PERIODONTITIS: CAUSAL LINKS AND TREATMENT IN THE CONTEXT OF DIABETES, SMOKING, AND IN-STENT RESTENOSIS

Summary of the PhD thesis

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PUBLICATIONS PROVIDING 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
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ABBREVIATIONS

BOP	bleeding on probing
CAL	clinical attachment level
DM	Diabetes Mellitus
FMBS	Full Mouth Bleeding Score
FMPS	Full Mouth Plaque Score
ISQ	Implant stability quotient
ISR	intergroup success rate
LMG	laser micro grooved
PCI	percutaneous coronary intervention
PI	plaque index
PPD	probing pocket depth
RFA	resonance frequency analysis
WHO	World Health Organization

I. INTRODUCTION

Periodontal disease is a chronic inflammatory condition of the tooth-supporting tissues, initiated by bacterial infection. In its severe form, it affects up to 11% of the global population, making it one of the most prevalent chronic diseases worldwide. Beyond its local effects on oral structures, periodontitis has increasingly been recognized as a contributor to systemic morbidity. A central question in current research is whether the associations between periodontal disease and systemic disorders are merely correlative or are mediated by causal mechanistic pathways.

In 2012, an international panel of experts from Europe and the United States reviewed the evidence on the most extensively studied links between periodontitis and systemic disease—namely diabetes mellitus, adverse pregnancy outcomes, and cardiovascular disease. Their consensus highlighted that periodontitis increases the bacterial and inflammatory burden of the host, thereby playing a role in the pathophysiology of metabolic and vascular disorders. Subsequent studies have strengthened this causal hypothesis, emphasizing shared inflammatory pathways, microbial dysbiosis, and genetic predispositions.

Diabetes mellitus (DM), characterized by chronic hyperglycemia due to impaired insulin secretion and/or insulin resistance, currently affects over 422 million people globally and accounts for approximately 1.6

million deaths each year, according to the World Health Organization. Individuals with diabetes are at higher risk of developing periodontal disease, particularly if glycemic control is poor. Conversely, periodontitis may aggravate glycemic dysregulation by increasing systemic inflammatory load, underscoring a bidirectional relationship between these two conditions. Although diabetes has traditionally been considered a relative contraindication for implant-based oral rehabilitation, advances in implant design and surgical protocols have increasingly allowed successful outcomes even in diabetic patients. A key factor in implant survival is osseointegration—the coordinated process of bone remodeling and healing that secures direct contact between implant and bone. Impaired wound healing and inflammation in diabetic individuals threaten this process and may reduce implant stability and longevity.

Another important mechanistic link between periodontitis and systemic disease is mediated by cathepsins, a family of lysosomal cysteine proteases. While they are essential for physiological processes such as tissue remodeling, angiogenesis, and wound repair, dysregulated cathepsin activity contributes to pathological tissue degradation and chronic inflammation. In periodontal tissues, cathepsin B has been implicated in collagen breakdown, while other cathepsins contribute to bone resorption and systemic complications.

Epidemiological and mechanistic studies also suggest that periodontitis is associated with cardiovascular disease, including atherosclerosis and in-stent restenosis (ISR). Both conditions share common risk factors such as diabetes and smoking, but they are also linked through inflammatory mechanisms. In periodontitis, disruption of the periodontal epithelium facilitates the translocation of pathogens, endotoxins, and inflammatory mediators into the bloodstream. These can contribute to endothelial dysfunction, smooth muscle proliferation, and ultimately vascular pathology. Taken together, these interconnections highlight the importance of considering periodontitis not only as a localized oral condition, but also as a systemic disease modifier. The present thesis investigates these links through three complementary studies: (1) a clinical trial evaluating the performance of laser micro-grooved implants in diabetic patients, (2) a case–control study on the relationship between periodontal disease and in-stent restenosis, and (3) a literature review of the role of cathepsins as potential molecular mediators at the intersection of oral and systemic diseases.

II. OBJECTIVES

This thesis investigated the clinical and molecular intersections between periodontitis, diabetes mellitus, and in-stent restenosis, with a focus on causal links and therapeutic implications. To achieve that end, three complementary studies were undertaken:

1. A clinical trial on laser micro-grooved implants in diabetic patients to assess whether specially designed laser micro-grooved implants and abutments improve peri-implant soft and hard tissue outcomes in moderately controlled type II diabetic patients. Radiographic and clinical parameters, including mean crestal bone levels and implant stability, were compared with non-diabetic controls over one year of functional loading.

2. A case–control study on periodontal disease and in-stent restenosis to determine whether patients undergoing percutaneous coronary intervention (PCI) for in-stent restenosis display more severe periodontal disease compared to those with de novo lesions and to healthy controls, thereby exploring shared inflammatory mechanisms.

3. A review of the role of cathepsins in oral disease to evaluate the role of cathepsins, particularly cathepsin B and S, in periodontal and systemic pathologies, and to assess their potential as molecular mediators linking diabetes, periodontitis, and cardiovascular disease.

