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PREFACE

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We thank all of the authors with whom we collaborated to publish their books across disciplines.

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Chapter 1

CURRENT KNOWLEDGE AND APPROACHES FOR THE USAGE OF PLATELET-RICH FIBRIN IN PERIODONTAL REGENERATION

Ece AÇIKGÖZ[1]

INTRODUCTION

Periodontal disease is a multifactorial and complex disease characterized by periodontal tissue destruction and the connective tissue attachment loss. The aim of periodontal therapy is to prevent the progression of periodontal disease by eliminating the existing inflammatory process and also to regenerate damaged periodontal tissues.

Periodontal regeneration is a difficult process that involves biological events such as adhesion, migration, proliferation, and differentiation[1]. Periodontal regenerative procedures include bone grafts, guided tissue regeneration, soft tissue grafts, and combinations of these procedures[2]. In addition to autogenic grafts, different biomaterials are used for periodontal tissue regeneration, such as allografts, xenografts, or grafts derived from synthetically produced alloplastic. However, there is no single material which is considered as the gold standard in periodontal intra-bony defects treatment[3]. It is crucial to note that although most of these biomaterials are promising in different aspects of regenerative dentistry, all of them can lead to foreign body reaction[4]. The generally accepted idea so far is that regenerative periodontal treatments can only recover some of the tissue volume

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and showed limited success for full periodontal regeneration[2]. Nevertheless, recently it was understood that true periodontal regeneration includes not only the periodontal ligament but also the alveolar bone, cementum, epithelium, and connective tissue. All the mentioned reasons lead us to look for new procedures based on new biomaterials, derived from autologous blood[5].

Wound healing is a multifactorial biological process in which many cellular events occur simultaneously and lead to repair or regeneration of damaged tissues[6]. The healing process includes 4 phases as hemostasis, inflammation, proliferation, and remodeling. These four aspects of wound healing have been identified as key ingredients for successful regeneration and various cell types are involved in each phase. One of the most important factors in these stages are platelets, cells that have been proven to be essential regulators of homeostasis through fibrin clot formation[7]. Vascularization, which is impaired in the wound healing process, leads to platelet aggregation, formation of fibrin, and growth factors release from platelets into tissues through molecular signals mediated by cytokines[3]. Key growth factors that are present in thrombocytes are vascular endothelial growth factor (VEGF), transforming growth factorβ- 1 (TGFβ-1) and platelet-derived growth factor AB (PDGF-AB)[8]. Additionally, fibrin, fibronectin, and vitronectin are also secreted from platelets and function as a matrix for connective tissue and adhesion molecules for greater cell migration[9]. All these roles that platelets play during the healing process have raised the question of whether they can be used to improve tissue recover in periodontal regeneration.

FROM FIBRIN GLUES TO PLATELET CONCENTRATES

In 1970, the first article of Matras was published on usage of fibrin glue to improve wound healing on skin. The fibrin glues were applied as tissue sealants, with fairly good outcomes. However, favorable clinical outcomes were not enough to enhance the advancement of this technique cause of economic concerns. The autologous fibrin glues were time-consuming and complicated to prepare; therefore, these techniques were never widely developed[10].

Evolving of the fibrin glue procedures into the platelet concentrates was a good chance to replace high priced fibrin glues with other autologous preparations. Since the presence of the autologous platelets reinforced with fibrin gel architecture, fibrinogen concentrates (fibrin glues) were impractical. Like fibrin glues, the procedure of platelet concentrate was first described for the treatment of skin ulcers[11]. But the usage of platelet concentrates in oral and maxillofacial surgery did not gain interest until Marx's study. In this study, Marx et al. used a common name as Platelet Rich Plasma (PRP) and offered a new concept named plasma rich growth factors[12].

In the last 20 years, platelet concentrates used alone or as a matrix for other graft materials and have been developed as a potential autogenous biomaterial in regenerative dentistry. Platelet concentrates are blood extracts, provided from processing a blood sample, commonly through centrifugation[13].

DEVELOPMENT OF PLATELET-RICH PLASMA

Platelet-rich plasma (PRP) is the first-generation scaffold and platelet concentrate derived from blood samples. The accepted mechanism of PRP therapy is to achieve the highest and largest quantities of growth factors from alpha granules of platelets. When alpha factors activated through injury and clot formation, they release transforming growth factor, epithelial cell growth factor, vascular endothelial growth factor, fibroblastic growth factor, platelet-derived growth factor, and insulin-like growth factor[14]. According to many studies, PRP has been shown to have an advantage on the tissue healing and regeneration processes[15].

Platelet-rich plasma preparation requires the additional use of coagulation factors and two separate cycles of centrifugation to maintain proper platelet concentration. Two centrifuge cycles can take between 30 minutes to 1 hour. Furthermore, bovine thrombin and calcium chloride must be added to PRP to provide gel form. Weak fibrin network, short releasing time of growth factors, and all mentioned above reduce the regenerative potential and clinical effectiveness of PRP[5, 7, 16].

Platelet-rich growth factor (PRGF) and platelet-rich plasma (PRP) contain secondary by-products known as both unnatural and inhibitors of wound-healing. Therefore, many studies have attempted to remove these anticoagulants (secondary products) and modify the centrifuge protocol. A few years later, platelet-rich fibrin (PRF) began to affect many medical fields significantly, including dentistry[4].

WHAT IS FIBRIN?

Plasma (55%) and cells (45%) are the main ingredients of blood and plasma contains soluble proteins, electrolytes, and metabolic wastes as well as water (92%). The most notable soluble ingredient of plasma is fibrinogen, a clotting protein[17]. When a vascular injury occurs, thrombin enzymatically converts fibrinogen to insoluble fibrin which acts as a matrix containing growth factors, structural glycoproteins, platelets, and cytokines. This three-dimensional structure acts as a network that seems favorable for the growth of periosteal cells and binds platelets and erythrocytes in clot formation. This first step is essential for wound healing and tissue regeneration[16, 18]. Currently, the natural fibrin scaffold formed at the initial stage of wound healing can be used alone or in combination with other biomaterials and grafts[16].

PLATELET-RICH FIBRIN

In 2001, the second-generation platelet concentrates were presented by Choukroun and colleagues due to the inconsistent outcomes and preparation difficulties of PRP and PRGF[19]. The most common formulation of second-generation platelet concentrates contains leukocytes and platelet-rich fibrin and usually termed L-PRF (leukocyte-and PRF)[16].

Three-dimensional matrix, locally harvested cells, and bioactive growth factors are the essential components to enhance tissue repair and PRF meets all these components. Because, fibrin serves as a scaffold that includes leukocytes, platelets, macrophages, and neutrophils, attracts regenerative cells to the damaged sites, and acts as a reservoir for growth factors that may be released along 10 to 14 days. PRF releases growth factors for a prolonged period of time in comparison with PRP[20]. In addition to these superiorities, PRF increases the proliferation of osteoblasts, gingival fibroblasts, and periodontal ligament cells, while selectively suppressing the proliferation of epithelial cells[21].

Another major superiority of this technique is the simplicity of preparation. Blood samples in 10 ml tubes are immediately centrifuged for 12 minutes at 2700 rpm[7]. Furthermore, the procedure requires neither anticoagulant, calcium chloride nor bovine thrombin like additives. The absence of anticoagulant means the activation of platelets that contact the tube walls and then the coagulation cascades start in a few minutes[9]. When entire blood is centrifuged at high spin without anticoagulants, three layers are obtained. These layers of tubes include platelet-poor plasma on the above, an intermediate layer named “buffy coat”, and red corpuscles at the base (Figure 1). The buffy coat is the layer where most leukocytes and platelets are concentrated and a fibrin clot obtained. It should be used immediately after its centrifugation to eliminate the risk of shrinkage of the fibrin clot through diffusion[22] (Figure 2).

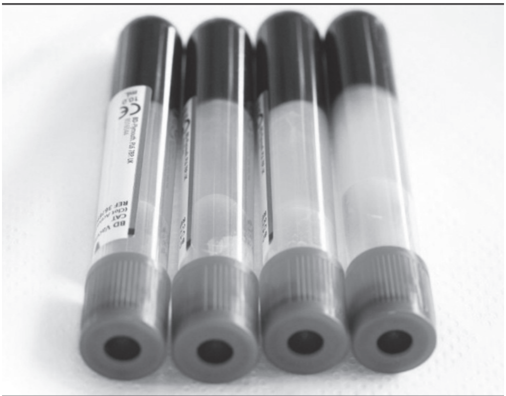

Figure 1. After centrifugation, three tube layers, consisting of PRP, buffy coat, and red corpuscles, are observed from top to bottom.

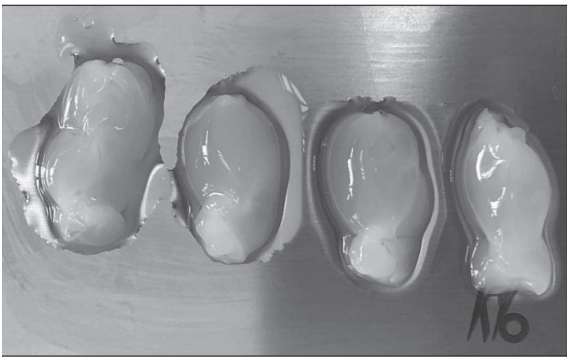

Figure 2. Platelet-rich fibrin obtained from the buffy coat should be applied to the defect sites quickly to prevent shrinkage that will occur over time.

The reduction in the centrifugation forces may lead to greater retention of cytokines and an increase in the number of leukocytes. Moreover, the significant slow release of the main growth factors from 1 week to 28 days has important effects on the healing process[23]. In recent years, alternative procedures based on different relative centrifugation forces including sticky bone, injectable PRF (I-PRF), advanced PRF (A-PRF), and titanium-prepared PRF (T-PRF) were improved upon to original Choukroun's method[24].

Advanced Platelet Rich Fibrin (A-PRF)

A-PRF and A-PRF+ have been improved over L-PRF to support more growth factor release in the wounded tissue (25). In 2014, Ghanaati et al. reported that cells inside the original PRF scaffold were gathered at the bottom. In principle, less centrifugation time increases the total count of cells that remain within the top layer of PRF and enables an advanced number of leukocytes "trapped" within the matrix[5].

Newer formulation of-PRF presented by Choukroun et al. (A-PRF+), does not only lower centrifugation speed but also centrifugation time (1300 rpm for 8 min). It increases the release of TGF-β1, PDGF-AB, PDGF-AA, PDGF-BB, VEGF, epidermal growth factor (EGF) and insulin-like growth factor (IGF) which are necessary for wound healing. Furthermore, A-PRF and A-PRF+ may indicate a significant increase in collagen1 synthesis which is the key factor during wound healing and remodeling[26].

In a study which is conducted by Fujioka-Kobayashi et al.[25], it is concluded that A-PRF demonstrates the highest values of growth factors at 1, 3, and 10th days. Additionally, it is claimed that the release of these factors after 10 days is three times higher when compared to L-PRF. A recently published study reported that the platelet distribution in A-PRF is more widespread and homogeneous compared with L-PRF[27].

Titanium-Prepared Platelet Rich Fibrin (T-PRF)

Although successful results have been reported with L-PRF, in recent years, some researchers have begun to worry about possible health problems that may arise from silica activators in blood collection tubes[28]. Therefore, in 2013, Tunalı et al. modified the primary L-PRF method by changing the glass-evacuated tubes with titanium which is more biocompatible material and named this modified technique as titanium-prepared PRF.

L-PRF and the T-PRF methods are very alike, but activation of the titanium-induced platelet provides prominent characteristics to T-PRF[8]. Based on scanning electron, light and fluorescence microscopy analysis, it was demonstrated that T-PRF has highly organized network throughout with sustained integrity, and fibrin network which may cover larger areas was thicker compared with L-PRF[24]. In a study conducted by Mitra et al.[29], it is reported that T-PRF had a better fibrin mesh with strong cellular entrapment than L-PRF. Furthermore, in another study published in 2020, it is concluded that T-PRF has a greater cellular distribution for B-lymphocytes, T-lymphocytes, neutrophils, monocytes, and platelets than L-PRF[30]. In conclusion, it can be stated that T-PRF may be an alternative option for L-PRF.

Injectable Platelet Rich Fibrin (I-PRF)

In general, it can be admitted that there are two types of platelet-rich fibrin according to their solid or liquid form. The solid PRF includes the original form of PRF introduced by Choukroun et al. and other PRF types improved in years by other studies. However, the liquid form is called i-PRF[20, 31].

Mourão et al.[32] was developed an injectable platelet-rich fibrin (i-PRF) based on the idea of slow centrifugal force that preparing PRF at higher speed but in a shorter time. This procedure provides a liquid that can be injected directly into the tissue and periodontal pockets or mixed with particulate bone grafts to increase an agglutinated "sticky bone". Sticky bone maintains stabilization of the graft in the bone defects, allows the graft to be easily handled and therefore, reduces bone loss during the healing period by supporting tissue healing[24].

The most significant outcome of this technique is being a suspension that can be manipulated like PRP without anticoagulation. Nevertheless, this type of PRF retains the capability to configure a slow-release matrix once applied to the tissue[31]. In 2017, Miron et al. have recommended that utilizing specific centrifugation tubes at a low speed of 700 rpm (60 g) with a shorter centrifugation time (3 minutes). In this study comparing PRP and i-PRF, it is demonstrated that i-PRF has the capability to release higher numbers of various growth factors, induce migration of fibroblasts and increase expression of PDGF, TGF-ß, and collagen1. Furthermore, they stated that PRP had dissolved entirely following 10 days whereas a further release of growth factors could still be expected from i-PRF[33].

The major advantages of i-PRF are forming fibrin clot, remaining an autologous product with the benefit, and sustaining comparable growth factor release. The only disadvantage of i-PRF is the requirement to apply within 15 minutes of collection[26].

CURRENT CLINICAL APPROACHES OF PRF IN PERIODONTOLOGY

Regeneration of destroyed tissue as a result of periodontal disease is the ultimate goal of periodontal therapy. Periodontal regeneration can be defined as the thorough restoration of lost or injured tissues to their unique structure and function by repeating the wound healing events associated with tissue formation[34].

PRF is an effective biomaterial for wound healing with native regenerative capacity that can be applied in various cases such as furcation involvements, periodontal intra-bony defects, peri-implant defects, gingival recessions, and sinus lift procedures. Also, in the periodontal tissue engineering field, it can be utilized as a scaffold for periosteal cells[24]. In the literature, many studies are investigating the application areas of PRF in periodontology, proposing new procedures, and stating the superiority of different techniques to another[5, 8, 13].

