SELINUS UNIVERSITY
OF SCIENCES AND LITERATURE

Periodontal Tissue Regeneration in Reconstructive/Regenerative Periodontal Surgery with or without the Adjunctive Use of Laser Devices. A Systematic Review of Literature and Meta-Analysis

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A DISSERTATION

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Declaration

TO WHOM IT MAY CONCERN:

I hereby declare that the present dissertation entitled:

“Periodontal Tissue Regeneration in Reconstructive/Regenerative Periodontal Surgery with or without the Adjunctive Use of Laser Devices. A Systematic Review of Literature and Meta-Analysis”

Which I am submitting for the Degree of Doctor of Philosophy

in Regenerative Cellular Therapy, is:

1) my own work except where states otherwise by reference or acknowledgment.

I also confirm that:

2) the thesis presented has not been submitted, in whole or in part, in any previous application for a degree or professional qualification.

Finally, I certify that

3) the work of the dissertation has not been presented to any other university or institute of learning.

Acknowledgements

Citation

“Learning Never Exhausts the Mind”

Leonardo Da Vinci

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Dedication

To my beloved Mom who still lends me a hand and has faith in me from above, your love and guidance have shaped me into the person I am today. Thank you for everything you've done for me.

Abstract

Background: Periodontal regeneration aims to restore lost tooth-supporting structures. Conventional regenerative approaches, while effective to some extent, often lack predictability and may cause postoperative discomfort. The adjunctive use of lasers has been proposed to enhance healing, reduce morbidity, and improve regenerative outcomes; however, their effectiveness need to be further assessed and explored.

Aim: This systematic review of literature and meta-analysis evaluated the effectiveness of regenerative periodontal therapy with or without the adjunctive use of lasers, focusing on clinical, radiographic, and patient-centered outcomes (PCOs).

Methods: An electronic and manual search was conducted across major databases including PubMed (MEDLINE), Scopus, and Web of Science, using carefully selected keywords and Medical Subject Headings (MeSH) terms to address the research question on the effectiveness of regenerative periodontal therapy with or without laser use. Out of 770 articles, 18 randomized controlled trials and controlled clinical studies comparing regenerative periodontal therapy with or without lasers were included, following predefined inclusion and exclusion criteria. Data extraction, qualitative assessment, and risk of bias evaluation were performed using standardized tools. Meta-analysis was conducted to assess evaluable outcomes such as probing depth (PD) reduction and clinical attachment level (CAL) gain. For the remaining outcomes, including bleeding on probing (BoP), gingival recession (GR), radiographic bone (RB) gain, and PCOs a descriptive synthesis was provided.

Results: Analysis revealed heterogeneity in sample size, follow-up period, and methodology. Meta-analysis demonstrated that adjunctive laser use provided modest but significant improvements in PD reduction (MD = +0.22 mm; p <; 0.001), while showed a statistically significant and clinically meaningful CAL gain (+0.99 mm). RB gain and PCOs presented variable findings across studies. Importantly, BoP and suppuration showed marked resolution postoperatively, underscoring the effectiveness of these

interventions in controlling inflammation. GR was generally minimal, reinforcing the safety profile of regenerative therapies with respect to marginal tissue preservation.

Conclusion: The adjunctive use of lasers in regenerative periodontal therapy may enhance clinical outcomes like PD, CAL, RB gain but evidence regarding PCOs and long-term stability remains inconclusive. The risk of bias assessment indicated that while several studies exhibited low risk, methodological inconsistencies like high heterogeneity limited the strength of pooled evidence and its generalisability to the larger population is inconsistent. Further large-scale, well-designed randomized controlled trials are warranted to establish definitive clinical recommendations.

Keywords: *regenerative periodontal therapy, lasers, systematic review, meta-analysis, clinical attachment level, probing depth, patient-centered outcomes.*

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iv. List of Abbreviations

AAP-	American Academy of Periodontology
BI-	Bleeding Index
BMPs-	Bone Morphogenetic Proteins
BoP -	Bleeding on Probing
CAF-	Coronally Positioned (Advanced) Flap
CAL-	Clinical Attachment Level
CBCT-	Cone-Beam Computed Tomography
CI-	Confidence Interval
CGF-	Concentrated Growth Factor
CO_2-	Carbon Dioxide
DBM-	Demineralized Bone Matrix
DFDBA-	Demineralized Freeze-Dried Bone Allografts
EDTA-	Ethylenediaminetetraacetic Acid
EGF-	Epidermal Growth Factor
EMD-	Enamel Matrix Derivative
EMP-	Enamel Matrix Protein
ePTFE-	Expanded Polytetrafluoroethylene
Er, Cr: YSGG-	Erbium,Chromium-doped: Yttrium, Scandium, Gallium, Garnet
Er:YAG-	Erbium-doped: Yttrium Aluminium Garnet
FDBA-	Freeze-Dried Bone Allografts
FGFs-	Fibroblast Growth Factors
FII-	Furcation Involvement Index
GaAlAs-	Gallium Aluminium Arsenide

Ga-As-	Gallium-Arsenide
GBI-	Gingival Bleeding Index
GBR-	Guided Bone Regeneration
GI-	Gingival Index
GR-	Gingival Recession
GTR-	Guided Tissue Regeneration
He-Ne-	Helium-Neon
Ho:YAG-	Holmium-doped: Yttrium Aluminium Garnet
IGFs-	Insulin-like Growth Factors
kDa-	KiloDalton
KTP-	Potassium Titanyl Phosphate
LANAP-	Laser-Assisted New Attachment Procedure
LILT-	Low-Intensity Laser Therapy
LLLT-	Low-Level Laser Therapy
MD-	Mean Difference
MeSH-	Medical Subject Headings
Nd:YAG-	Neodymium-doped: Yttrium Aluminium Garnet
Nd:YAP-	Neodymium-doped: Yttrium Aluminium Perovskite
NSPT-	Non-Surgical Periodontal Treatment
OFD-	Open Flap Debridement
OH-	Oral Hygiene
PCO-	Patient-Centered Outcomes
PD-	Probing Depth
PDGFs-	Platelet-Derived Growth Factors

PDL-	Periodontal Ligament
PGA-	Polyglycolic Acid
PI-	Plaque Index
PeI-	Periodontal Index
PrI-	Prediction Interval
PLA-	Polylactic Acid
PPD-	Probing Pocket Depth
PPE-	Personal Protective Equipment
PRF-	Platelet-Rich Fibrin
PRISMA-	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRP-	Platelet-Rich Plasma
PTH-	Parathyroid Hormone
RB-	Radiographic Bone
RevMan-	Review Manager
RCT-	Randomized Controlled Trial
SBI-	Sulcus Bleeding Index
SD-	Standard Deviation
SE-	Standard Error
SRP-	Scaling and Root Planing
TGF-β-	Transforming Growth Factor-Beta
VAS-	Visual Analog Scale
VEGF-	Vascular Endothelial Growth Factor
WHO-	World Health Organization
YAG-	Yttrium-Aluminum-Garnet

PART I - Introduction and Literature Review

CHAPTER 1- Introduction

I.1.1 Background of the Study

The aim of periodontal treatment encompasses both halting the progression of periodontitis caused by bacterial plaque along with its by-products and regenerating the loss of periodontal tissues during the evolution of the disease (Wang and Cooke, 2005; Behdin *et al*., 2015). Regenerative periodontal therapy combines advanced surgical techniques with biomaterials specifically designed to promote the regeneration of tooth-supporting structures. This approach results in the resolution of inflammation, reduction in probing pocket depth (PPD) and clinical attachment level (CAL) gain, and radiographic evidence of bone regeneration (Jepsen *et al*., 2008). Research suggests that the choice of biomaterials for regenerating periodontal tissues is crucial and should be guided by well-defined biological and clinical criteria. This concept requires robust preclinical research elucidating their mechanisms of action and detailed assessment of clinical effectiveness through human histological analysis and randomized controlled trials (RCTs) (Jepsen *et al*., 2008). According to available literature, guided tissue regeneration (GTR) with non-resorbable or bioresorbable membranes and enamel matrix derivative (EMD) are among the most well-documented treatment options for periodontal regeneration, either used alone or in addition to bone grafting materials (Sculean *et al*., 2008; Sanz *et al*., 2020). Although current evidence suggests that some regeneration occurs following conventional regenerative procedures, obtaining complete periodontal tissue regeneration remains challenging due to the complexities involved in biological processes and cellular interactions (Wang and Cooke, 2005). Consequently, while these procedures can be effective to varying degrees, they often lack predictability and are frequently associated with postoperative pain and discomfort.

To address these limitations and enhance periodontal healing, lasers (Light Amplification by Stimulated Emission of Radiation) have been introduced as adjunctive tools (Schwarz

et al.,2008; Behdin *et al*., 2015). Commonly used lasers in periodontal flap surgeries include carbon dioxide (CO_2), neodymium-doped, yttrium aluminum garnet (Nd:YAG), erbium-doped, yttrium aluminum garnet (Er:YAG), and diode lasers. These devices offer advantages over conventional surgical procedures, including precise tissue ablation, vaporization, effective hemostasis, periodontal pocket disinfection, and reduced postoperative morbidity (Behdin *et al*., 2015). While the use of laser as an adjunct to non-surgical periodontal therapy (NSPT) has shown promising improvements in clinical outcomes (Schwarz *et al*., 2008), their effectiveness in surgical periodontal therapy remains an area requiring further investigation.

I.1.2 Statement of the Problem

Conventional regenerative periodontal therapy often does not have enough of predictability and cause significant postoperative discomfort, limiting their effectiveness in achieving most favorable regenerative outcomes. Laser devices, as adjuncts in periodontal surgery, have shown several beneficial effects such as precision in tissue ablation, hemostasis, and reduced morbidity. However, their efficacy in surgical periodontal therapy remains inadequately explored, necessitating further research**.**

In light of this, the aim of this literature review is to assess and compare the efficacy of regenerative periodontal therapy with or without the laser use.

I.1.3 Objectives of the Study

The purpose of this literature review is to evaluate and compare the efficacy of regenerative periodontal therapy with or without the laser use.

Specific objectives:

- To evaluate and compare the effectiveness of regenerative periodontal therapy with or without the use of laser based on clinical parameters.
- To evaluate and compare the effectiveness of regenerative periodontal therapy with or without the use of laser based on the radiographic evidence of bone gain.

- To evaluate and compare the effectiveness of regenerative periodontal therapy with or without the use of laser in terms of patient-centered outcomes (PCOs).

I.1.4 Significance of the Study

The results of this research may give relevant insights for clinical decision-making process, enabling medical practitioners to make evidence-based, informed choices regarding the inclusion of lasers in regenerative periodontal surgical procedures to achieve improved long-term clinical outcomes. It may also support the development of treatment strategies that enhance clinical, radiographic, and PCOs. Furthermore, the study seeks to provide a more definite understanding of the advantages and limitations of conventional surgical approaches compared to those using adjunctive laser technology.

I.1.5 Scope of the Study

The study aims to synthesize and critically analyze the existing literature on periodontal tissue regeneration in reconstructive/regenerative surgical procedures, with a primary focus on evaluating clinical, radiographic, and PCOs with or without the adjunctive use of laser devices. Additionally, it seeks to assess the applicability and effectiveness of laser-assisted procedures to conventional surgical methods in various clinical scenarios.

I.1.6 Research Questions

In order to develop a clear focus on the project, the following research questions were addressed:

1. How does the use of lasers as an adjunct in regenerative periodontal therapy affect clinical parameters such PPD reduction, CAL gain, gingival recession (GR), bleeding on probing (BoP), and exudate compared to therapy without lasers?
2. Is there a significant difference in radiographic bone (RB) gain between patients undergoing regenerative periodontal therapy with the adjunctive use of lasers and those undergoing regenerative periodontal therapy alone?

3. How does the use of lasers in regenerative periodontal therapy impact PCO_S, including discomfort, aesthetics, and functional improvements, compared to therapy without lasers?

I.1.7 Organization of the Study

The thesis is organized as follows: **Part I** presents the Introduction and Literature Review, covering the study's background and providing a comprehensive review of theoretical concepts and existing literature. **Part II** outlines the Research Methodology, detailing the study's aims and design. **Part III** presents the Results and Discussion, with findings illustrated through figures and thoroughly analyzed. Finally, **Part IV** concludes the study with the Conclusion and Recommendations. Additional sections include the References with an Appendix List of Scientific Articles.

CHAPTER 2- Literature Review

I.2.1 Rationale of Regenerative Periodontal Therapy

Periodontal disease is a chronic inflammatory disorder that causes the gradual destruction of both hard and soft tissues surrounding the teeth, including the gingiva, periodontal ligament (PDL) and alveolar bone (Ivanovski, 2009). This pathological condition results in periodontal defects, characterized by substantial tissue loss, often exposing and contaminating the root cementum due to its direct contact with the oral environment. Once the inflammatory component of periodontitis is managed, the objective of periodontal therapy shifts toward the regeneration of destroyed tissues (Sanz *et al*., 2020).

Periodontal regeneration is termed as the reconstitution or rebuilding of lost or damaged periodontal structures in such a manner that their form and function are restored. This aspect differs from "new attachment," which refers to the creation of new cementum including inserting collagen fibers on a previously denuded surface of the root but does not necessarily imply complete periodontal regeneration. Notably, true periodontal regeneration can only be histologically confirmed, as it requires the restitution of all parts of periodontal tissues (Melcher, 1976).

The complexity of periodontal wound healing arises from the unique anatomical composition of the periodontium, which involves the interplay of soft and mineralized connective tissues. Unlike regular soft tissue healing, periodontal wound healing demands coordinated interactions among the four distinct periodontal components including, as mentioned above, gingival connective tissue, PDL, cementum, and alveolar bone. Conventional periodontal therapy primarily results in repair through collagenous scar formation, often referred to as a long junctional epithelium, which is frequently accompanied by apical migration of the gingival epithelium, thereby inhibiting true regeneration (Caton *et al*., 1980). Form a clinical standpoint, a successful periodontal treatment includes reduced PPD, resolution of inflammation (as evidenced by improvement in BoP and absence of suppuration), and reformation of a dento-gingival complex that supports proper oral hygiene (OH). Hypothetically, these clinical enhancements should be associated with CAL gain and radiographic evidence of bone

regeneration. These therapeutic outcomes can be achieved through an initial phase of oral prophylaxis, combined with patient motivation and OH instructions to maintain oral health and control associated risk factors such as smoking and diabetes. This is followed by NSPT, including subgingival instrumentation during subsequent visits (Sanz *et al*., 2020). However, in cases of deep periodontal pockets (≥4–5 mm with bleeding or ≥6 mm residual PDs) and persistent inflammation, further surgical intervention is required, along with long-term patient compliance including a periodontal maintenance program to achieve optimal clinical outcomes. Notwithstanding that, while surgical approaches such as resective periodontal therapy may be employed in cases of deep intrabony (angular) defects and Class II furcation involvement in molars to facilitate pocket reduction and improve maintainability, they are associated with significant attachment loss and increased soft tissue recession. Consequently, for periodontal defects characterized by angular bony defects with an intrabony component of ≥3 mm, as well as Class II furcation involvement in the mandibular and buccal maxillary regions, regenerative periodontal therapy is recommended over resective techniques to optimize periodontal regeneration and preserve attachment (Sanz *et al*., 2020).

I.2.2 Osseous Defects in Periodontal Disease

Based on clinical and skeletal observations, osseous defects resulting from periodontal disease can be broadly classified into three main types as confirmed by several authors (Papapanou and Tonetti, 2000; Siaili *et al*., 2018). Osseous defects are listed as following:

- **Suprabony (Supracrestal) Defects**: The base of the periodontal pocket is located coronal to the alveolar bone crest.
- **Infrabony (Subcrestal) Defects**: The base of the periodontal pocket extends apical to the alveolar bone crest. Infrabony defects can be further categorized into:
  - **Intrabony Defects**: These are well-defined osseous defects that primarily affect a single tooth. Based on the number of remaining bony walls intrabony defects are classified into One-wall defect, Two-wall defect, and Three-wall defect (**Figure 2.1**).

- **Craters**: Bowl- or cup-shaped defects in the interdental bone that affect the root surfaces of two adjacent teeth to an equal extent.

- **Interradicular (Furcation) Defects**: These defects involve bone resorption in the furcation area of multi-rooted teeth, leading to varying degrees of attachment loss (**Figures 2.2-2.3**).

According to a review by Pilloni and Rojas (2018) several classifications of furcation involvement do exist (**Tables from 2.1 to 2.10**). However, among the various classifying methods, Glickman's classification (1953), which considered horizontal attachment loss, was one of the earliest proposed systems. Tarnow and Fletcher (1984) later on refined this classification by incorporating the vertical component relative to each kind of horizontal furcation defect, calculated starting from the fornix of the furcation area. It is noteworthy to mention that currently the classification by Hamp *et al*. (1975) is the most extensively adopted because of its clarity and ease of application in clinical practice.

Table 2.1. Glickman's Classification (1953)

Grade	Description
Grade I	Incipient lesion with suprabony pocket and slight bone loss in the furcation area
Grade II	Loss of interradicular bone and pocket formation, but some alveolar bone and periodontal ligament remain intact
Grade III	Through-and-through lesion
Grade IV	Through-and-through lesion with gingival recession, making the furcation clinically visible

Table 2.2. Goldman's Classification (1958)

Grade	Description
Grade I	Incipient lesion
Grade II	Cul-de-sac lesion
Grade III	Through-and-through lesion

Table 2.3. Hamp *et al*.'s Classification (1975)

Degree	Description
Degree I	Horizontal attachment loss < 3 mm
Degree II	Horizontal attachment loss > 3 mm but not involving the total furcation width
Degree III	Through-and-through horizontal destruction of periodontal tissue in the furcation area

Table 2.4. Rosenberg's Classification (1986)

Type	Degree	Description
Horizontal	Degree I	Probing < 4 mm
Horizontal	Degree II	Probing > 4 mm
Horizontal	Degree III	Two or three furcations classified as Degree II
Vertical	Shallow	Slight lateral extension of an interradicular defect
Vertical	Deep	Internal furcation involvement without penetration into adjacent furcation

Table 2.5. Ramfjord and Ash's Classification (1979)

Class	Description
Class I	Tissue destruction < 2 mm (1/3 of tooth width)
Class II	Tissue destruction > 2 mm (>1/3 of tooth width)
Class III	Through-and-through involvement

Table 2.6. Goldman and Cohen's Furcation Classification (1988)

Degree	Description
Degree I	Involves furcation entrance
Degree II	Extends under the roof of the furcation
Degree III	Through-and-through involvement

Table 2.7. Tal and Lemmer's Furcation Involvement Index (FII) (1982)

Furcal Rating	Depth of Furcation
1	0 mm
2	1–2 mm
3	3 mm
4	≥ 4 mm

Table 2.8. Tarnow and Fletcher's Classification (1984)

Subclass	Vertical Bone Resorption
A	0–3 mm
B	4–6 mm
C	>7 mm

Table 2.9. Eskow and Kapin' s Classification (1984)

Grade	Subclass	Vertical Destruction
Grade I	A	>1/3 of the interradicular height
Grade I	B	2/3 of the interradicular height
Grade I	C	Beyond the apical third of interradicular height

Table 2.10. Walter *et al*.'s Modified Hamp *et al*.'s Classification (2009)

Degree	Description
Degree I	Horizontal attachment loss <1/3 of tooth width
Degree II	Horizontal loss of support 3–6 mm
Degree II–III	Horizontal loss >6 mm, but not through-and-through
Degree III	Horizontal through-and-through destruction

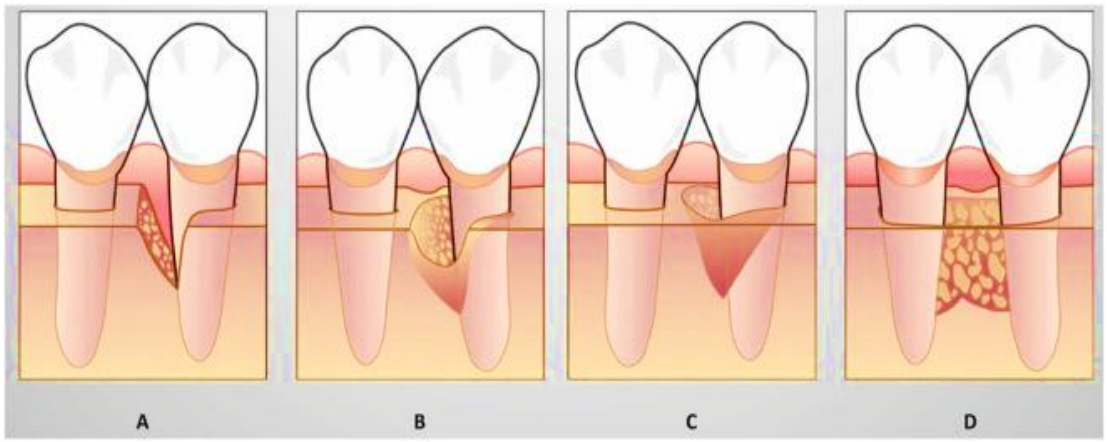

Figure. 2.1. *Infrabony defects. A. One-wall intrabony defect. B. Two-wall intrabony defect. C. Three-wall intrabony defect. D. Interproximal crater [source: (Papapanou and Tonetti, 2000)].*

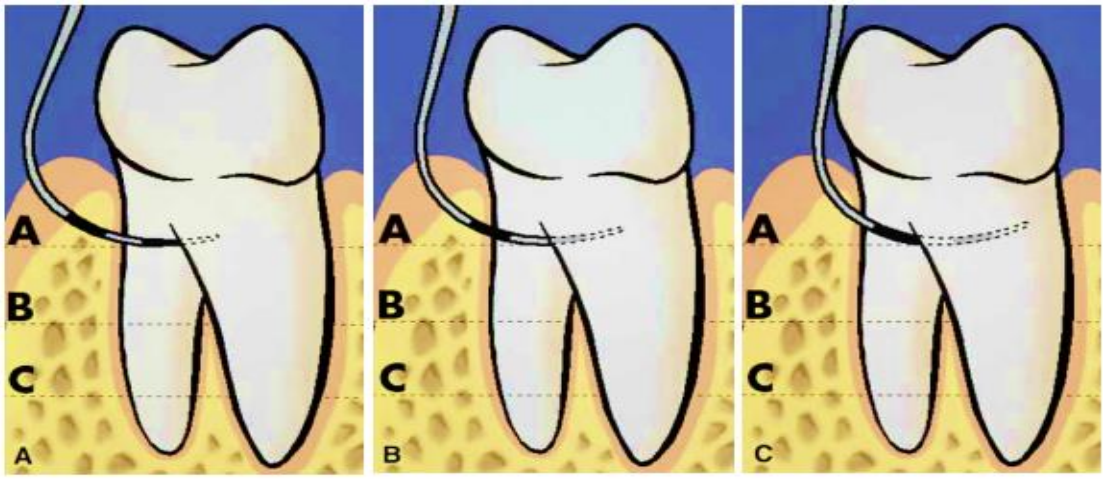

Figure.2.2. *Horizontal classification of furcation involvements. A. Class I, less than 3 mm of horizontal attachment loss. B. Class II, more than 3 mm of horizontal attachment loss but not through and through. C. Class III, through and through furcation involvement [source: (Papapanou and Tonetti, 2000)].*

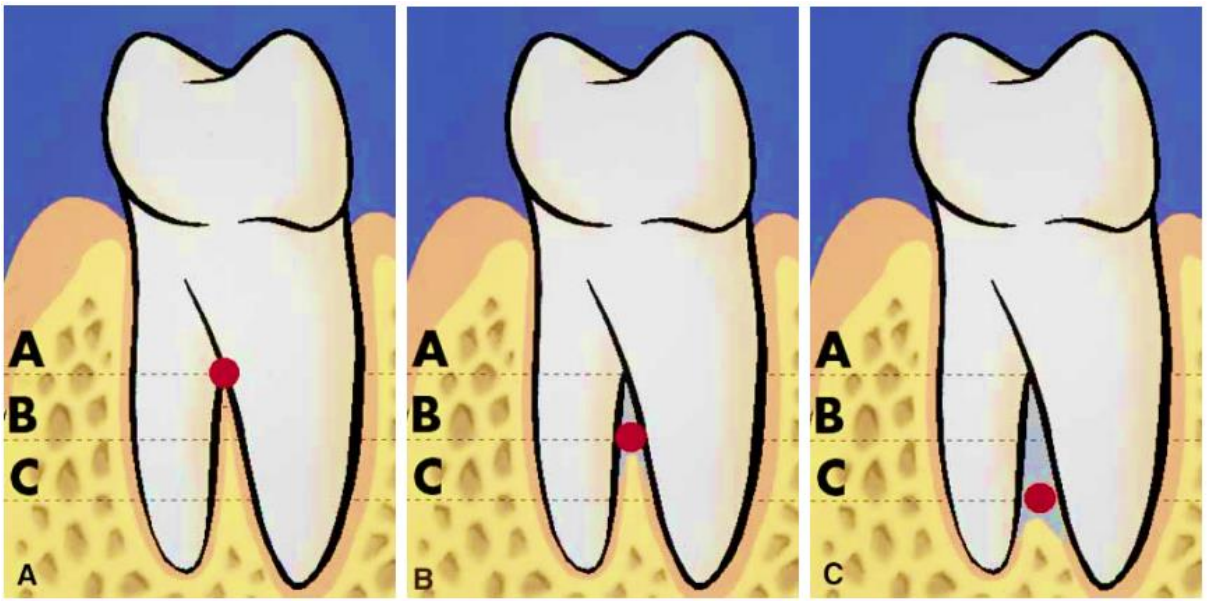

Figure 2.3. *Vertical classification of furcation involvements. A. Subclass A denotes furcation involvements with vertical bone bone loss of 3 mm or less. B. Subclass B denotes furcation involvements with vertical bone loss of 4 to 6 mm. C. Subclass C denotes furcation involvements with vertical bone loss from the fornix of 7 mm or more [source: (Papapanou and Tonetti, 2000)].*

I.2.3 Regenerative Periodontal Surgery: Indications for the Treatment

In line with Wang and Cooke (2005) indications for regeneration in periodontal surgery are as following:

- Narrow two or three wall intrabony defects.
- Class II molar furcation.
- Recession defects.
- Circumferential defects.

I.2.4 Regenerative Periodontal Surgery: Contraindications for the Treatment

Regenerative periodontal surgical procedure is contraindicated in the listed clinical scenarios as following (Wang and Cooke, 2005):

- Patients with medical conditions that contraindicate surgical intervention.
- Heavy chronic smokers.
- Poor OH.
- Increased tooth mobility.
- Periodontitis with horizontal bone loss.
- Defect depth < 4 mm.
- Width of attached gingiva at the defect site ≤ 1 mm.
- Presence of a thin gingival biotype at the defect site (≤ 0.5 mm).
- Furcation defects with short root trunks.
- Advanced periodontitis with minimal remaining bone support.
- Presence of multiple periodontal defects.

