From DEPARTMENT OF DENTAL MEDICINE
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LASER TREATMENT AND DISEASE CHARACTERISTICS OF PERI-IMPLANTITIS

Sebastian Malmqvist

Karolinska Institutet

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Cover illustration: Scanning electron microscope picture of a dental implant, by Anders Liljeborg, March 2017.

Laser treatment and disease characteristics of peri-implantitis

Thesis for Doctoral Degree (Ph.D.)

By

Sebastian Malmqvist

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Principal Supervisor:
Professor **Annsofi Johannsen**
Karolinska Institutet
Department of Dental Medicine
Division of Oral Diseases

Co-supervisors:
Dr. **Talat Qadri**
Kami Dental

Associate Professor **Elisabeth Almer Boström**
Karolinska Institutet
Department of Dental Medicine
Division of Oral Diagnostics and Rehabilitation

Professor **Anders Gustafsson**
Karolinska Institutet
Department of Dental Medicine
Division of Oral Diseases

Professor **Georgios N. Belibasakis**
Karolinska Institutet
Department of Dental Medicine
Division of Oral Diseases

Opponent:
Professor **Ola Norderyd**
Jönköping University
School of Health and Welfare

Examination Board:
Professor **Ingemar Abrahamsson**
University of Gothenburg
Sahlgrenska Academy
Institute of Odontology

Associate Professor **Annica Almståhl**
University of Gothenburg
Sahlgrenska Academy
Institute of Odontology
Department of Oral Microbiology and Immunology
&
Malmö University
Faculty of Odontology
Division 4 – Oral Health

Associate Professor **Anastasios Grigoriadis**
Karolinska Institutet
Department of Dental Medicine
Division of Oral Diagnostics and Rehabilitation

Dedication

To my late father, who inspired me to study.

To my supportive mother.

To my patient wife.

To my playful one-year-old son, who contributed with (assisted by autocorrect):

“Kitchen bath better ä rd med min bil med en millimeter boll är min egen? Och kvinn ok I'll know med Bill om må är Mumin är>6°6ûåå%ä\

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Popular science summary of the thesis

Replacing missing teeth with dental implants have become a popular treatment as it is a fixed solution compared to removable dentures. In some cases, the tissue surrounding the dental implant becomes inflamed, which can lead to a breakdown of the bone in which the implant is attached. This disease is called peri-implantitis. A poor oral hygiene, a history of tooth loss, smoking, and uncontrolled diabetes are some conditions that increases the risk to develop peri-implantitis. Treating peri-implantitis has proven to be difficult. Few studies have previously tested to treating peri-implantitis with infra-red laser.

In this thesis we have evaluated a specific infra-red laser's ability to safely treat peri-implantitis with emphasis on patients' experiences. The laser is of diode type and has a wavelength of 970 nm, which is just outside the visible light spectrum of 400-750 nm. We also have explored the immune response in peri-implantitis and compared it to its sibling disease in teeth; periodontitis (also known as tooth loss).

To safely use infra-red or blue laser on dental implants, one must use the laser in short intervals and apply a lot of cooling water during use. When we examined a titanium surface like that of dental implants in a specialized microscope, no surface alterations were noted with the use of a blue laser. Previous studies have not found any alterations when using similar intra-red lasers.

During interviews, it emerged that the patients were overall satisfied with their dental implants, but some were worried now that they had developed peri-implantitis. Some had felt or noticed signs of inflammation around their implants. The participants were also interviewed regarding their experience of receiving treatment for peri-implantitis with either infra-red laser or surgery. The worst part of both treatments was the injections of anesthesia. A downside of the surgery was the need for stiches, which is not required after laser treatment.

We could not confirm with statistics that the two treatments were equal in healing outcomes, but they had similar numbers of successful and unsuccessful healing patterns after 6 months. The surgery had some clinical advantages in severe cases of peri-implantitis.

The inflammation in peri-implantitis and periodontitis seem to be similar in immune cell composition and activity, but we found some tendencies for differences that are of interest to examine further.

Abstract

Peri-implantitis is an inflammatory disease which affects the soft and hard tissues surrounding dental implants. Current theory is that peri-implantitis is a counterpart to periodontitis, which is the inflammatory disease that destroys the tooth's supporting tissues. However, there are some key discrepancies and there is a need for more studies on the characteristics of peri-implantitis. If the disease is not stopped, there is a risk that the dental implant is lost. It has proven difficult to treat peri-implantitis with conventional nonsurgical or surgical treatments. This is also an area of peri-implantitis that needs further research.

The overall aim was to evaluate laser treatment of peri-implantitis, as well as explore the patients' experiences and disease characteristics.

In **study I**, we tested the safety of using diode lasers on dental implants by evaluating two different wavelengths 445 nm and 970nm. The temperature increase in dental implants were tested in two different models, one being a PM. Rigorous amounts of cooling water and limiting the continuous irradiation time to a maximum of 15-20s seemed to be key factors, depending on the power setting. We also assessed potential surface alterations on titanium discs in SEM but did not see any.

In **study II**, the patient's experiences and sensations were explored qualitatively in semi-structured interviews. We confirmed previous findings of positive associations of dental implants and added some perspectives to them with some negative experiences. In this group of patients, already diagnosed with peri-implantitis, some reported feeling symptoms, which could mean that with education on early signs of inflammation, the patient can also monitor their peri-implant health. The experiences of laser treatment and mucosal flap surgery were that of slight discomfort and for both the localized anesthesia was described as the worst part. Those that received surgery mentioned the sutures as a main source of discomfort. This we confirmed quantitatively in **study III**, where the surgery patients rated their discomfort significantly higher during the first week of healing than those in the laser group.

In **study III**, we could not establish equivalence in change of PPD and RBL between the laser treatment and mucosal flap surgery. Both treatments had similar numbers of unresponsive peri-implantitis lesions, but in the patients that improved in their PPD, the surgery had significantly higher pocket reduction.

There was basically no difference in change of RBL, BOP, biomarkers, and bacteria between the treatments.

In **study IV**, we found that the inflammatory profile and immune cell composition were similar between peri-implantitis and periodontitis. In homogenized soft tissue, peri-implantitis lesions had significantly higher levels of IL-1β, TNF-α, IL-4 IL-17A, IL-23, G-CSF, and BAFF, whereas periodontitis only had significantly higher levels of IL-1β, IL-4, and G-CSF, compared to non-disease controls. Although, peri-implantitis and periodontitis did not significantly differ, there was a tendency towards a stepwise increase in proportion of B cells, from lowest in controls to highest in peri-implantitis.

The results in this thesis show the potential for 970 nm diode laser in treating peri-implantitis. With unique clinical data a suggested role for the treatment modality could be initial stages of peri-implantitis where extensive pocket elimination is not as needed. The findings also support the need for further studies in assessing the patients self-monitoring of peri-implant conditions as well as the potential difference in B cell proportion and activity between peri-implantitis and periodontitis.

List of scientific papers

I. **Malmqvist S**, Liljeborg A, Qadri T, Johannsen G, Johannsen A. Using 445 nm and 970 nm Lasers on Dental Implants-An In Vitro Study on Change in Temperature and Surface Alterations. Materials (Basel). 2019 Nov 27;12(23):3934.

II. **Malmqvist S**, Erdenborg J, Johannsen G, Johannsen A. Patient's experiences of dental implants, peri-implantitis and its treatment-A qualitative interview study. Int J Dent Hyg. 2023 Apr 24. Epub ahead of print.

III. **Malmqvist S**, Qadri T, Lira-Junior R, Boström EA, Gustafsson A, Belibasakis GN, Silbereisen A, Johannsen G, Johannsen A. Treatment of peri-implantitis with either 970 nm diode laser or conventional mucosal flap surgery: a clinical randomized controlled trial. *Manuscript*.

