increased levels of hormones in the medications used have been reported to cause an increase in gingival inflammation and bleeding. (Haytaç, Çetin, & Seydaoğlu, 2004) Furthermore, a recent study has reported that the long-term use of doping medications containing high levels of testosterone may lead to gingival enlargement. (Özçelik, Haytaç, & Seydaoğlu, 2006)

Hematologic Diseases

All blood cells play critical roles in maintaining the health of periodontal tissues. While white blood cells are involved in inflammatory defense, red blood cells play a vital role in oxygenating tissues and meeting metabolic needs. Platelets, on the other hand, are essential for maintaining normal hemostasis mechanisms. In this context, the effects of both hematologic diseases and pathologies of hematopoietic organs on periodontal tissues are of significant clinical importance. (Klokkevold & Mealey, 2006)

Leukemia

Leukemia represents malignant neoplasms of white blood cells and is characterized by the abnormal infiltration of immature leukemic cells in the bone marrow, circulatory system, organs, and tissues in abnormal numbers and forms. (Klokkevold & Mealey, 2006) Leukemia is classified as either lymphoblastic or myeloblastic based on the affected cell type, and as acute or chronic based on the disease progression. Additionally, several subtypes have been defined within these main categories. (Jädersten & Hellström-Lindberg, 2009) In all forms of leukemia, bone marrow infiltration suppresses the production of erythrocytes, leukocytes, and platelets, leading to systemic symptoms such as anemia, increased susceptibility to infections, and bleeding in peripheral tissues. (Jädersten & Hellström-Lindberg, 2009) Gingival bleeding may be one of the initial clinical signs in leukemia patients.

In the periodontium, the intense production of endothelial adhesion molecules increases leukocyte migration and facilitates the infiltration of leukemic cells into these tissues. (Antmen et al., 2003) Dreizen et al. (1983) reported that 4% of leukemia patients exhibited gingival symptoms, with the majority of these cases occurring in patients with acute myeloid leukemia (AML) and chronic myeloid leukemia (CML). Gingival changes, including color alterations, increased bleeding, and frequently, gingival growths starting in the interproximal areas, can be observed as a result of leukemic cell infiltration. (Fowler, 1999) Histologically, the normal components of gingival connective tissue are replaced by leukemic cells. Infiltration of leukemic cells into the periodontal ligament and alveolar bone is less common but is typically associated with acute lymphoblastic leukemia (ALL). (Haytaç, Antmen, & Doğan, 2003) Radiologically, findings such as widening of the periodontal

ligament space, loss of lamina dura, and trabecular bone alteration can be observed. These changes, especially prominent in ALL patients, may present as widespread alveolar bone resorption, expansion of the maxilla and mandible, increased mobility, and migration. (Haytaç et al., 2003)

Anemia

Anemia is a condition characterized by a decrease in the number of erythrocytes and hemoglobin levels in the blood. (Lu & Wu, 2004) Anemias are typically classified based on hemoglobin content and the morphological characteristics of erythrocytes. (Altay et al., 1997) Acquired anemias, such as iron deficiency anemia, hemolytic anemia, and vitamin B12 deficiency anemia, generally develop due to factors such as inadequate nutrition, significant blood loss, infections, and pregnancy. In contrast, types such as thalassemia, sickle cell anemia, and aplastic anemia are inherited forms. (Brennan et al., 2001)

1. **Iron Deficiency Anemia;** a decrease in the amount of oxygen delivered to tissues can lead to significant findings not only systemically but also in the oral mucosa. Hypoxia resulting from insufficient circulating erythrocytes and hemoglobin can manifest clinically in the mouth through various signs. The most commonly observed among these signs are glossitis, angular cheilitis (cracking and inflammation at the corners of the mouth), and gingival pallor. (Bain & Hamburger, 2003)

2. **Mediterranean Anemia (Thalassemia);** thalassemias are hereditary forms of anemia that arise from mutations in the genes responsible for synthesizing the alpha and beta globin chains of the hemoglobin molecule. Thalassemia presents with a broad clinical spectrum, and in addition to hematologic findings, various oral and craniofacial anomalies may also be observed. Common conditions in these patients include gingival pallor, severe malocclusion due to skeletal deformities resulting from bone marrow activity, dental misalignment, and ectopic eruptions. (Al-Wahadni et al., 2002)

3. **Fanconi Anemia;** is a clinically and genetically heterogeneous disorder typically characterized by progressive aplastic anemia that usually begins around the age of 5 to 6 years. Aplastic anemia manifests with thrombocytopenia, neutropenia, and decreased hemoglobin levels. In addition to systemic symptoms, significant craniofacial and dental anomalies are also observed in individuals with Fanconi anemia. Frequently reported findings include severe skeletal extremity abnormalities, microdontia, dental hypoplasia, and taurodontism, which are congenital dental malformations. Furthermore, individuals with this condition are prone to developing gingivitis and aggressive periodontitis, as reported in the literatüre. (Nowzari et al., 2001; Açıkgöz et al., 2005)

Bleeding Disorders

Bleeding disorders are a group of diseases characterized by functional deficiencies in the hemostasis mechanism and are generally classified into two main categories: platelet function disorders and coagulation factor disorders. (Vassilopoulos & Palcanis, 2007)

Ø Platelet disorders, such as congenital thrombocytopenia, develop due to a reduction in platelet production or an increase in platelet destruction. Glanzmann thrombocytopenia, on the other hand, is characterized by genetic defects in platelet membrane receptors. (Toygar & GüzelDemir, 2007)

Ø Coagulation disorders include the most common conditions such as Von Willebrand disease, hemophilia A (factor VIII deficiency), and hemophilia B (factor IX deficiency).

In all these bleeding disorders, the most prominent clinical findings in periodontal tissues include increased bleeding tendency, spontaneous bleeding in the gingival connective tissue, and petechiae on the soft and hard palate and alveolar mucosa, independent of the microbial plaque accumulation. (Vassilopoulos & Palcanis, 2007)

Neutrophil Disorders

Polymorphonuclear leukocytes (particularly neutrophils) are central players in the inflammatory and immune defense systems. Neutrophils are short - lived, non-mitotic cells that differentiate from hematopoietic stem cells located in the bone marrow. To maintain healthy periodontal tissues, neutrophils must be both present in sufficient numbers and functionally effective. (Deas, Mackey, & McDonnell, 2003) The immune response that neutrophils generate against infectious agents occurs in six fundamental stages: accumulation around the vascular endothelium (marginalization), adhesion to the endothelium, migration to the infection site (chemotaxis), phagocytosis, and the intracellular elimination of microorganisms through phagolysosomes. (Deas, Mackey, & McDonnell, 2003) Any disruption at any stage of this process, or a reduction in neutrophil count, weakens the defense capacity against periodontal infections, increasing susceptibility to infections. Neutrophil deficiencies can be hereditary (primary immunodeficiencies), acquired (e.g., systemic diseases), or drug-induced.

Neutropenia is characterized by a decrease in the neutrophil count below the normal range. The normal adult neutrophil count ranges between 1800 - 8000 cells/μL. A decrease below 1000 cells/μL for more than six months is considered clinically significant neutropenia, increasing susceptibility to infections such as stomatitis, gingivitis, periodontitis, and cellulitis. When the neutrophil count falls below 500 cells/μL, there is a high risk of serious systemic infections such as pneumonia and sepsis. (Deas, Mackey, & McDonnell, 2003)

Chronic neutropenia is characterized by a long-term decrease in neutrophil count, while cyclic neutropenia fluctuates periodically. Congenital neutropenia typically manifests in the first year of life and is characterized by severe bacterial infections. Oral findings common to all types of neutropenia include ulcerations, pronounced gingival inflammation, gingival hyperplasia, spontaneous bleeding, severe alveolar bone loss affecting both primary and permanent teeth, deep periodontal pockets, mobility, migration, and early tooth loss. (Deas, Mackey, & McDonnell, 2003)

Functional Neutrophil Disorders

Chediak-Higashi Syndrome is characterized by the presence of abnormally large intracellular granules in neutrophils. This structural abnormality leads to impairments in key cellular functions such as chemotaxis, degranulation, and phagocytosis. (Bailleul-Forestier et al., 2008) Chronic Granulomatous Disease (CGD) is characterized by a deficiency in the NADPH oxidase enzyme, which plays a key role in the intracellular killing mechanism of neutrophils. This results in inadequate phagocytosis. (Buduneli, Baylas, Aksu, & Kütükçüler, 2001) In Hyper IgE Syndrome (HIES), neutrophil chemotaxis is impaired. These disorders share common clinical features, including recurrent bacterial and fungal infections, skin abscesses, oral ulcerations, severe gingivitis, and progressive periodontitis.

Leukocyte Adhesion Deficiency (LAD) results from structural defects in cell surface adhesion molecules such as CD11/CD18 (β2 integrins) and CD15, which are responsible for the migration of leukocytes to the vascular endothelium. This disorder impairs chemotaxis as well as bacterial adhesion and phagocytosis. (Waldrop et al., 1987) In LAD patients, common oral manifestations include acute gingival inflammation, gingival hyperplasia, significant alveolar bone loss, mobility, pathological migration, and early tooth loss, particularly affecting both primary and permanent dentition.

Papillon - Lefèvre Syndrome (PLS)

Papillon-Lefèvre Syndrome (PLS) is a rare autosomal recessive genetic disorder characterized by severe periodontitis and palmoplantar keratosis, which affect both primary and permanent dentition. The condition typically manifests between the ages of 2 and 4. Approximately 20% of cases also present with increased susceptibility to infections, lymphocyte and neutrophil dysfunctions, as well as intracranial calcifications. (Fıratlı, Gürel, Efeoğlu, & Badur, 1996) The genetic defect associated with PLS has been localized to the 11q14-q21 chromosomal region, which includes six genes, one of which is Cathepsin C. (Cagli et al., 2005) Cathepsin C is a lysosomal protease that plays a critical role in intracellular protein degradation and the activation of various leukocyte and mast cell granule serine proteases. This enzyme is present in epithelial tissues such as the lung, kidney, keratinized oral gingiva,

palms, soles, and knees, as well as in polymorphonuclear leukocytes, alveolar macrophages, and osteoclasts.

In PLS patients, Cathepsin C activity is reduced by more than 90%. (Nitta et al., 2005) Clinically, PLS is marked by the development of prepubertal periodontitis, typically around the ages of 2 to 4, often accompanied by severe inflammation around the primary teeth. This condition usually leads to the early loss of all primary teeth. After the eruption of permanent teeth, the inflammation reappears and similarly results in the loss of most teeth. Following significant alveolar bone destruction, only thin alveolar ridges remain. (De Vree, Steenackers, & De Boever, 2000)

Oral Complications Associated with Chemotherapy

Chemotherapy is a treatment modality designed to destroy tumor cells while minimizing toxicity to normal tissues. It exerts selective and toxic effects on rapidly proliferating cells by inhibiting cytoplasmic transport mechanisms, RNA transcription, DNA synthesis, and replication. (Simon & Roberts, 1991) Tumors composed of rapidly dividing cells are particularly sensitive to chemotherapy. In patients undergoing chemotherapy and/or radiotherapy for cancer treatment or in preparation for hematopoietic stem cell transplantation, numerous short- and long-term side effects can develop in the oral cavity. (Epstein & Schubert, 1999) The most common complications include bacterial, viral, and fungal infections due to reduced neutrophil activity, spontaneous gingival bleeding related to thrombocytopenia, as well as xerostomia and mucositis. (Doğan et al., 2007)

Mucositis arises as a result of the cytotoxic effects of chemotherapy on the oral and intestinal mucosa, which exhibit high mitotic activity. Clinically, mucositis can range in severity from mild erythema to extensive ulceration. (Dahllöf et al., 2001) These ulcerations can serve as portals of entry for microorganisms, thereby increasing the risk of septicemia. In patients receiving chemotherapy for acute leukemia, infections are among the leading causes of mortality. Oral infections are often the source of septicemia, occurring in 24 - 45% of neutropenic patients. (Sung et al., 2009) These infections are commonly associated with oral ulcers, periodontal diseases, pulpal infections, and bacterial foci in the paranasal sinuses. (Haytaç, Doğan, & Antmen, 2004)

Additionally, viral infections such as Herpes Simplex Virus, Varicella Zoster Virus, and Cytomegalovirus are frequently observed during chemotherapy. Fungal infections are associated with changes in the oral flora and conditions such as xerostomia induced by chemotherapy. (Kobayashi et al., 2008) Under normal conditions, the growth of *Candida albicans* is suppressed by other microorganisms and the immune system. However, in immunosuppressed patients, oral candidiasis often manifests as white, elevated, curd-like lesions that can be easily removed from the mucosal

surface; hemorrhagic areas may be observed following detachment of these lesions. (Jagarlamudi et al., 2000)

Dermatological Diseases

Mucocutaneous Disorders

A wide range of diseases affecting the skin and mucous membranes can lead to desquamative gingivitis, a clinical condition characterized by epithelial desquamation of the gingiva, erythema, ulceration, and/or vesiculobullous lesions. This presentation often serves as the first or early clinical manifestation of various dermatological disorders. Among the primary diseases associated with this condition are lichen planus and pemphigus vulgaris. For a definitive diagnosis, biopsy specimens obtained from the gingiva or oral mucosa must be examined using direct immunofluorescence (DIF) techniques. (Aguirre, Vasquez, & Nisengard, 2006)

Lichen Planus

Lichen planus is a chronic inflammatory disease primarily affecting the skin and mucosal surfaces, most commonly observed in individuals aged 40 to 70, with a higher prevalence among women. Although its etiology remains unclear, the most widely accepted pathogenic mechanism involves a cell-mediated autoimmune response directed against epithelial cell antigens. (A.A.P.P.P., 2003) The reported prevalence ranges from 0.1% to 4%. (Carrozzo, 2008; McCartan & Healy, 2008)

Oral involvement of lichen planus presents in various clinical forms, including reticular, papular, atrophic, ulcerative, bullous, and plaque - type lesions. (Lo Russo et al., 2008) The reticular form - characterized by bilateral white striations - is the most common and typically asymptomatic. (Carrozzo, 2008) Reticular, papular, and plaque forms usually cause only mild surface changes and do not elicit symptoms. In contrast, atrophic, ulcerative, and bullous forms - collectively referred to as *erosive lichen planus* - are often painful, especially during eating or tooth brushing, due to mucosal erosions accompanying the white lesions. (Mollaoglu, 2000) Desquamative gingivitis is frequently observed in erosive lichen planus, and the Nikolsky sign - indicating the ease of epithelial separation from the underlying connective tissue - is typically positive. (Aguirre, Vasquez & Nisengard, 2006) Lesions may also be present on the skin, genital mucosa, esophagus, and, rarely, ocular tissues. (A.A.P.P.P., 2003)

Histopathologically, lichen planus is characterized by epithelial acanthosis and hyperkeratosis, degeneration of basal cells, and a band-like infiltration of T-lymphocytes along the basement membrane. (Halmstrup & van Steenberge, 2003) Direct immunofluorescence (DIF) studies commonly reveal linear fibrin/fibrinogen deposits at the basement membrane and colloid

bodies, believed to be apoptotic epithelial cells, at the epithelial-connective tissue interface. These findings support the autoimmune nature of the disease, driven by a cellular immune response against basal keratinocyte antigens. (A.A.P.P.P., 2003) The primary goal of treatment is to suppress the exaggerated T-cell response and eliminate local irritants. Topical and systemic corticosteroids are often effective in managing the erosive form. Studies have demonstrated that individuals with lichen planus have a tenfold increased risk of developing squamous cell carcinoma, highlighting the need for regular clinical monitoring. (Gonzalez-Moles, Scully & Gil-Montoya, 2008)

Mucous Membrane Pemphigoid

Mucous membrane pemphigoid (MMP) is a chronic autoimmune disorder that predominantly affects women over the age of 50. Early clinical manifestations typically include desquamative gingivitis, vesiculobullous lesions, and ulcerations. These lesions most commonly originate in the oral mucosa and may later involve the nasal, conjunctival, pharyngeal, and genital mucous membranes. Histopathologically, MMP is characterized by subepithelial blister formation and vacuolization in the basal lamina, indicating separation of the epithelium from the underlying connective tissue. Unlike lichen planus, the inflammatory infiltrate in MMP is more heterogeneous, consisting of lymphocytes, neutrophils, and plasma cells. Direct immunofluorescence (DIF) analysis typically reveals a linear deposition of IgG and complement component C3 along the basement membrane zone, supporting the autoimmune nature of the disease. (Bozkurt et al., 1998) Due to its progressive course, MMP can lead to scarring and potential vision loss, particularly in cases with ocular involvement. Therefore, early diagnosis and appropriate immunosuppressive therapy are essential to prevent severe complications.