I.2.5 Regenerative Periodontal Surgery: Goals of the Treatment

According to the evidence, current regenerative surgical procedures are primarily centered on the treatment of intrabony and furcation defects. As reported by Cortellini and Tonetti (2022), the aims of periodontal regenerative therapy encompass:

- **Restoration of lost periodontium**: To regenerate key periodontal components, including root cementum, PDL, and alveolar bone, thereby re-establishing the structural and functional integrity of the periodontium.
- **PPD reduction**: To achieve a significant reduction in pocket depth, facilitating better periodontal health and long-term maintenance.
- **CAL gain**: To promote the attachment of periodontal tissues to the root and teeth surfaces, thereby enhancing overall periodontal stability.

- **Preservation of gingival architecture**: To preserve soft tissue integrity and aesthetics while reducing the risk of hypersensitivity and root exposure.
- **Effective utilization of biomaterial**: To apply biologically and clinically validated biomaterials that promote periodontal regeneration, resulting in predictable and evidence-based treatment outcomes.
- **Long-term stability and function**: To enhance the durability and function of the dentition, contributing to overall oral health and preventing the recurrence of the disease.

I.2.6 Regenerative Periodontal Surgery: Biologic Foundation of Treatment

Traditional periodontal surgeries, such as surgical debridement and resective procedures, are well-established methods for treating periodontal disease and halting its progression. However, studies indicate that these standard procedures usually heal through repair by forming connective tissue attachment or a long junctional epithelium, resulting in minimal regeneration of bone and tooth-supporting structures. Meanwhile, regenerative periodontal therapy intends to recreate lost periodontal tissues by promoting the regeneration of cementum, periodontal fibers, and alveolar bone (Alpiste Illueca *et al*., 2006). It was in 1976 that Melcher introduced the notion of compartmentalization, categorizing the periodontal connective tissues into four distinct compartments: the gingival corium, PDL, cementum, and alveolar bone. This foundational concept determined the development of GTR, which utilizes barrier membranes to selectively rule out undesirable epithelial and gingival connective tissue cells from the wound site. By excluding their entry, GTR facilitates the repopulation of the site by regenerative cells, such as PDL cells, bone cells, and cementoblasts, allowing for proper healing and periodontal regeneration (Wang and Cooke, 2005). Studies have confirmed that periodontal surgical wounds progress through the same phases as incisional wounds, forming a fibrin clot at the root surface that serves as a scaffold for connective tissue attachment. However, the unique anatomical and microbiological characteristics of the

periodontium, including the presence of an avascular root surface and diverse microbial flora, introduce complexities to the regenerative process (Cho *et al*., 2021).

The critical role of PDL cells in regeneration has been extensively investigated, with evidence suggesting their ability to differentiate into osteoblast-like and cementoblast-like cells, contributing to cementum and bone formation. Additionally, the maintenance of fibrin linkage and immobilization of the wound margins are essential for successful regeneration, as disruptions in these processes result in the formation of long junctional epithelium instead of new connective tissue attachment (Isaka *et al*., 2001). While early studies indicated that bone and gingival connective tissues lack regenerative capacity, later findings suggest that PDL cells play a predominant role, possibly through interactions with paravascular and osteoblastic cells. (Position Paper, 2005) Collectively, these findings emphasize the need for regenerative approaches that respect the natural biological sequence of periodontal healing in restoring the lost periodontal structures and functional attachment (Wang and Cooke, 2005; Siaili *et al*., 2018).

I.2.7 Regenerative Periodontal Surgery: Techniques Used for Regeneration

In line with the evidence commonly used techniques for periodontal regeneration include:

a. Root surface conditioning.
b. Coronally positioned (advanced) flaps (CAF).
c. Bone replacement grafts/ bone substitute materials.
d. GTR.
e. Biologic modifiers.
f. Enamel matrix proteins (EMP).
g. Lasers.

I.2.7.1 Root surface conditioning

The primary goal of root surface debridement is to remove bacterial biofilms and endotoxins. Adjunctive use of demineralizing agents, such as acids or ethylenediaminetetraacetic acid (EDTA), has been explored for the exposure of collagen

fibrils. Several reports have demonstrated that EDTA enhance periodontal regeneration by removing the smear layer and decalcifying cementum or dentin. This process may improve blood clot adhesion and stabilization, potentially supporting wound healing and regeneration (Polimeni *et al*., 2006). This process aims to promote mesenchymal cell attachment while inhibiting epithelial cell migration. Citric acid, initially used for its detoxifying properties, has been associated with adverse effects like root resorption and ankylosis. In contrast, EDTA, with its higher pH and gentler action, is considered more biocompatible. However, demineralization alone is not regenerative but serves as an adjunct to protocols like EMP application (Lowenguth and Blieden, 1993). In that respect, animal studies suggest that citric acid or tetracycline demineralization can induce mesenchymal cell differentiation into cementoblasts, promoting new connective tissue attachment (Crigger *et al*., 1978; Polson and Proye, 1982). However, human clinical trials have not shown significant improvements in periodontal regeneration. Similarly, systematic reviews indicate that citric acid, tetracycline, and EDTA offer no clinically meaningful benefits for chronic periodontitis, and their use as adjuncts to surgical debridement lacks strong evidence (Mariotti, 2003; Reynolds *et al*., 2003). In addition, histological studies report variable results, with some showing limited new connective tissue attachment after citric acid application. However, clinical trials found no added benefits when citric acid was used with surgical procedures, osseous grafts, or GTR (Renvert *et al*., 1985; Handelsman, 1991; Kersten *et al*., 1992). Furthermore, while EDTA minimizes tissue damage and promotes collagen exposure, human trials have not demonstrated significant clinical improvements compared to non-demineralized controls (Mariotti, 2003).

I.2.7.2 Coronally positioned (advanced) flaps (CAFs)

The periosteum is widely recognized for its regenerative potential due to its rich composition of osteoprogenitor cells (Wikesjö *et al*., 1991, 1992). This capacity is attributed to its cellular activity and its role as a physical barrier when repositioned. While treating mandibular Class II furcation defects, CAFs are utilized to position the flap margin distant from the critical healing area (the furcation site), thereby facilitating optimal healing

(Wikesjö *et al*., 1992). Re-entry studies have reported a mean bone fill ranging from 50% to 65% by volume in Class II mandibular furcation defects (Wikesjö *et al*., 1991). Among 46 evaluated defects, 22 demonstrated complete bone closure, indicating successful horizontal defect resolution. However, residual furcation involvement was often observed clinically prior to re-entry, highlighting the need for larger patient cohorts and extended follow-up periods to fully assess the technique's long-term efficacy (Wang and Cooke, 2005).

Several clinical studies have evaluated different flap management procedures to improve clot protection and wound stability (Andersson *et al*., 1994). For instance, CAFs have been adopted for the management of mandibular Class II furcation defects by securing the flap margin distant from the critical healing area during early healing (Bowers *et al*. 1989). Moreover, a comparative research assessing the efficacy of CAFs and expanded polytetrafluoroethylene (ePTFE) membranes in periodontal regeneration found no significant difference in clinical outcomes (Andersson *et al*., 1994). However, histologic evaluations demonstrated the creation of a novel connective tissue attachment in supracrestal periodontal defects using this approach (Stahl and Froum, 1991). Meanwhile, studies on the use of CAFs for Class III furcation defects reported enhancements in probing depths and attachment levels. However, complete resolution of Class III defects was not achieved, and the approach showed limited efficacy (Gantes *et al*., 1991; Garrett *et al*., 1994).

I.2.7.3 Bone replacement grafts/ bone substitute materials

Bone graft substitutes are broadly used in periodontal therapy to promote bone formation and periodontal regeneration. These materials are broadly categorized into autografts, allografts, xenografts, and alloplasts. Each category possesses distinct properties, including osteoconduction, osteoinduction, and osteogenesis, which influence their clinical efficacy (Reynolds *et al*., 2003). The rationale for using bone graft substitutes lies in their capacity to produce a scaffold for the generation of new bone and, ideally, to induce the regeneration of the periodontal attachment apparatus (Bosshardt, 2008). Different types of bone graft substitutes are displayed as follow:

- **Autogenous Bone Grafts.** Autogenous bone grafts represent the gold standard for their osteogenic potential, as they are sourced from the patient's own body. These grafts can be obtained from extraoral sites, such as the iliac crest, or intraoral sites, such as the maxillary tuberosity or healing extraction sites (Dragoo and Sullivan, 1973). Studies have reported a mean bone fill ranging from 1.2 to 3.4 mm when using iliac cancellous bone with marrow for the restoration of furcation, dehiscence, and intraosseous defects. However, the use of iliac grafts is limited by donor site morbidity, the possibility of root resorption, and the complexity of harvesting (Rosenberg, 1971; Hiatt and Schallhorn, 1973).

  Intraoral grafts have shown comparable efficacy to iliac grafts, with studies reporting bone fill ranging from 1.2 to 3.4 mm (Rosenberg, 1971; Hiatt and Schallhorn, 1973). Histologic evaluations of autogenous grafts have demonstrated some evidence of new connective tissue attachment, but the results are inconsistent, and the creation of a long junctional epithelium is often reported (Moskow *et al*., 1979). Despite their osteogenic potential, the necessity of a donor surgical site and associated morbidity limits the practicality of autogenous grafts in clinical practice (Miron *et al*., 2011).

- **Allogenic Bone Grafts**. Allogenic bone grafts, derived from human donors, are widely used in periodontal therapy. These grafts are available in two main forms: freeze-dried bone allografts (FDBA) and demineralized freeze-dried bone allografts (DFDBA). FDBA acts primarily through osteoconduction, providing a scaffold for new bone growth, while DFDBA has osteoinductive property due to the presence of bone morphogenetic proteins (BMPs) which get exposed over the process of demineralization (Rummelhart *et al*., 1989). Several clinical studies have reported bone fill ranging from 1.3 to 2.9 mm with FDBA and DFDBA as bone grafts (Ashfaq *et al*., 2024). Histologic evidence suggests that DFDBA may promote periodontal regeneration, with some studies showing new connective tissue attachment (Bowers *et al*., 1989). However, the biologic activity of DFDBA varies significantly between commercial preparations, influenced by factors such as donor age and processing methods. Stricter standards for bone bank preparations, including the use of younger

donors and assays to test inductive capacity, may improve the consistency and efficacy of allogenic grafts (Schwartz *et al*., 1998).

- **Alloplastic Materials.** Alloplastic materials are synthetic bone graft substitutes designed to promote bone healing controls through osteoconduction, with defect closure ranging from 1.6 to 3.5 mm (Lee *et al*., 2012). Commonly used alloplasts include hydroxyapatite, tricalcium phosphate, and bioactive glass (Ashfaq *et al*., 2024). Studies have reported significant improvement in the grafted sites compared to non-grafted sites. However, histological investigations have reported that alloplastic materials are encapsulated by connective tissue with minimal bone formation (Timothius *et al*., 2023). Moreover, bioactive glass, composed of calcium salts, phosphate, sodium salts, and silicon, forms a silica gel layer that facilitates the creation of a hydroxycarbonate-apatite layer, theoretically supporting osteoblast proliferation and bone formation (Fiume *et al*., 2018). However, clinical studies assessing bioactive glass have shown contrasting findings, and histologic evidence of periodontal regeneration is limited (Motta *et al*., 2023). Overall, alloplastic materials function primarily as non-irritating fillers, supporting periodontal repair rather than true regeneration (Vlasa *et al*., 2025).
- **Xenografts.** Xenografts, sourced from non-human species, are processed to remove cells and proteins, leaving an inert scaffold for bone growth. They are called anorganic bone due to the absence of organic components (Oryan *et al*., 2014). Clinical data on their use in periodontal defects are limited, with some studies showing results similar to DFDBA (Lee *et al*., 2020). However, xenografts are more commonly used for guided bone regeneration (GBR), sinus lifts, and ridge augmentation (Lotfazar *et al*., 2024). Histologic evidence of periodontal regeneration with xenografts is scarce, and concerns about the risk of prion transmission from bovine-derived products have been raised (Rodriguez and Nowzari, 2019). However, the World Health Organization (WHO) has classified bone as low-risk for prion diseases, and risk analysis estimates suggest that the risk of transmission is negligible (Position Paper, 2005).

Overall, despite the widespread use of bone graft substitutes, their ability to achieve true periodontal regeneration, defined by the formation of new connective tissue attachment, remains limited. Histologic evidence suggests that bone grafts and substitutes primarily support new bone formation rather than the regeneration of the periodontal attachment apparatus (Zhao *et al*., 2021). The creation of a long junctional epithelium is often detected, indicating repair rather than regeneration (Ramseier *et al*., 2012).

Future research should focus on developing materials with enhanced osteoinductive and regenerative properties. Stricter standards for bone bank preparations, as suggested by Wang and Cooke (2005), and the use of recombinant osteogenic factors, as mentioned in the Position Paper (2005), may improve the consistency and efficacy of bone graft substitutes. Additionally, more rigorous clinical and histologic studies are necessary to better comprehend the mechanisms of periodontal regeneration and the role of bone graft substitutes in this process (Luczak *et al*., 2024).

I.2.7.4 Guided tissue regeneration (GTR)

GTR is a well-established procedure in periodontal regeneration which has demonstrated superior efficacy in comparison to open flap debridement (OFD) in the treatment of intrabony and furcation defects. The primary goal of GTR is to promote the regeneration of periodontal structures, including new cementum, PDL, and alveolar bone, by selectively guiding cell repopulation through the use of barrier membranes. This approach is based on the hypothesis that cells originating from the PDL and adjacent bone have the greatest regenerative potential; similarly, excluding epithelial and gingival connective tissue cells is critical for successful healing (Murphy and Gunsolley, 2003).

The biologic principle underlying GTR includes the use of a physical barrier to prevent the apical migration of epithelium and the infiltration of gingival connective tissue into the healing wound. This allows cells from the PDL, cementum, and alveolar bone to repopulate the root surface and promote the creation of new attachment apparatus (Cho *et al*., 2021). Early animal studies, such as those by Nyman *et al*. (1982), demonstrated that mechanical exclusion of competing tissues could lead to the formation of new

cementum and connective tissue attachment on denuded root surfaces (Nyman *et al*., 1982). This foundational work paved the way for the development of barrier membranes in clinical practice. Relevant data from the evidence evaluating barriers membrane and GTR application in bone defects are reported in the following subheadings.

I.2.7.4.1 Types of barrier membranes

Barrier membranes used in GTR can be broadly classified into non-resorbable and bioabsorbable types.

- **Non-Resorbable Membranes.** The earliest non-resorbable ePTFE membrane has been extensively studied. These ePTFE membranes consist of a coronal collar that prevents epithelial migration and an occlusive segment that excludes gingival connective tissue. Studies by Becker *et al.* (1986) and others have shown significant bone fill (3.0–5.0 mm) in intraosseous defects treated with ePTFE, particularly in three-wall defects (Becker *et al*., 1986). However, the necessity of a second surgical procedure for the removal of non-resorbable membranes has limited their use in favor of bioabsorbable alternatives.
- **Bioabsorbable Membranes**. Bioabsorbable membranes made from collagen, such as polylactic acid (PLA) and polyglycolic acid (PGA), can degrade on their own, eliminating the need for a second surgery. A study by Sheikh *et al*. (2015) suggests that clinical outcomes with collagen membranes, including PPD reduction, CAL gain, and defect fill, are comparable to those of non-resorbable membranes. Additionally, their hemostatic properties and chemotactic effects on fibroblasts promote faster wound stabilization and primary closure, which are critical for successful regeneration (Zhang *et al*., 2023). GTR has been used to treat various periodontal defects, including intrabony defects, furcation defects, and marginal tissue recession.

I.2.7.4.2 Intrabony defects

Meta-analyses and systematic reviews, such as those by Murphy and Gunsolley (2003), have consistently shown that GTR results in significantly greater CAL gain and PPD reduction in comparison to OFD (Murphy and Gunsolley, 2003). The addition of bone graft

materials, such as DFDBA, does not appear to significantly enhance outcomes in intrabony defects, suggesting that GTR alone is sufficient for these cases (Vaid *et al*., 2021).

I.2.7.4.3 Furcation defects

GTR has shown variable success in the management of furcation defects. While mandibular Class II furcation defects respond well to GTR, maxillary Class II and Class III defects exhibit more modest and unpredictable outcomes (Becker *et al*., 1986; Murphy and Gunsolley, 2003). The combination of GTR with bone replacement grafts has been shown to enhance clinical improvements in furcation defects, particularly in vertical probing attachment level (Jepsen *et al*., 2002).

I.2.7.4.4 Root coverage and Recession defects

GTR-based root coverage techniques have demonstrated favorable results, with studies reporting 76.4% root coverage and complete coverage in 33.1% of cases (Al Hamdan *et al.*, 2003). However, connective tissue grafting techniques may offer advantages in areas with thin gingiva or minimal keratinized tissue. Despite its proven efficacy, GTR is not without limitations. Membrane exposure and bacterial contamination, particularly while using non-resorbable membranes, can compromise outcomes (Elgali *et al*., 2017). Additionally, the technique is sensitive and technically demanding, requiring careful patient and defect selection. The use of bioabsorbable membranes has mitigated some of these issues, but challenges remain, such as the need for bone fillers to prevent membrane collapse in large defects (Rider *et al*., 2021).

I.2.7.4.5 Growth modifiers

Growth modifiers or biologically active molecules involve extracellular matrix proteins, cell-attachment factors, mediators of cell metabolism and activity, and growth/differentiation factors. Growth factors play a critical role in regulating cell proliferation, cell activity, chemotaxis, and cell differentiation. Several growth factors, either alone or in combination, have been evaluated in animal models for their potential in periodontal regeneration (Galli

et al., 2021). Among the most studied, reported growth factors are insulin-like growth factors (IGFs), fibroblast growth factors (FGFs), epidermal growth factor (EGF), platelet-derived growth factors (PDGFs), vascular endothelial growth factor (VEGF), parathyroid hormone (PTH), transforming growth factor-beta (TGF-β), and BMPs (Sasikumar *et al.,* 2012). Clinical studies have examined the effectiveness of recombinant human PDGF-BB, platelet-rich plasma (PRP), and peptide P-15 in treating intraosseous and furcation defects (Dunn *et al*., 2000). BMPs, particularly BMP-2 and BMP-7, have shown promising results in promoting ectopic bone formation and new cementum formation (Hakki *et al*., 2010). Several studies involving animals have reported enhanced regenerative outcomes with BMP-2 and BMP-7 in the management of periodontal defects (Wikesjö *et al*., 1999; Wei *et al*, 2019). The first human trial involving osteogenin combined with DFDBA indicated a significant enhancement in the regeneration of a new attachment apparatus (Howell *et al*., 1997). However, concerns regarding a higher incidence of ankylosis in animal studies persist, particularly with BMP-2 (Lories *et al*., 2005).

Other growth factors, including TGF-β, PDGF, IGF, and FGF, fulfill an essential role in periodontal tissue regeneration. These factors act as mitogens or differentiation inducers, promoting cell proliferation and differentiation in periodontal tissues (Wang and Cooke, 2005). Human clinical trials involving recombinant PDGF and IGF have shown promising results in treating intrabony defects and furcations (Giannobile, 1996). One study found that purified recombinant human PDGF-BB, combined with bone allograft, led to significant regeneration of periodontal tissues in class II furcations and interproximal intrabony defects (McGuire and Scheyer, 2006).

Despite promising preclinical studies, the regular utilization of growth factors in regenerative periodontal surgery remains limited due to several critical challenges. One major hurdle is the complex mentioned anatomical architecture of the periodontium, making complete and predictable regeneration difficult (Bosshardt, 2008). Additionally, the effective dose of BMPs required for regeneration remains uncertain, with higher doses being associated with complications such as ankylosis (Wikesjö *et al*., 1999). Another significant challenge is the identification of an optimal carrier system that ensures the

sustained and controlled release of growth factors, as no ideal carrier has been established to date (Giannobile, 1996). Furthermore, the high cost of recombinant human BMPs raises concerns regarding their cost-effectiveness, especially for treating non-life-threatening periodontal defects (Kumara *et al*., 2021). These factors collectively hinder the widespread clinical application of growth factors in periodontal regeneration, despite their potential benefits.

I.2.7.4.6 Enamel matrix proteins (EMPs)

EMD has been investigated extensively for its role in periodontal regeneration and has been authorized by the U.S. Food and Drug Administration for the utilization in treating angular bony defects. EMD consists of a group of EMPs derived from developing porcine teeth and is primarily composed of three major protein fractions with molecular weights of 20, 13, and 5 kDa (McCombs, 2002). The protein extract is freeze-dried, solubilized in a propylene glycol alginate carrier solution, and applied to periodontal intrabony defects following debridement and root conditioning (Giannobile, 1996).

Histological studies have provided evidence supporting the regenerative potential of EMD. In a human dehiscence model, application of EMD led to significant periodontal regeneration (Sculean *et al*., 2007). However, clinical case reports have shown inconsistent histologic evidence of regeneration, with some studies failing to demonstrate the formation of new attachment (Laugisch *et al*., 2019). A case series of 10 patients reported varied results, where only three specimens showed periodontal regeneration, three exhibited new connective tissue attachment, and four healed with a long junctional epithelium (Lavu *et al*., 2015). Recently, an *in vivo* study suggested that EMD is an osteoconductive material rather than an osteoinductive one. This aspect indicates that EMD may promote bone healing without directly determining new bone formation (García-Gareta *et al*., 2015).

In addition, clinical trials and systematic reviews have reported significant improvements in probing measurements and RB fill following EMD application (Jepsen *et al*., 2008). A randomized, placebo-controlled, split-mouth trial comparing 1- and 2-walled defects

treated with EMD versus placebo over three years demonstrated statistically significant improvements in CAL and PD reduction in EMD-treated sites. However, long-term benefits and predictable outcomes remain uncertain, necessitating further research to clarify the regenerative mechanisms of EMD (Soleymanzadeh, 2015).

Compared to growth factors such as BMPs, the use of EMPs emerged somewhat late in periodontal regenerative treatment. Interestingly, EMD was introduced into clinical practice before extensive scientific studies were conducted to explain its regenerative effects (Rathva, 2011). Numerous clinical and histological studies have documented the formation of new cementum and bone with the insertion of connective tissue fibers following EMD application. The underlying biological concept suggests a relationship between EMPs and cementogenesis, although a direct causal link remains unproven (Sculean *et al*., 2008). While the use of EMD in periodontal therapy is promising, patient selection, defect characteristics, and proper postoperative care play crucial roles in determining clinical outcomes (Esposito *et al*., 2009). Furthermore, the clinician's experience and understanding of periodontal wound healing significantly influence treatment success. Additional research is required to elucidate the long-term efficacy, mechanism of action, and optimal clinical applications of EMD in periodontal regenerative procedures (Cho *et al*., 2021).

I.2.8 Lasers and Related Effectiveness in Periodontal Treatment

Over the past two decades, the application of lasers in dentistry has increased exponentially. Numerous scientific studies have been conducted in this field, significantly contributing to advancements in laser technology and its clinical applications in dentistry, and particularly in periodontology (Mathew *et al*., 2018). Laser devices and related aspects are thoroughly analyzed in the following sections.

I.2.8.1 Evolution of laser use in dentistry and in periodontal regeneration

Nowadays, lasers are employed either as an alternative to or in conjunction with conventional dental techniques. Lasers exhibit distinct properties, such as spatial

coherence and collimation, which make them highly suitable for dental applications, as these characteristics facilitate precise interactions with dental tissues (Romanos, 2015). Various types of lasers are used in the field of dentistry, and their selection depends on certain key factors, including their ability to penetrate tissues, energy output, duration of laser-tissue interaction, radiation power, and pulse length (Dostalova and Jelinkova, 2013). One of the earliest lasers used in dentistry was the ruby laser, introduced by Stern and Sognnaes in 1965. They applied the ruby laser to dental hard tissues and observed a reduction in enamel permeability to acid demineralization. However, subsequent studies revealed that ruby lasers generated excessive heat, leading to pulpal necrosis (Wigdor *et al*., 1995). Currently, lasers are particularly useful in soft tissue procedures and are extensively utilized in periodontal treatments. Their advantages include hemostasis, sterilization, minimal invasiveness, and precise tissue ablation. When used either alone or as an adjunct to conventional periodontal therapies, lasers have demonstrated enhanced healing outcomes and improved periodontal health (Behdin *et al*., 2015).

Among the various laser systems employed in periodontal therapy, the Nd:YAG laser has shown superior healing potential with minimal thermal damage to periodontal tissues, making it a promising option for periodontal treatments (Israel *et al*., 1997). While numerous studies make available evidence supporting the beneficial effects of lasers in NSPT (Schwarz *et al*., 2008), fewer studies have investigated their efficacy in regenerative periodontal surgeries. Further research is needed to establish their role and long-term clinical benefits in periodontal surgery.

I.2.8.2 Different types of lasers

Several types of lasers used in dentistry are reported. All these lasers can be grouped into different types based on its wavelength (**Figure 2.4**) and material used, based on its use on hard or soft tissues, based on output energy etc. (Verma *et al*, 2012; Dang and Rallan, 2013).

a) Based on wavelength:

- Visible light, 400nm to 750 nm: Argon and Diagnodent lasers.

- Infrared light, 750nm to 10000nm: CO_2, Er:YAG, Erbium,Chromium-doped: Yttrium Scandium Gallium Garnet (Er,Cr:YSGG), Nd:YAG, Diode.

b) Based on application of type of tissue:

- Hard tissue.
- Soft tissue.

c) Based on material used:

- Gas: CO_2.
- Solid: Er:YAG, Er,Cr:YSGG, Nd:YAG, Diode.

d) Based on Output Energy:

- Low-Output or Soft Lasers: These lasers emit cold (non-thermal) energy and are primarily adopted for the stimulation of cellular activity. Frequently used soft lasers in periodontics include Helium-Neon (He-Ne) and Gallium-Arsenide (Ga-As) lasers. These lasers improve tissue healing by minimizing inflammation, pain, and edema. As a result, they are clinically employed for pain management, ulcer healing, and the treatment of gingivitis, among other applications (Dang and Rallan, 2013).
- High output or hard lasers: Hard lasers, also referred to as surgical lasers can be applied to both hard and soft tissues in the oral cavity. The most frequently used hard lasers in periodontology involve CO_2, Argon, Nd:YAG, Er,Cr:YSGG , Holmium-doped, yttrium aluminium garnet (Ho:YAG), and Neodymium-doped, yttrium aluminium perovskite (Nd:YAP) (Ishikawa *et al*., 2009; Dang and Rallan, 2013).