IV. **Malmqvist S**, Clark R, Johannsen G, Johannsen A, Boström EA, Lira-Junior R. Immune cell composition and inflammatory profile of human peri-implantitis and periodontitis lesions. *Submitted*

Contents

List of abbreviations

AAP	American Academy of Periodontology
APC	Antigen precenting cells
aPDT	Antimicrobial photodynamic therapy
BAFF	B cell activating factor
BOP	Bleeding on probing
CD	Cluster of differentiation
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CW	Continuous wave
DC	Dendritic cell
EFP	European Federation of Periodontology
EQUATOR	Enhancing the quality and transparency of health research
FACS	Fluorescence-activated cell sorting
FWH	First week of healing
GCF	Gingival crevicular fluid
G-CSF	Granulocyte colony-stimulating factor
GIC	Glass ionomer cement
H&E	Hematoxylin & Eosin
HLA	Human leukocyte antigens
IL	Interleukin
LPS	Lipopolysaccharides
MMP	Matrix-metalloproteinase
OC	Osteoclast
OCT	Optimal cutting temperature compound
PI	Plaque index
PICF	Peri-implant crevicular fluid

PM	Pig mandible
PPD	Probing pocket depth
PROM	Patient reported outcome measures
RANK	Receptor activator of nuclear factor κ B
RANKL	Receptor activator of nuclear factor κ B ligand
RBL	Radiographic bone loss
RCT	Randomized controlled trial
RPMI	Roswell Park Memorial Institute
SD	Standard deviation
SEM	Scanning electron microscope
SOP	Suppuration on probing
SRQR	Standards of reporting qualitative research
T2DM	Type 2 diabetes mellitus
Th	T-helper cell
TOST	Two one-sided tests
VAS	Visual analogue scale

1 Introduction

Dental implants have become a wide-spread and popular treatment option to replace missing teeth (Klinge et al., 2018). The treatment restores chewing function and esthetics to a satisfactory degree, while also showing stability over time (Astrand et al., 2008; Coli et al., 2017). However, there are some essential differences between teeth and dental implants (Figure 1). Whereas a tooth is attached to the alveolar bone via the periodontal ligaments, the dental implant is attached directly to the bone via osseointegration (Coli et al., 2017). Like teeth, dental implants are susceptible to inflammation of the surrounding soft tissue, called peri-implant mucositis, due to oral bacteria (Heitz-Mayfield & Salvi, 2018). The similarities continue as teeth can develop periodontitis, inflammatory destruction of the surrounding bone, dental implant can develop peri-implantitis (Schwarz et al., 2018). At this stage, some differences are starting to show between the two situations. Peri-implantitis seems to progress faster, its lesions involve a larger area, and saucer-shaped defects are seen on radiographs instead of a mostly horizontal bone destruction of periodontitis (Heitz-Mayfield & Lang, 2010). Whether due to the gradually exposed threads of the implant or something in the mechanics of the peri-implantitis disease differs, it poses a challenge to successfully treat with conventional nonsurgical mechanical debridement (Renvert & Polyzois, 2018). Although, plaque control and supportive care is important, mucosal flap surgery has been suggested to be gold standard in treating an established peri-implantitis lesion (Herrera et al., 2023), but a less invasive option would be of interest.

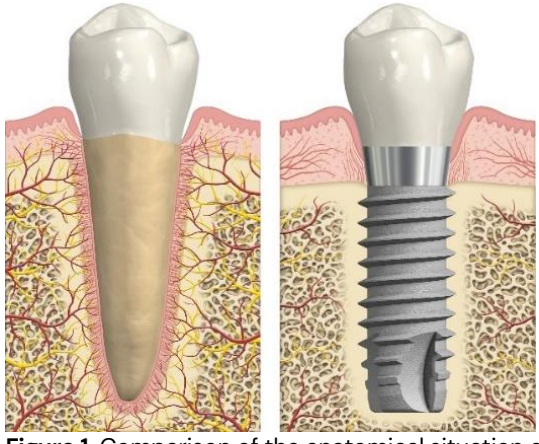


Figure 1. Comparison of the anatomical situation of teeth and dental implant. *Reprinted from Coli et al. (2017), with permission from John Wiley and Sons.*

2 Literature review

2.1 Definition and epidemiology of peri-implantitis

Peri-implantitis is a destructive inflammatory disease in which a dental implant gradually loses supporting bone. If untreated it may lead to the loss of the dental implant. There is a difference between early bone modulation after implant placement and the disease peri-implantitis. There have been a multitude of different case definitions through the years of what is considered peri-implantitis. On radiographs suggested definitions range from bone loss of ≥3 implant threads (Máximo et al., 2008) to change in bone level between >0.5 mm (Derks et al., 2016) to ≥3 mm (Papantonopoulos et al., 2015) after initial integration. Most definitions also include presence of bleeding on probing (BOP) or suppuration on probing (SOP) (Renvert et al., 2018). Some include different values for probing pocket depth (PPD) with suggestions from ≥4 mm (Renvert et al., 2014) to ≥6 mm (Koldsland et al., 2010). In 2018 the European Federation of Periodontology (EFP) and the American Academy of Periodontology (AAP) published a suggested definition after their consensus workshop the previous year (Renvert et al., 2018). They define peri-implantitis as visual signs of inflammation, an increase of PPD around the implant, and on radiographs visible progressive bone loss one year after placement of the implant-fixed prosthetic construction. In case of no initial radiographs to compare with one could use PPD ≥6mm with BOP and bone loss on radiographs of ≥3 mm as case definition of peri-implantitis.

The different case definitions with different cut off values regarding amount of bone loss have been discussed when trying to assess the prevalence of the disease (Derks & Tomasi, 2015; Kordbacheh Changi et al., 2019a; Krebs et al., 2019). The selection of the study participants for the estimation of the prevalence is also of importance. Recruiting from a university clinic, specialist clinic, or private or public general dentistry clinic seems to affect the prevalence, which is expected (French et al., 2019; Kordbacheh Changi et al., 2019; Vignoletti et al., 2019). In a meta-analysis by Lee et al. (2017) they reported a prevalence of 19.83% (95 % CI: 15.38-24.27%) on patient level and 9.25% (95 % CI: 7.57-10.93%) on implant level. In their analysis they include a variety of studies done in different settings in the hope that the over- and underestimations balance each other out.

Twelve million dental implants have been estimated to be installed yearly worldwide (Klinge, Klinge, et al., 2018). Assuming a prevalence of peri-implantitis of 9.25%, according to Lee et al. (2017), approximately 1.11 million implants yearly are at risk of being affected, which constitute a significant challenge for the dental sector.

2.2 Etiology & pathogenesis of peri-implantitis

The current most accepted theory is that peri-implantitis is mainly a dental plaque driven disease, similarly to periodontitis but around dental implants instead of teeth (Berglundh et al., 2018; Schwarz et al., 2018). There are some key similarities with bone loss starting marginally and that improvement of the individual's oral health has a prophylactic effect as well as improves the outcome of surgical treatments of peri-implantitis lesions (Lin et al., 2019). Peri-implantitis seems to be preceded by peri-implant mucositis, which like gingivitis is a reversible soft tissue inflammation, with the difference that peri-implant mucositis has a longer healing period (Berglundh et al., 2018; Salvi et al., 2012; Tomasi et al., 2016). A healing period of 12 weeks did not completely resolve the inflammation in the soft tissue around implants as seen in a study by Tomasi et al. (2016). The initial healing phase was characterized by formation of vascularized structures and recruitment of inflammatory cells. The further healing progression showed a decrease in density of T and B cell clusters and with the soft tissue forming a firm barrier around the implant, as epithelium cells and even connective tissue attach to the implant's surface, separating most of the peri-implant pocket and implant surface from the biofilm. One possible explanation for the longer healing period could be that the peri-implant tissue develops a stronger inflammatory response than its periodontal counterpart, which Salvi et al. (2012) has observed in experimental inflammation around implants and teeth. They also reported that a healing period of 3 weeks was not sufficient to fully reverse the inflammation (Salvi et al., 2012).

The mechanism and conditions explaining how peri-implant mucositis transitions into peri-implantitis are unknown (Schwarz et al., 2018). Histologically, fibroblasts and immune cell density have been seen to differ between peri-implant mucositis and peri-implantitis, with significantly higher density of immune cells and lower density of fibroblasts at peri-implantitis lesions (Karatas et al., 2019). In this aspect peri-implantitis and periodontitis lesions did not vary.

However, in a study by Carcuac & Berglundh (2014) they showed that the density of immune cells differed between peri-implantitis and periodontitis lesions. Also, peri-implantitis lesions had almost twice as large areas of infiltrated connective tissue as periodontitis, suggesting that the inflammatory process is spread deeper into the surrounding tissue around implants (Carcuac & Berglundh, 2014). Peri-implantitis tend to progress more rapidly and show typical saucer shaped defects on radiographs (Heitz-Mayfield & Lang, 2010). Periodontitis lesions tend to have a connective tissue fiber compartment walling off the alveolar bone from the infection while peri-implantitis lesions lack this boundary and could therefore be more susceptible to deeper spread of the infection into the bone. This anatomical difference might be the reason for the discrepancies in lesion size and shape (Coli et al., 2017).