Pemphigus Vulgaris

Pemphigus vulgaris is an autoimmune disorder characterized by the formation of blisters on the skin and mucous membranes. Oral lesions and blisters on the lips are often the first signs of the disease. These blisters rupture over time, leaving behind painful ulcerations. Minimal trauma to any area of the oral cavity can induce desquamation, making the mucosa highly sensitive. Histologically, pemphigus vulgaris is characterized by acantholysis and suprabasal blister formation. The basal cells, which form the base of the blister, are arranged in a “cobblestone” pattern, and keratinocytes that have undergone acantholysis can be seen in the fluid-filled blisters. Direct immunofluorescence (DIF) analysis typically shows IgG, IgA, and IgM deposits in the intercellular spaces, which are indicative of the autoimmune nature of the disease. It is believed that the autoimmune response targets desmoglein 3, a desmosomal adhesion molecule, in the pathogenesis of pemphigus vulgaris. (Akman, Kacaroglu, Yilmaz, & Alpsoy, 2008)

Behçet's Disease

Behçet's disease is a chronic, relapsing systemic vasculitis that can affect all organ systems. The exact etiology of the disease remains unclear, but it is believed that genetic predisposition, environmental factors, viral and bacterial infections, and immunological factors play a role in the pathogenesis of the disease. One of the most important clinical manifestations of Behçet's disease is oral aphthous lesions, which often present as the first sign of the disease. Aphthous ulcers are classified into minor, major, and herpetiform types. Minor ulcers are typically less than 10 mm in size, with a superficial lesion that can be easily sloughed. Major ulcers, on the other hand, are deeper, more painful, greater than 10 mm in size, and may take up to 30 days to heal. The diagnosis of Behçet's disease is made based on the presence of oral aphthae that recur at least three times a year, in addition to genital ulcers, skin lesions, and ocular involvement. (Mumcu et al., 2004)

Scleroderma

Scleroderma is a chronic disease characterized by the excessive accumulation of collagen in the skin and internal organs. While there are localized forms of the disease that affect only the skin and subcutaneous tissues, a systemic form exists that can impact all organ systems. In addition to excessive collagen production, widespread damage to vascular structures and dense mononuclear cell infiltration in perivascular tissues also play a role in the pathogenesis of the disease. Oral manifestations of scleroderma include restricted mouth opening, dry mouth, widespread gingival recession, and insufficient attached gingiva width, which are indicative of mucogingival problems. (Ozçelik et al., 2008)

Juvenile Hyaline Fibromatosis (JHF)

Juvenile Hyaline Fibromatosis (JHF) is a rare mesenchymal - origin disease characterized by the excessive accumulation of hyaline material in the skin and all soft tissues, although its exact etiology remains unclear. The lesions appear as nodules, papules, or tumor-like masses ranging from 1 to 5 mm in diameter, typically causing pain. The accumulation of hyaline material in internal organs is also a common feature of the disease. In JHF patients, widespread gingival hyperplasia, characterized by nodular formations in the gingiva, is commonly observed. (Hakkı, Balcı, Hakkı, Yılmaz, & Nohutcu, 2005)

Atopic Dermatitis

Atopic dermatitis is a chronic inflammatory skin disease that typically begins in infancy or early childhood, accompanied by genetic predisposition and triggered by various allergens. Clinically, it is characterized by erythema with indistinct borders, primarily affecting the nose and mouth areas,

particularly the cheeks, as well as the forehead and chin. Lesions may also develop on the scalp, neck, extensor surfaces of the extremities, and trunk. In these patients, mucogingival problems are often observed as well. (De Benedetto et al., 2009)

Ectodermal Dysplasia

Ectodermal dysplasia is an inherited condition affecting ectodermal tissues such as skin, hair, sweat and sebaceous glands, as well as teeth, leading to developmental abnormalities in these structures. Individuals with ectodermal dysplasia typically have fine, short, and sparse hair, as well as eyebrows and eyelashes that are thin. The skin is soft, smooth, and dry. Fine linear wrinkles may be observed around the eyes and mouth, while nails may exhibit thickening, discoloration, dark pigmentation, and deformities. Due to hypoplasia or aplasia of the salivary glands, dry mouth may occur, which can exacerbate inflammation in periodontal tissues. Additionally, tooth loss and mucogingival problems are common oral manifestations of the disease. (Yavuz et al., 2006)

Fibrous Dysplasia

Fibrous dysplasia is a mesenchymal-origin developmental anomaly of bone tissue, with an etiology that is not fully understood. The condition is characterized by the replacement of normal or inadequately developed bone tissue with fibrous tissue or the formation of irregular osteoid. In the affected bone regions, abnormal growth, deformities, and fractures may occur. When the facial and cranial bones are involved, serious complications such as hearing and vision loss may develop. In cases where the maxilla and mandible are affected, jaw bone enlargement can lead to malocclusion, tooth displacement, gingival hyperplasia, and increased gingival inflammation. (Alawi, 2002)

Sturge - Weber Syndrome (SWS)

Sturge - Weber Syndrome (SWS) is a rare, non - hereditary condition characterized by facial capillary malformations. The development of SWS occurs due to insufficient regression of the embryological venous plexus during the first trimester of pregnancy. The disease presents with clinical findings affecting the dermatological, neurological, and ocular systems. Capillary malformations and hemangiomas, typically presenting unilaterally on the face and often referred to as “port-wine stains” or nevus flammeus, are characteristic. These malformations commonly follow the distribution of the branches of the trigeminal nerve, with the maxillary and mandibular branches often involved. (Bhansali, Yeltiwar, & Agrawal, 2008)

The oral manifestations of SWS are characterized by widespread hemangiomas in the oral tissues. (De Benedittis et al., 2007) Red-to-purple growths can be observed on the gingiva, floor of the mouth, hard palate,

tongue, lips, and buccal mucosa. Patients may experience excessive gingival bleeding even with minimal stimulation. Additionally, some SWS patients on anticonvulsant medications due to neurological symptoms often report gingival hyperplasia as a side effect of these drugs.

Rothmund - Thomson Syndrome (RTS)

Rothmund-Thomson Syndrome (RTS) is an autosomal recessive disorder characterized by hypopigmentation and hyperpigmentation of the skin, macules, photosensitivity, and juvenile cataracts. Patients with RTS have an increased risk of developing skin and bone malignancies. Oral manifestations of the disease include microdontia, missing teeth, malocclusion, flat and shiny gingiva, spontaneous bleeding, a predisposition to periodontitis, and structural abnormalities such as disruption of the basal membrane continuity and separation of the epithelium from the connective tissue in the gingiva. (Haytaç, Oztunç, Mete, & Kaya, 2002)

Effect of Medication on the Periodontium

Drug - Induced Gingival Enlargement

Certain systemic medications can cause gingival enlargement as a side effect. These include phenytoin sodium, used as an anticonvulsant in epilepsy treatment; cyclosporine, an immunosuppressant used to prevent rejection following organ transplantation; and nifedipine, a calcium channel blocker used in the treatment of hypertension. The pathogenic mechanisms underlying gingival changes and enlargement observed with all three classes of drugs are similar. Enlargement typically begins in the interdental papillae and progresses to involve the entire free and attached gingiva in a painless manner. In advanced cases, it may cover the entire tooth surface, potentially impairing chewing and speech. (Ilgenli, Atilla, & Baylas, 1999)

Gingival enlargement caused by these medications tends to affect the labial surfaces of the upper and lower anterior teeth more frequently, and it has been reported that younger individuals are more commonly affected. The prevalence of drug-induced gingival enlargement varies between 8% and 80% in different studies. Factors such as the medication's dosage, duration of use, serum concentrations, patient age, oral hygiene, degree of gingival inflammation, and genetic predisposition are known to influence the development of gingival enlargement; however, the individual impact of these factors has not been fully established. (Seymour, Thomason, & Ellis, 1996)

The absence of gingival enlargement in edentulous areas highlights the importance of microbial dental plaque in the etiology of the enlargement, although the exact pathogenic effects remain unclear.

Bisphosphonate - Related Osteonecrosis of the Jaw (BRONJ)

Bisphosphonates (BP) are synthetic analogs of endogenous pyrophosphates and are primarily used to inhibit bone resorption. These agents are widely utilized in the treatment of osteopenia and early-stage osteoporosis, bone metabolic disorders such as Paget's disease, hypercalcemia associated with malignancies, and in conditions like metastatic breast and prostate cancers, as well as multiple myeloma. Although bisphosphonates do not have direct antineoplastic effects, they aim to enhance the quality of life of patients by controlling symptoms in these diseases. Intravenous (IV) forms of bisphosphonates, such as pamidronate and zoledronic acid, are used in the treatment of malignancies, and their clinical use began in the 2000s. For osteoporosis treatment, oral tablet forms are preferred.

Bisphosphonates exert their effects on bone by binding to hydroxyapatite crystals found on the surface of mineralized bone. (Marx, 2006) They inhibit the resorptive capacity of osteoclasts by inducing apoptosis, and also indirectly inhibit matrix metalloproteinases (MMPs) such as MMP-1 and MMP-3 by suppressing their production. These effects suggest that bisphosphonates are particularly effective during the early phase of bone resorption. (McCauley & Nohutcu, 2002)

During bone resorption, mature multinucleated osteoclasts stimulate the maturation of pre-osteoblasts toward bone formation via paracrine signaling. However, bisphosphonates induce osteoclast apoptosis before this signaling pathway, thereby disrupting the process. As a result, not only resorption but also bone remodeling is halted. This leads to an inability to remove old bone tissue and a failure to form new bone. Over time, osteocyte death occurs, hypermineralization develops, and cumulative mineral accumulation is observed in the bone matrix. Ultimately, necrotic bone tissue forms in the affected area. (Marx, 2006)

Repeated dosing of bisphosphonates leads to their cumulative accumulation in the bone mineral matrix. IV bisphosphonates can affect nearly the entire skeletal system within approximately 12 months, while oral formulations may take up to 48 months to reach similar levels of accumulation. (Marx, Sawatari, Fortin, & Broumand, 2005) In individuals using bisphosphonates for an extended period, particularly following traumatic dental procedures such as tooth extractions or periodontal surgery, the bone remodeling process in the alveolar bone does not begin. In addition, the affected bone becomes exposed in the form of sequestration, as the mucosal tissue in the area loses its vascular support. This condition is defined as bisphosphonate-related osteonecrosis of the jaw (BRONJ).

BRONJ was first reported in 2003, characterized by exposed bone limited to the jaws, resistant to surgical debridement and pharmacological

treatment, and complicated by secondary infection. With the increased use of bisphosphonates, the number of osteonecrosis cases has also risen. However, a universally accepted treatment algorithm for managing this complication has not been established. Treatment planning is based on the clinical size of the lesion and the patient's systemic condition, with different treatment protocols suggested according to various staging systems. Therefore, every patient using bisphosphonates and planning dental interventions should be comprehensively evaluated. Adequate information should be provided to the patient, and a multidisciplinary approach should be adopted by consulting the relevant specialist (oncologist, rheumatologist, etc.), while considering potential complications to carefully devise a treatment plan.

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Chapter 2

NEGLECTED FACTOR IN ENDODONTIC TREATMENT SUCCESS: TEMPORARY FILLING SELECTION AND APPLICATION TECHNIQUE

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1. Introduction

The success of endodontic treatment is closely related not only to the proper disinfection and filling of the root canal system, but also to the coronal sealing between treatment sessions. Root canal treatment often cannot be completed in a single session; especially in cases of persistent infection, presence of extensive periapical lesions or symptomatic cases, the treatment is divided into several sessions. In this process, if the pulp cavity is not temporarily closed, microorganisms and saliva from the oral environment may re-enter the canal system. Therefore, temporary filling materials have a critical role in preventing microleakage during treatment by creating a barrier between the root canal system and the oral cavity (Feliz Matos, Rodriguez Ide, Gonzalez, Pereyra, & Monzon Velez, 2013).

An ideal temporary filling material should have excellent sealing, appropriate mechanical strength, biocompatibility, easy applicability and easy removal at the end of treatment. In addition, the material should be resistant to abrasion, aesthetically acceptable and stable in the presence of moisture. Unfortunately, none of the materials used today can fulfil all of these properties at the same time. Therefore, the choice of material should be based on the characteristics of the clinical situation, the duration of treatment and the localisation of the tooth (Jacquot, Panighi, Steinmetz, & G'Sell, 1996).

Temporary filling materials have historically evolved in a wide range from zinc oxide-eugenol based products to advanced glass ionomer or resin modified materials. In particular, materials such as Cavit and IRM (Intermediate Restorative Material) have been used as standard temporary fillings in clinics for many years; however, in recent years, superior sealing and mechanical properties have been obtained thanks to nanotechnological additives, bioceramic ingredients and resin-based hybrid systems. In addition, the fact that today's materials have gained antibacterial properties and exhibit behaviours such as expansion in contact with saliva has enabled temporary fillings to become active protective systems rather than just passive barriers (Cruz et al., 2002).

The success of temporary filling materials used during endodontic treatment depends not only on the content of the material, but also on the application technique, thickness, cavity design and surface preparation. Various in vitro studies have shown that temporary fillings, especially those applied with a thickness of 3.5-4 mm, provide more effective sealing. In addition, factors such as the location of the tooth in the anterior or posterior region, the intensity of occlusal loads and moisture control directly affect the clinical performance of the material (Paulo et al., 2023).

In this chapter, the historical development, content characteristics, clinical usage areas, advantages and disadvantages of temporary filling materials used

in endodontic treatments will be discussed in detail. In addition, current literature findings comparing different materials in terms of impermeability and durability will be evaluated and recommendations that will shed light on material selection in clinical applications will be presented.

2. Basic Requirements of Temporary Filling Materials

2.1. Sealing (Prevention of Coronal Microleakage)

The most basic task of the temporary filling material is to create a physical barrier that prevents the re-entry of microorganisms, saliva and organic residues in the oral environment into the root canal system. Coronal leakage after root canal treatment is one of the leading causes of failure. The risk of re-invasion of oral microflora increases, especially when the waiting time between treatment sessions is prolonged.

Materials with hygroscopic expansion properties, such as Cavit, expand when in contact with water and adapt better to the cavity walls, thereby reducing micro-leakage. In contrast, zinc oxide-eugenol-based materials such as IRM, although they have higher mechanical strength, are not as effective as Cavit in terms of sealing (Balla, LoMonaco, Skribner, & Lin, 1991). Clinically, a filling thickness of at least 3.5-4 mm is considered critical for sealing. Thinner layers may be deformed by chewing forces and marginal gaps may occur.

2.2. Mechanical Strength and Abrasion Resistance

The temporary filling material must be resistant to occlusal loads, thermal changes and mechanical stresses during the treatment period. Poor mechanical properties can lead to fracture, collapse or separation of the material from the cavity.

Due to the intensity of occlusal forces, especially in posterior teeth, the temporary filling must have a high compressive strength (Webber, del Rio, Brady, & Segall, 1978). Materials such as IRM and TermpBond provide high compressive strength due to their zinc oxide-eugenol-based structure, but edge adaptation may be impaired due to the different coefficient of thermal expansion of these materials than dentin.

On the other hand, Cavit has a weaker structure against abrasion due to its water absorption feature and may lose edge integrity in long-term use. Therefore, Cavit is preferred for short-term temporary closures, while IRM or glass ionomer-based materials are recommended for long-term temporary restorations (Singla, Bogra, & Singal, 2012).

2.3. Biocompatibility (Biological Compatibility and Toxicity Status)

Temporary filling material should not cause irritation, cytotoxicity or inflammation in contact with pulp, periodontal ligament or mucosal tissues.

Eugenol, especially in zinc oxide-eugenol-based materials, can suppress cell proliferation at high concentration (Koagel, Mines, Apicella, & Sweet, 2008). In modern materials, this disadvantage is minimised with eugenol-free formulations or resin-added systems. Glass ionomer-based temporary materials reduce the risk of secondary caries thanks to fluorine release and provide advantages in terms of biocompatibility.