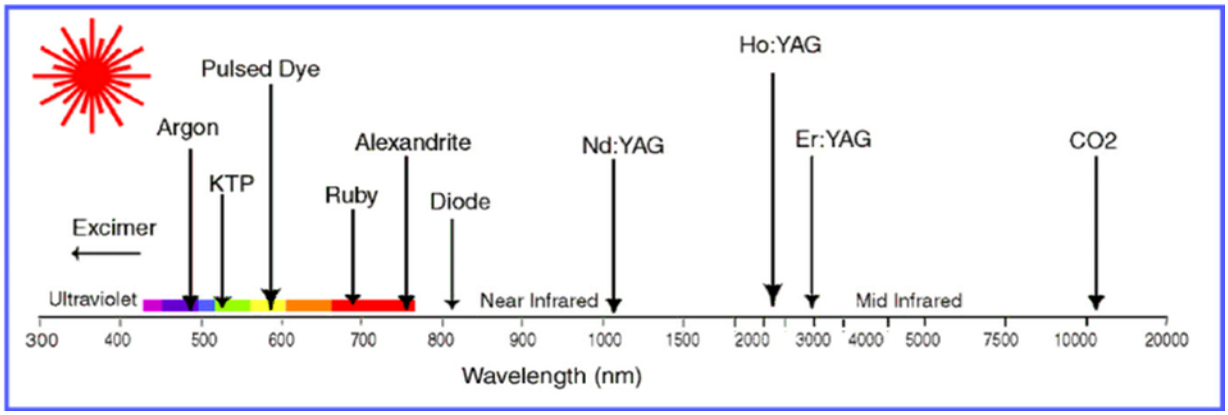

Figure 2.4. *Different types of lasers based on its wavelength. CO_2: Carbon Dioxide; Er:YAG: Erbium-doped: Yttrium Aluminium Garnet; Ho:YAG: Holmium-doped: Yttrium Aluminium Garnet; KTP: Potassium Titanyl Phosphate; Nd:YAG: Neodymium-doped: Yttrium Aluminium Garnet [source: (Peng et al., 2008)].*

I.2.8.3 Mechanism of action of lasers

Laser is a man-made monochromatic light with a single wavelength. A laser light is produced when an excited atom is stimulated and it emits a photon before it occurs spontaneously. The laser device converts electromagnetic energy into thermal energy and an emitted laser is monochromatic, coherent and collimated. These three main features help the laser to penetrate into tissues thereby making it a good tool in periodontal treatments (Dang and Rallan, 2013; Nazemisalman *et al*., 2015).

I.2.8.4 Parts of laser device

A laser device is made of three main components: an energy source, a lasing (or active) medium, and mirrors that function as an optical resonator (Kumara *et al*., 2021). The active medium can be a gas, solid, liquid, or solid-state semiconductor. However, liquid mediums are not used in dental applications. The energy source pumps energy into the lasing medium, while the optical resonators (mirrors) positioned at either end of the device cavity reflects the light waves back and forth, amplifying the laser beam (Convissar, 2010) (**Figure 2.5**).

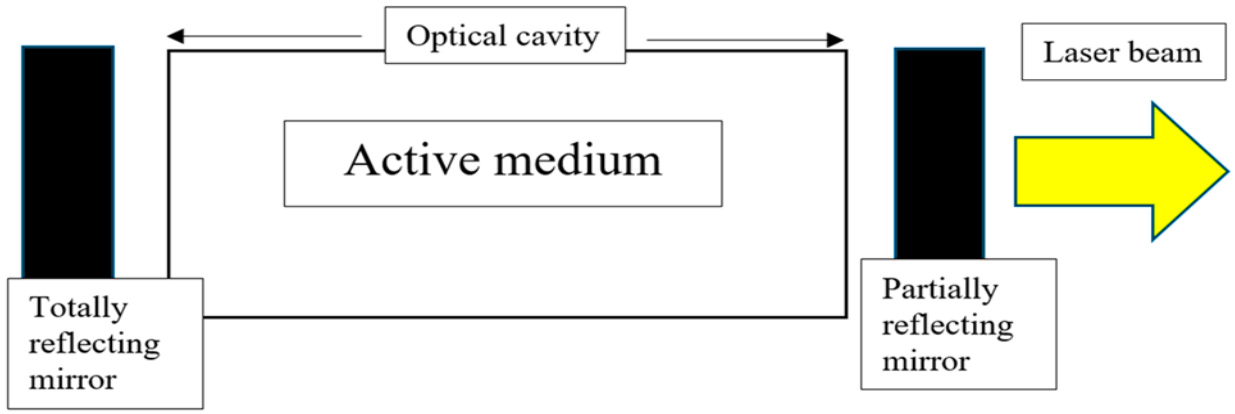

Figure 2.5. *Components of laser device [source:(Abu-Ta'a and Karameh, 2022)].*

I.2.8.5 Modes of operation of laser

Lasers operate in three distinct modes (Abu-Ta'a and Karameh, 2022) (**Figure 2.6**) listed as following:

- **Gated Pulse Mode**: In this mode, the laser produces periodic bursts of low-energy pulses at interrupted intervals. This intermittent delivery minimizes heat production, reducing the risk of thermal damage to surrounding tissues.
- **Continuous Mode**: In this mode, the laser emits a continuous wave of energy without interruption. While this allows for sustained energy delivery, it also leads to increased heat production, which can pose a risk of thermal damage to tissues.
- **Free-Running Pulse Mode (True Pulse Mode)**: This mode involves the emission of a significant amount of energy in a very short duration (microseconds), followed by a prolonged period of no energy output. This pattern allows for high peak power with minimal heat accumulation, making it suitable for precise and controlled tissue interactions.

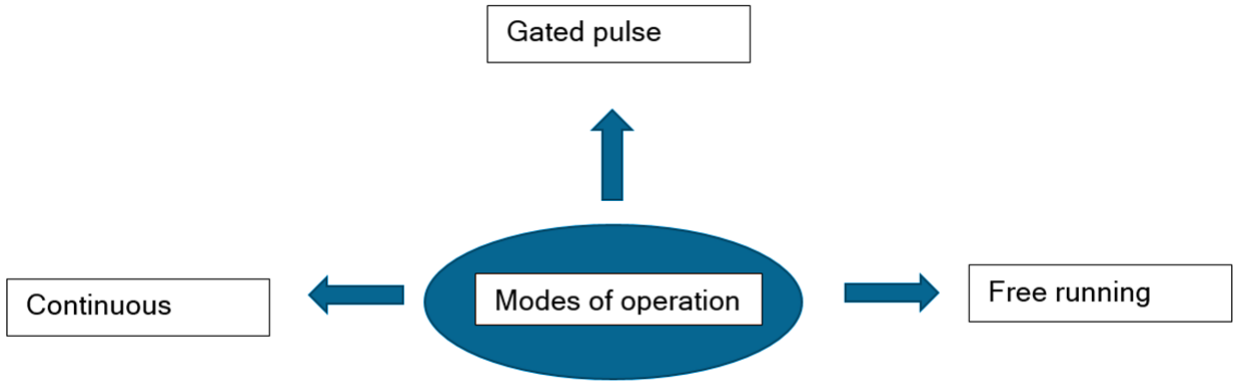

Figure 2.6. *Modes of operation of laser [source:(Abu-Ta'a and Karameh, 2022)].*

I.2.8.6 Tissue interaction of laser

Clinically, during the application of laser light to tissue, a photothermal reaction is induced, generating heat within the tissue. The biological effect of the laser depends on the degree of heat produced. If the temperature exceeds 60°C, the proteins within the cells coagulate. When the temperature rises above 100°C, it results in the loss of water content from the tissue, leading to tissue ablation (Frame, 1985; Abu-Ta'a and Karameh, 2022). When laser light interacts with target tissue, four types of interactions can occur, based on the laser wavelength and the optical properties of the tissue. These interactions are reflection, absorption, transmission, and scattering (Cobb, 2006).

- **Reflection**: The first interaction takes place in the event that the laser beam is redirected from the tissue surface. Reflected laser light can pose a significant risk to vision, so all personnel in the room must wear protective eyewear to prevent ocular damage.
- **Transmission**: In this interaction, the laser beam penetrates the tissue without having an effect on the target tissue. The extent of transmission is regulated by the wavelength of the laser beam.

- **Scattering**: Here, the laser light interacts with the tissue, causing the energy to disperse and weaken. Scattered radiation can generate unwanted heat, potentially damaging adjacent tissues.
- **Absorption**: This is the most critical interaction in periodontal applications. For laser light to be absorbed by tissue, specific light-absorbing molecules called chromophores must be present (Aoki *et al*., 2015). Chromophores interact with water, pigmented cells (such as melanin and hemoglobin) in soft tissues, and with hydroxyapatite crystals and water in hard tissues. The absorption of laser light also depends on the wavelength of the beam (Sulieman, 2005; Tracey, 2005).

I.2.8.7 Role of lasers in periodontics

As there are various types of lasers available, their penetration power varies relying on their wavelength and the type of tissue being treated. By carefully selecting and managing the wavelengths of these lasers, they can be effectively used for soft tissue debridement, sterilization, and even applied into periodontal pockets to facilitate tissue regeneration (Parker, 2007).

In minimally invasive periodontal surgeries, lasers are invaluable tools due to their ability to deliver focused and precise energy to the target tissue. This precision minimizes damage to surrounding tissues, provides hemostasis, and ensures a clear surgical field. When used in a focused beam, lasers are effective for making incisions and excisions, while an unfocused beam is suitable for ablation and hemostasis. Er:YAG and Er,Cr:YSGG lasers are particularly advantageous for ablation, excision, incision, sterilization, and decontamination of root surfaces. Since these lasers are absorbed by hydroxyapatite crystals, they can also be employed for efficient bone removal. By contrast, Nd:YAG and diode lasers have the ability to penetrate pigmented tissues, making them ideal for gingival depigmentation and the removal of chromogenic bacteria (Romanos, 2015).

I.2.8.8 Different types of lasers used in periodontics

This study has already discussed the various types and classifications of lasers used in dentistry. These lasers differ in their medium, wavelength, and delivery systems (Verma *et al*., 2012). Among them, the most commonly used lasers for periodontal therapies are Er:YAG, Er,Cr:YSGG , Nd:YAG, diode, and CO_2 lasers (**Table 2.11**).

a. **Diode lasers.** Diode Lasers utilize a solid-state semiconductor as the lasing medium, which typically consists of gallium, aluminum, arsenide, and sometimes indium. These components convert electrical energy into light energy. Diode lasers operate within a wavelength range of 810 nm to 980 nm (Prabhuji *et al*., 2011). They are equipped with a flexible fiber-optic delivery system and can operate in both continuous and gated pulse modes (Govila *et al*., 2011). The wavelength of diode lasers is primarily absorbed by hemoglobin and melanin pigments, making them highly effective for soft tissue applications such as ablation, coagulation, and depigmentation. Diode lasers are minimally absorbed by hydroxyapatite crystals in hard tissues, which allows for the safe removal of epithelial layers from periodontal pockets without damaging the teeth or periosteal bone (Hilgers and Tracey, 2004; Govila *et al*., 2011). As a soft tissue laser, diode lasers are versatile and can be used in various periodontal treatments, including periodontal pocket therapy, gingivitis management, and minor soft tissue surgeries such as frenectomy and operculectomy. They are also effective in treating peri-implantitis, crown lengthening, and gummy smile correction. Additionally, diode lasers can be utilized in certain hard tissue applications, such as root canal disinfection and teeth whitening (Govila *et al*., 2011). Diode lasers are cost-effective, provide excellent cauterization, and offer a clear operating field, along with sterilization benefits (Govila *et al*., 2011).

b. **Carbon Dioxide (CO_2) Lasers.** The active medium in a CO_2 laser is a gas, and it emits light at a wavelength of 10,600 nm. CO_2 laser can operate in continuous or gated modes and exhibits high absorption by water, making it particularly effective for soft tissue applications. Its shallow penetration depth, combined with its hemostatic properties, renders it a valuable tool in periodontics. However, in addition to water,

CO_2 lasers are also highly absorbed by hydroxyapatite crystals. Therefore, when used in the gingival region or periodontal pockets, care must be taken to protect adjacent teeth and bone from carbonization. A significant drawback of CO_2 lasers is their continuous mode of operation, which generates substantial heat and can cause thermal damage to surrounding tissues. Additionally, the delivery system for CO_2 lasers is bulky and costly (Garg *et al*., 2015).

c. **Erbium Laser.** Erbium lasers are available in two wavelengths: Er,Cr:YSGG and Er:YAG. Among the lasers used in periodontics, erbium lasers exhibit a high affinity for both water and hydroxyapatite crystals, making them suitable for hard tissue applications (Harashima *et al*., 2005). These lasers can also be adopted for soft tissue ablation, as soft tissues contain significant amounts of water. Erbium lasers are characterized by shallow tissue penetration and minimal scattering. When applied to hard tissues, these lasers generate considerable heat due to the lower water content in hard tissues compared to soft tissues. The Er,Cr:YSGG laser has a greater affinity for hydroxyapatite than water, making it more effective for hard tissue procedures. In contrast, the Er:YAG laser, with its higher affinity for water, is more efficient for soft tissue applications (Ishikawa *et al*., 2004). Both lasers produce heat during operation, necessitating the use of a water coolant to minimize thermal damage to adjacent tissues. The Er:YAG laser generates less heat and causes less collateral tissue damage compared to the Er,Cr:YSGG laser (Visuri *et al*., 1996). In periodontal treatments, Er:YAG lasers have demonstrated superior results. They are commonly used for decontaminating periodontal pockets, removing calculus, and ablating cementum and dentin surfaces (Aoki *et al*., 2024).

d. **Neodymium-doped, Yttrium Aluminium Garnet (Nd:YAG) laser.** The Nd:YAG laser utilizes a solid-state medium composed of yttrium-aluminum-garnet (YAG) crystals doped with neodymium ions. This laser shows a high affinity for pigmented tissues due to its wavelength, making it particularly effective in soft tissue procedures. Its ability to induce coagulation, achieve hemostasis, and enable precise tissue ablation makes it

a valuable tool in periodontal therapy and can be used in laser-assisted new attachment procedure (LANAP) (De Benedittis *et al*, 2007; Slot *et al*, 2009).

Table 2.11. Lasers Used in Periodontics

Laser	Medium	Wavelength	Delivery system
Diode	Semi-conductor	635nm-980nm	Optical fiber
CO_2	Gas	9600nm-10600nm	Waveguide, articulated arm
Nd:YAG	Solid	1064nm	Optical fiber
Er,Cr:YSGG	Solid	2780nm	Optical fiber
Er:YAG	Solid	2940nm	Opticalfiber, waveguide, articulated arm

CO_2: Carbon Dioxide; Er:YAG: Erbium-doped: Yttrium Aluminium Garnet; Erbium,Chromium-doped: Yttrium Scandium Gallium Garnet ; Nd:YAG: Neodymium-doped: Yttrium Aluminium Garnet; nm: Nanometer(s).

I.2.8.9 Supportive findings on laser use in periodontal regeneration

Lasers play an essential role in periodontal regenerative procedures by providing a dry operating field due to their hemostatic action, thereby enhancing visualization during surgery. Additionally, their sterilization and decontamination properties make them valuable in periodontal flap therapy (Coleton, 2004). Over the past decades, several researches have been performed to assess the efficacy of lasers in surgical periodontal therapies.

The most frequently adopted lasers for surgical periodontal procedures include CO_2, Er:YAG, Nd:YAG, Er,Cr:YSGG, and diode lasers, as they provide high power and precise cutting of periodontal soft tissues. These type of lasers are widely utilized for several treatments such as gingivectomy, gingivoplasty, surgical excision of gingival overgrowths, operculectomy, frenectomy, and subgingival curettage (Theodoro and Garcia, 2015).

Several studies have demonstrated that lasers yield desirable outcomes in NSPT. A review by Ohsugi *et al*. (2020) on the *in vitro* cytological response of periodontal tissues to laser application concluded that lasers enhance healing, reduce inflammation, and promote periodontal tissue regeneration. Their effects include coagulation, anti-inflammatory action, and decontamination. However, laser selection must be application-specific, as different lasers exhibit distinct tissue penetration depths. Nd:YAG and diode lasers, due to their high penetration power, can be used in a wide range of periodontal procedures, whereas Er:YAG and CO_2 lasers, which have lower penetration power, are more suitable for epithelial and connective tissue applications in non-surgical procedures and bone exposure in surgical flap therapy (Ohsugi *et al*., 2020).

A short-term clinical study was conducted on patients with chronic periodontitis and intrabony defects, where defects were treated either with GTR alone or in combination with low-level laser therapy (LLLT). The results demonstrated reduced PD, improved GR, and increased CAL, suggesting that LLLT, when used adjunctively with conventional therapies, enhances periodontal healing (Qadri *et al*., 2005).

In addition to regenerative therapies, low-power He-Ne and diode lasers have been effectively used for photoactivated dye disinfection in the treatment of periodontal pockets and peri-implantitis, as they generate minimal heat, thereby preserving surrounding tissues (Walsh, 2003).

A long-term study evaluating the effects of diode lasers on periodontal pocket therapy concluded that diode lasers, when combined with scaling and root planing (SRP), exhibited significant bactericidal effects and contributed to inflammation reduction (Moritz *et al*., 1998). Additionally, a study on rat jawbones demonstrated that the Er,Cr:YSGG laser provided precise cuts, safety, and accuracy when used for osteotomy and osteoplasty (Wang and Cooke., 2005).

A case series by Brown (2013) assessed the efficacy of lasers in LANAP and found that lasers offer a reliable alternative to conventional periodontal surgery, providing benefits such as reduced inflammation, effective hemostasis, and improved patient comfort compared to traditional methods (Brown, 2013).

An RCT examined the utilization of diode lasers as an adjunct to SRP in chronic periodontitis patients. Although significant improvements in clinical parameters (gingival index (GI), CAL, and periodontal index (PeI) were observed, the variation in bacterial reduction between the test and control groups was minimal (Caruso *et al*., 2008).

Furthermore, a study evaluating Er:YAG laser application in second-stage implant surgery compared two patient groups including one undergoing conventional surgery (control) and the other receiving Er:YAG laser treatment (test). The laser-treated group exhibited less postoperative pain and inflammation, lower necessity for local anesthesia, and enhanced tissue healing (Arnabat-Domínguez *et al*., 2003). **Table 2.12** shows studies supporting the use of laser in periodontal therapy.

I.2.8.10 Contradictory findings on laser use in periodontal regeneration

Although numerous studies support the efficacy of lasers in periodontal therapy, some research presents contradictory findings. A comparative study by Gokhale *et al*. (2012) assessed diode laser-assisted flap surgery versus conventional flap surgery. The results reported no significant change in clinical parameters between test and control groups, though bacterial colony formation was reduced with laser application (Gokhale *et al*., 2012).

A clinical study on 21 patients with 42 infrabony defects compared two groups including one treated with laser and EMP alongside flap surgery, and the other with EMP and EDTA following flap surgery. The results indicated similar clinical outcomes, suggesting that laser use did not significantly improve overall treatment results (Dilsiz *et al*., 2010). Similarly, a pilot study by Schwarz *et al*. (2003) analyzed the management of deep intrabony periodontal defects by combining Er:YAG laser and EMD versus SRP, EDTA, and EMD. The findings revealed no substantial clinical advantage of incorporating lasers with EMD over conventional approaches (Schwarz *et al*., 2003). **Table 2.13** summarizes studies that contradict the use of laser in periodontal therapy.

Table 2.12. Studies that Support the Use of Laser in Periodontal Therapy

St. No	Author & year	Laser used	Methodology	Conclusion
1.	Qadri *et al*., 2005	Low-level lasers	17 patients with moderate periodontitis underwent SRP and then after 1 week test group was treated with low-level lasers. Gingival crevicular fluids were examined after both treatments.	Low-level lasers improved the healing and reduced inflammation in PDL cells.
2.	Moritz *et al*., 1998	Diode	50 patients with periodontal pockets were divided into 2 groups (laser and control) after SRP and treated in 6 appointments for 6 months.	Laser group showed improved periodontal indices and reduced inflammation in adjunct with SRP.
3.	Wang and Cooke., 2005	Er,Cr:YSGG	Er, Cr:YSGG laser were used on rat jaw bones for osteotomy and osteoplasty.	Er, Cr:YSGG laser gave favorable results as they had precision cut and the method was also safe and accurate.
4.	Brown, 2013	Nd:YAG	Case series where lasers were used in LANAP.	There was reduced inflammation, effective haemostasis and more comfortable, compared to conventional method.
5.	Caruso *et al*., 2008	Diode	13 patients with untreated chronic periodontitis were randomly treated by SRP alone (control group) or by SRP + laser irradiation (test group).	Laser when used after scaling and root planning, showed improvement in clinical parameters but there was no much difference between the test and control group in case of reduction of pathogens present in periodontium.
6.	Arnabat-Domínguez *et al*., 2003	ER:YAG	20 patients were divided into 2 groups. One group (control group) underwent conventional 2nd stage of implant surgery and another group (test group) had ER:YAG.	The test group in which laser was used had less pain and post-operative inflammation, need for local anaesthesia was less, tissue healing was also great applied during the surgery.

Er:YAG: Erbium-doped: Yttrium Aluminium Garnet; Er,Cr:YSGG: Erbium, Chromium-doped: Yttrium Scandium Gallium Garnet ; LANAP: Laser-Assisted New Attachment Procedure; Nd:YAG: Neodymium-doped: Yttrium Aluminium Garnet; PDL: Periodontal Ligament; SRP: Scaling and Root Planing; St: Study.

Table 2.13. Studies that Contradict the Use of Laser in Periodontal Therapy

St. No	Author & year	Laser used	Methodology	Conclusion
1.	Gokhale *et al*., 2012	Diode	Comparative evaluation of use of diode laser along with flap surgery and conventional flap surgery	The results showed no much significant difference between these two groups in case of clinical parameters but it was found that colony forming bacteria were reduced when laser was applied.
2.	Dilsiz *et al*., 2010	Nd:YAG	21 patients having 42 infrabony defects were divided into two groups, in one group laser and EMP was used along with surgical flap therapy and second group was treated with EMP and EDTA after opening flap.	The results showed that both studies had similar outcome in case of clinical parameters and use of laser did not show much improvement in overall outcome of the treatment.
3.	Shwarz *et al*., 2003	Er:YAG	Treatment of deep intrabony periodontal defects with a combination of Er:YAG laser and EMD was compared with a combination of SRP, EDTA and EMD.	The use of laser in combination with EMD did not give much clinical outcome compared to the other group.

EMD: *Enamel Matrix Derivatives; EMP: Enamel Matrix Protein; EDTA: Ethylenediaminetetraacetic Acid; Er:YAG: Erbium-doped: Yttrium Aluminium Garnet; Nd:YAG: Neodymium-doped: Yttrium Aluminium Garnet; SRP: Scaling and Root Planing; St: Study.*

I.2.8.11 Advantages and Disadvantages/Limitations

Lasers offer numerous advantages in periodontal therapy, including improved healing and reduced post-operative discomfort. However, their application also presents certain limitations and challenges.

1) Advantages (Dostalova and Jelinkova, 2013; Romanos, 2015)

- **Enhanced sterilization and infection control**: Lasers exhibit bactericidal properties, reducing the risk of post-surgical infections.
- **Effective hemostasis**: The coagulative effect of lasers minimizes intraoperative bleeding, improving the surgical field's visibility.
- **Reduced inflammation and post-operative pain**: Lasers have an anti-inflammatory effect, leading to enhanced patient comfort.
- **Decreased need for anesthesia**: Many laser procedures can be performed with minimal or no anesthesia, reducing patient discomfort.
- **Absence of vibration, pressure, or noise**: Unlike conventional rotary instruments, lasers operate silently, improving the patient’s experience.
- **Accelerated wound healing with minimal scar formation**: Laser-induced biostimulation promotes fibroblast proliferation and collagen synthesis, leading to better tissue regeneration.
- **Reduced need for sutures**: Due to precise tissue ablation and minimal bleeding, many laser-assisted procedures do not require suturing.
- **Minimization of surgical instruments**: Laser procedures often reduce the number of traditional surgical tools required.
- **Versatility in hard and soft tissue applications**: Different laser types can be used for both gingival (soft tissue) and osseous (hard tissue) procedures.
- **Minimally invasive approach**: Laser therapy significantly preserves healthy tissue, resulting in less trauma and faster recovery.

2) Disadvantages and Limitations (Romanos, 2015; Abu-Ta'a and Karameh, 2022)

- **High cost of laser equipment**: The expense of laser devices makes them inaccessible for a large number of dental practitioners.
- **Variability in laser wavelengths and tissue interactions**: Different laser wavelengths have distinct tissue penetration depths and effects, necessitating careful selection for each procedure.
- **Potential thermal damage**: Some lasers generate excessive heat, requiring the use of cooling agents (e.g., air or water spray) to prevent tissue damage.
- **Risk of scattered radiation**: Laser procedures necessitate the use of personal protective equipment (PPE), such as laser-specific safety goggles, to protect both the operator and patient from accidental exposure.
- **Technique sensitivity**: Proper training is essential, as incorrect laser application can lead to thermal necrosis, excessive tissue removal, or delayed healing.
- **Contraindications in medically compromised patients**: Caution should be exercised with the use of lasers in patients with certain systemic conditions, such as uncontrolled diabetes or coagulation disorders, due to potential risks associated with altered healing responses.

PART II – Research Methodology

CHAPTER 3- Material and Methods

II.3.1 Study Design

This study evaluates laser effectiveness in conjunction with regenerative periodontal therapy in patients suffering from periodontitis in the form of a systematic review of literature.

This literature review was conducted in adherence with guidelines of the Cochrane Handbook for Systematic Reviews of Interventions (J.P.T. Higgins *et al*., 2019), ensuring a rigorous, transparent, and methodologically robust approach to the synthesis of evidence.

II.3.2 Search Strategy

A meticulous and systematic search was conducted through reputable databases, including PubMed (MEDLINE), Scopus, and Web of Science, using carefully selected keywords and Medical Subject Headings (MeSH) terms to address the research question on the effectiveness of regenerative periodontal therapy with or without laser use. The search was limited to clinical studies involving human subjects, published in English language exclusively, and encompassed articles up to and including April 2025. The search strategy employed a combination of MeSH terms and keywords, such as: ("Periodontal Diseases"[MeSH Terms] OR "Periodontal Attachment Loss"[MeSH Terms] OR "Alveolar Bone Loss"[MeSH Terms] OR "Periodontitis"[MeSH Terms] OR "Guided Tissue Regeneration, Periodontal"[MeSH Terms] OR "Bone Regeneration"[MeSH Terms]) AND ("Lasers"[MeSH Terms] OR "Laser Therapy"[MeSH Terms] OR "Carbon Dioxide Lasers"[MeSH Terms] OR "Erbium YAG Laser"[MeSH Terms] OR "Diode Laser"[MeSH Terms] OR "Neodymium-Doped Yttrium Aluminum Garnet Lasers"[MeSH Terms]) AND ("regenerative periodontal therapy"[Other Term] OR "periodontal flap"[Other Term] OR "bone graft"[Other Term] OR "barrier membrane"[Other Term] OR "clinical attachment level"[Other Term] OR "probing pocket depth"[Other Term] OR "radiographic

bone gain"[Other Term]) OR "patient satisfaction"[Other Term]) AND English [Filter] AND Clinical Trial[Filter] AND Humans[Filter]. This mentioned combination of terms/keywords was adopted during the search in PubMed. The same terms/key words and Boolean operators (OR, AND) were used in accordance with the various databases as specified above. The combinations of controlled terms (MeSH) and keywords adopted to perform the electronic search are listed in **Table 3.1**. Search results from the databases were efficiently imported into Mendeley Reference Manager, which streamlined bibliography compilation and eliminated duplicates, creating a comprehensive catalog of potentially relevant studies. Initial screening based on titles and abstracts was followed by a thorough evaluation of full-text articles. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist guided the screening process, ensuring the final selection adhered to rigorous standards and supported high-quality, transparent reporting of the systematic review. This methodical approach ensured precision and comprehensiveness in the research process.