Foreign body reaction has been suggested as an alternative explanation behind marginal bone loss around dental implants (Albrektsson et al., 2019), although this is a less explored and not as widely accepted theory. The theory suggests that a stable osseointegration is part of the foreign body reaction where the body encapsulates the implant in bone tissue. Implant failures are due to adverse or over reactions to the foreign nature of the implant or excess of accompanying prosthesis' cement. This line of thinking is not mentioned in the consensus report from EFP and AAP, who remain adamant that marginal bone loss in form of peri-implantitis is a plaque-driven disease (Schwarz et al., 2018). Albrektsson et al. (2019) drew parallels between dental and orthopedic implants in the sense that when there are infections around hip implants the bone resorption begins proximally and continues around the outline of the implant. They also highlight certain immunological cells which appear in both oral and orthopedic inflammatory reactions, which are associated with a foreign body reaction. Until further studies, one cannot conclude more than that a foreign body reaction could be part of a multifactorial explanation for the pathogenesis of peri-implantitis, but it seems unlikely that it is the sole explanation since the oral hygiene and supportive maintenance have been shown to have such a key role in preventing and treating peri-implantitis (Berglundh et al., 2019).

While the mechanism behind the development of peri-implantitis has not yet been identified, some risk factors for the disease have. History of periodontitis, smoking, diabetes mellitus, lack of regular supportive therapy, poor oral hygiene, lack of keratinized mucosa, excess cement, genetic factors, improper placement of implant or design of the construction, occlusal overload, titanium particles and

lastly viruses, have been explored as potential risk factors (Ahn et al., 2019; Ferreira et al., 2018; Karoussis et al., 2003; Lin et al., 2019; Schwarz et al., 2018; Stacchi et al., 2016) Overall, there is a limited amount of evidence for the different risk factors and due to the large amount of heterogeneity and high risk of bias in current studies, further prospective studies are necessary (Ferreira et al., 2018; Schwarz et al., 2018; Stacchi et al., 2016).

2.2.1 History of periodontitis

History of periodontitis has been associated with peri-implantitis in multiple studies. Implants installed to replace teeth extracted due to severe periodontitis had worse survival rates than implants installed after other extraction reasons, seen over a 10 year period (Karoussis et al., 2003). Ferreira et al. (2018) reported in their meta-analysis a significant increased risk for peri-implantitis in periodontitis patients when including both cross-sectional and cohort studies of sufficient quality, according to their criteria. However, when only using cohort studies the association was not significant, which shows the need for well performed prospective cohort studies. History of periodontitis is in itself a broad term which does not properly explain the current clinical inflammatory activity (Lin et al., 2019). Future studies should put emphasize on the severity and activity of the disease, so that the potential effect is not diluted with individuals with a reduced but now stable periodontium.

2.2.2 Smoking & diabetes mellitus

Few studies of sufficient quality have examined smoking as a risk factor (Stacchi et al., 2016). Karoussis et al. (2003) examined survival and clinical success in implants over a 10-year period and found that smoking showed no significant effect. However, Ahn et al. (2019) showed a significant odds ratio of 4.1 (95% CI: 1.44-11.66) for smokers developing peri-implantitis after 7 years of loading. Alqahtani et al. (2020) reported that smokers had significantly higher PPD and crestal bone loss than non-smokers. In the same study, type 2 diabetes mellitus (T2DM) seemed to have a larger impact on the peri-implant health than smoking. The consensus report from 2018 suggests that the evidence for smoking and T2DM is inconclusive (Schwarz et al., 2018). Yet, in a recent meta-analysis a cumulative risk ratio of 1.46 (95% CI: 1.21-1.77) was reported for having peri-implantitis in hyperglycemic individuals compared to those with normal glucose

levels (Monje, Catena, et al., 2017). They conclude that more studies should measure the glucose levels over the course of the study and not just using diagnosis or non-diagnosis as a way to examine the link between T2DM and peri-implantitis.

Overall, there seems to be more convincing evidence for T2DM as a risk factor than for smoking (Krebs et al., 2019; Monje, Catena, et al., 2017; Stacchi et al., 2016). Larger well-made prospective studies are needed to confirm that these suspected risk factors are a causal part of the pathogenesis of peri-implantitis.

2.2.3 Plaque control

Supportive therapy in terms of oral hygiene instructions and professional plaque removal reduced the risk of peri-implantitis by 75 %, when combining three studies in a meta-analysis (Lin et al., 2019). Compliance to the supportive therapy, with two or more sessions per year, has also affected the presence of peri-implantitis (Monje, Wang, et al., 2017). This highlights the importance of regularly recalling dental implant patients and taking the time to support them in their oral hygiene routines and technique (Cortellini et al., 2019). Prosthesis splinting has been seen to increase the risk of disease, possibly because it is harder to maintain plaque control under the inter-implant part of the prosthetic constructions than around a single crown on one implant (Ahn et al., 2019). Plaque index (PI) at the implants were only close to significant, in the previously mentioned study, which could be explained by the fact that the oral hygiene was reasonably good amongst the participants. Modifying the prosthesis contours to better fit interdental brushes decreased the mucosal inflammation in terms of BOP compared to only giving individualized instructions, in a prospective randomized controlled trial (RCT) by de Tapia et al. (2019). Giving professional instruction, regular follow-up recalls, and giving the patient the accessibility to maintain plaque control is of utmost importance in preventing and treating peri-implant diseases.

2.2.4 Keratinized mucosa

Lacking or having a thin keratinized mucosa around the implant have been reported to make oral hygiene more difficult for the patient resulting in higher plaque index and clinical signs of inflammation (Grischke et al., 2019). However, there are studies showing that the thickness of the keratinized mucosa does not

affect the presence of peri-implant diseases (Ahn et al., 2019; Lim et al., 2019). Whereas there are reports of association between peri-implantitis and thin or missing keratinized mucosa (Matarazzo et al., 2018; Vignoletti et al., 2019), others report that lack of keratinized mucosa did not influence the prevalence (Ahn et al., 2019). An argument could be made, that thin or lack of keratinized mucosa makes the home care harder for some patients, while some patients are still able to maintain an adequate oral hygiene. Degree of peri-implant bone loss at the time of treatment and thin or thick keratinized mucosa was shown to influence the results after surgical treatment of the peri-implantitis (Ravidà et al., 2020). In the same study they did also, conclude that the disease severity was associated with lack of keratinized mucosa, which could be confounding the relationship.

2.2.5 Excess cement

There is weak evidence towards higher prevalence-numbers of peri-implantitis with cemented rather than screw-retained implant prothesis (Staubli et al., 2017). The studies on this topic vary greatly in study design, type of prosthetic and implant system, observation period as well as definition and assessment of peri-implantitis, making a meta-analysis unsuitable as a method. Gram negative bacteria have been indicated to be more associated with cement-fixed prosthesis than screw-retained (Ramón-Morales et al., 2019). However, peri-implantitis was also more frequent in the cement retained group in that particular study and therefore one should interpret the results with caution. What seems to be important based on the available studies are avoiding submucosal crown margins, which makes detecting excess cement harder and it is mostly in those cases that peri-implantitis has a higher prevalence (Staubli et al., 2017). Submucosal placement of the crown margin also makes successful plaque control difficult for the patient, further increasing the risk of peri-implant diseases, and should therefore be avoided (Jepsen et al., 2015).

2.2.6 Other potential risk factors

Different gene polymorphisms have been suggested and associated with peri-implantitis with varying results (Fourmousis & Vlachos, 2019). With the pathogenesis of peri-implantitis not fully understood and the conflicting results of which genes that are associated with risk of peri-implantitis, no conclusion can be made regarding the role of the genes. It is, however, of interest to identify

these genes for potential early disease detection, future treatment modalities and risk assessment before implant placement.

In addition to diabetes mellitus, other systematic diseases have been statistically associated with peri-implantitis e.g., cardiovascular disease and rheumatoid arthritis (Renvert et al., 2014), but one should interpret this with caution due to the severe lack of studies and compensation for confounders.

Titanium and iron particles have been found in biopsies from tissue around dental implants (Fretwurst et al., 2016). It has been proposed that titanium ions could contribute to the dysbiosis of the biofilm around dental implants, which could lead to peri-implantitis (Souza et al., 2020). There is not enough evidence to support that either titanium particles or biocorrosion has any causal relationship with peri-implantitis (Mombelli et al., 2018).

