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EDITOR

Prof. Dr. Emin Caner TÜMER

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CONTENTS

CHAPTER 1

SALIVARY BIOMARKERS IN ORAL AND MAXILLOFACIAL DISEASES: DIAGNOSTIC AND PROGNOSTIC APPLICATIONS

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Introduction

Saliva has become one of the most promising diagnostic fluids in contemporary medicine and dentistry because of its noninvasive collection method, ease of storage, low cost, and ability to reflect both oral and systemic health conditions [1,2]. Historically, saliva was mainly considered important for lubrication, digestion, mastication, taste perception, and maintenance of oral homeostasis. However, advances in molecular biology and analytical technologies have dramatically changed this perspective. Saliva is now recognized as a biologically active fluid that contains thousands of proteins, peptides, enzymes, nucleic acids, electrolytes, metabolites, microorganisms, and extracellular vesicles capable of providing clinically significant information regarding physiological and pathological conditions [3].

In oral and maxillofacial diseases, early diagnosis and accurate prognostic assessment remain major clinical challenges. Many diseases affecting the oral cavity and maxillofacial region progress silently during their early stages and may only become clinically evident after significant tissue destruction or malignant transformation has occurred. Conventional diagnostic methods such as clinical examination, radiographic imaging, histopathological analysis, and invasive biopsy procedures remain the gold standard in many conditions, yet these approaches possess several limitations including patient discomfort, cost, delayed diagnosis, sampling errors, and inability to provide continuous monitoring [4].

The increasing interest in personalized medicine has accelerated the search for minimally invasive biomarkers capable of identifying disease before clinical manifestations become severe. Salivary biomarkers have therefore emerged as valuable candidates for screening, diagnosis, prognosis, therapeutic monitoring, and recurrence detection in oral and maxillofacial diseases [5]. Unlike blood collection, saliva sampling is painless, safe, repeatable, and suitable for chairside and community-based applications. These advantages are especially important in large-scale screening programs and longitudinal patient monitoring [6].

Recent progress in proteomics, genomics, transcriptomics, metabolomics, and microbiome analysis has enabled detailed characterization of salivary components associated with oral diseases [7]. High-throughput technologies including mass spectrometry, polymerase chain reaction (PCR), microarrays, next-generation sequencing (NGS), biosensor systems, and artificial intelligence-assisted data analysis have significantly improved the sensitivity and specificity of saliva-based diagnostics [8]. As a result, salivary biomarkers are increasingly

being investigated in oral squamous cell carcinoma (OSCC), oral potentially malignant disorders (OPMDs), periodontal diseases, peri-implantitis, salivary gland disorders, fungal infections, temporomandibular disorders, and odontogenic infections [9].

Another important aspect of salivary diagnostics is its ability to reflect systemic conditions. Because saliva contains serum-derived molecules that diffuse through salivary glands and gingival crevicular fluid, alterations associated with systemic inflammatory, metabolic, autoimmune, and neoplastic diseases may also be detected in saliva [10]. Consequently, saliva-based diagnostics may eventually bridge oral medicine and systemic health monitoring.

Despite substantial progress, several challenges remain before salivary biomarkers can become fully integrated into routine clinical practice. Variability in saliva composition, lack of standardized collection protocols, heterogeneity among analytical methods, and limited multicenter validation studies continue to restrict widespread clinical implementation [11]. Nevertheless, the rapidly growing body of evidence strongly supports the future role of salivary diagnostics in precision dentistry and oral medicine.

This chapter comprehensively reviews the biological basis, current evidence, diagnostic applications, prognostic significance, technological advances, limitations, and future perspectives of salivary biomarkers in oral and maxillofacial diseases.

Biological Basis of Salivary Diagnostics

Saliva is primarily produced by the parotid, submandibular, sublingual, and minor salivary glands. Whole saliva represents a complex mixture of glandular secretions, gingival crevicular fluid, microorganisms, epithelial cells, leukocytes, serum-derived proteins, and food remnants [12]. Although approximately 99% of saliva consists of water, the remaining 1% contains a wide range of biologically active molecules that are critically important for diagnostic applications [13].

Salivary composition is influenced by numerous physiological and environmental factors including age, circadian rhythm, hydration status, hormonal changes, medication use, smoking, stress, diet, and oral hygiene [14]. Flow rate variations may also alter the concentration of certain biomarkers. Therefore, standardization of collection conditions is extremely important in salivary biomarker studies.

Proteins are among the most extensively studied salivary biomolecules. Salivary proteins include enzymes, mucins, antimicrobial peptides, cytokines, growth factors, and immunoglobulins that participate in oral defense and tissue homeostasis [15]. Inflammatory processes, infections, and neoplastic transformation may significantly alter salivary protein profiles, thereby creating disease-specific signatures.

Salivary cytokines represent one of the most clinically relevant biomarker categories. Molecules such as interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF-α) play essential roles in inflammation, angiogenesis, tissue destruction, and immune regulation [16]. Elevated salivary cytokine levels have been identified in oral cancer, periodontal diseases, autoimmune disorders, and infectious conditions.

Genomic and transcriptomic biomarkers have also become increasingly important. Saliva contains human DNA, microbial DNA, messenger RNA (mRNA), and microRNA (miRNA), many of which remain stable despite the enzymatic environment of the oral cavity [17]. MicroRNAs are particularly attractive because of their small size, relative stability, and disease-specific expression profiles. Dysregulated miRNA expression has been associated with carcinogenesis, inflammatory diseases, and immune dysfunction.

Salivary metabolomics represents another rapidly expanding field. Metabolites are small molecules generated during cellular metabolic processes and may reflect real-time physiological alterations [18]. Cancer-associated metabolic changes, oxidative stress, microbial dysbiosis, and inflammatory activity can all produce distinct salivary metabolomic patterns.

Extracellular vesicles and exosomes have recently gained substantial attention in salivary diagnostics. These nano-sized vesicles are secreted by various cell types and contain proteins, nucleic acids, lipids, and signaling molecules [19]. Tumor-derived salivary exosomes may provide highly specific information regarding tumor progression, invasion, and metastasis.

The diagnostic potential of saliva is further enhanced by technological advances enabling highly sensitive biomarker detection at extremely low concentrations. Modern biosensor systems and lab-on-a-chip technologies may eventually allow rapid chairside analysis within minutes, thereby improving accessibility and clinical applicability [20].

Salivary Biomarkers in Oral Squamous Cell Carcinoma

Oral squamous cell carcinoma remains one of the most significant malignancies affecting the oral cavity and accounts for approximately 90% of oral cancers [21]. Despite advances in surgery, radiotherapy, chemotherapy, and targeted therapies, the overall survival rate has not improved substantially over recent decades. Delayed diagnosis remains one of the major causes of poor prognosis [22].

Traditional diagnostic methods rely primarily on clinical examination and histopathological confirmation obtained through biopsy. However, biopsy procedures are invasive and may not always identify early molecular alterations preceding visible lesions. Salivary biomarkers therefore offer a promising alternative for noninvasive screening and early detection [23].

Inflammatory cytokines are among the most extensively investigated salivary biomarkers in OSCC. Elevated levels of IL-6 and IL-8 have consistently been reported in saliva samples obtained from OSCC patients [24]. IL-8 is particularly important because it contributes to angiogenesis, tumor cell proliferation, migration, and metastasis. Increased salivary IL-8 concentrations have also been associated with advanced tumor stage and poorer prognosis.

Tumor necrosis factor-alpha and IL-1β are additional inflammatory mediators frequently elevated in OSCC patients. Chronic inflammation contributes significantly to carcinogenesis through induction of oxidative stress, genomic instability, and altered immune responses [25]. Consequently, inflammatory cytokine profiling may provide both diagnostic and prognostic information.

Proteolytic enzymes such as matrix metalloproteinases (MMPs) are critically involved in extracellular matrix degradation and tumor invasion. Increased salivary MMP-2 and MMP-9 activity has been associated with invasive tumor behavior and cervical lymph node metastasis [26]. These enzymes may therefore serve as indicators of aggressive disease.

Transcriptomic analysis has identified several salivary mRNA biomarkers associated with OSCC. Molecules including DUSP1, SAT1, OAZ1, IL8, and S100P have demonstrated promising diagnostic performance [27]. Salivary transcriptomics offers the advantage of detecting molecular alterations even before clinically detectable lesions develop.

MicroRNAs are also highly promising in oral cancer diagnostics. Salivary miR-21, miR-31, miR-184, and miR-125a have been shown to exhibit altered expression patterns in OSCC patients [28]. Some studies suggest that specific miRNA profiles may distinguish malignant lesions from benign inflammatory conditions with high sensitivity and specificity.

Oxidative stress biomarkers represent another important area of investigation. Reactive oxygen species contribute to carcinogenesis by inducing DNA damage, lipid peroxidation, and protein dysfunction [29]. Increased salivary malondialdehyde levels and altered antioxidant enzyme activities have been identified in OSCC patients, suggesting a significant role of oxidative imbalance in disease progression.

Recent research has additionally focused on salivary exosomes and extracellular vesicles. Tumor-derived exosomes contain proteins and nucleic acids reflecting the biological characteristics of cancer cells [30]. Exosomal miRNAs may provide highly specific diagnostic information and could potentially serve as biomarkers for treatment response and recurrence monitoring.

Salivary biomarkers may also play an important role in postoperative follow-up. Persistent elevation of inflammatory cytokines or tumor-associated miRNAs after treatment may indicate residual disease or recurrence risk. Consequently, saliva-based monitoring could become a valuable adjunctive tool in long-term oncological surveillance.

Salivary Biomarkers in Oral Potentially Malignant Disorders

Oral potentially malignant disorders comprise a heterogeneous group of lesions associated with an increased risk of malignant transformation. These include leukoplakia, erythroplakia, oral lichen planus, oral submucous fibrosis, and proliferative verrucous leukoplakia [31].

One of the major clinical challenges in OPMDs is the inability to accurately predict which lesions will progress to malignancy. Histopathological dysplasia grading remains the current standard, but it possesses significant interobserver variability. Salivary biomarkers may therefore provide additional objective information regarding malignant potential [32].

Elevated salivary cytokine levels have been observed in several OPMDs. Increased IL-6 and TNF-α levels may reflect chronic inflammatory activity and epithelial dysregulation [33].

Persistent inflammatory signaling contributes to cellular proliferation, angiogenesis, and DNA damage, thereby promoting carcinogenesis.

Oxidative stress also appears to play an important role in malignant transformation. Elevated salivary lipid peroxidation markers and altered antioxidant enzyme activity have been reported in leukoplakia and oral lichen planus patients [34]. Such findings support the role of oxidative imbalance in epithelial dysplasia progression.

MicroRNA profiling has emerged as a particularly promising approach in OPMD risk assessment. Altered salivary expression of miR-21, miR-31, and miR-184 has been associated with dysplastic transformation and increased cancer risk [35]. These biomarkers may eventually help identify high-risk lesions requiring closer surveillance or early intervention.

Oral lichen planus is another important disease in salivary biomarker research. This chronic inflammatory condition possesses recognized malignant potential and is strongly associated with immune dysregulation [36]. Elevated salivary cortisol levels have additionally been reported, suggesting a relationship between psychological stress and disease activity.

Proteomic analyses have also identified several proteins associated with malignant transformation risk. Although further validation studies are necessary, biomarker panels combining inflammatory cytokines, oxidative stress markers, and miRNAs may significantly improve prognostic assessment in OPMDs.

Salivary Biomarkers in Periodontal Diseases and Peri-Implantitis

Periodontal diseases and peri-implantitis are chronic inflammatory conditions characterized by destruction of tooth-supporting and implant-supporting tissues. Early diagnosis is critically important because tissue destruction is often irreversible once clinically detectable bone loss has occurred [37].

Traditional periodontal diagnostics primarily rely on probing depth measurements, bleeding on probing, clinical attachment loss, and radiographic bone assessment. However, these methods mainly reflect past destruction rather than current disease activity [38]. Salivary biomarkers may therefore provide more dynamic information regarding ongoing inflammation and tissue breakdown.

Interleukin-1β is among the most widely investigated salivary biomarkers in periodontal disease. Elevated IL-1β levels strongly correlate with periodontal inflammation and tissue destruction [39]. Similarly, increased TNF-α and IL-6 concentrations have been associated with active periodontal disease.

Matrix metalloproteinase-8 (MMP-8) is considered one of the most promising periodontal biomarkers because it directly reflects collagen degradation and connective tissue destruction [40]. Chairside tests detecting active MMP-8 have already been developed and may facilitate rapid periodontal screening.

Peri-implantitis shares many inflammatory characteristics with periodontal disease but may exhibit more aggressive progression patterns. Elevated salivary MMP-8, IL-1β, and IL-6 levels have been associated with peri-implant bone loss and implant failure risk [41]. Salivary diagnostics may therefore improve early peri-implant disease detection and maintenance protocols.

Microbiological biomarkers are also highly relevant in periodontal and peri-implant diseases. Salivary detection of periodontal pathogens such as Porphyromonas gingivalis and Tannerella forsythia may reflect microbial dysbiosis associated with disease activity [42].