Table 3.1. Search Strategy

PubMed Search Strategy
("Periodontal Diseases"[MeSH Terms] OR "Periodontal Attachment Loss"[MeSH Terms] OR "Alveolar Bone Loss"[MeSH Terms] OR "Periodontitis"[MeSH Terms] OR "Guided Tissue Regeneration, Periodontal"[MeSH Terms] OR "Bone Regeneration"[MeSH Terms]) AND ("Lasers"[MeSH Terms] OR "Laser Therapy"[MeSH Terms] OR "Carbon Dioxide Lasers"[MeSH Terms] OR "Erbium YAG Laser"[MeSH Terms] OR "Diode Laser"[MeSH Terms] OR "Neodymium-Doped Yttrium Aluminum Garnet Lasers"[MeSH Terms]) AND ("regenerative periodontal therapy"[Other Term] OR "periodontal flap"[Other Term] OR "bone graft"[Other Term] OR "barrier membrane"[Other Term] OR "clinical attachment level"[Other Term] OR "probing pocket depth"[Other Term] OR "radiographic bone gain"[Other Term]) OR "patient satisfaction"[Other Term]) AND English [Filter] AND Clinical Trial[Filter] AND Humans[Filter]

II.3.3 Eligibility Criteria- Inclusion and Exclusion Criteria

The inclusion criteria built on the PICOS framework (**Table 3.2**) specifically determined study eligibility for the research as shown below:

Study Question/PICOS Strategy:

- **Population/Problem:** Dentate patients with chronic or aggressive moderate to severe periodontal disease, with or without bleeding, exudate, furcation involvement, and GR, age≥18 years, with no restrictions of gender, ethnicity or socioeconomical status.
- **Intervention:** Periodontal tissue regeneration in reconstructive or regenerative periodontal surgical therapy using FDA (Food and Drug Administration)-approved CO_2, Nd:YAG, Er:YAG, or diode lasers as adjunctive tools.
- **Comparison:** Periodontal tissue regeneration in reconstructive or regenerative periodontal surgical therapy without the use of lasers as adjunctive tools.
- **Outcomes:**
  - **Primary Outcomes:** Clinical outcomes including PPD reduction, CAL gain, RB gain, GR, BoP, and exudate.
  - **Secondary Outcomes**: PCOs such as discomfort, aesthetics, and functional improvements.
- **Study Design:** Prospective, retrospective, randomized, or non-randomized studies involving regenerative periodontal therapy with various surgical approaches/techniques, with or without the use of lasers.

Studies were required to report factors such as the number of patients, number of defect sites, systemic conditions (e.g., smoking or other conditions that might influence outcomes), and the use of materials like bone grafts or barrier membranes.

Conversely, articles were excluded if they were case reports or case series with fewer than 10 patients, systematic reviews, pre-clinical animal studies, or studies focusing on non-surgical therapy (e.g., SRP). Studies with incomplete or missing information were also ruled out (**Table 3.3**).

Table 3.2. Inclusion Criteria

Selection Criteria	
Inclusion criteria	
Population/Problem	Dentate patients with chronic or aggressive moderate to severe periodontal disease, with or without bleeding, exudate, furcation involvement, and GR, age≥18 years, with no restrictions of gender, ethnicity or socioeconomical status.
Intervention	Periodontal tissue regeneration in reconstructive or regenerative periodontal surgical therapy using FDA-approved CO_2, Nd:YAG, Er:YAG, or diode lasers as adjunctive tools.
Comparison	Periodontal tissue regeneration in reconstructive or regenerative periodontal surgical therapy without the use of lasers as adjunctive tools.
Outcomes	**Primary Outcomes:** Clinical outcomes including PPD reduction, CAL gain, RB gain, GR, BoP, and exudate. **Secondary Outcomes**: PCOs such as discomfort, aesthetics, and functional improvements.
Study design	Prospective, retrospective, randomized, or non-randomized studies involving regenerative periodontal therapy with various surgical approaches/techniques, with or without the use of lasers

BoP: Bleeding on probing; CAL: Clinical Attachment Level; CO_2: Carbon Dioxide; Er:YAG: Erbium-doped: Yttrium Aluminium Garnet; FDA: Food and Drug Administration; GR: Gingival Recession; Nd:YAG: Neodymium-doped: Yttrium Aluminium Garnet; PCO: Patient-Centered Outcome; PPD: Probing Pocket Depth; RB: Radiographic Bone.

Table 3.3. Exclusion Criteria

Selection Criteria
Exclusion criteria
Abstracts
Case reports with fewer than 10 patients
Case series with fewer than 10 patients
Interviews
Letters to editor
Opinion articles
Review articles
Studies *in vitro*
Studies focusing on NSPT
Studies with incomplete or missing information
Pre-clinical animal studies
Unpublished studies
Updates

NSPT: Non-Surgical Periodontal Treatment.

II.3.4 Types of Outcomes Measured

This study systematically evaluated and compared the effectiveness of regenerative periodontal therapy with and without laser use through targeted clinical, radiographic, and PCOs. Clinical effectiveness was evaluated by measuring PPD reduction, CAL gain, GR, BoP, and exudate presence, reported as baseline, final, and changes in millimeters or percentages, to compare laser-assisted and non-laser-assisted periodontal regenerative surgical techniques. RB gain was quantified through changes in bone levels, expressed as baseline and final values or percentage increases, to evaluate bone regeneration outcomes. PCOs, including discomfort, aesthetics, and functional improvements, were

assessed via patient-reported measures such as pain levels, aesthetic satisfaction, and enhanced chewing or speaking function, reflecting treatment impact on quality of life.

II.3.5 Study Selection and Data Process

Eligibility assessment was performed on three levels of screening. In particular, a meticulously screening of titles and abstracts of studies retrieved via the predefined search strategy was performed. Furthermore, full-text article abstracts were assessed for relevance and compliance with inclusion criteria. Moreover, a thorough full-text screening was conducted in order to perform the critical appraisal of full articles. At the second and third levels of screening, an explanation for the exclusion of each study was given. Additionally, a hand search of potentially relevant articles identified during the process was undertaken to uncover further studies, boosting the comprehensiveness of the literature retrieval for the forthcoming systematic review.

For data extraction, a meticulously crafted form was developed using an MS Excel spreadsheet, tailored specifically to the objectives and variables outlined in our literature review. This structured tool was thoughtfully designed to capture a comprehensive range of critical data points. Study characteristics and clinical outcomes were extracted, including the author and year of publication, study design, number of patients in the test and control groups, patient age, and the presence of systemic conditions. Information regarding the number and type of periodontal defects, the type and wavelength of laser used, the surgical technique employed, and the duration of follow-up was also collected. Clinical outcomes included baseline and final values, as well as changes in PPD, CAL, and RB gain. Inflammatory indicators such as BoP and suppuration were recorded as percentages at baseline and follow-up, along with their respective reductions. GR was noted at both time points, including any increase observed. PCOs, such as discomfort, aesthetic satisfaction, and functional improvement, were also documented when available. This approach ensured that all essential information was captured systematically and with a high degree of accuracy.

II.3.6 Qualitative and Quantitative Analysis of Included Studies

III.3.6.1 Qualitative analysis

The methodological quality of the included studies was independently evaluated using the Cochrane Risk of Bias tool (RoB 2.0) for RCTs (Sterne *et al*., 2019) and the ROBINS-I tool for non-randomized studies, as appropriate (Sterne *et al*., 2016). Each domain (random sequence generation, allocation concealment, blinding of participants and assessors, incomplete outcome data, selective reporting, and other potential sources of bias) was assessed and categorized as low risk, high risk, or unclear risk. The results of this assessment were graphically presented using Review Manager (RevMan)-generated risk of bias summary tables and traffic light plots, which provided a graphic outline of the distribution of bias across all included studies. This allowed clear identification of domains most prone to methodological limitations and ensured transparency in the interpretation of pooled outcome.

III.3.6.2 Quantitative analysis

A systematic meta-analysis was performed to quantitatively synthesize the outcomes of the included studies. For this purpose, the RevMan 5.4 software (RevMan, 2020) was used. Continuous variables (e.g., PPD reduction, CAL gain) were expressed as MDs with corresponding 95% confidence intervals (CIs)**.** When studies reported outcomes using different measurement scales, standardized mean differences (MDs) were calculated to ensure comparability. Heterogeneity among the included studies was evaluated using the Cochran's Q test and quantified with the I^2 statistic**.** An I^2 value greater than 50% was interpreted as indicative of substantial heterogeneity.

Forest plots were generated in RevMan to visually represent the combined effect estimates. Each study was plotted with its respective effect size and 95% CI, with the weight of each study determined by sample size and variance. The pooled estimate was displayed as a diamond, where the center indicated the overall effect and the width represented the CI. Publication bias and small study effects were investigated through funnel plot analysis. Symmetry of the funnel plot suggested minimal publication

bias, whereas marked asymmetry was interpreted cautiously as potential bias or heterogeneity.

II.3.7 Analyzing and Presenting Results- Evidence Table Structure

Given the diversity in study designs and laser types, the analysis was categorized into two distinct subgroups:

- **Group 1:** Regenerative periodontal surgery (GTR/EMP/Bone substitutes/CAFs) with laser treatment.
- **Group 2**: Regenerative periodontal surgery GTR/EMP/Bone substitutes/CAFs) without laser treatment.

The data extracted from the included studies, including summaries of treatment procedures and laser parameters were presented in well-structured tables. Moreover, results were organized in tables according to treatment modalities, follow-up durations, and outcome measures to facilitate clear and comprehensive reporting.

II.3.8 Ethical Consideration

The present research is a review that utilizes publicly accessible materials as evidence and does not involve the collection of any private, sensitive, or confidential information from participants. Therefore, ethical approval was not required.

PART III – Results and Discussion

CHAPTER 4- Contents and Results

III.4.1. Literature Search Results

A comprehensive literature search was conducted to identify studies evaluating regenerative periodontal therapy with or without adjunctive laser use. A total of 770 articles were retrieved from electronic databases, including PubMed, Scopus, and Web of Science. After the removal of duplicates, 250 articles remained. Initial title screening excluded 187 studies that were not relevant to regenerative periodontal surgery or laser applications. The abstracts of the remaining 63 studies were reviewed, and 25 were excluded based on the predefined inclusion and exclusion criteria. Full-text analysis was performed for 38 studies, of which 20 were excluded for the following reasons: not primary clinical studies (n = 6) (Sculean *et al*., 2004; Alagl, 2015; Al-Falaki *et al*., 2016; Jonnalagadda *et al*., 2018; El Sharaki, 2023; Dervisbegovic *et al*., 2025), animal or pre-clinical studies (n = 3) (Pinheiro *et al*., 2003; Bosco *et al*., 2016; Rossi *et al*., 2024), use of PRF/PRP (n = 4) (Thalaimalai *et al*., 2020; Ebada *et al*., 2020; Hatab *et al*., 2023, Satpathy *et al*., 2023), inappropriate study design (n = 2) (Gilio, 2003; Salarmaaf *et al*., 2018), and incorrect intervention (n = 5) (Soares *et al*., 2014; Bereşescu *et al*., 2015; Yan *et al*., 2018; de Souza Fonseca *et al*., 2023; Olazábal and Glikel, 2023). Ultimately, 18 studies were included in this review. The selection process of the studies is displayed in **Figure 4.1**, whereas **Table 4.1** shows the excluded articles following full-text evaluation and outlines the reasons for exclusion.

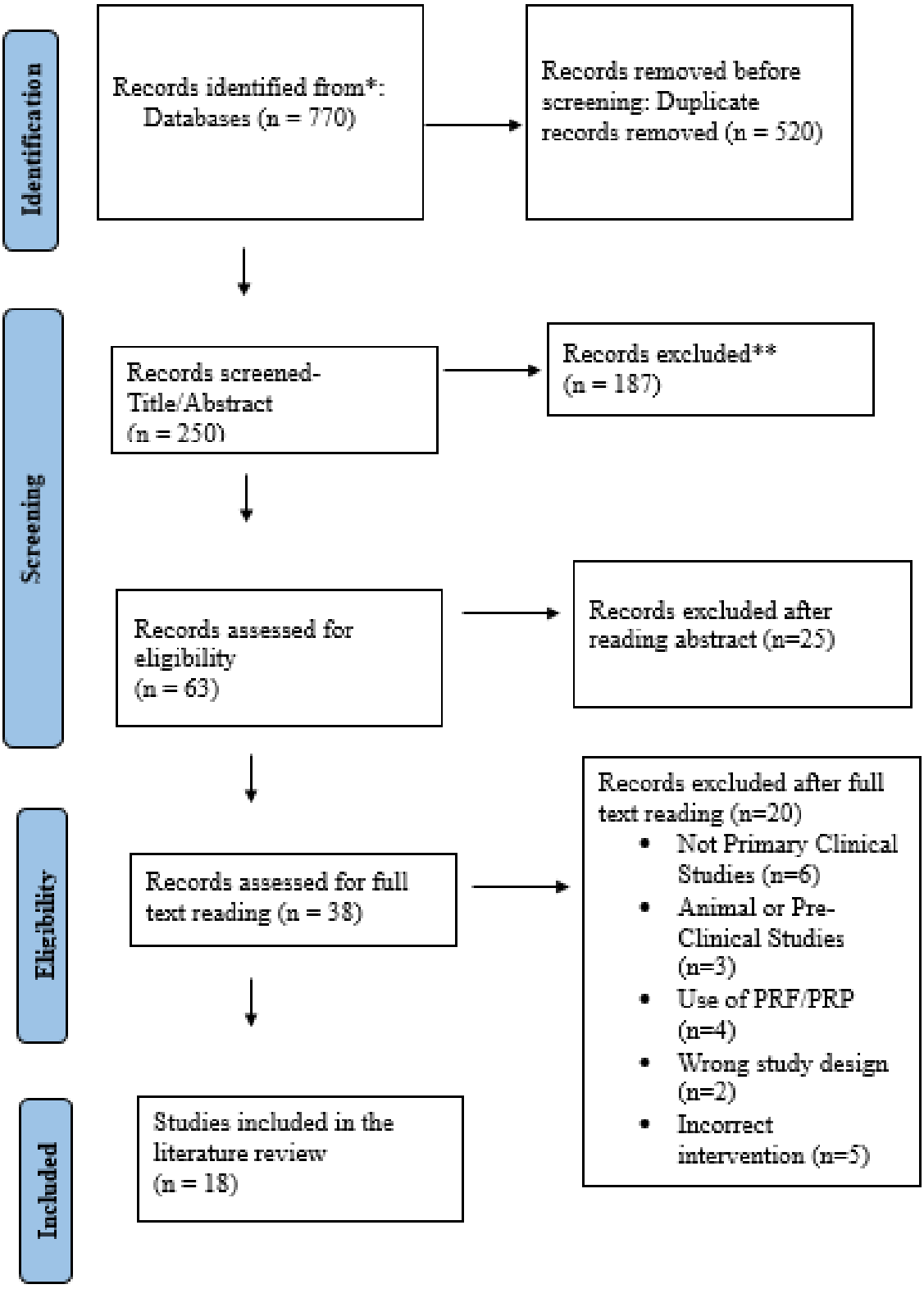

***Figure 4.1**. Selection process of the studies. Illustration via PRISMA 2020 flow diagram [source: (Page et al., 2021)].*

Table 4.1. Studies Excluded following Full-Text Analysis and Reasons for Exclusion

Author/ Year	Reason for Exclusion
Gilio, 2003	Case report (not a clinical study with ≥10 patients).
Pinheiro *et al.,* 2003	Conducted on an animal model (Wistar rats).
Soares *et al.,* 2014	It is a secondary review article and not a primary clinical study.
Alagl, 2015	No reporting on the type of laser or its wavelength.
Bereşescu *et al.,* 2015	Primarily histological, limited reporting of clinical outcomes (no result table provided).
Al-Falaki *et al.,* 2016	Laser-only therapy without adjunctive regenerative biomaterial.
Bosco *et al.,* 2016	Pre-clinical animal study.
Jonnalagadda *et al.,* 2018	Focus is on conventional flap surgery, not regenerative periodontal surgery (no biomaterials used).
Salarmaaf *et al.,* 2018	Case report (single patient).
Yan *et al.,* 2018	The study is a systematic review/ meta-analysis.
Ebada *et al.,* 2020	Use of PRF.
Thalaimalai *et al.,* 2020	Use of PRF.
de Souza Fonseca *et al.,* 2023	Only 1 patient met inclusion criteria.
El Sharaki, 2023	The study compares laser therapy vs PRP without mention of surgical regenerative procedures.
Hatab *et al.,* 2023	Use of PRF.
Olazábal and Glikel, 2023	This is a systematic review/ literature review and is published in Spanish.
Satpathy *et al*., 2023	Use of PRP in combination with hydroxyapatite. crystals.
Rossi *et al*., 2024	Pre-clinical animal study conducted on rats.
Sculean *et al*., 2004	Er: YAG laser is used for debridement, not to induce or enhance periodontal regeneration.
Dervisbegovic *et al.,* 2025	Non-surgical periodontal therapy study focusing on SRP.

Er: YAG: Erbium-doped: Yttrium Aluminium Garnet; PRF: Platelet-Rich Fibrin; PRP: Platelet-Rich Plasma; SRP: Scaling and Root Planing.

III. 4.2 Summary of the Evidence- Characteristics of Included Studies

III. 4.2.1 Study design

Among the 18 included studies, 17 articles were RCTs which are considered as the gold standard to minimize bias by random allocation of participants. (Danish *et al*., 2024; Dharani *et al*., 2024; Vinaya *et al*., 2023; Amitha *et al*., 2022; Gangolu *et al*., 2022; Attia *et al*., 2019; Gamil *et al*., 2019; Gupta *et al*., 2019; Doğan *et al*., 2016, 2014; Singh *et al*., 2015; Ozturan *et al*., 2011; Dilsiz *et al*., 2010; Hazzaa *et al*., 2010; AboElsaad *et al*., 2009; Ozcelik *et al*., 2008; Schwarz *et al*., 2003). The remaining one prospective case series (Schwarz *et al*., 2006) was a non-randomized clinical study.

Several trials used a split-mouth design, which enabled comparisons within subject, reducing inter-individual variability (Vinaya *et al*., 2023; Gangolu *et al*., 2022; Amitha *et al*., 2022; Attia *et al*., 2019; Gupta *et al*., 2019; Singh *et al*., 2015; Doğan *et al*., 2014; Ozturan *et al*., 2011; Dilsiz *et al*., 2010; AboElsaad *et al*., 2009; Ozcelik *et al*., 2008), while others adopted a parallel-group approach to prevent carry-over effects (Gamil *et al*., 2019; Hazzaa *et al*., 2010; Schwarz *et al*., 2003). Blinding was implemented in some studies to reduce observer bias (Amitha *et al*., 2022; Ozcelik *et al*., 2008).

III.4.2.2 Number of study participants

Across the 18 clinical studies on periodontal regenerative therapies published between 2003 and 2024, a total of 316 participants were enrolled, with sample sizes ranging from 10 to 40 patients, reflecting notable variation in study scale and statistical power. The smallest cohorts were reported by Dharani *et al*. (2024) (n = 10), Singh *et al*. (2015) (n = 10; 3 females, 7 males), and Ozturan *et al*. (2011) (n = 10), while the largest was by Vinaya *et al*. (2023) (n = 40). Moderate sample sizes were observed in Danish *et al*. (2024) (n = 15), Amitha *et al*. (2022) (n = 15; 14 males, 1 female), and Attia *et al*. (2019) (n = 15; 11 females, 4 males). About articles from Gangolu *et al*. (2022) and Gupta *et al*. (2019), each report studied 12 participants, whereas Doğan *et al*. (2014) included 13 (7 males, 6 females). Larger mid-range cohorts included Gamil *et al*. (2019) (n = 32), Doğan *et al*. (2016) (n = 25), Dilsiz *et al.* (2010) (n = 21; 9 males, 12 females), Hazzaa *et al*. (2010) (n = 17), AboElsaad *et al*. (2009) (n = 20; 15 females, 5 males), Ozcelik *et al*. (2008) (n = 22;

12 males, 10 females), Schwarz *et al.* (2006) (n = 15; 7 males, 8 females), and Schwarz *et al.* (2003) (n = 22; 12 males, 10 females). Overall, the evidence base comprises of small- to medium-sized trials.

III.4.2.3 Gender distribution

Gender distribution was reported in 11 of the 18 studies. Male-dominant cohorts were observed in Amitha *et al.* (2022), which enrolled 14 males and 1 female, Doğan *et al.* (2016) with 15 males and 10 females, Singh *et al*. (2015) with 7 males and 3 females, and Ozcelik *et al*. (2008) with 12 males and 10 females. Female-dominant cohorts were noted in Attia *et al.* (2019), which included 4 males and 11 females, Dilsiz *et al.* (2010) with 9 males and 12 females, Ozturan *et al.* (2011) with 4 males and 6 females, and AboElsaad *et al*. (2009) with 5 males and 15 females. Nearly balanced cohorts were seen in Doğan *et al.* (2014), which reported 7 males and 6 females, Schwarz *et al.* (2004) with 7 males and 8 females, and Schwarz *et al.* (2003) with 12 males and 10 females. The remaining seven studies (Danish *et al*., 2024; Dharani *et al*., 2024; Vinaya *et al*., 2023; Gangolu *et al*., 2022; Gupta *et al*., 2019; Gamil *et al*., 2019; Hazzaa *et al*., 2010) did not provide gender-specific data. Heterogeneity in data restricted sex-based comparisons.

III.4.2.4 Study samples- Age of participants

Age distribution in most studies reported age ranges, while few reports provided mean ages with standard deviations (SDs). Broad adult cohorts were seen in Danish *et al.* (2024) (18–60 years), Gangolu *et al*. (2022) and Gupta *et al.* (2019) (20–65 years each), Dharani *et al*. (2024) (20–50 years). Middle-aged focus was noted in Vinaya *et al*. (2023) (35–60 years), Gamil *et al*. (2019) (28–51 years), Dilsiz *et al.* (2010) (33–46 years; mean 39.2 ± 4 years; 9 males, 12 females), and Ozcelik *et al*. (2008) (31–49 years). Younger cohorts included Attia *et al*. (2019) (25–37 years), Singh *et al*. (2015) (21–36 years; mean 27 ± 5.41 years; 3 females, 7 males), and Hazzaa *et al*. (2010) (22–37 years). Balanced young–middle-aged groups were enrolled by Amitha *et al*. (2022) (20–55 years), Doğan *et al*. (2016) (26–52 years), and Doğan *et al*. (2014) (26–49 years). Older cohorts were represented by Schwarz *et al*. (2006) (mean 49 ± 12 years; 7 males, 8 females) and Schwarz *et al*. (2003) (32–61 years; 12 males, 10 females). AboElsaad *et al*. (2009) (33–

57 years) spanned middle to older age groups, while Ozturan *et al*. (2011) (mean 34 years) reflected a younger population. Overall, age ranges varied from narrow (e.g., 25–37 years) to broad (e.g., 20–65 years), with four studies reporting mean ages for greater precision.

III.4.2.5 Smoking and systemic health status

Across the 18 included studies, 14 articles included non-smokers to lower the risk of confounding effects of smoking on periodontal regeneration and healing. Meanwhile, Schwarz *et al*. (2003, 2006) each enrolled six smokers, introducing potential variability. Two studies (Vinaya *et al*., 2023; Gupta *et al*., 2019) did not document smoking status.

All studies included healthy participants without any systemic conditions. This aids in the comparability across trials but restricts the applicability of findings to populations with comorbidities.

III.4.2.6 Intervention/Comparison groups: Test (T) / Control (C)

The 18 clinical studies evaluating periodontal regenerative therapies from 2003 to 2024 used varying group allocations to compare adjunctive laser therapy with standard regenerative interventions. Among the selected articles, 17 studies employed two-group designs, while one (Schwarz *et al*., 2006) was a non-controlled case series.

Dharani *et al*. (2024) included 20 patients, with the test group (n = 10) receiving concentrated growth factor (CGF) plus laser therapy and the control group (n = 10) receiving CGF alone. Similarly, Danish *et al*. (2024) enrolled 20 patients, with 10 in the test group treated with bioactive glass and Gallium Aluminium Arsenide (GaAlAs) laser, and 10 in the control group treated with bioactive glass alone. Vinaya *et al*. (2023) allocated 80 patients into two equal groups, where the test group received bone graft plus laser and the control group received bone graft alone. Gangolu *et al*. (2022) assigned 24 patients into two groups of 12 each, comparing hydroxyapatite grafts with and without adjunctive laser therapy. Amitha *et al*. (2022) enrolled 30 patients, with the test group (n = 15) undergoing CAF with LLLT and the control group (n = 15) receiving CAF alone. Attia *et al*. (2019) also included 30 patients, equally divided between a test group that underwent regenerative therapy using bioactive glass + collagen membrane with laser

irradiation and a control group that received graft material without laser. In the same year, Gamil *et al*. (2019) studied 32 patients, assigning 16 to a test group that received OFD with demineralized bone matrix (DBM) plus laser, and 16 to a control group treated with OFD and DBM alone. Gupta *et al*. (2019) evaluated 24 patients, equally divided between biomaterial with laser and biomaterial alone.

Doğan *et al*. (2016) included 33 patients, with 17 in the test group receiving GTR with laser and 16 in the control group treated with GTR alone. Singh *et al*. (2015) studied 40 patients divided equally into CAF with LLLT and CAF alone. In a similar design, Doğan *et al.* (2014) included 26 patients, allocating 13 to GTR with LLLT and 13 to GTR alone. Ozturan *et al*. (2011) examined a larger cohort of 74 patients, evenly divided between CAF with low-intensity laser therapy (LILT) and CAF alone. Dilsiz *et al*. (2010) included 42 patients, with 21 in each group comparing EMDs with and without adjunctive laser therapy.

Hazzaa *et al*. (2010) enrolled 20 patients, where the test group (n = 10) received DBM with laser in combination with OFD, and the control group (n = 10) received DBM with OFD alone. AboElsaad *et al*. (2009) studied 40 patients, assigning 20 to bioactive glass with laser and 20 to bioactive glass alone. Similarly, Ozcelik *et al*. (2008) included 22 patients, with 10 in the test group receiving EMD with laser and 12 in the control group treated with EMD alone. In contrast, Schwarz *et al*. (2006) presented a prospective case series of 15 patients without a control group. An earlier study by Schwarz *et al*. (2003) included 22 patients, equally divided between a test group receiving EMD plus laser and a control group treated with only EMD.