Another implant related factor is the type of surface of the dental implant, machined implant surface or modified rough surface. For the initial osseointegration the rough modified surface seems preferable whereas it has been seen to later on increase the risk for peri-implantitis and a recurrence of the disease post-treatment (Bosshardt et al., 2017; Carcuac et al., 2020).

As with periodontitis, there has not been any single bacteria species that has been causally associated with peri-implantitis (Charalampakis & Belibasakis, 2015). Current theories of both diseases are that there is an ecological shift in the composition of species in the biofilm toward a more pathological flora. However, there are reports of both traditional and new pathogens in the peri-implant microflora (Sanz-Martin et al., 2017). Which species that are present in the peri-implant flora seem to be affected by adjacent teeth and implant sites, periodontal disease activity, as well as if the patient has been edentulous (Robitaille et al., 2016). Further studies are needed to assess the microbiome's role in peri-implantitis with a clearer focus on how peri-implant species partake in the etiology of the disease, rather than just trying to identify periodontal pathogens (Charalampakis & Belibasakis, 2015; Robitaille et al., 2016).

It is largely unclear if viruses play any role in the development or progression of peri-implantitis. The few studies that have investigated the association between viruses and healthy or peri-implantitis sites, show large heterogeneity and risk of bias (Akram et al., 2019). A slight significant increase of risk was seen for Epstein-

Barr virus but should be interpreted with caution due to the low quality of the available evidence.

2.3 Patients' experiences of dental implants

The positive impact of dental implants on patients' quality of life have been shown in many studies (Jan Derks et al., 2015; Elsyad et al., 2019; Farzadmoghadam et al., 2020; Øzhayat & Gotfredsen, 2020). Derks et al. (2015) has demonstrated, in a large questionnaire study with ~3800 participants, that the majority of the patients receiving implants were satisfied with the overall and aesthetic results as well as the cost of the treatment, after a minimum of 6 years of use. Older patients were more satisfied with the treatment and those who had received their implant treatment at a specialist clinic were more satisfied with chewing ability. The extent of the rehabilitative need also affected the feeling of improved chewing function and self-confidence, in terms of a more extensive reconstruction leading to a more satisfied patient. This is not surprising since a greater treatment need would also mean a larger function gained. Farzadmoghadam et al. (2020) showed that both oral health and general health related quality of life improved with implant treatment. Improvement in chewing, appearance, comfort, stability of the prosthesis, ease of speaking as well as decreased shyness or embarrassment over dental status have been reported as results of the implant treatment (Elsyad et al., 2019; Øzhayat & Gotfredsen, 2020). Both general and oral pain were reduced by implant treatment (Farzadmoghadam et al., 2020), but are likely linked together and affected by the oral disease/problem resulting in the extraction of the tooth and subsequent implant placement. A small percentage of individuals receiving dental implants are not satisfied with the result or feel that the treatment has had a negative effect on them (Jan Derks et al., 2015; Øzhayat & Gotfredsen, 2020), which is important to remember when dealing with the individual patient in a clinical setting.

Qualitative studies have shown the details of how the patients experience undergoing dental implant treatment as well as the importance of implant fixed prosthetics are for the individual (Abrahamsson et al., 2017; Johannsen et al., 2012; Kashbour et al., 2017). At first, when losing teeth, the patients describe a feeling of amputation and a negative impact on their social lives (Johannsen et al., 2012). Some blamed themselves and expressed feelings of shame of their oral

status, whilst others blamed their previous dentist for their status. The transitional period with temporary removable prothesis was frustrating with increased difficulty in chewing and a fear that the prothesis would show or fall out when socializing (Johannsen et al., 2012). The patients tended to overestimate the surgical trauma of the implant placement and were prepared for it to be a painful and difficult ordeal (Kashbour et al., 2017). On the other hand, the discomfort of the post-surgery healing period was often underestimated. Discomfort with the sutures and bleeding from the wound, swelling, pain, and bruising were the most commonly described symptoms.

In the end receiving the dental implants with fixed prosthesis improved the quality of life and chewing ability as well as a feeling that the process was worthwhile (Johannsen et al., 2012). There seems to be a mixture of feelings towards the implants and their prosthesis once in place where some view it as their own teeth and others as something foreign and not quite like their old teeth (Abrahamsson et al., 2017; Johannsen et al., 2012). There was some concern about the cost of the treatment, which was described as extensive but overall worth it (Johannsen et al., 2012). The implants were seen as a lifelong solution to replace their missing teeth (Abrahamsson et al., 2017; Johannsen et al., 2012). A variance of different thoughts about the need and expected oral hygiene procedures, has been described. Some were not prepared that the implants required such thorough and time-consuming cleaning and maintenance (Johannsen et al., 2012). The fixed prosthesis could in itself be a hinderance for proper oral hygiene, as some expressed that accessibility was a problem due to its design (Abrahamsson et al., 2017). Others described an anxiety to clean around the implants and under the prosthesis as instructed by their dental hygienist or dentist, in fear of damaging the implants or surrounding tissues. A few had not understood the importance of the daily oral hygiene procedures until being diagnosed with peri-implantitis and meeting a periodontist.

2.4 Treatment of peri-implantitis

As the current paradigm in peri-implantitis is that it is a plaque-driven disease with similarities to periodontitis, treatment options similar to those of periodontitis have been explored (Renvert & Polyzois, 2018). However, there are some key anatomical differences between a periodontal and peri-implant pocket which is believed to explain the faster progression of peri-implantitis.

Treatment of peri-implantitis comes with the challenges of the larger lesions (Carcuac & Berglundh, 2014), saucer-shaped bone defects (Heitz-Mayfield & Lang, 2010) and the threaded implant surface (Renvert & Polyzois, 2018).

2.4.1 Non-surgical treatment

Nonsurgical debridement of implants has been tested with plastic, titanium and steel curettes, ultrasonic scalers, air-abrasive devices as well as lasers (Renvert & Polyzois, 2018). The nonsurgical debridement should of course be accompanied by oral hygiene instructions and supportive therapy (Lin et al., 2019). The conventional non-surgical therapy with curettes and ultrasonic scalers shows conflicting results in terms of disease resolution (Nart et al., 2020; Renvert et al., 2009; Roos-Jansåker et al., 2017). Renvert et al. (2009) noticed no difference between using either curettes or ultrasonic scaler on clinical variables. PPD at worst site and, mean PPD at implant site showed no statistically significant change for either treatment option but showed a reduction in BOP. Roos-Jansåker et al. (2017) also reported a reduction of BOP around the dental implants, but they did however see a reduction in mean PPD and clinical attachment level (CAL), as a result of nonsurgical treatment with an ultrasonic scaler. Improved clinical variables of BOP, SOP and PPD were also noted by Nart et al. (2020) as well as a slight improvement of the bone level assessed on radiographs. It should be noted that they used a mixture of treatments together, ultrasonic scaler, curettes, air-abrasive device, and systemic antibiotics for a week. This occurs relatively commonly in studies of nonsurgical treatment (Bassetti et al., 2014; Mayer et al., 2020; Nart et al., 2020), which makes it hard to draw conclusions as to which part or parts together that has an effect. Cost effectiveness could potentially be improved by excluding one or more superfluous treatment steps. In a meta-analysis by Schwarz et al. (2015), antibiotic adjunctive to nonsurgical treatment showed significant improved weighted mean difference favoring its use in terms of BOP, but not PPD. The authors also noted that there was no significant difference between using air-abrasive device or ultrasonic scaler compared to curettes.

Few studies have investigated the effects of chlorhexidine as an adjunct to nonsurgical treatment of peri-implantitis. Chlorhexidine chips inserted into the peri-implant pocket, with 6 repeated chip placements, has been reported to provide some adjunctive effect to mechanical debridement (Machtei et al., 2012). A meta-analysis of the effect of chlorhexidine as a gel or chip inserted into

the peri-implant pocket showed a non-significant tendency to favoring the chip (Faggion et al., 2014), but further studies are required to assess this with more certainty.

