Periodontitis: Causal Links and Treatment in the Context of Diabetes, Smoking, and In-Stent Restenosis

PhD Thesis

by

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PUBLICATIONS FORMING THE BASIS OF THE THESIS

1. **Dharmarajan L,** Prakash PS, Appukuttan D, Crena J, Subramanian S, Alzahrani KJ, Alsharif KF, Halawani IF, Alnfiai MM, Alamoudi A, Kamil MA. The Effect of Laser Micro Grooved Platform Switched Implants and Abutments on Early Crestal Bone Levels and Peri-Implant Soft Tissues Post 1 Year Loading among Diabetic Patients—A Controlled Clinical Trial. Medicina. 2022 Oct 15;58(10):1456.

SJR rank: Q2 / IF: 2.6

2. Nagy FT, Gheorghita D, **Dharmarajan L**, Braunitzer G, Achim A, Ruzsa Z, Antal MÁ. Oral Health of Patients Undergoing Percutaneous Coronary Intervention—A Possible Link between Periodontal Disease and In-Stent Restenosis. Journal of Personalized Medicine. 2023 Apr 28;13(5):760.

SJR rank: Q2 / IF: 3.4

3. **Dharmarajan L**, Anuja S, Elango P, Babu A. Role of Cathepsin in Oral Disease. European Journal of Molecular and Clinical Medicine.2020 ISSN 2515-8260 Volume 7, Issue 4

Summed IF: 6.0

PUBLICATIONS NOT RELATED TO THE SUBJECT OF THE THESIS

1. Nath S, Pulikkotil SJ, **Dharmarajan L**, Arunachalam M, Jing KT. Effect of locally delivered doxycycline as an adjunct to scaling and root planing in the treatment of periodontitis in smokers: A systematic review of randomized controlled trials with meta-analysis and trial sequential analysis. Dental research journal. 2020 Jul;17(4):235.

SJR ranking: Q2

2. Nagendrababu V, Ahmed HM, Pulikkotil SJ, Veettil SK, **Dharmarajan L**, Setzer FC. Anesthetic efficacy of Gow-Gates, Vazirani-Akinosi, and mental incisive nerve blocks for treatment of symptomatic irreversible pulpitis: A systematic review and meta-analysis with trial sequential analysis. Journal of endodontics. 2019 Oct 1;45(10):1175-83.

IF: 4.2 SJR ranking: Q1

3. Gopinath VK, Pulikkotil SJ, Veettil SK, **Dharmarajan L**, Prakash PS, Dhar V, Jayaraman J. Comparing the clinical and radiographic outcomes of pulpotomies in primary molars using bioactive endodontic materials and ferric sulphate–a systematic review and meta-analysis of randomized clinical trials. Journal of Evidence-Based Dental Practice. 2022 Aug 6:101770.

IF: 3.6 SJR ranking: Q1

4. Jasmine Crena, **Lalli Dharmarajan**, PSG Prakash, Sangeetha Subramaniam, Devapriya Apukuttan. p53 and c-Myc in Reprogramming Energy Metabolism in Metastasis. Journal of Molecular Biology. Volume 11:11, 2022

IF: 5.6 SJR ranking: Q1

5. Nagendrababu V, Duncan HF, Tsesis I, Sathorn C, Pulikkotil SJ, **Dharmarajan L**, Dummer PM. Preferred reporting items for systematic reviews and meta-analyses for abstracts: best practice for reporting abstracts of systematic reviews in Endodontology. International Endodontic Journal. 2019 Aug;52(8):1096-107.

IF: 5,0 SJR ranking: Q1

6. Nagendrababu V, Narasimhan S, Faggion Jr CM, Dharmarajan L, Jacob PS, Gopinath VK, Dummer PM. Reporting quality of systematic reviews with network meta-analyses in Endodontics. Clinical Oral Investigations. 2023 Mar 13:1-9.

IF: 3.4 SJR ranking: Q1

7. Gopinath VK, Shetty RM, Renugalakshmi A, Dharmarajan L, Prakash PS, Jayaraman J. Reporting Quality of the Abstracts for Randomized Controlled Trials in Pediatric Dentistry. European Journal of Dentistry. 2023 Aug 8.

SJR ranking: Q1

8. Nazar NSBM, Ramanathan A, Ghani WMN, Rokhani FB, Jacob PS, Sabri NEB, Hassan MS, Kadir K, Dharmarajan L. Salivary metabolomics in oral potentially malignant disorders and oral cancer patients-a systematic review with meta-analysis. Clin Oral Investig. 2024 Jan 16;28(1):98. doi: 10.1007/s00784-023-05481-6.

IF: 3.4 SJR ranking: Q1

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ABBREVIATIONS

PSD: Polymicrobial Dysbiotic Model

PD: Periodontal Disease

IL: Interleukin

TNF: Tumour Necrosis Factor

DM: Diabetes Mellitus

OPG: Osteoprotegerin

CDC: Centers for Disease Control and Prevention

LMG: Laser Micro Grooved

MCBL: Mean Crestal Bone Level

R-PGM: Relative Position of the Gingival Margin

FMPS: Full Mouth Plaque Score

FMBS: Full Mouth Bleeding Score

PPD: Periodontal Probing Depth

S-SPS: Site-Specific Plaque Scores

S-SBS: Site-Specific Bleeding Scores

PISD: Peri-Implant Sulcus Depth

ISQ: Implant Stability Quotient

I. INTRODUCTION

Periodontal disease is a chronic inflammation of the tooth-supporting tissues caused by bacteria [1]. In its severe form, it affects up to 11% of the global population and remains one of the most prevalent diseases [2]. Approximately 10% of adults are affected by this severe form of oral disease, which represents a major socioeconomic and public health burden [3]. This chronic inflammatory disease (CID) progressively undermines the structural integrity of the tissues that support the teeth. It is associated with several chronic systemic disorders, including Alzheimer's disease, non-alcoholic fatty liver disease, cardiovascular disease, type 2 diabetes mellitus (T2DM), inflammatory bowel disease, and certain cancers [4].

It is essential to determine whether the association between periodontitis and its comorbidities is merely correlative or mediated by causal mechanistic pathways [5]. To understand the causal relationship, a panel of specialists from the USA and Europe examined the evidence in 2012, focusing on the most extensively studied links—namely, diabetes, adverse pregnancy outcomes, and cardiovascular diseases—between periodontal and systemic disorders. They concluded that periodontitis increases the bacterial load, which causes a major inflammatory reaction in the body and it is believed to play a role in the pathophysiology of diabetes, cardiovascular diseases and other inflammatory conditions [6-8].

Recent research suggests that periodontitis may increase an individual's susceptibility to comorbidities. Even after accounting for potential confounding factors, an independent association remains between periodontitis and these conditions, which share common inflammatory effector pathways, hereditary predispositions, oral microbial interactions, and acquired risk factors with periodontitis [9-11].

I.1. Signatures of the Oral Microbiome in the Periodontal Tissues

Microbial cells within the oral bacteriome communicate to coordinate their activities. These interactions include competition with other microorganisms, signaling interference for competitive advantage during colonization, horizontal gene transfer, synergistic metabolic cooperation, and resource competition [11]. The oral environment provides conditions that allow bacterial colonization and growth. These microorganisms have the ability to form biofilms [12]. Alterations in the natural oral microbiome can disrupt the symbiotic relationship between microbial colonization and the host, thereby affecting both oral and systemic health. Pathogenic

bacteria in subgingival plaque biofilms can disrupt the host–microbe equilibrium, leading to disease. This imbalance is referred to as "dysbiosis" [13, 14]. A model known as Polymicrobial Synergy and Dysbiosis (PSD) has been developed to describe the contemporary understanding of the pathophysiology of periodontitis [15]. The PSD model posits that periodontal disease results from a synergistic polymicrobial community rather than a single pathogen. The members or functional genes of this community shape and stabilize a dysbiotic microbiota, thereby disrupting host homeostasis [16]. Evolving interactions between microbes and host factors have led to the development of updated microbial models of periodontal pathogenesis. These models propose that tissue destruction is not caused by a few specific periodontal pathogens, but rather by the collective activity of pathogenic microbial communities [15]. These microbial communities include putative pathogens such as the gram-negative bacteria *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia*. Researchers consistently link these bacteria to the development and advancement of periodontitis in greater anaerobic regions. Conversely, in healthy gingival plaque, other bacterial species predominate. Historically, the development of periodontitis has been attributed to a triad of oral anaerobic bacteria known for their virulence characteristics and robust association with disease-affected sites [17]. For example, *P. gingivalis* manipulates the host immune response to modify the oral microbiota and cause pathobiont-mediated inflammatory periodontal bone loss [18]. Although not inherently pathogenic, certain commensals such as *Streptococcus gordonii* facilitate the colonization of *P. gingivalis* and are therefore considered secondary pathogens [19]. Animal models of periodontitis support the notion that *P. gingivalis* collaborates with other periodontal organisms; inoculating *P. gingivalis* in combination with accessory pathogens or other keystone-like pathogens (e.g., S. gordonii or T. forsythia) results in greater alveolar bone loss than inoculation with *P. gingivalis* alone [20]. The synergy described may not be limited to manipulation of the host response; rather, it may involve cooperative interspecies communication that enhances bacterial fitness and promotes dysbiosis. Communication between periodontal bacteria induces reciprocal transcriptomic and proteomic responses in vitro, which modulate virulence factor production, nutrient uptake, and other metabolic processes [20]. Compared to supragingival microbial communities, subgingival biofilms adhere more tightly to root surfaces, where they are better protected from shear forces and ambient oxygen [21]. This allows the biofilms to stimulate host inflammation, which can lead to periodontal disease and tooth loss[22].

I.2. Inflammatory Mechanisms Linking Periodontitis and Systemic Disease

A physiological acute inflammatory response to supragingival and subgingival plaque is mediated by innate immune cells such as fibroblasts, epithelial cells, neutrophils, macrophages, complement proteins, and neuropeptides. Resident cells release cytokines such as TNF-α, IL-1β, and IL-6, which promote cell migration to sites of infection, upregulate neutrophil adhesion molecules, and enhance proinflammatory cytokine synthesis within vessels [23]. Immunological homeostasis is regulated through both microbiome-dependent and microbiome-independent mechanisms [24]. In this immune system, neutrophils act as surveillance cells, with IL signaling being downregulated during microbial inflammation[25].

To summarize, the emerging model of polymicrobial synergy and dysbiosis posits that accessory pathogens initially undermine the host immune response, which is then overactivated by pathobionts. This establishes a connection between the breakdown of homeostasis and the induction of destructive inflammation in susceptible individuals. The subsequent section delineates the precise molecular mechanisms through which periodontal bacteria modulate the host response in order to induce dysbiotic inflammation. Periodontal inflammation and its causal link

Neutrophils are essential for maintaining periodontal health. Their dysfunction leads to severe periodontitis, characterized by increased neutrophil infiltration and aberrant inflammation.A finely regulated balance between neutrophils and proinflammatory cytokines is needed for periodontal immunity [26]. This highlights how periodontal bacteria manipulate neutrophils through the release of harmful components. Modulation of the microbiota and targeting of host neutrophils provide mechanistic insights into periodontal comorbidities, including those influenced by nutritional factors [27]. Neutrophils employ both oxidative and non-oxidative mechanisms, including the production of cathepsins, a class of lysosomal cysteine proteases [28]. Inflammatory and infectious insults alter the expression of Cathepsin S and other autophagy-associated molecules, which play catabolic and immunomodulatory roles and influence osteoblast differentiation and bone remodeling. Overexpression of cathepsins contributes to vascular and metabolic complications associated with periodontal disease [29]. For example, the synergistic activity of pathogens and their secreted molecules helps maintain a dysbiotic, heterotypic microbial community. This community acts as a collective virulence factor, triggering a tissue-destructive and non-resolving host response [29].