Recently, clinical trials about PRF have shown significant outcomes of osseous growth in intra-bony defects. Since PRF is already a natural matrix for osteoblastic conduction, it can be used with or without bone graft materials and can also stimulate tissue regeneration 3-6 months after application to the periodontal pocket. In two different studies, Thorat et al.[35] and Sharma and Pradeep[36] reported that PRF-treated sites had greater reduction in pocket depth, greater clinical attachment gain, and greater intra-bony defect filling than only open-flap-debridemented sites. Furthermore, Mitra et al.[29] demonstrated that noticeable clinical and radiographic improvements according to baseline values at both PRF and T-PRF treated intra-bony defects after 9 months. A recent meta-analysis is reported that conventional flap surgery with L-PRF compared to conventional flap surgery alone showed significant differences such as greater bone filling in intra-bony defects (1.7 mm), clinical attachment gain (1.2 mm), and probing depth reduction (1.1 mm). Besides, the positive effects of L-PRF on soft and hard tissue healing and reduction of postoperative discomfort were reported[13]. In a research that investigates the effect of PRF in extraction sockets treated with or without membrane, Simon et al. found that sites treated with PRF alone or PRF with membrane showed more rapid healing and had osseous filling by 3 weeks[37]. Similar to intra-bony defects, many studies indicated that peri-implant defects treatment with PRF provides greater bone formation and better clinical outcomes than conventional flap surgery[38, 39].

In guided tissue regeneration, the membrane does not only act as a shield against penetration of epithelial cells but also can release growth factors that improve the osteoblasts activity and promote the healing of the gingival tissue. When PRF is flattened, it can be applied as a barrier membrane in bone grafting procedures[31]. L-PRF membranes do not have any contraindications, they can be recommended in all cases (even in patients under anticoagulant therapy), they always promote soft tissue healing and reduce the necrosis risk of the flap after surgery. As opposed to other guided bone regeneration membranes, L-PRF membranes act as competitive barriers, that's why they should not be used as a cell-proof shield. L-PRF membranes let cells migrate through, and as a consequence promote angiogenesis and interactions between the gingival flap and the bone[10]. The number of membranes within a site and the convenient blood volume may affect the clinical outcome[13]. Simonpieri et al. [40, 41], in a two-part publication, introduced an innovative technique with using PRF membranes, freeze-dried bone allografts, metronidazole solution (0.5%) together. In this technique, small quantity of 0.5% metronidazole solution provides effective protection to the graft material against bacterial contamination while the membrane component of PRF preserves the surgical site and enhances soft tissue healing.

Furcation defects are considered difficult areas for the treatment due to low accessibility to the operation region and anatomical irregularities. Therefore, these defects are generally treated surgically to allow appropriate root planing, osseous recontouring, and periodontal regeneration. In many studies, it is reported that the combination of PRF and bone grafts has remarkable outcomes in periodontic-endodontic furcation defects. Especially with early grade II furcation treatment usually shows great results[24, 42]. A meta-analysis published in 2019 showed that autologous platelet concentrates may be advantageous in the treatment of furcation defects in adjunct to bone graft or open flap debridement[43]. However, in another meta-analysis published in 2020, Tarallo et al. stated that all the studies reported favorable results with the addition of PRF to conventional flap techniques for the treatment of grade 2 furcation defects. According to these meta-analyses, PRF has positive effects on soft tissue and hard tissue healing such as reducing vertical furcation depth, vertical pocket depth, and vertical clinical attachment loss[42]. Additionally, in another meta-analysis, statistically significant differences are found in favor of L-PRF again[13].

Manipulation of the tissue is the basic concept in soft tissue surgery. The L-PRF membrane can be adapted and sutured to soft tissue, therefore can open *new horizons in gingival surgery.* The slowly release of growth factors and blood proteins derived from the L-PRF membrane during root covering promotes two important biological mechanisms such as impregnation and induction. Initially, the surface layer of the root is impregnated with blood proteins and secondly, the release of growth factors continues long enough to stimulate cell induction phenomenon. The short term outcome is a rapid wound closure with the reduction of post-surgical edema and pain. Subsequently, the long term result occurs not only as a firm root covering but also as thicker gingiva[10, 44]. Many studies have suggested the use of PRF membranes as an alternative approach to connective tissue grafts for the treatment of gingival recessions. Uzun et al.[45] reported that T-PRF is a safe and effective material for the treatment of multiple Miller Class I and II gingival recession defects. Eren and Atilla[46] treated gingival recessions with coronally advanced flap procedure by using PRF or subepithelial connective tissue graft and they announced development in all parameters with both techniques. In a meta-analysis conducted by Castro et al.[13], stated that L-PRF may be an alternative to a connective tissue graft (CTG) when it was compared with a connective tissue graft and similar results were noted for pocket reduction, clinical attachment level gain, gingival recession reduction and enhancement of keratinized tissue width. Also, in a recent study, the histological assessment revealed earlier angiogenesis and tissue maturation at PRF compared with CTG[47]. At the same time, in a study published in 2020, a statistically significant difference was detected in favor of subepithelial CTG only in keratinized mucosa width thus PRF membranes were decided to be a promising option to autogenous gingival grafts in the treatment of Miller class I and II gingival recessions[48]. Similarly, according to the results obtained from another meta-analysis, it is indicated that the use of PRF in combination with coronally advanced flap (CAF) significantly improves relative root coverage when compared with CAF alone. However, it did not improve the keratinized mucosa width[49]. Considering all the studies mentioned above, PRF may be preferred as an alternative approach to connective tissue grafts for the treatment of gingival recessions and only in specific cases with narrow keratinized mucosa, the use of CTG might be selected instead of PRF.

CONCLUSION

Platelet-rich fibrin has gain popularity in periodontal regeneration due to ease of application, low costs, and providing a completely autologous reservoir for growth factors. PRF is an effective healing biomaterial with native regenerative capacity that can be applied in various cases in periodontology such as furcation involvements, periodontal intra-bony defects, peri-implant defects, and gingival recessions. T- PRF is recently developed by changing the glass-evacuated tubes with titanium which is a more biocompatible material. Furthermore, recent modifications of the centrifugation speeds and times (A-PRF) improved the regenerative potential of PRF and provided a liquid formulation for injection (i-PRF). Nowadays, current knowledge and approaches are being developed continuously to improve the clinical results of regenerative procedures utilizing platelet concentrates but further studies are needed in order to achieve satisfactory outcomes.

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Chapter 2

CURRENT MANAGEMENT METHODS OF DEEP CARIOUS LESIONS

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INTRODUCTION

Caries is an infectious disease that causes destruction of dental hard tissues after a certain period of time, when favorable conditions occur with the presence of bacteria, fermentable carbohydrates, plaque, acidogenic and aciduric microorganisms. Bacterial metabolism by-products cause mineral loss from the tooth surface and initiate enamel demineralization. Underlying dentin will be affected if the demineralization continues to progress. In dentin tissue, demineralization is more rapid due to the high tubular structure and lower mineral content. Further demineralization of dentin results in cavitation[1].

Caries reaching the inner third or quarter of dentin are defined as deep caries and have a higher risk of pulp exposure[2]. Clinically it is impossible to measure the residual dentin thickness thereby the radiographic assessment is valid (Figure 1). Yet, to determine the deep dentin caries accurately in mm is a difficult procedure due to the x-ray distortion of the dental radiograph and generally, the dentist evaluates the depth of caries at the radiography with his/her clinical experience. However, x-ray mesh grids specialized for intra-oral films, the software programs and measurement methods can be used to show the existing carious tissue.

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Researchers have reported that the invasion of dentinal tubules by cariogenic microorganisms and thermal damage during mechanical caries removal, chemical irritation of restorative materials, or acidic agents applied to the dentin can cause pulpal reactions[3, 4]. Therefore, the residual dentin thickness, depth of caries are of great importance to avoid from these negative situations.

There are different treatment approaches in the management of deep caries to maintain pulpal vitality (Figure 2). While caries are completely removed in conventional approaches, less invasive methods are accepted today highlighting that complete removal of soft dentin may not be necessary.

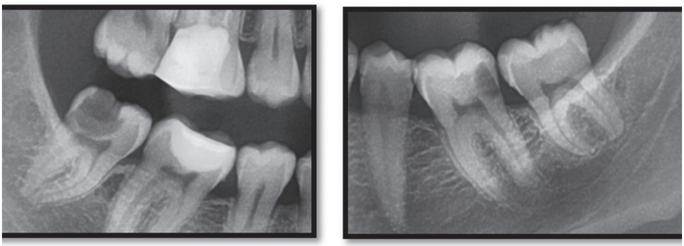

Figure 1. Radiological diagnosis of deep dentin caries

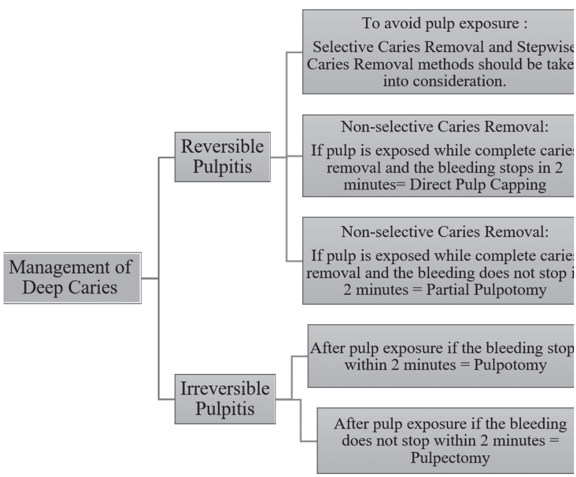

Figure 2. Management methods of deep caries

1. NON-SELECTIVE CARIES REMOVAL

In 1908, G.V. Black was claimed that it is better to expose the pulp than to leave it covered with softened dentin. Nevertheless, this approach causes excessive tissue loss and is now considered overtreatment[5].

The complete removal of softened dentin in order to eliminate both the biofilm and the microorganisms within the carious lesion was recommended in this technique. However, it is impossible to eliminate all the bacteria since a few will remain even if all soft dentin is removed. Additionally, it is repoted in several studies that bacterial counts under sealed restorations were drastically reduced[6-8]. This indicates that complete caries removal is not essential to eliminate all the bacteria under the sealed restoration.

Non-selective Caries Removal technique has some disadvantages, such as the risk of pulp expose, weakening of the tooth structure with excessive tissue removal, or reduced vitality[9]. To overcome these disadvantages, alternative strategies were developed.

2. SELECTIVE CARIES REMOVAL

In deep carious lesions, non-selective caries removal puts the pulp at risk of exposure that is why other strategies should be considered[10]. Incomplete caries removal is a non-invasive technique that allows pulp to be protected from mechanical hazards of complete excavation. Selective caries removal technique includes complete removal of the carious lesion from the cavity margins and peripheral cavity walls but limited removal from the pulpal floor[6].

The clinical assessment of carious dentin was subjective and differs from infected to affected dentin depending on the clinician. Consequently, some methods are developed to ease the selective removal of the caries lesion. One of these methods is polyamide polymer burs. Polymer burs are tougher than infected dentin, and softer than affected dentin. Thus, while removing infected dentin, the burs remain intact, and when it comes to healthy tissue, the burs will undergo deformation which prevents excessive tissue removal[11, 12].

Another method for selective caries removal was chemomechanical caries removal technique. In this technique, a solution was applied onto the caries, allowing it to soften the tissue, and scraping it off with blunt hand instruments. This technique has advantages included removal of infected dentin tissue only, absence of pain (no need for local anesthesia) and absence of negative mechanical removal effects to the pulp, due to heat and pressure[13]. However, chemomechanical caries removal methods are thought to affect the adhesion of restorative materials. On the contrary, Haak et al. stated that chemomechanical caries removal has no adverse effects on adhesion when modern bonding systems are used. They also claimed that smear layer-dissolving or smear layer-modifying bonding systems could benefit from chemomechanical pretreatment[14].

Subjective nature of clinical assessment of carious dentin led to caries dye (acid red in propylene glycol) development that can differentiate infected from affected dentin[5]. The infected dentin includes irreversibly damaged collagen fibers and dead odontoblastic processes that would never remineralize[15]. However, the deepest layer of affected dentin was hard as a result of remineralization. Caries detector dyes can discriminate these tissues. The dye-stained dentin indicates infected tissue and should be removed. Yet in some studies, it was revealed that not all dye-stained dentin was infected and dyes may lead to overpreparation[16, 17]. Although caries detector dyes have an important role in the education of undergraduates, their clinical acceptance is limited.

The major problem of selective caries removal technique is how much caries will be left in the cavity. Selective removal to leathery, hard dentin is often preferred. However, soft dentin can be left over the pulp to avoid exposure and maintain vitality. In this cases, care must be given to terminate preparation on non-carious tissue in peripheral enamel and dentin to ensure adequate adhesion[2, 10]. The amount of residual caries is important for bond strength because adhesion depends on the type of dentin. In a study conducted by Yoshiyama et al.[18], the bond strengths of adhesives to hard dentin were significantly higher than to affected dentin, and these values were both significantly higher than to infected dentin. The lower bond strengths to affected dentin may not be crucial, since such lesions are surrounded by noncarious dentin or enamel. However, Hevinga et al. stated that the fracture strength of teeth restored after partial caries removal was significantly reduced[19]. This can be explained by the lower value of the young module of carious dentin which can lead to greater deformation in the dental restoration complex, causing increased sensitivity to higher marginal stresses and fatigue failure[20]. On the contrary, in a study conducted by Silva et al.[21], it is demonstrated that maintaining the demineralized, softened dentin tissue under the composite resin restoration had no significant effect on the development of enamel cracks and fracture strength of the restoration. Therefore, it can be concluded that there is no difference between non-selective or selective carious removal techniques on the biomechanical behavior of bulk-fill composites in the class II restorations. The reason for these conflicting results can be differences in the extent and depth of caries, cavity configurations, and the materials used.

Since, there is a lack of standardization for the degree of excavation and residual caries, investigating selective caries removal is challenging. While Lula et al.[22] and Phonghanyudh et al.[23] removed only superficial necrotic dentin from the pulpal floor and left the soft dentin, Casagrande et al.[24] removed all of the soft dentin from the pulpal floor and left the leathery dentin. Therefore a healthy comparison cannot be achieved among the current studies.

Many studies indicated that the selective caries removal technique had a significantly lower risk of pulp exposure compared with non-selective caries removal technique[9, 24, 25]. In a 3-year follow-up study, Casagrande et al.[24] reported that there was no statistically significant difference in two methods by the aspect of pulpal complications but selective caries removal group showed higher frequency of restorative failures (15.4 %) compared to non-selective technique (2.0 %). In a meta-analysis conducted by Li et al.[9], results demonstrated that the pulpal symptoms and failure of the selective technique might be comparable to that of non-selective technique, with a decreased pulp exposure risk.

Even if the clinical survival of selective and non-selective caries removal technique is quite similar, the majority of dentists prefer complete removal of caries since they think residual caries may progress or infect the pulp[26]. The advantages of minimal invasive caries removal techniques should be highlighted in dental education, and long-term clinical studies are required to convince the clinicians to the performance of incompletely removed caries.

3. STEPWISE CARIES REMOVAL

Stepwise excavation is a selective caries removal technique for deep caries management with two-visit. The necrotic and disorganized dental tissue is removed during the initial excavation, leaving soft dentin over the pulpal floor to avoid pulp exposure. The cavity is temporarily sealed with a glass-ionomer based restorative material to allow the pulp to recover and produce tertiary dentin. In the second visit, the cavity is re-opened and the residual caries are removed[27]. The aim of this procedure is to lead carious dentin to change into arrested carious dentin over time. With a calcium hydroxide based material or hydraulic calcium silicate cement, the soft and wet appearance of carious dentin becomes darker, drier, and harder[1, 28]. After several months, second-stage excavation is carried out to firm dentin which makes the procedure safer and easier.