III.4.2.7 Types and number of defects

Across the 18 included studies different categories of periodontal defects were evaluated. A total of 10 studies investigated intrabony or deep intrabony defects, with defect numbers ranging from 10 to 80, including 10 (Dharani *et al*., 2024), 24 (Gangolu *et al*., 2022), 30 (Attia *et al*., 2019), 24 (Gupta *et al*., 2019), 26 (Doğan *et al*., 2014), 42 (Dilsiz *et al*., 2010), 20 (Hazzaa *et al*., 2010), 44 (Ozcelik *et al*., 2008), 15 (Schwarz *et al*., 2006), and 11 (Schwarz *et al*., 2003), with Vinaya *et al*. (2023) contributing the largest sample of 80

bilateral defects. Two studies focused on infrabony defects, reporting 30 defects (Danish *et al*., 2024) and 40 bilateral defects (AboElsaad *et al*., 2009). Three studies examined GR defects, with 30 (Amitha *et a*l., 2022), 40 (Singh *et al*., 2015), and 74 (Ozturan *et al*., 2011) defects, the latter being the largest soft tissue cohort. One study addressed Class II furcation defects, reporting 33 cases (Doğan *et al*., 2016). Overall, these investigations highlight variations in both defect types and sample sizes, reflecting the heterogeneity of the available data.

III.4.2.8 Type of laser- Wavelength- Power setting

Various lasers were used as adjuncts in periodontal regenerative treatments, with specific wavelengths and power settings influencing their efficacy. Diode lasers (588–980 nm) were most frequently applied. Shorter wavelengths (588–635 nm, 0.12–0.1 W) targeted superficial tissue effects in addition to CAF procedures, EMD applications, and DBM (Ozcelik *et al*., 2008; Ozturan *et al*., 2011; Gamil *et al*., 2019). Wavelengths of 810–980 nm, with power settings ranging from 0.3–3 W, enhanced deeper healing when combined with CGF, bone grafts, CAF, or biomaterials (Dharani *et al*., 2024, 810 ± 20 nm, 0.5 W; Vinaya *et al*., 2023, 810 nm, 2.5 W; Amitha *et al*., 2022, 810 nm, 0.12 W; Gangolu *et al*., 2022, 980 nm, 3 W; Gupta *et al*., 2019, 810 nm, 2.5 W). GaAlAs lasers (660–870 nm, 0.025–0.1 W) were employed with bioactive glass, CAF, or DBM to promote biostimulation in infrabony defects (Danish *et al*., 2024, 660 nm, 0.025 W; Attia *et al*., 2019, 870 nm, 0.08 W; Singh *et al*., 2015, 810 nm, 0.3 W; Hazzaa *et al*., 2010, 870 nm, 0.1 W; AboElsaad *et al*., 2009, 830 nm, 0.04 W). Nd:YAG lasers (1064 nm, 0.1–1 W) were used with GTR or EMD for deep tissue regeneration (Doğan *et al*., 2016, 1064 nm, 0.1 W; Doğan *et al*., 2014, 1064 nm, 0.1 W; Dilsiz *et al*., 2010, 1064 nm, 1 W). Er:YAG lasers (2.94 µm, 1.36 W) provided ablative effects with or without EMD (Schwarz *et al*., 2003, 2006). Overall, diode and GaAlAs lasers dominated for biostimulation, Nd:YAG for deeper penetration, and Er:YAG for ablation.

III.4.2.8 Follow-up time

Most studies had a short- to medium-term follow-up period, evaluating the efficacy of regenerative procedures with or without lasers at three and six months (Danish *et al*.,

2024; Dharani et al., 2024; Vinaya *et al*., 2023; Gangolu *et al*., 2022; Gupta *et al*., 2019). Several studies restricted follow-up to six months, making it the most common assessment duration (Amitha *et al*., 2022; Gamil *et al*., 2019; Doğan *et al*., 2014, 2016; Singh *et al*., 2015; Hazzaa *et al*., 2010; AboElsaad *et al*., 2009; Schwarz *et al*., 2003, 2006). In contrast, only few studies extended to nine or 12 months (Attia *et al*., 2019; Ozturan *et al*., 2011; Dilsiz *et al*., 2010; Ozcelik *et al*., 2008), highlighting the scarcity of long-term data. **Table 4.2** presents the characteristics of the 18 selected articles.

Table 4.2. Characteristic of Included Studies

Study Information **Author/Year** **Study type** **Study design**	***Patient Characteristics*** **Number of patients(n)** **Age** **Gender** **Smoking status** **Systemic health** **No. and type of periodontal defects,** **Groups (Test/Control)**	***Regenerative Procedure***	***Laser characteristics/ parameters*** **Laser type** **Wavelength** **Watt**	***Findings Observed***
-Dharani *et al.,* 2024 -RCT -Split-mouth	-n. patients: 10 -Age: 20-50 years -Male/Female: ND -Smokers: No -Systemic Health: No Type -Number of Defects: 10 intrabony defects -Groups: T. (CGF + laser): 10; C. (CGF): 10	-CGF membrane	-Diode laser -810 ± 20 nm -0.5 W	-Follow-up: 3 and 6 months -Mean PD Reduction: T: 5.3 ± 0.28 mm; C: 4.0 ± 0.34 mm -Mean CAL Gain: T: 5.30 ± 0.44 mm; C: 4.0 ± 0.25 mm -RB Gain: T: 2.122 ± 0.178 mm; C: 1.987 ± 0.155 mm -BoP Reduction: 52.14 ± 2.74% (GBI, no separate distinction for groups) -Suppuration Reduction: ND -Recession Increase: ND -Patient Outcomes: No Comment: -Comment: PPD and CAL from Friedman test; BoP as GBI
-Danish *et al.,* 2024 -RCT, -Parallel, double-blinded split-mouth trial	-n. patients: 15 -Age: 18-60 years -Male/Female: ND -Smokers: No -Systemic Health: No -Type and Number of Defects: 30 infrabony defects -Groups: T. (bioactive glass and GaAlAs laser): 10; C. (bioactive glass): 10	-Bioactive Glass	-GaAlAs laser -660 nm - 25 mW	-Follow-up: 3 and 6 months -Mean PD Reduction: T: 4.75 ± 0.98 mm; C: 4.70 ± 1.05 mm -Mean CAL Gain: T: 4.38 ± 0.91 mm; C: 3.85 ± 1.19 mm -RB Gain: T: 5.60 mm; C: 3.77 mm -BoP Reduction: ND -Suppuration Reduction: ND -Recession Increase: ND -Patient Outcomes: No
-Vinaya *et al.,* 2023 -RCT -Split-mouth trial	-n. patients: 40 -Age: 35-60 years -Male/Female: ND -Smokers: ND -Systemic Health: No	-Bone graft ([HA + β-TCP)	Diode laser 810 nm 2.5 W	-Follow-up: 3 and 6 months -Mean PD reduction: T: 4.10 ± 0.40 mm; C: 4.24 ± 0.74 mm -Mean CAL Gain: T: 3.21 ± 0.02 mm; C: 1.24 ± 0.04 mm -RB gain: ND -BoP reduction: ND -Suppuration reduction: ND

	-Type and Number of Defects: 80 (bilateral defects in 40 patients), intrabony defect -Groups: T (bone graft + laser): 40; C (bone Graft): 40			-Recession increase: T: 1.30 ± 0.22 mm; C: 0.20 ± 0.38 mm -Patient outcomes: None of the patients reported any adverse reaction -Comment: Recession increase value as mentioned in study
-Gangolu *et al*., 2022 -Randomized prospective clinical trial -Split-mouth	-n. patients: 12 -Age: 20-65 years -Male/Female: ND -Smokers: No -Systemic Health: No -Type and Number of Defects: 24 bilateral intrabony defects -Groups: T (graft + laser): 12; C (only grafts): 12	-HA graft	-Diode laser -980 nm -3 W	-Follow-up: 3 and 6 months -Mean PD reduction: T: 2.00 ± 2.04 mm; C: 2.08 ± 1.82 mm -Mean CAL Gain: T: 2.00 ± 3.38 mm; C: 2.08 ± 3.25 mm -Radiographic Bone Gain: T: 1.201 mm; C: 0.498 mm (linear bone fill) -BoP Reduction: ND -Suppuration Reduction: ND -Recession Increase: ND -Patient Outcomes: No
-Amitha *et al.,* 2022 -Prospective randomized clinical trial -Split-mouth	-n. patients: 15 (14 males and 1 female) -Age: 20–55 years -Male/Female: 14 males, 1 female -Smokers: No -Systemic Health: No -Type and Number of Defects: 30 GR -Groups: T (CAF procedure + LLLT): 15; C (CAF procedure): 15	-CAF	-Diode laser -810 nm -120 mW	-Follow-up: 6 months -Mean PD Reduction: Showed no difference between T and C -Mean CAL Gain: T: 3.1 ± 0.98 mm; C: 2.0 ± 1.09 mm -RB Gain: ND -BoP Reduction: ND -Suppuration Reduction: ND -Recession Increase: T: 2.90 ± 0.934 mm; C: 1.77 ± 1.04 mm -Patient Outcomes: Yes (VAS scale: patients experienced less pain) -Comment: PD: no major alterations
-Attia *et al.,* 2019 -Prospective RCT -Split-mouth	-n. patients: 15 (11 females and 4 males) -Age: 25-37 years -Male/Female: 4 males, 11 females -Smokers: No -Systemic Health: No -Type and Number of Defects: 30 intrabony defect -Groups: T (regenerative therapy with laser irradiation): 15; C (regenerative therapy): 15	-Bioactive Glass + Collagen Membrane	-GaAlAs diode laser -870 nm -80 mW	-Follow-up: 9 months -Mean PD Reduction: T: 64.57% (64.57 ± 9.37); C: 64.95% (64.95 ± 10.07) -Mean CAL Gain: T: 59.77 ± 12.1%; C: 38.83 ± 7.56% (baseline to 9 months % change) -RB Gain: ND -BoP Reduction: ND -Suppuration Reduction: ND -Recession Increase: ND -Patient Outcomes: No -Comment: CAL values for C group not mentioned

-Gamil *et al.,* 2019 -Prospective RCT -Parallel-group	-n. patients: 32 -Age: 28-51 years -Male/Female: ND -Smokers: No -Systemic Health: No -Type and Number of Defects: 2 or 3-wall intrabony defect around premolar or molar teeth -Groups: T (OFD + DBM + laser): 16; C (OFD + DBM): 16	-DBM	-Diode laser -635 nm -100 mW	-Follow-up: 6 months -Mean PD Reduction: T: 4.2 ± 1.04 mm; C: 3.9 ± 1.14 mm -Mean CAL Gain: T: 4.31 ± 1.06 mm; C: 2.72 ± 1.27 mm -RB Gain: T: 4.5 ± 0.86 mm; C: 2.6 ± 1.20 mm -BoP Reduction: ND -Suppuration Reduction: ND -Recession Increase: ND -Patient Outcomes: No
-Gupta *et al,* 2019 -Prospective RCT -Split-mouth	-n. patients: 12 -Age: 20-65 years -Male/Female: ND -Smokers: ND -Systemic Health: No -Type and Number of Defects: 24 intrabony defect -Groups: T (biomaterial + laser): 12; C (biomaterial): 12	-Bioactive Glass	Diode laser 810 nm 2.5 W	-Follow-up: 3 and 6 months -Mean PD Reduction: T: 3.91 ± 0.66 mm; C: 4.08 ± 0.90 mm -Mean CAL Gain: T: 3.16 ± 0.57 mm; C: 3.25 ± 0.62 mm -RB Gain: T: 0.95 ± 0.68 mm; C: 1.33 ± 0.57 mm -BoP Reduction: ND -Suppuration Reduction: ND -Recession Increase: T: 0.66 ± 0.65 mm; C: 0.75 ± 0.96 mm -Patient Outcomes: No
-Doğan *et al.,* 2016 -Prospective RCT -Split-mouth	-n. patients: 25 (15 males, 10 females) -Age: 26-52 years -Male/Female: 15 males, 10 females -Smokers: No -Systemic Health: No -Type and Number of Defects: 33 class II furcation defects -Groups: T (GTR + laser): 17; C (GTR): 16	-GTR with Equine bone graft and collagen resorbable equine membranes	-Nd: YAG -1064 nm -100 mW	-Follow-up: 6 months -Mean PD Reduction: T: 2.75 ± 0.67 mm; C: 2.73 ± 0.68 mm -Mean CAL Gain: T: 2.61 ± 1.56 mm; C: 2.16 ± 0.95 mm -RB Gain: ND -BoP Reduction: ND -Suppuration Reduction: ND -Recession Increase: ND -Patient Outcomes: No
-Singh *et al.,* 2015 -Prospective RCT -Split-mouth	n. patients: 10 (3 females and 7 males) Age: 21-36 years (mean: 27 ± 5.41 years) Male/Female: 7 males, 3 females Smokers: No Systemic Health: No	-CAF	-GaAlAs Diode laser -810 nm -0.3 W	-Follow-up: 6 months -Mean PD Reduction: ND -Mean CAL Gain: T: 4.05 ± 1.093 mm; C: 3.05 ± 1.29 mm -RB Gain: ND -BoP Reduction: ND -Suppuration Reduction: ND -Recession Increase: T: 2.3 ± 0.590 mm; C: 1.40 ± 1.21 mm -Patient Outcomes: No

	Type and Number of Defects: 40 GRs Groups: T (SCAF + LLLT): 20; Control (SCAF): 20			-Comment: Root coverage (T: 90%; C: 30%)
-Doğan *et al.,* 2014 -Prospective RCT -Split-mouth	-n. patients: 13 (7 males and 6 females) -Age: 26-49 years Male/Female: 7 males, 6 females -Smokers: No -Systemic Health: No -Type and Number of Defects: 26 intrabony defects -Groups: T (GTR + LLLT): 13; C (GTR): 13	-GTR	-Nd:YAG -1064 nm -100 mW	-Follow-up: 6 months -Mean PD Reduction: T: 3.38 ± 0.27 mm; C: 3.02 ± 0.42 mm Mean -CAL Gain: T: 2.91 ± 0.43 mm; C: 2.26 ± 0.34 mm -RB Gain: ND -BoP Reduction: T: 0.53 ± 0.49; CI: 0.24 ± 0.57 (SBI) -Suppuration Reduction: ND -Recession Increase: T: −0.49 ± 0.67 mm; C: −0.76 ± 0.70 mm -Patient Outcomes: No -Comment: BoP as SBI
-Ozturan *et al.,* 2011 -Prospective RCT -Split-mouth	-n. patients: 10 (6 females and 4 males) -Age: 34 years (mean) - Male/Female: 4 males, 6 females -Smokers: No -Systemic Health: No -Type and Number of Defects: 74 GRs -Groups: T (CAF + LILT): 37; C (CAF): 37	-CAF	-Diode laser -588 nm -120 mW	-Follow-up: 12 months -Mean PD Reduction: T: 0.34 ± 0.31 mm; C: 0.20 ± 0.17 mm -Mean CAL Gain: T: 2.83 ± 0.85 mm; C: 2.47 ± 0.57 mm -RB Gain: ND -BoP Reduction: ND -Suppuration Reduction: ND -Recession Increase: T: 2.57 ± 0.77 mm; C: 2.27 ± 0.48 mm -Patient Outcomes: No -Comment: Decrease in GR
-Dilsiz *et al.,* 2010 -Prospective RCT -Split-Mouth	-n. patients: 21 (9 males and 12 females) -Age: 33-46 years (39.2 ± 4 years) -Male/Female: 9 males, 12 females -Smokers: No -Systemic Health: No -Type and Number of Defects: 42 intrabony defects without furcation involvement -Groups: T (EMP + laser): 21; C (EMP): 21	-EMP	-Nd:YAG -1064 nm -1 W	-Follow-up: 6 and 12 months -Mean PD Reduction: T: 4 ± 0.8 mm; C: 4.4 ± 0.9 mm -Mean CAL Gain: T: 2.6 ± 1.2 mm; C: 3.0 ± 1.1 mm -RB Gain: ND -BoP Reduction: T: 90.48%; C: 95.24% -Suppuration Reduction: Absent -Recession Increase: T: 1.5 ± 0.7 mm; C: 1.4 ± 0.6 mm -Patient Outcomes: No
-Hazzaa et al., 2010	-n. patients: 17 Age: 22-37 years	-DBM	-GaAlAs diode laser	-Follow-up: 6 months

-Prospective RCT -Parallel-group	-Male/Female: ND -Smokers: No -Systemic Health: No -Type and Number of Defects: 20 intrabony defect -Groups: T (DBM + laser + OFD): 10; C (DBM + OFD): 10		-870 nm -100 mW	-Mean PD Reduction: T: 3.9 ± 1.1 mm; C: 2.3 ± 1.49 mm -Mean CAL Gain: T: 3.3 ± 1.2 mm; C: −2.0 ± 1.70 mm -RB Gain: T: 5.6 ± 1.5 mm; C: 4.9 ± 1.6 mm -BoP Reduction: ND -Suppuration Reduction: ND -Recession Increase: ND -Patient Outcomes: No
-AboElsaad *et al*., 2009 -Prospective RCT -Split-mouth	-n. patients: 20 (15 female and five male) -Age: 33-57 years Male/Female: 5 males, 15 females -Smokers: No -Systemic Health: No -Type and Number of Defects: 40 bilateral infra-bony defects -Groups: T (Bioactive Glass + laser): 20; C (Bioactive Glass): 20	-Bioactive Glass	-GaAlAs laser -830 nm -40 mW	-Follow-up: 6 months -Mean PD Reduction: T: 5.07 ± 0.71 mm; C: 5.25 ± 0.53 mm -Mean CAL Gain: T: 2.21 ± 0.92 mm; C 2.60 ± 1.10 mm -RB Gain: T: 3.1 ± 0.5 mm; C: 2.9 ± 0.4 mm (defect fill) -BoP Reduction: ND -Suppuration Reduction: ND -Recession Increase: ND -Patient Outcomes: No
-Ozcelik *et al.,* 2008 -Prospective RCT -Split-Mouth Blinded Placebo	-n. patients: 22 (12 males, 10 females) -Age: 31-49 years -Male/Female: 12 males, 10 females -Smokers: No -Systemic Health: No -Type and Number of Defects: 44 intra-bony defects (22 treated with EMD + LLLT; 22 treated with EMD), deep intrabony periodontal defects -Groups: T (EMD + Laser): 10; C (EMD): 12	-EMD	-Diode Laser -588 nm -Watt: ND	-Follow-up: 12 months -Mean PD Reduction: T: 3.6–5.6 mm; C: 3.4-4.6 mm -Mean CAL Gain: T: 3.1–5.1 mm; C: 2.8-3.7 mm -RB Gain: ND -BoP Reduction: T: 1.0–1.3; C: 1.0–1.3 (BI) -Suppuration Reduction: ND -Recession Increase: T: 1.7-1.3 mm; C: -0.6 to -0.8 mm -Patient Outcomes: Yes (reduced pain) -Comment: Values in ranges
-Schwarz *et al.,* 2006 -Prospective Case Series -Non-Controlled Clinical Study	-n. patients: 15 (7 men; 8 women) -Age: 49 ± 12 years -Male/Female: 7 males, 8 females -Smokers: Yes (6 individuals) -Systemic Health: No -Type and Number of Defects: 15 intrabony defect	-EMD	-Er:YAG -2.94 µm -1.36 W (calculated)	-Follow-up: 6 months -Mean PD Reduction: 3.9 ± 0.9 mm -Mean CAL Gain: 3.0 ± 1.2 mm -RB Gain: ND -BoP Reduction: 0.67 -Suppuration Reduction: ND -Recession Increase: 0.9 ± 0.6 mm

	-Groups: No T/C (case series)			-Patient Outcomes: No -Comment: Case series, no groups
-Schwarz *et al.,* 2003 -Prospective RCT -Parallel-Group	n. patients: 22 (12 men and 10 women) Age: 32-61 years -Male/Female: 12 males, 10 females -Smokers: Yes (6 individuals) -Systemic Health: No -Type and Number of Defects: 11 intrabony defect, deep intrabony periodontal defects -Groups: T (EMD + Laser): 11; C (SRP + EDTA + EMD): 11	-EMD	-Er:YAG -2.94 µm -1.36 W (calculated)	-Follow-up: 6 months -Mean PD Reduction: T: 4.0 ± 1.44 mm; C: 4.1 ± 0.94 mm -Mean CAL Gain: T: 3.2 ± 1.91 mm; C: 3.3 ± 1.63 mm -RB Gain: ND -BoP Reduction: T: 35%; C: 26% -Suppuration Reduction: Not Observed -Recession Increase: T: 0.8 ± 1.35 mm; C: -0.8 ± 1.27 mm -Patient Outcomes: No

β-TCP: β-tricalcium phosphate; BI: Bleeding Index; BoP: Bleeding on Probing; C: Control; CAF: Coronally Advanced Flap; CAL: Clinical attachment Level; CGF: Concentrated Growth Factor; DBM: Demineralized bone matrix putty; EDTA: Ethylenediaminetetraacetic Acid; EMD: Enamel Matrix Derivative; EMP: Enamel Matrix Protein; ERL: Erbium:Yag Laser: Er:YAG: Erbium-doped: Yttrium Aluminium Garnet; GaAlA: Gallium Aluminium Arsenide; GBI: Gingival Bleeding Index; GR: Gingival Recession; GTR: Guided Tissue Regeneration; HA: Hydroxyapatite; HPD: horizontal probing depth;LILT: Low Intensity Laser Therapy; LLLT: Low Level Laser Teraphy; ND: No Data; Nd:YAG: Neodymium-doped: Yttrium Aluminium Garnet ; OFD: Open Flap Debridement; PD: Probing Depth, RB: Radiographic Bone; RCT: Randomized Controlled Trial; SBI:Sulcus Bleeding Index; SCAF: Semilunar Coronally Advanced Flap; SRP: Scaling and Root Planing; T: Test; VAS: Visual Analog Scale.

III.4.3 Critical Appraisal- Quality Assessment- Risk of Bias Assessment

The risk of bias for the included articles (n = 18) was assessed using standardized tools appropriate to each study design. For RCTs, the Revised Cochrane Risk-of-Bias Tool for Randomized Trials (RoB-2) was employed (Sterne *et al*., 2019). For non-randomized studies, the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool was applied (Sterne *et al*., 2016).

Of the 18 included studies, 17 were RCTs and were evaluated with the RoB-2 tool (Danish *et al*., 2024; Dharani *et al*., 2024; Vinaya *et al*., 2023; Gangolu *et al*., 2022; Amitha *et al*., 2022; Attia *et al*., 2019; Gamil *et al*., 2019; Gupta *et al*., 2019; Doğan *et al*., 2016; Singh *et al*., 2015; Doğan *et al*., 2014; Ozturan *et al*., 2011; Dilsiz *et al*., 2010; Hazzaa *et al*., 2010; AboElsaad *et al*., 2009; Ozcelik *et al*., 2008; Schwarz *et al*., 2003). The remaining one study was a prospective case series (Schwarz *et al*., 2006), which was assessed using the ROBINS-I tool. Report on risk of bias assessment of included studies is thoroughly detailed in **Tables 4.3-4.4** and **Figures 4.2-4.3** respectively.