In addition, factors such as pH value, monomer release and ion solubility of the material directly affect biocompatibility. In clinical practice, biocompatible materials should be preferred especially in large cavities or in areas where pulp exposure is imminent (Hashem et al., 2024).

2.4. Ease of Application and Removal

In terms of clinical efficacy, the temporary material is expected to be easily mixable, adaptable to the cavity and hardenable in a short time. These properties are especially important for time management in endodontic treatments.

Cavite is a practical material because it is ready to use and self-curing. In contrast, materials such as IRM are prepared as a powder-liquid mixture, which can create variability depending on operator experience (Naseri, Ahangari, Shahbazi Moghadam, & Mohammadian, 2012). During the removal of the material at the end of the treatment, the root canal filling or dentin should not be damaged. Especially if resin-added materials harden too much, the removal process may become difficult. Therefore, it is recommended to apply the temporary filling only at the required thickness and to control the hardening time.

2.5. Radiopacity (Radiographic Visibility)

Radiopacity allows the temporary filling to be clearly distinguished on radiography. This feature is important for checking whether the material is in place, marginal cavities or cavities within the cavity.

Radiopacity is usually achieved by additives such as barium sulphate, bismuth oxide or strontium glass. These additives do not affect the sealing properties of the material, but can reduce mechanical strength if the formulation is out of balance (Ermis, Yildirim, Yildiz, & Gormez, 2014). Glass ionomer and resin-modified materials show adequate radiopacity in their modern formulations. Radiographic evaluation is also of clinical importance to recognise overflow of canal media or inadequate filling thickness (Lachowski, Botta, Lascala, Matos, & Sobral, 2013).

2.6. Aesthetic Properties (Colour Harmony and Opacity)

When temporary filling materials are used especially in anterior teeth, aesthetic appearance also becomes important. Patient satisfaction is enhanced

if the material is translucent, close to the tooth colour.

Some materials (e.g. Cavit and IRM) are white or light grey, which can be conspicuous in aesthetic areas. Therefore, composite-based temporary materials (e.g. Clip F, Fermit N) are preferred for aesthetic restorations (Yannikakis, Zissis, Polyzois, & Caroni, 1998). Aesthetic harmony is important not only for appearance but also for the optical stability of the material, as discolouration or pigment absorption can be perceived as clinical failure. (Prasad, Alva, & Shetty, 2014).

2.7. Stability and Chemical Stability in Humidity

The oral environment is characterised by constant changes in humidity, saliva and temperature. Therefore, the hydrophilic stability of the temporary filling material must be high.

The cavity expands in contact with moisture, which is advantageous in terms of sealing, but may lead to mechanical weakening in long-term use. In contrast, IRM is more dimensionally stable in the presence of moisture, but its marginal adaptation may deteriorate over time.

The solubility of the material should be low and it should not react chemically with intra-canal media. For example, some materials in contact with calcium hydroxide may lose hardness due to ion exchange.

2.8. Antibacterial Properties

Some temporary filling materials show antibacterial effect thanks to the active ingredients they contain. For example, IRM containing eugenol provides short-term antibacterial effect. However, long-term contact is not recommended due to the cytotoxic effects of eugenol.

New generation materials have gained antibacterial properties with silver nanoparticles, chlorhexidine or chitosan additives. These materials not only act as a passive barrier, but can also reduce the activity of residual bacteria.

This feature is especially valuable in multi-session treatments as a supportive factor for the effect of the intra-canal medication.

2.9. Compatibility with Final Restorative Materials

The temporary filling material should be chemically or physically compatible with the final restoration (composite, glass ionomer, ceramic, etc.). Especially eugenol-containing materials may reduce the success of the composite restoration by inhibiting resin polymerisation.

Therefore, eugenol-free temporary materials should be preferred in cases where composite restoration is planned. In addition, cleaning the cavity walls with solvent or alcohol after removal of the temporary filling prevents surface contamination and increases bond strength (Hitij & Fidler, 2013).

2.10. Thermal Expansion, Dimensional Stability and Physical Properties

The coefficient of thermal expansion of the temporary materials should be close to the surrounding tooth tissue. Excessive expansion or contraction causes edge leakage.

In addition, condensation stress caused by temperature changes can lead to cracking or separation of the material, especially in the occlusal region.

Moisture absorption behaviour is also an important factor: Cavite expands because it is hygroscopic, which is an advantage in the short term and a weakness in the long term. In contrast, IRM has low moisture absorption, which improves dimensional stability (Ermis et al., 2014).

2.11. Additional Clinical Features

The material must not release taste, odour or irritants. This problem is more evident especially in materials containing phenolic components.

In addition, the surface roughness should be low, preventing plaque accumulation. High surface roughness increases the risk of secondary infection by increasing bacterial adhesion (Emamieh, Ghasemi, & Torabzadeh, 2011). Finally, the fact that the temporary filling is economical, easily available and has a long shelf life is preferred for clinical application.

3. Types of Temporary Filling Material

Temporary filling materials are divided into different classes according to their content and physical properties. Historically, the first materials used were zinc oxide-eugenol-based systems, while zinc sulphate, glass ionomer, resin modified and bioceramic additive materials have been developed over time. Each type of material has its own advantages and limitations (Mickevičienė, Lodienė, & Venskutonis, 2020).

3.1. Zinc Oxide-Eugenol (ZOE) Based Materials

Composition and Hardening Mechanism

ZOE-based materials contain zinc oxide (ZnO) in powder form and eugenol (phenolic compound) in liquid phase. When the powder and liquid are mixed, zinc eugenolate is formed as a result of an acid-base reaction. This reaction is exothermic and the material hardens at room temperature.

Most known examples: IRM (Intermediate Restorative Material), Kalzinol, Cavitec, ZOE Cement (Topçuoğlu, Düzgün, Akyüz İ, & Manolya Özdemır, 2025).

Advantages

- Suitable mechanical strength and pressure resistance

- Antibacterial effect (especially from eugenol)

- Relatively low cost

- Easy to mould and remove

Disadvantages

- Sealing properties are weaker than materials such as Cavit

- May cause irritation or temporary sensitisation of pulp tissue due to eugenol content

- Inhibits the polymerisation of resin-based restorations

- Resolution and colour change may occur with prolonged use

Clinical Use

ZOE-based materials are generally preferred for short-term temporary closures in posterior teeth. In cases where composite restorations are planned, eugenol-free modifications (e.g. IRM-E) should be preferred.

3.2. Zinc Sulphate Based Materials (Cavit Type Products)

Composition and Mechanism

Cavit-type materials (Cavit, Cavit-G, Cavit-W, Cavit-N) mainly contain zinc oxide, zinc sulphate, calcium sulphate, glycol acetate and polyvinyl acetate. The material hygroscopically expands by absorbing water; this expansion increases mechanical adaptation to cavity walls and reduces microleakage (Webber et al., 1978).

Advantages

- Excellent impermeability (especially in short-term applications)

- Ready to use, no mixing required

- Self-hardening, completes polymerisation in the presence of moisture

- Ease of application and removal

Disadvantages

- Low mechanical strength, may fracture under occlusal load

- Tends to wear and collapse with prolonged use

- When over-expanded with moisture, it may cause micro-cracks in the cavity walls

Clinical Use

Cavit-type materials are the most commonly used temporary filling in cases requiring a short waiting period between single sessions. It is especially

preferred in anterior and small posterior cavities. The thickness should be at least 3.5 mm.

3.3. Glass Ionomer Based Temporary Filling Materials

Composition and Reaction Mechanism

Glass ionomer materials are a mixture of aluminofluorosilicate glass and polyacrylic acid. Hardening takes place through an acid-base reaction, resulting in adhesion to dentin through ionic bonds. Temporarily used samples: Ketac™ Silver, Fuji IX, AquaCem (Spadone, Gallarda, Fischman, & Olié, 1999).

Advantages

- Chemical binding to dentin
- Reducing the risk of secondary caries by fluorine release
- Moderate mechanical strength and abrasion resistance
- High moisture tolerance

Disadvantages

- Hardening time is long
- Excessive humidity or saliva contamination may weaken binding
- Tendency to crack under high occlusal stress

Clinical Use

Glass ionomer-based materials can be used for long-term temporary restorations or for cavity floor sealing in combination with temporary filling. It is also preferred for temporary solutions in pedodontic cases.

3.4. Resin and Composite Modified Temporary Materials

Composition and Properties

These materials contain methacrylate monomers (e.g. UDMA, Bis-GMA) and filler particles. Polymerisation is initiated by light or chemically.

The most known examples: Fermit N, Clip F, Luxatemp, Protemp, Structur 2 (Creugers, De Kanter, Verzijden, & Van't Hof, 1998).

Advantages

- High mechanical strength
- Aesthetically superior appearance
- Low resolution and high dimensional stability
- Easy to shape, can be applied in one step

Disadvantages

- High cost
- Dentin may be damaged during removal
- Sealing properties are not as strong as Cavit
- Pulp irritation may occur due to heat increase in some materials

Clinical Use

Resin modified materials are frequently used in the preparation of aesthetic temporary restorations, veneers or ceramic crowns, especially in the anterior region. In endodontics, it is suitable for temporary closure after root canal treatment in the aesthetic area.

3.5. New Generation (Nanotechnological and Bioceramic Additive) Materials

Composition and Innovations

Temporary filling materials developed in recent years strengthen traditional structures with biological and nanotechnological additives. These materials are;

- Nanoparticle doped zinc oxide,
- Bioceramic (calcium silicate) based systems,
- Antibacterial agents (e.g. chlorhexidine, silver nanoparticles),
- It stands out with its self-healing properties.

Advantages

- High biocompatibility and antibacterial effect
- Long-term dimensional stability
- Remineralisation potential by ion release (Ca^{2+}, Si^{4+}) in some systems
- Increased sealing and mechanical performance

Disadvantages

- Clinical use is still limited and costly
- Difficulty in removal and high stiffness may be a problem
- Long-term clinical data are limited

Clinical Use

New generation temporary materials are preferred especially in high-risk endodontic cases and long-term temporary closures. The potential of bioceramic-containing systems to reduce residual inflammation after treatment has been reported in the literature (Dhar & Kaur, 2021).

4. Points to be Considered During Application

The clinical success of temporary filling materials depends not only on the properties of the material but also on the correct application technique. The main points to be considered during the application process are summarised below:

4.1. Cavity Preparation and Cleaning

Before temporary filling, the cavity walls should be cleaned from canal irrigant residues and saliva isolation should be ensured.

- If sodium hypochlorite or EDTA residue remains on the surface, material bonding weakens.

- Moisture should be controlled with cofferdam or cotton rolls.

4.2. Closing the Channel Mouth (Base Application)

In cases where a medikament is placed, the canal openings should be covered with PTFE (Teflon) tape or a temporary base that is not affected by moisture.

- Cotton pellets are not recommended; they may leave fibres and reduce the filling thickness.

- PTFE provides a smooth surface and facilitates material removal.

4.3. Thickness of the material

Studies have shown that for effective sealing, the thickness of the temporary filling should be at least 3.5-4 mm.

- Thinner layers may leak or collapse with chewing pressure.

- Especially in Cavit type materials, this thickness is critical.

4.4. Edge Adaptation and Compression

The material should be adapted to the cavity walls with light pressure.

- Especially Cavit should not be over pressurised as it expands by absorbing water.

- When applying IRM or GIC, marginal integrity should be ensured with a spatula.

4.5. Occlusion Control

After application, occlusal high contacts should be checked.

- Excessive load causes the material to break or crack.

- If necessary, high points should be corrected with articulation paper.

4.6. Hardening and Contamination

Ambient humidity should be sufficient for moisture-curing materials such as Cavit.

However, for glass ionomer or resin modified materials, excessive humidity adversely affects bonding.

- Therefore, a controlled humidity environment should be provided according to the type of material.

4.7. Removal Phase

When removing the temporary filling:

- The cavity wall must not be damaged,

- There should be no leakage into the canal mouth,

- For resin-based systems, the surface should be cleaned with alcohol or chlorhexidine.

4.8. Clinical Summary

- Thickness should be ≥ 4 mm.

- PTFE tape should be used as the base.

- Isolation is a must.

- High occlusion must be corrected.

- Humidity control should be adjusted according to the type of material.

5. Points to be Considered During Application

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However, for glass ionomer or resin modified materials, excessive humidity adversely affects bonding.

- Therefore, a controlled humidity environment should be provided according to the type of material.

5.7. Suspension Phase

When removing the temporary filling:

- The cavity wall must not be damaged,

- There should be no leakage into the canal mouth,

- For resin-based systems, the surface should be cleaned with alcohol or chlorhexidine.

5.8. Clinical Summary

- Thickness should be ≥ 4 mm.

- PTFE tape should be used as the base.

- Isolation is a must.

- High occlusion must be corrected.

- Humidity control should be adjusted according to the type of material.

6. Conclusion

Temporary filling materials, although often overlooked in the success of endodontic treatment, are of vital importance in ensuring coronal sealing between treatment sessions. Re-invasion of microorganisms during root canal treatment is one of the most common causes of treatment failure. Therefore, the temporary filling material should be considered not only as a passive barrier isolating the duct system from the external environment, but also as a biologically and mechanically active protective element (Balla et al., 1991).

Although no material has all the ideal properties at the same time, a high success rate can be achieved by making the appropriate choice according to the clinical conditions.

- Cavit and similar zinc sulphate-based materials provide superior sealing between short-term treatments.

- IRM and glass ionomer-based materials offer mechanical strength and stability in long-term temporisation.

- Resin-modified or bioceramic-added materials are an alternative in cases with aesthetic requirements or in complicated cases.

- The double barrier technique (GIC + Cavit or IRM) stands out as the most reliable approach, especially in long-term treatments.

Success in clinical applications is possible with the application of appropriate thickness, good isolation, control of occlusal loads and correct material selection according to the duration of treatment, rather than the chemical content of the material.

As a result, the selection of temporary filling material should not be considered as a "routine procedure" but as a strategic part of the treatment plan. This approach will preserve not only the biological success of the endodontic treatment but also the long-term functional integrity of the tooth.

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Chapter 3

FUNCTIONAL AND AESTHETIC ADVANTAGES AND DISADVANTAGES OF BRACKET TYPES

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Introduction

The primary aim of orthodontic treatments today is to ensure that brackets adhere firmly and permanently to the tooth surface. The micromechanical bonding approach to the enamel surface was first defined by Buonocore in 1955. This technique aims to increase the bonding strength of adhesive systems by creating microscopic irregularities on the enamel surface using an acid etching method. (Buonocore, 1955) Newman (1965), It has been noted that bonding brackets directly to the enamel surface not only provides an aesthetic benefit but also reduces the risk of demineralisation.

Nowadays, fixed orthodontic treatments are carried out by bonding brackets to the tooth surface or restorative materials using adhesive systems, ensuring that orthodontic forces are effectively transmitted to the teeth. (Proffit, Fields & Larson, 2019). The success of this treatment method depends on various factors, such as the mechanical strength of the bracket materials used, patient compliance, and adequate oral hygiene. (Millett et al., 2003). The bonding strength of brackets is influenced by variables such as the surface preparation method, the type of adhesive used, and the physical properties of the bracket. (Öztürk & Malkoç, 2006). Nowadays, stainless steel and ceramic brackets are among the most frequently preferred systems in orthodontic treatments. In line with increasing aesthetic expectations, the use of ceramic brackets has become more widespread, particularly in adult patients. (Eliades & Athanasiou, 2002). Ceramic brackets offer high biocompatibility, chemical resistance and aesthetic advantages as they are manufactured from polycrystalline or monocrystalline aluminium oxide. (Karamouzos et al., 1997). On the other hand, studies have shown that the bonding strength of ceramic brackets to enamel is often higher than that of stainless steel brackets. (Russell, Way & Reese, 1995). However, despite all these aesthetic advantages, stainless steel brackets are still considered the gold standard in orthodontic treatment. (Kusy, 2002). With the increasing demand for orthodontic treatment, new generation aesthetic systems such as transparent, ceramic and sapphire brackets have been developed for individuals who prioritise aesthetic concerns. (Eliades & Papageorgiou, 2018). At the same time, arch wires produced from flexible alloys such as nickel-titanium also increase treatment success by providing more controlled and constant force application during treatment. (Andreasen et al., 2001).