In recent decades, research on periodontitis and its association with systemic disorders has increased significantly. Randomized clinical trials are unlikely to definitively establish a causal

relationship between periodontitis and other inflammatory diseases. Randomized studies evaluating the effects of periodontitis therapy on systemic comorbidities such as diabetes mellitus (DM) or cardiovascular disease (CVD) would require long-term follow-up and face significant ethical constraints. Thus, health authorities must evaluate the cumulative plausibility of a causal link between periodontitis and its comorbidities, a conclusion likely to rely on indirect evidence [29, 30]. For example, the synergistic activity of pathogens and their molecular products sustains a dysbiotic, heterotypic microbial community, which acts as a collective virulence factor that triggers a tissue-destructive and non-resolving host response [15].

I.3. Diabetes and Periodontal Disease

Chronic hyperglycemia caused by insulin secretion and/or insulin resistance is a hallmark of diabetes mellitus (DM). Chronically elevated blood sugar levels have been linked to both microvascular and macrovascular complications. According to the World Health Organization, diabetes mellitus affects 422 million people worldwide and causes 1.6 million deaths annually. The global prevalence of diabetes is projected to reach 629 million by 2045. Most diagnosed diabetes cases, 90%-95%, are T2DM, which affects about 380 million people worldwide, 8.8% of those aged 20–79 [31, 32].

In addition, peripheral neuropathy, retinopathy, nephropathy, and atherosclerotic cardiovascular, peripheral arterial, and cerebrovascular diseases are potential long-term complications of T2DM [33]. Additionally, people with diabetes mellitus have an increased risk of developing periodontal disorders, which can worsen in those with poorly controlled diabetes. Conversely, individuals with periodontitis have a higher risk of developing diabetes mellitus, as periodontal inflammation may increase systemic inflammatory burden [34].

Chronic hyperglycemia is therefore associated with impaired bone metabolism, hyperinflammatory responses, and impaired wound repair [35]. Increased osteoclastic activity also promotes autoimmune responses in tissues, leading to bone resorption and disruption of osteoblastic function. Reduced sensitivity of the parathyroid glands disrupts calcium and phosphorus homeostasis. This imbalance impairs cellular function and compromises the extracellular matrix of bone [36].

During callus formation, hyperglycemia inhibits collagen synthesis, increases osteoclastic activity and induces apoptosis of bone lining cells; these events impair osseointegration. During callus formation, hyperglycemia inhibits collagen synthesis, increases osteoclastic activity and induces

apoptosis of bone lining cells; these events impair osseointegration. (i.e., bone-to-implant contact, which is essential for implant stability and survival as part of dental rehabilitation) [37].

Although numerous studies have investigated the bidirectional relationship between diabetes mellitus and oral conditions such as periodontitis, and evaluated treatment outcomes like implant survival [38], significant gaps remain in the quantity and quality of research focused specifically on the impact of diabetes mellitus on the oral microbiome. Furthermore, diabetes-induced hyperglycemia may exacerbate dysfunction of periodontal ligament stem cells (PDLSCs) [39, 40]. The adverse effects of diabetes on bone metabolism have raised concerns about the long-term viability of dental implants in diabetic patients[41].

Although diabetes mellitus has historically been considered a relative risk factor for implant-based dental rehabilitation, dental implant surgery has, over the past several decades, become one of the most reliable and effective methods for oral rehabilitation[38]. Understanding the molecular pathways linking these two diseases may pave the way for design modifications that reduce bone loss, enhance osseointegration in diabetic individuals, and enable more precise treatment strategies. Diabetes mellitus increases susceptibility to severe periodontitis by influencing microbial composition and exerting synergistic effects with host immune factors, including neutrophil dysfunction, Th17/Treg imbalance, an exaggerated inflammatory response to bacterial challenge (via cytokines, miRNAs, and AGEs/RAGE), oxidative stress and reactive oxygen species, alveolar bone resorption driven by the RANKL/OPG ratio, and epigenetic modifications. Reduced collagen synthesis, increased collagen breakdown activity, RANKL-mediated enhanced osteoclastogenesis, and reduced bone regeneration are among the possible pathophysiologies of increased periodontal tissue deterioration in diabetic patients. As an antagonist of RANKL, osteoprotegerin (OPG) inhibits osteoclast formation and contributes significantly to bone protection. RANKL primarily mediates alveolar bone resorption through its receptor RANK. Their effect on bone metabolism is determined by the RANKL/OPG ratio. The RANKL/OPG signaling pathway plays a central role in periodontal tissue loss and inflammation in diabetic patients[42].

Osseointegration refers to the coordinated process of bone remodeling and healing that establishes direct contact between the implant surface and living bone following placement. Implant stability and the long-term absence of inflammation depend on successful osseointegration. Several studies have reported that diabetes negatively affects implant survival [43-45].

I.4. Cathepsins and the Periodontal Tissues

Protein degradation is facilitated by a class of globular lysosomal proteases known as cathepsins. In addition to proteolysis, they perform a variety of biological functions, including angiogenesis, wound healing, proenzyme activation, apoptosis, bone remodeling, and resorption. Physiological equilibrium is maintained through the regulated release of inactive cathepsins and the action of endogenous inhibitors. Pathogenic bacteria may also produce cathepsin-like proteases, which function as virulence factors contributing to disease. Neutrophils are a primary cellular source of cathepsins, which play a key role in eliminating intracellular pathogens and mediating tissue degradation at sites of inflammation [46].

Cathepsin B plays a role in collagen degradation in the periodontal tissue of individuals with periodontitis. Research by Li et al. found that cathepsin B may reduce type III and IV collagen levels under oxidative stress and in periodontitis by repeatedly activating the TLR2/NF-κB signaling pathway. Research has shown that in fibroblasts, NF-κB forms a complex with IκBα and remains in an inactive state in the cytoplasm as a dimer consisting of the p50 and p65 subunits. When fibroblasts are stimulated with LPS, a TLR2 agonist, NF-κB becomes activated, leading to phosphorylation and subsequent proteolytic degradation of the IκBα subunit. Additionally, cathepsin B contributes to the degradation of IκB, prolonging NF-κB activation by preventing its nuclear export. This process may prolong NF-κB activation, increase oxidative stress, and suppress the synthesis of type III and IV collagen by fibroblasts. Given its role in collagen degradation, inhibition of cathepsin B may represent a promising strategy for periodontal tissue repair and for slowing the progression of periodontitis [47].

I.5. Cardiovascular Events Associated with Periodontal Disease

A growing body of epidemiological research supports a possible link between periodontal disease and atherosclerosis, which share several common risk factors. The pathophysiology of both periodontal disease and atherosclerosis is well documented, with inflammation likely serving as the key connecting mechanism. Such organisms, along with their toxins and breakdown products, are often found in infected periodontal pockets. These organisms can trigger humoral, immune, and inflammatory responses, enter the bloodstream, and contribute to atherogenesis and thromboembolic events [48].

Infectious pathogens can impact atherosclerotic processes through a variety of potential routes. In periodontitis, bacterial plaque damages the periodontal epithelium, facilitating the entry of oral pathogens and their toxic byproducts, endotoxins and exotoxins, to enter the bloodstream. Oral

pathogens can directly invade the arterial wall, triggering inflammatory responses that contribute to endothelial dysfunction. This process promotes the proliferation of vascular smooth muscle cells and the infiltration of inflammatory cells, both of which contribute to the pathogenesis of atherosclerosis [49].

Vascular inflammation is driven by elevated levels of cytokines, chemokines, and adhesion-promoting molecules. This inflammatory cascade is initiated by endothelial signaling. Heart failure has been associated with alterations in serine protease activity in various pathological conditions, including obesity-related hypertrophy, pressure overload, diabetes-induced cardiac changes, and age-related cardiac dysfunction [50].

Among these mediators, arachidonic acid metabolites are especially important, as they enhance the permeability-inducing effects of other pro-inflammatory signals from both endogenous and exogenous sources. During the immune response, neutrophils release various substances that contribute to edema formation, with TNF-α being particularly significant [51]. In addition to the pro-angiogenic and permeability-enhancing substances mentioned earlier, neutrophils also promote edema by disrupting vascular endothelial integrity via reactive oxygen species and serine proteases [52].

It is well established that periodontal disease causes lesions in periodontal tissues. These lesions can serve as entry points for pathogens into the bloodstream. There are both direct and indirect routes by which bacteria or infection-related molecules enter the bloodstream. The “direct pathway” refers to the entry of bacteria into the bloodstream, whereas the “indirect pathway” involves the translocation of pathogen-associated molecules such as cytokines, chemokines, and bacterial debris. These pathways contribute to inflammation and atherosclerosis through three primary mechanisms:

First, infections cause inflammation, endothelial damage, and upregulation of adhesion molecules. As a result, they promote smooth muscle cell proliferation and platelet aggregation.

Second, activation of the innate immune system affects the liver, increasing the production of acute-phase proteins and cholesterol via pro-inflammatory cytokines. This contributes to systemic inflammation and dyslipidemia.

Third, activation of the adaptive immune system leads to the production of antibodies, which in turn contribute to atherosclerosis and chronic inflammation [53].

Thus, inflammation serves as a mediating and causal link between vascular and metabolic diseases, acting through serine proteases involved in these pathological processes. Targeted

therapies, such as specifically designed implant placements for diabetic individuals and assessments of periodontal status in patients undergoing in-stent restenosis treatment, may offer dual benefits. These include enabling personalized drug therapy by accounting for individual risk factors and periodontal condition, particularly through understanding molecular characteristics such as serine proteases like cathepsin.

II. OBJECTIVES

This thesis presents three studies aimed at investigating the clinical and molecular intersections between periodontitis, diabetes mellitus, and in-stent restenosis, with a particular focus on therapeutic implications and shared pathogenic pathways.

The first study aimed to evaluate the impact of laser micro-grooved implants and abutments on peri-implant tissue health and systemic glycemic control in moderately controlled diabetic patients. Radiographic and clinical parameters, including mean crestal bone loss and HbA1c levels, were assessed over a one-year functional loading period to determine whether these specifically designed implants offer improved outcomes in diabetic implant therapy.

The second study explored the association between periodontal disease severity and in-stent restenosis in patients undergoing percutaneous coronary intervention. The study investigated whether patients with restenotic lesions exhibit a distinct periodontal profile compared to those with de novo lesions, and whether this association may reflect overlapping inflammatory mechanisms shared with diabetes.

The third study involved a comprehensive literature review of the role of cathepsins—particularly cathepsin B and S—as potential molecular mediators linking periodontitis, diabetes, and cardiovascular disease. The aim was to assess whether dysregulated cathepsin expression could serve as a shared therapeutic target and diagnostic biomarker across these interconnected conditions.