Table 4.3. Risk of Bias Assessment Tool used for Included Studies

S.No	Name	Year	Study Design	RoB Tool Used
1	Dharani *et al.*	2024	Randomized Controlled trial	RoB-2
2	Danish *et al.*	2024	Randomized Controlled trial	RoB-2 (Randomized Trials)
3	Vinaya *et al.*	2023	Randomized Controlled Trial	RoB- 2 (Randomized Trials)
4	Gangulo *et al.*	2022	Prospective Randomized Split-Mouth Clinical Trial	ROB-2 (Randomized Trials)
5	Amitha *et al.*	2022	Prospective Randomized Split-Mouth Clinical Trial	ROB-2 (Randomized Trials)
6	Attia *et al.*	2019	Prospective, Randomized, Controlled Split-Mouth Clinical Trial	ROB-2 (Randomized Trials)
7	Gamil, *et al.*	2019	Prospective Randomized Parallel-Group Clinical Trial	ROB-2 (Randomized Trials)
8	Gupta *et al.*	2019	Prospective Randomized Controlled Split-Mouth Clinical Trial	ROB-2 (Randomized Trials)
9	Doğan *et al.*	2016	Prospective Randomized Controlled Clinical Trial	ROB-2 (Randomized Trials)
10	Singh *et al.*	2015	Prospective Randomized Controlled Split-Mouth Clinical Trial	ROB-2 (Randomized Trials)
11	Doğan *et al.*	2014	Prospective Randomized Controlled Split-Mouth Clinical Trial	ROB-2 (Randomized Trials)
12	Ozturan *et al.*	2011	Prospective Randomized Controlled Split-Mouth Clinical Trial	ROB-2 (Randomized Trials)
13	Dilsiz *et al.*	2010	Prospective Randomized Controlled Split-Mouth Clinical Trial	ROB-2 (Randomized Trials)
14	Hazzaa *et al.*	2010	Prospective Randomized Controlled Parallel-Group Clinical Trial	ROB-2 (Randomized Trials)
15	AboElsaad *et al.*	2009	Prospective Randomized Controlled Split-Mouth Clinical Trial	ROB-2 (Randomized Trials)
16	Ozcelik *et al.*	2008	Prospective Randomized Blinded Split-Mouth Placebo-Controlled Clinical Trial	ROB-2 (Randomized Trials)
17	Schwarz *et al.*	2006	Prospective Case Series (Non-Controlled Clinical Study)	ROBINS-I (Non-Randomized Study)
18	Schwarz *et al.*	2003	Prospective Randomized Controlled Parallel-Group Clinical Trial	ROB-2 (Randomized Trials)

Table 4.4. Detailed Report on Risk of Bias Assessment of Included Studies

S.No	Name	Year	Study Design	Overall Risk of Bias	Key Concerns / Comments
1	Dharani *et al.*	2024	Randomized controlled trial	Low	Randomization method clearly stated; But unclear how it was conducted; outcome assessors were blinded but no information about participants blinding; outcome data complete; hence low risk; no selective reporting observed. Assessor blinding not mentioned.
2	Danish *et al.*	2024	Prospective Randomized Clinical Study	Moderate	Unclear sequence generation and concealment in randomization. While prospective and blinding described, the study lacks details for same raising possibility of bias from knowledge of treatment allocation. Low risk for attrition. Selective reporting as no protocol to compare outcomes. Outcomes reported match expectations. Unclear assessor blinding. Moderate risk of bias due to confounding, missing information about baseline comparability and intervention fidelity.
3	Vinaya *et al.*	2023	Randomized Controlled Trial	Low Risk	Clearly described randomization; Allocation concealment not described. Concerns regarding assessor blinding; minimal missing data; pre-defined outcomes reported. Low attrition.
4	Gangolu *et al.*	2022	Prospective Randomised Split-Mouth Clinical Trial	Some Concerns	Randomization and allocation seem adequate (coin toss, split-mouth), but blinding is not mentioned. Operator was aware of interventions, increasing performance/detection bias risk. Small sample size (n=12 per group), single-center, no microbiological confirmation. Short-term follow-up (6 months), selection bias
5	Amitha *et al.*	2022	Prospective Randomized Split-Mouth Clinical Trial	Some Concerns	Adequate randomization (coin toss described) but allocation concealment not clarified; single-blinding (patients unaware of side, but operator and assessor blinding unclear). All enrolled patients completed follow-up; selective reporting not evident. Small sample (n=15), split-mouth design, possible carry-over effects. Short duration (6 months). Primary outcomes objectively reported, but potential outcome assessment bias.
6	Attia *et al.*	2019	Prospective, Randomized, Controlled Split-Mouth Clinical Trial	Some Concerns	Randomization: Allocation sequence via sealed envelopes; methods described, but details on allocation concealment and blinding (patient/operator/assessor) are limited. Blinding: Only bone density measurements stated to be assessor-blinded; otherwise, risk of performance/detection bias (no explicit blinding of operator or clinical assessors). Sample Size: Small (15 patients, 30 sites); split-mouth limits inter-patient variability, but increase in possible carry-over effect. Follow-up: Up to 9 months; relatively short for long-term periodontal therapy. Selective Reporting: All major outcomes (PD, CAL, bone density) are reported; low risk of selective reporting. Other: Statistical methods appropriate; dropouts not reported (all patients completed); no microbiological assessments. Generalizability limited to population with chronic periodontitis and malocclusion.
7	Gamil, *et al.*	2019	Prospective Randomized Parallel-Group Clinical Trial	Some Concerns	Randomization: Computer-generated, but details on allocation concealment not described. Blinding: Not mentioned, operator/outcome assessor blinding unclear. Sample Size: Small (16/group); no dropouts. Follow-up: 6 months post-surgery. Reporting: All key

					clinical and radiographic outcomes reported. Other: Group comparability ok at baseline; only non-smokers; possible performance/detection bias where blinding likely not feasible; antibiotics and standardized protocols used for all patients. Generalizability somewhat limited; no microbiological/histological outcomes.
8	Gupta *et al.*	2019	Prospective Randomized Controlled Split-Mouth Clinical Trial	Some Concerns	Randomization: Split-mouth design with random assignment, but method details on random sequence generation and allocation concealment are not fully described, raising possible selection bias concerns. Blinding: No mention of blinding of operator, outcome assessors, or participants. Potential performance and detection bias due to open-label design. Sample Size: Small (n=12 patients, total 24 defects). Follow-up: 6 months, adequate short-term but no long-term data. Reporting: All clinical and radiographic parameters reported as planned. No microbiological assessments. Other: Split-mouth design reduces intersubject variability but possible cross-over effect not discussed. Clinical outcomes stable with well-described measurements and appropriate statistical analysis.
9	Doğan *et al.*	2016	Prospective Randomized Controlled Clinical Trial	Some Concerns	Randomization: Randomization process described but lacking clear details on allocation concealment; possible selection bias. Blinding: No explicit mention of blinding of participants, operator, or outcome assessors; this introduces risk of performance and detection bias. Sample Size: Moderate (33 defects in 25 patients), split into two groups. Follow-up: Six months, adequate for early clinical/bio-chemical outcomes but no long-term data. Reporting: All clinical (PPD, CAL, HPD) and biochemical markers (ALP, OC) outcomes reported as pre-specified. Other: Single-center study; split groups were clinically comparable at baseline. The adjunctive use of LLLT showed statistically significant improvements in some clinical and biochemical outcomes at 6 months.
10	Singh *et al*.	2015	Prospective Randomized Controlled Split-Mouth Clinical Trial	Some Concerns	Randomization: Allocation by coin toss was stated but details on allocation concealment and sequence generation were not described, raising possible selection bias risk. Blinding: No indication of operator or outcome assessor blinding; patients likely unaware of laser application only, leading to possible performance and detection bias. Sample Size: Small (10 patients, 40 defects), limiting power and generalizability. Follow-up: 6 months, adequate short-term but no long-term data. Outcomes: Clinical parameters (GR depth and width, CAL, KT width, PD) fully reported, showing statistically significant improvements with LLLT adjunct. Other: Split-mouth design reduces inter-patient variability but potential carry-over effect is possible. No microbiological or histological analyses. No report of dropouts; all patients completed follow-up. Statistical analyses appropriate. Single center study.
11	Doğan *et al.*	2014	Prospective Randomized Controlled Split-Mouth Clinical Trial	Some Concerns	Randomization: Randomized split-mouth design; method of random sequence generation and allocation concealment is not clearly detailed, raising potential selection bias concerns. Blinding: No explicit mention of blinding of patients, operators, or outcome assessors; possible performance and detection bias given open treatment nature. Sample Size: Small (13 patients, 26 defects); all completed the study with no reported

					losses. Follow-up: 6 months, suitable for short-term outcomes but limits long-term conclusions. Reporting: All clinical periodontal parameters (PPD, CAL, GR, PI, SBI) measured at baseline, 3 months, and 6 months, reported as planned. Other: Split-mouth design reduces inter-patient variability but potential crossover effects not discussed. Use of equine bone and membrane with LLLT adjunct showed statistically significant improvements in PPD reduction, CAL gain, and reduction in GR and bleeding compared to GTR alone. Antibiotics and postoperative care standardized. Single-center study limits generalizability.
12	Ozturan *et al.*	2011	Prospective Randomized Controlled Split-Mouth Clinical Trial	Some Concerns	Randomization: Random allocation was by coin toss conducted by a separate staff member to maintain operator blinding; this partially addresses allocation concealment, but detailed description of sequence generation was limited. Blinding: Operator was blinded to treatment allocation during surgery (laser application performed by another staff member), and patients likely unaware of which side received laser; no explicit mention of outcome assessor blinding. Potential performance/detection bias remains. Sample Size: Small (10 patients, 74 recession defects), but power calculation was performed. Follow-up: 12 months, providing adequate short-to-medium term data. Reporting: Comprehensive clinical parameters reported (GR depth and width, KT width, CAL, PD). Outcomes favored laser adjunct with statistically significant improvements in multiple parameters. Other: Split-mouth design controls inter-subject variability but possible crossover/systemic effects not addressed. Study was single center, limiting generalizability. Postoperative care standardized including antibiotics and chlorhexidine.
13	Dilsiz *et al.*	2010	Prospective Randomized Controlled Split-Mouth Clinical Trial	Some Concerns	Randomization: Split-mouth design with random allocation of 42 intrabony defects in 21 patients. Method of random sequence generation and allocation concealment not fully detailed, raising possible selection bias concerns. Blinding: Described as double-masked; the assessor was masked, but operator blinding is unclear as same surgeon performed both treatments in the same session. Patients likely blinded due to split-mouth design. Sample Size: Moderate (21 patients), all completed follow-up. Follow-up: 6 and 12 months; adequate for short- to medium-term assessment. Reporting: Clinical periodontal parameters (PD, CAL, RC, BoP) were comprehensively measured and reported. No microbiological or histologic outcome data included. Other: Split-mouth design controls patient-level confounders but carries potential risk of crossover systemic effects, which were not addressed. Standardized postoperative care minimized confounding. No significant clinical benefit from Nd:YAG laser root conditioning over EDTA conditioning with EMP was found in this study.
14	Hazzaa *et al.*	2010	Prospective Randomized Controlled Parallel-Group Clinical Trial	Some Concerns	Randomization: Defects divided into two groups (10 defects each); randomization method not clearly detailed, allocation concealment unclear.

15	AboElsaad *et al.*	2009	Prospective Randomized Controlled Split-Mouth Clinical Trial	Some Concerns	Randomization: Split-mouth design with random allocation by coin toss to assign infra-bony defects (40 defects in 20 patients) to treatment with bioactive glass plus laser versus bioactive glass alone. Random sequence generation and allocation concealment not fully described, raising possible selection bias.
16	Ozcelik *et al.*	2008	Prospective Randomized Blinded Split-Mouth Placebo-Controlled Clinical Trial	Some Concerns	Randomization: Allocation of contralateral defects to EMD+LLLT or EMD alone was by coin toss; no detailed description of sequence generation or allocation concealment with possible selection bias. Blinding: Patients blinded (sham laser in controls); outcome examiner blinded; however, operator not blinded, introducing some risk of performance bias.
17	Schwarz *et al.*	2006	Prospective Case Series (Non-Controlled Clinical Study)	Serious Risk	Randomization/Control: No control group; participants (n=15) all received ERL + EMD, so no comparative analysis possible. Selection Bias: Consecutive patient recruitment not clearly stated; unclear if selection was consecutive or convenience sampling.
18	Schwarz *et al.*	2003	Prospective Randomized Controlled Parallel-Group Clinical Trial	Some Concerns	Randomization: Random allocation to ERL+EMD or SRP+EDTA+EMD after baseline matching, but no detail on sequence generation or allocation concealment with possible selection bias. Blinding: Outcome: Examiner was blinded and calibrated; operator blinding not feasible; patient blinding not reported with possible performance bias.

ALP: Alkaline Phosphatase; BoP: Bleeding on Probing; CAL: Clinical Attachment Level; EDTA: Ethylenediaminetetraacetic Acid; EMD: Enamel Matrix Derivative; EMP: Enamel Matrix Protein; ERL: Erbium:Yag Laser: GR: gingival recession; GTR: Guided Tissue Regeneration; HPD: Horizontal Probing Depth; KT: Keratinized Tissue LLLT: Low Level Laser Teraphy; Nd:YAG: Neodymium-doped: Yttrium Aluminium Garnet; OC: Osteocalcin; PD: Probing Depth; PI: Plaque Index, PPD: Probing Pocket Depth; RC: Recession; SBI: Sulcus Bleeding Index; SRP: Scaling and Root Planing.

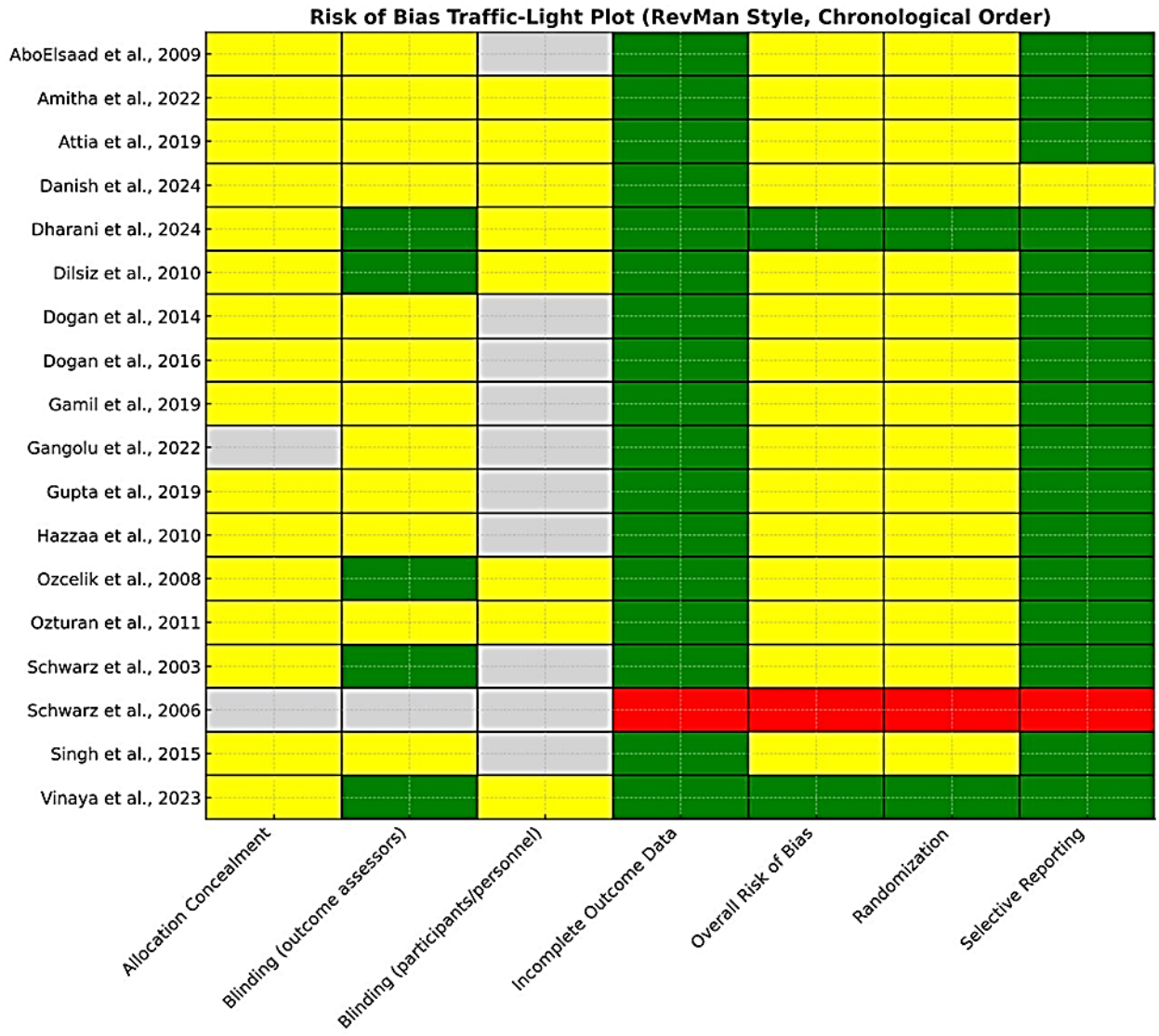

Figure 4.2*. Illustrative representation of Risk of bias assessment report using traffic light plot. Risk Levels: Low Risk (Green): No major issues. Some Concerns (Yellow): Minor Issues. High Risk (Red): Major issues (e.g., no control group, no blinding). Serious Risk (Red): Extreme Issues (e.g., no comparative analysis).*

Study (Author, Year)	Randomization	Allocation Concealment	Blinding (participants/personnel)	Blinding (outcome assessors)	Incomplete Outcome Data	Selective Reporting	Overall Risk of Bias
Dharani et al., 2024	Low	Unclear	Unclear	Low	Low	Low	Low
Danish et al., 2024	Some concerns	Unclear	Unclear	Unclear	Low	Some concerns	Moderate
Vinaya et al., 2023	Low	Unclear	Some concerns	Low	Low	Low	Low
Gangolu et al., 2022	Some concerns	Adequate	Not mentioned	Unclear	Low	Low	Some concerns
Amitha et al., 2022	Some concerns	Unclear	Unclear	Unclear	Low	Low	Some concerns
Attia et al., 2019	Some concerns	Unclear	Unclear	Partial	Low	Low	Some concerns
Gamil et al., 2019	Some concerns	Unclear	Not mentioned	Unclear	Low	Low	Some concerns
Gupta et al., 2019	Some concerns	Unclear	Not mentioned	Unclear	Low	Low	Some concerns
Dogan et al., 2016	Some concerns	Unclear	Not mentioned	Unclear	Low	Low	Some concerns
Singh et al., 2015	Some concerns	Unclear	Not mentioned	Unclear	Low	Low	Some concerns
Dogan et al., 2014	Some concerns	Unclear	Not mentioned	Unclear	Low	Low	Some concerns
Ozturan et al., 2011	Some concerns	Partial	Partial	Unclear	Low	Low	Some concerns
Dilsiz et al., 2010	Some concerns	Unclear	Partial	Low	Low	Low	Some concerns
Hazzaa et al., 2010	Some concerns	Unclear	Not mentioned	Unclear	Low	Low	Some concerns
AboElsaad et al., 2009	Some concerns	Unclear	Not mentioned	Unclear	Low	Low	Some concerns
Ozcelik et al., 2008	Some concerns	Unclear	Partial	Low	Low	Low	Some concerns
Schwarz et al., 2006	High	Not applicable	Not blinded	Not applicable	High	High	High
Schwarz et al., 2003	Some concerns	Unclear	Not mentioned	Low	Low	Low	Some concerns

Figure 4.3. *Tabular representation of risk of bias assessment using RevMan software. RevMan: Review Manager.*

III.4.4. Outcomes

Based on the study inclusion criteria, the following clinical parameters/outcomes were observed in the selected studies:

- Primary outcomes: PPD reduction, CAL gain, RB gain, GR, BoP, and suppuration.
- Secondary outcomes: discomfort, aesthetics, and functional improvements.

All the selected studies compared changes of specific clinical outcomes as displayed in **Table 4.5** which evidences the frequency of reported primary outcomes of the included articles. Furthermore, studies with suitable numerical data only were considered for meta-analysis and the variables were assessed at baseline, three- six- nine- 12-month follow-up period as shown in **Table 4.6**. Due to heterogeneity in data reporting/assessment methods and indices used, meta-analysis was possible for PPD and CAL only. For the remaining outcomes, descriptive assessment and synthesis were provided. Given the amount of articles involved in the meta-analysis (superior to 10), funnel plots to present publication bias were also provided.

Table 4.5. Frequency of Reported Primary Outcomes of the Included Studies

Authors/Year	PPD	PPD Change	CAL	CAL Change	BoP	BoP Change	Rec	Rec Change	Radiographic Bone Gain
Dharani *et al.*, 2024	+	+	+	+	+	+	NR	NR	+
Danish *et al.*, 2024	+	+	+	+	NR	NR	NR	NR	+
Vinaya *et al.*, 2023	+	+	+	+	NR	NR	+	+	NR
Gangolu *et al.*, 2022	+	+	+	+	NR	NR	NR	NR	+
Amitha *et al.*, 2022	+	+	+	+	NR	NR	+	+	NR
Attia *et al.*, 2019	+	+	+	+	NR	NR	NR	NR	NR
Gamil, *et al.*, 2019	+	+	+	+	+	NR	NR	NR	+
Gupta *et al.*, 2019	+	+	+	+	NR	NR	+	+	+
Doğan *et al.*, 2016	+	+	+	+	NR	NR	NR	NR	NR
Singh *et al.*, 2015	NR	NR	+	+	NR	NR	+	+	NR
Doğan *et al.*, 2014	+	+	+	+	+	+	+	+	NR
Ozturan *et al.*, 2011	+	+	+	+	NR	NR	+	+	NR
Dilsiz *et al.*, 2010	+	+	+	+	+	+	+	+	NR
Hazzaa et al., 2010	+	+	+	+	NR	NR	NR	NR	+
AboElsaad *et al.*, 2009	+	+	+	+	NR	NR	NR	NR	+
Ozcelik *et al.*, 2008	+	+	+	+	+	+	+	+	NR
Schwarz *et al.*, 2006	+	+	+	+	+	+	+	+	NR
Schwarz *et al.*, 2003	+	+	+	+	+	+	+	+	NR
Total	17 (94.44%)	17 (94.44%)	18 (100%)	18 (100%)	6 (33.33%)	5 (27.78%)	9 (50%)	9 (50%)	5 (27.78%)

BoP: Bleeding on Probing; CAL: Clinical attachment Level; PPD: Probing Pocket Depth; Rec: Gingival Recession.

Table 4.6. List of Studies and Outcomes Selected for Meta-Analysis

Authors / Year	Test vs Control Groups	Clinical Parameters Observed	Timelines Considered	Inclusion in Meta-Analysis
Dharani *et al.*, 2024	T: CGF + Laser; C:CGF	Mean PD reduction, CAL gain, RB gain, BoP	3 and 6 months	Mean PD reduction, CAL gain
Danish *et al.*, 2024	T: Bioactive Glass + GaAlAs Laser; C: Bioactive Glass	Mean PD reduction, CAL gain, RB gain	3 and 6 months	Mean PD reduction, CAL gain
Vinaya *et al.*, 2023	Test: Bone Graft + Laser; Control: Bone Graft	Mean PD reduction, CAL gain, Rec	3 and 6 months	Mean PD reduction, CAL gain
Gangulo *et al.*, 2022	Test: Graft + Laser; Control: Graft only	Mean PD reduction, CAL gain, RB gain	3 and 6 months	Mean PD reduction, CAL gain
Amitha *et al.*, 2022	T: CAF + LLLT C: CAF	Mean PD reduction, CAL gain, Rec	6 months	CAL gain
Attia *et al.*, 2019	T: Regenerative Therapy + Laser; C: Regenerative Therapy	Mean PD reduction, CAL gain	9 months	Mean PD reduction, CAL gain
Gamil *et al.*, 2019	T: OFD + DBM + Laser; C: Same without laser	Mean PD reduction, CAL gain, RB gain, BoP	6 months	Mean PD reduction, CAL gain
Gupta *et al.*, 2019	T: Biomaterial + Laser C: Biomaterial	Mean PD reduction, CAL gain, RB gain, Rec	3 and 6 months	Mean PD reduction, CAL gain
Doğan *et al.*, 2016	T: GTR + Laser; C: GTR	Mean PD reduction, CAL gain, BoP	6 months	Mean PD reduction, CAL gain
Singh *et al.*, 2015	T: SCAF + LLLT C: SCAF	CAL gain, Rec, BoP	6 months	CAL gain
Doğan *et al.*, 2014	T: GTR + LLLT; C: GTR	Mean PD reduction, CAL gain, Rec, BoP	6 months	Mean PD reduction, CAL gain
Ozturan *et al.*, 2011	T: CAF + LILT; C: CAF	Mean PD reduction, CAL gain, Rec	12 months	Mean PD reduction, CAL gain
Dilsiz *et al.*, 2010	T: EMP + Laser C: EMP	Mean PD reduction, CAL gain, Rec, BoP	6 and 12 months	Mean PD reduction, CAL gain
Hazzaa *et al.*, 2010	T: DBM + Laser + OFD C: Same without laser	Mean PD reduction, CAL gain, RB gain	6 months	Mean PD reduction, CAL gain
AboElsaad *et al.*, 2009	T: Bioactive Glass + Laser; C: Bioactive Glass	Mean PD reduction, CAL gain, RB gain	6 months	Mean PD reduction, CAL gain
Ozcelik et al., 2008	T: EMD + Laser C: EMD	Mean PD reduction, CAL gain, BoP, Rec	12 months	Mean PD reduction, CAL gain
Schwarz *et al.*, 2003	Test: EMD + Laser; C: SRP + EDTA + EMD	Mean PD reduction, CAL gain	6 months	Mean PD reduction, CAL gain

BoP: Bleeding on Probing; C: Control; CAF: Coronally Advanced Flap CAL: Clinical attachment Level; CGF: Concentrated Growth Factor; DBM: Demineralized bone matrix; EDTA: Ethylenediaminetetraacetic Acid; EMD: Enamel Matrix Derivative; EMP: Enamel Matrix Protein; GaAlA: Gallium Aluminium Arsenide; GTR: Guided Tissue Regeneration; LILT: Low Intensity Laser Therapy; LLLT: Low Level Laser Teraphy; PD: Probing Depth; RB: Radiographic Bone; Rec: recession; SRP: Scaling and Root Planing; T: Test; OFD: Open Flap Debridement; SCAF: Semilunar Coronally Advanced Flap.

III.4.4.1 Descriptive synthesis- Comparison of primary and secondary outcomes

III.4.4.1.1 Probing Depth (PD)

Assessment of PD outcomes in the 18 included studies showed consistent reductions following interventions. Initial PDs ranged from 5.9 to 8.83 mm, with final values reduced to 1.2–4.7 mm, resulting in mean reductions of 2.0–5.3 mm (Danish *et al*., 2024; Dharani *et al*., 2024; Vinaya *et al*., 2023; Gamil *et al*., 2019; Gupta *et al*., 2019; Dilsiz *et al*., 2010; AboElsaad *et al*., 2009; Schwarz *et al*., 2003, 2006). Considerable reductions of more than 5 mm were shown by Dharani *et al*. (2024) and AboElsaad *et al*. (2009), while Attia *et al.* (2019) observed percentage-based improvements of ~65%. In contrast, Ozturan *et al.* (2011) reported minimal reductions, and Amitha *et al.* (2022) found no difference between groups. Overall, test groups generally outperformed controls, as demonstrated by Hazzaa *et al.* (2010).

III.4.4.1.2 Clinical Attachment Level (CAL)

Assessment of CAL outcomes in the 18 included studies demonstrated considerable gains, with test groups generally outperforming controls. Initial CAL values ranged from 4.35 to 11.00 mm, with final values reduced to 0.3–8.78 mm, resulting in gains of 1.24–5.30 mm. The highest gains were reported by Danish *et al*. (2024) (4.38 ± 0.91 mm, test), Dharani *et al*. (2024) (5.30 ± 0.44 mm, test), and Gamil *et al.* (2019) (4.31 ± 1.06 mm, test). Percentage improvements were noted by Attia *et al.* (2019), with 59.77 ± 12.1% gain in the test group versus 38.83 ± 7.56% in controls. In contrast, lower gains were observed in Gangolu *et al.* (2022) (2.00 ± 3.38 mm, test) and AboElsaad *et al*. (2009) (2.21 ± 0.92 mm, test). Hazzaa *et al.* (2010) reported a loss in the control group (-2.0 ± 1.70 mm), while Attia *et al.* (2019) did not provide control group data. Overall, test groups showed superior CAL improvements (e.g., Amitha *et al*., 2022: 3.1 ± 0.98 mm vs. 2.0 ± 1.09 mm), although outcomes varied depending on baseline CAL severity and type of intervention.

III.4.4.1.3 Bleeding on Probing (BoP) and Suppuration

Assessment of BoP was described in 7 of the 18 included studies, with reductions ranging from 26% to 95.24%. Higher reductions were observed in Dilsiz *et al*. (2010) (test: 90.48%, control: 95.24%), Schwarz *et al*. (2006) (67%), and Dharani *et al*. (2024) (52.14 ± 2.74%, gingival bleeding index (GBI)). Moderate reductions were reported by Schwarz *et al*. (2003) (test: 35%, control: 26%), while Doğan *et al.* (2014) recorded lower values (test: 0.53 ± 0.49, control: 0.24 ± 0.57, sulcus bleeding index (SBI)). Complete elimination of BoP was noted by Ozcelik *et al.* (2008), with both groups improving from 1.0–1.3 to 0.0 (bleeding index (BI)). Overall, six of the seven studies demonstrated greater reductions in test groups compared with controls, except for Dilsiz *et al.* (2010), where controls outperformed test groups. The absence of BoP data in 11 of the 18 studies limits a comprehensive evaluation of this outcome. Meanwhile, suppuration, when reported (e.g., Dilsiz *et al*., 2010; Schwarz *et al*., 2003), was consistently eliminated post-treatment, reinforcing the capacity of regenerative approaches to control local infection.

III.4.4.1.4 Gingival Recession (GR)

Assessment of GR was reported in 10 of the 18 included studies. Initial values ranged from 1.1 to 4.42 mm, with final values ranging from 0.1 to 4.20 mm. Most studies observed improvement in GR, with the largest decreases reported by Amitha *et al*. (2022) (test: 2.90 ± 0.934 mm, control: 1.77 ± 1.04 mm), Ozturan *et al.* (2011) (test: 2.57 ± 0.77 mm, control: 2.27 ± 0.48 mm), and Singh *et al*. (2015) (test: 2.3 ± 0.590 mm, control: 1.40 ± 1.21 mm). In contrast, worsening of GR was reported by Doğan *et al.* (2014) (test: −0.49 ± 0.67 mm, control: −0.76 ± 0.70 mm), Schwarz *et al*. (2003) (control: −0.8 ± 1.27 mm), and Ozcelik *et al*. (2008) (control: −0.6 to −0.8 mm). Schwarz *et al.* (2006) reported a modest decrease (0.9 ± 0.6 mm), while Gupta *et al.* (2019) observed smaller decreases (test: 0.66 ± 0.65 mm, control: 0.75 ± 0.96 mm). Ozcelik *et al*. (2008) further showed mixed outcomes, with decreases in test groups (1.3–1.7 mm) but increases in controls (−0.6 to −0.8 mm). The absence of GR data in eight of the 18 studies limits a comprehensive evaluation of this outcome.