1. BRACKETS

Braces are used as one of the fundamental components of treatment in orthodontics, a specialised field of dentistry. Derived from the English word "brace," this term refers to the function of binding. In orthodontic treatment, they can be defined as devices that are bonded to the tooth surface and have channels (slots) through which orthodontic wires pass. Although they

are usually made of stainless steel, types made of ceramic or plastic-based materials are also available for aesthetic reasons.(Khan, 2015). Orthodontic braces are effectively used to correct malocclusions, crooked teeth, diastema, open and crossbites, deep bites, gaps between teeth, and other abnormalities in the structure of the teeth and jaw.(Proffit et al., 2019). These brackets can be of different types, such as cosmetic brackets used for aesthetic purposes, lingual brackets placed on the tongue side, or traditional structural brackets. (Eliades & Athanasiou, 2002). Additionally, during orthodontic treatment, auxiliary devices such as clear aligners and elastic bands are used alongside braces to help move the teeth and jaw into their desired position(Kravitz et al., 2008).

2. HISTORY OF BRACKETS

Dental and jaw disorders have been among the health issues that have attracted the attention of different societies throughout history. The earliest information on orthodontic practices can be found in written sources belonging to Ancient Egypt and Ancient Greece. Aulus Cornelius Celsus, a physician and thinker who lived in ancient times, suggested that the position of teeth could be changed by applying regular finger pressure.(Celsus, M.S. 25, akt. Proffit et al., 2019). During the Middle Ages, when Islamic civilisation flourished, significant advances were made in orthodontics. Ali bin Abbas, who lived in the 10th century, argued that teeth causing irregularities in dental alignment should be extracted.(Kieser, 2000). During the Middle Ages, when Islamic civilisation flourished, significant advances were made in orthodontics. Ali bin Abbas, who lived in the 10th century, argued that teeth causing irregularities in dental alignment should be extracted. (Altan, 2012These examples demonstrate that the historical roots of orthodontics run quite deep. During the Ottoman period, Sabuncuoğlu Şerefeddin, known by the title of chief physician, served in the court of Sultan Mehmed the Conqueror and, in his medical works, addressed various dental diseases as well as congenital cleft lip and palate problems.(Altan, 2012). Pierre Fauchard, who laid the foundations of modern dentistry, carried out numerous treatments on patients using the removable orthodontic appliances he developed in the 18th century. During this period, he recorded in detail the treatment cases of 12 different patients. (Ring, 1985). In the 19th century, Edward H. Angle established a scientific classification system in orthodontics, defining the fundamental types of malocclusion recognised today, and is regarded as the founder of modern orthodontics. (Proffit et al., 2019). Throughout the 20th century, orthodontic treatment techniques have advanced further; with the widespread use of metal brackets, applications involving intraoral and extraoral appliances have become systematic. Clinical data obtained from applications targeting malocclusions during this period have provided significant experience in treatment planning. (Graber et al., 2017). Throughout

the 20th century, orthodontic treatment techniques have advanced further; with the widespread use of metal brackets, applications involving intraoral and extraoral appliances have become systematic. Clinical data obtained from applications targeting malocclusions during this period have provided significant experience in treatment planning. (Papadimitriou et al., 2018).

3. BRACKET TYPES

The most commonly used type of bracket in orthodontic treatments is metal brackets. During the treatment process, after the brackets are placed on the teeth, the orthodontist monitors the patient at regular intervals and makes the necessary tension adjustments to the wires. This ensures that the teeth are gradually guided into the desired position over time. (Proffit et al., 2019). The most commonly used type of bracket in orthodontic treatments is metal brackets. During the treatment process, after the brackets are placed on the teeth, the orthodontist monitors the patient at regular intervals and makes the necessary tension adjustments to the wires. This ensures that the teeth are gradually guided into the desired position over time. (Eliades & Athanasiou, 2002).

3.1. Metal Brackets

3.1.1. Stainless Steel Brackets

Stainless steel is an alloy containing at least 10.5% chromium by weight, also known as "inox steel" in metallurgical literature.(Deger et al., 2016). This material is classified into different types based on its crystalline structure and is particularly favoured for the production of brackets used in orthodontic applications. Orthodontic brackets must possess a certain degree of hardness, durability and elasticity in order to transmit the necessary force to the teeth via wires. Stainless steel stands out as the most commonly used bracket material in orthodontics, as it meets these requirements at an optimal level. (Proffit et al., 2019). Austenitic stainless steel, in particular, stands out from other types of stainless steel due to its advantages such as high corrosion resistance, low production cost and superior formability. (Kusy, 1997). Due to these properties, the most commonly used type of steel in the manufacture of orthodontic brackets and wires is austenitic stainless steel. The elements present in stainless steel alloys directly affect the material's mechanical and chemical properties. Carbon increases the hardness and strength of the alloy, but high levels of carbon can lead to the formation of chromium carbides, which can cause localised corrosion in the oral environment. (Deger et al., 2016). Chromium, on the other hand, provides resistance to oxidation. Thanks to the passive chromium oxide layer formed on the surface of stainless steel, it prevents oxygen from reaching the internal structure and thus prevents surface corrosion.(Kusy, 1997). Chromium, on the other hand, provides resistance to oxidation. Thanks to the passive chromium oxide layer formed

on the surface of stainless steel, it prevents oxygen from reaching the internal structure and thus prevents surface corrosion. (Wataha, 2000). Manganese, like nickel, contributes to the formation of an austenitic structure and can therefore be used as an alternative to nickel.

Various elements present in stainless steel alloys play an important role in shaping both mechanical and chemical properties. Nitrogen supports the formation of the austenitic phase by exhibiting a nickel-like effect and increases the stability of this phase. (Deger et al., 2016). Molybdenum improves the alloy's overall corrosion resistance by increasing its resistance to pitting corrosion in particular. Titanium, on the other hand, stabilises the free carbon within the material by forming carbides with carbon atoms, thereby increasing its resistance to corrosion (Wataha, 2000). Phosphorus not only enhances the alloy's corrosion resistance but also stands out for its ability to reduce sintering (compaction) temperature. Niobium and tantalum control carbide formation by binding carbon, thereby preventing the degradation of the passive layer and increasing corrosion resistance. Copper is added to the alloy to increase the material's mechanical strength by providing precipitation hardening (Kusy, 1997). Selenium and sulphur improve the workability of steel and its usability in the production process; however, it is known that these elements can have adverse effects on hardness and mechanical strength.

3.1.2. Titanium Brackets

Titanium is a metal widely used in dentistry due to its superior biocompatibility and high corrosion resistance (Wataha, 2000). Thanks to these qualities, titanium brackets have been developed as an alternative to stainless steel brackets, particularly for individuals with nickel sensitivity (Kusy, 1997). Alloyed titanium is preferred in orthodontics because it exhibits greater mechanical strength compared to pure (unalloyed) titanium. Today's titanium bracket systems are generally manufactured from grade 2 alpha titanium or grade 4 titanium materials in the alpha-beta phase (Deger et al., 2016). The bracket base is made from grade 2 titanium, which has a softer structure, while the wing (slot) section, which requires greater rigidity and torque resistance, is produced from alpha-beta titanium. These two different types of titanium are joined together using laser welding to form a single unit. Thus, while the wing section of the bracket provides the necessary rigidity, the base section is kept more flexible to facilitate mechanical separation. This design aims to optimise both clinical durability and ease of application. Ensuring these features in clinical applications is of great importance for the success of the treatment. Titanium and titanium alloy brackets exhibit a much higher level of corrosion resistance compared to stainless steel brackets, thanks to the naturally formed passive protective titanium dioxide (TiO_2) layer on their surfaces (Wataha, 2000). This oxide layer, which forms naturally on the surface of titanium, is chemically more stable and longer lasting than

the chromium oxide film found on stainless steel (Kusy, 1997). This passive layer ensures that titanium-based brackets exhibit superior performance against corrosion, particularly in electrochemically active environments such as the oral cavity. For this reason, titanium and its alloys are among the preferred materials in orthodontics, due to their biocompatibility as well as their superior corrosion resistance.

During sliding mechanics in orthodontic treatments, the passive titanium dioxide layer on the surface of titanium maintains its structural stability. Therefore, when titanium brackets are used with stainless steel archwires, effective and controlled tooth movement can be achieved, as is the case with stainless steel brackets (Kusy, 1997). Furthermore, the alloyed titanium materials used in the production of titanium brackets have a lower coefficient of friction compared to pure titanium. This reduces friction between the bracket and the wire, contributing to more efficient operation of the sliding mechanisms (Proffit et al., 2019).

3.1.3. Chromium Cobalt Brackets

Cobalt-chromium brackets were introduced for orthodontic use in the mid-1990s as an alternative material to stainless steel brackets. (Kusy, 1997). These brackets are generally manufactured using casting or metal injection moulding (MIM) techniques in terms of production method. Cobalt-based brackets used in orthodontics today are selected from alloy types that are particularly resistant to wear. The corrosion resistance of cobalt-chromium alloys increases significantly as the chromium content increases; therefore, there is an inverse relationship between chromium content and corrosion risk (Wataha, 2000). Cobalt-based alloys are generally divided into three groups; this classification is based on the composition and structural properties of the alloys.

- Cobalt-based wear-resistant alloys
- Cobalt-based high-temperature alloys
- Cobalt-based corrosion-resistant alloys

Today, special cobalt-based alloys with high resistance to wear are preferred in the production of orthodontic brackets. In these alloys, the nickel content, which could pose a risk in terms of biocompatibility, is kept low (Wataha, 2000). When evaluated in terms of friction resistance, cobalt-chromium brackets can produce lower friction than stainless steel brackets when used with stainless steel arch wires (Kusy, 1997). However, when compared to titanium brackets, the same CoCr brackets exhibit higher friction values when used with both stainless steel and beta-titanium wires. Furthermore, as the chromium content in these alloys increases, corrosion resistance improves due to the contribution of the passive chromium oxide layer formed

on the surface, and the material's resistance to intraoral conditions increases significantly.

3.2. Ceramic Brackets

Ceramic brackets were first used in orthodontics in the early 1980s and, in response to demand from patients particularly concerned about aesthetics, became widely marketed from the mid-1980s onwards (Eliades & Athanasiou, 2002). Ceramic typically consists of glass, clay, precious stone derivatives and various metal oxides, and this structure gives the material high hardness. Ceramic is a harder material than both enamel and stainless steel. Thanks to its transparent or semi-transparent properties, ceramic brackets offer a significant aesthetic advantage. Furthermore, due to being an inert material, ceramic brackets are considered a safe choice, particularly for individuals with allergies to metals such as nickel or chromium (Wataha, 2000). Compared to plastic brackets, ceramic brackets offer higher bonding strength, superior wear resistance, better colour stability and an improved aesthetic appearance. However, the excessive hardness of ceramic, its high bonding force and brittle structure can lead to certain clinical disadvantages. These disadvantages include bracket breakage during debonding, structural damage to tooth enamel or restorative surfaces, and an increased risk of tooth surface wear (Kusy, 1997). Ceramic brackets, despite their high aesthetic advantages, also have certain mechanical and clinical limitations. The torque transfer capacity of these brackets is lower compared to metal brackets, and this can reduce treatment effectiveness, particularly in cases requiring advanced root movements (Kusy, 1997). Ceramic brackets are contraindicated in individuals with enamel cracks or hypoplastic and hypocalcified tooth structure, as they exhibit high adhesion strength. (Eliades & Athanasiou, 2002). These brackets cannot be removed as easily as metal brackets because they adhere to surfaces via ionic and covalent bonds. Ceramic brackets are classified into two groups based on the aluminium oxide structure used: monocrystalline (single-crystal) brackets and polycrystalline (multi-crystal) brackets. Monocrystalline brackets generally offer a more transparent and aesthetic appearance, while polycrystalline brackets are more opaque. However, the high hardness, strong adhesion, and brittle structure of ceramic brackets create some clinical disadvantages. The main disadvantages are as follows:

High rigidity makes the debonding (removal) process of the bracket more difficult; this situation can lead to the bracket breaking and consequently causing cracks or structural damage to the tooth enamel. Additionally, the risk of wear on the opposing tooth increases over time. (Kusy, 1997).

· During long-term orthodontic treatment processes, and particularly in the moist and acidic environment inside the mouth, stress corrosion causes discolouration in ceramic brackets.(Eliades & Athanasiou, 2002).

· Ceramic is considered the third hardest material after natural diamond and corundum, and has a higher hardness than stainless steel wires. This can lead to increased friction and wear on the wire in wire-bracket interactions. As the third hardest material, ceramic is harder than stainless steel wires.

· Due to the brittle nature of ceramic, there is a risk of breaking the ceramic bracket when attaching wires to the bracket slot. Ceramic brackets have weak torque properties.

· The brittle nature of ceramic poses certain limitations in orthodontic applications. There is a risk of cracking or breaking the ceramic bracket, particularly when placing or attaching archwires to the bracket slot (Eliades & Athanasiou, 2002). Furthermore, ceramic brackets have a lower torque transmission capacity compared to metal brackets. This can make treatment control more difficult, particularly in cases requiring root movement (Kusy, 1997).

· The high bonding strength of ceramic brackets limits their use in certain clinical situations. In particular, ceramic brackets are contraindicated in patients with enamel cracks, restorations, devitalised teeth, or hypoplastic or hypocalcified tooth surfaces.(Eliades & Athanasiou, 2002). In these patient groups, there is a high risk of damage to tooth structures during the debonding process.

· Ceramic brackets manufactured in larger sizes to increase fracture resistance may cause soft tissue irritation or injury to the lip and cheek mucosa, particularly in individuals with limited space in the vestibular region.

· Ceramic brackets adhere to surfaces via ionic and covalent bonds. This type of bond is much stronger than the mechanical adhesion found in metal brackets, making the removal (debonding) of ceramic brackets clinically more difficult and requiring special techniques.

3.3. Plastic Brackets

Plastic brackets were first commercially introduced in 1963 by Morton Cohen and Elliott Silverman (Cohen & Silverman, 1963, akt. Kusy, 1997). These brackets are manufactured in transparent or semi-transparent forms to meet patients' increasing aesthetic expectations and have become one of the alternative aesthetic materials in orthodontics. They are generally manufactured using the plastic injection moulding technique. They are particularly advantageous as an alternative to metal brackets for individuals with nickel allergies (Wataha, 2000). However, the clinical use of plastic brackets also has certain disadvantages. The absorption of oral fluids weakens the mechanical properties of the material over time and causes deterioration in durability and colour stability. This situation can lead to increased bacterial colonisation and, consequently, undesirable outcomes such as bad breath.

Polycarbonate-based, filler-free plastic brackets exhibit significantly lower durability compared to stainless steel brackets; this durability is further reduced by liquid absorption, leading to more frequent wing fractures (Kusy, 1997).

The requirement for some traditional plastic brackets to undergo special primer applications before being bonded to teeth or restorative surfaces can complicate clinical procedures. Furthermore, various studies in the literature have reported that the shear bond strength of plastic brackets is lower compared to other conventional brackets such as metal and ceramic (Eliades & Athanasiou, 2002).