The time interval between two sessions can affect the success of stepwise caries removal technique. When the carious dentin becomes hardened, a shrinkage of the tissue will leave a void beneath the restoration and this situation may affect the durability of temporary restoration. However, the outcome of the study conducted by Mertz-Fairhurst et al.[29], indicated that the interval between initial and final excavation is not critical and it could be appropriate to wait more than 6-12 months for the second excavation.

Even if calcium hydroxide based liner material commonly placed under temporary restorations after first excavation, as reported previously by Pereira et al.[30], the calcium hydroxide liner does not improve the short-term outcomes compared to the use of resin-modified glass-ionomer (RMGI) alone. On the other hand, some studies reported less inflammatory cells with calcium hydroxide compared to the RMGI after 60 days. Yet, they claimed no significant difference clinically[31]. RMGI can cause mild pulpal reactions when used in the treatment of deep caries; however, the inflammation decreases over time, proving that the material is biocompatible.

In the stepwise excavation technique, pulp exposure frequency is lower than one-visit selective and non-selective caries removal techniques. Leksell et al. stated that the frequency of pulp exposure during non-selective caries removal was 40% and this rate was decreased to 17.5% in stepwise caries removal technique[32]. Bjørndal et al. reported that the stepwise excavation had a significantly higher success rate (74.1%) than of the non-selective caries removal group (62.4%) due to the fewer pulp exposures (17.5%) than direct complete excavation (28.9%)[33]. However, there was no statistically significant difference in terms of pulp vitality at the short term follow-up studies with two techniques[32, 33].

Stepwise caries removal technique requires two appointments to complete the treatment and temporary restoration can result in microleakage or discomfort to the patient; furthermore, there is a high risk of pulp exposure during the second excavation[27]. The two-visit nature of this technique may cause patients to drop out of treatment. When these disadvantages are taken into consideration, the question of whether we should re-enter these cavities has been raised. There is insufficient evidence of the need to re-enter the cavity and further excavation, whereas the studies that did not re-enter indicated any adverse consequences.

In 5 years of a follow-up study conducted by Maltz et al., selective caries removal technique (80%) presented a significantly higher success rate compared with stepwise excavation (56%). This low success rate of stepwise caries removal technique is due to the fact that some patients prone to do not attend the second appointment can negatively impact the clinical performance of this technique. If the stepwise excavation procedure was completely performed, both techniques can present similar success rates[34].

As a result of the microbiological analysis conducted by Orhan et al.[35], in the selective caries removal technique with indirect pulp capping the bacterial growth rate was 63.8% in dentin samples. The bacterial growth rate in the initial excavation of the stepwise caries removal technique was 100%, and it is drastically reduced to 44% in the second appointment. The reported bacterial growth after the final excavation was as low as 2.2%. In the direct pulp capping group, the bacterial growth rate was 25.6%. As a result, bacterial colonization has been shown to decrease the most in the stepwise caries removal technique. However, Kidd suggested that a successfully sealed restoration affects prognosis rather than residual microorganisms. Sealing the cavity interferes with the activity in the biofilm and persistent microorganism can be irrelevant. Therefore, Kidd recommends to focus on proper restoration rather than residual caries[5]. Studies showed that when radiographically detectable caries that extends into the middle third of dentin with no cavitation was placed over with a fissure sealant, the number of microorganisms was significantly reduced[36, 37]. This fissure sealant studies also support the Kidds sealed caries approach.

In a study conducted by Alves et al.[38], residual caries in teeth treated with selective caries removal monitored for 10 years and most of the residual caries remained unchanged or remineralized. In the %77 of cases, tertiary dentin detected in the radiographic analysis. The results showed that the proper sealing of carious dentin can promote tertiary dentin deposition and induce remineralization. Unchanged or decreased lesion depth in the radiographic evaluation was the evidence of arrested caries. However, some researchers claimed that leaving soft dentin over the pulp may lead to inflammation and necrosis[39, 40]. Even if caries is expected to be arrested with the sealed restoration without access to fermentable carbohydrates, the microorganism in the affected dentine is dominated by asaccharolytic anaerobic bacteria that may derive nutrients from proteins and glycoproteins from the demineralized collagen of dentin and the pulp tissue fluids.

The minimal invasive caries removal techniques are important since it is well documented that the success rate decreased when the pulp exposed. Al-hiyasat et al. stated that the success of direct pulp capping was 60% after 3 years and it was only %33.3 if the expose occurred during caries removal[41]. Therefore direct pulp capping was only successful when the pulp exposed traumatically or mechanically. If pulp expose occurs during caries removal, it is considered infected and partial pulpectomy was the treatment of choice.

Atraumatic restorative treatment (ART) is another minimally invasive caries removal technique aimed to arrest the caries progression. After removal of the carious tissue with hand instruments, the subsequent restoration with glass-ionomer cement is completed. The survival of ART restorations ranges from 93% and 62% and this technique can be applied in non-clinical settings with low cost[42]. In a study conducted by Singhal et al. microbial counts in cavities submitted to non-selective, selective caries removal and ART and reported that the microbiology of the ART technique resulted in a greater reduction of *Streptococcus mutans* and *Lactobacillus* spp. counts as compared to non-selective and selective techniques in which caries removed by using burs. The explanation of this could be that removing caries by using rotary instruments can cause bacterial invasion into the dentinal tubules. Since the carious tissue was removed with hand instruments in ART technique, residual microorganisms were low[43]. However, the restoration longevity was decreased in ART due to the inadequate mechanical retention as a result of used hand instruments' nature.

The comparison of deep caries management techniques is challenging due to multi factors that can affect success rates. Factors such as the materials used, patient-related factors (age, systemic diseases, oral hygine and diet habits), the depth and condition of caries can affect the pulpal prognosis and restoration success. In addition, the lack of adequate randomized controlled split-mouth studies in the literature and the lack of standardization among the current studies also prevents us to assess the techniques properly. Due to the ethical difficulties, setbacks in patient follow-up studies and lack of histological investigations, the qualified studies in this subject are quite a few. Therefore, further studies are needed to discriminate the advantage and disadvantages of each technique and to decide appropriate technique to particular case.

RESULTS

In deep carious lesions, to maintain the pulp vitality was the initial goal of the clinicians. If the residual dentin thickness was unreliably thin, alternative caries removal techniques should be considered as selective or stepwise caries removal. Every caries removal technique has advantages and disadvantages compared to one another. However, if the proper case was selected, adequate sealing was achieved and biocompatible materials were preferred, the restoration success will be improved.

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Chapter 3

DISTRACTION OSTEOGENESIS IN ORAL AND MAXILLOFACIAL SURGERY

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INTRODUCTION

Although orthognathic surgical procedures and traditional reconstruction procedures are frequently used in the correction of craniofacial deformities, many limitations are encountered in the acute movements of osteotomized bone fragments and over-stretched soft tissues. In addition, more than one surgical procedure is generally required in large skeletal disorders and especially in patients with syndrome. In these cases where many procedures should be postponed until the child grows, there is a great risk for psychosocial problems as well as secondary deformities with postponing treatment. Traditional osteotomies performed to correct severe craniofacial deformities require a long stay in the hospital and pose a risk for infection and relapse.(1)

These limitations and risks have led researchers to look for new methods to correct excessive anteroposterior, transversal and vertical deformities. After examining the results obtained by the distraction osteogenesis of the endochondral bones, it has

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been suggested that the membranous bones of the craniofacial complex can also be successfully distracted.[1] On top of that, distraction osteogenesis has found application in the craniofacial complex and has started to be used as a valid treatment option in the correction of craniofacial deformities.[2,3]

Distraction osteogenesis is the process of new bone formation in the space by applying a graded stretching force to the space between the two bone segments separated from each other.[4]

This process begins when the distraction force is applied to the callus of healing between the segments of separated bones and continues as long as the tissue is stretched.[5]

The use of distraction osteogenesis in oral and maxillofacial surgery has been widely used for the correction of bone deformities in the last thirty years.

INDICATIONS OF DISTRACTION OSTEOGENESIS

Common indications for distraction osteogenesis in the mandible can be summarized as mandibular hypoplasias due to congenital deformities such as Nager syndrome, Treacher Collin syndrome, Piere Robin syndrome, Cranofacial scoliosis and Hemifacial microsomia, and mandibular asymmetry of temporomandibular joint ankylosis.[6]

In addition, there are many indications for application: obstructive sleep apnea, mandibular stenosis, maxillary stenosis, mid-facial developmental retardation, cleft lip slits, bone loss due to a pathology (tumor resections, bone loss due to a large cystic formation), increasing the height of the fibula graft, elevating osteointegrated implants, maxillary arch shortness, poorly healed bone as a result of trauma, atrophic alveolar crest.[3,7-15]

CONTRAINDICATIONS OF DISTRACTION OSTEOGENESIS

Cases with insufficient bone volume and density, patients with weak immune system, osteoporosis, radiotherapy, diabetes are the main contraindications.[1,3,16,17]

DISTRACTION OSTEOGENESIS TECHNIQUES

Distraction Osteogenesis is divided into two as callotasis and physeal distraction depending on where the applied pulling forces affect:

a. Callotasis

It is formed by the gradual stretching of the callus formed around the bone segments formed after osteotomy. Clinically, callotasis consists of three successive periods, the latent period, the distraction period and the consolidation period. Callotasis is classified into three groups according to the number of distraction-tension regions:[(18)]

1. Monofocal Distraction Osteogenesis: It is a technique in which bone segments on both sides of the incision line are removed from each other by a single incision made into the bone. Here regeneration occurs in one region.
2. Bifocal Distraction Osteogenesis: It is a technique in which a vascularized bone piece that is separated from the remaining bone segment in the case of a wide bone defect is progressively moved towards the defect. The new bone transport is formed during the movement of the disc and the bone segment that is transported closes the defect region.
3. Trifocal Distraction Osteogenesis: It is a distraction osteogenesis technique in which two transport discs are created and brought closer to each other after osteotomies performed in the segment on both sides of the defect region in cases with very large bone defects.

b. Physeal Distraction

It is the distraction of bone growth plates. In this technique, it is divided into two depending on the distraction rate between growth plates:

1. Distraction epiphysiolysis: It is a fast physeal distraction technique performed in growth regions at a rate of 1–1.5 mm per

day. With rapid and increasing tension, fractures are formed in the growth plates. The epiphysis is then separated from the metaphysis and the growth plate is replaced by the trabecular bone formed.

2. Chondrodiatasis: Osteogenesis is accelerated by increasing the biological activities of cartilage cells with a tension created at a rate of approximately 0.5 mm daily without creating a fracture.

BIOMECHANICAL STEPS OF CLINICAL APPLICATION OF DISTRACTION OSTEOGENESIS

- Detailed preoperative planning including sensitive corrections of angular deformities
- Selection of the appropriate distraction apparatus, whose constant properties are known in different loading conditions
- Selection of pins in appropriate diameter and design
- Atraumatic bone incision (corticotomy) in the most appropriate area
- Carefully forming the bone and pin interface and preventing pin loosening that may develop later
- Creating a stable external fixation configuration

Choosing the distraction rate and rhythm that fit the biological process of the dystraction osteogenesis

- In case of delayed osteogenesis, periodic break in activation and even reverse movement (compression)

Maintenance of conservative fixation after the completion of the distraction

Inductive bone grafting in delayed consolidation cases

- Distraction of the distraction apparatus after adequate maturation of the new bone
- Protection of distracted bone from excessive stress during the remodeling period

CLASSIFICATION OF TREATMENT MODELS OF DISTRACTION OSTEOGENESIS

There are four types of distraction treatment methods:

1- Extension procedures only
2- Corrective distraction osteotomies (used in cases where there is a false fusion, such as pseudoarthrosis cases.)
3- Bone segment transfer
4- Stimulation of bone growth region by distraction in applications in children [19,20]

BIOLOGICAL BASIS OF DISTRACTION OSTEOGENESIS

Distraction application involves the interaction of mechanical and biological factors that affect each other. The biological and mechanical forces that shape regeneration play a key role in determining the position of the appliance.

The biological forces affecting the bone regeneration morphology result from the neuromuscular sheath surrounding the region. Mechanical forces, which are under the control of the clinician, occur by activation of the distraction apparatus.[17,19]

The classic idea in the bone formation mechanism is that different tissue types can be formed or remodeling under a specific pressure or loading condition. Chondrogenic and fibroblastic expressions of osteogenic cells are considered to be the result of an unfavorable mechanical environment that causes indirect bone formation (endochondrial ossification) and even fibrous attachment. The presence of direct intramembranous bone formation that occurs during distraction is thought to be a response to osteogenic cells against the applied tensile force.

In fact, the primary target of the applied tensile force may be the induction of angiogenesis, which is known to occur before osteogenic activity, rather than osteoblasts.

The force applied during distraction therapy may increase systemic osteoblast stimulating factors that increase osteoblast activity systemically and locally. Holbein et al. stated that the serum of patients with distraction osteogenesis had mitogenic effects on osteoblastic cells. No effect has been observed in sera from patients in the traditional osteotomy control group. Studies have also shown that there is a difference in serum concentrations of the transforming growth factor (TGF) among patients. On the other hand, the groups showed a similar increase in platellet-derived whole factor (PDGF).[21]

The rate is known as the distance in which bone segments are moved, and the rhythm is known as the number of movements of bone segments per unit time. Many studies indicate that the daily rate of 1-2 mm results in adequate osteogenesis in craniofacial distraction osteogenesis. The rate of distraction is usually 1 mm per day. Some researchers try to prevent early consolidation by applying 2 mm distraction to young patients a day. Others try to prevent fibrous attachment by applying 0.5 mm distraction to elderly patients per day.[22,23]

The distraction applied daily can also be applied at once or in sections. Its application in sections is more advantageous as it helps the formation and development of tissues. In addition, frequent daily distraction in small pieces speeds up the formation of new bone, as a result of the biochemical analysis of this application and the observation that the released substances for osteoblast formation and maturation increase is a proof of this. In addition to increased osteogenesis, split distraction protocols provide less injury to soft tissue and increased vascularization.[3,17,19]

Distraction osteogenesis begins with the formation of a repair callus. Callus forms the new bone with the effect of tensile forces.[3]

The distraction process is examined in 5 clinical stages according to the morphological process and remodeling of the new bone formation:

- Surgical period
- Latent period
- Distraction period
- Consolidation period
- Remodeling period [24]

Surgical Period: It includes the decortication of the bone or the complete osteotomy procedure. The important point in doing this procedure is the necessity of working with conventional methods so as not to disturb the nutrition of the bone. To minimize the risk of delayed consolidation, the corticomy should cause minimal damage to the endosteum and periosteum. In this way, it is aimed to maximize regeneration.[25,26]

Latent Period: To optimize the response of osteogenic tissue to distraction, a latent period has been proposed for early callus formation. It refers to the start of traction after the osteotomy and the process in which callus formation is allowed. Callus formation occurs with the formation of good vascularized granulation tissue with proliferation of endosteal and periosteal cells in the end regions of bone fragments. The events observed in the latent period are the same as those occurring in fracture healing. Traditionally, fracture healing consists of four phases. These include: inflammation, soft callus formation, hard callus formation and remodeling.[2,27]

There are several opinions about the ideal process for maximal osteogenic activity during this period. It is 5-7 days according to Ilizarov, 7 days according to Synder, and 10 days according to Califona. In young patients, this period can be shortened or the consolidation phase can be started without applying.[28,29]