Probiotics have been tested as an adjunct to mechanical debridement in both peri-implant mucositis and peri-implantitis (Fawaz Alqahtani et al., 2019; Galofré et al., 2018; Laleman et al., 2020; Peña et al., 2019). There are a few studies that have tested mainly *Lactobacillus reuteri* strains which show no or limited effect on clinical variables in peri-implant mucositis (Fawaz Alqahtani et al., 2019; Galofré et al., 2018; Peña et al., 2019) and no effect on peri-implantitis (Galofré et al., 2018; Laleman et al., 2020). Potentially other species of probiotics or combinations of different species could have a clinically relevant effect, but current evidence does not support the use of probiotics in treating peri-implant diseases.

Similarly to severe periodontitis, nonsurgical treatments and oral hygiene instructions are suggested as a first treatment option to peri-implantitis, and after an initial healing period, surgical treatment of residual or nonresponding peri-implant pockets should be evaluated (Renvert & Polyzois, 2018).

2.4.2 Surgical treatment

Most advanced peri-implantitis lesions require surgical treatment to achieve disease resolution. In general terms, the treatment consists of an elevation of a peri-implant mucosal flap, to expose the peri-implant lesion, then the granulation tissue is removed and implant surface decontaminated (Renvert & Polyzois, 2018). Mucosal flap surgery, also called access flap surgery, has been combined with various methods for decontamination of the implant surface such as titanium curettes, air-abrasive devices, titanium brushes, lasers, and removing the implant's threads (implantoplasty). It is still unclear, which method that is most effective in decontaminating the implant surface. Titanium brushes have in a randomized controlled trial shown improved PPD and BOP values, at the 6 month and 1 year follow-ups, when used to decontaminate the implant surface during surgery (de Tapia, Valles, et al., 2019). Various chemical decontaminations have also been suggested such as chlorhexidine, hydrogen peroxide, and local and systemic antibiotics (Carcuac et al., 2017; de Waal et al., 2015; Jepsen et al., 2016). Neither of these have shown any long-term benefits.

Depending on the clinician's assessment of the bone defect, if it has bone walls to warrant regenerative approaches, such can be included in the treatment e.g., filling the defect with bone substitute or autogenous bone (Renvert & Polyzois, 2018). Tomasi et al. (2019) reported in a meta-analysis that regenerative treatment had favorable results in terms of marginal bone level gain and bone defect fill compared to open flap surgery. However, there were no significant differences between treatments in terms of PPD and BOP reduction. The authors also discussed if the marginal bone level gain was clinically relevant since it is hard to distinguish graft material from newly formed bone on radiographs. On the other hand, a case report by Kim et al. (2018) analyzed a peri-implant site, which previously had received regenerative treatment with bone substitute, by post-mortem histological and radiographical assessment. This unique case showed that new bone formation and osseointegration was possible after regenerative treatment.

Another approach, to treat the peri-implantitis caused bone defect, would be resective treatment where the bone is recontoured with a bur (Renvert & Polyzois, 2018). A combination of resective treatment and implantoplasty has shown promising early results, but further studies evaluating the method is needed (Bianchini et al., 2019). Englezos et al. (2018) confirms the finding that resective surgery is an effective option and emphasize the importance that the patients comply with oral hygiene instructions. The method has the disadvantage of resulting in clinically noticeable recession of the mucosa which is an aesthetic issue in anterior implants.

Both resective and regenerative surgical procedures show promising early results, but more studies are needed to confirm these findings, assess prognostic indicators for treatment choice and fine tune the treatment protocols (Renvert & Polyzois, 2018; Schwarz et al., 2015).

2.5 Laser treatment

The most commonly researched individual wavelength of laser, for use in periodontology, is the 2940 nm Er:YAG laser, which is used to remove mineralized deposits as it has a wavelength that absorbs well in hydroxyapatite (Figure 2; Cobb, 2017; Schwarz et al., 2009). Other lasers that have been evaluated in treating peri-implantitis are diode lasers (660 nm to 980 nm) and

Nd:YAG (1064 nm) (Abduljabbar et al., 2017; G. H. Lin et al., 2018). Diode lasers and Nd:YAG absorb better in hemoglobin and melanin, which makes them more suited to be used to treat soft tissue. The CO_2 laser is mostly used for removal of soft tissue through ablation, as its use on hard tissues tend to result in excessive carbonization (Schwarz et al., 2009).

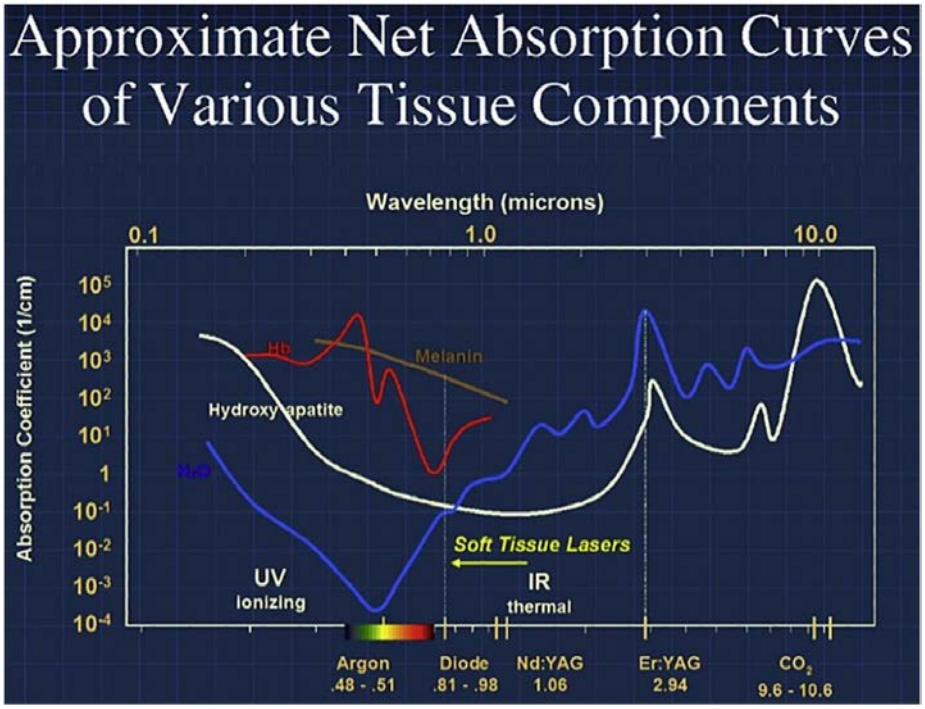


Figure 2. Overview of how different wavelengths of lasers, commonly used in periodontology, absorbs in different components of tissue. *Reprinted from (Low & Mott, 2014), with permission from Elsevier.*

It is not only where the light is absorbed that affects the treatment, how deep the light penetrates the tissues and the power settings used play a large role as well (Aoki et al., 2015). With the use of a lower power setting one can stimulate the healing of the soft tissues through photobiomodulation, also called low-level laser therapy (Aoki et al., 2015; Schwarz et al., 2009). Whereas higher power settings allow the operator to remove tissues through ablation and makes it possible for surgical uses of the laser. Together with power setting one often uses an appropriate tip to either spread the light over a larger area, in low-level laser therapy, or focus it for a narrow and selective cutting or ablative removal of tissue (Schwarz et al., 2009).

Another important setting is whether the laser uses continuous wave (CW) or pulsed mode. Conventionally it is suggested to use pulsed mode, but *in vitro* studies have seen favorable fibroblast proliferation in CW when used at comparable energy densities as pulsed with a 980 nm diode laser (Khalaj et al., 2023). Further studies are needed to explore the differences between the CW and pulsed modes, whether the even energy flow of CW or the higher peak power with microbreaks for the tissue of pulsed is preferable (8 3).