III. MATERIALS AND METHODS

III.1. Effect of laser micro grooved (LMG) implants on bone levels and peri-implant soft tissues in diabetic patients

III.1.1. Participants

Participants were enrolled based on study group allocation (Figure 1). Participants were categorized as either systemically healthy (control group) or type II diabetic (test group) based on their allocation. Patients aged 30 to 60 years with missing premolar or molar teeth in the mandibular arch, and with adequate bone height (≥13 mm) and width (≥6 mm), were included in the study. Moderately controlled diabetic patients (HbA1c 8.1–10%) were included in the trial. Sample size was calculated based on prior studies [54]. Accounting for a 20% dropout rate, the final sample included 20 edentulous sites, with 10 laser micro-grooved (LMG) platform-switched implants and abutments allocated per group.

The primary objective was to assess changes in mean crestal bone levels (MCBL), measured radiographically at the mesial and distal aspects, at baseline (immediately post-restoration) and one year after functional loading in both non-diabetic (control) and diabetic (test) groups. Additionally, implant survival rates one year after functional loading were compared between diabetic and non-diabetic groups. Secondary objectives included: (1) assessing the relative position of the gingival margin (R-PGM) around LMG platform-switched implants with LMG abutments at baseline, six months, and one year after functional loading in both diabetic and non-diabetic patients; and (2) comparing implant stability quotient (ISQ) values prior to prosthesis placement using resonance frequency analysis.

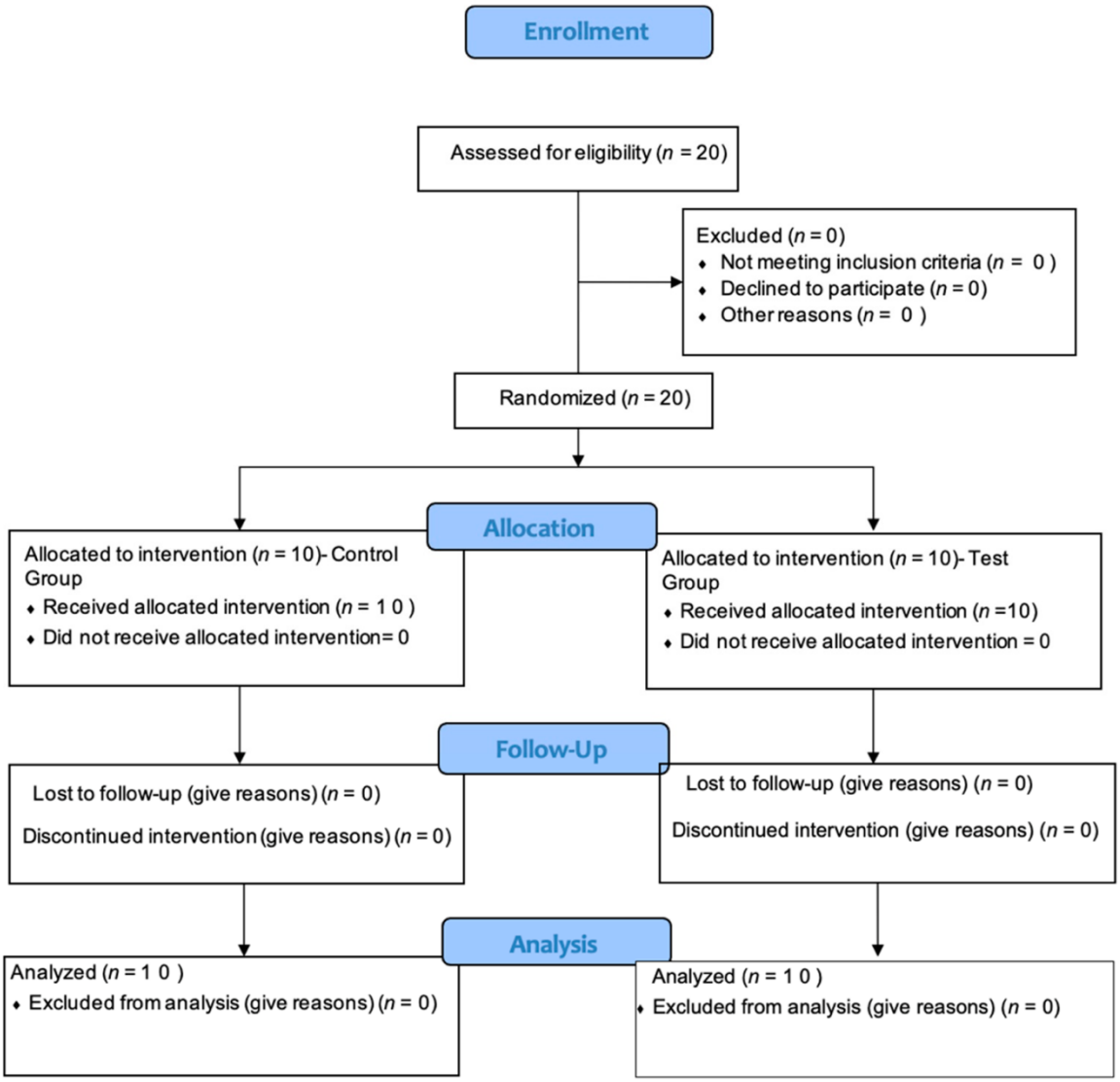

Figure 1. Consort flow diagram of the study.

This study hypothesized that laser micro-grooved platform switched implants and abutments could reduce mean crestal bone loss and peri-implant attachment loss in moderately controlled diabetic 1-year post-functional loading to levels comparable to non-diabetics.

III.1.2. Clinical Parameters

Full Mouth Plaque Score (FMPS) [55] and Full Mouth Bleeding Score (FMBS) [55] were recorded at two time points: baseline (prior to implant placement) and one year after functional loading. Periodontal Probing Depth (PPD) [55] was also assessed at these two time points.

Clinical Attachment Level [56] was evaluated both before implant placement and one year following functional loading.

Site-specific parameters included Site-Specific Plaque Scores (S-SPS) [55], which were recorded at baseline, six months, and one year after functional loading. Site-Specific Bleeding Scores (S-SBS) [56] were recorded at the same time points.

Peri-Implant Sulcus Depth (PISD) [56] was assessed at baseline, six months, and one year after functional loading.

The Relative Position of the Gingival Margin (R-PGM) [56] was evaluated at baseline, six months, and one year following functional loading.

Implant Stability Quotient (ISQ) [57-59] was measured immediately after implant placement, prior to prosthetic restoration.

III.1.3. Radiographic Parameters

Radiovisiography (RVG) [56] was used to measure changes in mesial and distal Mean Crestal Bone Levels (M-MCBL and D-MCBL) immediately after restoration (baseline) and one year after functional loading. Implant Success Rate (ISR) was assessed one year after functional loading [60].

III.1.4. Randomization

The controlled clinical trial included patients who met the inclusion and exclusion criteria. Inclusion criteria were: male or female patients aged 30 to 60 years, with edentulous mandibular premolar or molar sites and adequate bone height (≥13 mm) and width (≥6 mm). The test group consisted of moderately controlled diabetic patients with HbA1c levels between 8.1 and 10. Accounting for a 20% dropout rate, the sample size was increased to 20 edentulous sites, with 10 LMG platform-switched implants allocated per group. All clinical measurements were performed by a single calibrated examiner to minimize examiner bias. Standard preoperative examinations and initial therapy were conducted. Eligible patients who consented to participate were allocated

into two groups. Twenty edentulous sites, distributed across patients meeting inclusion criteria, were selected for implant placement.

III.1.5. Interventions

All surgical interventions were performed by a calibrated operator who was blinded to the patients' diabetic status. An independent calibrated examiner, blinded to recruitment group and clinical details, evaluated all radiographic parameters. Local anesthesia (2% lignocaine with 1:80,000 adrenaline) was administered, followed by a 30-second rinse with 0.12% chlorhexidine. A mid-crestal incision was made under local anesthesia, followed by minimal flap elevation. Pilot osteotomy preparation was performed using a drill at 950 rpm and 35 Ncm torque. An implant surgical kit was used to prepare the osteotomy sites and place the implants. Implants were placed with insertion torque exceeding 35 Ncm following final osteotomy preparation.Implant Stability Quotient (ISQ) was measured using resonance frequency analysis (RFA) with the PenguinRFA device (Integration Diagnostics, Gothenburg, Sweden). A transducer was attached to the implant collar, and a threshold value of ≥60 was used to confirm primary stability [57-59]. An ISQ value exceeding 60 was considered sufficient for immediate loading. All implants were placed equicrestally (Preoperative and surgical procedures are shown in Figures 2–5). Prosthetic abutments were placed, and immediate functional loading was performed (Figures 6–7). The same surgical protocol was followed for both control and test groups. After surgery, all patients were instructed to rinse with 0.2% chlorhexidine digluconate twice daily for two weeks. Ibuprofen (500 mg) was prescribed for postoperative pain management.

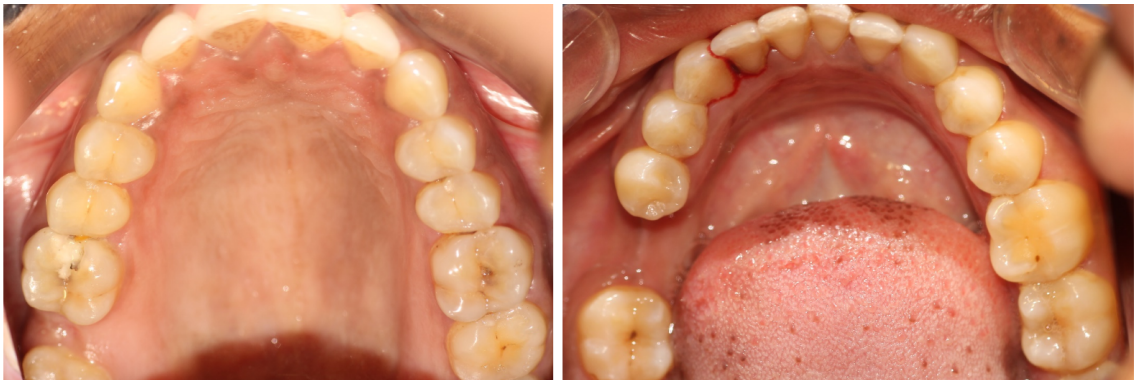

Figure 2. Preoperative status.