Distraction Period: The distraction process begins by pulling the bone segments in separate directions with external or internal appliances. This action leaves the repair callus under tension. This tension activates skeletal growth factors and transforms capillary cells into osteogenic cells, resulting in new bone formation.[30]

The values of three variables should be determined during the distraction period. These are: the rate of distraction, the rhythm, and the total time required for distraction.[31]

Rate; The amount of daily activation applied to the appliance, and the rhythm; Indicates how many parts of daily activation applied to appliance.[30]

The rate of distraction is approximately 1 mm per day, regardless of species, bone segment distracted and age. The rhythm of the distraction changes as 1 turn per day or 0.25 mm 4 times a day. The total time required for distraction varies depending on the patient and the size of the deformity and the achievement of the desired clinical goals.[10]

Consolidation Period: It is the period from lifting the pulling forces to removing the distraction devices. This period includes the mineralization of immature bone. The distraction apparatus is left at the last stage brought on and the bone is stabilized until the new bone has sufficient strength. Usually 6-8 weeks is enough. According to Ilizarov, this period should not be less than the period in the distraction period.[3]

Remodeling Period: Remodeling is the period when full functional loading is performed on the newly formed bone. During this period, both cortical bone and bone marrow are restored. Havers channels are also remodeled. It takes a year or a little more for the formed bone to fully level with the normal bone. In maxillofacial applications, implants are placed following the 3-month consolidation period. Prosthesis is applied 3 months after implants.[17]

MANDIBULAR DISTRACTION AND APPLIANCES

Clinical distraction osteogenesis applications to the mandible have proven to be a major improvement in the treatment of various craniofacial deformities. Experimental applications in animal mandibular were pioneers in distraction osteogenesis in human mandible by McCarthy et al.[19] The first experimental distraction study for the craniofacial skeleton was performed in 1973 by Synder et al.[32] Then, in 1977, they practiced Michielli and Miotti in Italy.[33] Until 1990, no study on this subject has been observed. Karp et al. performed unilateral angular osteotomy in the canine mandible.[34]

These researchers found that a very well-organized bioprocess emerged in the enlarged region of the cortical bone formation and histological examination of the area of expansion. In 1992, McCarthy et al. presented the results of the first clinical mandibular lengthening that they successfully performed in four young patients using a bicortical osteotomy and rigid external fixator.[35]

Although there are various details in mandibular distraction applications, the basic principles that must be taken into consideration are:

- Adequate bones must be available for osteotomy and appliance placement.
- Depending on the size of the space required for placement of the apparatus and the amount of mouth opening available, the required clearance can be achieved through an intraoral or extraoral approach.
- A number of factors should be considered when deciding between internal and external appliances. While external appliances allow multi-directional distraction control, this cannot be done with existing internal appliances, whereas external appliances can cause significant scar formation on the face and therefore different distraction vector applications can be preferred to permanent external scars with a series of internal distraction appliances.
- The location of the appliance and / or orientation determines the distraction vector, not the osteotomy of the mandible.
- Before performing an osteotomy, the appliance must be temporarily replaced. Because the proximal segment is mobile after osteotomy, it is difficult to insert the appliance. The osteot-

omy line does not need to be perpendicular to the distraction vector, but should be placed so as not to damage the nerve and developing dentition.

- Buccal corticomy is performed with a special saw, and the greenstick fracture in the lingual is created with a suitable osteotome and the inferior alveolar nerve is protected.
- Before closing the zone, the appliance should be tested and the patient should be told by emphasizing the direction of use of the part used to activate the appliance.

MIDDLE FACE DISTRACTION AND APPLIANCES

Indications of maxillary distraction;

1- Patients with moderate and severe retrusions with large advances requiring large advances.
2- Patients who do not need intermediate bone grafts that need to stretch forward and down
3- Early treatment for growing patients.[36]

Although there are various details in maxillary distraction applications, the basic principles that must be taken into consideration are:

- With the use of external appliances, preoperative preparation typically involves inserting a palatal appliance to guide the distraction vector.
- Osteotetomy should be done conventionally and mobilization of the middle face should be completed.
- To protect the developing dentition at the infraorbital foramen level in children with milk or mixed dentition, typical LeFort I osteotomy should be modified and taken up.
- Midface advances and frontofacial advances at LeFort III level can be done with external or internal appliances depending on the conditions. Internal appliances are placed at the level of the zygoma body and arc. External appliances need palatal apparatus and additionally wires from zygoma, nasal root and supraorbital regions.[37]

BIOLOGICAL BASIS OF DISTRACTION OSTEOGENESIS

In 1993, Rachimel et al presented the findings of the midfielder enhancement they made in the bay with external distractors. For the 43 mm expansion in the lateral maxilla and 36 mm expansion in nasofrontal junction, 2 mm expansion was made daily.[(1)]

Molina and Ortiz-Monisterio presented the use of an orthodontic protraction mask combined with Le Fort I osteotomy for distraction osteogenesis.[(38)] After applying this technique, Polley and Figueroa realized that the elastic face mask is not rigid enough to achieve the desired forward movement. They developed an adjustable rigid external distraction (RED) system for maxillary advancement. Indications for use; Some cases and treatments that require major improvement are cleft palates that have resulted in scarring. A crocheted occlusal splint is prepared in advance and a large LeFort osteotomy is performed. Immediately after the closure, the distraction device is placed symmetrically and fixed with 2-3 head screws. The guide wire is connected to the horizontal bar in the distractor by extraoral hooks extending from the splint. There is a 3-4 day latent period and the distraction rate is 1 mm per day. The horizontal bar of the appliance can be adjusted up or down to allow for versatile control of vertical movements with horizontal movements. The consolidation period is 2-3 weeks after the appliance is removed. With this appliance, LeFort I osteotomy, LeFort III osteotomy and monoblock osteotomies can be used. [(1,39,40,41)]

Molina designed a one-way orbital malar distractor used with Le Fort III osteotomy. The arm in the appliance itself is soft, this provides comfort and function. The active part of the arm extends percutaneously behind the ear and can provide 25 mm of enlargement. At the front end of the appliance, there is a fulcrum that provides flexibility in the displacement of the appliance behind the zygomatic bone.[(1)]

Chin and Toth designed their own internal appliances for use in the maxillofacial complex. The patients' skeletons used computed tomography information to plan the surgery and design their distractors. Chin and Toth's method for distraction is different from the principles published by Ilizarov in several ways. First, a full thickness osteotomy is performed without preserving the periosteum. Secondly, the latent period is not expected; however, distraction is started directly without closing the operation site.[42]

In 1997, Cohen et al. Developed a system called the Modular Internal Distraction System (MIDS). It is the first internal distraction appliance approved by the FDA. The first generation system includes expansion screws capable of 15mm and 30mm distraction. The flexible activation wire can be inconspicuously away from the operative area, behind the ear, between the hair, or inside the mouth. MID can be easily adapted for mid-face distraction. Appliances are generally well tolerated by patients. Besides all these, a major operation is required to remove the appliance and the amount of tissue removed is disadvantages of the appliance.[43,44,45]

With the currently used internal appliances, midface advances at LeFort I level are limited; because the adaptation and orientation of the appliances in a limited space is limited due to the difficulty of properly adjusting the appliances in the space. Fixation of the apparatus may damage the developing dentition. External multi-directional appliances are preferred because they allow more control in distraction application.[37] However, external appliances have disadvantages such as cumbersome, uncomfortable and poorly tolerated by the patient.[46] This led the researchers to search for new intraoral appliances.

In 2004, Yamaji et al developed a new appliance called LeFort I internal distractor for use in mid-face hypoplasias. This appliance includes the top and bottom plates placed under and above the LeFort I osteotomy. The top plate is U-shaped while the bottom plate is U-shaped. The anterior and posterior ends of the plates are fixed with screws to the priform protrusion and zygomatic support. The distraction screw is placed parallel to the sagittal plane in the maxillary sinus. The activation bar is attached to the distraction screw with a multi-purpose ligament and extends into the mouth along the maxillary buccal sulcus. This new appliance is designed to show some problems with traditional internal appliances. Advantages of the appliance; Placement of the distraction screw in the maxillary sinus facilitates the placement of the screw parallel to the sagittal plane and provides a wide room for changes in the vertical direction, and this localization is more tolerable by the patient since it does not cause regression in the buccal tissues. Disadvantages of the appliance; An additional application is required to remove the appliance, sufficient bone support is required for loading, and the distraction vector cannot be controlled, as with conventional internal appliances; however, the appliance allows precise control of the distraction vector for better occlusal results.[(46)]

Maxillary stenosis cases can be corrected by methods such as slow orthodontic expansion, rapid palatal expansion, rapid palatal expansion supported by surgery, and two-segment LeFort I type osteotomy with expansion. As a result of such treatments, unwanted movements may be observed in the supporting teeth and long retention and over correction may be required to prevent skeletal relapse.[(37)] To prevent these disadvantages, for the first time in 1999, Mommaters introduced a bone-assisted transpalatal distractor (TPD) for maxillary expansion. This appliance has 3 advantages. The first is that the forces are directly attached to the bone so that orthodontic movements are not required, the second is that by changing the telescopic distraction module given in four different sizes, the amount of distraction can be easily changed during the activation phase, and the third advantage is that it allows the teeth to be braced and leveled immediately in the retention phase after treatment. The disadvantage of the apparatus is that the functional components are loosened or damaged.[(47,48)]

CURRENT DEVELOPMENTS IN APPLIANCES

Distraction appliance has disadvantages such as causing the scar, requiring second surgery to remove it, prolonging treatment time, risk of infection around the appliance. These disadvantages prompted the researchers to make new discoveries.

Resorbable materials largely replace titanium and metal implants in pediatric craniofacial applications. In 1999, Cohen and his friends introduced a new mid-face distractor, which can be partially resorbed.(49) In 2001, Cohen and his friends performed Le Fort III distraction with a partially resorbable appliance. MID system is used in this process. The difference from classical MID is that Macropore meshes can be resorbed instead of titanium meshes. Only the distraction screw and wire need to be removed from the appliance. Since a resorbable stabilizer is used, the distraction wire and screw do not require a consolidation phase and can be removed after the distraction phase.(43,44,45)

In 2002, Burstein et al. developed three types of single-stage distraction appliance based on the LactoSorb resorbable implant system. The first appliance they developed (MOF Apparatus) is used for mid face, orbital and frontal bone distraction. The MOF appliance can be easily applied in any osteotomy design and can combine frontal and orbital bone expansions. The second appliance is the Mandibular Adolescent Appliance (MA Appliance) that can be used in older children and adolescents with sufficient bone volume. The third appliance is used for mandibular distraction in newborns, infants and young children with very low bone volume. (MI Appliance).(49)

Various agents are used clinically and experimentally as distraction osteogenesis mediators. In one study, the effects of calcium sulfate, hyalunaric acid and chitosan on distraction osteogenesis in early bone consolidation were investigated in canine models, and materials combined with calcium sulfate and calcium sulfate were found to be partially effective in early bone consolidation.(50)

Today, distraction osteogenesis is used safely in many treatment methods such as the treatment of skeletal deformities and providing the proper bone volume for implant treatment.

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Chapter 4

INVESTIGATION OF THE COLOR STABILITY OF CURRENT COMPOSITES: NEW DEVELOPMENTS, NEW MATERIALS

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The increasing interest in aesthetics today and the fact that dental health is an indispensable part of aesthetics have caused patients to demand longer-lasting aesthetic restorations. For this reason, composite resins have become frequently preferred materials by physicians[1,7].

One of the essential factors in the aesthetic success of current restorative materials is its compatibility with natural teeth. Dentistry needs to ensure color harmony between teeth and restoration. Cosmetic fillers are asked to maintain their color in oral conditions because coloration is one of the most critical aesthetic failures. To prevent this, color stability, which is one of the main factors of renewals in composite restorations, cannot be maintained. The effects of chemical and physical components on restorative materials can be predicted to make these restorations more aesthetic and long lasting[1].

There are many internal and external factors such as insufficient polymerization, water absorption, chemical reaction, nu-

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tritional habits, oral hygiene, and surface smoothness of restoration that affect the degree of coloration. Color changes due to the composite material structure are classified as internal colorings, and color changes caused by physician errors that may occur during the application of the restoration[2].

Fillers also have an important effect on the coloring of composite materials. It is known that composite materials with low filler content have less color stability. Fillers may separate from the resin matrix due to the abrasion of the resin composite. For this reason, external coloration may occur in the restoration as the surface roughness increases[3].

CLASSIFICATION OF DISCOLORATION IN COMPOSITE RESINS

Color changes occurring in composite resins arise due to various reasons. In composite resins, there are two types of coloration, internal and external. Internal stainings are permanent colorings that occur depending on the composite's structure, filler content, water absorption, and polymerization method. External stainings occur due to factors such as finishing and polishing processes during the application of the restoration, staining materials, surface roughness and hardness, poor oral hygiene, water absorption[2].

INTERNAL STAINING:

The internal colorations observed in composite resins material are realized according to the material's content and structure. Factors affecting the color of the material used in restorative dental materials that are polymerized with light include many features such as polymerization, matrix content, and filler properties[2].

Structure of Composite Resin

In dentistry, composite resins consist of three primary phases structurally. These phases, the organic polymer matrix phase, is called the inorganic phase and the intermediate phase. Bis-GMA (bisphenol A glycyl-ether-methacrylate), Bis-EMA (ethoxylated bisphenol A dimethacrylate), TEGDMA (triethylene glycol dimethacrylate) and UDMA (urethane dimethacrylate) are the most commonly used oligomers in much composite resin organic matrixes[2,4-6]. It is said that the color stability of composite resins containing UDMA is better than composites containing other monomers[7].

In auto polymerizing composites, the initiator is dibenzole peroxide, while the accelerator is aromatic tertiary amines. In composites that are polymerized with light, 450-550 nm wavelengths are used as the initiators, which show their effect by absorbing light[8]. When the composites are chemically polymerized, colorations are observed due to the chemical change of the tertiary aromatic amines. Moisture, UV (Ultraviolet) light, and oxidation can be listed among the materials that accelerate this deterioration. The most commonly used initiator type in light-polymerized composite resins; The chromophore group, which is yellow and stable, is camforoquinone. It is reported that the use of camforoquinone at high levels in the resin structure causes discoloration[9,10]. Concerning resin storage form, color changes can be observed in composite resins kept in a hot environment for a long time[11].

Water Absorption of Composite

Water absorption plays an essential role in the clinical success of composite resins. Hydrophilic composite materials showing water absorption are thought to be more prone to coloration. Microcracks are seen in the composite resin due to excessive water absorption or cavities formed in the filling and matrix interface, causing dye penetration and coloration. Also, composites with the main monomer content of Bis-GMA, compared to composites containing UDMA and Bis-EMA (ethoxylated bisphenol A glycol dimethacrylate), show greater water absorption and thus increase the probability of coloration[8].

Water absorption in resins with necessary filler Bis-GMA is 0% - 1%. Due to the TEGDMA added to these resins' structures to regulate their viscosity, this ratio may increase to 3-6%. TEGDMA contains ethoxy groups that are hydrophilic in the center, and therefore the surface hydrophilicity of the composite material also increases. As a result, Bis-GMA and TEGDMA structures show high water absorption due to the affinity of water. Due to the hydrophobic group in the structure of Bis-EMA, water absorption is low. In addition to these, TEGDMA is reported to show a high rate of water absorption compared to Bis-EMA, Bis-GMA, and UDMA[12,13].