4. A FUNCTİONAL COMPARİSON OF BRACKET TYPES

One of the most important factors affecting the bonding strength of orthodontic brackets is the material from which the bracket is manufactured. In the mid-1980s, ceramic brackets were introduced into clinical use to meet aesthetic expectations and quickly became widespread (Eliades & Athanasiou, 2002). Although numerous studies have been conducted on ceramic brackets due to their aesthetic advantages, metal brackets are still considered the gold standard in orthodontic treatment thanks to their high mechanical strength, flexibility and ease of debonding (Kusy, 1997). Eslamian and colleagues (2012) reported that the shear bond strength of ceramic brackets is significantly higher than that of metal brackets. However, this high bond strength does not always provide a clinical advantage. Particularly during debonding, excessive bond strength can cause irreversible damage to the tooth enamel or restorative surface. The low ductility of ceramic materials leads to the direct transmission of force to the underlying layers, increasing the risk of structural damage. Therefore, careful clinical techniques should be used during the application and removal of ceramic brackets (Eslamian et al., 2012). Lai and colleagues (1999) demonstrated in their study that the most important variable affecting the bonding strength of orthodontic brackets to composite resins is the type of bracket rather than the type of adhesive used. Indeed, the geometric structure of the bracket base is one of the main factors determining the bonding force. Bracket bases can be produced in different shapes and surface roughnesses, such as bead-shaped, wide round-bottomed, irregularly patterned, or metal mesh-based. These designs directly affect bonding performance by increasing mechanical interlocking with the adhesive material. The effect of bracket base designs on bonding strength may vary depending on the type of cement used. While some basic surface designs exhibit high performance with certain adhesive systems, they may not yield the same results with different types of cement. Therefore, it is not always clinically possible to determine the base design that provides the best bonding (Lai et al., 1999). Irregular and widely pitted base designs containing small glass particles integrated into polycrystalline alumina limit mechanical

interlocking because they do not create undercut structures where adhesive resins can mechanically bond. In contrast, designs consisting of moncrystalline beads distributed homogeneously across the base surface allow for better mechanical locking of the adhesive resin thanks to the undercut structures. This structure contributes to achieving higher shear bond strength in particular (Eliades & Athanasiou, 2002). Therefore, modifying bracket base designs in adults with restorative materials on their buccal surfaces has become important in terms of clinical success. The continuous introduction of new bracket base structures and adhesive cement types to the market has made systematically evaluating all existing combinations a highly complex and time-consuming process (Eliades & Athanasiou, 2002). Further clinical and laboratory studies are required to understand how different base designs interact with various restorative surfaces. With the increasing number of adult patients in modern orthodontics, it has become necessary to bond brackets not only to enamel surfaces but also to different restorative materials such as composite resins, amalgam, and porcelain. In this context, approaches aimed at achieving optimal bonding to restorative materials with minimal surface preparation have become an important area of research in recent years. Viwattanatipa and colleagues (2008) compared the bond strength of orthodontic appliances applied to five different types of composite resins, including flowable, condensable, hybrid, and nanofil composites; under the same bonding protocol, they obtained results ranging from 6.9 MPa for nanofil composites to 12.99 MPa for hybrid composites. These findings revealed that the type of composite has a significant effect on bonding strength. Similarly, Crumpler and colleagues (1989) also reported that different composite resins exhibited different bond strength values in restoration repairs. However, the number of studies in the literature examining the relationship between the bonding strength of brackets to composite surfaces and the viscosity or filler particle size of composite resins is quite limited. This situation makes it difficult to establish standardised bonding protocols for the different composite materials used in clinical practice. Deniz and colleagues (2020) compared various surface roughening methods applied for bonding orthodontic brackets to direct and indirect composite surfaces in their study, aiming to determine the most suitable protocol. On direct composite surfaces, the highest average surface roughness was obtained in the group treated with bur roughening (2.62 μm). This group was followed by the sandblasted group (2.11 μm) and the orthophosphoric acid-treated group (0.16 μm). Similarly, on indirect composite surfaces, the highest surface roughness was also achieved with milling (3.01 μm), followed by sandblasting (1.37 μm) and orthophosphoric acid application (0.02 μm). These differences in surface roughness also affected the bond strength. Indeed, the highest shear bond strength on direct composite surfaces was again observed in the milling group (12.64 MPa), followed by the orthophosphoric acid group (12.04 MPa) and the sandblasting group (10.65

MPa) (Deniz et al., 2020). The findings indicate that surface roughening protocols play a critical role in the bonding success of orthodontic brackets to composite surfaces. However, this situation also reveals that the current data is insufficient, particularly in terms of different composite resin types and structural properties; therefore, it emphasises the need for more comprehensive and controlled studies in this field. In the study, the group treated with orthophosphoric acid (5.18 MPa) and the control group (5.85 MPa) were determined to be the groups with the lowest average shear bond strength values. On indirect composite surfaces, the highest bond strength value of 15 MPa was obtained in the group where surface roughening was applied with a bur. This group was followed by the orthophosphoric acid-treated group (12.04 MPa) and the sandblasted group (10.20 MPa), respectively. Similarly, in another study, the shear bond strength of orthodontic brackets bonded to three different bulk-fill composites was examined, and the orthophosphoric acid-treated group (6.62 MPa) and the control group (4.25 MPa) showed the lowest averages. In this study, although there was no statistically significant difference in bond strength between the different composite groups, significant differences were observed between the composite surfaces and the natural tooth surface (control group). According to the findings of the study, the average shear bond strength values of orthodontic brackets bonded to composite surfaces ranged from 2.55 MPa to 3.40 MPa In contrast, the average bond strength measured on brackets applied to the natural tooth surface (control group) was 9.92 MPa. The Adhesive Remnant Index (ARI) value was determined to be 3 in all composite groups, indicating that the adhesive had largely separated from the tooth surface. In the control group, ARI values ranged from 0 to 3. The bond strength values achieved by the three different bulk-fill composite materials examined fell below the minimum threshold value of 6–8 MPa predicted by Reynolds for orthodontic brackets to provide clinically adequate bonding (Reynolds, 1975). This highlights the importance of surface modification when bonding brackets to composite restorations. Mechanical surface roughening processes traditionally involve diamond burr application and sandblasting (air abrasion) techniques. Various studies have shown that both methods can significantly increase bonding strength. Bayram and colleagues (2011) reported that surface roughening with diamond burrs yielded an average shear bond strength of 10.6 MPa, while sandblasting yielded 10.3 MPa; in contrast, the control group without surface treatment had a value of only 2.8 MPa. Similarly, Bishara and colleagues (2003) reported a bond strength of 6.1 MPa in the control group, 9.4 MPa with diamond bur application, and 7.8 MPa with air abrasion. These findings clearly demonstrate the effect of surface preparation on bonding success. Viwattanatipa and colleagues (2008) reported that an average shear bond strength of 6.5 MPa was obtained in the control group without mechanical surface preparation, whereas this value was measured as 17.1 MPa when diamond bur roughening

was applied and 15.0 MPa when the air abrasion method was used. These findings demonstrate that mechanical surface modifications have a significant effect on the bond strength of orthodontic brackets to composite surfaces. Similarly, Riberio and colleagues found that mechanical surface roughening was the most effective approach for increasing the bond strength of brackets to composite surfaces. Eslamian and colleagues (2012) also compared the effects of different surface treatments on the bonding of metal brackets to composite surfaces in their study and stated that milling was the most suitable method in terms of both effectiveness and cost. Valizadeh and colleagues (2020) evaluated the bonding strength of metal brackets to old composite surfaces that had undergone surface modification, using different adhesive groups. According to their results, the bonding strength was ranked as follows: no surface preparation <laser application <milling roughening <sandblasting. This result demonstrates the decisive effect of surface morphology on bonding quality. Laser technology was first used in the dental field in 1960 with the development of the ruby laser by Maiman and has undergone significant development over time. Today, laser systems are used in clinical applications as an alternative surface roughening method to create micro-level changes on tooth and dental material surfaces (Wigdor et al., 1993).

Laser applications increase the interaction between the adhesive and the area where orthodontic brackets will be bonded by creating micro- and nano-level roughness on the surface of dental materials. This technology has been successfully used to modify both tooth and restorative material surfaces prior to bracket bonding. Studies in the literature show that laser surface treatments significantly increase bond strength, particularly on porcelain surfaces. In the same study, the most frequently observed Adhesive Residue Index (ARI) score in the milling and sandblasting groups was reported as 3. This finding indicates that a strong bond was achieved between the adhesive and the composite surface in the samples from these groups. However, the disadvantage of this situation is that additional clinical procedures are required to remove the adhesive remaining on the composite surface after debonding and to re-polish the surface; this can place an additional time burden on the clinician. In contrast, the most commonly observed ARI scores in the laser and control groups were reported as 0 and 1. Although the bond strength obtained in these groups was lower compared to the bur and sandblasting groups, it was stated that cleaning the composite surface after debonding was more practical and time-efficient. Hammad and Banna, and Eslamian and colleagues (Eslamian et al., 2009) In the studies conducted, it was demonstrated that the surface abrasion method using a bur provided the highest shear bond strength (SBS) value among all groups. This is thought to be related to the deep craters and irregular grooves formed on the composite surface as a result of the abrasive processes, which significantly increase

the adhesion capacity and micromechanical interlocking of orthodontic adhesives. In contrast, some studies have shown that sandblasting with aluminium oxide (Al_2O_3) particles provides higher bond strength than other techniques. Najafi et al. (2019) stated that sandblasting with Al_2O_3 particles creates micro-pores on the composite surface, which increases the surface area for adhesive bonding and improves bonding strength. On the other hand, it has been reported that during diamond bur abrasion, both macro and micro porosities can form on the bonding surface, which may result in tissue loss on the composite surface, potentially leading to adverse effects in terms of plaque accumulation and secondary caries risk. Among temporary restoration materials, indirect composite materials are recommended for long-term prosthetic and orthodontic treatment requirements due to their superior mechanical strength and aesthetic properties. In this context, a study conducted by Borzangy investigated the effect of different surface roughening methods applied to temporary crowns made of indirect composite and the thermal cycling process on the shear bond strength of metal and ceramic brackets. The study concluded that both types of brackets could tolerate orthodontic forces at a clinically acceptable level. Applying silane to indirect composite temporary crown surfaces after etching with hydrofluoric acid or sandblasting can significantly increase the bonding strength of orthodontic brackets (Borzangy, 2017). Furthermore, comparative studies have reported that ceramic brackets exhibit higher bond strength values compared to metal brackets (Eslamian et al., 2009). However, these methods also have certain limitations. In particular, in clinical situations where it is undesirable to abrade highly polished aesthetic composite restoration surfaces, the applicability of such mechanical surface preparation techniques may be limited. Therefore, alternative surface preparation methods must be evaluated in terms of both preserving aesthetic integrity and ensuring adequate bonding. The literature suggests not only mechanical surface roughening techniques but also various chemical surface modification methods, such as phosphoric acid application, hydrofluoric acid surface etching, silanisation, and the application of various bonding agents or adhesive promoters. However, compared to dental enamel, the effect of traditional phosphoric acid etching on composite restoration surfaces has been reported to be limited. This situation makes it difficult to achieve micromechanical retention on composite surfaces. Some studies have shown that the hydrofluoric acid etching method is effective in achieving clinically adequate bond strength. For example, studies conducted by Bayram et al. (2011) and Viwattanatipa et al. (2008) reported shear bond strength (SBS) levels of 7.2 MPa and 13.0 MPa, respectively, following hydrofluoric acid application. When compared to the shear bond strength (SBS) values of 2.8 MPa and 6.5 MPa obtained in control groups without surface preparation, it can be seen that the values obtained with hydrofluoric acid application are significantly higher. However, it is also reported that these values fall short of

the SBS levels achieved using diamond burr or air abrasion methods. Brosh and colleagues (1997) reported that the use of hydrofluoric acid resulted in the lowest bonding strength when compared to other surface treatments. Hydrofluoric acid is a highly aggressive chemical that can cause serious tissue damage if it comes into contact with soft tissues during application. Therefore, soft tissue barriers must be used during the procedure, which prolongs the clinical process and is a disadvantage for the clinician. On the other hand, silane application is considered an effective adhesive promoter, particularly in bracket bonding to porcelain surfaces. However, whether this effectiveness is equally valid in older composite resin restorations remains a subject of debate in the literature. Eslamian and colleagues (2009), in their study evaluating the effect of applying silane to composite surfaces on the bond strength of orthodontic brackets, reported that silane application did not significantly increase bond strength. Similarly, Brosh and colleagues (1997) also observed no statistically significant difference between groups where silane was used and those where it was not. Consequently, the functional performance of brackets depends on the combination of material type, base geometry, surface preparation, and adhesive system. It is important to evaluate these parameters together and determine the most appropriate strategies for each patient in order to increase clinical success (Valizadeh et al., 2020).

5. AESTHETİC EVALUATİON OF BRACKET TYPES

Aesthetic braces are devices developed to make orthodontic treatment less noticeable. Thanks to their tooth-coloured structure, they attract less attention than metal braces (Souza et al., 2013). These brackets offer a suitable alternative for individuals who place particular importance on their appearance and therefore have reservations about orthodontic treatment (Van Wezel et al., 2015). One of the most important advantages of aesthetic braces is that they allow the natural appearance of the teeth to be largely preserved throughout the treatment processn (Pinzan-Vercelino et al., 2014).

Aesthetic braces offer various advantages in orthodontic treatment in terms of both effectiveness and comfort. These advantages include the controlled direction of tooth movement, shortening of treatment time, no adverse effects on speech function, and easy-to-clean structures. All these features provide patients with a more comfortable treatment process (Souza et al., 2013). However, the fragile structure of aesthetic brackets and the difficulty of the removal process are considered to be among the main disadvantages of these systems (Van Wezel et al., 2015). Although metal braces provide effective results in orthodontic treatment, some individuals do not prefer them due to aesthetic concerns (Souza et al., 2013). This situation has gradually reduced the frequency of use of metal braces over time (Van Wezel et al., 2015). Considering that appearance has a significant impact on individuals, those with aesthetic concerns may hesitate to begin orthodontic

treatment. Despite their desire to start treatment, these individuals may delay the process due to aesthetic concerns, which can lead to psychological issues such as low self-esteem, avoidance of social interactions, and feelings of worthlessness (Pinzan- Vercelino et al., 2014; Souza et al., 2013). Over time, in line with the increasing demands of individuals who want to have a healthy mouth structure and gain an aesthetic appearance, manufacturers have turned to developing alternative products that are less noticeable in terms of aesthetic appearance but provide similar treatment results to metal brackets (Van Wezel et al., 2015). With the development of transparent braces, patients who are highly concerned about appearance have begun to prefer this type of aesthetic braces (Pinzan-Vercelino et al., 2014). In line with evolving aesthetic expectations, transparent braces have become increasingly popular in orthodontic treatment. Offering a more aesthetically pleasing appearance, these braces are less noticeable than metal braces, thereby increasing patient satisfaction (Souza et al., 2013). Transparent structures are manufactured from materials that are close to tooth colour or colourless, rather than having a metallic appearance, thus offering a more suitable option for individuals with aesthetic concerns (Van Wezel et al., 2015). These types of brackets, which are visually less noticeable, are particularly popular among adult patients (Pinzan-Vercelino et al., 2014). Studies show that clear brackets are one of the most preferred systems among aesthetic bracket types. (Souza et al., 2013). Orthodontic treatment is a method of treatment that aims to correct the misalignment of teeth using brackets fixed with special adhesives that do not damage the surface of the teeth (Van Wezel et al., 2015). The ceramic brackets developed within this scope stand out as structures designed to eliminate the aesthetically undesirable appearance of metal brackets. (Pinzan-Vercelino et al., 2014). The surface structures of ceramic brackets are rougher than those of metal brackets, resulting in higher friction forces when they come into contact with the wires. (Souza et al., 2013). This increased friction can lead to a longer treatment period, particularly in cases where oral hygiene is inadequate. Furthermore, if regular and effective brushing is not performed, discolouration and staining may occur around ceramic brackets. Sapphire brackets share similar physical and aesthetic properties with ceramic brackets and have similar advantages and disadvantages. In treatments using this type of bracket, careful cleaning around the bracket is of great importance. Maintaining oral hygiene and brushing teeth regularly using the correct technique are fundamental requirements for the success of the treatment process.