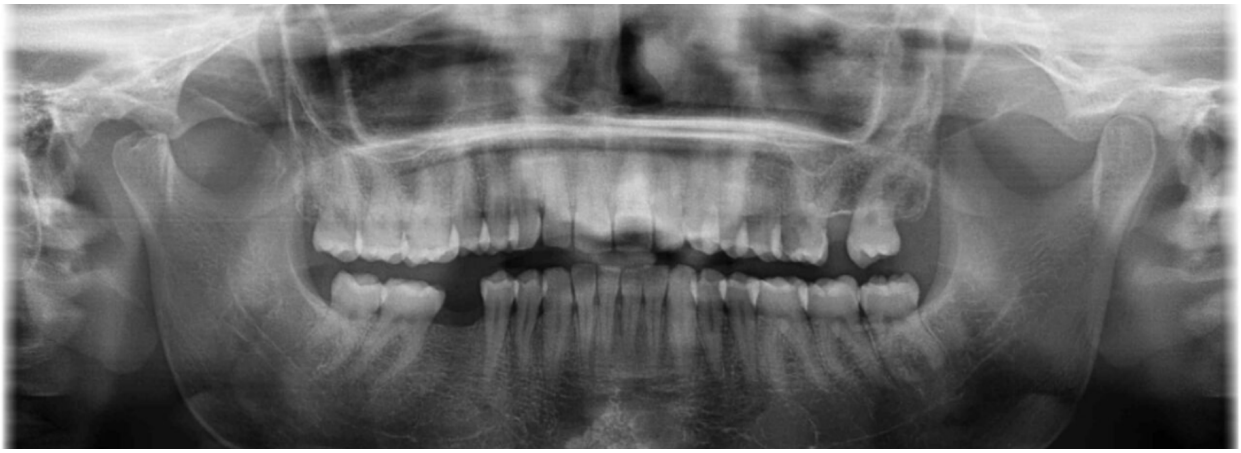

Figure 3. Preoperative OPG

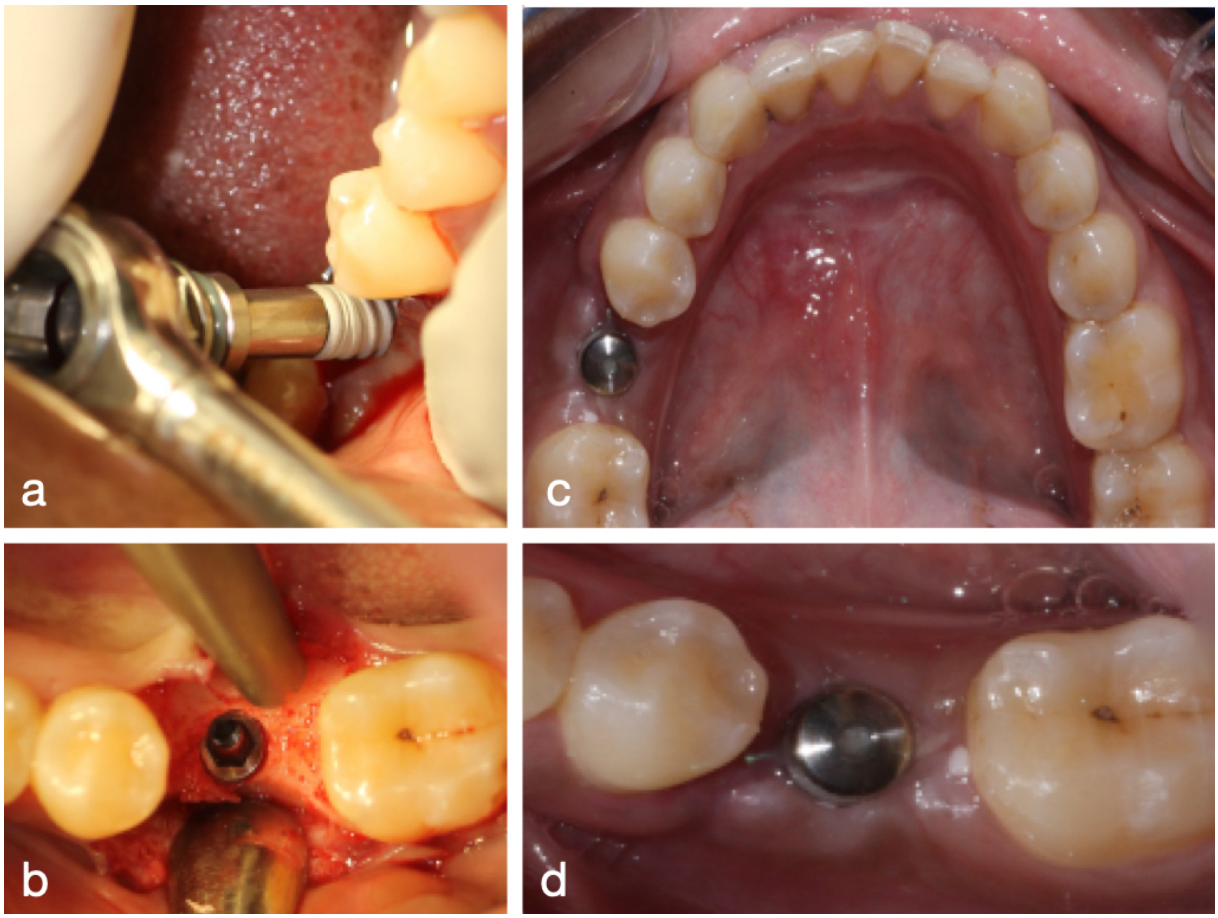

Figure 4. Implant placement procedure: (a) implant insertion, (b) implant in situ, (c–d) placement of healing cap.

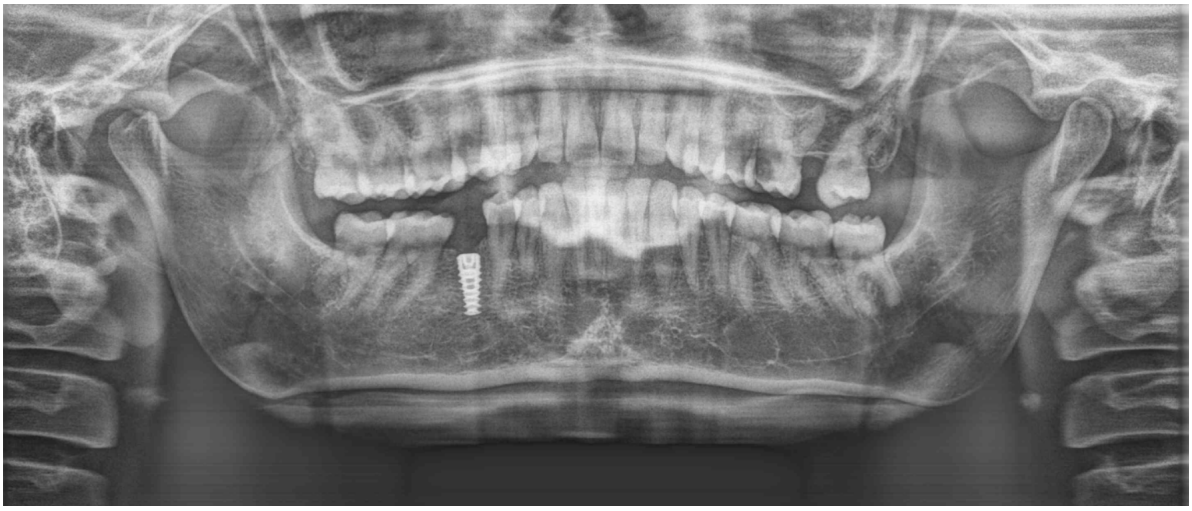

Figure 5. Postoperative OPG

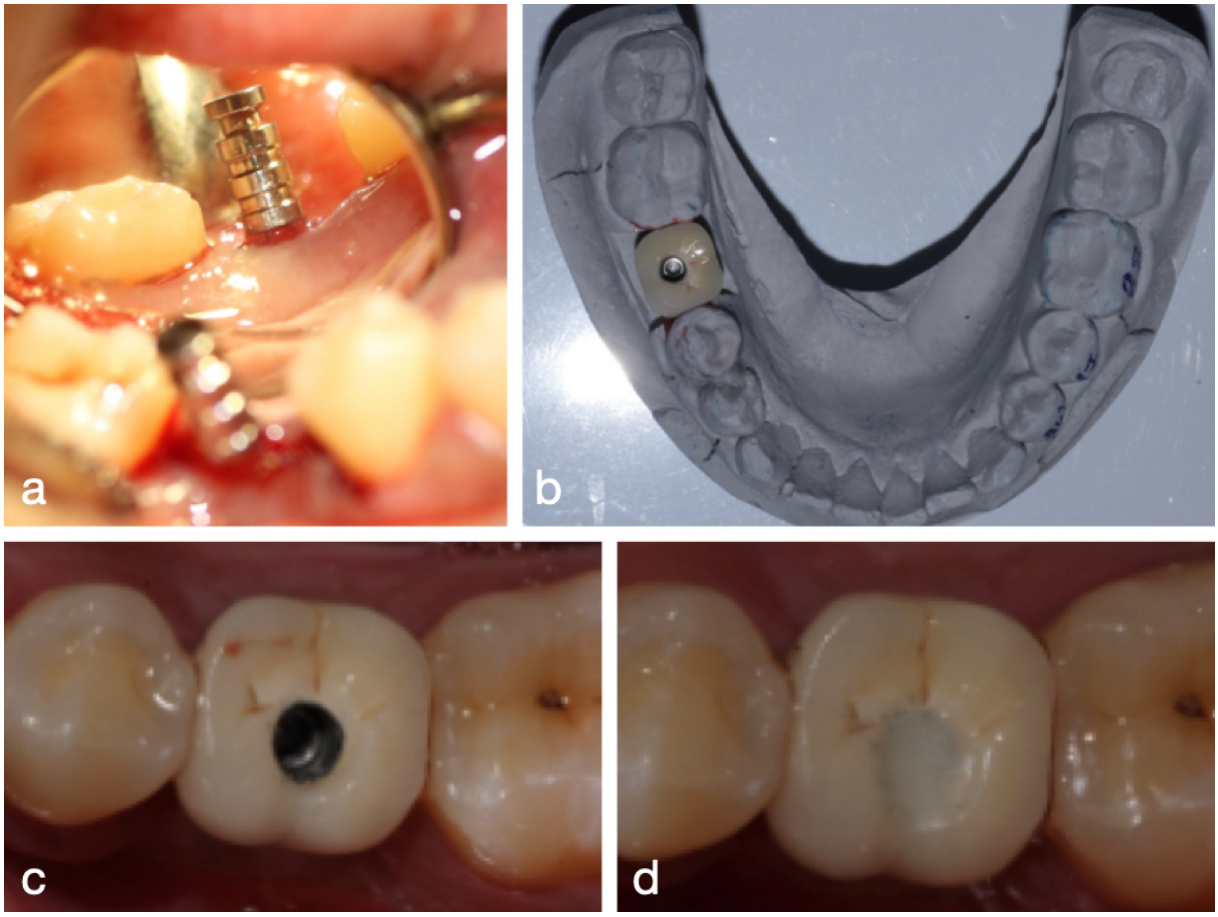

Figure 6. Restorative procedures: (a) impression coping, (b) screw-retained restoration on stone model, (c) restoration in situ, (d) restoration with composite resin plug.

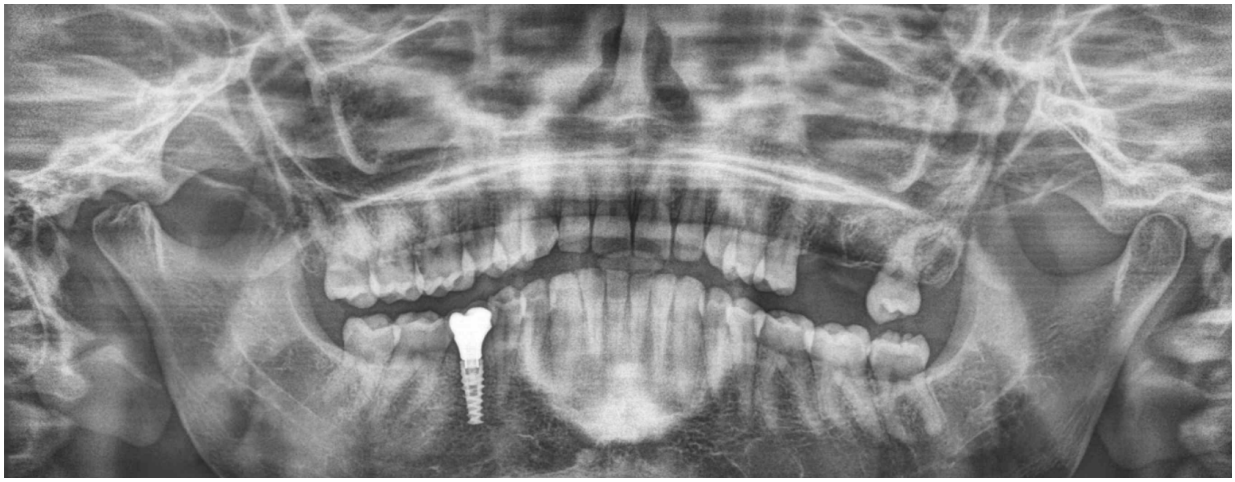

Figure 7. Control OPG

III.1.6. Statistical Analysis

Statistical *analysis* was conducted using SPSS version 21.0 (Armonk, NY: IBM Corp.). The Wilcoxon signed-rank test was used to determine whether there were significant differences between paired samples (baseline and one-year values). The Mann–Whitney U test was applied to assess differences between independent groups at the same time points. For intergroup comparisons of continuous variables—such as FMPS, FMBS, PPD, CAL, S-SPS, S-SBS, PISD, R-PGM, MCBL, ISR, and ISQ—a Student's t-test was used. Intragroup comparisons of these clinical and radiographic parameters were analyzed using paired t-tests. A p-value of <0.05 was considered statistically significant in all analyses.