III. METHODS

III.1. Clinical trial: Laser micro-grooved implants in diabetic patients

A controlled clinical trial was designed to evaluate the effect of laser micro-grooved (LMG) implants and abutments on peri-implant bone and soft tissue levels in moderately controlled type II diabetic patients, compared with non-diabetic controls. Eligible participants were 30–60 years of age with mandibular premolar or molar edentulous sites and adequate bone dimensions. The diabetic test group included patients with HbA1c levels between 8.1–10%.

All surgeries were performed by a calibrated operator using a standardized protocol. Implants were placed equicrestally with insertion torque >35 Ncm, and stability was verified using resonance frequency analysis (ISQ $\geq$ 60). Immediate functional loading with prosthetic abutments was carried out.

Clinical (plaque and bleeding scores, probing depth, gingival margin, peri-implant sulcus depth, attachment level) and radiographic (mesial and distal crestal bone levels) parameters were assessed at baseline, six months, and one year. Statistical analyses included intra- and intergroup comparisons, with significance set at $p < 0.05$.

III.2. Case–control study: Periodontal disease and in-stent restenosis

Ninety patients undergoing percutaneous coronary intervention (PCI) at the University of Szeged were recruited: 51 treated for de novo lesions and 39 for in-stent restenosis (ISR). A healthy control group of 90 age- and gender-matched individuals was also included. Patients with systemic inflammatory diseases, fewer than four teeth, or critical illness were excluded.

Periodontal examinations were performed 48 hours after PCI by a periodontal specialist. The following parameters were recorded at six sites per tooth: plaque index (PI), bleeding on probing (BOP), probing pocket depth (PPD), clinical attachment level (CAL), and number of missing teeth. Periodontal status was staged as healthy, early, moderate, or severe.

Statistical analyses employed chi-square tests, logistic regression, and multinomial regression to explore associations between periodontal disease severity, diabetes status, and restenosis.

III.3. Methods of the review

A systematic literature review was conducted to assess the role of cathepsins in periodontal and systemic disease. Electronic databases (PubMed, Scopus,

EBSCOHOST) and grey literature sources (Google Scholar, conference proceedings) were searched using combinations of the keywords cathepsins, oral disease, dental, dentistry. No restrictions on publication year were applied, but only English-language studies were included.

Two independent reviewers screened titles, abstracts, and full texts. Reference lists of included papers were also hand-searched. The review synthesized evidence regarding cathepsin expression and activity in oral tissues, their involvement in periodontal and systemic pathology, and their potential as biomarkers or therapeutic targets.

IV. RESULTS

IV.1. Clinical trial: Laser micro-grooved implants in diabetic patients

Both diabetic and non-diabetic groups demonstrated good peri-implant health during the one-year follow-up. Plaque and bleeding indices decreased significantly in both groups after one year of functional loading ($p < 0.001$), with no intergroup differences. Probing pocket depth remained stable, with no attachment loss observed. Crestal bone levels showed minimal changes: in the control group, mesial and distal bone loss averaged 0.16–0.17 mm; in diabetics, 0.21–0.22 mm. These changes were statistically significant within groups but not between them. Implant survival rate was 100% in both groups, with no failures. Implant stability (ISQ values) remained high (>74) and comparable between groups. **Laser micro-grooved implants and abutments supported stable bone and soft tissue conditions, even in moderately controlled diabetics.**

IV.2. Case–control study: Periodontal disease and in-stent restenosis

Significant differences were observed between patients undergoing PCI and healthy controls.

Periodontal status was strongly associated with PCI group membership ($p < 0.001$). Patients in the PCI group had more missing teeth and more severe periodontitis, despite similar plaque indices. Diabetes

mellitus and periodontal disease severity were independent predictors of PCI status. Among PCI patients, those with restenotic lesions (ISR) had notably more severe periodontitis than those with de novo lesions ($p < 0.01$). **Severe periodontitis (stage 4) was present in 64% of ISR patients. Severe periodontal disease was significantly overrepresented in PCI patients, particularly in those with restenosis, suggesting shared inflammatory pathways between PD and vascular pathology.**

IV.3. Results of the review

The literature review confirmed the broad involvement of cathepsins in both oral and systemic pathology.

Cathepsin B contributes to collagen degradation and prolonged inflammatory signaling in periodontal tissues. Cathepsin S regulates antigen presentation and periodontal tissue remodeling, linking immune dysregulation with systemic inflammation. Cathepsin K is central to bone resorption, with elevated activity in peri-implantitis and osteoclastic bone loss. Dysregulated cathepsins have been implicated in systemic conditions such as diabetes, atherosclerosis, and cancer. Circulating cathepsins, together with their inhibitors (e.g., cystatin C), show promise as biomarkers for systemic disease and may represent therapeutic targets. **Cathepsins are not only mediators of oral tissue destruction but also potential molecular links between periodontal disease, diabetes, and cardiovascular complications.**

V. 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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