Polymerization Method of Composite

Insufficient polymerization in composite resins causes poor color stability of the material. In cases where it is not polymerized sufficiently, the failure of the camhoroquinone used as the initiator to completely change its color from yellow to colorless causes yellow colorings in the composite resin structure. Over time, it has been reported that yellow color marks turn brown as a result of oxidation of amines with photo-activation of the material[9].

Time and preferred light devices in polymerization are also very effective in stainings. With the decrease of dimensional stability and monomer-polymer conversion, an increase in color change is observed. However, additional polymerization was found to be ineffective on all composite resins. Composite resins are reported to change color when they interact with chemicals and food dyes if they are not polymerized adequately[14-16].

External Staining:

External discolorations are generally caused by consuming colored food and drinks and poor oral hygiene. Besides, faults in contact with the blood and moisture, finishing and polishing through external tools or insufficient insulation, cause external discoloration[2].

Discoloration of the Composite Resin with Water Absorption and Coloring Agent

Composite resins can absorb water as well as absorb liquids with other pigments that can cause discoloration[17]. Water is thought to be a means of transporting coloring agents into the resin matrix. Filling particles in the composite resin cannot absorb water. Therefore, the more organic matrix the composite resin contains, the more water it absorbs[18].

There are many in vitro studies on foods and beverages such as coffee, tea, red wine, juice, cola, and ketchup that we consume in daily life. The results of the studies determined that these substances cause discoloration on the restoration surfaces. Alcohol, which is known to cause deterioration on the surface of composite materials, causes more coloration, creating a rougher surface[19,20].

The Effect of Finishing and Polishing on the Coloring of Composite Resin

Composite resins formed by filler particles with the hard structure embedded in the soft organic matrix have a heterogeneous structure[21]. The surface may remain rough due to not completing the finishing and polishing processes of composite resin restorations. As a result, it has been reported that increased plaque accumulation, gingival inflammations, secondary caries formation, and coloration can be observed[22].

The filler particles in the composite resins are hard from the resin matrix. During the finishing-polishing process, the resin matrix is easily separated and remains in the form of protrusions on the surface of the harder filler particles. Therefore, they cause the surface to become rough[23]. Organic matrix and inorganic fillers with different hardness in the composite resin are desired to be abraded in the final stage of the restoration, so it aims to minimize the coloration of the restoration by obtaining smooth surfaces [24].

Also, composite resins with large filling particles can increase surface roughness and increase coloration. As the filler particle sizes in the composite resin decrease in size, the surface roughness decreases, and resistance to coloration increases[25].

Effect of Mouthwashes and Toothpastes on Discoloration

It has been reported that mouthwashes used as a therapeutic antimicrobial agent or applied for whitening also cause color changes in teeth and restorations[26]. Elhejazi et al. evaluated the effect of 2 mouthwashes (Listerine, Orasept, Emuflor) on the color stability of 2 composite resins and one compomer material, one of which is ormoser based. They found that the Ormoser-based composite resin had the highest color change, and the gargle named Emuflor caused the most staining in all restorations. The researchers reported that the color factors and fluoride added to the mouthwashes are responsible for the staining[27].

In a study conducted by Öngöl et al., They found higher color change, especially in the Listerine and Chlorhexidine groups. In a study they did, Lee et al. concluded that the ΔE value of compomer samples kept in various mouthwashes (Listerine, Peridex, Rembrandt Age Defying, and Distilled water) for 24 hours and seven days was lower than 3.3. Toothpastes can also change the color properties, surface roughness, and hardness of restorative materials. Roopa et al. As a result of their application of whitening toothpastes to compomers and composite samples, they achieved a significant color change in both materials[29].

EVALUATION OF COLOR

Color Concept

Color is the physicochemical and psychophysical perception of light energy reflected from objects by an observer's vision system[30,31]. Color perception may vary depending on factors such as light source, observed object, and observer[32].

Color Analysis Systems

Color systems are used to define the color parameters of objects. In dentistry, mostly Munsell and CIE Lab (Commission International de I'Eclairage) and CIEDE 2000 color systems are used[33].

CIE L * a * b * Color System

Today, the CIE Lab color system is one of the most preferred color measurement systems in dentistry. In the CIE L * a * b * system developed in 1976 by the Commission Internationale de L'Eclairage (International Enlightenment Commission), three different variables are used: L *, a *, and b *. In this way, a material, restoration, or color change of the natural tooth can be expressed numerically (ΔE). The L * value and the 'Value' in the Munsell color system are proportional to each other and relate to the lightness-darkness, brightness, or light reflection rate of the color. Pure black 0 means pure white 100 L *. L * value of lighter colored objects is higher, and the L * value of dark-colored objects is lower. The a * coordinate is related to the locations of the red and green colors in the Munsell color system. The positive value of a * defines red and negative value represents green.

Similarly, b * coordinate is related to the places of yellow and blue colors. The positive value of b * indicates yellow, and the negative value indicates the amount of blue[34]. The most important advantage of the system is that color differences of the same or different objects can be calculated over time.

The amount of color change is expressed as ΔE and calculated as follows;

$$\Delta E = [(\Delta L^*)^2 + (\Delta a^*)^2 + (\Delta b^*)^2]^{1/2}$$

In this formula, ΔL *, Δa *, and Δb * represent the difference between the CIE L * a * b * color variables of the two objects[35].

The human eye is limited in perceiving these color differences and cannot detect ΔE values below 1. ΔE values between 1 and 3.3 are clinically perceptible but acceptable color differences. The most considerable clinically acceptable ΔE value is 3.7[36].

Current Composite Resin Restorative Materials

Composite resins are versatile materials that allow dentists to make direct aesthetic restorations. These materials have high fracture resistance and surface hardness, low abrasion, water absorption and solubility, low polymerization shrinkage, good biocompatibility, maintain tooth structural integrity, prevent fracture or crack formation, have anti-carious properties, color compatibility and stability. To provide these properties, composite resins have undergone many changes over the years. For this, many composite resin types are presented to the market by making changes in both the monomers that make up the organic polymer matrix phase of the composite resins and the inorganic filler particles[37,38].

Nanocomposite Resins

Microfill-filled composite resins are preferred in anterior tooth restorations because of their polishability. However, they are insufficient in posterior restorations because they are not robust against the masticatory forces. However, hybrid composites are more resistant to chewing forces if they cannot be polished as well as microfill composite resins. In dentistry today, composite resins containing micrometer and nanometer-sized filler particles are frequently used to restore both anterior and posterior teeth. These two properties are combined in nanocomposite resins[2].

Inorganic fillers on the surface of composite materials cause surface roughness due to the material moving away from the resin matrix during the clinical life of the material and creating a gap in that area. Since nano-filled composite resins contain small filler particle sizes, they are expected to undergo a lower degree of superficial coloring when they leave the surface compared to other materials. According to some researchers, increasing filler ratio in this type of composites caused less coloration due to decreasing the rate of organic matrix[39].

The composition and size of the filler particles is an important factor affecting the surface roughness of composite resins and is therefore associated with external coloring.

Therefore, it is expected that nanocomposites with a small particle size will obtain a smoother surface and less surface discolorations[2].

Ormosers

Structural changes have been made in the organic matrix of composites in the ormoser material (consisting of the first syllables of the words "organic modified ceramics") produced to improve the physical properties of traditional composites. In ormosers, inorganic-organic copolymers of urethane and thioether oligo methacrylate alkoxysilane are formed. The abrasion resistance of these materials is much higher than conventional composite resins. Unlike traditional composites, ormosers reduce dimethacrylate monomers using methacrylate polysiloxane as the main component in the organic matrix, thereby reducing the likelihood of an allergic reaction. In addition to the silaned inorganic filler particles, the ormosers contain an inorganic-organic copolymer. The advantages of the ormoser are low polymerization shrinkage, high abrasion resistance, biocompatible material, and protective against caries[40-42]. Awliya et al. In their studies comparing the color stability of ormoser-based and dimethacrylate-based composite resins, they found that ormoser samples were more resistant to discoloration[43].Ayad has shown that ormocer composites are significantly lower in color sensitivity than nanophil composite resins. Ren et al. Evaluated the color change of Ceram X Universal, which is an ormoser composite, which is kept in dyeing beverages after the thermal cycle, and reported that Ceram X Universal showed a lower color change compared to nanophil composite resin materials[44].

Bulk-fill Composite Resins

Bulk-fill composite resins, a new generation nanohybrid composite type, contain ytterbium trifluoride, barium glass, cocoxide, proacrylate, zirconium/silica particles. It is stated that these composites can be polymerized with a thickness of 4 mm. The material type of the composite also constitutes the name of the technique. It is known that the clinical study time decreases, and patient-physician comfort increases by applying this material as a single layer (bulk). The barium and ytterbium particles in the inorganic structure of this material increase the radioopacity and allow the effect of the light device to reach deep[45]. The contents of ytterbium trifluoride, barium aluminum silicate glass, and zirconium silica particles in these composite resins increase their transparency, allowing the light device to reach deeper [46].

Barutcigil et al. evaluated nanohybrid, bulk-fill posterior composite, and ormoser-based bulk-fill composite restorative materials in distilled water, coffee, and red wine. They evaluated the color change after 24 hours, one week, and three weeks. They found that Admira Fusion Xtra, which is an Ormoser based composite restorative material, changed more colors than other bulk-fill composite resins. The color change of Bulk-fill composite resins increased over time in red wine and coffee, while the color change of nanohybrid composite resin remained constant in red wine and coffee one week later[47].

Fiber-reinforced Composite Resins

These materials, which contain fiber in their structure, mimic the dentin tissue's stress-absorbing feature, allowing direct restoration of large class II restorations. It is stated that the fibers prevent the formation of cracks or stop the crack progression, which is one of the critical causes of failure[48].

Its contents; There are different fiber types such as glass fiber, polyester fiber, carbon fiber, aramid fiber, and ultra-high molecular weight polyethylene fiber, which are used to improve the mechanical properties of composite resin[49]. Tunçdemir et al. found that fiber reinforcement led to color and translucency parameter change in both anterior and bulk-fill resin composites. These changes were below the visual perceptibility threshold. The chemical composition of composite resins, such as the composition and quality of the resin matrix, the type and amount of initiator, inhibitor, and filler, are essential factors in the color change of composites. Composite resins containing fillers with a larger filler particle size may be more sensitive to water-induced discoloration. Therefore, they detected more total color changes in the posterior composite material, which has a filler particle size larger than the anterior composite. Ribbond (polyethylene fiber) reinforced posterior composite showed the most significant total color change, while EverStick (glass fiber) reinforced composite showed the lowest value. These color change results are associated with chemical structures[50,51].

Nanoceramic Composite Resins

Today, nanoceramic composites, which have nano-fillers in their structure and ceramic particles in addition to traditional glass particles, can be preferred. The particles in the structure of nanoceramic composites are homogeneously dispersed in the organic matrix. Ceramic nanoparticles are organically modified and consist of a polysiloxane backbone. Although used in the dentistry sector, these modified ceramics are preferred in various industrial areas as coatings due to their high resistance to abrasion, corrosion, and scratch resistance[52].

Self-adhesive Composite Resins

It is used in self-adhesive composite resins, small class I and V cavities, cervical lesions, and porcelain repairs that minimize technical precision. Self-adhesive fluid composite resins include the functional monomer GPDM (glycerophosphatdimetacrylate), which serves to roughen enamel and dentin. HEMA (hydroxyethyl methacrylate), another functional monomer that enhances the wettability and resin penetration of most adhesives[53,54]. These composites also contain acidic monomers such as 4-methacryloxyethyl trimellitate (4-META) and 2- (methacryloyloxyethyl dihydrogen phosphate (10-MDP) and pentaerythritol penta acrylate monophosphate (PENTA)55.

An ideal composite resin should exhibit a high degree of conversion and minimal polymerization shrinkage. Monteiro et al.

stated that different monomer contents and photoinitiator systems significantly affect the color stability of self-adhesive composite resins. The 2MP (2-methacryloyloxyethyl phosphate) based group showed the weakest color stability, while the use of BAPO (phenyl bis 2,4,6-trimethyl benzoyl phosphine oxide produced) provided the best color stability for acidic monomer based groups. This monomer has a large linear and reticulated molecular structure with many hydroxyl groups, making it susceptible to degradation and water absorption. Besides, the hydrophilicity of 2MP can disrupt molecular stability, creating pores in the polymer and causing discoloration[56].

Silorans

A monomer called siloran has been developed to reduce polymerization shrinkage in composite resins. Silorane; is a hybrid monomer system containing siloxane and oxirane, in which ring-opening polymerization of silorans is performed instead of polymerization of free radicals of dimethacrylate monomers[57]. The hydrophobic properties of siloxane to the material are useful in the long-term mechanical durability of composite resin in the mouth. Due to this hydrophobic property, the water absorption of the material is low, showing less coloration[58]. Studies show that less shrinkage occurs when compared to methacrylate-based composites, and siloran based systems are superior to edge compatibility and microleakage aspects[59].

The low polymerization shrinkage is the main advantage of the silo. In the most commonly used methacrylate-based composite resins, shrinkage occurs during polymerization, which causes stress on the cavity walls. This stress causes leakage, secondary caries development, post-op sensitivity, and marginal coloration[60-62].

Perez et al. reported that these systems' optical properties are different compared to the dimethacrylate based composites in their studies in which the optical properties of the silos are evaluated[63]. They reported that color changes for siloran-based composites were due to changes in the Δa * and Δb * coordinates. They specifically stated that the color difference in dimethacrylate-based composites generally results from ΔL * and Δb *. When they look at the translucency values, they report that siloran based composites show the lowest value[64].

Giomers

Giomers are called hybrid composite materials. It has fluoride release and storage properties and is reported in studies of remineralization in dentin tissue[65,66].

The PRG (pre-reacted glass ionomer) particles in its structure are formed as a result of the acid-base reaction occurring in an aqueous medium between the fluoroaluminacilicate glass particles and polyalkenoic acid. The name "Giomer" is derived from the words "Glass ionomer + polymer"[67]. PRG particles responsible for fluoride release are available in two different forms: surfactant (S-PRG) and all particle active (F-PRG)[63]. Because they contain resin, show more positive aesthetic properties than traditional glass ionomers, and resin-modified glass ionomers[68].

The ability of giomers to inhibit demineralization is similar to that of glass ionomer cements[69]. An in-vitro study investigating the long-term fluoride release of this material found that fluoride release was deficient in the first few days, but fluoride release increased significantly after 21 days[70]. The absorption and coloration of giomers are considerably higher compared to nanohybrid resin composites, which negatively affect their aesthetic properties[71].

Resin Modified Glass Ionomer Cement

RMGIC have polymerization similar to composite resins. In their structure, they also contain an acid-base reaction as in the glass ionomer. Also, most of these materials have substantially dark polymerization or autopolymerization resin properties. As a result, they provide a complete polymerization of the places that light cannot reach due to undesired reasons[72].