Advances in microbiome analysis have significantly improved understanding of periodontal pathogenesis. Rather than focusing on single pathogens, modern approaches evaluate complex microbial community shifts and host-microbe interactions. Future biomarker panels may therefore combine inflammatory, proteolytic, and microbiological markers to improve diagnostic accuracy.

Salivary Biomarkers in Salivary Gland Diseases

Salivary gland disorders constitute an important subgroup of oral and maxillofacial diseases and include inflammatory, autoimmune, obstructive, infectious, and neoplastic conditions. Because saliva is directly produced by the salivary glands, alterations in salivary composition may provide highly valuable diagnostic information regarding glandular dysfunction and disease progression [43].

Sjögren syndrome represents one of the most extensively studied autoimmune diseases in salivary biomarker research. This chronic autoimmune disorder is characterized by lymphocytic

infiltration of the salivary and lacrimal glands, leading to xerostomia and keratoconjunctivitis sicca. Diagnosis is often delayed because symptoms may initially be nonspecific and conventional diagnostic procedures such as salivary gland biopsy are invasive [44].

Numerous salivary biomarkers have been investigated in Sjögren syndrome. Elevated salivary levels of IL-6, IL-17, TNF-α, β2-microglobulin, lactoferrin, and various autoantibodies have been identified in affected patients [45]. Proteomic analyses have also demonstrated alterations in salivary gland proteins associated with immune activation and epithelial dysfunction. These findings suggest that saliva may eventually serve as a noninvasive alternative to biopsy in selected cases.

Salivary flow rate reduction itself may additionally function as an important functional biomarker in glandular diseases. Quantitative and qualitative changes in saliva production may reflect disease severity, glandular destruction, and therapeutic response [46].

Obstructive salivary gland diseases such as sialolithiasis and chronic sialadenitis may also alter salivary biochemical composition. Increased inflammatory cytokines, oxidative stress markers, and bacterial products may be observed in chronic inflammatory glandular disorders [47].

Salivary gland neoplasms represent another area of growing interest. Although research remains relatively limited compared with oral cancer, several studies have identified distinct salivary proteomic and metabolomic profiles associated with benign and malignant salivary gland tumors [48]. Biomarkers capable of differentiating pleomorphic adenoma from malignant salivary tumors could potentially improve preoperative planning and risk assessment.

Another important application involves monitoring radiation-induced salivary gland dysfunction in head and neck cancer patients. Radiotherapy frequently damages salivary glands, resulting in xerostomia, dysphagia, oral infections, and reduced quality of life. Salivary biomarkers may assist in evaluating glandular injury severity and regenerative response following treatment [49].

Regenerative medicine approaches involving stem cells, tissue engineering, and growth factor therapy are increasingly being investigated for salivary gland repair. Salivary biomarkers may therefore play a future role in monitoring regenerative outcomes and therapeutic effectiveness.

Salivary Biomarkers in Oral Candidiasis and Other Oral Infections

Oral candidiasis is one of the most common opportunistic fungal infections affecting the oral cavity and occurs particularly in immunocompromised individuals, denture wearers, diabetic patients, elderly individuals, and patients receiving antibiotics or corticosteroids [50]. Candida albicans remains the predominant pathogen, although non-albicans Candida species are increasingly being identified in resistant infections.

Saliva plays a critical protective role against fungal colonization through mechanical cleansing and antimicrobial activity. Salivary proteins such as histatins, defensins, lysozyme, lactoferrin, calprotectin, and secretory immunoglobulin A contribute to antifungal defense mechanisms [51]. Reduced salivary flow or impaired salivary antimicrobial activity may therefore predispose individuals to candidiasis.

Altered salivary cytokine profiles have been reported in oral candidiasis patients. Increased IL-1β, IL-6, and TNF-α levels reflect local inflammatory responses to fungal invasion [52]. Salivary oxidative stress markers may additionally increase during active infection due to inflammatory tissue damage and microbial metabolism.

Quantitative salivary Candida analysis may also provide diagnostic and prognostic information. Elevated fungal load in saliva may correlate with disease severity, recurrence risk, and treatment response [53]. Molecular diagnostic techniques such as PCR-based Candida detection have improved sensitivity and specificity compared with conventional culture methods.

The emergence of antifungal resistance has further increased interest in salivary biomarker research. Resistant Candida strains may produce distinct inflammatory and metabolic profiles, potentially enabling earlier therapeutic adjustment [54].

Beyond candidiasis, salivary biomarkers have also been investigated in bacterial and viral oral infections. Odontogenic infections and deep fascial space infections may cause substantial elevations in inflammatory biomarkers such as C-reactive protein, IL-6, and TNF-α [55]. Because severe odontogenic infections can progress rapidly and become life-threatening, early biomarker-based assessment may improve risk stratification and treatment planning.

Salivary diagnostics additionally gained major attention during the COVID-19 pandemic because saliva-based viral detection demonstrated high diagnostic utility while minimizing

healthcare worker exposure [56]. This experience significantly accelerated interest in saliva as a diagnostic fluid for infectious diseases.

Future approaches may combine microbial detection, inflammatory cytokine analysis, and metabolomic profiling to create highly accurate saliva-based infectious disease diagnostic platforms.

Salivary Biomarkers in Temporomandibular Disorders

Temporomandibular disorders (TMDs) comprise a heterogeneous group of musculoskeletal and neuromuscular conditions affecting the temporomandibular joint (TMJ), masticatory muscles, and associated structures. TMDs are multifactorial disorders influenced by biomechanical, inflammatory, psychological, hormonal, and genetic factors [57].

Diagnosis of TMDs remains challenging because symptoms vary widely among patients and objective diagnostic biomarkers are limited. Clinical examination and imaging remain essential, but salivary biomarkers may provide additional insight into underlying pathophysiological mechanisms [58].

Stress-related biomarkers are among the most extensively investigated salivary parameters in TMD patients. Salivary cortisol, alpha-amylase, and chromogranin A have been associated with psychological stress and sympathetic nervous system activation [59]. Elevated cortisol levels are frequently observed in patients with chronic myofascial pain and stress-related parafunctional habits such as bruxism.

Inflammatory cytokines may also contribute to TMJ pathology. Elevated salivary IL-6, IL-1β, and TNF-α levels have been identified in patients with inflammatory TMDs and degenerative joint disease [60]. These cytokines may participate in cartilage degradation, synovial inflammation, and pain sensitization.

Oxidative stress appears to play an additional role in TMD pathogenesis. Increased oxidative damage markers and reduced antioxidant capacity have been identified in some chronic TMD patients [61]. Such findings suggest that oxidative imbalance may contribute to joint degeneration and chronic pain development.

Another emerging area involves salivary neuropeptides and pain mediators. Molecules such as substance P and calcitonin gene-related peptide may reflect nociceptive activation and central sensitization processes [62]. Biomarker analysis may therefore eventually help differentiate inflammatory, muscular, and neuropathic TMD subtypes.

The integration of biomarker analysis into TMD management could potentially improve personalized treatment approaches. Patients demonstrating predominantly inflammatory biomarker profiles may benefit more from anti-inflammatory therapies, whereas stress-related biomarker patterns may indicate a stronger role for behavioral and psychological interventions.

Salivary Biomarkers in Bone Healing and Regenerative Processes

Bone regeneration and wound healing are fundamental aspects of oral and maxillofacial surgery. Salivary biomarkers may provide important information regarding postoperative healing, osseointegration, inflammatory response, and regenerative activity following surgical procedures [63].

Inflammatory cytokines and growth factors are particularly relevant in bone healing assessment. Molecules such as transforming growth factor-beta (TGF-β), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and bone morphogenetic proteins (BMPs) participate in angiogenesis, osteogenesis, and soft tissue regeneration [64].

Dental implant therapy represents one of the most important clinical applications of bone healing biomarkers. Successful osseointegration depends on balanced inflammatory and regenerative responses. Elevated salivary inflammatory markers may indicate impaired healing or early peri-implant disease development [65].

Platelet concentrates such as platelet-rich fibrin (PRF) and concentrated growth factors (CGF) have become increasingly popular in oral surgery because of their regenerative potential. Salivary biomarker analysis may help evaluate the biological effects of these regenerative approaches and monitor tissue healing dynamics [66].

Bone grafting procedures, guided bone regeneration, sinus augmentation, and reconstructive maxillofacial surgeries may also influence salivary cytokine and growth factor levels. Monitoring such biomarkers may improve understanding of individual healing responses and help identify patients at increased risk of complications [67].

Medication-related osteonecrosis of the jaw (MRONJ) is another important condition in which salivary biomarkers may provide significant diagnostic and prognostic information. Increased inflammatory cytokines, altered bone metabolism markers, and microbial dysbiosis have been reported in MRONJ patients [68]. Early biomarker-based detection may potentially improve prevention and management strategies.

Future regenerative medicine approaches involving stem cells, tissue engineering, and biomaterial-based therapies may further increase the importance of salivary biomarker monitoring in oral surgery and implantology.

Artificial Intelligence and Salivary Biomarker Analysis

The rapid development of artificial intelligence (AI) and machine learning technologies has significantly influenced salivary biomarker research. Salivary diagnostics frequently involve large and complex datasets generated from proteomics, genomics, transcriptomics, metabolomics, and microbiome analysis [69]. Conventional statistical methods may not always adequately identify complex multidimensional relationships within such datasets.

Machine learning algorithms can analyze large biomarker datasets and identify disease-specific patterns with high accuracy. AI-assisted models have demonstrated promising performance in oral cancer detection, periodontal disease classification, and microbiome analysis [70].

Deep learning systems may additionally improve image-based salivary biosensor interpretation and facilitate automated diagnostic workflows. Integration of AI into point-of-care salivary diagnostics could eventually enable rapid chairside disease screening within routine dental practice [71].

Another important advantage of AI involves predictive analytics. Machine learning models may help predict malignant transformation risk, peri-implantitis progression, treatment response, and recurrence probability based on salivary biomarker profiles [72].

Personalized medicine is likely to become increasingly dependent on AI-supported biomarker analysis. Individualized risk assessment and treatment planning based on integrated salivary biomarker panels may significantly improve clinical outcomes in oral and maxillofacial diseases.

Nevertheless, important challenges remain regarding data standardization, algorithm transparency, external validation, and ethical considerations. Large multicenter datasets and interdisciplinary collaboration will be essential for successful clinical translation.

Limitations and Challenges of Salivary Biomarkers

Despite the remarkable progress achieved in salivary diagnostics, several important limitations continue to restrict the routine clinical implementation of salivary biomarkers in oral and maxillofacial diseases. One of the primary challenges involves biological variability. Salivary composition may fluctuate significantly depending on age, gender, circadian rhythm, hydration status, dietary habits, smoking, alcohol consumption, stress, systemic diseases, medication use, and oral hygiene practices [73]. Such variability may influence biomarker concentrations and complicate interpretation of results.

Saliva collection methodology represents another major issue. Stimulated and unstimulated saliva samples may demonstrate substantially different biochemical profiles. Furthermore, collection time, storage conditions, centrifugation protocols, and sample contamination can all affect analytical outcomes [74]. Lack of standardized protocols therefore remains a significant obstacle to reproducibility and multicenter comparison.

Another important limitation is the relatively low concentration of some biomarkers in saliva compared with serum. Although technological advances have significantly improved detection sensitivity, highly specialized laboratory equipment may still be required for accurate analysis of low-abundance molecules [75]. This may increase costs and reduce accessibility in routine clinical settings.

The heterogeneity of oral diseases also complicates biomarker validation. Oral squamous cell carcinoma, periodontal diseases, autoimmune disorders, and infectious conditions may all involve overlapping inflammatory pathways and biomarker profiles. Consequently, a single biomarker rarely demonstrates sufficient specificity for definitive diagnosis [76]. For this reason, current research increasingly focuses on multimarker panels combining cytokines, proteomic signatures, microRNAs, microbial profiles, and metabolomic data.

Many existing studies additionally involve relatively small sample sizes and cross-sectional designs. Large prospective multicenter trials remain limited. Without external validation across different populations and geographic regions, clinical applicability remains uncertain [77].

Economic considerations also play an important role. Although saliva collection itself is inexpensive, advanced molecular analyses such as proteomics, transcriptomics, and next-generation sequencing may still be costly and technically demanding. Wider adoption of portable biosensor technologies and point-of-care systems will therefore be necessary to improve accessibility [78].

Ethical and data-management considerations have become increasingly relevant with the integration of artificial intelligence and multi-omics technologies. Salivary biomarker databases may contain sensitive genetic and health-related information requiring appropriate privacy protection and ethical oversight [79].

Despite these limitations, continuous technological progress and increasing interdisciplinary collaboration are expected to gradually overcome many of these barriers. As analytical technologies become more affordable, standardized, and automated, salivary diagnostics will likely become increasingly integrated into clinical oral healthcare.