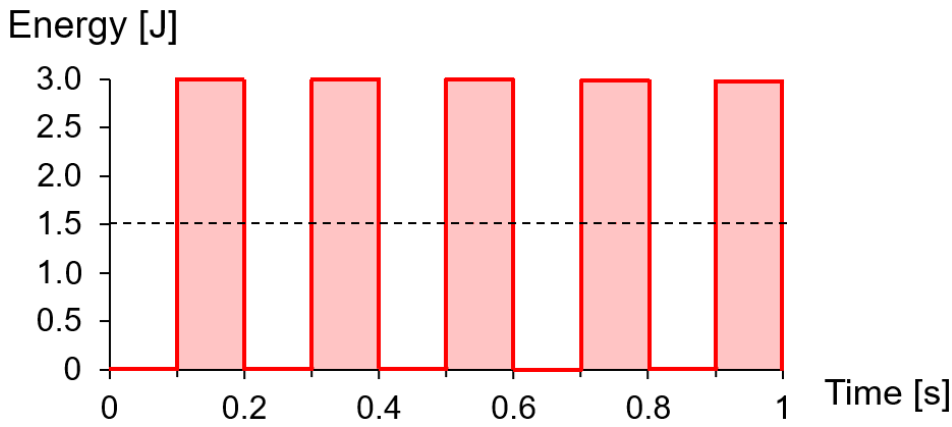


Figure 3. Comparing continuous wave (dotted line) with pulsed mode (red line) frequency 5 Hz and 50% duty cycle, both having the same average power. *Illustration by Sebastian Malmqvist.*

Erbium lasers (Er:YAG and Er,Cr:YSGG) has been used in treating both periodontitis and peri-implantitis (Alpaslan Yayli et al., 2022; Schwarz et al., 2011; Schwarz et al., 2003; Schwarz et al., 2005). In a pilot study by Schwarz et al. (2005) they noted a significantly larger average reduction in BOP around nonsurgical Er:YAG debrided implants compared to a combination of plastic curettes and 0.2 % chlorhexidine gel. Other clinical variables did not differ significantly between groups but were reduced at 6 months after treatment compared to baseline. Renvert et al. (2011) showed no significant differences between nonsurgical use of Er:YAG laser compared to an air-abrasive device. Both studies used the same device settings 100 mJ/pulse and 10 Hz (energy density 12.7 J/cm^2) (Renvert et al., 2011; Schwarz et al., 2005). Using Er:YAG laser to debride the implants during mucosal flap surgery showed no adjunctive effect at 6 months or 4 years after treatment (Schwarz et al., 2013; Schwarz et al., 2011). Another aspect to keep in mind when assessing treatment modalities is cost-effectiveness. The Er:YAG laser being a quite expensive piece of equipment,

compared to mechanical debridement, air-abrasive device, adjunctive use of chlorhexidine chip and debridement combined with local antibiotics, has that as a hurdle to overcome even if it would show a promising clinical effect, which it currently does not (Listl et al., 2015).

Nd:YAG have only been tested on peri-implant disease in a single study by Abduljabbar et al. (2017). They did not define peri-implantitis or peri-implant mucositis but used the broad term; peri-implant disease. At 3 months they reported a significant difference in the reduction of PI, BOP and PPD for the Nd:YAG laser compared to plastic curettes. This significant difference was not seen at the 6 months follow-up. This single study suggests a potentially faster healing, but more studies are needed to confirm if there is a positive effect rather than random favorable outcome in this single study.

Lerario et al. (2016) evaluated a diode laser with 810 nm, use at 1 W, pulsed with 50 Hz frequency and an energy density of 24.87 J/cm^2. Irradiating the peri-implantitis sites two times for 30 s each and repeating every 4 months of the 12-month study. In the control group 0.5 % chlorhexidine gel was applied in the peri-implant pocket. Both groups received mechanical debridement with titanium curettes and ultrasonic scaler with a plastic-coated tip as well as rinsed with 0.2 % chlorhexidine mouth rinse for 1 min and was recalled every 4 months for supportive therapy. The diode laser resulted in a significantly better clinical outcome in terms of BOP and PPD after a year compared to the control group.

Mettraux et al. (2016) used a higher power setting and did three repeats of laser irradiation per site with 810 nm laser (2.5 W, 50 Hz, 10 ms), but showed no significant clinical differences after two years. They administered supportive mechanical treatment for both groups and repeated the laser treatment for the active group at 1-month intervals and increased it gradually and individually up to 6 months. Arisan et al. (2015) did not see a significant adjunctive effect to nonsurgical mechanical debridement with the settings: energy density, 3 J/cm^2, power density 400 mW/cm2, energy 1.5 J. All three studies had few participants (27, 15, and 10) and a large amount of heterogeneity in their treatment protocols and follow-up times, which makes it hard to draw any overall conclusions.

The use of 980 nm diode laser as adjunct to mucosal flap surgery was explored by Papadopoulos et al. (2015). The laser was applied with 0.8 W in pulsed mode to disinfect the exposed implant surface. The frequency and irradiation time

were not stated in this study. This pilot study of 16 patients (8 per group) did not show any significant adjunctive effect of the 980 nm diode laser.

The use of antimicrobial photodynamic therapy (aPDT), that utilizes a 660 nm laser at 100 mW and a photosensitizer gel (phenothiazine chloride), which when activated by the light becomes antimicrobial, has not been noted to have a significant adjunctive effect (Bassetti et al., 2014). The study was a randomized controlled trial with 40 participants and was followed up at 3, 6, 9 and 12 months. Both groups received mechanical debridement with titanium curettes, submucosal cleaning of the implant with air-abrasive device, irrigation of the pocket with 3% hydrogen peroxide and oral hygiene instruction. The laser group had the gel in the peri-implant pocket for 3 min, then it was irradiated with the laser for 10s and this procedure was repeated one week later. The control group instead received minocycline hydrochloride microspheres as antimicrobial adjunctive treatment. Another study has investigated aPDT, with 670 nm at 150 mW and methylene blue as photosensitizer, as adjunct to mucosal flap surgery (Albaker et al., 2018). A single aPDT treatment session of 10 s did not lead to any significant adjunctive effect to the surgery at 6 or 12 months. These two variants of aPDT have not shown promising results, but it is possible that finding the right combination of wavelength and photosensitizer could have an effect.

In the general research field of lasers in periodontology there are a lot of review, case, and in vitro studies. Relatively few clinical studies have been performed and those that exist vary in treatment protocol and follow-up time (Cobb, 2017). There is overall a very limited amount of evidence available for assessing the effects of lasers in treating peri-implantitis directly or as adjunctive to nonsurgical or surgical therapy (G.-H. Lin et al., 2018). Future studies should be conducted as randomized controlled trials of high quality with clearly stated laser settings, treatment protocol and not combining several modalities, to be able to contribute with any meaningful insight into lasers role in peri-implantitis treatment.

3 Research aims

3.1 Overall aim

The overall aim was to evaluate laser treatment of peri-implantitis, as well as explore the patients' experiences and disease characteristics.

3.2 Specific aims

- To evaluate the safety of using a 445 nm laser on dental implants by comparing it with a laser with a 970 nm wavelength. (**study I**)
- To explore peri-implantitis patients' sensations, expectations, and experiences of dental implants, the disease, as well as undergoing treatment with laser or mucosal flap surgery. (**study II**)
- To compare the healing of peri-implantitis lesions 6 months after treatment with either diode laser or conventional mucosal flap surgery, primarily looking at equivalence for probing pocket depth and radiographic bone loss, but also differences in other clinical variables, patient reported outcomes, and inflammatory and microbial response. (**study III**)
- To assess the immune cell composition of peri-implantitis and periodontitis lesions along with their corresponding inflammatory profile in soft tissues and crevicular fluid. Additionally, to evaluate the impact of smoking on the immune-inflammatory profile in these lesions. (**study IV**)

4 Materials and methods

4.1 Study designs

To investigate the overall research aim, four studies (I-IV) were planned, covering the different aspects of the diode laser treatment and the disease peri-implantitis. Firstly, we set out to explore safety parameters in using diode laser on dental implant and to optimize them for use on patients, in an *in vitro* study (**study I**). To do this we compared two different wavelengths of diode lasers 445nm and 970nm. The main potentially hazardous effect of using lasers on dental implants is deleterious temperature increase in the surrounding tissue and secondary hazardous effect being alteration of the implant surface, with extensive melting.

Based on the findings we devised a treatment protocol used in **study II** and **III**. To gain a deeper understanding of how the patients with peri-implantitis experience the laser treatment and the disease, we interviewed 18 patients undergoing treatment in a qualitative study (**study II**). The patients' experience was also explored in a quantitative way by PROM in **study III**, were they rated their pain, discomfort, and satisfaction on a VAS.

The quantitative evaluation of the laser treatment was done in a parallel arm RCT (**study III**) with conventional mucosal flap surgery as control intervention. Apart from PROM, the evaluation consisted of clinical, radiographic, immunological, and microbiological outcomes.

The disease characteristics of peri-implantitis that were explored in this thesis were the subjective experience of having the disease, as mentioned above, as well as characterization of the immune profile from biopsies and peri-implant crevicular fluid (**study IV**). In this laboratory study we compared the immune profile of peri-implantitis with periodontitis and non-disease controls, gathered during surgeries of either lesion or implant placement in a healthy region.