Thanks to their resin content, they are more aesthetic and durable compared to traditional glass ionomer cements. Adhesion to dental tissue is slightly less than conventional glass ionomers. Still, they are more advantageous because they form smoother surface properties and are easier to apply thanks to the capsule-gun system. Bonding before use is not recommended as it will reduce fluoride release[73].

Savas et al. reported that the restorative materials they tested showed significant color changes after 28 days of immersion in four types of solution. After immersion in different solutions, they observed the least effect on Glasiosite, a composite resin modified with a polyacid.GCP Glass Fill, a traditional high-viscosity glass ionomer cement with nanofluoride / hydroxyapatite, was more prone to color changes. Equia, a high viscosity conventional glass ionomer cement, and Ketac N100, a resin-modified glass ionomer cement with nanoparticles, follow this. They attribute this result to high staining sensitivity due to the high water absorption rate or surface texture. According to the water absorption results, there is the lowest water absorption level in Glasiosite among the materials tested. With Ketac N100, they observed that the highest values are available in GCP Glass Fill100[74].

Smart Monochromatic Composite Resins

Today, there is no single material that will meet all the requirements to reach the ideal material, but the studies on this subject are ongoing. These materials, called "smart" developed for this purpose, support the remaining tooth structure to the extent possible and can be changed by factors such as temperature, humidity, pH, stress[75].

Smart materials have features such as the ability to return to their original state even after removing the stimulus, piezoelectric property, thermotherapeutic properties like shape memory alloys or shape memory polymers, thermochromic property, photochromic property, magnetorheological property, sensitivity to biofilm formation. Today, burs, adhesives, and composites are produced with smart technology. Structurally colored, universally produced composites containing only one composite color tone and classic VITA tones have smart chromatic technology that gives the color “physical” dimension [76-78].

Today, a composite resin named “Omnichroma”(Tokuyama, Tokyo, Japan), which contains 260 nm spherical supra nano spherical fillers in the same size, produced with smart chromatic technology, has been put on the market. Thanks to this technology, it offers a wide variety of color matching features that cover a single color tone. It is stated that Omnichroma provides a successful color matching by creating a structural color similar to natural teeth from yellow to red. Structural color is expressed only by the physical properties of light (refraction, refraction, scattering, etc.). While creating a structural color from yellow to red, it combines the color of the adjacent tooth and its reflected light during the additive color mixing process, increasing the success of Omnichroma to adapt to natural teeth. Using the structural color with this system, the use of pigments and dyes becomes unnecessary in this system. In traditional composites, color selection increases the time spent in the seat and makes the color selection process subjective. Elimination of this situation in smart technology is also a critical advantage75-78.

Although smart monochromatic composite resin provides convenience for the physician by reducing the time spent in the clinic’s shade selection, in vitro and in vivo studies are needed to evaluate the color stability.

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Chapter 5

NEW APPROACHES IN REPAIR OF AESTHETIC RESTORATIVE MATERIALS

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One of the aims of restorative dentistry is to provide it happen functional and aesthetic restorations. Developments in new restorative materials and the increasing interest in aesthetics composite resin restorations that can mimic natural teeth' appearance have become frequently preferred by dentists [1].

Composite resin and porcelain are suitable materials for indirect restorations due to their aesthetic appearance, long clinical life, durability, less microleakage, and postoperative sensitivity. Nowadays, there is a wide variety of ceramic materials and systems for indirect restorations such as laminate veneers, inlays and onlays. Its advantages include superior aesthetic properties, adequate fracture resistance against occlusal forces, excellent connection resistance between the tooth and ceramic surfaces, and production techniques facilitated using CAD / CAM (computer-aided design manufacturing) to increase the use of full ceramic systems [2].

Composite resins bonded to the dental tissue with adhesive systems fail due to their structural properties deteriorating over

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time and degradation of the adhesive layer. The secondary caries development, coloration, abrasion, restoration or tooth fracture formation can also be seen as a result of the microleakage that may occur on the adhesive surface [3]. Although Academy of Operative Dentistry European Section (AODES) sees composite resins with appropriate content and properties as the "preferred material" for use in posterior teeth minimally invasive dentistry applications, AODES states that composite resins are still lacking some properties. The AODES highlights the importance of performing refurbishment and repair techniques to extend the longevity of restorations [4].

Restoration repair is a minimally invasive treatment performed by removing the part that failed in the old restoration and placing the new composite on the surface. The three factors that form a successful repair process are the surface preparation methods used in the repair process, the adhesive systems used, and the compatibility of the tooth surface with the repair composite [5,6].

SURFACE PREPARATION METHODS USED IN THE REPAIR OF COMPOSITE RESINS

The repair process's success depends on the strength of the bonding between old and new composite resin materials [7]. Due to the oxygen barrier layer, the bonding between the two composite layers does not polymerize [6,8]. The water absorbed by diffusion by the composite resin in the oral environment adversely affects the binding of the new composite to the old composite. The aging and water absorption causes the oxygen inhibition layer to disappear, and the unsaturated double carbon-carbon bonds to decrease. For this aim, various surface preparation protocols should be applied to the old composite resin surface. These chemomechanical surface treatments are abrasion with carbide or diamond burs, hydrofluoric or phosphoric acid roughening, adhesive resin applications, laser roughening, tribochemical silica coating and air abrasion [9].

Most studies reveal that increasing the surface roughness of the old composite resin is effective in repair strength [5]. Mechanical bonding is provided by increasing the surface roughness. This process increases unreacted methacrylate groups. As a result, the superficial layer of the old composite resin is removed to obtain a clean connection surface with high energy, and filler particles are exposed to [10].

Surface Roughening by Bur Cutting

The method frequently used in the clinic for roughening composite surfaces is roughening with diamond burs. Then, adhesive systems used in composite resin repair can be used by roughening with phosphoric acid [11]. Oskoee et al. reported that the bond strength values obtained on diamond bur roughened and laser-roughened surfaces were higher than other groups in their studies investigating the effect of various surface treatments on the repair bond strength of composites [12].

Surface Roughening by Acid Etching

The phosphoric or hydrofluoric acid is typically used for roughening surfaces. However, there are conflicting data about the effectiveness of acid roughening on the bond strength of repaired surfaces in the literature. Phosphoric acid is a weak acid. It cannot create sufficient surface roughness on the composite resin surface [13]. In many in vitro studies, it has been shown that etching with acid does not have a sufficient effect on the repair bond strength values. While the resin material must be partially or completely removed in the repair of composite restorations, tissue loss may also occur in enamel and dentin in some cases [14]. Phosphoric acid acts on enamel and dentin but does not directly affect the surface properties of composites, ceramics and metals. Loomans et al. concluded that phosphoric acid alone did not affect the roughness of the resin composite [15].

Gupta et al. used 4 dıfferent acıds for use in the repair mechanism: 30% citric acid, , 7% maleic acid, 10% hydrofluoric acid and 37% phosphoric acid. According to the results, they observed that the best repair bond strength was in hydrofluoric acid [16]. Hydrofluoric acid attacks and dissolves the glass filler particles that are exposed, unlike phosphoric acid. Thus, it reduces the irregularities available for silane bonding without affecting the resin matrix. It has been noted that hydrofluoric acid's effect largely depends on the composition of the filler particles in the material. Therefore, roughening with hydrofluoric acid is considered convenient for composite repair [17]. It has been found that sufficient concentration is between 4%-10% to obtain suitable repair bond strength values [16]. However, hydrofluoric acid has been limited concerning the dangers of oral hydrofluoric acid [18].

Surface Roughening by Air Abrasion and Tribochemical Silica Coating

Air abrasion is used to clean the substrate surface, change the surface topography, and increase the surface area of the linkage, surface energy, and wettability. Afterward, it is recommended to apply silane, followed by the adhesive used with it [19].

Sandblasting is a tribochemical silica coating system. Tribochemical method means creating a chemical bond using mechanical energy. The tribochemical silica coating process is the embedding of silica-coated alumina particles under pressure by spraying to achieve a more chemically reactive surface and is recommended as an effective method to increase the adhesion of the resins to the restoration. Generally, it is used for repairing ceramics and nanoceramics with composite resins. With this method, restoration is roughened in the laboratory (RocatecTM, 3M / ESPE, Germany) or the clinic (CojetTM, 3M / ESPE, Germany). For intraoral procedures, such as direct repair of fractures of CoJet, metal-ceramic, and all-ceramic restorations with composite resin or adhesive cement, Rocatec is designed for laboratory use [20].

Various reports have reported that sandblasting with 50 μm aluminum oxide said that the repair composite provides superior surface roughness and wetting potential compared to chemical processes. It shows adequate bond strength values for composite repair [9,21,22,23].

Chemical Bonding

While the surface roughness provides the micro-mechanical retention of the repair composite, intermediate materials such as adhesive resin, silane coating agents, or flowable resin composite are still required to provide wetting of the surface and subsequent permanent bonding between the old and repair resin composite [22,24]. Reactive monomers are exposed to surface preparation methods, and chemical connections are established with the monomers included in the repair material. The superficial composite resin layer that is contaminated with the mouth environment is removed [25].

Silane has a bifunctional molecule structure and has an essential place in all composite resin structures as bonding agent. The silanol group of the silane agent forms a chemical bond with silica modified surfaces. The other end of the silane, the methacrylate group, reacts with the methacrylate groups of the adhesive and composite resin. It briefly initiates chemical reactions by providing physical adhesion [26]. The silane provides the wettability by reducing the adhesion and contact angle of the inorganic and organic matrix. Silanes increase repair bond strength by increasing the surface energy, which is the prerequisite of wetting optimized for close contact between resin composites. The adhesive use after silanization is recommended for ideal attachment without micro gap [27]. The most common silane used in contemporary dentistry applications is the 3-trimethoxysilylpropylmethacrylate (MPS). Many in vitro studies using silane in composite repairs have shown that this agent has positive effects on repair bond strength values [27,28]. In contrast, Nassoohi et al. They found that using silane in composite repair caused the weakest bonding strength[9].

Surface Roughening by Laser

Due to the frequent use of lasers in dentistry recently, the technique of surface preparation with lasers has been on the came agenda [29,30]. The laser makes changes in surface topography to create sufficient bonding in the repair of composite resins. Although this situation is similar to other mechanical treatment methods, laser is considered to be more conservative than other mechanical treatment alternatives [21,31].

The studies on the use of Erbium yttrium aluminum garnet (Er: YAG) and neodymium yttrium aluminum garnet (Nd: YAG) lasers for caries removal, cavity preparation, surface roughening applications and periodontal processes have been conducted. The Erbium laser family has two different wavelengths: Er: YAG laser (2940 nm) and (Er, Cr: YSGG) laser (2780 nm). The advances in laser technology have shown Er: YAG laser as a method of surface preparation in the repair process [12]. Oskoee et al. evaluated the effectiveness of different lasers on surface roughness in their studies. According to the results, Er, Cr: YSGG laser showed more successful repair binding strength values than Nd: YAG and CO2 lasers without creating a smear layer [30].

Alizadeh Oskoee et al. reported mechanical surface treatments, i.e. diamond burs, air abrasion, and Er, Cr: YSGG laser. They compared the effects of the siloran-based composites on the repair bond strength that repair bond strength values of laser and bur treatments were significantly higher [12]. Similar findings were obtained in another study using the same treatment protocols for repair a methacrylate-based resin composite and reporting that the laser-treated group had the highest bonding values [31].

Murray et al. suggested laser treatment as an appropriate treatment option for advanced repair bonding forces [32]; similarly, Rossato et al. found that laser and bur treatment in the repair process gave similar results [33].

EVALUATION OF THE IMPACT OF DEVELOPMENTS IN THE CONTENT OF COMPOSITE RESINS ON REPAIR PROCESS

It has been reported that the effectiveness of repair treatment of composite resin restorations depends on the structure of the existing composite resin to be repaired, and it has been argued that it should be restored with composite resins of similar structure. However, most of the time, physicians do not know which type of composite resin the restoration they will perform before was done [17]. According to the results of their study, Ribeiro et al. reported that high shear bond strength was obtained after the bonding of composite resins with similar organic and inorganic structure to each other [34]. Shahdad and Kennedy stated that shear bond strengths obtained by repair restoration with composite resins with the same organic matrix do not show significantly higher values compared to repair with composite resins with different types of organic matrix [35].

Bis-GMA (Bisphenol A diglycidylmethacrylate) molecules in the structure of composite resins have a higher viscosity, and low conversion degree, smaller and flexible TEGDMA (Triethylene glycol dimethacrylate) is used as a diluent monomer and increases the degree of conversion. The modified monomer Bis-EMA (Ethoxylated bisphenol A dimethacrylate) has been shown to increase the degree of conversion and reduce water absorption. It has been claimed that resin composites' water saturation reduces existing free radicals, thereby reducing repair bonding forces [36].

The most used composite resins in dentistry are methacrylate-based composite resins. The contraction of these composite resins during polymerization creates stress on the cavity walls. This stress causes leakage, secondary caries development, post-operative sensitivity, marginal coloration, and cracks in the enamel. To overcome these problems, siloran based composite resins containing monomers with low polymerization shrinkage have been developed in recent years [37]. The polymerization mechanism of the siloran resin composites is based on the photo cationic ring-opening, which is different from the radical reaction found in methacrylate materials. The photo-cationic ring-opening is significantly lower than methacrylate composites (4%), reducing polymerization shrinkage to almost 1% [38].

It has its adhesive system consisting of two components for better bonding of siloran based composites to dental tissue. The first component is a self-etch primer. The hydrophilic structure of the first component is important for adhesion to the tooth tissue. To connect the siloran-based (hydrophobic) composite to the dental tissue, it is necessary to coat it on the hydrophilic primer layer with a hydrophobic adhesive layer. The second component serves this work. An adhesive system containing hydrophobic dimethacrylate monomer without hydrophilic 2-hydroxyethyl methacrylate (HEMA) monomer should be used for bonding siloran-based composite resins [39]. There are many types of research on the repair protocol of siloran based composite resins. Composite resin is hydrophobic due to its siloxane molecules. Therefore, it is recommended to be treated with a hydrophobic adhesive system during the repair process [40].

The factors that determine the surface characteristic of the existing and defective composite resin restoration are the type, size, distribution, organic matrix structure, polymerization degree, and hardness of the material's filler particles. The parameter that most affects the repair bond strength is the property of the filler particles of the material. Composite resins containing particles with a large filler size are known to react more extensively with functional monomers of adhesive systems [24]. In the literature, it is recommended to repair composite resins with composite resins of the same structure [41].

Lührs et al. have stated that the repair protocols of methacrylate-based composite resins can be applied in repairing composite resins based on siloran [42]. According to the study of Oskoee et al. on the use of laser in the surface preparation protocol of siloran based composites, Er, Cr: YSGG reported as the most effective laser [30]. Lima et al. showed that composite resins' surface preparation based on siloran has similar repair bond strength values after sandblasting with diamond burs and aluminum oxide [13].