Future Perspectives

The future of salivary biomarker research appears highly promising and may fundamentally transform diagnostic approaches in oral and maxillofacial medicine. The growing emphasis on minimally invasive and personalized healthcare strongly supports the continued development of saliva-based diagnostic systems [80].

One of the most important future directions involves the integration of multi-omics approaches. Combining proteomics, transcriptomics, metabolomics, microbiomics, and exosome analysis may provide a more comprehensive understanding of disease biology than single biomarker evaluation alone [81]. Such integrated biomarker panels are expected to improve diagnostic accuracy, prognostic reliability, and treatment prediction.

Point-of-care technologies are likely to play a major role in future clinical implementation. Portable biosensor devices capable of rapidly detecting multiple salivary biomarkers could allow chairside screening within minutes [82]. Such systems may become particularly valuable for oral cancer screening, periodontal risk assessment, and monitoring of chronic inflammatory diseases.

Artificial intelligence and machine learning will probably become increasingly important in salivary diagnostics. AI-assisted systems may identify complex biomarker interactions that are difficult to recognize using traditional analytical methods [83]. Predictive algorithms could potentially estimate malignant transformation risk, peri-implantitis progression, or postoperative complication probability based on individualized biomarker profiles.

Another promising area involves liquid biopsy applications. Salivary exosomes, circulating tumor DNA, and tumor-associated microRNAs may provide real-time information regarding tumor dynamics, metastasis, therapeutic response, and recurrence [84]. Such approaches could significantly improve noninvasive cancer monitoring and personalized oncological management.

Salivary diagnostics may additionally become integrated with digital dentistry and telemedicine platforms. Remote saliva collection and cloud-based biomarker analysis could eventually facilitate large-scale population screening and long-term disease monitoring [85].

Regenerative medicine applications may further expand the role of salivary biomarkers. Biomarker-guided evaluation of bone healing, implant osseointegration, tissue engineering outcomes, and stem cell therapies may contribute to more predictable surgical results [86].

As research continues to progress, it is likely that saliva-based diagnostics will transition from experimental applications to routine clinical tools within oral and maxillofacial practice. Collaboration among dentists, oral surgeons, molecular biologists, bioengineers, data scientists, and industry partners will be essential for successful clinical translation.

Conclusion

Salivary biomarkers represent one of the most rapidly evolving areas in oral and maxillofacial medicine and possess substantial diagnostic and prognostic potential. Saliva is a complex biological fluid containing numerous proteins, cytokines, nucleic acids, metabolites, microorganisms, and extracellular vesicles capable of reflecting both local and systemic pathological changes.

Current evidence demonstrates promising applications of salivary biomarkers in oral squamous cell carcinoma, oral potentially malignant disorders, periodontal diseases, peri-implantitis, salivary gland diseases, fungal infections, temporomandibular disorders, and regenerative

processes. Inflammatory cytokines, matrix metalloproteinases, oxidative stress markers, microRNAs, proteomic signatures, and exosomal components have all shown significant potential for disease detection and monitoring.

One of the greatest advantages of saliva-based diagnostics is its noninvasive nature. Saliva collection is painless, inexpensive, repeatable, and suitable for chairside applications, making it highly attractive for large-scale screening and longitudinal monitoring. Advances in proteomics, genomics, metabolomics, biosensor technologies, and artificial intelligence have significantly improved the sensitivity and specificity of salivary analyses.

Nevertheless, important challenges remain regarding standardization, biomarker validation, reproducibility, and clinical integration. Biological variability, methodological heterogeneity, and limited multicenter validation studies continue to restrict widespread implementation. Future research should therefore focus on standardized protocols, large prospective clinical trials, multimarker panel development, and AI-assisted predictive modeling.

Overall, salivary diagnostics are expected to become an increasingly important component of precision dentistry and personalized oral healthcare. Continued technological innovation and interdisciplinary collaboration will likely enable saliva-based biomarker systems to play a central role in early diagnosis, prognosis assessment, therapeutic monitoring, and individualized treatment planning in oral and maxillofacial diseases.

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CHAPTER 2

ENDODONTIC MANAGAMENT PROTOCOLS ACCORDING TO PREGNANCY TRIMESTERS

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1. INTRODUCTION

Pregnancy is a unique period during which significant physiological, hormonal and immunological changes occur in a woman's body. These changes directly affect not only general health but also oral and dental health. In particular, the increased levels of oestrogen and progesterone during pregnancy lead to increased gingival vascularity, changes in the inflammatory response, and increased sensitivity of periodontal tissues to bacterial irritants. As a result, an increase in pregnancy gingivitis, periodontal diseases and oral infections may be observed.

Oral infections and dental pain that arise during pregnancy not only adversely affect the mother's quality of life, but are also significant in terms of foetal health. Indeed, it has been reported that periodontal infections and odontogenic inflammation may be associated with obstetric complications such as preterm birth, low birth weight and pre-eclampsia [1]. It is thought that, in particular, uncontrolled acute dental infections may have adverse effects on the maternal-foetal balance by increasing the systemic inflammatory response.

Endodontic pathologies are among the most common dental emergencies encountered during pregnancy. Acute pulpitis, necrotic pulp, apical abscesses and widespread odontogenic infections may require urgent intervention due to severe pain, infection and stress. However, although there was previously a widespread view that dental treatment should be postponed during pregnancy, current scientific evidence indicates that necessary dental and endodontic procedures can be performed safely using appropriate clinical protocols. The American College of Obstetricians and Gynaecologists (ACOG) and the American Dental Association (ADA) emphasise that necessary dental treatments should not be postponed during pregnancy and can be safely carried out with appropriate protective measures. (ACOG, 2013; ADA, 2020).

When planning endodontic treatment during pregnancy, the trimesters must be taken into account. As the first trimester is the organogenesis period, it is considered more sensitive in terms of foetal development, whilst the second trimester is regarded as the safest period for dental treatment. In the third trimester, patient positioning, maternal comfort and the risk of supine hypotensive syndrome come to the fore. Furthermore, issues such as the use of radiography, the choice of local anaesthetics, irrigation protocols and the prescription of medication must also be carefully assessed from the perspective of foetal safety.

Failure to bring endodontic infections under control can often pose a greater risk than the treatment itself. Indeed, the literature indicates that untreated dental pain and infections can lead to an increase in maternal stress hormones, which may have significant consequences for both maternal and foetal health[2]. For this reason, the primary aim of endodontic treatment during pregnancy is to control the infection, relieve pain and ensure the safety of both mother and baby.

In this section, trimester-based endodontic treatment protocols for pregnant women are discussed in line with the current literature; the principles of clinical approach by trimester, safe endodontic practices, medication use, radiography protocols and clinical management strategies are examined in detail.

2. Endodontic Emergencies During Pregnancy and Their Clinical Significance

The physiological, hormonal and immunological adaptations that occur during pregnancy lead to specific changes in the oral microbiota and host response, thereby accelerating the progression of existing dental infections. In particular, pregnancy-related episodes of nausea and vomiting, changes in dietary habits, and the resulting poor oral hygiene create a favourable environment for the exacerbation of pulp and periapical pathologies. Acute pulpitis, pulp necrosis, symptomatic apical periodontitis and odontogenic abscesses are among the most frequently encountered clinical presentations during this period; due to their potential for severe pain and systemic spread, they are classified as major dental emergencies requiring urgent intervention.

The clinical management of endodontic emergencies during pregnancy is of strategic importance, as it is not limited to controlling local tissue damage and acute pain in the tooth, but also directly affects the maintenance of maternal and foetal health. Indeed, the literature reports that uncontrolled chronic and acute odontogenic infections may enter the systemic circulation and exacerbate the maternal inflammatory response. It is noted that this systemic inflammation caused by periodontal and odontogenic infections may be associated with major obstetric complications such as preterm birth, low birth weight and pre-eclampsia[1]. Offenbacher and colleagues have demonstrated, using clinical data, that periodontal and odontogenic infections may be a "previously unrecognised independent risk factor for preterm low birth weight"[1].

On the other hand, the secondary neuroendocrine stress response induced by severe odontogenic pain leads to marked increases in maternal catecholamine and cortisol levels. It is thought that this condition may have a direct adverse effect on foetal physiology by influencing the dynamics of the uteroplacental circulation[2].In this context, with the aim of eliminating the risk of infection and the stress response, the American Dental Association (ADA) emphasises that dental emergencies arising during pregnancy should be treated without delay, in accordance with appropriate clinical protocols (ADA, 2020). Consequently, endodontic management during pregnancy is a vital clinical parameter in terms of both pain control and the preservation of maternal-foetal integrity [3].

2.1. Acute Pulpitis

During pregnancy, the acceleration of caries progression due to hormonal fluctuations and a decline in oral hygiene standards increases the incidence of pulp pathologies. Acute irreversible pulpitis, which is frequently encountered during this period, is an endodontic emergency characterised by irreversible inflammation of the pulp tissue, leading to severe acute pain attacks. Clinically, it is characterised by a spontaneous, throbbing pain response that is prolonged in response to hot and cold thermal stimuli and intensifies to a level severe enough to wake the patient from sleep at night[4]. This persistent pain pattern caused by acute pulpitis significantly elevates anxiety and systemic stress levels in pregnant patients. Given the potential adverse physiological consequences that untreated dental pain and infections may have on the maternal-foetal unit [2], establishing urgent pain control is a priority.

In this regard, in accordance with the guidelines of the American College of Obstetricians and Gynaecologists (ACOG), procedures such as pulpotomy or pulpectomy—which involve surgical intervention within the hard tissues—should be safely performed under adequate local anaesthesia to reduce pulp pressure and remove infected tissue (ACOG, 2013).

2.2. Necrotic Pulp and Apical Periodontitis

As the inflammatory process progresses, leading to complete necrosis of the pulp tissue within the root canal system, this results in the spread of bacterial colonisation to the periapical tissues and the development of symptomatic apical periodontitis. At this clinical stage, the patient complains not so much of spontaneous pain as of severe sensitivity, particularly during mastication, and vertical percussion pain[5]. Clinical examination reveals signs of localised

inflammation, accompanied by periapical radiolucencies detected on radiographic examination. Leaving such intracanal infections untreated during pregnancy carries the risk of progression to acute apical abscess formation. The literature reports that failure to control endodontic infection foci poses a far greater risk to the patient than the clinical treatments to be administered. Therefore, the disinfection of the root canal system via chemomechanical preparation, the provision of intracanal drainage where necessary, and the meticulous implementation of safe irrigation protocols must be carried out without delay. The primary aim of treatment is the mechanical elimination of the local source of infection and the reduction of the systemic inflammatory burden.

2.3. Acute Apical Abscess

An acute apical abscess, which develops when a pulp infection fails to localise within the periapical tissues and instead spreads to the surrounding tissues, causing a purulent reaction, is considered one of the most critical endodontic emergencies requiring urgent intervention during pregnancy [6]. The clinical presentation is quite dramatic, leading to severe spontaneous pain, marked intraoral or extraoral swelling, a mass with fluctuation on palpation, systemic fever and regional lymphadenopathy. In advanced cases, the spread of infection beyond anatomical barriers into the facial sinuses exponentially increases the risk of systemic complications and maternal morbidity.

The first step in the clinical management of such acute infections is to ensure urgent drainage via root canals or a surgical incision in the intraoral area, thereby evacuating the purulent exudate from within the tissue. In addition to mechanical and surgical endodontic interventions, antibiotic therapy should be initiated without delay in cases where the infection shows signs of systemic spread. Amoxicillin and penicillin derivatives, whose safety during pregnancy has been established, are among the safest pharmacological agents to be preferred as a first-line treatment[7].

2.4. Common Odontogenic Infections and Cellulitis

Cellulitis resulting from the spread of odontogenic infections to the facial compartments and deep cervical spaces is a clinical emergency that poses serious life-threatening risks to maternal and foetal health. The progression of this aggressive condition leads to major complications such as acute airway obstruction, widespread systemic infection (sepsis),

uncontrolled increase in maternal-foetal stress, and an inevitable need for hospital admission. Failure to aggressively control cellulitis and widespread odontogenic infections in the early stages may pave the way for life-threatening obstetric crises. The treatment approach requires the implementation of surgical decompression and emergency drainage protocols, aggressive intravenous antibiotic therapy, and close monitoring of the patient's general systemic condition in a hospital setting. In the management of infections of this extent, close multidisciplinary collaboration with the relevant obstetrician and an obstetric consultation process are of paramount importance to minimise the risk of complications.

2.5. Basic Principles in the Management of Endodontic Emergencies During Pregnancy

The primary clinical objective in the management strategy for endodontic emergencies encountered during pregnancy is to rapidly control maternal pain, prevent the spread of infection and systemic complications, minimise acute anxiety and the stress response in the expectant mother, and thereby ensure the maximum possible protection of foetal safety. When managing this process, the gestational trimester in which the patient is currently in must be carefully considered; the use of unnecessary and uncontrolled medication with teratogenic potential must be strictly avoided; protective equipment (lead aprons and thyroid shields) must be used in accordance with the ALARA principles during diagnostic radiography; and care must be taken to ensure correct patient positioning to prevent compression of the inferior vena cava. Joint consensus reports from the American Dental Association and the American College of Obstetricians and Gynaecologists confirm that emergency dental treatment can be safely and successfully performed at any stage of pregnancy, provided that local infection foci are addressed before they develop into systemic problems, and in accordance with appropriate clinical and protective protocols (ACOG, 2013; ADA, 2020). The fundamental principle of the endodontic approach during pregnancy is the simultaneous elimination of the infection focus and the assurance of maternal-foetal safety.