III.4.4.1.5 Radiographic Bone (RB) Gain

Assessment of RB gain was reported in seven of the 18 included studies, with values ranging from 0.498 mm to 5.60 mm. The highest gains were observed in Danish *et al*. (2024) (test: 5.60 mm, control: 3.77 mm), Hazzaa *et al*. (2010) (test: 5.6 ± 1.5 mm, control: 4.9 ± 1.6 mm), and Gamil *et al*. (2019) (test: 4.5 ± 0.86 mm, control: 2.6 ± 1.20 mm). Moderate improvements were reported by AboElsaad *et al*. (2009) (test: 3.1 ± 0.5 mm, control: 2.9 ± 0.4 mm), while lower gains were noted in Dharani *et al*. (2024) (test: 2.122 ± 0.178 mm, control: 1.987 ± 0.155 mm) and Gangolu *et al*. (2022) (test: 1.201 mm, control: 0.498 mm). Six of the seven studies reported greater RB gain in test groups compared to controls, with the exception of Gupta *et al*. (2019), where controls showed higher gain (1.33 ± 0.57 mm vs. 0.95 ± 0.68 mm). The absence of radiographic data in 11 of 18 studies limits comprehensive evaluation of this outcome.

III.4.4.1.6 Patient-Related Outcomes

Assessment of patient-related outcomes was reported in only three of the 18 studies. Vinaya *et al*. (2023) noted no adverse reactions among patients, suggesting minimal discomfort. Amitha *et al*. (2022) reported reduced pain measured using the Visual Analog Scale (VAS), while Ozcelik *et al*. (2008) documented reduced pain but did not specify the parameters used. No studies addressed aesthetics or functional improvements. The absence of PCOs data in 15 studies limits a comprehensive evaluation of this outcome.

III.4.4.1.7 Overall synthesis

The collective findings of evidence from 2003 to 2024 highlight a consistent pattern: regenerative modalities reliably achieve 3–5 mm reductions in PD, 2–5 mm gains in CAL, and measurable RB fill. Adjunctive use of biologics or lasers may enhance outcomes modestly, though the magnitude of benefit varies by study. Importantly, BoP and suppuration show marked resolution postoperatively, underscoring the effectiveness of these interventions in controlling inflammation. GR is generally minimal, reinforcing the safety profile of regenerative therapies with respect to marginal tissue preservation.

III.4.4.2 Meta-Analyses of the outcomes: synthesis of results

III.4.4.2.1 Meta-analysis- The effect of adjunctive laser uses in regenerative periodontal therapy in terms of probing pocket depth (PPD) reduction

A meta-analysis was conducted to compare the reduction in PD between studies evaluating regenerative periodontal therapy with or without adjunctive laser use. Out of the 18 studies, 15 met the inclusion criteria for quantitative synthesis. Studies like Amitha *et al.* (2022) were excluded as test and control group showed no difference, Singh *et al.* (2015), and Schwarz *et al.* (2006) lacked sufficient data. Forest plot interpretation of PD reduction is shown in **Figure 4.4**. Using Review Manager 5.4 software (RevMan, 2020), the forest plot synthesised MD across selected 15 studies between test and control groups. The mean reduction in PD with SD were taken in consideration. The blue dots signify the MD and the horizontal lines indicate the 95% CIs. The blue diamond indicates the cumulative effect of studies. The dotted vertical red line is the null line.

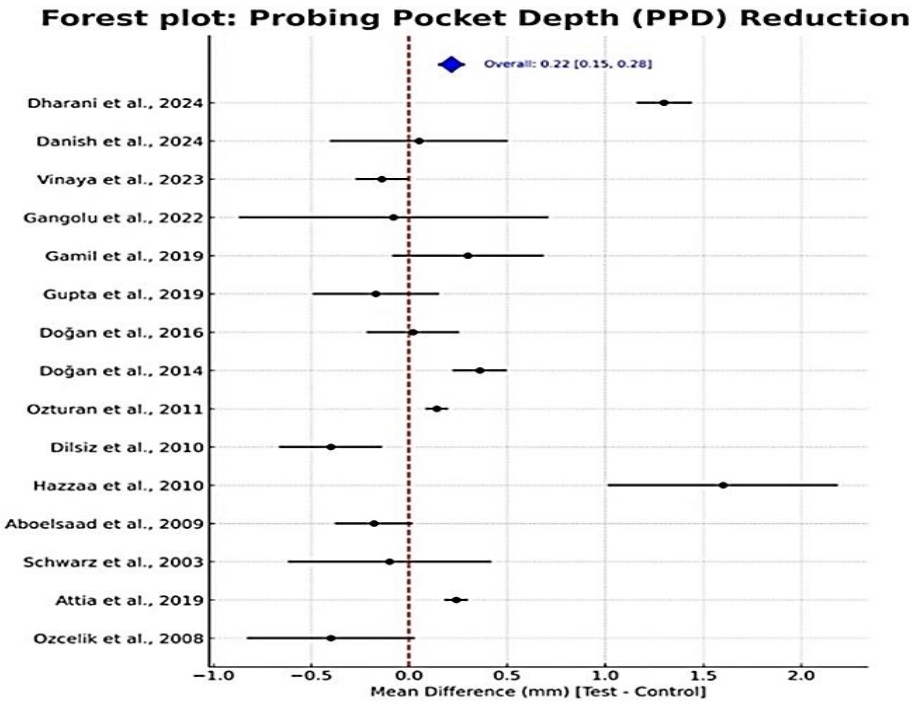

Figure 4.4. *Forest plot interpretation of PPD reduction. Pooled MD: 0.22 mm (95% CI 0.15 to 0.28). PD: Probing Pocket Depth; MD: Mean Difference.*

III.4.4.2.2 Clinical relevance of findings

1. Pooled Mean Difference (MD)

The pooled MD of +0.22 mm suggests that laser adjunctive therapy is slightly favorable compared to conventional therapy in terms of PD reduction.

Some studies such as Dharani *et al.* (2024) and Hazzaa *et al.* (2010) clearly favored the test group with CIs not crossing the null line. However, the majority of studies, while numerically favoring the test, had CIs that crossed the line of no effect, indicating no statistically significant difference. Several trials (Dilsiz *et al*., 2010; AboElsaad *et al*., 2009; Gupta *et al*., 2019) suggested little to no difference, or even slight benefit of control. Overall, the general trend suggests that the test group achieved an equal or marginally greater PD reduction compared to control. However, the effect is small in magnitude and may not reach clinical significance.

2. Heterogeneity

A high degree of inconsistency was observed across studies ($Q = 88.57$, $df = 13$, $p < 0.001$; $I^2 = 85.3\%$; $\tau^2 = 0.123$). This implies that the variation between studies was much greater than expected by chance alone. Such heterogeneity likely reflects:

- ✓ Differences in study populations (age, disease severity, defect type).
- ✓ Variation in laser parameters (wavelength, power, exposure time).
- ✓ Different adjunctive regenerative materials or surgical protocols.
- ✓ Follow-up duration.
- ✓ Methodological quality and risk of bias.

3. Clinical Implications

Although a small benefit is suggested, the effect size is statistically significant but clinically modest (only ~0.2 mm) Given the substantial heterogeneity, the results cannot be generalized across all clinical contexts. Certain patient subgroups or specific laser protocols may show benefit, but this is not consistently demonstrated in the pooled evidence.

4. Model Summary

Pooled Effect Size Test

- ✓ Estimate (MD): +0.22 mm (Test – Control).
- ✓ Standard Error (SE): 0.034.
- ✓ 95% CI: 0.15 to 0.28 mm.
- ✓ $p < 0.001$ → Statistically significant, but modest effect size.

Residual Heterogeneity (Cochran's Q)

- ✓ $Q = 88.57$, $df = 13$, $p < 0.001$.
- ✓ $I^2 = 85.3\%$ (substantial heterogeneity).
- ✓ $\tau^2 = 0.123$ (between-study variance).

5. Interpretation

a. Pooled Effect Size and Confidence Interval (CI)

- ✓ The pooled effect size (+0.22 mm) favors laser adjunctive therapy.
- ✓ While statistically significant, the absolute magnitude is small, raising questions about its clinical importance.

b. Prediction Interval (PrI)

- ✓ The wide 95% PI implies that future studies may report effects ranging from minimal benefit to no effect.
- ✓ This variability reduces certainty in applying findings across all clinical contexts.

c. Heterogeneity

- ✓ Substantial heterogeneity ($I^2 = 85\%$) indicates that outcomes are strongly influenced by differences between studies.
- ✓ Results cannot be assumed to apply uniformly; study-specific variables (population, technique, laser settings) play a major role.

d. Implications

- ✓ The available evidence indicates that laser adjuncts provide, at best, a small additional PD reduction compared to conventional therapy.
- ✓ Given the heterogeneity, conclusions should be interpreted cautiously.
- ✓ Publication bias and small-study effects cannot be excluded.

6. Conclusion

This meta-analysis of 15 studies found a small but statistically significant pooled benefit of laser-assisted therapy for PD reduction (MD = +0.22 mm; $p < 0.001$). However, the effect size is modest, and the substantial heterogeneity ($I^2 = 85\%$) limits generalizability. Thus, current evidence does not conclusively demonstrate a clinically meaningful advantage of laser adjunctive therapy over conventional approaches in periodontal regenerative surgery.

III.4.4.2.3 Funnel plot of probing depth (PD)

The funnel plot is a key tool in meta-analysis used to visually estimate the presence of publication bias or small-study effects. It displays individual studies' effect sizes (here, residual values possibly representing standardized MDs in PD reduction on the horizontal axis against their SEs on the vertical axis.

- ➢ Each point represents an individual study included in the meta-analysis.
- ➢ SE increases down the Y-axis (i.e., smaller, less precise studies appear lower).
- ➢ Symmetry (studies evenly spread on both sides of the mean effect) suggests publication bias is less likely; marked asymmetry may indicate bias or small-study effects.

Funnel Plot Interpretation of PD reduction is shown in **Figure 4.5**.

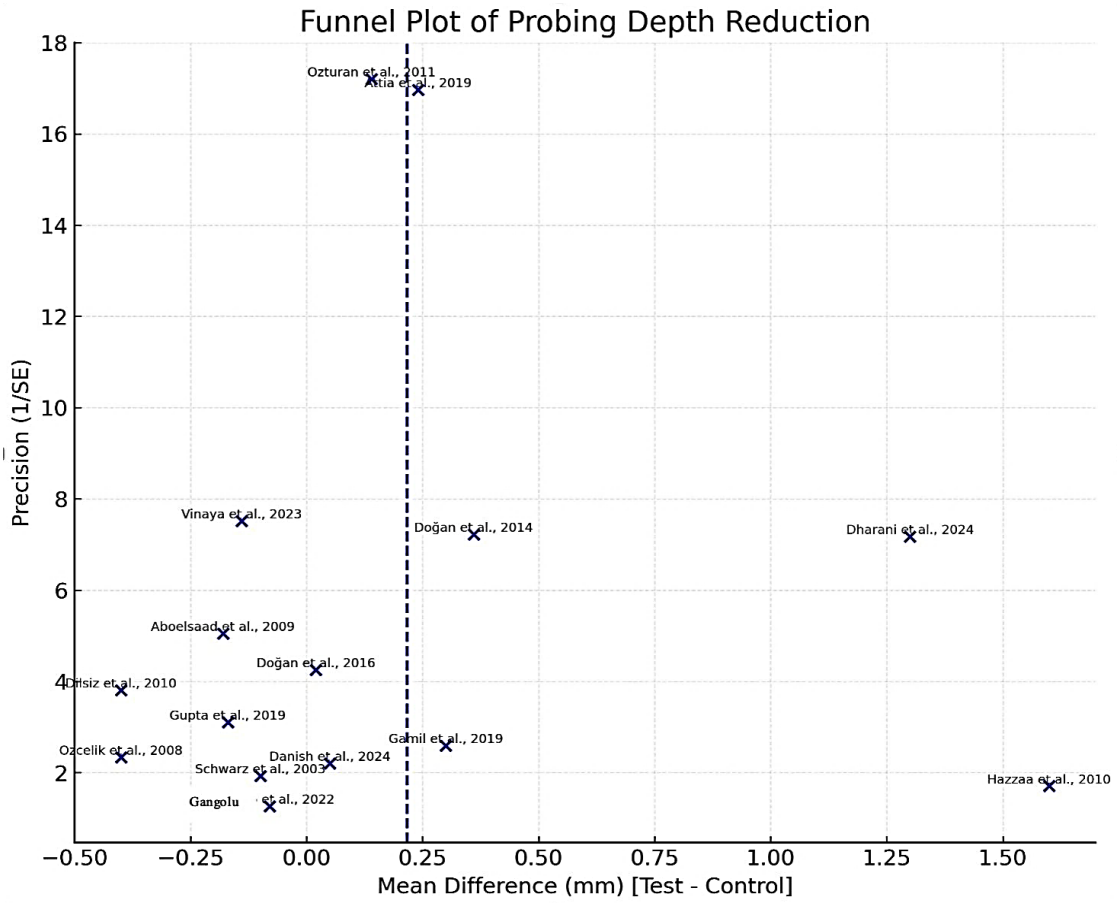

Figure 4.5. *Funnel plot interpretation of PD reduction. PD: Probing Depth.*

❖ Key Observations

1. Scatter/Symmetry

- ✓ The studies are scattered across both sides of the mean effect (vertical dotted line).
- ✓ However, the distribution is asymmetrical.
- ✓ More studies fall to the left (negative/near-zero MD) with smaller effect sizes.
- ✓ Fewer studies appear on the right, except for a few with large positive effects (e.g., Dharani *et al*., 2024; Hazzaa *et al*., 2010).
- ✓ This asymmetry suggests a possibility of publication bias or true heterogeneity in study effects.

2. **Standard Error (SE) / Study Precision**

- ✓ Precision (1/SE) increases as we move up the plot (y-axis).
- ✓ Larger studies (high precision) cluster around the center near the mean effect (Ozturan *et al*., 2011; Attia *et al*., 2019).
- ✓ Larger, more precise studies are plotted higher (with smaller SEs, closer to the top), while smaller, less precise studies are distributed lower.
- ✓ Smaller studies (low precision, bottom part of the funnel) show more variability and wider scatter, which is expected.

3. Outliers / Influential Studies

- ✓ Hazzaa *et al*. (2010) (far right, low precision) stands out as a strong positive outlier.
- ✓ Dharani *et al*. (2024) also shows a larger effect size compared to others but is more accurate, so it still lies within expected variation.
- ✓ On the left side, Ozcelik *et al*. (2008) and Gangolu *et al*. (2022) show relatively negative or near-null effects with low precision, also lying outside the main cluster.

These outliers may drive heterogeneity in the overall meta-analysis.

4. Interpretation- Conclusion

The funnel plot shows some degree of asymmetry, raising concern about publication bias or selective reporting. Larger, more precise studies (higher up) are closer to the null or mean effect, suggesting that smaller, less precise studies are exaggerating effects (both in positive and negative directions). Outliers (Hazzaa *et al*., 2010, Dharani *et al*., 2024, Ozcelik *et al*., 2008, Gangolu *et al*., 2022) contribute to this asymmetry.

Overall, while there is evidence of an effect, the funnel plot suggests caution in interpretation due to possible bias and heterogeneity.

III.4.4.2.4 Meta-analysis- The effect of adjunctive laser uses in regenerative periodontal therapy in terms of clinical attachment level (CAL) gain

A meta-analysis was conducted to compare the changes in terms of CAL gain between studies evaluating regenerative periodontal therapy with or without adjunctive laser use. Out of the 18 studies, 17 met the inclusion criteria for quantitative synthesis. Schwarz et *al*. (2006) lacked sufficient data. **Figure 4.6** displays forest plot interpretation of CAL gain. Using Revman software, the forest plot synthesised MD across selected 17 studies between test and control groups. The mean change in CAL with SD were taken in consideration. The blue dots signify the MD and the horizontal lines indicate the 95% CIs. The orange diamond indicates the cumulative effect of studies. The dotted vertical line is the null line.

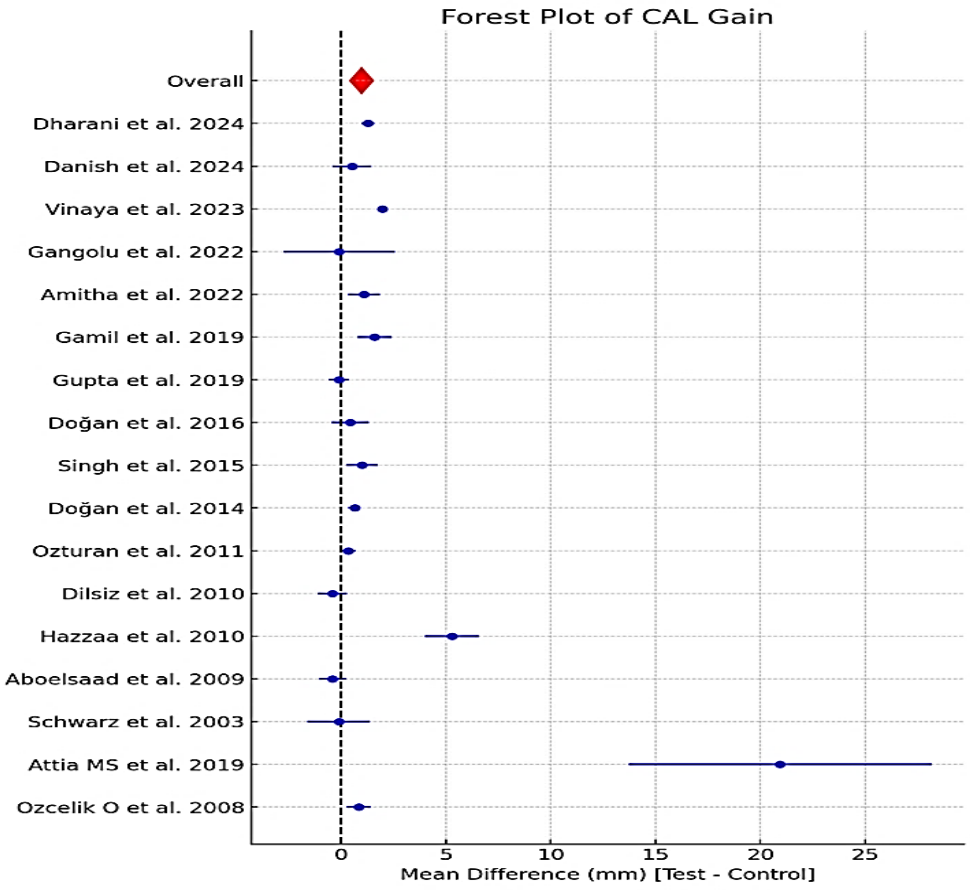

Figure 4.6. *Forest plot interpretation of CAL gain. CAL: Clinical Attachment Level.*

III.4.4.2.5 Clinical relevance of findings

1. Pooled Mean Difference (MD)

The pooled MD in CAL gain was +0.99 mm (95% CI: 0.43 to 1.55 mm), significantly favoring the test group compared to control. Various reports (Danish *et al*., 2024; Dharani *et al*., 2024; Amitha *et al*., 2022; Gamil *et al*., 2019; Singh *et al*., 2015) clearly favored the test intervention with CIs not crossing the null line. Some studies (Gangolu *et al*., 2022; Gupta *et al*., 2019; Schwarz *et al*., 2003) suggested little to no difference, with CIs crossing the line of no effect. Hazzaa *et al.* (2010) and especially Attia *et al.* (2019) appear as outliers, reporting much larger positive differences compared to other trials.

Overall, the evidence indicates that adjunctive/test interventions provide a clinically meaningful improvement in CAL gain compared to controls.

2. Heterogeneity

Substantial heterogeneity was observed ($Q = 447.5$, $df = 16$, $p < 0.001$; $I^2 \approx 96.6\%$; $\tau^2 = 1.17$). This means that the variation between studies is far greater than expected by chance alone. Likely causes include:

- ✓ Differences in regenerative materials and adjuncts used.
- ✓ Variability in defect type (one–three wall intrabony defects, combined defects).
- ✓ Study design and sample size.
- ✓ Follow-up durations.
- ✓ Patient-related factors (age, smoking, OH, baseline CAL).

3. Clinical Implications

A +1 mm CAL gain is clinically meaningful in regenerative periodontal therapy and represents a substantial improvement compared to the small effect seen in PD reduction. However, due to the very high heterogeneity, the magnitude of benefit cannot be generalized to all patients or protocols. Certain techniques or patient subgroups may yield much higher benefits (as seen in Attia *et al*., 2019), while others may show negligible improvement.

4. Model Summary

Pooled Effect Size Test

- ✓ Estimate (MD): +0.99 mm (Test – Control).
- ✓ SE: ≈ 0.29 mm.
- ✓ 95% CI: 0.43 to 1.55 mm.
- ✓ $p < 0.01$ → Statistically significant.

Residual Heterogeneity *(Cochran's Q)*

- ✓ $Q = 447.5$, $df = 16$, $p < 0.001$.
- ✓ $I^2 = 96.6\%$ (very high heterogeneity).
- ✓ $\tau^2 = 1.17$ (between-study variance).

5. Interpretation

a. Pooled Effect Size and Confidence Interval (CI)

- ✓ The pooled effect (+0.99 mm) favors test interventions.
- ✓ Statistically significant and clinically relevant.

b. Prediction Interval (PrI)

- ✓ 95% PI: –1.20 to +3.20 mm → future studies could find no effect, or a substantially larger gain.

c. Heterogeneity

- ✓ Very high heterogeneity ($I^2 \approx 97\%$) indicates outcomes vary widely between studies.
- ✓ Study-specific factors (protocols, populations, methods) play a major role.

d. Implications

- ✓ Evidence supports test interventions as beneficial for CAL gain.
- ✓ However, because of outliers and large variability, results must be interpreted with caution.
- ✓ Subgroup analysis is essential to identify which approaches and patients benefit most.

6. Conclusion

This meta-analysis of 17 studies shows that adjunctive/test interventions yield a statistically significant and clinically meaningful CAL gain (+0.99 mm). However, very high heterogeneity (I^2 = 96.6%) reduces certainty, and outcomes may vary greatly across settings. While promising, these findings require careful application in clinical practice, with emphasis on patient selection and tailored protocols.

III.4.4.2.6 Funnel plot of clinical attachment level (CAL) gain

The funnel plot below displays the distribution of MDs in CAL gain (**Figure 4.7**).

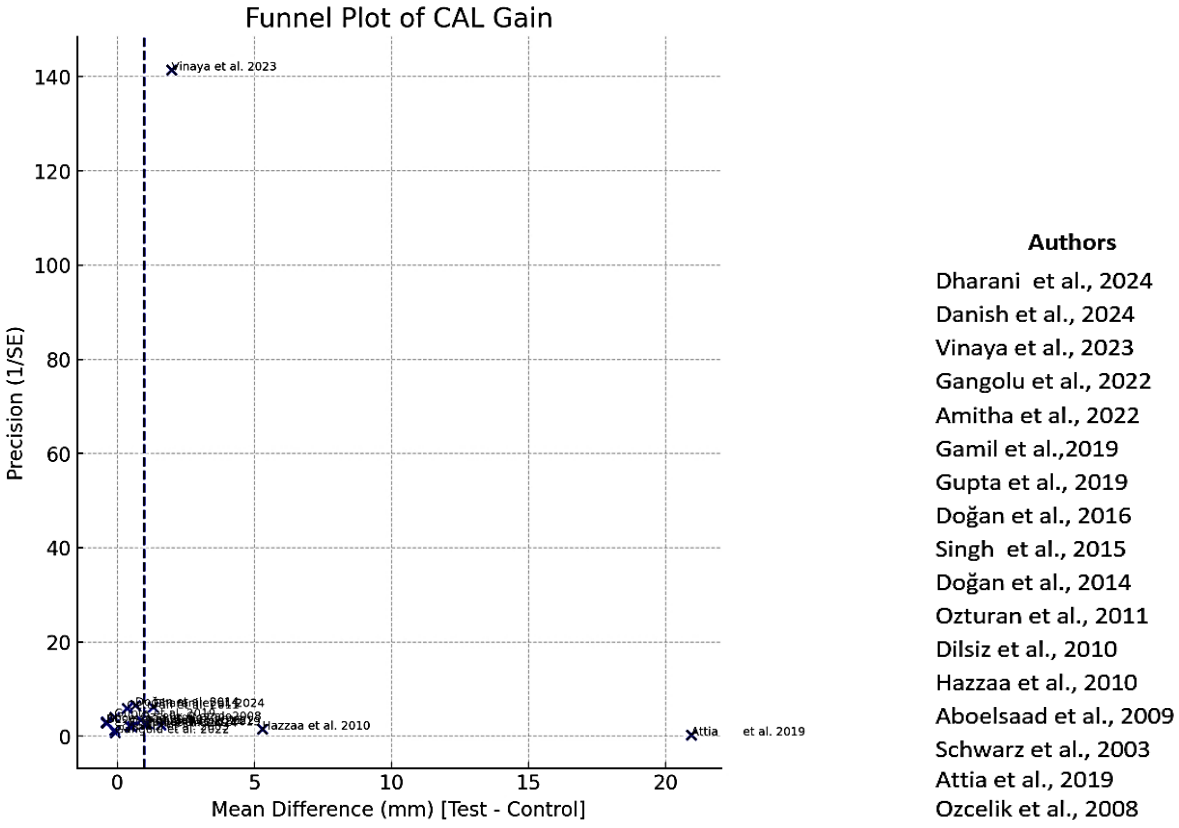

Figure 4.7. *Funnel plot interpretation of CAL gain. CAL: Clinical Attachment Level.*

❖ **Key Observations**

1. Scatter / Symmetry

- ✓ Most studies are distributed around the pooled MD line, but the funnel is not perfectly symmetrical.
- ✓ Vinaya *et al*. (2023) is positioned at the top of the funnel due to its extremely high precision (large sample size, very narrow SE), effectively anchoring the pooled estimate.
- ✓ Danish *et al*. (2024), Dharani *et al*. (2024), Singh *et al*. (2015), Doğan *et al.* (2014, 2016), Ozturan *et al*. (2011) and several others cluster symmetrically near the MD, suggesting moderately precise studies.
- ✓ Hazzaa *et al*. (2010) lies distinctly to the right with low precision, indicating a disproportionately large CAL gain estimate compared to most studies.
- ✓ Attia *et al.* (2019) is positioned at the far right and bottom of the funnel, a clear outlier with very large effect size and very low precision, strongly contributing to the observed asymmetry.
- ✓ Despite these outliers, there is no “empty tail” (i.e., no missing cluster of studies), which suggests limited but not absent publication bias.