Orthodontic appliance manufacturers began to take aesthetic concerns into account from the mid-1970s onwards. In line with this, the metal materials initially used in bracket bases were replaced with plastic polymers, which, despite having lower hardness compared to steel, offered acceptable clinical

properties. Over time, the industry shifted towards developing materials that offered higher aesthetic performance; in this context, polycrystalline ceramics, acrylic polymers and moncrystalline ceramic materials, known as "sapphire", began to be used in bracket production. Today, monocrystalline ceramic (sapphire) brackets stand out as one of the most superior options in terms of aesthetic appearance (Pinzan-Vercelino et al., 2014). In the development of aesthetic orthodontic wires, a problem distinct from traditional orthodontic appliances has been encountered: the need to preserve the mechanical properties of the wire in addition to ensuring its aesthetic appearance. As a solution to this problem, archwires produced from traditional metal alloys such as stainless steel, titanium-molybdenum and nickel-titanium (NiTi) have been coated with aesthetic materials or painted since the 1970s (Van Wezel et al., 2015). The first coating materials applied include Teflon and epoxy resin (Pinzan-Vercelino et al., 2014). In order to make orthodontic wires more aesthetically acceptable, some manufacturers have developed nylon-based wires reinforced with silicone. Products such as Optiflex (Ormco, Orange, CA, USA) and Optis T (TP Orthodontics, Westville, IN, USA) have attracted attention in this regard (Souza et al., 2013). Although these wires offer an excellent aesthetic appearance, they have been found to be inadequate in terms of clinical performance and are recommended by manufacturers only for limited indications and short-term use. Due to the failure to achieve the desired results in clinical use, these wires have been withdrawn from the commercial market. Today, however, the rhodium bath technique, used in jewellery production, has begun to be applied as an innovative approach in the production of aesthetic orthodontic wires (Van Wezel et al., 2015). Nowadays, aesthetic orthodontic wires and brackets are extensively researched and compared in terms of numerous physical and clinical characteristics, such as friction coefficients, surface roughness, mechanical durability, and aesthetic stability during the treatment process (Souza et al., 2013). The advantages and limitations of these materials have been explained in detail in various studies in the literature. Recently, Pinzan-Vercelino and colleagues conducted a cross-sectional study based on the opinions of members of the general public to evaluate the aesthetic perception of metal archwires with and without aesthetic coatings, reporting that epoxy resin-coated wires had the most aesthetic appearance. However, it has been noted that, to date, no study has directly compared the perceived attractiveness of different types of aesthetic wires by both lay individuals and dentists (Souza et al., 2013). In this regard, the present study aims to analyse the aesthetic appeal of different types of aesthetic orthodontic wires based on the assessments of both dentists and members of the general public (Van Wezel et al., 2015).

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Chapter 4

BISPHOSPHONATE - RELATED OSTEONECROSIS OF THE JAW (BRONJ)

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Bisphosphonates (BPs) are natural derivatives formed by the esterification of two phosphate groups of inorganic pyrophosphate. The oxygen atom present in inorganic pyrophosphate is replaced by a hydrolysis-resistant carbon atom in bisphosphonates, which confers structural stability and resistance to degradation. The presence of phosphate and hydroxyl groups facilitates the interaction of bisphosphonates with the bone matrix, thereby contributing to their high affinity for osseous tissue. (Mariotti, 2008)

BPs are synthetic drugs that exhibit antiresorptive effects in various bone pathologies characterized by increased fragility. They are widely used in conditions such as multiple myeloma, osteoporosis, bone metastases of solid tumors, osteitis deformans (Paget's disease), primary and secondary hyperparathyroidism, and osteogenesis imperfecta. Bisphosphonates can be administered either orally or intravenously (IV). IV formulations are primarily preferred in cancer-related conditions and lesions associated with multiple myeloma, whereas oral formulations are generally used for the treatment of osteopenia and osteoporosis, and less commonly for disorders such as Paget's disease and osteogenesis imperfecta. (Brozoski et al., 2012; Saldanha et al., 2012) Osteoporosis is one of the most prevalent metabolic bone diseases worldwide, and the widespread nature of this condition has led to a marked increase in the use of BPs in recent years. Bisphosphonates are among the most frequently prescribed medications for the treatment of osteoporosis on a global scale. (Reid, 2011; Hellstein et al., 2011)

Bisphosphonates help prevent complications such as pathological bone fractures, pain, loss of bone mass, and tumor-associated hypercalcemia by inhibiting bone resorption, thereby improving the patient's quality of life. (Hinchy et al., 2013) In the presence of osteoporosis, bisphosphonates are highly effective in preventing hip and vertebral fractures. (Reid, 2011; Suresh, Pazianas & Abrahamsen, 2014) Despite their numerous beneficial effects, the most severe adverse event associated with this drug class is the development of osteonecrosis of the jaws. This condition was first reported in 2003, when BRONJ cases were observed in 36 patients treated with Zometa (zoledronic acid) and Aredia (pamidronate). (Marx, 2003) Since its initial description, the increasing number of reported cases has led to BRONJ being recognized as a growing epidemiological concern.

Bisphosphonates

Bisphosphonates are the most commonly used antiresorptive drugs in bone metabolic disorders where osteoclastic resorption plays a pathogenic role. They reduce bone resorption by suppressing osteoclastic activity and increase bone mineral density. (Moinzadeh et al., 2013) Bisphosphonates can be administered either orally or intravenously (IV). When administered orally, the bioavailability is considered to be between 1% and 5% due to low

absorption in the gastrointestinal system. In contrast, approximately 50% of the drug administered intravenously reaches bone tissue. Bisphosphonates that enter the bloodstream rapidly accumulate in bone tissue, where they bind to the bone mineral matrix; around 40% of the absorbed dose is excreted in the urine within the first 24 hours without undergoing metabolism. The half-life of different types of bisphosphonates in the human skeleton ranges from 3 months to ≥10 years. Due to these characteristics, bisphosphonate therapy can last for many years, and similarly, side effects associated with the drug may persist over extended periods. During osteoclastic bone resorption, bisphosphonates that are released from the bone mineral matrix are internalized into osteoclasts through endocytosis. Osteoclasts are the primary target cells for bisphosphonates. However, studies have also shown that some phagocytic cells can internalize bisphosphonates, albeit at lower levels. (Mariotti, 2008; Yamashita, McCauley & Van Poznak, 2010; Brozoski et al., 2012)

The chemical structure of bisphosphonates is similar to pyrophosphate. Pyrophosphates are hydrolyzed within the cell to be used in various cellular functions. Bisphosphonates internalized by osteoclasts are resistant to dissolution, which prevents the activation of enzymes targeting pyrophosphate in osteoclast cells. Bisphosphonates are classified into two subgroups, based on whether or not they contain a nitrogen atom. These subgroups have different mechanisms of action on osteoclasts. The first generation of bisphosphonates (e.g., etidronate, tiludronate, and clodronate) do not contain a nitrogen chain or hydroxyl group, and therefore have a lower specificity for bone compared to later generations. Nitrogen-free bisphosphonates are metabolized into cytotoxic analogs of ATP in osteoclast cells, competing with binding sites on the cell surface. This results in a decrease in the number of functional osteoclasts and consequently reduces bone resorption rates. The second group of bisphosphonates, containing nitrogen (e.g., alendronate, pamidronate, ibandronate, risedronate, and zoledronate), suppress osteoclastic activity through a different mechanism. These drugs inhibit the enzyme farnesyl pyrophosphate synthase, which is involved in the biosynthesis of cholesterol and other sterols. Additionally, these bisphosphonates bind to hydroxyapatite crystals in the bone matrix, preventing crystal breakdown and thus reducing bone resorption. (Ebetino et al., 2011)

The affinities of these drugs for bone and their therapeutic effectiveness can vary. Zoledronate, a nitrogen-containing compound, is considered the most potent bisphosphonate in inhibiting bone resorption. Although bisphosphonates from different groups act through various molecular mechanisms, the ultimate result is the reduction of osteoclastic activity and increased osteoclast apoptosis. (Yamashita, McCauley & Van Poznak, 2010)

Bisphosphonate - Related Osteonecrosis of the Jaw; BRONJ

Bisphosphonates, which are highly beneficial in the treatment of severe clinical conditions such as metastatic bone cancer and osteoporosis, can lead to certain side effects during or after the treatment process. One significant adverse effect of bisphosphonates is osteonecrosis of the jaw, first described in 2003 in patients receiving intravenous (IV) applications and later in 2006 in those receiving oral applications. (Shannon J, Modelevsky & Grippo, 2011; Janovská, 2012; Diniz-Freitas et al., 2012) The American Association of Oral and Maxillofacial Surgeons (A.A.O.M.S.) and the American Society for Bone and Mineral Research (ASBMR) define BRONJ cases as the presence of exposed bone surface and bone necrosis in the maxillofacial region, unhealed within 8 weeks, in patients using bisphosphonates without a history of radiation therapy. (Ruggiero, 2011; Sigua-Rodriguez et al., 2014) (Figure 1)

Although the exact mechanism of BRONJ remains unclear, several hypotheses have been proposed. The most widely accepted hypothesis is that bisphosphonates negatively impact the bone remodeling process and wound healing. Bisphosphonates, which are potent inhibitors of osteoclastic activity, significantly slow down the bone remodeling process and increase bone mineral density. The effective suppression of osteoclastic activity disrupts the physiological cycle in bone, preventing the healing of micro-damages caused by normal chewing forces or dental extractions. Over time, this can lead to the development of necrosis in the bone. Furthermore, the recent report that denosumab, a drug targeting osteoclastic activity through a completely different mechanism from bisphosphonates, can also lead to osteonecrosis in the jaw, supports the hypothesis that the inhibition of osteoclastic activity may be a fundamental factor in the development of this pathology. Additionally, it is noteworthy that this drug class has inhibitory effects on angiogenesis, which can impair local blood circulation and create an ischemic environment, potentially triggering necrosis development in conjunction with metabolic changes resulting from the suppression of osteoclastic activity.

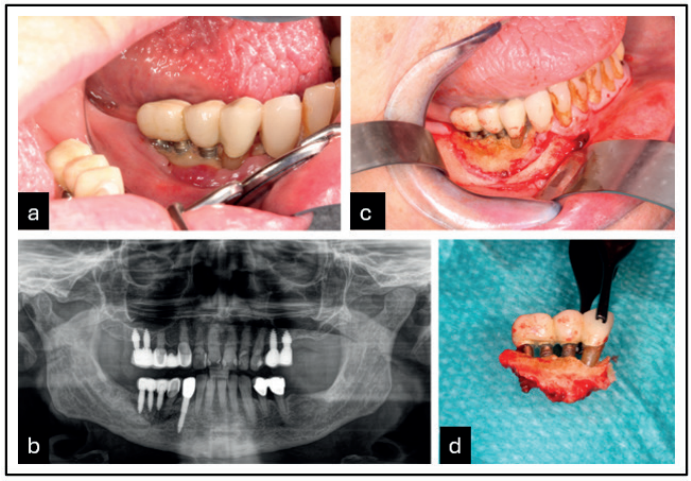

Figure 1. *BRONJ observed in the mandible after the placement of implants. Exposed bone in the oral cavity (a), bone sequestrum visible on the panoramic radiograph (b), exposure of the sequestrum during the procedure (c), removal of the bone sequestrum (d). (Jelin-Uhlig S, Weigel M, Ott B, Imirzalioglu C, Howaldt HP, Böttger S, Hain T. Bisphosphonate-Related Osteonecrosis of the Jaw and Oral Microbiome: Clinical Risk Factors, Pathophysiology and Treatment Options. Int J Mol Sci. 2024 Jul 24;25(15):8053)*

In addition to all these mechanisms, it has been suggested that bisphosphonates (BF) may have a direct toxic effect on soft tissues, which could lead to fenestrations in the oral mucosa and expose the underlying bone. On the other hand, the fact that only a small proportion of individuals using bisphosphonates develop osteonecrosis of the jaw suggests that genetic differences in drug metabolism or skeletal system homeostasis may contribute to this process. To definitively elucidate all these proposed mechanisms regarding the etiopathogenesis of this pathological condition, evidence-based clinical and basic science research is required. (Ruggiero, 2011; Yamashita & McCauley, 2012)

BRONJ Diagnosis Criteria (A.A.O.M.S., Current Definition)	
1	**History of Antiresorptive Drug Use:** Use of Osteoclast Inhibiting Agents such as Oral or IV Bisphosphonates or Denosumab
2	**No History of Head and Neck Radiotherapy to the Jaw Area:** For the diagnosis to be made, the patient must not have received radiotherapy to the relevant area. Similarly, the presence of malignant disease affecting the region must also be excluded.
3	**Presence of Exposed Bone in the Jaw-Face Area for More than 8 Weeks Without a History of Radiotherapy or Metastatic Disease:** This is identified during clinical examination or radiographic assessment. It is usually painful, but can also be asymptomatic.

Table 1. *BRONJ diagnosis criteria (A.A.O.M.S., Current Definition)*

Risk Factors

Necrotic lesions, although often emerging after tooth extractions or dento-alveolar surgical interventions, may, in some cases, occur without any triggering event prior to such procedures. The incidence of BRONJ is reported to range from 1 - 10% with IV administration and 0.001 - 0.01% with oral administration. The higher likelihood of BRONJ development in patients receiving IV bisphosphonates suggests that this risk increases with the dose and efficacy of the drug. However, it should also be considered that individuals with metastatic bone disease may be using corticosteroids or chemotherapy agents concurrently. The American Association of Oral and Maxillofacial Surgeons (A.A.O.M.S.) has categorized the risk factors for BRONJ into five main groups. (Yamashita & McCauley, 2012)

1. Drug-Related Risk Factors: The efficacy of bisphosphonates is stronger in zoledronate and pamidronate than in oral bisphosphonates. In IV administration, the duration of exposure and bioavailability are higher compared to oral applications. Prolonged treatment increases the risk of BRONJ development.

2. Local Risk Factors: Tooth extraction, implant placement, and periodontal surgeries that involve bone are considered within the scope of dentoalveolar surgery. According to AAOMS reports, dentoalveolar surgeries are not limited to specific cases. Anatomical structures such as torus and existing dental diseases can increase the risk of BRONJ. Patients using bisphosphonates who undergo dentoalveolar surgery are seven times more likely to develop BRONJ compared to those who do not undergo such procedures. Traumatic and deep dental surgeries are significant risk factors for BRONJ development. (Vescovi et al., 2010) It has been reported that 60% of BRONJ cases in the literature developed following tooth extractions or surgical procedures involving the jaw.

3. Local Anatomy: When the distribution of BRONJ lesions is examined, 65% of cases are found in the mandible, 28.4% in the maxilla, 6.5% in both jaws, and 0.1% in extraoral locations (external auditory canal). (Khan et al., 2015) It is known that lesions are seen more frequently in the mandible than in the maxilla, approximately at a 2/1 ratio, and are more common in areas covered by thin mucosa, such as bone prominences or regions overlying the mylohyoid line. However, a specific study assessing BRONJ risk related to anatomical structures has not yet been reported.

- Mandible (lingual torus, mylohyoid prominence)
- Maxilla (palatal torus)

4. Comorbid Conditions: In patients using IV bisphosphonates, the presence of accompanying inflammatory conditions such as periodontal

disease or dental abscesses increases the risk of BRONJ development by about seven times. Demographic and systemic factors (age, race, and cancer diagnosis) have been reported as risk factors for BRONJ; however, gender is suggested not to influence this condition. White race has been associated with a higher risk compared to black race, and the risk of BRONJ increases with age. (Ruggiero et al., 2022) Studies also show that renal disease, low hemoglobin levels, obesity, and diabetes may increase the risk of BRONJ. It is suggested that the type of malignant disease does not directly affect the risk, but the presence of metastasis can increase the risk. The relationship between cancer treatment drugs and BRONJ risk is conflicting. Smoking may be associated with an increased risk, while alcohol consumption does not appear to affect the risk. The probability of BRONJ development in patients using only bisphosphonates is 1.1%, whereas in patients using bisphosphonates and anti-angiogenesis drugs, this rate can reach 16%. (Christodoulou et al., 2009)

5. Genetic Factors: In patients using IV bisphosphonates for multiple myeloma treatment, polymorphism in the cytochrome P450-2C8 (CYP2C8) gene has been reported to increase the risk of BRONJ. Recent studies have suggested that genes such as COL1A1, RANK, MMP2, OPG, OPN, FDPS, and VEGF could be potential candidates for susceptibility to BRONJ development. (Vescovi et al., 2010)

6. Preventive Treatments: AAOMS recommends that patients undergo a comprehensive dental examination and complete necessary treatments before starting bisphosphonate therapy. Current studies highlight that IV bisphosphonate administration and procedures targeting the dental and jaw regions are the two most prominent risk factors for BRONJ. Optimizing the bisphosphonate dose can help prevent pathological fractures while reducing the risk of BRONJ. Although preventive dental treatments before initiating therapy may reduce the risk of BRONJ to some extent, they cannot entirely eliminate it. (Thumbigere-Math et al., 2012)

Diagnosis and Clinical Features of BRONJ

BRONJ clinically resembles osteoradionecrosis (ORN) and can often progress asymptomatically for an extended period. Pain, swelling in the soft tissues, inflammation, increased mobility, and the formation of fistulas are typical symptoms. Other symptoms such as difficulty chewing and speaking, trismus, halitosis, and recurrent abscesses may also be observed. (Saldanha, Shenoy, Eachampati, & Uppal, 2012) In some patients, atypical findings such as dull pain, numbness, lower lip anesthesia, and a sensation of fullness in the jaw may occur. Before becoming clinically apparent, BRONJ may present with changes in the periodontal tissues, non-healing mucosal lesions, increased mobility, unexplained tissue infections, and fistula formation that cannot be attributed to periodontal disease or pulp infection. (Khosla et al., 2007)