3. Endodontic Treatment Protocols in the First Trimester

The first trimester, covering the first 13 weeks of pregnancy, is the most critical developmental period during which the processes of embryogenesis and organogenesis occur simultaneously and the foetus is at its most vulnerable to teratogenic agents. During this stage, when the foetal organ systems are forming at a rapid pace, the period between the 2nd and 8th weeks is considered the most vulnerable to external stimuli. In the past, there was a widespread belief that all dental treatments should be postponed entirely to avoid teratogenic effects.

However, current clinical evidence clearly indicates that uncontrolled odontogenic pain and infection pose a significantly higher risk profile than the therapeutic intervention itself, and emphasises that emergency interventions should not be delayed. Severe neurogenic pain caused by endodontic emergencies encountered during the first trimester—such as acute irreversible pulpitis, necrotic pulp, symptomatic apical periodontitis and acute apical abscess—can lead to dramatic increases in maternal catecholamine and cortisol levels, thereby disrupting uteroplacental blood flow. Therefore, to protect the foetus from physiological stress, it is recommended that the necessary endodontic interventions to eliminate the pain be performed immediately.

The fundamental philosophy of the clinical approach during this period is based on the eradication of the infection, with preference given to shorter-term palliative treatments rather than invasive procedures requiring lengthy sessions. Non-urgent elective endodontic procedures, as well as extensive restorative or aesthetic procedures, should be postponed until the second trimester[3].The duration of procedures such as pulpotomy, pulpectomy or intra-canal drainage, which are performed only when absolutely necessary, should be kept to the absolute minimum. To prevent the swallowing of irrigation solutions during the procedure and to completely eliminate the risk of aspiration, rubber dam isolation should be used as standard practice.

The use of radiography in diagnostic procedures should be restricted to cases where it is strictly necessary. The radiation exposure to the foetus from modern digital radiographs taken with appropriate protective equipment (lead apron and thyroid shield) is minimal and clinically safe. The use of local anaesthesia to manage pain is essential to prevent maternal stress. The most commonly used and proven safe local anaesthetic during pregnancy is lidocaine preparations containing epinephrine. It has been reported that controlled doses of epinephrine, administered whilst avoiding intravascular injection, do not cause any clinically significant adverse effects on uteroplacental circulation[8].In terms of pharmacological management, paracetamol should be used as an analgesic; in cases requiring antibiotic therapy, penicillins, amoxicillin and clindamycin should be preferred. The use of antibiotics from the tetracycline group, which inhibit foetal bone development and cause irreversible discolouration of the teeth, should be avoided throughout the entire pregnancy [7].

4. Endodontic Treatment Protocols in the Second Trimester

The second trimester, spanning weeks 14 to 27 of pregnancy, is a stage in which the process of organogenesis is largely complete, the risk of spontaneous abortion has statistically decreased, and the symptoms of nausea typically subside. During this period, the volume of the uterus has not yet reached a size that would prevent the patient from assuming an optimal position on the dental unit. Taking all these physiological advantages into account, the second trimester is considered the safest period for planning routine root canal treatment and other necessary endodontic procedures. Guidelines from the American Dental Association and the American College of Obstetricians and Gynaecologists clearly state that all necessary dental treatments can be safely performed during this period (ACOG, 2013; ADA, 2020).

In root canal treatment procedures, it is of the utmost importance to carefully determine the working length in order to prevent irritation of the apical tissues. The use of a rubber dam is mandatory to prevent irrigation solutions from coming into contact with oral tissues and to eliminate the risk of aspiration. During endodontic disinfection, as the apical extrusion of sodium hypochlorite into the periapical tissues can lead to serious tissue damage and inflammation, it is essential that the irrigation procedure is carried out at low pressure using irrigation needles with lateral holes.

As inadequate local anaesthesia may trigger maternal stress and impair foetal circulation , complete and deep anaesthesia must be achieved using lidocaine with epinephrine. To maintain the maximum safety margin, recommended dose limits must not be exceeded, and aspiration must always be performed prior to injection. In medical prescribing, paracetamol, amoxicillin and penicillin-group antibiotics remain the first choice; the use of NSAID-group analgesics should be avoided[7]. During radiographic follow-ups, the use of digital systems equipped with lead aprons and thyroid protectors, combined with a minimum number of images, keeps foetal radiation exposure to very low levels (ADA, 2020). Furthermore, even during this comfortable period when patient tolerance is high, it is recommended that sessions be kept short in order to preserve uteroplacental haemodynamics [2].

5. Endodontic Treatment Protocols in the Third Trimester

The third trimester, which spans the period from the 28th week of pregnancy until delivery, is a stage characterised by significant anatomical changes in the maternal cardiovascular system due to the acceleration of foetal growth. During this period, the focus of

treatment planning is on maintaining maternal comfort, postponing elective procedures until after delivery, and performing emergency interventions only in cases of acute infection or pain.

The most critical obstetric risk associated with endodontic procedures in the third trimester is the pressure exerted by the expanding uterus on the inferior vena cava as a result of the patient lying on their back (in the fully supine position) for an extended period in the dental chair. This pressure can obstruct venous return, potentially triggering the "supine hypotensive syndrome", characterised by hypotension, dizziness, nausea and syncope. To prevent this high-risk condition, the patient must not be kept in the fully supine position; instead, a pillow should be placed under the right hip to shift the weight of the uterus away from the veins, thereby achieving a slight left lateral position[3].Position changes should be kept to a minimum, and appointments should be scheduled in short time slots to prevent maternal discomfort, ensuring the patient is given frequent breaks to rest.

In endodontic emergencies that cannot be delayed—such as acute pulpitis, necrotic pulp and the formation of an apical abscess—procedures must be completed swiftly using a rubber dam, and the treatment should be divided into several short sessions if necessary. To prevent the devastating stress caused by uncontrolled pain on the mother-foetus unit [2], pain management must be carried out with the utmost care. However, the choice of analgesics is much more limited during this period; whilst paracetamol remains the safest option [9], the use of non-steroidal anti-inflammatory drugs (NSAIDs) is strictly contraindicated due to the risk of causing premature closure of the foetal ductus arteriosus during the intrauterine period[7]. Before commencing treatment for any surgical procedure or widespread infection, consultation with the relevant obstetrician must be sought (ACOG, 2013), whilst radiographic procedures should be carried out using digital sensors without compromising the ALARA principles (ADA, 2020).

6. Protocols for Medication, Anaesthesia and Radiography in Endodontic Treatment for Pregnant Women

When planning endodontic treatment during pregnancy, dental pharmacotherapy, the use of local anaesthetics and radiological procedures must be assessed with the utmost care in terms of maternal and foetal safety. The fact that many pharmacological agents prescribed in clinical practice have the potential to cross the placental barrier and interfere with foetal development, and that uncontrolled exposure to radiation poses teratogenic risks, necessitates that all clinical steps be designed in accordance with current medical guidelines. However, data

from the American College of Obstetricians and Gynaecologists (ACOG) confirm that necessary dental interventions can be safely performed throughout pregnancy provided appropriate protective measures are taken and rational drug selection is employed (ACOG, 2013).

6.1. Management of Local Anaesthesia and Analgesia

Ensuring deep and adequate anaesthesia during endodontic procedures is of critical importance not only for the success of the treatment but also for the inhibition of maternal stress and the establishment of pain control[10]. This is because it is known that uncontrolled dental pain can lead to the release of endogenous catecholamines, thereby disrupting uteroplacental haemodynamics. The local anaesthetic agents most commonly and safely used during pregnancy are lidocaine preparations combined with epinephrine[11]. It has been reported that controlled doses of epinephrine, administered strictly via aspiration in accordance with the principle of the minimum effective dose and to avoid intravascular injection, do not result in clinically significant morbidity in the foetal circulation[8].

It should be noted that local anaesthetic agents containing felipressin—which could be considered as an alternative to epinephrine (e.g. prilocaine + felipressin)—may trigger uterine contractions due to their oxytocic effects and are strictly contraindicated during pregnancy[12].

In postoperative pain management, however, foetal safety categories are the determining factor. Paracetamol is considered the safest agent for relieving pain of pulp and periapical origin throughout pregnancy [13]. However, the use of non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, naproxen and diclofenac carries a risk of serious obstetric complications, particularly from the 20th week of pregnancy onwards. It has been reported that the use of NSAIDs may lead to premature closure of the foetal ductus arteriosus, the development of oligohydramnios and prolonged labour; therefore, these medicines should not be prescribed[7].

6.2. Antibiotic Therapy and Root Canal Irrigation Protocols

In conditions such as facial cellulitis or lymphadenopathy, where acute endodontic infections tend to enter the systemic circulation, the use of antibiotics is a medical necessity. In such cases, penicillin derivatives, amoxicillin and cephalosporins—which have been proven to be safe for the foetus (Category B)—should be the first-line choice[3]. In pregnant patients with a penicillin allergy, clindamycin (Category B) should be considered a safe alternative.

However, agents in the tetracycline and doxycycline groups are strictly contraindicated throughout all stages of pregnancy, as they exhibit an affinity for calcified tissues, thereby inhibiting foetal bone development and causing intrinsic discolouration and enamel hypoplasia in permanent dentition.

In root canal irrigation—a key component of infection control—the migration of chemical solutions (particularly sodium hypochlorite) into the periapical tissues can cause severe cellular toxicity and acute inflammatory reactions. To prevent this complication, irrigation procedures must be carried out in a highly controlled manner at low pressure, using side-ported needles that prevent apical extrusion, and within a carefully calculated working length.

6.3. Radiography and the ALARA Principle

In situations requiring radiographic examination, such as establishing an endodontic diagnosis and determining the working length, the fundamental philosophy is the ALARA (As Low As Reasonably Achievable) principle. In accordance with this principle, radiographic exposure should be limited to essential cases only, unnecessary repetitions should be avoided, and protective equipment such as lead aprons and thyroid shields must be used. According to the guidelines of the American Dental Association (ADA), the radiation dose to the embryo or foetus from dental radiographs taken with high-speed digital sensors and appropriate shielding is extremely low, and such radiographs can be safely performed during pregnancy (ADA, 2020).

7. Clinical Management and Safety Protocols

The endodontic approach in pregnant patients requires a multidisciplinary management plan that goes beyond standard dental procedures, focusing on the preservation of maternal-foetal haemodynamics, the prevention of potential obstetric complications, and the maximisation of patient comfort. A comprehensive medical history is the first and most important step in determining the patient’s trimester, the presence of systemic conditions such as gestational diabetes or hypertension, and high-risk pregnancy factors. Particularly in cases with a history of pre-eclampsia, bleeding disorders, or complicated infections requiring surgical intervention, a medical consultation with the patient’s obstetrician must be arranged prior to commencing endodontic procedures (ACOG, 2013).

Appointment scheduling should be adjusted to account for the physiological demands of pregnancy. Dental procedures should be planned in short sessions; lengthy procedures should be interspersed with frequent rest breaks to ensure they do not strain the patient's physical tolerance; and for patients experiencing severe morning sickness (hyperemesis), appointments should be rescheduled for later in the day [3]. In the later weeks of pregnancy (particularly during the third trimester), to eliminate uterine pressure on the inferior vena cava and the associated risk of supine hypotensive syndrome, positioning the patient in a slight left lateral decubitus position (or by placing a support under the right hip) rather than in a fully supine position on the dental unit is a vital ergonomic rule for haemodynamic stability[14].

In the context of operational safety, rubber dam isolation is an indispensable standard. By preventing mucosal contact with and the swallowing of irrigation solutions, as well as reducing the risk of instrument aspiration to zero, this system is the strongest link in the infection control chain. Finally, it should not be forgotten that increased anxiety and severe dental pain can trigger maternal stress hormones, leading to fluctuations in blood pressure and uteroplacental perfusion disorders. It is therefore of the utmost importance that the clinician establishes an empathetic, explanatory communication to ensure a calm treatment environment and guarantees pain management through pharmacological means[2].

8. Conclusion

Pregnancy is a delicate physiological phase that requires tailored clinical approaches to dental treatment planning due to the effects of hormonal, immunological and cardiovascular changes. During this period, exacerbated odontogenic infections and secondary acute pulp pain not only reduce the expectant mother's quality of life but may also trigger obstetric complications such as preterm birth and low birth weight through an increased systemic inflammatory cascade[1].