2. Standard Error (SE) / Study Precision

- ✓ Larger, more precise studies (e.g., Vinaya *et al*., 2023) appear at the top of the funnel, close to the pooled effect size.
- ✓ Smaller, less precise studies are located toward the bottom, showing greater scatter as expected.
- ✓ The vertical spread widens as precision decreases, which is consistent with a funnel-shaped distribution.

3. Outliers / Influential Studies

- ✓ Attia *et al*. (2019) is the most influential outlier, with an exaggerated effect size well beyond the cluster of other studies.

- ✓ Hazzaa *et al*. (2010) also shows an unusually large CAL gain with low precision, deviating from the general pattern.
- ✓ All other studies remain within the expected scatter, contributing normally to the pooled estimate.

4. Interpretation- Conclusion

The funnel plot shows that larger, high-quality studies (e.g., Vinaya *et al*., 2023; Dharani *et al*., 2024) cluster near the pooled mean, providing consistent evidence for CAL gain. Smaller studies show more variability, with some exaggerating the benefit (positive outliers such as Hazzaa *et al*., 2010 and Attia *et al*., 2019). This asymmetry may indicate small-study effects or publication bias, where smaller studies with large positive results are more likely to be published. However, asymmetry could also reflect true heterogeneity driven by:

- ✓ Different defect morphologies (1–3 wall, combined defects).
- ✓ Variation in adjunctive materials or regenerative protocols.
- ✓ Differences in follow-up times.
- ✓ Patient-related characteristics (smoking, baseline CAL, OH).

To summarize, the funnel plot indicates moderate asymmetry, primarily influenced by two outlier studies (Hazzaa *et al*., 2010 and Attia *et al*., 2019). Larger, precise studies support a consistent CAL gain, while smaller studies occasionally report exaggerated benefits. While publication bias cannot be excluded, the asymmetry is more likely due to true methodological and clinical heterogeneity across studies. Compared with PD reduction, CAL gain shows a robust pooled effect and remains clinically meaningful, even when accounting for small-study effects.

III.4.4.2.7 Overall synthesis of meta-analysis

Adjunctive laser use in regenerative periodontal therapy demonstrates a statistically significant but modest improvement in PD reduction (+0.22 mm) and a more robust, clinically meaningful gain in CAL (+0.99 mm), representing a greater benefit than PD

reduction. However, the considerable heterogeneity observed in both outcomes (I^2 = 85.3% for PD and 96.6% for CAL) limits the generalizability of these results. Funnel plot analyses further indicate potential publication bias or small-study effects, particularly for CAL gain, with certain outliers exerting notable influence. Collectively, these findings suggest that while the adjunctive use of lasers offers limited justification when evaluated solely on PD reduction, it provides a substantial and clinically meaningful advantage in CAL gain, thereby supporting its potential role in regenerative periodontal therapy. Nonetheless, patient-specific factors and variations in treatment protocols must be considered, and further well-designed studies are needed to establish the optimal conditions for laser application.

CHAPTER 5- Discussion

This meta-analysis was conducted to systematically evaluate the effectiveness of regenerative periodontal therapy performed with and without adjunctive laser application. The primary objective of periodontal therapy extends beyond halting disease progression to restoring lost periodontal tissues, thereby re-establishing both structural integrity and functional capacity (Wang and Cooke, 2005; Jepsen et al., 2008). Despite advancements in regenerative techniques, including GTR, EMDs, and bone graft substitutes, clinical outcomes remain heterogeneous and often unpredictable (Sculean *et al*., 2004; Sanz *et al.,* 2020).

Adjunctive laser therapy has been proposed to enhance regenerative outcomes by facilitating root surface and wound decontamination, reducing microbial burden, and exerting photobiomodulatory effects that may promote tissue repair (Schwarz *et al*., 2008; Behdin *et al*., 2015). To explore this potential, data from 18 clinical studies were synthesized to assess the impact of adjunctive laser use on key clinical outcomes, including PD reduction, CAL gain, BoP, GR, RB gain, and patient-reported outcomes. By integrating research spanning two decades, this investigation provided an extensive evaluation of the adjunctive benefits of laser therapy in regenerative periodontal procedures and offers insights to guide future research and clinical practice.

The included studies (2003–2024) captured over two decades of advancements in both laser technology and regenerative biomaterials. Early investigations focused on experimental laser applications, whereas recent trials employed advanced protocols and devices, thereby offering both historical and contemporary perspectives. By synthesizing evidence across diverse study designs and time periods, this research enhances the reliability of conclusions and provides clinicians and researchers with a robust understanding of the evidence base, surpassing the limitations of individual studies.

A systematic review and meta-analysis methodology was employed to address the heterogeneity present in the literature on regenerative periodontal therapy with adjunctive laser use. Individual RCTs and clinical studies often face limitations such as small sample

sizes, short follow-up periods, and methodological inconsistencies, which reduce their generalizability (Page *et al.,* 2021). A systematic review offers a structured framework to appraise and integrate diverse findings, while meta-analysis quantifies treatment effects through data pooling, thereby improving statistical power and precision (Higgins *et al*., 2019).

This methodology is particularly well-suited to the variability in laser parameters, defect morphologies, and regenerative adjuncts across studies. Meta-analytic synthesis, using measures such as the I^2 statistic, distinguishes true treatment effects from study-specific variability and assesses result consistency. By applying consistent inclusion criteria, this approach minimizes selective reporting and aligns with evidence-based periodontology, integrating high-quality research evidence with clinical expertise and patient values (Sanz *et al*., 2020). Furthermore, funnel plots and heterogeneity analyses were employed to evaluate publication bias and methodological differences, ensuring a rigorous and clinically relevant assessment of adjunctive laser therapy.

According to the inclusion and exclusion criteria, 18 studies were included in this research. Of these, 17 were RCTs and one was a prospective case series (Schwarz *et al*., 2006). The predominance of RCTs underscores the robustness of the evidence base, as RCTs are widely considered as the gold standard for assessing the effectiveness of interventions (Cioffi and Farella, 2011). The frequent use of split-mouth designs, as seen in certain studies such as Vinaya *et al.* (2023) and Ozcelik *et al.* (2008), helped minimize inter-individual variability, thereby enhancing the precision of treatment effect estimates (Lesaffre *et al*., 2009).

However, variability in sample sizes, ranging from 10 to 40 participants (total n = 316), raises concerns about statistical power, particularly in smaller trials such as those by Dharani *et al*. (2024), Singh *et al*. (2015), and Ozturan *et al.* (2011), each of which enrolled only 10 participants. Such studies may have limited capacity to detect clinically meaningful differences in periodontal regeneration outcomes, thereby contributing to heterogeneity in the overall findings (Yu *et al*., 2015). In contrast, larger trials including Vinaya *et al*. (2023) (n = 40) and Gamil *et al.* (2019) (n = 32), likely provided greater statistical robustness and

more reliable conclusions. This variability in cohort size underscores the need for standardized guidelines in periodontal regenerative research to ensure greater consistency in study design and outcome reporting.

Although there is no conclusive evidence of inherent constitutional differences in susceptibility to periodontal diseases between genders, a systematic review by Shiau and Reynolds (2010) reported a higher predisposition among men. This was attributed to behavioral and lifestyle factors such as poor OH practices, irregular dental visits, and certain habits like smoking and tobacco chewing. Moreover, sex chromosome-related genes and sex hormones, including estrogens, progesterone, and androgens, play a role in the differential regulation of immune responses between sexes (Klein and Flanagan, 2016; Ioannidou, 2017).

Unlike Shiau and Reynolds (2010), the present review did not reveal a clear gender predilection, as only 11 of the 18 studies reported gender-specific data. Of these, four studies demonstrated a male-dominant cohort, with Amitha *et al*. (2022) showing the most skewed distribution. Four studies, in contrast, were female-dominant, in particular AboElsaad *et al.* (2009). Three studies, including Schwarz *et al*. (2003, 2006) and Doğan *et al*. (2014), described relatively balanced gender distributions. However, the omission of gender data in seven studies (Danish *et al*., 2024; Dharani *et al*., 2024; Vinaya *et al*., 2023; Gangolu *et al*., 2022; Gupta *et al*., 2019; Gamil *et al*., 2019; Hazzaa *et al*., 2010) represents a significant limitation, as it precludes meaningful sex-based comparisons.

With respect to age, periodontal disease is more commonly observed in older populations, particularly individuals over 45 years of age (Iwashimizu *et al*., 2024). While aging itself does not directly cause periodontal disease, it increases the risk of periodontal attachment loss and alveolar bone resorption upon exposure to etiologic factors (Jain and Bhavsar, 2021). In opposition to this evidence, however, studies included in this investigation enrolled participants across a wide age spectrum, ranging from younger cohorts (e.g., Singh *et al*., 2015: 21–36 years) to middle-aged groups (e.g., Vinaya *et al*., 2023: 35–60 years) and older populations (e.g., Schwarz *et al*., 2006: mean 49 ± 12 years). Inconsistencies in age reporting, with some studies presenting ranges and others

reporting means, further complicated direct comparisons across trials. Furthermore, since smoking and systemic health conditions are known to impair wound healing and affect the efficacy of periodontal treatment (Borojevic, 2012), most studies included only non-smokers and systemically healthy individuals to minimize potential confounding effects on periodontal regeneration and healing.

Based on the controlled selection of participants, the 18 clinical studies evaluating periodontal regenerative therapies employed varying group allocations to compare adjunctive laser therapy with standard regenerative interventions. The primary outcomes assessed included PPD reduction, CAL gain, GR, BoP, and RB gain, while the secondary outcomes focused on patient-centred measures such as discomfort, aesthetic results, and functional improvements.

Assessment of PD outcomes in the included studies reported consistent reductions, with a pooled MD of +0.22 mm (95% CI: 0.15–0.28, $p < 0.001$), evidencing that adjunctive laser use was associated with a statistically significant but clinically modest reduction in PD compared with regenerative therapy alone. In periodontal practice, reductions smaller than 0.5 mm are unlikely to influence prognosis, guide treatment decisions, or affect long-term tooth survival (Cortellini and Tonetti, 2002). Accordingly, while the statistical evidence is strong, adjunctive lasers appear to provide only minor additional benefits in PD reduction when combined with regenerative procedures. Moreover, the high heterogeneity ($I^2 = 85.3\%$) further reflects variability in patient populations, defect morphologies, laser types, power settings, and regenerative adjuncts. Some trials, such as Dharani *et al.* (2024) and Hazzaa *et al.* (2010), reported clinically relevant reductions in PD, possibly due to optimized parameters or favorable defect characteristics. In contrast, studies like Dilsiz *et al*. (2010) and AboElsaad *et al*. (2009) found little or no benefit, underscoring inconsistency across the evidence base. Taken together, these findings suggest that while adjunctive lasers may yield incremental improvements under certain conditions, they cannot be expected to consistently produce substantial changes in PD.

Contrary to PD, assessment of CAL outcomes in the included studies reported more meaningful improvements with adjunctive laser use. The pooled MD of +0.99 mm (95% CI: 0.43–1.55, $p < 0.001$) demonstrates a statistically significant gain that is clinically relevant, as it suggests regenerative healing beyond simple pocket reduction and contributes to improved tooth stability over time. Gains of this magnitude are widely considered indicative of regeneration rather than repair, and are associated with improved tooth stability, reduced recurrence of periodontal breakdown, and increased tooth survival (Jepsen *et al*., 2008; Cortellini and Tonetti, 2002).

However, the analysis also revealed very high heterogeneity ($I^2 = 96.6\%$), reflecting substantial variability across the included studies. Differences in surgical protocols, defect morphologies, regenerative adjuncts, and patient-related characteristics likely contributed to this inconsistency. Outlier influence was also evident; for example, Hazzaa *et al*. (2010) reported disproportionately large attachment gains that may have skewed the pooled estimate. Despite these variations, the general trend across diverse settings supports the adjunctive value of lasers in improving CAL. From a clinical standpoint, even an average gain of around 1 mm can improve prognosis, reduce the risk of future disease progression, and enhance the predictability of regenerative therapy.

With regard to BoP as clinical parameter, reductions were observed across seven studies (ranging from 26% to 95.24%), consistently favoring the laser-assisted groups. This improvement emphasizes that lasers may aid in modulating inflammation within periodontal tissues and enhance local inflammatory control. The bactericidal properties of lasers, particularly diode and Nd:YAG wavelengths, likely explain these outcomes, as they facilitate root surface decontamination and reduce microbial colonization within the periodontal pocket (Al Asmari, and Alenezi, 2025; Fiegler-Rudol *et al*., 2025). In addition, their photobiomodulatory effects have been shown to reduce inflammatory mediators and promote a more favorable healing environment. From a clinical perspective, reduced BoP is significant, as persistent bleeding is strongly associated with active disease and future attachment loss. Although the degree of improvement varied between trials, the overall

trend suggests that lasers can play a useful role in achieving and maintaining periodontal stability by controlling inflammation (Schwarz *et al*., 2008).

In addition, data from 10 studies reported a mixed picture with regard to GR. While some investigations, such as Amitha *et al.* (2022), demonstrated improvements in gingival stability following laser-assisted regenerative therapy, others, including Doğan *et al.* (2014), reported greater recession in laser-treated sites. These discrepancies likely reflect differences in flap design, surgical technique, and energy parameters used in different studies. In cases where excessive thermal energy or aggressive de-epithelialization occurred, gingival margin recession may have been exacerbated. Moreover, diode and Nd:YAG lasers tend to penetrate deeper and cause relatively higher thermal effects and result in thicker coagulation layer on surfaces that are treated compared to superficially absorbed lasers, causing delayed wound healing (Aoki *et al*., 2015). Conversely, protocols emphasizing minimally invasive laser application and optimal biomaterial support may have contributed to improved soft tissue preservation. Clinically, GR is a double-edged outcome as even in the presence of attachment gain, worsening recession in aesthetically sensitive areas can compromise patient satisfaction. Thus, the role of lasers in influencing gingival margins requires further investigation through standardized surgical protocols and long-term follow-up.

With regard to RB gain, seven of the 18 included studies reported outcomes, with values ranging from 0.498 mm to 5.60 mm. In most cases, greater improvements were observed in laser-assisted groups, suggesting that adjunctive laser use may contribute positively to osseous regeneration. Radiographic presence of bone fill, although not a direct histological confirmation of regeneration, remains an important surrogate marker of periodontal healing and prognosis (Kreisler *et al*., 2003). Lasers may enhance bone regeneration by facilitating thorough root surface debridement, reducing bacterial contamination, and stimulating osteoblastic activity through photobiomodulation (Aoki *et al*., 2015). However, variability in radiographic assessment methods, including periapical radiographs, digital subtraction techniques, and cone-beam computed tomography (CBCT), complicates cross-study comparisons. Despite these methodological

differences, the trend toward improved bone fill in test groups parallels clinical attachment and PD outcomes, reinforcing the potential regenerative advantage of adjunctive laser use. Overall, RB gain findings, though variable, further suggest a role for lasers in promoting osseous healing.

With respect to PCOs, only three studies reported these findings, reflecting a major limitation in the current evidence base. Among these, Amitha *et al*. (2022) and Ozcelik *et al.* (2008) observed reduced postoperative pain and discomfort in the laser groups, whereas Vinaya *et al.* (2023) found no significant differences between groups. The scarcity of data on esthetics, function, and quality of life is concerning, particularly as these outcomes are increasingly prioritized in contemporary periodontology. Lasers may provide advantages in reducing intra- and postoperative discomfort due to their minimally invasive and hemostatic properties, potentially enhancing patient acceptance and satisfaction (Romanos and Nentwig, 1999; Aoki *et al*., 2015; Al Asmari and Alenezi, 2025). However, without consistent and systematic reporting of PCOs, it remains difficult to draw definitive conclusions. The paucity of patient-reported outcomes highlights a significant gap in the literature. Few studies systematically assessed pain, esthetic satisfaction, or functional results, underscoring the necessity for subsequent investigations to integrate validated PCO measures. Such estimations reflect the real-world impact of periodontal interventions more directly than clinical or radiographic endpoints alone (Sanz *et al*., 2020). Findings from a recent meta-analysis by Zhao and Zhao (2021) align with these observations. In details, adjunctive LLLT by in periodontal surgery was shown to reduce pain and analgesic use in the early postoperative period, with benefits evident by day three. By day seven, however, no significant improvement in pain control was observed, suggesting that outcomes may be influenced by factors such as laser parameters, surgical technique, and concomitant medication use.

Due to the lack of previous meta-analyses and reported data, direct comparisons with existing literature are limited. Nevertheless, studies with related findings provide context. A narrative review on the adjunctive use of lasers in conventional flap surgery reported improvements in key parameters such as CAL, BoP, and plaque index (PI), alongside

reduced postoperative discomfort in laser-treated sites. However, significant heterogeneity in reported outcomes and an overall lack of unifying evidence limit broad support for the adjunctive use of lasers in periodontal therapy (D'Albis *et al*., 2025). Similarly, a systematic review and meta-analysis by Yan *et al.* (2018) evaluating the adjunctive use of lasers in flap graft techniques for GR found clinical advantages in terms of PD and CAL, but no additional benefit in root coverage or esthetics.

Long-term and clinical studies also provide insights. A 15-year follow-up study by Crespi *et al*. (2011) showed significant reductions in PD and CAL by combining CAF with CO_2 lasers, compared with the modified Widman flap procedure. The authors attributed these improvements to the ability of CO_2 lasers to remove the smear layer and bacterial cells from affected root surfaces. Similarly, Sculean *et al*. (2004) demonstrated that the adjunctive use of Er:YAG lasers in intrabony defect treatment improved clinical parameters at six months; however, their efficacy was comparable to mechanical debridement alone. Contrary to the findings of the present meta-analysis, a systematic review and meta-analysis by Behdin *et al*. (2015) concluded that the available literature on dental lasers as an adjunct to resective or regenerative periodontal therapy is inadequate and does not demonstrate superiority over conventional methods. More recently, a narrative review by Zisis *et al*. (2025) suggested that adjunctive laser use in resective surgery may offer additional benefits, but emphasized that evidence in regenerative contexts remains insufficient and warrants further investigation. Meanwhile a consensus report by the American Academy of Periodontology (AAP) concluded that adjunctive laser use does not provide significant benefits beyond those achieved with conventional surgical treatments alone (Mills *et al*., 2018). Variability in laser parameters and application techniques across studies continues to hinder the development of standardized clinical recommendations (Cobb, 2006). Furthermore, lasers such as CO_2 and Nd:YAG potentially lead to the risk of thermal damage to root surfaces, which may compromise treatment outcomes (Dentino *et al*., 2013).

Overall, the present meta-analysis synthesized two decades of evidence directly comparing regenerative therapy with and without adjunctive lasers, thereby contributing

to the advancement of current knowledge. The inclusion of recent high-quality trials such as Danish *et al.* (2024) and Dharani *et al.* (2024) strengthens the evidence base by incorporating contemporary protocols and improved laser technology, which may explain the more consistent results observed in newer studies. These benefits are also consistent with the biological rationale for laser use. Experimental research has demonstrated that lasers may enhance periodontal healing and regeneration through multiple mechanisms, including reduction of bacterial contamination, stimulation of fibroblast proliferation, promotion of angiogenesis and collagen formation, and modulation of inflammatory mediators (Aoki *et al.*, 2015; Behdin *et al*., 2015). Collectively, these findings suggest that while earlier studies reported mixed results, the cumulative evidence increasingly supports the adjunctive role of lasers in regenerative procedures. Nevertheless, further well-designed long-term studies are necessary to validate and extrapolate these results.

III.5.1 Strengths of the Study

A key strength of this meta-analysis is its comprehensive literature search strategy. From 770 initially identified articles, 18 studies met the inclusion criteria and were analyzed, spanning more than two decades (2003–2024). This broad timeframe ensured that both early exploratory investigations and more recent trials incorporating advanced laser technologies were included, thereby providing a balanced and representative synthesis of the available evidence. By applying predefined eligibility criteria and systematic screening methods, the review minimized selection bias and strengthened the robustness of its conclusions (Moher *et al*., 2009).

Another major strength lies in the design of the included studies. Seventeen of the 18 trials were RCTs, widely regarded as the gold standard in clinical research (K.M. Higgins *et al*., 2024). The predominance of RCTs enhanced the internal validity of the review by reducing confounding factors and minimizing potential bias. Furthermore, systematic risk of bias assessments was conducted, ensuring a transparent appraisal of methodological quality across studies. This rigorous evaluation enhances the credibility and reliability of the findings (Sanz *et al*., 2020). Finally, the inclusion of meta-analyses for two primary

outcomes, such as PD reduction and CAL gain, represents an additional strength. By quantitatively pooling data, the review achieved more precise effect estimates than individual studies alone could provide. While PD reduction was modest (+0.22 mm), CAL gain was both statistically significant and clinically meaningful (+0.99 mm). These quantitative insights provide valuable guidance for clinicians and underscore the potential role of adjunctive lasers in regenerative periodontal therapy (Jepsen *et al*., 2008; Cortellini and Tonetti, 2002).

III.5.2 Limitations of the Study

Despite its strengths, the study has several important limitations, the most prominent being the high degree of heterogeneity across the included trials. For PD reduction, heterogeneity was I^2 = 85.3%, and for CAL gain I^2 = 96.6%, indicating substantial variability. This variability can be attributed to multiple methodological and biological factors. Firstly, laser type and parameters differed considerably between studies. Diode, Nd:YAG, Er:YAG, and Er,Cr:YSGG lasers each interact differently with hard and soft tissues due to variations in wavelength absorption and energy delivery (Ishikawa *et al*., 2009; Romanos, 2015). Differences in output power, mode of operation (continuous vs. pulsed), and duration of exposure likely contributed to inconsistent outcomes. Secondly, variability in defect morphology (e.g., intrabony, furcation, or recession-type defects) may have influenced the healing potential and regenerative response (Cortellini and Tonetti, 2002). Thirdly, regenerative adjuncts used in combination with lasers, such as EMDs, CGFs, or bioactive glass, differed across studies, complicating isolation of the laser effect (Sanz *et al*., 2020). Methodological differences, including split-mouth versus parallel-group designs, lack of blinding, and varied follow-up durations, further contributed to heterogeneity. Finally, patient-related variables such as smoking status, age, and systemic health conditions are known to influence periodontal healing and may explain some of the between-study variation (Lang *et al*., 2018; Siaili *et al*., 2018). Collectively, these sources of heterogeneity restrict the generalizability of the pooled results and suggest that laser efficacy may be context-dependent.

Another limitation relates to potential publication bias. The funnel plot analysis for PD reduction demonstrated an asymmetrical distribution, suggesting that smaller studies with more favorable results for adjunctive lasers may be overrepresented in the literature, while neutral or negative studies could remain unpublished. Such bias can artificially inflate pooled estimates and must be considered when interpreting clinical significance. Similarly, for CAL gain, the funnel plot also showed asymmetry, with outliers such as Hazzaa *et al*. (2010) and Attia *et al*. (2019) reporting unusually large improvements. These outcomes may reflect methodological differences or selective reporting. Nonetheless, despite the potential influence of publication bias, the overall direction of effect across studies remained consistent, strongly supporting the conclusion that adjunctive lasers contribute meaningfully to attachment gain. The observed asymmetry, therefore, underscores the need for more large-scale, rigorously designed trials to confirm the durability and generalizability of these benefits. A further limitation is the underreporting of key clinical outcomes. While PD and CAL were consistently documented, secondary outcomes were often missing. For instance, BoP was reported in only seven of the 18 studies, and patient-related outcomes such as pain, aesthetics, and quality of life were reported in just three studies. This limited reporting prevented meta-analyses of these outcomes and restricted the comprehensive evaluation of adjunctive laser therapy (Sanz *et al*., 2020).

Finally, the scope of the review was narrowed by the exclusion of certain types of studies, such as those involving platelet-rich fibrin (PRF), PRP, or animal models. Although these exclusions were necessary to ensure methodological rigor and maintain a focus on human clinical outcomes, they may have limited the breadth of available evidence. Furthermore, the small sample sizes in several included studies reduced statistical power and might have exaggerated treatment effects.

III.5.3 Future Implications

The findings of this meta-analysis highlight several important directions for future research. First, the high levels of heterogeneity observed across studies underscore the need for larger, multi-center RCTs. Such trials would increase statistical power, minimize

the influence of small-study effects, and improve the generalizability of results across diverse patient populations and clinical settings. By involving multiple centers, these studies could also account for operator variability and enhance external validity.

Second, future research should place greater emphasis on PCOs such as postoperative pain, aesthetic satisfaction, and oral health–related quality of life. These outcomes are often underreported, despite being highly relevant to patients' daily experiences and treatment decisions. Incorporating validated patient-reported outcome measures into trial designs would align clinical research with the priorities of contemporary periodontal practice, ensuring that therapies are evaluated not only for biological efficacy but also for their impact on patient well-being. Furthermore, surgical re-entry or histologic evaluation, considered the gold standard for assessing true periodontal regeneration, was lacking in most of the included studies due to ethical constraints. Future investigations focusing on histological analysis would provide more definitive evidence on the regenerative efficacy of lasers in periodontal therapy.

Third, research into the cost-effectiveness of adjunctive laser therapy should be required. While lasers offer potential clinical advantages, they also involve substantial capital investment and operational costs. Evaluating the economic value of lasers in comparison with conventional regenerative methods would provide essential insights for clinicians, policymakers, and healthcare systems considering their wider adoption. Cost-effectiveness analyses that balance clinical outcomes with financial implications are critical to guide evidence-based resource allocation.

Finally, the development and adoption of standardized laser protocols and defect classification systems would greatly facilitate future meta-analyses and evidence synthesis. At present, variability in laser type, wavelength, power settings, and application protocols complicates cross-study comparisons and contributes to heterogeneity. Similarly, consistent classification of periodontal defects (e.g., intrabony, furcation, or recession-type lesions) is critical for evaluating treatment outcomes across different clinical scenarios. Establishing consensus on these standards would enhance

methodological consistency and allow for more meaningful comparisons and pooled analyses in future research.

PART IV- CHAPTER 6- Conclusions and Recommendations

This meta-analysis synthesized two decades of clinical evidence comparing regenerative periodontal therapy with and without adjunctive laser use. Findings indicate that adjunctive lasers significantly improve CAL, with modest benefits in PPD reduction, while additional gains in BoP and RB fill support the biological rationale for laser-assisted regeneration. However, inconsistencies in GR outcomes, underreporting of PCOs, and high heterogeneity due to variations in laser parameters, defect morphologies, and adjunctive materials limit the generalizability of results. Potential publication bias and small sample sizes further warrant cautious interpretation. Overall, the cumulative evidence suggests that lasers hold promise as adjuncts in regenerative procedures, but well-designed, multicenter, long-term RCTs with standardized protocols, histological validation, and systematic reporting of PCOs are required before routine clinical adoption can be recommended.

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