In cases where defective restoration is not known to be a siloran-based composite resin, it has been reported that it can be repaired with methacrylate-based composite resins and shows adequate repair bond strength [43]. As a result of using silorane-based composite resins in the repair of methacrylate-based composite resins, lower repair bond strengths are obtained [41]. According to the studies of Bacchi et al., siloran-based composite resins show lower repair bond strength compared to methacrylate-based composite resins, due to the less reactivity of the siloran groups after polymerization [44]. If the composition of the material is unknown, it is recommended to apply with phosphoric acid roughening, sandblasting (Al_2O_3 in sizes of 30 µm and 50 µm), silane, and adhesive systems [17]. Previous studies have reported that silane application is mandatory for the adhesion of methacrylate-based adhesives to silorane surfaces [45]. Wiegand et al. suggest that silane application is not necessary when silorane composite and compatible silorane adhesive system is used in the repair mechanism [40].

It is claimed that nanocomposites have promising physicomechanical properties due to their high content of filling particles. Due to its high filler content, nanocomposite resins, which have lower water absorption rate compared to other composites, are less sensitive to aging and more suitable for repair [7]. Nassoohi et al. reported that the microhybrid resin composite may have a better repair bonding strength compared to nanocomposites, and nanofil and nanohybrid types are less different from each other [9]. Moncada et al. reported that hybrid composites provide better repair strength than micro filled resins [46].

EVALUATION OF THE IMPACT OF DEVELOPMENTS IN ADHESIVE SYSTEMS ON REPAIR PROCESS

Adhesive restorations provide better transmission and distribution of functional stresses to the tooth with their potential to strengthen weakened tooth tissue while reducing marginal discoloration and fractures, secondary caries, and even microleakage, which can lead to the development of pulpal pathology.

The adhesive systems can be classified as total-etch adhesives, self-etch adhesives, and glass ionomer-based adhesives. In recent years, new single-stage self-etch adhesive systems, also known as universal or multi-mode systems, have been released. They are single-stage self-etch adhesives produced with the 'all-in-one' concept. It gives physicians a chance to choose with adhesive strategy: etch & rinse can be applied with self-etch and selective etch technique. This approach combines the advantages of enamel etch & rinse technology and the additional chemical bonding of apatite crystals of dentin simplified self-etch procedure [47]. Some researchers report that some functional monomers (Bis-GMA (bisphenol A glycidyl methacrylate), HEMA (hydroxyethyl methacrylate), GPDM (glycerol di methacrylate ester), MEP-P (methacryloxyethyl phenyl hydrogen phosphate), MMP (Methacryloyloxypropyl dihydrogen phosphate), MEP (methacryloxyethyl dihydrogen phosphate), PENTA-P (dipentaeritrolpentaakrilol dihydrogen phosphate), 4-META (4-methacryloxyethyl trimellitate anhydride), MAC-10 (metakriloloksialkil asit fosfat), 10-MDP (10 metakriloyloksidesil dihydrogen phosphate) in self-etch and universal adhesives increase the bond strength of adhesive systems [48]. However, manufacturers of universal adhesives claim that those containing silane improves bonding to glass ceramics or composite resins without additional preparation procedures. The 10-MDP monomer has been reported to play an important role in achieving a chemical connection between the enamel and dentin and a stable and durable interface [49]. Yoshida et al. reported that the 10-MDP functional monomer included in the adhesive content provides an adequate and permanent bonding. They also stated that thanks to the HEMA, a hydrophilic monomer, it can wet the composite resin surface better and penetrate more into the retentive areas [50]. Since the PENTA functional monomer in adhesive systems contains polymerizable double bonds, they form various calcium-phosphate complexes and build nanolayer structures that strengthen the hybrid layer of the adhesive and facilitate the spread of the adhesive by wetting the surface [51]. In a study conducted by Staxud et al. the bond strength values obtained with universal adhesives were found to be similar to the bond strength of the groups applied post-silane adhesives [27]. In their study, Fornazari et al. suggested that the bond strength of a silane-containing universal adhesive is as effective as silane + adhesive application and eliminates the need for a separate silane application [52].

For the adhesive systems to provide sufficient adhesion clinically, the required repair bond strength values should be similar to the bond strength values of the adhesive systems to the enamel (15-30 MPa). Therefore, according to most researchers, repair bond strength should be above 18 MPa [53].

Bayrak et al. stated that the solvent and filler content of adhesive systems have more effect on their shear bond strength than their pH [54]. In a study conducted, Teixeira said that adhesive systems containing fillers showed higher repair bond strength than those without fillers [55]. It is thought that the reason for this is that the adhesive systems containing filler have adequate tensile strength and relieve shrinkage stresses between the materials [56].

NEW APPROACHES IN REPAIRING CERAMIC BASED MATERIALS WITH COMPOSITE RESINS

Nowadays, there is a wide variety of ceramic materials and systems for indirect restorations such as laminate veneers, inlays, onlays [2]. Although ceramics are the most preferred indirect restoration material in clinical practice, there are also hybrid-ceramic and nanoceramic resin materials developed by different companies. The advantages of dental ceramics such as not being affected by oral chemical events, color stability, high resistance to abrasion, low thermal conductivity, biocompatibility, ideal aesthetic properties, and production techniques facilitated by using CAD / CAM (computer-aided design/manufacturing) have increased its use by dentists 78. Localized fractures frequently appear in indirect restorations applied in the clinic. In this case, restoration should either be wholly refurbished or repaired as a treatment option [58].

It is necessary to obtain a strong micromechanical connection between the restoration fracture surface and the different structure of hydrophobic resin-based composite or resin cement for the oral repair to be successful. Since this connection also includes chemical interaction, it is necessary to choose suitable surface treatments for exposed cracked surfaces of different types of materials [59]. Surface treatments applied mechanically or chemically to the restoration materials; sandblasting with aluminum oxide particles (Al_2O_3), burs, hydrofluoric acid (HF), and phosphoric acid roughening, silane and metal primers application, tribochemical silica coating can be listed [60].

Wiegand et al. reported that roughening with burs generally showed the highest bond strength values in their study. Based on this finding, it may be suggested to roughening the surface with diamond burs before repairing hybrid ceramics with composites [61]. Although roughening by bur is a quick and easy method, Jain et al. suggested that roughening with diamond milling creates sharp surface roughness on the ceramic surface and causes microfractures causing an increase in stress concentration and subsequent fracture formation on the ceramic surface [62].

It is recommended to use acid roughening on glass-ceramic (silicate materials) surfaces. It is difficult to protect the undamaged surfaces during sanding of the restoration with aluminum oxide particles [63]. In surface roughening by acid, HF acid, phosphoric acid or acidified phosphate fluoride (APF) gel can be used. Among these gels, HF acid is more durable than phosphoric acid and is the most commonly used agent for porcelain roughening. HF acid can be used for surface roughening of silica-based porcelain. HF acid cannot be used for surface roughening of metal or oxide ceramic materials with a silica content of less than 15% by volume [64]. As a result of his work, Acar Ö stated that HF acid does not increase the success of connection in hybrid ceramic material (Vita Enamic). This result indicates that the material contains a high proportion of leucite and zirconia crystals and that the entire structure shows a substantially composite formation [65].

Tribochemical silica; It is a system used in the clinical environment for repairing metal porcelain and full porcelain restoration fractures to coat silica on the surface. With the tribochemical silica coating process, the silica content of the ceramic increases, and many structures are exposed so that the silane bonding agent can react. The covalent bonds have been reported between silane application and ceramic-composite. Also, silane agents provide to increase the wettability of the glassy structure of composite resins while at the same time strengthening the physical, chemical, and mechanical bonding between composite resin and porcelain [18]. Silanes, by their nature, create a strong connection between ceramics containing silica and composite resins, while they cannot provide strong connections with silica-free dental restorative materials [66]. Since aluminum, aluminum/zirconium or zirconium ceramics have a high crystal content; silica coating is recommended because acid roughening can not affect their durable structure.

For this reason, the silica coating process; ındicated for acid-resistant ceramics with low silica content [67]. Stawarczyk et al. found the highest value in the group in which they used Universal Bond and tribochemical silica coating in their study, where they applied different surface treatments on CAD / CAM resin nano ceramic (Lava Ultimate) and compared various bonds with composite resin. Some of the universal adhesives contain MDP and silane, capable of bonding to different surfaces such as glass or non-glass ceramics and metals [68].

Metal primer is an agent used to strengthen the bonding between metal and resin. The functional monomers contained in it can be attached to both resin and metal. Metal primers interact differently depending on the type of metal used. The metal primer suitable for the metal type must be selected by the clinician [69]. Because the bifunctional phosphate monomers (10 methacryloloxidesyl dihydrogen phosphate-.MDP or 4-. Methacryloxyethyl trimethylate anhydride) in the product, one end connects to the metal oxide or oxide ceramic surface and the other ends to the resin material with a direct chemical connection [70].

The bonding resistance of the ceramic and repair composite resin interface depends more on the type of repair composite than the surface treatment. Hybrid composite resins exhibit higher bond strength than composites with microfill fillers. Microfil composites are preferred for repairing superficial fractures at the level of enamel porcelain, and condensable and hybrid composites for repairing deep fractures at the posterior region where chewing pressure is high [71].

WHAT AWAITS US IN COMPOSITE REPAIR IN THE FUTURE?

While dental materials often fail after a period of use, nature manages to renew most of the biological materials it uses. Nature has inspired new technologies such as self-healing and repair mechanisms that can increase material survival. All self-healing systems have shown promising results for self-repair and crack inhibition, suggesting a long life for dental composite restorations. These new materials can heal cracks, restore load-bearing ability, inhibit oral bacterial pathogens, reduce or eliminate biofilm acids, increase biofilm pH, and regenerate lost tooth minerals. Also, its effects are stated to be durable and long-lasting [72].

Self-healing approaches are bio-inspired or biomimetic mechanisms. Nature's self-healing ability inspired engineers and chemists who aimed to restore the mechanical properties of a material by suggesting different healing approaches [73]. Self-healing composite systems include self-healing hollow fibers and microcapsules. The microcapsules of the dicyclopentadiene (DCPD) monomer in the polyurea-formaldehyde (PUF) shells are dispersed in a polymer host and breaks when exposed to a load causing crack propagation. Healing agents (DCPC) is drawn along the fissure line, where it encounters a faulty chemical catalyst (usually ruthenium-based 'Grubbs') in the polymer matrix. This chemical catalyst initiates polymerization and recovery occur [72] (Figure 1).

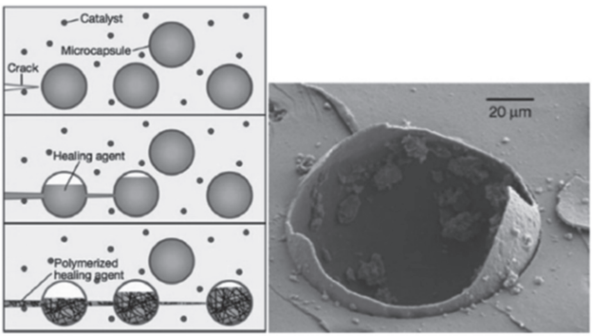

Figure 1: Typical method of microcapsule approach (Left), SEM image showing ruptured microcapsule (Right)

One of the first self-healing synthetic materials reported has some resemblance to resin-based dental materials as it is resin-based. This is an epoxy system containing resin-filled microcapsules [74]. If a crack occurs in the epoxy composite material, some microcapsules are destroyed and release the resin. The resin then fills the crack and reacts with a Grubbs catalyst dispersed in the epoxy composite, causing polymerization of the resin and repair of the crack. Similar systems have been shown to have a longer mission cycle under on-site mechanical stress than similar self-healing systems [75].

It is clear how effective such an approach is for application in dental composites. Dental composites using this technology can be expected to have a longer mission cycle and improved clinical performance. The problems may arise from the potential toxicity of resins in microcapsules and the catalyst that should be present in the composite. However, the amounts of these agents required to repair microcracks in the dental composite seem quite small and maybe below the toxicity threshold. The self-healing mechanism based on microcapsules may be more promising, so the composites repaired in this way can perform better than those improved with macroscopic repair approaches; some of these have not been shown to cause satisfactory mechanical properties of the repaired composite [76].

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Chapter 6

REGENERATIVE ENDODONTIC TREATMENT

Faruk ÖZTEKİN[1]

Regenerative endodontic treatment involves biological replacement of damaged, diseased or incomplete dentin-pulp complex cells, as long as possible, by maintaining their physiological functions with living cells of the same origin. The potential of regenerative dentistry is highly dependent on advances in biological therapy, which benefit from growth and differentiation factors that stimulate or accelerate natural biological regeneration. For this purpose, tissue engineering was used [1].

TISSUE ENGINEERING

Tissue engineering includes biological treatment strategies that aim to regain damaged or partially lost tissue in terms of structure, function and physiology[2].

Regenerative endodontic treatment is based on 3 basic principles of tissue engineering[3]:

1. Appropriate sources of stem / progenitor cells
2. Growth factors that can promote stem cell differentiation
3. Scaffolding suitable for regulation of cell differentiation

STEM CELLS

Stem cell is a non-specialized cell that has the ability to divide on its own and differentiate into various tissue cells. The most important feature of stem cells is their ability to renew themselves [4].

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The use of stem cells for regenerative purposes has become widespread in recent years. These cells have a wide range of potential uses in cardiology, including myocardial infarction, spinal cord injuries, and burn treatment in plastic surgery. In dentistry, it is aimed to maintain regeneration by preserving mesenchymal stem cells and dental pulp stem cells of apical papilla, which are left behind by regenerative endodontic treatment application [5].

TISSUE SCAFFOLD

The tissue scaffold determines the shape of the tissue to be regenerated by creating a three-dimensional structure and micro environment that mimics the extracellular matrix [1]. Since pulp stem cells must be organized in a three-dimensional structure and supported by vascularization; The use of biological tissue scaffolds consisting of porous polymers is needed [2].

Since tissue scaffolds are imitation of the extracellular matrix, growth factors to help differentiate stem cells and proliferate; Nutrients for their nutrition and development should also contain antibiotics to prevent bacterial growth [6]. Tissue scaffolds should be able to selectively bind to cells, localize them and be resorbed [7].

There are three types of tissue scaffolding used. These are natural tissue scaffolds (collagen and glycosaminoglycan), synthetic tissue scaffolds (polylactic acid, polyglycolic acid, polylactic-co glycolic acid), mineral tissue scaffolds (hydroxyapatite and calcium phosphate). Natural tissue scaffolds are mostly used in regenerative endodontics [8].

GROWTH FACTORS

The third component of tissue engineering is growth factors. Growth factors affect the cellular activities of all dental pulp cells, including progenitor / stem cells, including migration, proliferation, differentiation and apoptosis [9]. It is accepted that many growth factors and extracellular matrix protein, which are usually expressed and secreted during primary and secondary dentinogenesis, play a role in dental repair and dentine regeneration [10].

NEW TISSUE FORMATION MECHANISM

Regenerative endodontics procedures are based entirely on cellular reactions. After the bleeding in the root canal, stem cells from the apical papilla act quickly [11]. These cells need to differentiate, multiply and produce dentin in order to regenerate the pulp tissue [12]. The formation of new tissues formed in the root apex and canal cavity has been tried to be explained with different mechanisms [13]. One of these is the possibility that the few pulp cells that remain alive at the apical end of the root canal form a new matrix and differentiate into odontoblasts that will allow the root to grow and thicken [14]. However, it is stated that stem cells or bone marrow in the apical papilla may also be effective in the root development mechanism. In addition, it is thought that stem cells originating from periodontal ligament and dental pulp stem cells may play a role in the root development [15].