Current evidence-based medical data indicates that the risks posed to the foetus by delayed treatment are significantly higher than those associated with the stress of treatment itself; it demonstrates that endodontic procedures can be safely completed at any stage of pregnancy with accurate diagnosis, appropriate pharmacotherapeutic agents and protective radiological measures (ACOG, 2013). The primary objective is to bring the infection under control as a matter of urgency during the first trimester whilst avoiding unnecessary procedures; to complete routine procedures during the second trimester, which is the safest period; and, during the third trimester, to ensure palliative emergency management through correct

positioning and short appointments in order to protect maternal haemodynamics. The dentist's full mastery of maternal physiology, risks of foetal teratogenicity, ALARA radiography principles, and the operational safety provided by rubber dam isolation is the sole guarantee that endodontic treatment in pregnant women will result in a complication-free and multidisciplinary success.

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CHAPTER 3

PHOTOBIOMODULATION AND LASER-ASSISTED THERAPIES IN ORAL SURGERY

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Introduction

Technological advances have significantly transformed contemporary oral and maxillofacial surgery, leading to the development of minimally invasive therapeutic approaches aimed at improving tissue healing, reducing postoperative morbidity, and enhancing clinical outcomes. Among these innovations, photobiomodulation (PBM) and laser-assisted therapies have gained considerable attention because of their biological effects on cellular metabolism, inflammation, angiogenesis, tissue regeneration, and pain modulation [1].

Photobiomodulation, formerly referred to as low-level laser therapy (LLLT), involves the application of low-intensity laser or light-emitting diode (LED) light to stimulate biological processes without causing thermal tissue damage [2]. Unlike surgical lasers that cut or ablate tissues through photothermal effects, PBM primarily acts through photochemical and photobiological mechanisms [3]. The therapy has been increasingly investigated in oral surgery for wound healing enhancement, reduction of postoperative pain and edema, nerve regeneration, implant osseointegration, management of medication-related osteonecrosis of the jaw (MRONJ), temporomandibular disorders, and treatment of oral mucosal lesions [4].

The biological effects of PBM are mainly mediated through the absorption of photons by mitochondrial chromophores, particularly cytochrome c oxidase [5]. This interaction increases mitochondrial activity, adenosine triphosphate (ATP) synthesis, reactive oxygen species modulation, and transcription factor activation, thereby influencing cellular proliferation, collagen synthesis, angiogenesis, and inflammatory responses [6]. Such effects have generated growing interest in PBM as an adjunctive therapeutic modality in oral and maxillofacial surgery.

Laser-assisted therapies additionally encompass a broad range of applications involving high-power surgical lasers such as diode, erbium, Nd:YAG, and CO_2 lasers. These systems may be used for soft tissue surgery, bone surgery, decontamination, peri-implant therapy, and management of oral lesions [7]. Compared with conventional surgical instruments, laser-assisted procedures may offer advantages including reduced bleeding, improved visualization, decreased postoperative pain, bacterial reduction, and enhanced patient comfort [8].

In implant dentistry and regenerative oral surgery, PBM has become increasingly important because of its potential effects on bone metabolism and osseointegration. Experimental and

clinical studies have suggested that laser therapy may stimulate osteoblastic activity, enhance angiogenesis, accelerate bone maturation, and improve implant stability [9]. Similarly, laser-assisted decontamination techniques have been investigated in peri-implantitis treatment and MRONJ management.

The use of PBM in nerve regeneration has also emerged as a promising field. Inferior alveolar nerve and lingual nerve injuries remain significant complications of oral surgery procedures such as third molar extraction, implant placement, orthognathic surgery, and trauma management [10]. PBM may promote axonal regeneration, reduce inflammatory injury, and improve functional neural recovery.

Despite increasing evidence supporting PBM and laser-assisted therapies, important controversies remain regarding optimal treatment parameters, wavelength selection, energy density, irradiation duration, and treatment frequency [11]. Lack of standardized protocols continues to limit direct comparison between studies and restricts broader clinical consensus.

This chapter reviews the biological principles, mechanisms of action, clinical applications, therapeutic outcomes, limitations, and future perspectives of photobiomodulation and laser-assisted therapies in oral surgery.

Biological Mechanisms of Photobiomodulation

The therapeutic effects of photobiomodulation are primarily based on the interaction between light energy and cellular photoreceptors. The most widely accepted mechanism involves absorption of photons by cytochrome c oxidase within the mitochondrial respiratory chain [12]. This process stimulates electron transport activity and increases ATP production, thereby enhancing cellular energy metabolism.

Enhanced ATP synthesis may significantly influence cellular proliferation, migration, protein synthesis, and tissue repair processes [13]. PBM additionally modulates reactive oxygen species production at controlled levels, activating intracellular signaling pathways associated with growth factor release and gene transcription.

Another important mechanism involves nitric oxide dissociation from cytochrome c oxidase. Nitric oxide release may improve local microcirculation and vasodilation, thereby increasing

oxygen delivery and nutrient transport to damaged tissues [14]. Enhanced angiogenesis is considered one of the major contributors to accelerated wound healing following PBM therapy.

Photobiomodulation also exerts anti-inflammatory effects through modulation of cytokine activity. Studies have demonstrated reductions in pro-inflammatory mediators such as TNF-α, IL-1β, and prostaglandin E2 following laser irradiation [15]. Simultaneously, PBM may stimulate anti-inflammatory cytokines and growth factors involved in tissue repair.

Fibroblast activation represents another critical therapeutic mechanism. PBM stimulates fibroblast proliferation and collagen synthesis, both of which are essential for soft tissue healing and wound maturation [16]. Increased collagen organization may improve tissue strength and reduce scar formation.

In bone tissue, PBM influences osteoblastic differentiation, alkaline phosphatase activity, and mineralized matrix formation [17]. Experimental studies have additionally demonstrated increased expression of bone morphogenetic proteins and osteogenic transcription factors following laser therapy.

Analgesic effects of PBM are multifactorial and may involve modulation of nerve conduction velocity, reduction of inflammatory mediators, release of endogenous opioids, and suppression of nociceptor activity [18]. These mechanisms contribute significantly to postoperative pain control following oral surgery procedures.

The biological response to PBM is highly dependent on treatment parameters including wavelength, power output, energy density, irradiation time, pulse frequency, and tissue characteristics [19]. Excessively low energy levels may produce insufficient biological stimulation, whereas excessive energy may inhibit cellular activity, a phenomenon commonly referred to as the biphasic dose response.

Laser Systems Used in Oral Surgery

Various laser systems have been introduced into oral and maxillofacial surgery, each characterized by specific wavelengths and tissue interactions. The most commonly used systems include diode lasers, Nd:YAG lasers, erbium lasers, and CO_2 lasers [20].

Diode lasers are among the most widely utilized systems in dentistry because of their relatively compact size, affordability, and effectiveness in soft tissue applications. Common wavelengths range from approximately 810 to 980 nm [21]. Diode lasers demonstrate strong absorption by melanin and hemoglobin, making them highly effective for soft tissue incision, coagulation, bacterial reduction, and photobiomodulation.

Nd:YAG lasers operate at a wavelength of 1064 nm and exhibit deep tissue penetration [22]. They are frequently used for soft tissue surgery, periodontal therapy, bacterial decontamination, and coagulation procedures. Because of their thermal effects, careful parameter control is necessary to minimize collateral tissue damage.

Erbium lasers, including Er:YAG and Er,Cr:YSGG systems, demonstrate high absorption in water and hydroxyapatite [23]. These characteristics make erbium lasers highly suitable for hard tissue applications such as bone cutting, cavity preparation, implant surface decontamination, and osseous surgery. Compared with rotary instruments, erbium lasers may produce reduced vibration, noise, and thermal injury.

CO_2 lasers emit light at approximately 10,600 nm and are strongly absorbed by water-containing tissues [24]. They are widely used in oral soft tissue surgery because of their precise cutting ability, excellent hemostasis, and superficial tissue penetration. CO_2 lasers are commonly applied in management of oral lesions, frenectomies, biopsies, and mucosal surgery.

The selection of an appropriate laser system depends on the intended clinical application, tissue type, depth of penetration required, thermal characteristics, and desired biological effect [25]. In many clinical situations, laser-assisted surgery may improve patient comfort and reduce postoperative morbidity compared with conventional scalpel-based techniques.

Photobiomodulation and Wound Healing

One of the most extensively investigated applications of PBM in oral surgery involves enhancement of wound healing. Oral surgical procedures frequently produce tissue injury associated with inflammation, edema, pain, and delayed healing [26]. Accelerating tissue repair while minimizing postoperative complications remains a major clinical objective.

PBM has demonstrated beneficial effects during all major phases of wound healing including inflammation, proliferation, and remodeling [27]. During the inflammatory phase, laser therapy

reduces excessive inflammatory mediator release and improves local circulation. This may decrease postoperative swelling and discomfort.

During the proliferative phase, PBM stimulates fibroblast proliferation, collagen synthesis, angiogenesis, and epithelialization [28]. Enhanced fibroblast activity contributes to more rapid connective tissue repair and improved wound stability.

Several clinical studies have reported accelerated healing following tooth extraction, periodontal surgery, mucogingival procedures, and implant surgery when adjunctive PBM was applied [29]. Reduced postoperative pain and edema are among the most consistently reported clinical benefits.

Laser-assisted wound healing may be particularly valuable in medically compromised patients such as diabetics, smokers, elderly individuals, and immunocompromised patients, all of whom may demonstrate impaired healing capacity [30].

Photobiomodulation has additionally been investigated in management of oral mucositis associated with chemotherapy and radiotherapy. Oral mucositis represents one of the most debilitating complications of cancer therapy and significantly affects quality of life [31]. PBM has demonstrated substantial efficacy in reducing mucositis severity, pain intensity, and healing duration.

Another important area involves soft tissue grafting and periodontal plastic surgery. Enhanced vascularization and collagen maturation following PBM may improve graft survival and esthetic outcomes [32].

Although many studies support the positive effects of PBM on wound healing, variability in treatment protocols remains a major limitation. Standardization of wavelength, dosage, irradiation timing, and treatment frequency is still needed to establish universally accepted clinical guidelines.

Photobiomodulation and Pain Control After Oral Surgery

Postoperative pain remains one of the most common concerns following oral surgical procedures and may significantly affect patient comfort, quality of life, nutritional intake, and functional recovery. Conventional pain management primarily relies on nonsteroidal anti-

inflammatory drugs (NSAIDs), corticosteroids, and opioid analgesics. However, pharmacological approaches may be associated with gastrointestinal complications, allergic reactions, drug interactions, and concerns regarding opioid overuse [33]. Consequently, nonpharmacological adjunctive approaches such as photobiomodulation have gained increasing interest in postoperative pain management.

The analgesic effects of PBM appear to involve several biological mechanisms. Laser irradiation may reduce peripheral nociceptor activity, modulate inflammatory mediator release, increase endogenous endorphin production, and improve local circulation [34]. Inflammatory cytokines such as prostaglandin E2, TNF-α, and IL-1β are reduced following PBM, thereby decreasing inflammatory pain signaling.

Third molar surgery represents one of the most extensively studied areas in postoperative PBM research. Impacted mandibular third molar extraction is commonly associated with pain, edema, and trismus [35]. Multiple clinical studies have demonstrated that adjunctive PBM may reduce postoperative pain intensity and analgesic consumption following third molar surgery.

Reduction of postoperative edema is another important clinical benefit. Laser therapy may improve lymphatic drainage and microcirculation while simultaneously reducing vascular permeability [36]. Several studies have reported reduced facial swelling following PBM application after dentoalveolar surgery.

Trismus reduction has also been investigated extensively. Postoperative muscular inflammation and edema may limit mouth opening after oral surgery. PBM may decrease muscle spasm and inflammatory edema, thereby improving functional recovery [37].

Temporomandibular disorder management represents another important indication for PBM-based analgesia. Chronic TMD pain is often multifactorial and difficult to manage. Studies have reported reduced pain intensity, improved mandibular movement, and enhanced muscle relaxation following laser therapy [38].

The noninvasive nature of PBM and its minimal adverse effects make it particularly attractive for repetitive applications in chronic pain management. Nevertheless, variability among treatment parameters and placebo-controlled study designs continue to create controversy regarding optimal protocols and long-term efficacy.

Photobiomodulation and Nerve Regeneration

Peripheral nerve injury represents a significant complication in oral and maxillofacial surgery. Inferior alveolar nerve, lingual nerve, and mental nerve injuries may occur following third molar extraction, implant placement, orthognathic surgery, trauma, tumor surgery, and local anesthesia administration [39]. Such injuries may lead to paresthesia, dysesthesia, hypoesthesia, pain, speech difficulties, and substantial reduction in quality of life.

Conventional management of nerve injuries includes observation, corticosteroid therapy, microsurgical repair, and supportive rehabilitation. However, functional recovery may be unpredictable and incomplete. Photobiomodulation has therefore emerged as a promising adjunctive therapy for enhancing neural regeneration [40].

Experimental studies suggest that PBM may stimulate axonal growth, Schwann cell proliferation, mitochondrial activity, and nerve conduction [41]. Increased ATP production and modulation of oxidative stress may improve cellular survival within injured neural tissues.

Laser therapy may additionally reduce inflammatory edema surrounding damaged nerves, thereby decreasing compression-related ischemia [42]. Improved local microcirculation and angiogenesis may further support neural repair.