III.2. Study on Periodontal Disease and In-Stent Restenosis

III.2.1. Study Participants

Participants (n = 90) were recruited from the Invasive Cardiology Unit of the Department of Internal Medicine, University of Szeged, during percutaneous coronary intervention (PCI). Of these, 51 underwent intervention for de novo lesions, while 39 received treatment for in-stent restenosis. The healthy control group (n = 90) consisted of individuals undergoing routine lung screening in the same city and timeframe. All participants were unpaid volunteers who could withdraw from the study at any time. The PCI and control groups were matched for age and gender.

The indication for PCI was determined by an interventional cardiologist in accordance with local protocol and European Society of Cardiology (ESC) guidelines [61]. Patients diagnosed with in-stent restenosis—defined as a ≥50% re-narrowing of the artery lumen inside or adjacent to the stent—were eligible for inclusion [62]. Relevant medical data were obtained from hospital and patient records. Standard post-PCI laboratory evaluations were also collected. A structured questionnaire was used to gather demographic information and smoking status. Smoking status was self-reported and classified into current smokers and former smokers.

Exclusion criteria included conditions known to affect periodontal health such as chronic systemic inflammatory diseases, excessive alcohol consumption, substance abuse, estrogen deficiency, and the presence of fewer than four remaining teeth. Patients in critical condition were also excluded. The study aimed to investigate the hypothesis that periodontal disease may be more prevalent among patients requiring PCI for restenotic lesions, thereby suggesting a possible association between periodontal health and restenosis risk.

III.2.2. Clinical Parameters

Although the pathological progression of periodontal disease is well understood, its clinical staging remains a subject of debate [63]. In this study, the staging system proposed by Fernandes and colleagues was applied [64]. The following parameters were recorded: number of missing teeth (excluding third molars), plaque index (PI), bleeding on probing (BOP), probing pocket depth (PPD), and clinical attachment level (CAL). This protocol has been used in multiple prior publications by this research group [65-67]. Based on these parameters, participants were categorized as periodontally healthy, or as having early, moderate, or severe periodontitis.

A comprehensive full-mouth periodontal examination was performed by a periodontal specialist 48 hours after percutaneous coronary intervention. Using Williams periodontal probes (Hu-Friedy Manufacturing Co., Chicago, IL, USA), PPD, CAL, and BOP were measured at six distinct sites per tooth.

III.2.3. Statistical Analysis

Statistical analysis was performed using SPSS version 21.0 (IBM, Armonk, NY, USA). Unless otherwise specified, continuous variables were expressed as means and standard deviations, while categorical variables were reported as frequencies. Depending on the data distribution,

comparisons between groups were conducted using one-way ANOVA, Kruskal–Wallis ANOVA, or the chi-square test. The Shapiro–Wilk test was used to assess normality, and Levene's test was applied to evaluate homogeneity of variance.

The overall level of statistical significance was set at $p = 0.05$. Where applicable, Bonferroni correction was used to adjust for multiple comparisons. Hypothesis testing was conducted using the chi-square test, as well as logistic and multinomial logistic regression analyses [48].

III.3. Review of the Role of Cathepsins in Oral Disease

In order to identify pertinent studies regarding the role of cathepsins in oral disease, two reviewers conducted a thorough literature search in the Scopus, EBSCOHOST, and PubMed electronic databases. The grey literature search was also conducted. We used Google Scholar to look at unpublished papers, conference proceedings, and other forms of grey literature. The search strategy entailed the use of a combination of the following keywords: "Cathepsins," "Oral Disease," "dental," and "dentistry." In order to encompass a comprehensive array of pertinent literature, criteria were implemented to only include articles published in English, with no limitation on the publication year. Supplementary searches were conducted within the reference listings of the included papers.

IV. RESULTS

IV.1. Study on the Effect of Laser Micro-Grooved Implants on Bone Levels and Peri-Implant Soft Tissues in Diabetic Patients

The mean age of participants in the control group was 38.62 ± 5.06 years, while that of the test group was 42.62 ± 5.34 years. The control group comprised five male and five female participants, whereas the test group included four males and six females. There were no statistically significant differences in age or gender distribution between the groups ($p = 0.46$ and $p = 0.17$, respectively).

Both Full Mouth Plaque Scores (FMPS) and Full Mouth Bleeding Scores (FMBS) showed a marked reduction over the study period, decreasing from 15% to 10% and from 11% to 8%, respectively, in both the control and test groups after one year of functional loading ($p = 0.001$) (Table 1). Intergroup comparisons of FMPS and FMBS at each time point revealed no statistically

significant differences (p = 0.52). Probing Pocket Depth (PPD) decreased slightly from 2.94 mm to 2.90 mm in the control group and from 2.88 mm to 2.63 mm in the test group after one year, although these changes were not statistically significant (p = 0.90). No attachment loss was observed in either group throughout the study period. Intergroup comparisons of PPD at both baseline and one year post-loading similarly revealed no statistically significant differences (p = 0.43 and p = 0.39, respectively).

Table 1. Intergroup and intragroup comparison of clinical parameters at baseline and one year after functional loading.

Clinical Parameter		Control Group (Group 1)	Test Group (Group 2)	*p* Value
PPD	Baseline	2.94 ± 0.16	2.88 ± 0.12	0.43
	1 Year	2.90 ± 0.10	2.63 ± 0.14	0.39
p value		0.90	0.66	
CAL	Baseline	0.00	0.00	-
	1 Year	0.00	0.00	-
p value		-	-	-
Full mouth plaque scores (FMPS) (%)	Baseline	15.74 ± 2.26	15.15 ± 1.85	0.52
	1 Year	10.62 ± 1.38	10.70 ± 1.30	0.32
p value		≤0.001 **	≤0.001 **	
Full mouth bleeding scores (FMBS) (%)	Baseline	11.80 ± 1.20	11.49 ± 1.51	0.51
	1 Year	8.61 ± 0.39	8.53 ± 1.47	0.86
p value		≤0.015 *	≤0.015 *	

Abbreviations: PPD = Probing Pocket Depth; CAL = Clinical Attachment Level; FMPS = Full Mouth Plaque Score; FMBS = Full Mouth Bleeding Score. Level of significance: p=0.05

Within both the control and test groups, site-specific plaque scores (SS-PS) demonstrated a consistent reduction over time (Table 2). Specifically, plaque scores decreased from 9% at baseline to 8% at six months and 6% at one year following functional loading. The reduction from baseline to one year was statistically significant ($p < 0.05$). Similarly, site-specific bleeding scores (SS-BS) declined comparably in both groups over the same period. In the control group, SS-BS decreased from 9% at baseline to 8% at six months and 6% at one year, while the test group exhibited a reduction from 9% to 7% and then 6%. Both groups showed a substantial and statistically significant decrease in SS-BS by the end of the one-year follow-up.

Table 2. Intergroup comparison of site-specific clinical parameters at baseline, 6 months, and one year after functional loading.

Clinical Parameter		Control Group (Group 1)	Test Group (Group 2)	*p* Value
S-SPS	Baseline	9.37 ± 6.63	9.37 ± 6.63	1.0
	6 months	8.30 ± 6.70	8.70 ± 6.30	0.90
	1 year	6.25 ± 4.75	6.25 ± 4.75	1.0
S-SBS	Baseline	9.37 ± 6.63	9.37 ± 6.63	1.0
	6 months	8.50 ± 6.50	7.50 ± 5.50	0.66
	1 year	6.37 ± 4.63	6.25 ± 4.75	0.77
PISD	Baseline	2.11 ± 0.58	2.03 ± 0.56	0.80
	6 months	2.09 ± 0.11	2.04 ± 0.13	0.67
	1 year	2.06 ± 0.55	2.07 ± 0.50	0.73

Abbreviations: S-SPS = Site-Specific Plaque Scores; S-SBS = Site-Specific Bleeding Scores; PISD = Peri-Implant Sulcus Depth; Level of significance: p=0.05

An intergroup comparison was conducted to evaluate differences in site-specific plaque scores (SS-PS) between the control and test groups. The results indicated that plaque scores were virtually identical across all time points: baseline (9% vs. 9%), six months (8% vs. 8%), and one year (6% vs. 6%). These similarities were not statistically significant. Likewise, site-specific bleeding scores (SS-BS) showed minimal variation between the groups. At baseline, SS-BS was 9% in both groups; at six months, scores were 8% in the control group and 7% in the test group; and at one year, both groups recorded 6%. None of these differences reached statistical significance.

Peri-Implant Sulcus Depth (PISD) assessments within both groups showed a slight reduction from baseline to one year post-loading, though no statistically significant changes were observed at any individual time point. When comparing the control and test groups, PISD values were comparable at all intervals: 2.11 mm vs. 2.03 mm at baseline, 2.09 mm vs. 2.04 mm at six months, and 2.06 mm vs. 2.07 mm at one year, respectively. These differences were not statistically significant.

No peri-implant attachment loss was recorded in either group throughout the study period. Additionally, the Relative Position of the Gingival Margin (R-PGM) remained unchanged in both groups across all evaluated time points. Mean R-PGM values were 3.37 ± 0.20 mm in the control group and 3.53 ± 0.30 mm in the test group, with no statistically significant differences observed.

Radiographic assessment of Mean Crestal Bone Level (MCBL) in the control group revealed minimal early crestal bone loss over the one-year period following functional loading. Specifically, changes were observed from 0.00 mm to 0.16 mm on the mesial aspect and from 0.00 mm to 0.17 mm on the distal aspect. Both changes were statistically significant, with p-values of < 0.003 and < 0.001, respectively. Similarly, the test group demonstrated a slight but statistically

significant bone loss, with mesial MCBL changing from 0.00 mm to 0.21 mm and distal MCBL from 0.00 mm to 0.22 mm over the same period ($p < 0.001$ for both measurements, as shown in Table 1). However, intergroup comparisons revealed no statistically significant differences in mesial or distal MCBL after one year of functional loading.

Analysis of the Implant Survival Rate (ISR) showed that all implants in both the control and test groups remained intact after one year, yielding a 100% survival rate with no failures reported. Implant Stability Quotient (ISQ) measurements were also comparable between groups: 74.50 in the control group and 74.25 in the test group. Both values exceeded the minimum threshold required for immediate loading, and no statistically significant difference was observed between groups ($p = 0.92$).