In cases where the maxilla is affected, maxillary sinusitis, either due to or independent of an oroantral fistula, may accompany the BRONJ condition. Additionally, BRONJ-associated jaw fractures have also been reported in the literature. Bilateral fractures are rare but should be considered as a potential complication. Rarely, fistulas opening to the outside of the mouth and bone sequestration reaching the skin surface may be observed. In some cases, sequestration may be eliminated spontaneously without the patient's awareness. The exposed bone surface in BRONJ can provide an environment conducive to secondary infections, potentially leading to osteomyelitis. (Gupta et al., 2013)

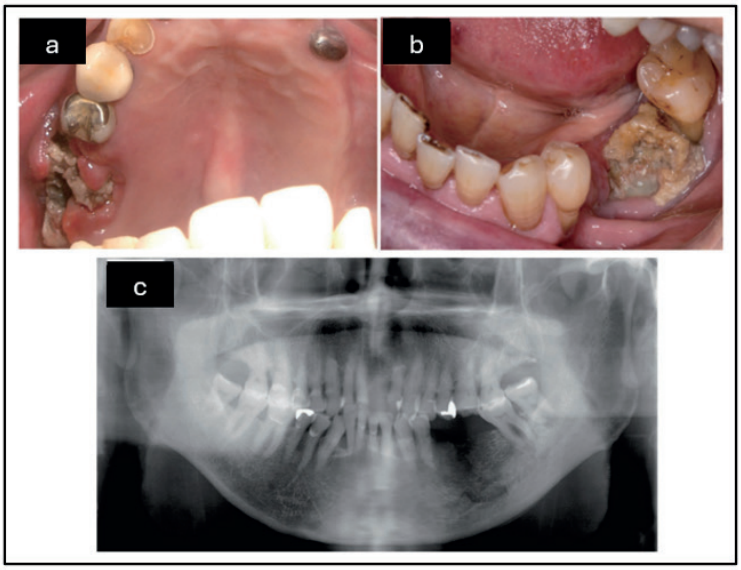

Figure 2. *BRONJ case; necrotic bone area exposed in the maxilla (a), necrotic bone exposed in the left mandible (b), panoramic radiograph of the case shown in (b) (c). (Shibahara T. Antiresorptive Agent-Related Osteonecrosis of the Jaw (ARONJ): A Twist of Fate in the Bone. Tohoku J Exp Med. 2019 Feb;247(2):75-86)*

Among radiographic findings, bone loss and resorption in the alveolar bone, which cannot be associated with periodontitis, are noteworthy. Significant changes are observed in the trabecular bone structure, where dense mesh-like bone formation and immature bone tissue can be seen in extraction sockets. Thickening or blurring of the periodontal ligament, along with the thickening of the lamina dura and narrowing of this area, may also occur. Additionally, narrowing of the inferior alveolar canal may be observed radiographically. (Arce, Assael, Weissman, & Markiewicz 2009)

Panoramic radiographs, cone-beam computed tomography (CBCT), and computed tomography (CT) are imaging methods that can be used for the diagnosis of BRONJ. Periapical and panoramic radiographs may fail to detect changes associated with early-stage osteonecrosis. (Gupta et al., 2013) Panoramic radiographs may not distinguish osteonecrosis from metastatic osteoblastic lesions. However, as osteosclerosis is associated with chronic osteomyelitis, the presence of osteolysis and osteosclerosis together may assist in diagnosis on panoramic radiographs. The two-dimensional nature of the imaging makes it challenging to define the boundary between necrotic and healthy bone tissue, potentially leading to the omission of early-stage lesions. Nevertheless, it is recommended to review traditional radiographs in initial assessments. In cases where exposed bone necrosis is not clinically present, scintigraphy, PET scanning, or magnetic resonance imaging (MRI) may help in detecting affected areas of bone at an early stage. CT techniques offer the advantage of accurately assessing intrabony changes, periosteal reactions, and soft tissue involvement. In BRONJ cases, CT images may reveal osteolytic and osteosclerotic areas depending on the stage of the disease. Denser bone structures indicate necrotic lesions, while lytic areas often signal infected lesions-commonly associated with pus and soft tissue edema. However, distinguishing malignant metastatic osteolysis from benign osteolytic changes on CT can be challenging.

CBCT, which offers three-dimensional imaging specific to the jaw and facial regions, is an increasingly popular technology that can be used as an alternative to CT. This method provides more precise positioning information with lower radiation doses and can be useful in early detection of periapical and periodontal pathogens, which are known to be risk factors for BRONJ but may not be detectable with conventional radiographs. Although CBCT is primarily optimized for implant planning and placement, no standardized protocol has yet been developed for BRONJ diagnosis. (Arce, Assael, Weissman, & Markiewicz 2009)

In the diagnosis of BRONJ, evaluating bone morphology, soft tissue condition, and bone function through various imaging techniques is crucial. In this context, functional imaging methods such as scintigraphy may be useful in detecting areas of increased remodeling. These techniques, although highly sensitive, have low specificity and may serve a supportive role in early diagnosis. Positron emission tomography (PET), a non-invasive method, provides reliable results, particularly in the diagnosis of acute or chronic osteomyelitis. However, there is insufficient evidence to support the routine use of PET scans in BRONJ patients. Nevertheless, PET scans performed for systematic follow-up in oncological patients may aid in the early detection of BRONJ development before clinical symptoms manifest. (Belcher et al., 2014)

Biochemical Tests and Histopathology in BRONJ Diagnosis

The serum level of CTX (C-terminal cross-linking telopeptide of type 1 collagen), a collagen degradation product, can be considered as a risk indicator for the development of BRONJ. Serum CTX and urinary NTX (N-telopeptide of type 1 collagen) are recognized as markers of bone resorption. Elevated levels of these markers indicate increased bone turnover. Although serum CTX levels are used as an early determinant in BRONJ diagnosis, there is still no consensus on the reliability and consistency of this test. (Herrmann & Seibel 2008)

Marx et al. classified patients based on their CTX levels for the assessment of BRONJ risk.

≥ 150 pg/mL	It does not present a risk.
< 150 pg/mL	It presents a risk.
< 100 pg/mL	High risk.

Table 2. *Classification of patients according to their CTX levels in BRONJ risk assessment. (Marx, 2012)*

Research has shown that there may be an increase in CTX levels after periods of interruption in medication use. Furthermore, it has been reported that the risk of BRONJ is three times higher in patients with CTX levels below 150 pg/mL. (Hutcheson et al., 2014) However, some studies suggest that there is no correlation between CTX values and the development of BRONJ. It is also known that CTX values are influenced not only by BF usage but also by other diseases and medications affecting bone and connective tissue metabolism. (Kim et al., 2013) In BRONJ biopsies, no specific histopathological pattern has been identified for the disease, but bone lesions similar to those seen in osteomyelitis are commonly observed. It can be partially distinguished from osteoradionecrosis by the lower collagen synthesis and fibrosis, as well as more intense inflammatory infiltration in the bone marrow. (Marx, 2012)

In the necrotic bone layer, lacunae of osteocytes, bacterial colonies in bone marrow spaces – often Actinomyces species – and polymorphonuclear leukocytes (PMNLs) are observed. In perinecrotic regions, a prominent inflammatory response and apoptotic osteocytes can be found in the bone marrow spaces. As the severity of inflammation increases, new bone formation decreases, while there is an increase in the number of TRAP (+) cells. It has been observed that the necrotic and inflammatory areas in the bone develop before the clinically observable necrotic bone tissue, indicating that changes in the bone tissue of BRONJ lesions occur earlier than changes in the soft tissue. (Lesclous et al., 2009)

Stages of BRONJ

In order to guide prognosis and treatment planning, a staging system for BRONJ lesions was first proposed in 2006 and updated by the AAOMS in 2009. With this update, it was acknowledged that patients using oral or IV BF without clinically evident necrotic bone findings were also included in the risk group. (Table 3) In risk assessment, the potency of the drug, duration of treatment, and surgical interventions involving teeth or alveolar bone should be prioritized factors.

Stages of BRONJ	
Stage 0 (Suspicious Stage/ Prodromal Period)	Ø There is no exposed necrotic bone. Ø Clinical findings; tooth and sinus pain, paresthesia, flattening of the alveolar ridge. Ø Radiographic findings; irregular trabeculation, widening of the periodontal space, sclerosis of the lamina dura. Ø Osteonecrosis is not observed, but there are signs that may indicate the early stages of BRONJ.
Stage 1	Ø There is exposed necrotic bone that has not healed for more than 8 weeks. Ø No signs of infection are present. Ø Typically asymptomatic. Ø Radiographic findings may be present, but there is no significant inflammation or infection.
Stage 2	Ø Exposed necrotic bone is present along with signs of infection (pain, erythema, swelling, fistula, purulent discharge). Ø Infected necrotic bone may spread. Ø Radiographically, areas of osteolysis or sclerosis may be observed.
Stage 3	Ø In addition to exposed necrotic bone and infection, complications such as pathological fractures, extraoral fistulae, sinusitis extending beyond the maxillary sinus floor, and widespread bone destruction in the jaw are present. Ø Surgical intervention is generally required.

Table 3. *BRONJ stages (A.A.O.M.S. 2022)*

The likelihood of patients in the first or second stage progressing to the third stage cannot be precisely predicted; however, this progression is generally variable and may depend on the duration of BF treatment and whether the patient is still continuing the medication.

It has been reported that approximately 25 - 40% of BRONJ cases develop spontaneously without any trauma or triggering factor. (Sigua-Rodriguez et al., 2014) The spontaneous onset of lesions is often associated with the posterior regions where the oral mucosa is thinner, and this condition is attributed to potential anatomical or physiological characteristics.

In spontaneously developed lesions, the most commonly observed initial finding is mucosal changes that develop into slowly healing ulcers, often

accompanied by discomfort such as numbness or a burning sensation. Pain is frequently present, typically due to bacterial-induced necrotic bone infection. These symptoms emerge before osteonecrosis becomes clinically apparent, and early recognition of these signs is crucial for timely preventive measures. (Otto, Hafner, & Grötz, 2009)

Treatment Management

The first step in managing these patients is prioritizing ongoing oncological treatment and supporting the therapy. The second step involves pain relief, preventing secondary infections, and maintaining the patient's quality of life by preventing the expansion of lesions or the formation of new necrotic areas. (Gupta S, Gupta H, Mandhyan, & Srivastava, 2013) For patients using IV and long-term oral bisphosphonates, prophylactic antibiotic use is recommended for all procedures involving the jawbones. In large-scale screenings, it has been indicated that antibiotic treatments reduce the risk of developing BRONJ. (Khan et al., 2015)

Preventive Treatments

Treatment interventions vary depending on the stage of the disease.

1. Patients starting IV bisphosphonate therapy:

Ø The goal is to minimize the risk of BRONJ development. Bisphosphonate therapy should be postponed until dental treatments are completed and oral health is restored.

Ø Teeth that are in poor prognosis and irreparable should be extracted.

Ø During this process, necessary surgeries should be completed, and bisphosphonate therapy should be delayed until mucosal healing occurs (14 - 21 days) or bone healing is achieved, depending on the patient's systemic condition.

Ø For patients using removable partial or complete dentures, mucosal trauma areas should be eliminated.

Ø The importance of oral hygiene and regular check-ups should be emphasized, and the patient should be instructed to seek clinical help in case of pain, swelling, or the formation of necrotic areas.

2. Patients using IV bisphosphonates without any symptoms:

Ø Improved oral hygiene should be maintained, and surgical requirements should be avoided.

Ø Any procedure that could damage the bone should be avoided.

Ø Irreparable teeth can be treated with coronectomy and root canal therapy for the remaining roots.

Ø Implant procedures should be avoided in oncology patients using high doses of bisphosphonates or frequent dosages.

3. Patients using oral bisphosphonates without any symptoms:

Ø BRONJ occurs much less frequently compared to patients using IV bisphosphonates. Surgical procedures are not contraindicated, but patients should be informed about the potential effects on bone healing.

4. Patients with BRONJ:

Ø In patients with BRONJ, the treatment goal is to relieve pain, control infections in hard and soft tissues, and minimize the likelihood of further necrosis formation in the bone.

Ø Since new necrotic areas may develop, elective surgical procedures should be avoided.

	Treatment Recommendations	
	Clinical Features	**Treatment**
Stage 0	Patients on IV or long - term oral bisphosphonates without BRONJ development	Ø O. H. M. Ø Preventive Dental Treatments Ø CHX Mouthwash
Stage 1	Asymptomatic, no inflammatory changes in the soft tissue, and no exposed bone is observed.	Ø O. H. M. Ø Preventive Dental Treatments Ø CHX Mouthwash
Stage 2	Exposed bone, pain, inflammation in the surrounding soft tissues, and/or secondary infections are present.	Ø O. H. M. Ø Local Debridement Ø Oral Antibiotics Ø CHX Mouthwash
Stage 3	In addition to exposed bone, pain, inflammation in the surrounding soft tissues, and/or secondary infections, there is a risk of oral fistula or jaw fracture.	Ø Treatment similar to Stage 2 Ø IV Antibiotics usage in advanced cases Ø Major Resection

Table 4. *A.A.O.M.S. Treatment recommendations for BRONJ. (CHX: Chlorhexidine, O.H.M.: Oral Hygiene Motivation)*

Surgical Treatment

In BRONJ patients, if the current condition is not progressing, pain can be managed with conservative methods, and bisphosphonate therapy has been paused or discontinued, conservative treatments should be continued instead of surgical intervention. (Khan et al., 2015)

Surgical debridement for the removal of necrotic bone may be effective to varying degrees depending on the situation. However, in some cases, due to the pharmacological effects of bisphosphonates on bone tissue, it may be difficult to completely remove the lesion and reach healthy and viable bone

boundaries. Therefore, surgical treatment should be postponed as much as possible. In areas where bone is exposed, mobile bone fragments that could cause discomfort to the patient and lead to irritation of surrounding soft tissues can be removed, while preserving the surrounding soft tissues. (Ruggiero et al., 2006) In BRONJ cases observed in the mandible, neurological symptoms such as hyperesthesia, paresthesia, and numbness, resulting from the involvement of the inferior alveolar nerve, may regress after the surgical removal of necrotic areas and appropriate antibiotic therapy. (Otto, Hafner, & Grötz, 2009)

The extraction of teeth that do not exhibit symptoms associated with exposed bone or necrotic areas can be considered, as this procedure does not exacerbate the existing necrosis. During tooth extractions or surgical treatment of BRONJ lesions, the application of autologous platelet-rich fibrin (PRF) membranes can support primary wound healing. (Soydan & Uckan, 2014)

Hyperbaric Oxygen (HBO) Therapy

Hyperbaric oxygen therapy is based on administering purified oxygen to patients in specially designed pressurized chambers, and it is known to have positive effects on soft and hard tissue healing in ischemic conditions. However, there is no consensus on the effectiveness of HBO therapy in BRONJ patients. When HBO is applied for 40 days in addition to traditional BRONJ treatment (local debridement, antibiotics, and antiseptic gargles), it has been shown to support lesion healing and improve the quality of life of patients. (Freiberger et al., 2012) Nevertheless, the existing evidence is insufficient to recommend routine use of HBO therapy in BRONJ patients.

Teriparatide Treatment

Teriparatide, a parathyroid hormone analogue, has shown promising results in the treatment of BRONJ lesions. The application of teriparatide not only facilitates the complete healing of necrotic areas but also provides positive effects such as bone regeneration. (Yoshiga et al., 2013) Teriparatide therapy, in addition to increasing osteoblastic activity, can also enhance angiogenesis activity, which is reduced due to bisphosphonate (BF) use. However, since the use of teriparatide analogs is contraindicated in patients with metastatic bone lesions, this treatment is considered an appropriate option solely for treating necrotic lesions in patients using BFs due to conditions like osteoporosis. (Thumbigere-Math, Gopalakrishnan, & Michalowicz 2013) Non-surgical interventions such as platelet-rich plasma (PRP) and bone morphogenetic proteins (BMP) have been applied in some limited cases; however, there is currently no evidence-based data to support their routine use in BRONJ treatment.