Animal studies have demonstrated accelerated nerve regeneration and improved functional recovery following laser irradiation after peripheral nerve injury [43]. Histological analyses frequently reveal increased axonal density, improved myelin organization, and enhanced neural maturation in laser-treated groups.

Clinical studies involving inferior alveolar nerve injuries have also shown promising outcomes. Patients receiving adjunctive PBM following nerve injury have demonstrated improvements in sensory recovery, tactile perception, and pain reduction [44]. Similar benefits have been reported in lingual nerve injuries.

Implant-related nerve injuries represent another important application area. Early PBM intervention following neurosensory complications may potentially improve recovery outcomes and reduce chronic neuropathic pain development [45].

Despite encouraging findings, standardized treatment protocols remain lacking. Variability in wavelength selection, dosage, timing of intervention, and treatment duration complicates direct comparison between studies. Further randomized controlled clinical trials are therefore necessary to establish evidence-based recommendations.

Photobiomodulation and Implant Osseointegration

Dental implant therapy has become a predictable and widely accepted treatment modality for oral rehabilitation. Successful implant therapy depends largely on osseointegration, defined as the direct structural and functional connection between living bone and the implant surface [46].

Osseointegration involves complex biological events including inflammation, angiogenesis, osteoblastic differentiation, bone remodeling, and mineralization. Numerous factors such as systemic disease, smoking, bone quality, surgical trauma, and infection may negatively affect this process [47].

Photobiomodulation has been increasingly investigated because of its potential to enhance bone healing and implant stability. Experimental studies suggest that PBM stimulates osteoblastic proliferation, collagen synthesis, alkaline phosphatase activity, and mineralized matrix deposition [48].

Laser irradiation may additionally increase expression of osteogenic growth factors including bone morphogenetic proteins, transforming growth factor-beta, and vascular endothelial growth factor [49]. Enhanced angiogenesis is considered particularly important during early osseointegration because adequate vascular supply is essential for bone regeneration.

Animal studies have frequently demonstrated improved bone-to-implant contact and increased peri-implant bone density following PBM application [50]. Histomorphometric analyses often reveal accelerated bone maturation and enhanced trabecular organization in laser-treated groups.

Clinical studies have also reported improved implant stability quotient (ISQ) values following adjunctive PBM [51]. Such findings suggest that laser therapy may accelerate implant stabilization during the early healing period.

Immediate implant placement and immediate loading protocols may particularly benefit from enhanced osseointegration support. PBM may additionally be advantageous in compromised situations involving poor bone quality, smokers, elderly patients, diabetics, or medically compromised individuals [52].

Another important application involves sinus augmentation and guided bone regeneration procedures. Laser therapy may enhance graft integration and accelerate bone maturation in augmented areas [53].

Nevertheless, not all studies have demonstrated uniformly positive outcomes. Differences in laser parameters, implant systems, patient characteristics, and evaluation methods may contribute to inconsistent findings. Additional high-quality randomized clinical trials remain necessary to clarify the long-term clinical significance of PBM in implant dentistry.

Laser-Assisted Peri-Implantitis Therapy

Peri-implantitis is a biofilm-associated inflammatory disease characterized by peri-implant mucosal inflammation and progressive bone loss [54]. Management of peri-implantitis remains clinically challenging because of implant surface complexity and difficulties in achieving effective decontamination.

Laser-assisted therapies have gained substantial interest in peri-implantitis treatment because of their antimicrobial effects and ability to decontaminate implant surfaces [55]. Various laser systems including diode, Nd:YAG, Er:YAG, and CO_2 lasers have been investigated for this purpose.

Er:YAG lasers are among the most extensively studied systems because of their high affinity for water and minimal thermal damage to implant surfaces [56]. Studies suggest that Er:YAG laser decontamination may effectively reduce bacterial load while preserving implant surface integrity.

Diode lasers additionally demonstrate antimicrobial and anti-inflammatory effects and may improve soft tissue healing around implants [57]. Combined use of mechanical debridement and laser therapy has been associated with reductions in probing depth, bleeding on probing, and microbial colonization.

Photobiomodulation may also contribute to peri-implantitis management through modulation of inflammation and stimulation of tissue healing [58]. Improved fibroblast activity and angiogenesis may support peri-implant soft tissue repair following decontamination procedures.

Although laser-assisted peri-implantitis therapy appears promising, complete disease resolution remains difficult in advanced cases. Surgical regenerative approaches are often required in combination with decontamination procedures. Long-term maintenance and biofilm control remain essential for treatment success.

Photobiomodulation and Medication-Related Osteonecrosis of the Jaw

Medication-related osteonecrosis of the jaw is a severe complication associated primarily with antiresorptive and antiangiogenic medications such as bisphosphonates and denosumab [59]. MRONJ is characterized by exposed necrotic bone, impaired wound healing, chronic infection, and pain.

Management of MRONJ remains challenging because of compromised bone remodeling and reduced vascularity. Conservative treatment approaches often include antimicrobial therapy, chlorhexidine rinses, pain management, and limited surgical debridement [60].

Photobiomodulation has emerged as a potential adjunctive therapy because of its anti-inflammatory, angiogenic, analgesic, and regenerative properties. PBM may stimulate local microcirculation, reduce inflammation, and enhance tissue repair within necrotic areas [61].

Several clinical reports have demonstrated improvements in pain control, mucosal healing, and quality of life following adjunctive PBM in MRONJ patients [62]. Laser-assisted surgical debridement has additionally been investigated to improve removal of necrotic tissue while minimizing thermal injury.

Er:YAG and diode lasers are among the most frequently used systems in MRONJ management [63]. Laser-assisted surgery may improve bacterial reduction and promote more favorable soft tissue healing compared with conventional approaches.

Combination protocols involving surgery, antimicrobial therapy, platelet concentrates, and PBM appear particularly promising [64]. Regenerative adjuncts such as platelet-rich fibrin may further enhance tissue repair when combined with laser therapy.

Nevertheless, current evidence remains limited by relatively small sample sizes and heterogeneity among protocols. Additional controlled clinical studies are necessary to establish standardized treatment recommendations and determine long-term therapeutic effectiveness.

Applications of Laser-Assisted Therapies in Soft Tissue Surgery

Laser-assisted soft tissue surgery has become increasingly popular in oral and maxillofacial practice because of its precision, hemostatic properties, and minimally invasive nature. Conventional scalpel surgery often produces intraoperative bleeding, postoperative discomfort, and edema, whereas laser systems may improve surgical visibility and patient comfort [65].

Diode and CO_2 lasers are among the most frequently used systems for oral soft tissue procedures including frenectomies, fibroma excision, operculectomies, gingivectomies, biopsy procedures, and treatment of vascular lesions [66]. Laser energy produces simultaneous incision and coagulation, thereby reducing intraoperative bleeding and improving visualization of the surgical field.

Reduced postoperative pain is another important advantage of laser-assisted surgery. Thermal sealing of sensory nerve endings and lymphatic vessels may contribute to decreased pain and edema following laser procedures [67]. Consequently, some patients require lower postoperative analgesic consumption compared with conventional surgery.

Laser-assisted procedures may additionally reduce bacterial contamination within the surgical field. This antimicrobial effect may contribute to improved wound healing and reduced postoperative infection risk [68]. Such properties are particularly advantageous in medically compromised patients and contaminated oral environments.

In oral mucosal lesion management, laser excision may provide excellent tissue control and esthetic outcomes. Leukoplakia, papillomas, mucoceles, pyogenic granulomas, and vascular lesions have all been successfully treated using laser-assisted techniques [69]. However, appropriate laser parameter selection remains essential to avoid excessive thermal tissue damage and histopathological artifact formation.

CO_2 lasers are especially effective for superficial mucosal surgery because of their shallow penetration depth and precise cutting capability [70]. Erbium lasers may additionally be used for combined soft and hard tissue applications, particularly in periodontal and peri-implant surgery.

Patient acceptance of laser-assisted procedures is generally high because of reduced bleeding, minimal suturing requirements, decreased postoperative discomfort, and shorter recovery periods [71]. Nevertheless, adequate operator training and understanding of laser-tissue interactions are essential to ensure safe and predictable outcomes.

Limitations and Challenges of Photobiomodulation and Laser Therapy

Despite the growing popularity of PBM and laser-assisted therapies in oral surgery, several important limitations and controversies remain. One of the major challenges involves the lack of standardized treatment protocols. Considerable variability exists among studies regarding wavelength selection, power output, irradiation duration, pulse frequency, treatment intervals, and energy density [72].

The biphasic dose-response phenomenon further complicates treatment optimization. Low laser doses may produce insufficient biological stimulation, whereas excessively high doses may inhibit cellular activity or produce unwanted thermal effects [73]. Consequently, determination of optimal parameters remains one of the most important research priorities in PBM.

Another limitation involves variability in tissue penetration among different laser wavelengths. Penetration depth depends on tissue composition, pigmentation, vascularity, and wavelength characteristics [74]. Therefore, clinical outcomes may vary significantly depending on anatomical location and tissue type.

The quality of available evidence also remains heterogeneous. Although many studies report beneficial outcomes, differences in methodology, sample size, placebo control, and follow-up duration may affect reliability and reproducibility [75]. High-quality randomized controlled clinical trials are still required in several application areas.

Cost and equipment availability may additionally limit widespread implementation. Advanced laser systems may require substantial financial investment and specialized training [76]. Operator experience plays a critical role in achieving safe and effective clinical outcomes.

Safety considerations are also important. Improper laser use may cause thermal injury, delayed healing, excessive tissue carbonization, ocular damage, or unintended damage to adjacent anatomical structures [77]. Appropriate protective measures and adherence to safety protocols are therefore mandatory during laser-assisted procedures.

Despite these limitations, continuing technological improvements and increasing clinical experience are expected to further refine laser applications and improve evidence-based protocol development.

Future Perspectives

The future of photobiomodulation and laser-assisted therapies in oral surgery appears highly promising. Continuous technological advances, improved understanding of laser-tissue interactions, and increasing interest in minimally invasive therapies are expected to expand clinical applications substantially [78].

Artificial intelligence and digital technologies may play a major role in future laser therapy optimization. AI-assisted systems could potentially determine individualized treatment parameters based on patient-specific tissue characteristics, disease severity, and biological responses [79]. Such personalized approaches may significantly improve therapeutic predictability.

Another important future direction involves integration of PBM with regenerative medicine. Combination approaches involving stem cells, platelet concentrates, biomaterials, growth factors, and laser therapy may enhance tissue regeneration and accelerate healing in complex surgical procedures [80].

Nanotechnology-based photosensitive materials and targeted phototherapy systems are also being investigated. Such technologies may allow selective activation of regenerative or antimicrobial pathways while minimizing collateral tissue effects [81].

Wireless portable PBM devices and chairside biosensor integration may additionally increase accessibility and facilitate postoperative home-based therapy protocols [82]. These developments could improve patient compliance and reduce clinical workload.

Further research is also expected in the fields of neural regeneration, peri-implant disease management, bone engineering, and MRONJ therapy. As evidence continues to accumulate, PBM may become a routine adjunctive modality in many oral surgery procedures.

Standardization of clinical guidelines remains critically important for future progress. International collaboration and multicenter clinical trials will be essential to establish universally accepted evidence-based treatment protocols [83].

Conclusion

Photobiomodulation and laser-assisted therapies have become increasingly important components of modern oral and maxillofacial surgery. Through photochemical and photobiological mechanisms, PBM influences cellular metabolism, inflammation, angiogenesis, collagen synthesis, and tissue regeneration without causing significant thermal damage.

Current evidence supports the beneficial effects of PBM in wound healing enhancement, postoperative pain reduction, edema control, nerve regeneration, implant osseointegration, peri-implantitis management, and adjunctive MRONJ therapy. Laser-assisted surgical techniques additionally provide important advantages including improved hemostasis, reduced bacterial contamination, enhanced surgical precision, and improved patient comfort.

Among the most promising applications are postoperative recovery after dentoalveolar surgery, management of temporomandibular disorders, enhancement of implant stability, and support of regenerative surgical procedures. Experimental and clinical studies suggest that PBM may significantly influence both soft tissue and bone healing processes.

Nevertheless, important challenges remain regarding treatment parameter standardization, protocol reproducibility, and long-term evidence quality. Variability among wavelengths, energy densities, irradiation times, and treatment frequencies continues to limit direct comparison between studies.

Future developments involving artificial intelligence, regenerative medicine, biosensor integration, and personalized laser protocols are expected to further expand the role of PBM and laser-assisted therapies in oral surgery. Continued interdisciplinary research and high-

quality clinical trials will be essential for establishing standardized evidence-based recommendations.

Overall, photobiomodulation and laser-assisted therapies represent highly promising adjunctive approaches capable of improving clinical outcomes, reducing postoperative morbidity, and supporting minimally invasive patient-centered oral surgical care.