IV.2. Study on Periodontal Disease and In-Stent Restenosis

Table 3 presents a comparison of clinical and demographic characteristics between the PCI group and healthy controls, including intergroup statistical analyses. A chi-square test revealed a significant association between group membership and periodontal status ($\chi^2 = 35.207$, df = 6, $p < 0.001$), indicating that periodontal condition was strongly related to whether individuals belonged to the PCI or control group. The analysis also identified a statistically significant difference in the number of remaining teeth between groups ($p < 0.001$), while no significant difference was found in plaque index.

Table 3. Comparison of clinical and demographic characteristics between PCI patients and healthy controls.

Parameter	PCI	Healthy controls	Sig. (p)
Age	63.2 ± 10.0	67.3 ± 9.9	0.89
Gender (male)	63 (70)	63 (70)	1
Diabetes mellitus	29 (32)	4 (4)	<0.0001
Hypertension	82 (92)	12 (13)	<0.0001
Hyperlipidemia	67 (72)	0 (0)	<0.0001
Chronic renal disease	10 (11)	0 (0)	<0.0001
Active smoker	16 (18)	24 (27)	0.21
Former smoker	18 (20)	13 (14)	0.43
Number of teeth	14.08 ± 6.99	19.71 ± 5.73	<0.0001
Plaque index (0–3)	2 (1–3)	2 (1–2)	0.40
Periodontal status (1–4)	3 (2–4)	2 (2–3)	<0.0001

Level of significance: p=0.05

To further explore this association, a logistic regression model was employed, incorporating background variables known to influence systemic and periodontal health: periodontal status,

diabetes mellitus, smoking, and plaque index. Group membership (PCI patient or control) was used as the dependent variable to determine which factors were significantly associated with PCI status. The analysis identified both diabetes mellitus ($p < 0.001$) and periodontal status ($p < 0.05$) as significant predictors.

Although diabetes is widely recognized in the literature as a risk factor for periodontal disease, this association was not confirmed in the present sample. A chi-square test revealed no statistically significant relationship between diabetes and periodontal status ($\chi^2 = 3.049$, df = 3, $p = 0.384$), suggesting that in this cohort, each variable independently contributed to PCI risk.

To assess whether group membership (patient vs. control) was associated with the severity of periodontal disease, a multinomial logistic regression analysis was conducted using periodontal disease stage as the independent variable. The results demonstrated a strong association between periodontal status and group classification ($p < 0.001$). Calculated odds ratios were as follows: stage 2, OR = 2.154 (95% CI: 0.42–11.08); stage 3, OR = 3.13 (95% CI: 0.61–16.04); and stage 4, OR = 15.27. While increasing periodontal severity tended to raise the likelihood of being in the PCI group, this association reached statistical significance only for stage 4 ($p < 0.01$), where the odds of being classified as a PCI patient were 15.27 times higher compared to individuals with healthier periodontal conditions.

PCI patients were further stratified into two subgroups based on the type of lesion treated: 51 patients received PCI for de novo lesions, and 39 patients for in-stent restenotic lesions. Baseline clinical and procedural characteristics did not differ significantly between these subgroups. Although the sample size limited the power for detailed comparisons, the analysis aimed to investigate whether the severity of periodontal disease was associated with restenosis (Table 4).

A comparison of periodontal disease (PD) stage frequencies between the two subgroups revealed a statistically significant association between lesion type and periodontal disease severity ($\chi^2 = 13.77$, df = 3, $p < 0.01$). Notably, stage 4 periodontitis was present in 64.1% of patients with restenotic lesions. In contrast, although there were no patients classified as periodontally healthy, the distribution of PD stages among those with de novo lesions was more evenly spread. Tooth count and plaque index were comparable between the two subgroups, with no significant differences observed.

Table 4. Comparison of clinical and periodontal parameters between patients with restenotic and de novo PCI lesions.

Periodontal condition	PCI Restenotic lesions (n-39)	PCI Patients with De Novo Lesions (n=51)	Sig. (p)
Number of teeth	13.8 ± 7	14.3 ± 7.1	0.74
Plaque index (0–3)	2(1–3)	2(1–3)	0.83
Periodontal status (1–4)	4(3–4)	3(2–4)	<0.01

IV.3. Review of the Role of Cathepsins in Oral Disease

Cathepsins, a group of globular lysosomal proteases, are primarily involved in protein degradation but also participate in a wide array of biological processes, including bone resorption, apoptosis, wound healing, angiogenesis, proenzymatic activation, and bone remodeling. Their dysregulation has been implicated in the pathogenesis of numerous systemic diseases, such as cancer, bronchial asthma, atherosclerosis, neurological disorders, rheumatoid arthritis, and osteoarthritis. This thesis underscores the relevance of cathepsins in a variety of oral pathologies, including periodontitis, odontogenic cysts, ameloblastoma, salivary gland tumors, and malignant melanoma.

Cathepsins also mediate immune responses in periodontitis, with established links to systemic diseases. In bacteria-stimulated cells, cathepsin B contributes to Toll-like receptor (TLR) signaling, promoting the production of interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), and amyloid β. Cathepsin S plays a critical role in MHC class II maturation, enabling CD4+ T-helper cells to secrete interferon-gamma (IFN-γ) and interleukin-17 (IL-17). Additionally, cathepsin K is involved in the activation of the TLR/autophagy pathway, leading to the generation of type I interferons.

These cathepsin-mediated proinflammatory processes, initially associated with periodontitis, may propagate systemically and contribute to the development of cardiovascular diseases such as atherosclerosis, aneurysm formation, restenosis, and neovascularization. Advances in understanding cathepsin function have been greatly supported by the development of gene knockout models and specific enzyme inhibitors. Inflammatory cytokines have been shown to regulate cathepsin expression and activity in cultured vascular cells and macrophages.

Furthermore, cathepsins are being explored as potential diagnostic biomarkers. Circulating levels of cathepsins S, K, and L, as well as their endogenous inhibitor cystatin C, have shown promise for identifying conditions such as coronary artery disease, aneurysms, adiposity, peripheral arterial disease, and coronary artery calcification. The mechanistic involvement of cathepsins in

atherosclerotic cardiovascular disease (ASCVD) highlights their potential as both diagnostic markers and therapeutic targets.

V. DISCUSSION

V.1. Clinical Performance of Laser-Microgrooved Implants in Diabetic Patients

Titanium alloys are widely used in medical device fabrication due to their excellent biocompatibility, corrosion resistance, and superior mechanical properties. Their bioactivity is attributed to the presence of a dense, coherent nanometric TiO_2 passivation layer, which enhances their performance in biological environments [68, 69]. Recently, the field of implant dentistry has introduced metal ingots as potential materials; however, these remain in the early stages of development and require further research before clinical application.

Substantial research has focused on the microstructural enhancement of dental implants, particularly through laser-based surface modification and the incorporation of titanium nanotubes. These advancements have demonstrated promising results in optimizing peri-implant parameters and improving implant survival rates [70, 71].

The study hypothesized that surface-modified implants incorporating Laser-Lok technology could benefit moderately controlled diabetic patients, who frequently experience impaired soft and hard tissue healing around dental implants. This design facilitates optimal cellular interaction, enabling osteoblasts and fibroblasts to align and attach within the laser-etched microchannels. Consequently, a stable osseointegration bond forms along the implant collar, while a biological seal is established at the abutment interface. Additionally, the surface architecture produces a cold-welding effect at the crest module, which reduces inflammatory infiltration and promotes soft tissue sealing. Collectively, these features help limit microbial colonization and enhance overall implant stability.

One year after functional loading, probing pocket depth decreased consistently in both the control and test groups, maintaining comparable levels without statistically significant differences. Clinical attachment loss was absent in both cohorts, indicating the absence of active periodontal disease across the study population. Site-specific plaque scores on the abutment surfaces also showed no statistically significant differences between groups from baseline to six months and from six months to one year. However, both groups exhibited a substantial and statistically

significant reduction in plaque accumulation from baseline to one year. This parallel reduction is likely attributable to the uniform design of the implants and abutments used in both groups.

Similarly, site-specific bleeding scores followed comparable trends across both groups. Haemorrhage scores decreased significantly from baseline to one year in each group, though intergroup comparisons at all measured time points showed no statistically significant differences. These findings suggest that the application of laser-microgrooved surfaces enhances connective tissue adaptation, facilitating rapid formation of a robust mucosal barrier at the implant collar. This structural adaptation may contribute to reduced plaque accumulation and gingival inflammation.

Evaluations of peri-implant sulcus depth within and between the control and test groups revealed only negligible reductions, with measurements remaining nearly identical across all time points. No statistically significant differences were observed. Additionally, neither group exhibited any peri-implant attachment loss. These findings support the conclusion that Laser-Lok implants combined with laser micro-grooved abutments facilitate the formation of a robust mucosal barrier at the implant–abutment interface [72, 73]. This barrier closely resembles the connective tissue attachment observed in natural dentition, where gingival collagen fibres are oriented perpendicularly to the tooth surface. In this study, resistance to probing was similarly attributed to perpendicular collagen fibre orientation relative to the abutment surface, coinciding with minimal sulcus depth and an absence of attachment loss.

Previous research by Ferraris et al. [74, 75] demonstrated that micromachined surfaces featuring horizontal channels of 3 or 10 μm in depth promote contact guidance mechanisms that inhibit epithelial downgrowth. Likewise, histological evidence from Nevins et al. [76] indicated that perpendicular orientation of connective tissue fibres along the implant surface effectively prevents apical migration of gingival epithelial cells and fibroblasts.

Across all three time points, the gingival margin remained stable and consistently positioned coronal to the implant crown in both study groups. This stability was maintained both within groups over time and between groups, suggesting a favorable soft tissue response. Furthermore, mesial and distal mean crestal bone level measurements taken immediately after restoration and one year after functional loading revealed no radiographic evidence of bone loss. Although slight crestal bone loss was observed in both groups over the one-year period, the changes in mesial and distal bone levels were statistically significant within groups, but not between them. Importantly, the degree of early crestal bone loss remained well below the thresholds proposed by Albrektsson

[77] as acceptable for implant success. Consistent with this, the implant survival rate in both groups was 100%.

Both groups demonstrated comparable implant stability and achieved a 100% implant survival rate [57-59]. An immediate loading protocol was implemented for both diabetic and non-diabetic patients, as the ISQ values exceeded the clinically acceptable threshold. Although the literature on the immediate functional outcomes of single-tooth implants remains limited, existing studies suggest that standard placement protocols, when accompanied by sufficient primary stability, may serve as a reliable therapeutic approach.

The application of laser micro-grooved implant surfaces in this study likely contributed to the prompt restoration of patient function and aesthetics. Based on this observation, we hypothesized that Laser-Lok technology may promote enhanced integration of both hard and soft tissues, thereby supporting the feasibility of immediate loading protocols. Specifically, we investigated whether ISQ, a key indicator of primary stability, could be improved through the use of Laser-Lok-modified surfaces in diabetic patients.

To more thoroughly assess the benefits of Laser-Lok technology in medically compromised populations, future research should include stratified comparisons among diabetic patients with poor, moderate, and good glycemic control. The current study was limited by its small sample size, which restricts the generalizability of the findings. Accordingly, further investigations with larger cohorts and additional prospective parameters are necessary to validate and expand upon these preliminary results.