4.2 *In vitro* tests of safety

In **study I** we used two wavelengths of diode laser 445 nm and 970 nm to explore how different settings and protocols affects the temperature increase around the dental implant and those wavelengths' potential for surface alterations on the titanium surface. The laser device SiroLaser Blue has those two

wavelengths incorporated in the same machine, which made it convenient to use in this study. To ensure that the actual power output from the laser was consistent over the study period and for the different tests, we measured the output with a power meter. The actual output was slightly higher than the set power and did not change meaningfully during the study. Two models were used: one for its repeatability, the glass ionomer cement (GIC) model; the other for its anatomical accuracy, the pig mandible (PM) model. Change in temperature was measured every second with four thermocouples, connected to a multimeter. The measurement points were similar on the two different models used: next to the irradiation site, halfway down the implant, apical part of the implant, and inside - as seen in Figure 4 for PM model. To account for the room temperature a fifth thermocouple was placed in the air approximately 0.5 m away from the model. The relevant thresholds for temperature increase in **study I** was 10 °C and 20 °C, based on previous studies on dental implants and temperature increase in animal models (Eriksson & Albrektsson, 1984; Trisi et al., 2015). Between tests the temperature was allowed to reset to a stable room temperature.

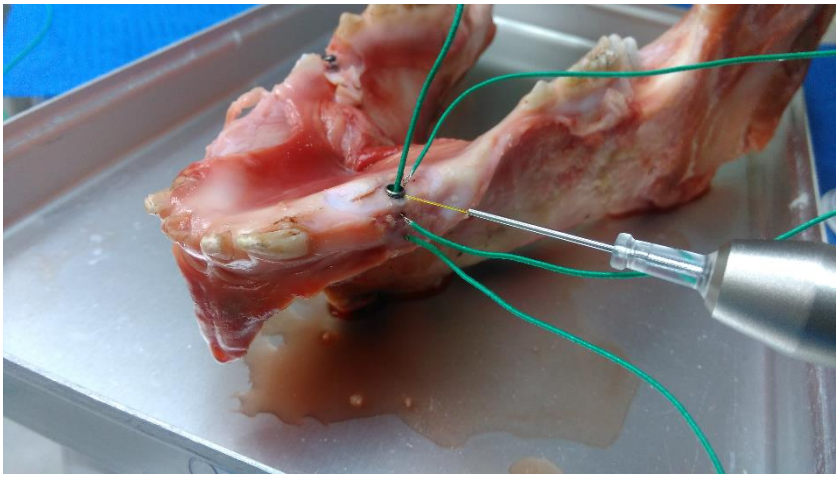


Figure 4. A dental implant placed in a pig mandible with the four thermocouples measuring the temperature at different sites of the implant. *Figure from **study I**: Malmqvist et al. 2019 CC-BY.*

4.2.1 Set up of the glass ionomer cement model

A dental implant (Astra Tech OsseoSpeed EV 3.6 × 11 mm) was placed in a block of GIC with the dimensions 28×20×13 mm and holes for the thermocouples to reach the previously mentioned sites. As GIC has similar thermal conductivity as human bone, it makes it decent material for narrowing down the tests to use on

the PM model. GIC having thermal conductivity between 0.30–0.64 W/mK (Fukase et al., 1992) whereas human cortical bone 0.68 W/mK and human bone marrow 0.42 W/mK (Feldmann et al., 2018). The parameters that were tested are detailed in Table 1 and the tests were repeated three times for both wavelengths, the laser handpiece mounted on a stand, and with 2 min of irradiation.

Table 1. Overview of the tests of different parameters on the GIC model, which were repeated three times each.

No.	Purpose	Power setting [W]	Distance [mm]	Irradiation mode
1	Different power settings	0.5, 1.0, 1.5 & 2.0	1	CW
2	Different irradiation modes	0.5 (pulsed mean 0.51)	1	CW & pulsed 10 Hz 17% duty cycle
3	Different distances	1.0	0, 1, 2, 3	CW
4	Manual sweeping motion and angled apically (20° from the implant) similarly as used on patients	1.0	0–1	CW
5	Manually applying 20.0 ml of water evenly throughout irradiation	1.0 & 2.0	1	CW
6	30s irradiation then application of 5.0 ml water × 4	1.0	1	CW
7	30s irradiation then application of 2.5 ml water × 4	1.0	1	CW
8	15s irradiation then application of 2.5 ml water × 8	1.0	1	CW

Abbreviations: GIC, glass ionomer cement; CW, continuous wave;

4.2.2 Set up of the pig mandible model

The PM model had the same type of implant, as the GIC model, placed in an edentulous region of the mandible and even though it is a bone level type it was placed 2mm above the bone level to have an area to irradiate. For this model three repeats of test no. 1 (Table 1) with only 1.0 W power were done to compare the models and then three clinical simulations with movement of the laser fiber like test no. 4 together with interval and water from no. 6.

4.2.3 Surface alteration tests

To better discern potential surface alteration titanium discs were used, with both machined and acid-etched surfaces, instead of dental implants. The surface was examined with a scanning electron microscope (SEM) (FEI Nova 200 Dual Beam; located at Albanova NanoLab, KTH, Stockholm). The discs had the dimensions 10 mm diameter and 2mm thickness and were marked to facilitate matching the before and after irradiation pictures (Figure 5). Magnifications ranged from 75× (500 µm scale bar) to 25000× (1 µm scale bar). Before taking the control pictures the discs were cleaned in an ultrasonic bath filled with isopropanol. Discs with both surface structures were irradiated with the 445 nm laser at 1 mm distance with 2.0 W power setting in CW mode for 4 min.

Figure 5. The two kinds of titanium discs, machined and acid-etched, used for the surface alteration test with markings to easier align the before and after SEM pictures. *Figure from **study I**: Malmqvist et al. 2019, CC-BY.*

4.3 Study populations

All participants were recruited from the same specialist dental clinic (Danakliniken Specialisttandvård, Stockholm, Sweden). Patients referred to the clinic, between September 2019 to November 2021, for surgical treatment of peri-implantitis were screened for inclusion in **study III**. Inclusion criteria were at least one dental implant with peri-implantitis (PPD ≥ 6 mm, BOP/SOP site, ≥ 2 mm RBL) and be ≥ 18 years old. Participants were excluded if they had received any antibiotic treatment or peri-implantitis treatment 6 months prior to baseline, as well as any contraindication for performing oral surgery. Based on a power analysis for equivalence in change of PPD between laser treatment and surgery

as well as with a margin for dropouts, 50 participants were planned to be included in the study. However, due to the coronavirus disease 2019 (COVID-19) pandemic we recruited the eligible patients within the above-mentioned time interval.

Out of the pool of patients having received treatment in **study III**, participants were strategically selected for interviews in **study II**. This was done to try to improve the richness of the interview answers by selecting participants with different ages, disease severity and treatment received. Recruitment took place between October 2019 and February 2021 and interviews was stopped when saturation of the interview answers was reached, and this decision was taken after discussions in the research group in consensus.

For **study IV** participants were recruited from June 2019 to March 2022. The peri-implantitis group had similar criteria as in **study III** but were to have at least 3mm bone loss to include a bit more established disease. Periodontitis group had to have stage III-IV periodontitis. Non-disease control group had to have periodontally healthy conditions, defined as no BOP, < 4mm PPD, and no bone loss, in the region of sampling. Additionally, exclusion criteria for all groups were: having used anti-inflammatory medicine in the last 2 weeks, antibiotics within 3 months, known genetic diseases affecting the oral cavity, and oral cancer.

4.4 Laser treatment and mucosal flap surgery

Patients who passed the screening for eligibility for **study III** were assigned to either of the two treatment groups via block randomization stratified for initial mean PPD around the worst affected dental implant. Most of the peri-implantitis patients in the surgery group in **study III** were included in **study IV**. There were, however, some patients that had such severe disease that the prognosis were too poor or that at least one of their dental implants were slated for extraction, that were not included in **study III** but were eligible for **study IV**. Some of the participants in **study III** were not included in **IV** due to scheduling conflict, as gathering and processing the biopsies in an as similar as possible way required multiple research group members present.

In **study III** all participants were given oral hygiene instructions after baseline examination, after treatment, at the early follow-up, and after the 6 months follow-up, which were individually adapted based on their abilities and oral

situation. Participants in both groups were instructed to rinse with 0.2% chlorhexidine solution until their first follow-up visit.