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CHAPTER 4

ABSOLUTE ISOLATION IN RESTORATIVE DENTISTRY: RUBBER DAM APPLICATIONS AND THEIR IMPACT ON CLINICAL SUCCESS

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1. GENERAL INFORMATION

Absolute isolation of the operative field is regarded as one of the fundamental procedures in modern restorative dentistry. This concept was first introduced in 1864 by dentist Sanford Christie Barnum, and the isolation method based on the use of a rubber sheet was presented as an innovative approach for restorative treatments. Over time, this technique has developed into an important clinical procedure, particularly for improving the success of adhesive restorations. Absolute isolation separates the tooth to be treated from the oral environment by means of a rubber barrier, thereby preventing saliva, blood, and other oral contaminants from reaching the working field. As a result, a drier, cleaner, and more controlled operative environment is established, improving the performance of restorative materials and the long-term success of restorations. In addition, rubber dam use is widely preferred in contemporary restorative dentistry because it improves visibility of the operative field, protects soft tissues, and enhances patient safety (Alkhatib, Bissasu, & Daud, 2023).

Today, the majority of procedures performed in restorative dentistry are based on adhesive systems. Therefore, the clinical success of restorations is closely related not only to the properties of the material used but also to the strength and continuity of the bond formed between the dental tissues and the restorative material. Achieving adequate and durable adhesion plays a key role in preventing marginal gap formation, bacterial leakage, postoperative sensitivity, secondary caries, and restoration loss (De Munck et al., 2005; Jacquot et al., 2012).

In addition to appropriate material selection, adhesive protocols and application techniques must be followed meticulously to improve clinical outcomes and ensure the long-term success of restorations. The quality of the resin-adhesive-tooth interface is influenced by the chemical composition of adhesive agents, polymerization protocols, and the accuracy of clinical application steps, as well as by the environmental conditions to which the materials are exposed. In particular, factors such as temperature and humidity may affect the success of adhesive procedures and the durability of bonding; therefore, controlling these conditions during application is of considerable importance (Bicalho et al., 2015; Finger & Tani, 2002).

The amount of saturated water vapor contained in exhaled air is an important environmental factor that is often overlooked during adhesive restorative procedures. However, the moisture transferred to the oral environment through respiration has been reported to be approximately 27 mg/dm³, and this level is considered to have potential adverse effects, particularly on the sensitive bonding interface where adhesive systems are applied (Varègne, Ferrus, Manier, &

Gire, 1986). Maintaining an ideal moisture balance on enamel and dentin surfaces during adhesive procedures is critical for bonding success. Accordingly, it should be considered that additional moisture originating from exhaled air may affect surface wetting by the adhesive material, monomer infiltration, solvent evaporation, and polymerization efficiency. Because dentin is structurally a moist substrate with a high organic content, the bonding interface becomes more susceptible to changes in environmental humidity (Falacho et al., 2023; Plasmans, Creugers, Hermsen, & Vrijhoef, 1994).

The intraoral environment is a dynamic structure that continuously varies in terms of temperature and humidity. The mean intraoral temperature has been reported to be approximately 30°C, while relative humidity is approximately 80%; however, humidity levels may range from 74% to 94%. This variability requires adhesive protocols to be applied with greater precision under clinical conditions than in laboratory settings. Relative humidity may be influenced by several factors, including the position of the teeth within the dental arch, whether the patient breathes through the mouth or nose, salivary flow, the degree of isolation of the working field, and the use of protective isolation methods such as rubber dam (Falacho et al., 2023; Plasmans et al., 1994). Particularly in the posterior region, where moisture control is more difficult and exposure to respiratory air is greater, the risk of contamination during adhesive procedures may increase. Therefore, restorative procedures should consider not only salivary isolation but also the control of moisture originating from respiration; the stability of the bonding interface should be supported through appropriate isolation methods. The clinical appearance before and after rubber dam isolation in the posterior region is shown in Figure 1A-B.

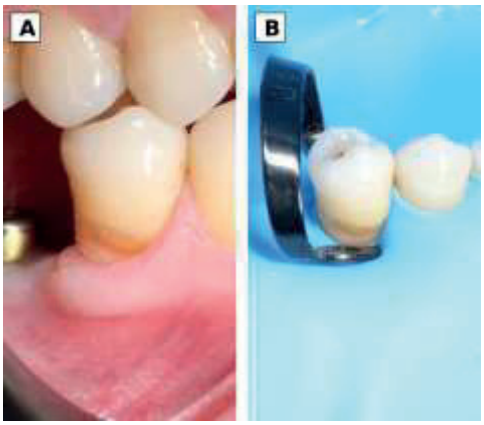

Figure 1A-B. Clinical appearance before rubber dam isolation in the posterior region (A) and control of the operative field after isolation (B).

Rubber dam isolation is considered one of the most effective methods for controlling the operative field in restorative dentistry. One of its most important advantages is that it reduces the level of moisture in the operating field, thereby creating a more stable and controlled environment for adhesive procedures. Preventing contaminants such as saliva, blood, and gingival crevicular fluid from reaching the working area contributes to the effective application of adhesive materials on enamel and dentin surfaces, more controlled evaporation of solvents, and the more reliable formation of the bonding interface. This is particularly important in procedures involving resin-based restorative materials, because adhesive systems are highly sensitive to moisture contamination, and even small amounts of contamination on the bonding surface may lead to clinical problems such as microleakage, reduced bond strength, marginal discoloration, postoperative sensitivity, and restoration failure (Ahmad, 2009; Haruyama et al., 2014).

In restorative dentistry, rubber dam isolation is regarded as a fundamental method that increases the predictability of clinical procedures, particularly in adhesive applications. Nevertheless, absolute isolation is not always implemented as a routine step in daily practice. Although it is strongly supported in the literature and by clinical authorities, rubber dam usage rates have not reached the expected level. This indicates a marked discrepancy between the scientific acceptance of the method and its application in clinical practice (Comunello et al., 2025).

Reasons for clinicians' avoidance of rubber dam use include concerns regarding patient acceptance, the belief that application time will be prolonged, technical difficulties, additional costs, and established habits. For this reason, relative isolation methods such as cotton rolls, saliva ejectors, high-volume suction systems, and lip-cheek retractors are preferred in some restorative procedures. Although these methods may reduce visible fluid contamination to a certain extent, they may be limited in controlling the moisture introduced into the oral environment through the patient's respiration. However, in adhesive protocols, the moisture balance of the bonding surface is one of the critical factors that directly affects the success of the restoration (Comunello et al., 2025; Madarati et al., 2018).

Effective isolation is not limited solely to the placement of a rubber dam sheet. For a successful clinical outcome, appropriate material selection, the correct isolation strategy, and careful execution of the technique should be considered together. Isolation procedures performed without planning or without adequate mastery of the clinical steps may result in time loss, reduced patient comfort, and difficulties during application. Similarly, even when the clinician

has sufficient technical knowledge, the selection of an inappropriate clamp, dam sheet, or auxiliary isolation material may reduce the effectiveness of the procedure. Therefore, rubber dam isolation should be regarded as a comprehensive clinical approach in which material, strategy, and technical components are managed together (Shakibaie, Conejo, & Abdulqader, 2025; Yu, 2022).

The long-term success of adhesive restorative treatments does not depend solely on the properties of the selected restorative material. The quality of the interface formed between dental tissue, the adhesive system, and the resin material is affected by the chemical composition of the adhesive, the application protocol, the solvent removal step, polymerization conditions, and environmental factors. Therefore, isolation should not be considered merely a mechanical auxiliary procedure that keeps the operative field dry, but rather a critical clinical step that supports bond strength, marginal integrity, and the clinical longevity of restorations (Comunello et al., 2025).

Nevertheless, the effect of absolute isolation provided by rubber dam or relative isolation provided by methods such as cotton rolls, saliva ejectors, and high-volume suction on clinical outcomes remains an important topic of discussion in restorative dentistry. From the clinician's perspective, the main question is to what extent the isolation method affects clinical outcomes such as the long-term success of restorations, marginal adaptation, secondary caries development, and restoration loss. Although relative isolation methods may appear practical and sufficient in some clinical situations, the success of adhesive procedures may be adversely affected when intraoral moisture cannot be fully controlled. Therefore, particularly in adhesive restorations where moisture control is critical, rubber dam isolation should be considered not merely an auxiliary procedure but a fundamental clinical step that enhances treatment quality and predictability (Ahmad, 2009).

Clinical examples of cavity preparation performed under rubber dam isolation in the posterior region are shown in Figure 2A-C.

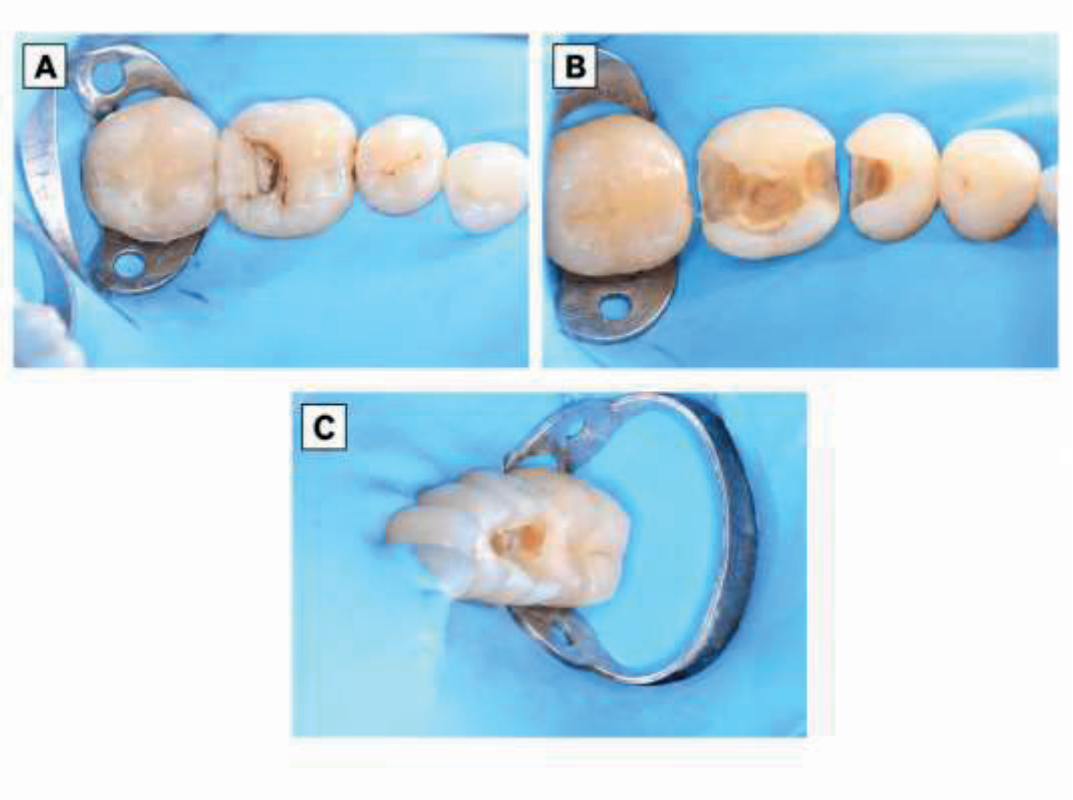

Figure 2A-C. Clinical appearance of a carious lesion under rubber dam isolation in the posterior region (A), appearance after cavity preparation (B), and evaluation of the preparation from a different angle (C).

Although conventional rubber dam isolation is a fundamental procedure in restorative dentistry for achieving moisture control and adhesive success, complete adaptation of the dam around the tooth may be difficult in some clinical situations. In particular, cervical substance loss, deep carious lesions, anatomical irregularities, or procedures close to the gingival margin may lead to the formation of microgaps in the isolation area. In such cases, light-curing resin-based liquid rubber dam materials can be used as auxiliary barriers that support conventional rubber dam isolation. Initially used to protect gingival tissues during bleaching procedures, these materials are currently also considered for closing gaps between the rubber dam sheet and the tooth, strengthening isolation, and creating a temporary barrier in the cervical region (Malcangi et al., 2023). Among liquid rubber dam materials, OpalDam™ is a light-curing methacrylate-based passive adhesive resin barrier used particularly to protect gingival tissues and adjacent teeth during tooth bleaching procedures. Similarly, Top dam is a directly applicable, light-curing composite-based gingival barrier material designed to provide an impermeable seal for the isolation and protection of soft tissues. Both materials are considered auxiliary isolation materials that are easy to apply clinically and practical to remove after the procedure. Owing to these properties, they may be used as supportive materials for conventional rubber dam

application or as an alternative barrier option in limited areas, particularly in certain clinical situations where absolute isolation is not required or relative gingival isolation is considered sufficient (Kharouf et al., 2024).