This study represents the first clinical and radiographic evaluation of immediately loaded laser micro-grooved implants and abutments in moderately controlled diabetic patients. Future studies comparing outcomes across varying levels of diabetic control will be essential to fully determine the clinical utility of this technology in implant-based rehabilitation.

V.2. Periodontal Disease and Coronary Artery Disease

Coronary artery disease (CAD) remains a leading global cause of morbidity and mortality. As such, interventional cardiology continues to be an essential and evolving area of clinical research and innovation [78]. Despite advancements in technology, including the widespread use of drug-eluting stents, in-stent restenosis remains a significant clinical challenge. ISR rates vary widely, ranging from 3% to 30%, depending on the type of stent employed and the clinical context [79]. Risk factors for ISR are multifactorial, encompassing patient-related variables, lesion characteristics, and procedural aspects. Among the systemic risk factors most frequently

associated with ISR are advanced age, female sex, diabetes mellitus, and chronic kidney disease [80].

Periodontal disease (PD) is a chronic inflammatory condition initiated by bacterial infection of the tooth-supporting structures. In its severe form, PD affects up to 11% of the global population, making it one of the most widespread chronic diseases [81]. Notably, periodontal disease and cardiovascular diseases share multiple common risk factors, such as diabetes, smoking, and systemic inflammation. An expanding body of epidemiological evidence supports a potential association between periodontitis and atherosclerosis, suggesting that these conditions may be linked through shared inflammatory pathways [82-84].

The progression of both diseases has been extensively investigated in the context of inflammatory mechanisms, which are now believed to represent a key biological connection. In periodontitis, infected subgingival pockets serve as reservoirs for pathogenic microorganisms, their metabolic byproducts, and proinflammatory mediators [85]. These substances may translocate into systemic circulation, where they can trigger immunological, inflammatory, and humoral responses, contributing to atheroembolic and thromboembolic processes.

This study assessed the periodontal health of patients undergoing percutaneous coronary intervention (PCI). When compared to healthy controls, individuals receiving PCI for significant coronary artery lesions exhibited a notably higher prevalence of moderate to severe periodontitis. Furthermore, substantial variation in periodontal indices was observed between PCI patients treated for in-stent restenosis and those treated for de novo lesions. Specifically, patients with restenosis demonstrated a greater prevalence of severe periodontitis. These findings suggest a potential correlation between in-stent restenosis and periodontal disease.

Previous research has established a strong association between periodontal disease and angiographically confirmed coronary artery disease, both in stable presentations and in cases of acute coronary syndromes [86-89]. However, it remains unclear whether periodontitis itself serves as an independent risk factor for coronary artery disease, or whether the observed association is largely mediated by common risk factors such as age, sex, smoking, diabetes mellitus, hypertension, obesity, low socioeconomic status, and psychological stress [90].

Our age- and gender-matched case–control study adds further evidence to the growing body of literature supporting a link between periodontal disease and CAD. Importantly, our findings indicate that diabetes mellitus—despite being a prominent shared risk factor for both conditions—did not account for the association observed in our study population.

While a significant difference in periodontal status was noted between PCI patients and healthy controls, no meaningful difference was found in plaque index (PI). Although oral hygiene, as reflected by PI, is a well-recognized contributor to periodontal disease [91], it is also known that hospitalization may negatively affect patients' oral care routines [92, 93]. However, given the absence of a difference in PI, poor oral hygiene does not appear to explain the disparities in periodontal status observed in this study.

V.3. Periodontal Disease and In-Stent Restenosis

The relationship between periodontal disease and in-stent restenosis (ISR) remains an underexplored aspect of coronary artery disease (CAD). Most existing research has focused on periodontal disease in the context of new coronary lesions. For example, Fukushima et al. [94] identified an association between periodontal disease at baseline and an increased risk of future major adverse cardiac events (MACE) in patients with CAD undergoing percutaneous coronary intervention (PCI) with drug-eluting stents. However, that study defined MACE primarily in terms of non-target lesion myocardial infarction and mortality, and lacked the statistical power to assess ISR specifically. In another study conducted 24 months after drug-eluting stent implantation, Wu et al. found a positive, independent association between oral infections, triglyceride index (a marker of insulin resistance), and ISR in patients with acute coronary syndrome [95].

Restenosis exhibits a distinct pathophysiology compared to de novo coronary artery lesions [62]. Interventions such as stent implantation or balloon dilation cause vascular injury that initiates a localized inflammatory response. This response promotes the proliferation, migration, and activation of smooth muscle cells, macrophages, and endothelial cells [96]. These processes lead to re-endothelialization, neointimal hyperplasia, and eventually neoatherosclerosis, which narrows the stented lumen once again [97]. The present findings introduce the novel hypothesis that chronic periodontal disease may contribute to the development of ISR within this specific patient population.

Although the precise mechanisms connecting periodontal disease to ISR remain to be fully elucidated, several plausible biological pathways have been proposed. Chief among these is the well-established inflammatory cascade that underlies the progression of both CAD and periodontal disease [83]. Inflammatory markers such as C-reactive protein, matrix metalloproteinase-2, and tumor necrosis factor-beta are often elevated in individuals with periodontal disease and have been implicated in restenosis risk as well [96].

Endothelial dysfunction, a recognized contributor to ISR, has also been linked to periodontal disease [97]. This dysfunction may occur through two principal mechanisms. First, oral pathogens associated with periodontal disease may invade vascular tissues directly, triggering an inflammatory response [97, 98]. Second, elevated systemic levels of trimethylamine N-oxide—a proatherogenic metabolite produced by the oral microbiota—may impair endothelial function [99].

In addition to their role in hemostasis, platelets also act as key mediators of inflammation. Certain periodontal pathogens, such as *Porphyromonas gingivalis*, are known to induce and maintain platelet aggregation through hemagglutinin domain proteins like HgP44 [100]. Platelet activation, in turn, may promote both restenosis and atherosclerotic progression [101]. Although the precise mechanisms underlying this phenomenon remain unclear, several biological pathways have been proposed to explain the association between periodontal disease and in-stent restenosis (ISR) [62]. The most widely accepted explanation involves a shared inflammatory pathway that contributes to the progression of both coronary artery disease (CAD) and periodontal disease [85].

Inflammatory markers—including C-reactive protein, matrix metalloproteinase-2, and tumor necrosis factor-beta—have been shown to be elevated in Parkinson's disease and may contribute to an increased risk of restenosis [98]. Parkinson's disease is also strongly associated with endothelial dysfunction, a known risk factor for ISR [99]. This dysfunction may arise via two primary mechanisms: first, oral pathogens may directly invade vascular tissues and elicit an inflammatory response [98] [100]; second, elevated systemic levels of trimethylamine N-oxide, a proatherogenic metabolite produced by the oral microbiota, may accumulate in the bloodstream and impair vascular function [101].

In addition to their established role in hemostasis, platelets play a central role in inflammation. Periodontal pathogens such as *Porphyromonas gingivalis* can induce and sustain platelet aggregation through the hemagglutinin domain protein HgP44 [102]. This platelet activation may, in turn, contribute to the pathogenesis of both restenosis and atherosclerosis [103].

Porphyromonas gingivalis can also alter gene expression in vascular smooth muscle cells, enhancing their ability to migrate and proliferate [104]. The proliferation and migration of smooth muscle cells are critical processes in the development of neointimal hyperplasia, which ultimately leads to in-stent restenosis (ISR) [96].

In conclusion, it is important to note that, similar to atherosclerosis and Parkinson's disease, ISR and periodontal disease (PD) have been associated with several common underlying medical

conditions, including—but not limited to—diabetes mellitus, chronic renal disease, age, gender, and multivessel coronary disease [80, 90]. Accordingly, the question arises as to whether PD is an independent risk factor for ISR, or whether the observed association is attributable to shared risk factors, as has been debated in the context of PD and atherosclerosis [23].

Current guidelines recommend the use of local antiproliferative agents delivered via drug-eluting stents and balloons. Additionally, they emphasize the role of intravascular imaging in identifying mechanical substrates beneath the vessel surface and guide interventional treatment strategies based on those findings [105].

Nevertheless, a growing body of research has turned attention to the prevention of restenosis through the systemic administration of anti-inflammatory agents, in addition to conventional local pharmacological and mechanical approaches. Existing evidence [89, 106, 107] clearly demonstrates the beneficial effect of periodontal therapy on surrogate markers of systemic inflammation, particularly interleukin C-reactive protein (ILCRP) and tumor necrosis factor-alpha (TNF-α). This observation raises the possibility that periodontal treatment may help reduce systemic inflammation, thereby contributing to a multidisciplinary approach to ISR prevention.

Further prospective, randomized clinical trials are necessary to validate this potential effect. More broadly, our findings underscore the importance of screening for compromised oral hygiene and underlying periodontal disease in patients at elevated cardiovascular risk, particularly those undergoing coronary interventions for restenosis.

Because this study is subject to the inherent limitations of cross-sectional, case–control research, it does not permit causal inference. Patient enrolment was intentionally biased to include individuals undergoing percutaneous coronary intervention (PCI) for in-stent restenosis (ISR). Consequently, the possibility of investigator bias cannot be excluded, and unmeasured confounding factors may have influenced the results.

Comparisons were made between patients undergoing PCI for ISR, healthy controls, and other PCI patients with similar clinical and procedural characteristics. However, this approach did not allow for consideration of lesion-specific or procedural aspects of the initial coronary intervention, which may influence restenosis development.

Although the ISR and de novo lesion PCI groups did not show significant differences in baseline clinical characteristics, the relatively small sample size precluded a formal multivariate analysis. Therefore, the presence of underlying medical conditions potentially affecting the outcomes cannot be definitively ruled out.

V.4. The Role of Cathepsins in Oral Disease

V.4.1. The Structure of Cathepsins

Papain, a cysteine protease derived from *Carica papaya*, was among the first dozen protein crystal structures to be successfully crystallized. Its structure, in combination with that of actinidin, provided the first insight into the three-dimensional (3D) configuration of this class of enzymes. Subsequent advances enabled the extraction of cysteine cathepsins from various tissues, including cathepsins B, H, L, S, X, and C. In contrast, the expression systems used for the remaining cathepsins were distinct [108].

V.4.2. Cathepsin Structure Activation and Inhibition

Cathepsins are initially produced as inactive zymogens, in which the prodomain obstructs the enzyme's active site, thereby preventing substrate hydrolysis [109]. Activation of cathepsins requires modification of the zymogen, specifically through the removal of the prodomain. In the endoplasmic reticulum, the inactive signal peptide is cleaved, and the resulting protein is glycosylated into a proenzyme before being transported to the Golgi apparatus [108]. Within the Golgi, mannose residues are phosphorylated to form mannose-6-phosphate, which is then directed to the lysosomes via the mannose-6-phosphate receptor pathway [3].

Acidification within the late endosome facilitates the separation of the prodomain from the active site, resulting in the formation of active cathepsins. Thus, the prodomain functions as an autoinhibitory domain. Activation occurs exclusively via autocatalytic or transactivation mechanisms within lysosomes. Both acidic pH and the presence of glycosaminoglycans accelerate the activation process. Matrix metalloproteinases also contribute to cathepsin activation by regulating proteolytic processing [109]. These enzymes modulate cathepsin activity by interacting with and altering the active site.