With regenerative endodontic treatment, it is aimed to maintain revascularization of the remaining apical papilla by protecting mesenchymal stem cells and dental pulp stem cells [16]. Growth factors released from dentin can chemically attract stem cells in the periapical region or remaining healthy pulp tissue. After the cell selection, these cells settle, attach, multiply, differentiate and eventually form new tissue [17]. In studies, blood has been used as a tissue scaffold because it contains different growth factors that will help new tissues to grow [18]. The blood clot can provide differentiation and growth due to the growth factors it contains. It can also stimulate the maturation of fibroblasts, odontoblasts, and cementoblasts, and has an important role in regeneration [19]. Intracanal bleeding that can be used as a tissue scaffold or platelet-rich plasma (PRP) or platelet-rich fibrin (PRF) taken from the patient its use is considered to have a positive effect on the outcome of regenerative endodontic therapy [20].

Advantages of Regenerative Endodontic Treatment

Regenerative Endodontic Treatment is an inexpensive biotechnology where current hand tools and drugs can be used. In addition, the technique of application of treatment is simpler than traditional methods. As the infection is under control, there is no need for re-sessions as in apexification with calcium hydroxide. As the tooth regains its vitality, root development continues and the lateral dentin walls are strengthened due to the new dentin / hard tissue accumulation [8].

Disadvantages of Regenerative Endodontic Treatment

The disadvantages of regenerative endodontic therapy are the case reports showing that the blood clot provides regeneration of the pulp tissue; the source of the regenerated tissue has not yet been determined [21].

Regenerative Endodontic Treatment Methods

Methods being developed in regenerative endodontics; Revascularization of the root canal, stem cell therapy, scaffold implant, pulp implant, injectable tissue scaffold applications, three-dimensional cell software and gene therapy [1].

Revascularization

The term revascularization is used to reconstitute vascularization in the pulp cavity after traumatic injury [22]. In this technique, regeneration of tissues such as dentin, cementum, periodontal ligament, bone, that is, the regeneration of pulp rather than vascularization in the canal cavity. Regeneration of the pulp restores the functional properties of the tooth while providing, immature continues root development in teeth, prevents the formation of apical periodontitis and eliminates the formed periodontitis [13]. In this method, it is aimed to completely disinfect the necrotic root canal and to create a fibrin matrix by forming a blood clot. The open end of the root of the immature tooth allows new tissues to form in the pulp chamber [23].

Stem Cell Therapy

The easiest way to obtain cells with regeneration potential in dentistry is to inject the stem cells into the canal after the apexes are opened and the root canal is disinfected. Adult stem cells can be obtained from various tissues such as skin, cheek mucosa, adipose and bone tissue [24].

The advantages of adult stem cell therapy are that the autogenous stem cells are easy to manufacture and administer and have the potential to stimulate new pulp regeneration. The disadvantages are that the cells survival time and rates are low. When it is desired to create a new and functional pulp tissue, it is not possible to achieve high success only by injecting stem cells into the pulp chamber without scaffolding and bioactive signal molecules [19].

Pulp Implantation

After the pulp tissue is prepared in laboratory conditions, transplanting it into a shaped and disinfected root canal system is called a pulp implantation method [19]. The pulp tissue reproduced in culture medium is grown in vitro in a biodegradable polymer nanofiber layer or into the root canal system on the extracellular matrix protein layer such as collagen-1 or fibronectin [25].

Tissue Scaffolds Implantation

Pulp stem cells should be supported with a three-dimensional structure that will support cell organization and blood supply. This can be achieved with a tissue scaffold with a porous polymer structure where pulp stem cells can be buried [26]. A suitable scaffold should ensure cell growth and differentiation, cell adhesion should be increased and should provide a three-dimensional physical, chemical and biological environment suitable for cell migration [19].

The content of the tissue scaffold; The growth factors that ensure the proliferation, differentiation and rapid tissue formation of the stem cell, the foods that ensure the survival and growth of the cell and antibiotics that prevent the growth of bacteria in the root canal. The tissue scaffold should be able to be resorbed by the surrounding tissues without requiring new surgical practice. It should have a high porosity and a sufficient pore width suitably to allow cell nutrition and diffusion [27].

Injectable Tissue Scaffolds

Since pulp, which is a tissue engineering product in root canal systems, does not require structural support, soft three-dimensional scaffolding matrices have been brought to the agenda. The most important example, hydrogel, is an injectable tissue scaffold applied by syringe [28]. Hydrogels; It is an injectable tissue scaffold that can be applied with a syringe, it is non-invasive and can be easily applied to the root canal system.

Three Dimensional Cell Smear

In this technique; Theoretically, a special device is used to reconstruct the pulp tissue and distribute the cell layers into the hydrogel, and then the resulting structure is surgically implanted. The advantage of this method is that different cells are located exactly in place. The three-dimensional cell spreading technique can fully mimic natural pulp tissue [19].

Gene Therapy

Gene therapy; is a treatment that defines gene transplantation for somatic cells to express growth factors, morphogens, transcription factors and extracellular matrix molecules [29]. The goal of gene therapy is to ensure that the body produces the substance it needs in a healthy way, rather than delivering the necessary chemical from outside the body [19]. As a result of studies, it has been found that gene therapy cannot progress as part of endodontic therapy and some unwanted health problems may occur during gene therapy [30].

IN-CANAL DRUGS USED IN REGENERATIVE ENDODONTIC TREATMENT

Calcium Hydroxide

Calcium hydroxide is a dental material used in many fields such as direct and indirect pulp coatings, amputation, root canal treatments, repair of iatrogenic root perforations, apexification, treatment of resorbations and root fractures. Successful results were obtained for many years with the use of this material presented to dentistry by Hermann in the 1920s [31].

Calcium hydroxide shows its main effect by decomposing to Ca + 2 and OH- ions. The high alkaline nature of calcium hydroxide is associated with its hydroxyl ions and their release into the medium, and these highly reactive free radicals form the basis of the bactericidal property of calcium hydroxide [32].

Calcium hydroxide; It is frequently used in endodontics due to its easy manipulation, alkaline pH, antibacterial effect and hence accelerating recovery [31]. In resorptive defects converts local environmental factors to ideal conditions for recovery [32]. It neutralizes acid products and activates alkaline phosphatase, contributing to hard tissue formation [33]. It is preferred for intra-canal disinfection due to its hydroscopic feature and anti-inflammatory effect [34].

Calcium hydroxide is ineffective in eliminating Enterococcus faecalis (E.faecalis), which is the most important bacterium in treatment resistant infections, although it is a commonly used canal because of its antimicrobial efficacy and biocompatibility feature against endodontic pathogens [31].

Antibiotic Pastes

Systemic antibiotic administration is based on patient compliance with dose regimens followed by absorption through the gastrointestinal tract and distribution through the circulatory system to bring the drug to the infected area. Therefore, the infected area needs a normal blood supply; this does not apply to teeth with necrotic pulp and teeth without pulp tissue. Therefore, local application of antibiotics in the root canal system may be a more effective method of drug delivery [35]. More effective concentrations are obtained than those found in the systemic circulation after oral administration with local antibiotic applications [36].

Metronidazole, which is an effective antibiotic for anaerobes, has been chosen as the intra-canal drug because it constitutes the compulsory anaerobes as the majority of bacteria infecting the root canal system. In teeth with periradicular infection, metronidazole alone cannot eliminate all bacteria due to the variety of bacteria in the root canals. Therefore, it is used in combination with ciprofloxacin and minocycline [37]. Due to the color change caused by minocycline in teeth, some authors recommend modifying this antibiotic and using cefaclor instead of TAP or eliminating minocycline [14].

Disadvantages of antibiotic pastes used inside the canal, such as color change, cytotoxicity, sensitization, development of resistance and difficulty in removing from the root canal should be taken into account . In order to eliminate or reduce these disadvantages, it has been proposed to use antibiotic pastes at lower concentrations [38].

CALCIUM SILICATE BASED CEMENTS USED IN REGENERATIVE ENDODONTIC TREATMENT

Mineral Trioxide Aggregate (MTA)

MTA was first described by Lee, Monsef and Torabinejad in 1993 [39]. It was stated that MTA has a good sealing property, offers an excellent prognosis in the long term, is relatively easy to manipulate and promotes tissue regeneration as well as high biocompatibility [40].

Chemical Composition

MTA consists of tricalcium silicate, tricalcium aluminate, tricalcium oxide, silicate oxide and bismuth oxide [41]. The most important structural difference with Portland cement is that it does not contain potassium and its structure contains bismuth oxide [40]. Bismuth oxide was added to the material to improve its structural properties and provide radiopacity.

Tulsa Dental (Dentsply, USA) launched the white MTA preparations on the market in 2002, since the first MTA was gray in color, causing unwanted color changes in the front teeth. White and gray MTA differ in iron, aluminum and magnesium oxide contents [40].

The desired consistency of MTA is achieved by mixing 3 parts of powder and 1 part of liquid. Mixing can be done on paper or glass with a metal or plastic spatula. Adding more or less water during its preparation causes a decrease in the final hardness of the material. After the mixture, the MTA carrier is placed in the desired place and condensed with a moist cotton pellet. Since irrigation after MTA placement may cause material to flow away, all irrigation procedures must be completed before MTA placement [42].

Clinical Use and Physical Properties

Due to its properties such as biocompatibility and bacterial sealing, MTA is seen as an ideal material for the protection, repair and maintenance of pulp and therefore it is used in many dental treatments in pediatric dentistry.

Clinical uses of MTA [42];

- As a pulp coating material,
- As an amputation material,
- As repair material for the repair of furcation and root perforations,
- In the treatment of apexification, in order to ensure apical occlusion,
- Repairing the resorption zones in the root,
- As retrograde filler
- As repair material in root fractures

Physical properties of MTA;

1) Compressive Strength: MTA shows the lowest resistance to compressive forces in the first 24 hours compared to amalgam, IRM (Intermediate Restorative Material) and Super-EBA. However, after 21 days, the pressure was reported to increase to 67.3 megapascals (MPa), and its resistance was comparable to IRM and Super-EBA, but significantly lower than amalgam [40].
2) Radiopacity: The average radiopacity for MTA is reported to be equivalent to 7.17 mm thick aluminum. Although this value is lower than IRM, Super EBA, amalgam and gutta percha, it is sufficient to be easily seen radiographically [43].
3) Marginal Adaptation and Sealing Ability: This feature is critical in retrograde filling, perforation repair, pulp coating and pulpotomy procedures. Bates et al. [44] found MTA more successful than other retrograde filling materials. Expansion of MTA during hardening may be the reason for its excellent sealing property [45].
4) Solubility: Fridland et al. [46] It was stated that as the powder / water ratio changes, its solubility changes, and the high powder / water ratio increases the smoothness and solubility of MTA. In addition, bismuth oxide added to MTA has been reported to decrease the solubility of MTA [40].
5) Biocompatibility: In Torabinejad and Kettering's [47](135) studies, it was found that MTA is not mutagenic and is very low cytotoxic compared to Super-EBA and IRM. MTA does not cause an inflammatory reaction in direct contact or causes minimal infection. It also has the effect of inducing tissue regeneration [48].
6) Tissue Regeneration: MTA provides regeneration in periodontal tissues and has osteoconductive and osteoinductive properties, thereby inducing the formation of dentin, cement, and hard tissue [40].

7) Antibacterial and antifungal properties: Contrary results were obtained from the studies on the antibacterial properties of MTA. These contradictory results are thought to depend on the type of MTA used and the powder / liquid ratio of MTA. It can be considered a good antibacterial agent, especially against E.faecalis and Streptococcus sanguis, thanks to its good sealing properties and preventing microleakage. In some studies, it has been reported that MTA has an antibacterial effect on some facultative bacteria while it is not effective on anaerobes [40].

Disadvantages of MTA

The biggest disadvantages of MTA are the long hardening time, the difficulty of application, the powder / liquid ratio being adjusted manually, the same ratio cannot be obtained every time, the potential of coloration especially in the front teeth, the presence of toxic elements in its component, the high cost and the difficult to disassemble after insertion. In addition, the necessity of placing damp cotton after the use of MTA prevents the use of a single session [40]. One of the disadvantages is poor chemical bonding to dentine [49].

Biodentine

Biodentine is a calcium silicate based material produced in 2009 with the slogan 'instead of dentin [50].

Composition and Hardening Reaction

Biodentine powder part consists of tricalcium silicate (main component), calcium carbonate (filler), zirconium oxide (radiopacity provider), dicalcium silicate, calcium oxide, iron oxide. The liquid part consists of a water-soluble polymer (water reducing agent) and calcium chloride. Although tricalcium silicate is a common substance in both MTA and Biodentine, it consists of the monoclinical form of MTA and triclinic form of Biodentine [51]. The hardening time of Biodentine is 12 minutes and thus, it provides restoration and becomes intraorally functional in a single session. This allows for use in pediatric dentistry.

Physical and Mechanical Properties

Compressive strength is considered as one of the main physical properties of calcium silicate based cements.Biodentine-like products have a wide range of uses in vital pulp treatments. Accordingly, it is essential that it has a sufficient compressive strength against external forces [52]. Compared to other tricalcium silicate cements, Biodentine's higher compressive strength is attributed to the low water / cement ratio provided by the water-soluble polymer in the liquid part. Such as Biodentine's bending strength (34 MPa), elastic modulus (22,000 MPa) and Vickers hardness (60 HV) its physical properties are higher than MTA but show similar values to dentin. It has an inhibitory effect on Biodentine microorganisms with its high alkaline pH. In addition to alkaline pH, it provides disinfection in the area surrounding hard and soft tissues [53].

Biodentine maintains the vitality of the pulp and promotes the healing process. The effect of Biodentine on activation, differentiation and dentin regeneration of projection cells and Biodentine has been found to provide dentin regeneration by differentiating the progenitor cells to odontoblasts [53].

The micromechanical adhesion of Biodentine is caused by the alkaline effect during the hardening reaction. High pH leads to dissolution of organic tissues outside the dentinal tubules. The alkaline area between Biodentine and dental hard tissue creates an environment where Biodentine can enter the exposed dentin tubules. Thus, with the connection formed with countless tubules, a magnificent sealing is provided [50].

Clinical Use

Biodentine is a calcium silicate based material, and it draws great attention with its similarity to MTA and its applicability in cases where MTA is indicated. Biodentine endodontically root perforations, apexification, resorptive lesions and endodontic surgery; It is also a material that can be used as a retrograde filling material in addition to dentin in pulp coating [50].

Endosequence Root Repair Material (ERRM)

In order to overcome the disadvantages of MTA, new calcium silicate based cements have been introduced with similar basic components and biological effects [54]. ERRM (Brassaler, Savannah, USA) is a bioceramic material with paste and injector paste forms that are produced ready-to-use and do not need mixing. It can be used in root perforation repair, regenerative treatments, retrograde fillings [55].

According to the manufacturer, it consists of calcium silicate, monobasic calcium phosphate, zirconium oxide, tantalum oxide, propylene fillers and thickeners. High alkaline pH is partly responsible for its antibacterial property. Bioceramics refer to the combination of calcium silicate and calcium phosphate, valid for biomedical or dental use [56].The pH of the bioceramic materials during placement reaches 12.8. ERRM has a strength of 70-90 MPa. The material also has excellent radio opacity [55].

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