In the in vitro study by Kharouf et al. (2024), two different liquid rubber dam materials were reported not to allow methylene blue infiltration over periods of 30, 60, and 90 minutes and to provide an effective seal at the interface between the tooth surface and the material. However, Top dam showed higher bond strength to enamel than OpalDam, although this may make removal of the material more difficult at the end of the procedure. In addition, while no marked surface changes were observed with 3% sodium hypochlorite, 17% EDTA, or artificial saliva, 37% phosphoric acid and bleaching agents were reported to cause microporosity and morphological changes on the material surface. Therefore, liquid rubber dams should be regarded not as substitutes for conventional rubber dam, but as auxiliary materials that reinforce isolation, particularly in adhesive restorations, bleaching applications, and situations in which rubber dam adaptation is insufficient.

2. RUBBER DAM SET COMPONENTS

For rubber dam isolation to be applied correctly and effectively in clinical practice, a basic set must be prepared. A standard rubber dam set consists of a rubber dam sheet, punch forceps, clamp, clamp forceps, rubber dam frame, lubricant, rubber dam napkin, and dental floss (Borges, Torres, Benetti, & Bakhshandeh, 2019; Yu, 2022). Rubber dam sheets are generally produced in different colors, thicknesses, and sizes. Because single-tooth isolation is usually sufficient in endodontic procedures, 5×5-inch sheets may be used, whereas 6×6-inch sheets are more advantageous in restorative procedures when multiple teeth need to be isolated simultaneously (Browet & Gerdolle, 2017). Punch forceps are used to create holes with diameters appropriate for the teeth to be isolated, and the creation of smooth, round, tear-resistant holes is important for isolation success. Clamps are the main retentive elements that stabilize the rubber dam sheet on the tooth, and appropriate clamp selection directly affects the success of isolation. Clamp forceps allow the clamp to be opened and safely placed on the tooth. The rubber dam frame maintains the tension of the sheet and contributes to lip and cheek retraction. In addition, lubricant facilitates the passage of the sheet through contact areas and around tooth contours, whereas rubber dam napkins reduce direct contact between the sheet and the patient's skin and improve patient comfort by absorbing saliva accumulation. Dental floss

is used both for controlling contact areas and for securing the clamp against possible aspiration or swallowing (Ahmad, 2009; Borges et al., 2019).

A clinical example in which multiple posterior teeth are isolated simultaneously is presented in Figure 3.

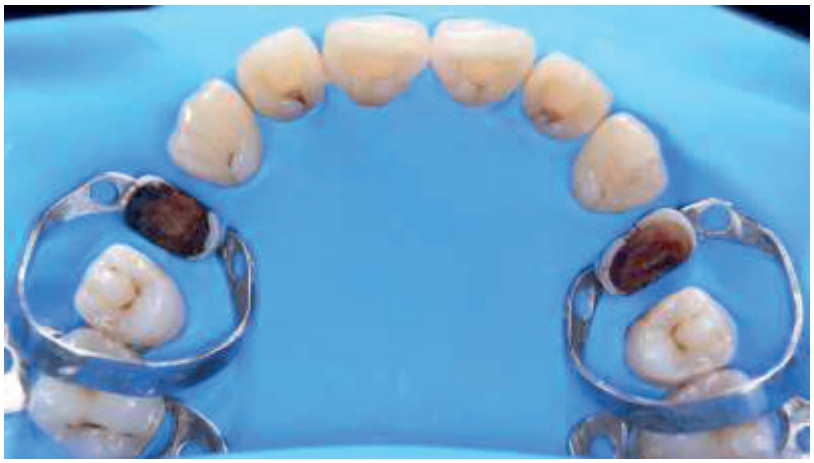

Figure 3. Clinical appearance of bilateral multiple-tooth isolation in the posterior region.

3. TYPES OF RUBBER DAM SHEETS

Rubber dam sheets can be classified into different types according to their material properties, elasticity, latex content, and ease of use. Conventional latex rubber dam sheets have been widely used for many years because of their high elasticity and good adaptation in the cervical region. However, latex-free alternatives should be preferred in patients with latex allergy. Non-latex rubber dam sheets developed for this purpose are particularly important in patients with a history of allergy because they reduce the risk of latex reactions, have a powder-free structure, and, in some products, show greater tear resistance (Alani & Patel, 2026; Sakhare & Goyal, 2023). Hygenic rubber dam is a synthetic, powder-free, medium-thickness dam type developed for patients with latex allergy. Derma dam is a non-latex rubber dam type designed to reduce the likelihood of allergic reactions and dermatitis owing to its low surface protein content. Flexi dam has an elastic plastomer structure and is a latex-free, highly flexible, tear-resistant sheet; it contributes to obtaining a dry working field by providing good adaptation in the cervical region. Contrasting color options such as blue and purple may help provide clearer visualization of the operative field, particularly during esthetic restorative procedures (Ballal, Khandelwal, & Saraswathi, 2013; Lozada, Junqueira, Rondón, Carlo, & Soares, 2024; Sengupta, Pandit, Gandhe, Gujrathi, & Chaubey, 2019).

4. TYPES OF RUBBER DAM FRAMES

Rubber dam frames are auxiliary components that maintain the tension of the sheet and keep the operative field open. Young-type frames are among the conventional metal frames, whereas plastic and radiolucent frames may offer advantages particularly in endodontic procedures requiring radiographic imaging. Because of their transparent structure, plastic frames do not obstruct the field of view; however, some models may be bulkier than metal frames. The articulated frame developed in modern systems provides clinical convenience because its foldable structure facilitates radiographic exposure, administration of additional local anesthesia, or removal of intraoral fluids. New frame systems such as Safe-T-frame aim to increase patient comfort through locking mechanisms that securely hold the rubber dam sheet and edge designs that help reduce fluid leakage. Such frames may make clinical application more tolerable by reducing the discomfort that conventional frames can cause around the nose and mouth (Ahlers, 2003; Bhuva, San Chong, & Patel, 2008; Kamath, 2019; Sakhare & Goyal, 2023).

5. PRE-FRAMED RUBBER DAM SYSTEMS

In conventional rubber dam application, the sheet, punching procedure, clamp, and frame are prepared separately, whereas pre-framed systems have been developed to shorten the procedure time and facilitate application. Insti dam is a system that incorporates a flexible and radiolucent nylon frame and eliminates the need for a separate frame. Its prefabricated hole design shortens placement time, and the ability of the frame to bend when radiographs are required provides clinical convenience. Handi dam is also one of the pre-framed rubber dam types that eliminates the need for a conventional frame and can be applied quickly and easily. Dry dam is an alternative system in which a small rubber dam sheet is supported by an absorbent paper layer and elastic bands passing over the ears; it may be used for rapid isolation particularly in the anterior region, but it has limited use for posterior tooth isolation and bleaching procedures. Framed Flexi dam, with its non-latex structure and integrated flexible frame, aims both to increase patient comfort and to eliminate the risk of latex allergy (Haruyama et al., 2014; Rahul et al., 2024; Sengupta et al., 2019; Wong, Zou, Zhou, Li, & Wang, 2021).

6. ANATOMICAL AND SPECIALLY DESIGNED RUBBER DAM SYSTEMS

In recent years, in addition to conventional flat rubber dam sheets, three-dimensional systems that better adapt to anatomical structures have also been developed. OptiDam is a rubber dam

system designed to adapt to oral anatomy through its three-dimensional form and nipple-like protruding design. It has different versions for anterior and posterior use. In this system, application can be performed by cutting the protruding areas without the need for separate marking of tooth positions or a conventional punching procedure. This feature may reduce application time while improving the field of view and working comfort. OptraDam is a system that combines the advantages of lip and cheek retraction with rubber dam isolation. Owing to its anatomical shape, high elasticity, and inner ring design, it can be applied in most cases without the need for a separate frame or clamp. The ability to create a broad working field, increase patient comfort, and provide isolation in both arches simultaneously offers important advantages in restorative procedures (BaHammam et al., 2025; Kapitán, Sustova, Ivancakova, & Suchánek, 2014; Sezen Erhamza, Küçük, & Malikov, 2025; Tiwari et al., 2023).

7. TYPES OF RUBBER DAM CLAMPS

Clamps are the most important components that enable the rubber dam sheet to attach to the tooth, and they should be selected according to the position of the tooth, crown morphology, eruption status, and existing tissue loss. In general, clamps are classified as winged and wingless. Winged clamps are suitable for placement together with the rubber dam sheet, whereas wingless clamps may be preferred particularly in the posterior region, in patients with thick cheeks, or in situations where the working field is limited because they are less bulky. Different numbered clamps are used for anterior teeth, premolars, and molars; in addition, special clamp types may be selected for asymmetric molars, partially erupted teeth, short clinical crowns, or teeth with crown preparations. It is recommended that clamps be secured with dental floss against the risk of fracture or dislodgement (Bhuva et al., 2008; Bud, 2024; Doshi, Shah, Kumar, Shah, & Kotecha, 2023; Klubcharoen, Phumpatrakom, & Krajangta, 2025; Sengupta et al., 2019).

In anterior restorations, appropriate clamp selection and cervical adaptation of the rubber dam sheet are important for maintaining a stable operative field and sustaining moisture control. Clinical examples of clamp stabilization in the anterior region are shown in Figure 4A-B.

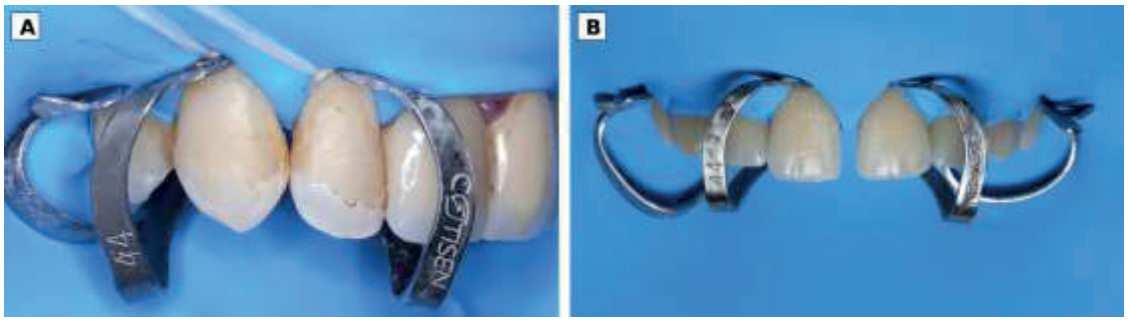

Figure 4A-B. Clinical appearance of clamp stabilization, cervical adaptation, and operative field control during rubber dam isolation in the anterior region.

8. MODIFIED AND ADVANCED CLAMP TYPES

Because clinical conditions are not always ideal, modified clamp types are required in some special situations. Clamps with long protective extensions help protect soft tissues by retracting the cheek and tongue in addition to providing isolation. The Tiger clamp provides better stabilization particularly in partially erupted, fractured, or poorly retentive teeth owing to its serrated jaw structure. The S-G (Silker-Glickman) clamp is a special clamp type with an anterior extension that can be used in teeth with severe substance loss; while it provides rubber dam retraction around the tooth to be treated, the clamp can be placed on the adjacent tooth. The Super clamp is a system with special extensions that facilitate single-tooth isolation and protect the cheek and tongue, and it can be used particularly in the premolar and molar regions. Gold-colored clamps are designed to increase retention through diamond-particle structures on their jaw surfaces. These special clamp options may improve isolation success particularly in challenging cases involving short clinical crowns, partial eruption, fractured teeth, or subgingivally located restorative margins (Bhomavat, Manjunatha, Rao, & Kidiyoor, 2009; Hegde, 2014; Nugroho & Utami, 2020; Sakhare & Goyal, 2023).

9. RUBBER DAM ACCESSORIES

Various auxiliary accessories may be used to improve the effectiveness of rubber dam isolation and patient comfort. Cushees are soft thermoplastic clamp cushions that reduce direct contact between the clamp and the tooth or gingiva. These accessories increase patient comfort and may reduce trauma to enamel, restorations, and soft tissues. They also contribute to reducing leakage by improving clamp stability. Wedjets are elastic stabilization cords made of natural latex rubber and are used to retain the rubber dam sheet particularly in interproximal areas. They may offer a more comfortable alternative to conventional metal clamp use and provide

practical advantages especially in the isolation of anterior teeth ((Sengupta et al., 2019; West, Chivian, Arens, & Sigurdsson, 2018).

CONCLUSION

In conclusion, isolation protocols play a critical role in achieving successful and long-lasting treatment outcomes in restorative dentistry. Particularly in adhesive restorations, protecting the bonding interface from saliva, blood, gingival crevicular fluid, and respiration-related moisture is of great importance for ensuring marginal integrity, reducing microleakage, preventing postoperative sensitivity, and increasing the clinical longevity of restorations. Rubber dam isolation is one of the most effective methods for meeting these requirements and should be regarded as an indispensable clinical step in restorative procedures because it enhances control of the operative field, improves visibility, protects soft tissues, and contributes to patient safety. However, isolation success does not depend solely on the placement of the rubber dam sheet; the appropriate selection and clinically appropriate use of the dam sheet, clamp, frame, auxiliary accessories, and, when necessary, supportive materials such as liquid rubber dam are required. Therefore, rubber dam isolation should be considered not merely as a technical auxiliary procedure but as one of the main determinants of adhesive success, clinical predictability, and the long-term success of restorative treatments.

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