Endogenous inhibitors such as cystatins, thyropins, and serpins also play a key role in regulating cathepsin function. Cystatins represent the most diverse group of endogenous cathepsin inhibitors and primarily target cysteine proteases. These intracellular proteins inhibit enzymatic activity by binding non-covalently to the active site, creating a partial blockage. The cystatin family includes three major subtypes: type 1 (stefins), type 2 (cystatins), and type 3 (kininogens). In contrast, serpins are capable of inhibiting both cysteine and serine proteases [110].

The first identified member of the extensive family of lysosomal cysteine peptidases was cathepsin B [111]. The *CTSB* gene, located on chromosome 8p22.1, encodes this enzyme, which is the most widely expressed cathepsin. Cathepsin B is found in abundance in macrophages and gingival crevicular fluid [112]. It has also been identified in granular duct cells and gingival fibroblasts of the submandibular gland. Functionally, cathepsin B is involved in various cellular processes, including apoptosis, antigen synthesis, and proteolysis. It also serves as a key activator of trypsin in cases of acute pancreatitis [113]. Additionally, cathepsin B contributes to the degradation of collagen and other non-collagenous matrix proteins, playing a significant role in the formation of resorption lacunae in deciduous teeth [114].

Dipeptidyl peptidase I, also known as cathepsin C, is encoded by the *CTSC* gene located on chromosome 11q14. This exogenous salivary peptidase is responsible for cleaving dipeptides from the N-termini of peptides [115]. It plays an important role in the activation of platelet factor XIII and various serine proteases within inflammatory cells.

Cathepsin D is a proteinase known to stimulate collagenolytic activity and bone resorption, and is intricately associated with tumour progression. It has been detected in macrophages, epithelial cells, and fibroblasts in various normal tissues [116]. Acting as a mitogen, cathepsin D contributes to the remodeling and renewal of epithelial structures. In the oral cavity, it is present in gingival fluid and has been identified in the junctional epithelium and oral mucosa of rats.

Cathepsin G, synthesized predominantly by neutrophils, plays a key role in the degradation of tissues at inflammatory sites and in the clearance of intracellular pathogens. It also participates in platelet activation, promoting platelet aggregation and thrombus formation [112]. Cathepsin G expression has been documented in various myeloid cell populations, including dendritic myeloid cells, plasmacytoid dendritic cells, B cells, and murine microglia. Elevated levels of cathepsin G have been observed in the synovial fluid of patients with rheumatoid arthritis, contributing to increased enzyme concentration and activity [117].

Cathepsin K, a member of the lysosomal cysteine protease family, is primarily expressed in osteoclasts and plays a crucial role in bone resorption and remodeling. Its catabolic activity enables the degradation of both bone and cartilage. In deciduous teeth, cathepsin K is present in odontoclasts, where it facilitates the breakdown of extracellular dentin collagen during physiological root resorption [112]. In addition to its role in skeletal tissues, cathepsin K has been associated with vascular pathology, including the degradation of blood vessel integrity and the destabilization of atherosclerotic plaques [118]. Cathepsin K inhibitors serve as important tools for investigating its role in conditions such as obesity and adipogenesis and are being explored for

potential therapeutic applications [118]. The enzyme is also implicated in the pathogenesis of osteoarthritis. Moreover, its expression has been documented in malignant cells from breast, lung, thyroid, and melanoma tumors. Notably, cathepsin K has been linked to increased invasive potential in prostate cancer [118].

Cathepsin L is known for its broad substrate specificity, cleaving various components of the extracellular matrix, including fibronectin, collagen, and laminin. It is believed to participate in several biological functions, such as intracellular protein turnover, antigen processing and presentation, and bone resorption [108, 119].

Cathepsin S, another lysosomal cysteine protease, is predominantly expressed by professional antigen-presenting cells (APCs), including dendritic cells and B cells. It plays a key role in tissue repair and maintenance through the degradation of extracellular matrix molecules such as collagen, elastin, fibronectin, laminin, and proteoglycans [120]. In addition to regulating osteoblast differentiation and bone remodeling, cathepsin S facilitates cell migration [120]. Cathepsin S is involved in a wide range of physiological and pathological processes, including cancer, autoimmune diseases, allergic inflammation, asthma, diabetes, obesity, and both cardiovascular and respiratory disorders [120].

Nuclearly localized variants of cathepsin L are involved in regulating cell cycle progression [108]. Active cathepsin L has also been implicated in cardiac signal transduction pathways [109]. Cathepsin V, also known as cathepsin L2, shares high homology with cathepsin L but exhibits restricted tissue expression, being primarily localized to the thymus and testis. In particular, human thymic cortical epithelial cells express cathepsin V specifically [121].

The upregulation of cathepsin V in stenotic aortic valves and atherosclerotic plaques suggests its involvement in the degradation of elastin laminae within diseased blood vessels. Furthermore, the physiological degradation of myelin basic protein has been found to correlate with elevated expression and activity of cathepsins B, D, and S in patients diagnosed with multiple sclerosis [116].

V.4.3. Cathepsins in Oral Disease

Dental caries, a microbiological disease, develops when the organic matrix dissolves and the inorganic matrix undergoes demineralization. Matrix metalloproteinases (MMPs) are primarily implicated in the pathogenesis of dental cavities. According to current theory, colocalized cysteine cathepsins may accelerate caries progression by activating latent MMPs and interacting with them. Carious dentin has been shown to contain higher levels of cathepsin B antibodies compared to

healthy enamel, with greater cathepsin B expression associated with deeper carious lesions. MMP-20, MMP-2, and possibly cathepsin B have also been identified in dentinal fluid, particularly in areas with high dentinal tubule density, suggesting that they may be involved in lesion activity Periapical lesions surrounding the apex of the tooth are caused by pulp inflammation, which becomes visible due to the host immune response [122].

Osteoclasts predominantly express cathepsin K, a protease involved in bone resorption and remodeling. Given its central role in bone metabolism, cathepsin K has been the target of research aimed at developing highly selective inhibitors for the treatment of osteoporosis [118].

Oral lichen planus, a chronic mucosal disease, is mediated by T cells. Studies have shown that cathepsin K inhibitors can block dendritic cell signaling of Toll-like receptor (TLR)-mediated cytokines in psoriasis. In oral lichen planus, the activation of TLR4 and TLR9, along with the concurrent expression of cathepsin K in certain dendritic cells, suggests that cathepsin K contributes to increased cytokine activity in these cells during disease progression [123].

In oral lichen planus lesions, inflammatory cells stained with cathepsin B have been observed to secrete stromal proteases, which may expose epithelial cells to neoplastic transformation [124].

In certain cases, the inflammatory process associated with peri-implantitis may contribute to implant failure by damaging the tissues surrounding the implant. According to Yamalik et al., cathepsin K activity is elevated in peri-implantitis and peri-mucositis compared to healthy peri-implant tissues. Increased expression of receptor activator of nuclear factor kappa-B ligand (RANKL) promotes the generation of active osteoclasts, which subsequently facilitate cathepsin K expression and lead to bone resorption .

Periodontitis is a prevalent chronic inflammatory condition characterized by progressive destruction of the teeth, alveolar bone, and surrounding connective tissue. In this context, cathepsin S has been shown to promote the migration and proliferation of periodontal ligament cells, contributing to lesion closure. This finding suggests that the cysteine protease cathepsin S may play a significant role in periodontal tissue remodeling and repair [75].

Cathepsin G has also been found to be more prevalent in adult periodontitis. Promatrix metalloproteinase-8, a latent neutrophil-derived procollagenase, can contribute both directly and indirectly to periodontal tissue destruction, exacerbating disease progression. The observed correlation between periodontal pocket depth and these enzymes supports their role as inflammatory biomarkers in periodontitis [11, 125].

The intensity of cathepsin D staining has been assessed across different layers and in the stroma or capsular wall of various odontogenic cysts. Distinct staining patterns were observed in both the stromal and epithelial components. In radicular cysts, staining intensity increased progressively from dentigerous cysts to odontogenic keratocysts (OKC), suggesting a correlation between rising expression levels and increasing lesion aggressiveness [112]. In the separation zone of OKC, a significant presence of granular staining was noted. This finding suggests that cathepsin B may play a key role in the epithelial–connective tissue separation observed in OKC.

Granular cell ameloblastomas exhibit unique staining and discharge patterns compared to other ameloblastoma subtypes, which may explain their aggressive behavior, recurrence tendencies, and metastatic potential [112]. Cathepsin D, a proteinase involved in bone resorption and collagen degradation, is heavily implicated in the biological progression of cancers. Its ability to degrade the extracellular matrix is a recognized marker of aggressiveness in oral squamous cell carcinoma. Physiologically, cathepsin D is thought to promote the self-destruction of senescent or damaged epithelial cells. This enzyme has been detected in the epithelium, connective tissue, and stroma of odontogenic cysts and tumors [2].

Cancer is a multistage process characterized by genetic alterations, and systemic immune proteases, including cathepsins, play regulatory roles in metastasis and invasion. Cathepsins facilitate tumor progression by degrading extracellular matrix components and disrupting intercellular communication. Cathepsin B, in particular, has been associated with uncontrolled proteolysis and has been implicated in tumor development, invasion, and metastasis through its remodeling effects on connective tissue and basement membranes [112].

Conversely, although cathepsin C is upregulated during pancreatic islet carcinogenesis, it does not appear to contribute functionally to neoplastic progression in that context. However, both cathepsin B and cathepsin C show increased expression and enzymatic activity in numerous tumor types [125].

Cathepsin D expression has also been detected during the transformation of epithelial dysplasia into oral squamous cell carcinoma, and its expression is correlated with both tumor progression and invasiveness [126]. Changes in the intracellular trafficking of cathepsin D—from lysosomal compartments to the invasive front of tumors—have been linked to mutations in the p53 gene. Additionally, cancer cells secrete procathepsin D, which enhances invasion and metastasis by acting through mitogenic pathways [126].

In samples from patients with oral tongue squamous cell carcinoma (OTSCC), cathepsin K was detected in the majority of tumors, although it was absent in some dysplastic regions adjacent to carcinoma tissue. Cathepsin K was not present in the morphologically normal epithelium of the tongue but was found in both stromal cells and malignant tissues [127].

Overexpression of cathepsin L in oral cancer has been strongly associated with tumor progression. Its expression is linked to lymph node metastasis and poor prognosis, indicating that cathepsin L may serve as a robust biomarker for predicting cancer outcomes [128].

VI. CONCLUSIONS

Based on the studies that form the foundation of the present thesis, we draw the following conclusions, which we also consider the novel findings of our work:

1. Laser-Lok implants with laser micro-grooved, platform-switched abutments were found to reduce plaque accumulation one year after functional loading in both diabetic and non-diabetic patients, thereby decreasing inflammation and microbial load.

2. The findings confirm that moderately controlled diabetic patients are not contraindicated for dental implant placement in terms of implant survival rate and stability.

3. The added benefit of microtexturing on implant and abutment surfaces may offer a clinical advantage in diabetic individuals by helping to counteract pathological changes associated with metabolic disorders.

4. Within an immediate implant loading protocol, laser micro-grooved implants and abutments may reduce or prevent peri-implant mean crestal bone loss in moderately controlled diabetic patients.

5. Patients undergoing percutaneous coronary intervention (PCI) for restenotic lesions were found to exhibit more severe forms of periodontal disease compared not only to healthy controls but also to patients treated for de novo lesions.

6. These results underscore the importance of periodontal screening and care in PCI patients, which may contribute to the prevention of future cardiovascular events, including restenosis.

7. Cathepsins play a critical role in the pathogenesis of both systemic and oral diseases and may serve as biomarkers for various oral pathologies.

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APPENDIX