Dental Implant Surgery

In contemporary dentistry, dental implant-supported treatment options are increasingly preferred over conventional prosthetic approaches for the rehabilitation of partial and total edentulism. (Javed & Almas, 2010) Dental implant surgery is an invasive procedure involving both soft and hard tissues and is considered among the interventions that carry a risk for the development of BRONJ. Peri-implant bone necrosis can occur in patients who initiated bisphosphonate (BF) therapy prior to implant placement, as well as in those who began BF treatment years after implant insertion. This may reflect the potential impact of BF use during the osseointegration process or may result from the negative effects of BF on the ongoing bone remodeling processes around osseointegrated implants. (Lazarovici et al., 2010; Kwon et al., 2014)

Effects of Bisphosphonates on Peri-implant Hard Tissues

The inhibitory effects of bisphosphonates (BPs) on osteoclastic activity have led to the hypothesis that they may positively influence bone regeneration through local or systemic applications. Animal studies have demonstrated that high-dose systemic or local BF administration can enhance bone formation around orthopedic implants and improve the mechanical properties of the bone - implant interface. (Aspenberg & Astrand, 2002; Peter, Zambelli, Guicheux, & Pioletti, 2005) In vivo studies have shown that dental implants can successfully osseointegrate in animal models treated with intravenous BFs, with greater bone - implant contact observed compared to control groups. (de Oliveira et al., 2014) However, the absence of adverse effects associated with BF use in animal models limits the direct applicability of these findings to humans, likely due to significant physiological differences in bone metabolism between species.

Numerous case reports have documented BF - associated complications involving dental implants. These cases have yielded various histopathological findings related to BRONJ lesions. In a case reported by Kim and Kwon (2014), BRONJ developed approximately three years after a sinus augmentation and implant placement procedure in a patient receiving oral BF therapy, necessitating implant removal. Histological analysis of the implant and grafted site revealed an absence of osteoclasts and osteocytes in the necrotic bone tissue, along with a dense inflammatory cell infiltrate within the bone lacunae. Similarly, in another case reported by Yuan et al. (2012), a patient who received dental implants approximately ten years prior and began oral BF therapy three years before the onset of symptoms developed BRONJ. In this case, severe bone loss that was not consistent with typical peri-implantitis led to implant removal. Histopathological examination showed intense inflammatory cell infiltration, bacterial biofilms, bone sequestration, and necrotic areas surrounding the implant. Due to persistent complaints and

suppuration, another implant - without radiographically detectable bone loss - was also removed. Despite 100% bone - implant contact, the surrounding bone contained empty lacunae devoid of connective tissue. These findings suggest that BF use may alter bone remodeling processes, resulting in excessive bone - implant contact without maintaining the dynamic balance between hard and soft tissues.

In summary, BRONJ can develop around implants both in the early postoperative period and long after successful osseointegration. This is likely due to the long-term effects of bisphosphonates on bone metabolism, which may disrupt the physiological remodeling processes of peri-implant tissues.

Histopathologically, BRONJ lesions surrounding dental implants have been classified into three main patterns. (Table 5)

Lesion Type	Histopathological Features	Clinical Manifestation
Complete necrosis	The implant is surrounded by completely necrotic bone.	Radiographically significant bone loss; surgical debridement may be required.
Inflammation and Osteolysis	Intense inflammatory cell infiltration, increased osteoclastic activity.	Pain, swelling, pus discharge; often accompanied by signs of infection.
Necrosis and Sequestration	Formation of sequestrum in block form in necrotic bone areas.	Mobile bone segments; decrease in implant stability.

Table 5. *Histopathological classification of BRONJ lesions around implants. (Kwon et al., 2014)*

Recognition of these lesion types is important in the clinical decision-making process. Particularly in late-stage BRONJ cases, pathological bone remodeling may persist around the implant despite successful osseointegration. Therefore, the necessity of long-term follow-up for patients with a history of bisphosphonate therapy should be emphasized.

It has become evident that bone alterations resulting from long-term BF use can pose significant risks for dental implant therapy. Accordingly, when evaluating the suitability of implant treatment in individuals receiving BF therapy, not only the medication itself but also the patient's systemic medical history, the type of BF used (aminobisphosphonate vs. non-aminobisphosphonate), the route of administration (oral or intravenous), the duration of use, and other local and systemic risk factors must be assessed comprehensively. (Madrid & Sanz, 2009)

Dental Implant Applications in Cancer Patients Undergoing Bisphosphonate Therapy

Dental implant placement is generally not considered appropriate in patients receiving intravenous bisphosphonate (IV BF) therapy for metastatic

cancer. Due to the nature of the malignancy and adjunctive therapies such as chemotherapy, radiotherapy, and prolonged corticosteroid use, implant treatment is not routinely planned for this patient group. Even in cases where cancer treatment has shown favorable outcomes, implant placement is discouraged in patients who are not receiving chemotherapy but continue IV BF therapy. Furthermore, even after discontinuation of IV BF, implant planning should be avoided due to the drug's long-term effects on bone tissue. (Madrid & Sanz, 2009)

Akman et al. reported early failure of two out of five implants placed in the anterior mandibular region of a patient who had completed chemotherapy for prostate cancer 18 months earlier but was still undergoing IV BF therapy. In the same case, bone tissue consistent with bisphosphonate-related osteonecrosis of the jaw (BRONJ), classified as stage 1, was identified around one of the clinically successful implants. Following consultation with the oncology team, IV BF therapy was temporarily discontinued, and the patient underwent regular dental follow-up. After one year, erythema and purulent discharge were observed in the peri-implant soft tissue of one initially asymptomatic implant. Despite a five-day course of antibiotics (amoxicillin + clavulanic acid, 1 g twice daily) and chlorhexidine mouthwash, no clinical improvement was achieved. In this case, the patient's medical status had not been thoroughly evaluated, and ongoing IV BF therapy had been overlooked. As a result, two implants failed within the first postoperative year, and BRONJ developed around the remaining two implants.

Dental Implant Applications in Patients Using Bisphosphonates for Osteoporosis Treatment

The risk of developing bisphosphonate-related osteonecrosis of the jaw (BRONJ) associated with oral bisphosphonates (BF), commonly used in the treatment of osteoporosis, is significantly lower (0.001% - 0.01%) compared to intravenous (IV) bisphosphonates (1% - 10%). (Javed & Almas, 2010) However, individuals using BFs for osteoporosis represent a significant portion of the patient population frequently encountered by dental practitioners. Dental implant procedures are often planned and carried out in this age group to address the prevalent issue of partial or complete edentulism. (Yip et al., 2012)

Most studies evaluating implant success in patients using oral BFs consist of case reports, case series, and retrospective analyses. A meta-analysis reported a very low risk of BRONJ in patients taking oral BFs. Risk factors identified in these studies include the duration of BF use, concurrent corticosteroid therapy, diabetes mellitus, and smoking. Additionally, dental implant therapy is not recommended for cancer patients on BFs, and there is insufficient evidence supporting the evaluation of C-terminal telopeptide (CTX) levels or the discontinuation of BF therapy. A large-scale study

investigating implant outcomes in patients using oral BFs reported an implant success rate of over 99%, with a BRONJ incidence of 1 in 5000. (Goss, Bartold, Sambrook, & Hawker, 2010)

Among patients who developed BRONJ, it has been shown that oral BF use exceeding five years significantly increases the risk. Furthermore, cases of osteonecrosis have also been reported in patients who initiated oral BF therapy after implant placement. (López-Cedrún et al., 2013) A 2014 review noted that oral BF therapy may increase the risk of BRONJ in implant patients, particularly in those who began or continued BF therapy during the peri-implant period. (Holzinger et al., 2013)

In recent years, IV administration of 5 mg zoledronic acid one to four times annually has been proposed as an alternative to weekly oral BF therapy for osteoporosis. (Ruggiero et al., 2009) This regimen has been shown to exert a faster effect on bone remodeling compared to oral treatment. (Deeks & Perry, 2008) Annual administration of 5 mg IV zoledronic acid has been demonstrated to improve bone mineral density and significantly reduce the risk of vertebral fractures. (Black et al., 2007) In the literature, case reports describe the development of BRONJ in 10 patients who received this IV BF regimen for osteoporosis. All cases involved additional risk factors such as corticosteroid use, diabetes mellitus, smoking, and a history of prolonged oral BF therapy prior to IV administration. (Katz & Ordoveza, 2014)

Bisphosphonate Use in Children

Currently, the majority of research and knowledge related to bisphosphonate-related osteonecrosis of the jaw (BRONJ) is predominantly associated with diseases in older populations, such as osteoporosis, breast cancer, and prostate cancer. However, there is also a significant number of pediatric and adolescent patients using oral or intravenous (IV) bisphosphonates for the treatment of bone diseases such as osteogenesis imperfecta and fibrous dysplasia. (Annibali, Bignozzi, Ottolenghi, & Polimeni, 2012; Christou, Johnson, & Hodgson, 2013) In this patient population, there is a frequent need for dental interventions due to conditions such as rapidly progressing caries and issues related to third molar teeth. Additionally, treatment options such as decoronation or tooth extraction, which are often employed in older patients, may not always be suitable for children and adolescent patients. Therefore, the development of specialized and individualized dental approaches for children receiving bisphosphonate therapy is essential.

In pediatric and adolescent patients requiring bisphosphonate treatment, preventive approaches, such as the application of fluoride gels, should be prioritized. Moreover, extracting third molar teeth before root development is complete may be an effective strategy for preventing serious complications,

such as BRONJ development or associated jaw fractures. (Annibali, Bignozzi, Ottolenghi, & Polimeni, 2012)

Other Drugs That Can Cause Bone Necrosis Similar to BRONJ

Denosumab

Denosumab is a drug developed with indications similar to bisphosphonates, but it operates through a different mechanism of action. By inhibiting osteoclastic activity through a distinct pathway from bisphosphonates, denosumab behaves as an analogue of osteoprotegerin, binding to RANK and inhibiting the activity of RANKL; this process prevents the differentiation of macrophage-derived precursor cells into osteoclasts. (Sivolella, Lumachi, Stellini, & Favero, 2013) Recently introduced into clinical practice, denosumab has been reported in case studies and research to potentially cause atypical femur fractures and osteonecrosis of the jaw (ONJ) similar to bisphosphonates. Large - scale studies have shown that the incidence of osteonecrosis related to denosumab is comparable to that of BRONJ. (Aghaloo, Dry, Mallya, & Tetradis, 2014) When denosumab treatment is interrupted, its effects on bone metabolism dissipate more quickly compared to bisphosphonates. Therefore, in patients using denosumab, an "drug holiday" before invasive dental procedures that may lead to necrosis could yield more favorable outcomes than in patients on bisphosphonates. (Malan, Ettinger, Naumann, & Beirne, 2012)

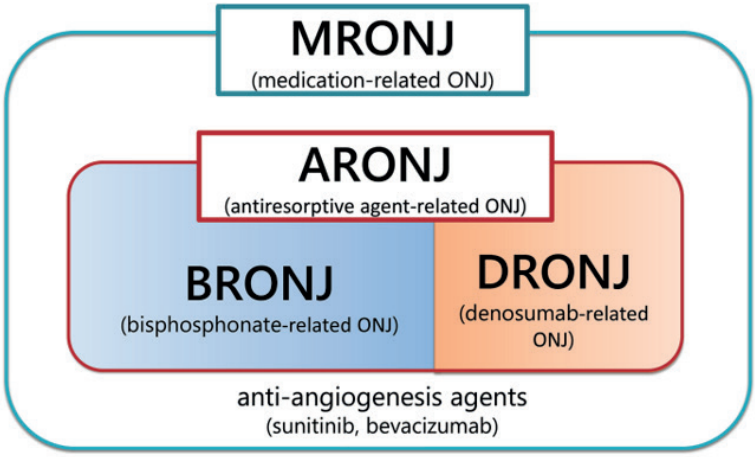

Figure 3. *Diagram of Osteonecrosis. (Shibahara T. Antiresorptive Agent-Related Osteonecrosis of the Jaw (ARONJ): A Twist of Fate in the Bone. Tohoku J Exp Med. 2019 Feb;247(2):75-86)*

Bevacizumab

Bevacizumab, a recombinant monoclonal antibody that binds to vascular endothelial growth factor (VEGF) to inhibit angiogenesis, is used in the treatment of metastatic colorectal, breast, lung cancers, and glioblastoma. In addition to known side effects such as vascular complications and delayed wound healing, it has also been reported in various studies to potentially cause osteonecrosis in the jawbone. (Magremanne & Reychler 2014)

Dental Implant Surgery in Patients Using Bisphosphonates	
1.	Dental implant surgery is considered a significant interventional risk factor for the development of BRONJ.
2.	In patients receiving intravenous bisphosphonates during cancer treatment, the risk of BRONJ development is high, and therefore, dental implant procedures are generally not recommended.
3.	In patients using oral bisphosphonates, the risk of BRONJ development associated with dental implant procedures has been reported to be very low. However, similar to patients using oral bisphosphonates before or during implant treatment, there is also a possibility of BRONJ development in individuals who begin bisphosphonate therapy years after implant surgery.
4.	Factors that increase the risk of BRONJ development in patients using oral bisphosphonates include the type of medication used, treatment duration, concurrent corticosteroid use, diabetes mellitus, smoking, and existing periodontal diseases. Especially in patients using oral bisphosphonates for more than three years, or in cases of use for less than three years with the presence of additional risk factors, it is recommended to temporarily interrupt medication ('drug holiday') following medical consultation and to evaluate serum CTX levels.
5.	In osteoporotic patients who do not carry a high fracture risk, when dental implant surgery is planned, a temporary interruption of bisphosphonate therapy for 3 to 6 months ('bisphosphonate holiday') may be considered. This approach is recommended as a preventive measure to reduce the risk of BRONJ development.
6.	A serum C-telopeptide (CTX) level below 150 ng/ml has been associated with an increased risk of BRONJ development. However, there is insufficient and conclusive evidence in the literature regarding the reliability and clinical validity of CTX levels in predicting BRONJ risk.
7.	Patients with risk factors for BRONJ development should be thoroughly informed about the potential complications associated with implant therapy and the preventive measures that can be taken. Additionally, alternative non-implant treatment options should be offered to this patient group. For those who are selected for implant placement, it is crucial to establish a comprehensive follow-up protocol that includes regular clinical check-ups.

Table 6. *Dental implant surgery in patients with a history of or currently undergoing bisphosphonate therapy*

Conclusion

With the increase in average life expectancy and the growing elderly population, there has been a significant rise in the number of patients using bisphosphonates (BF) for the treatment of osteoporosis. Furthermore, as expectations for maintaining and improving quality of life increase, the demand for dental treatments, including invasive procedures, has also risen among the elderly population. Despite their known side effects, bisphosphonates remain the most commonly used drug group for osteoporosis treatment today.

On the other hand, effective chemotherapy protocols used in malignancies such as breast and prostate cancer, as well as multiple myeloma, have significantly extended survival rates. Bisphosphonates are also among the treatment options for preventing complications such as hypercalcemia and pathological fractures caused by bone metastases in these patients.

Current knowledge is still insufficient to fully explain the mechanisms of BRONJ development, make an early diagnosis, and establish effective treatment approaches. Various hypotheses have been proposed to elucidate the pathophysiology of the disease, but the formation process of BRONJ remains unclear. In animal studies conducted in this regard, challenges are encountered in creating effective and reliable experimental systems that can accurately model the disease.

Conservative approaches are generally recommended for the treatment of BRONJ lesions, and these approaches are typically aimed at halting disease progression rather than improving the current clinical situation. Recent studies suggest that parathyroid hormone derivatives may provide potential benefits in the treatment of BRONJ lesions in patients using bisphosphonates due to osteoporosis. However, this drug group is not a suitable treatment option for patients using bisphosphonates due to bone metastases. Studies on hyperbaric oxygen therapy have reported conflicting results. Additionally, the fact that most clinical publications on BRONJ consist of case reports and retrospective studies limits the development of evidence-based effective treatment protocols.

The increasing importance of dental applications for patients using bisphosphonates and the limited current knowledge on BRONJ further highlight the need for preventive approaches. In this context, informing patients and their families about the treatment process and potential risks, along with ensuring regular clinical follow-ups, is of great importance.

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