The laser treatment consisted of removal of diseased epithelium, granulation tissue, and sub- and supramucosal biofilm, around the affected dental implant, with a 970 nm diode laser (SiroLaser Blue) and steel curettes. Prior to treatment, localized anesthesia was given. Power setting used was 1.2 W in CW mode with a 320 μm fiber diameter and throughout the treatment sterile saline solution (0.9% NaCl) was manually applied, to keep the overall temperature in the surrounding tissue in check, based on the findings in **study I**. The laser tip was continuously moved back and forth during activation to avoid potential local thermal deleterious effects.

As control intervention conventional mucosal flap surgery was carried out under localized anesthesia. The mucoperiosteal flap was elevated after a reverse bevel incision, inflamed tissue was removed, and the exposed surface of the dental implant was brushed with a titanium brush (NiTi Brush Pocket). In **study IV** the same treatment was performed but could also include bone recontouring and post-treatment use of antibiotics, as the sampled tissue or PICF were not affected by those extra steps, although would meriting exclusion from **study III**. Suture removal was performed between 7 to 12 days post-surgery.

4.5 Capturing the patient's experiences

4.5.1 Qualitative patient experience

The methodology utilized in **study II** were quantitative content analysis (Graneheim & Lundman, 2004), which has an epistemological approach that is a combination of phenomenology and hermeneutics (Graneheim et al., 2017). The analysis of the latent and manifest content was done at a low to moderate level of abstraction and presented in a concrete descriptive way.

The semi-structured interviews were done between October 2019 and February 2021, and used an interview guide with questions covering three themes (Table 2). These covered both the subjective disease characteristics and the opinions of the laser treatment, among those that received that.

Table 2. The interview guide used in **study II** with the three themes of the interviews. As the interviews were semi-structured there was a possibility for the interviewer to ask spontaneous follow-up questions.

Theme	Topic of the questions
Dental implants	Reason for receiving dental implant(s)
	Period of having dental implant(s)
	Opinion of having teeth
	Dental implant vs removable prosthesis
	Information about implant maintenance
Peri-implantitis	Time of receiving the diagnosis
	Reaction to diagnosis
	Knowledge – previous and now
	Notice the disease
	Perceived reasons for getting peri-implantitis
Treatment of peri-implantitis	Expectations beforehand of the treatment
	Describing the treatment experience – before, during and after
	[If laser:] Difference between this and previous surgeries
	Information about the treatment
	Perception of the implants post-treatment
	Change in implant maintenance
	Recommending the treatment
Other	Anything else you want to mention about your implants?

Interviews took between 20 to 40 min and were conducted in an office setting by two members of the research group that were not involved in the clinical examinations or treatments in **study III**. Transcription and analysis of the interviews were done in batches of 5-7 interviews per batch, to improve the possibility to ask follow-up questions to further the richness of the material. The interview material was analyzed separately by the group members and then the finalized categories and subcategories with representative condensed quotes were decided upon jointly.

4.5.2 Quantitative patient experience

To compliment the qualitative findings of the patient experience of peri-implantitis and its treatment, PROMs was graded by the participants on a 100 mm visual analogue scale (VAS) covering the domains of pain, discomfort, and satisfaction (**study III**). Pain and discomfort were assessed at baseline, directly after treatment, at the early follow-up visit (7-12 days after treatment), and at the 6 months examination. Satisfaction was at the same timepoints except baseline, as they had not received any treatment yet. The questions were explained and read verbally to the participants, who then were given time to grade their experiences on the VAS in their own time without interference. The participants could also ask for additional explanations during their grading.

4.6 Quantitative comparison of the treatments

All outcomes were measured at baseline and 6 months after treatment, except for PROM which had additional measuring timepoints. The patients were not blinded to which treatment they received and only RBL and analysis of immunological markers were blinded for the assessors.

Clinical variables were PI, BOP, SOP, and PPD and were measured on four sites per implant. They were analyzed on full mouth and affected implants levels. RBL was measured on periapical radiographs and summarized as a mean for the implant and per site - mesial and distal. The patients need for potential further care or follow-up were noted at the 6 months follow-up based on the healing of the treated area. Mean change in PPD and RBL were regarded as primary outcomes and assessed against a predefined zone of equivalence of ±1.0 mm for the mean difference in change to follow-up between the treatments. Differences in clinical variables, RBL, levels of inflammatory markers, and $\log_{10}$ counts of selected periodontal pathogens were treated as secondary outcomes.

Stimulated saliva and PICF were collected from the participants to analyze for levels of IL-1β, MMP-8, and S100A8/A9. Stimulated saliva was collected during 5 min of chewing of a piece of paraffin. PICF was sampled by paper strip inserted for 30 s in the peri-implant pocket of the implant with the severest RBL, Periotron value was measured and registered directly after, and then the paper was placed in an Eppendorf tube. The procedure was done both mesially and distally. Both exudates were stored on ice in a polystyrene box until aliquoted and frozen at -80 °C until analysis. Cytokines were measured with enzyme-

linked immunosorbent assay (ELISA) kits and read in a microplate spectrophotometer.

Submucosal samples of the biofilm were collected to assess the $\log_{10}$ counts of *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Tannerella forsythia*, and *Treponema denticola* by means of quantitative real-time polymerase chain reaction (qPCR), as described by Greenwood et al. (2020). The bacterial species were selected as a proxy for a dysbiotic pathogenic biofilm as they are classically chosen periodontal pathogens which has also been linked to peri-implantitis (Charalampakis & Belibasakis, 2015; Schwarz et al., 2018). Medium sized sterile paper points were inserted for 30 s in the same peri-implant pocket as for PICF, both mesially and distally, and then pooled together in an Eppendorf tube.

4.7 Characterizing the immune profile

4.7.1 PICF and GCF

To characterize the immune profile soft tissue biopsies, PICF, and gingival crevicular fluid (GCF) were used.

PICF and GCF were collected for 30 s with paper strips from the worst affected site in the area scheduled for surgical treatment for the disease groups and the closest healthy periodontal pocket in the non-disease group. The strips were placed in Eppendorf tubes and stored on ice during continued sampling and transportation. The tubes were frozen and stored at -80 °C until analysis. The analysis was done with multiplex immunoassay of the panel of biomarkers in Table 3, all of which has been linked to peri-implantitis and periodontitis disease activity.

Table 3. Panel of biomarkers used for testing PICF and GCF, including which cell that produces them and their function (Chmielewski & Pilloni, 2023; Fernandes & Gomes, 2016; Flores et al., 2022; H. Li et al., 2021; Luo et al., 2013; Zouali, 2017). Red marking for pro-inflammatory and green marking for anti-inflammatory.

Biomarker	Produced by	Function
IL-1β	Macrophages	Increased OC activation & formation. Modulating inflammatory response, pyrogen, pain hypersensitivity, cell proliferation
IL-4	Th2 cells & NK cells	Decreased OC generation, RANK down-reg.
IL-10	Monocytes & Th2 cells	Decreased RANK signaling and OC formation. Anti-inflammatory agent and TNF-α regulation.
IL-17A	Th17 cells	Production of chemokines which recruits neutrophils and monocytes, promotes inflammatory responses of IL-1β and TNF-α
IL-23	DCs & epithelium cells	Stimulates Th17 cell mediated inflammatory response
G-CSF	Endothelium cells & macrophages	Neutrophil stimulation and recruitment
TNF-α	Epithelium cells, DCs, fibroblasts, macrophages & neutrophils	Mobilization of OC precursors and activation. Immune cell signaling and modulation and response to bacterial LPS
BAFF	DCs & macrophages	Promotes B cell survival, which increases expression of RANKL and OC activity.

Abbreviations: IL, interleukin; OC, osteoclast; Th, T helper; RANK, receptor activator of nuclear factor κ B; TNF-α, tumor necrosis factor alpha; DC, dendritic cell; G-CSF, granulocyte colony-stimulating factor; LPS, lipopolysaccharides; BAFF, B-cell-activating factor; RANKL, receptor activator of nuclear factor κ B ligand.

4.7.2 Soft tissue biopsies

For the peri-implantitis and periodontitis groups, soft tissue biopsies of respective lesion were harvested, during mucosal flap surgery or extraction of implant or tooth, from the same site that was sampled for PICF or GCF. For the non-disease control group, the participants were to receive a dental implant adjacent to a periodontally healthy tooth and the soft tissue biopsy was harvested from part of the periodontal pocket of that tooth during flap elevation. The biopsies designated for histology and multiplex immunoassay were placed in tubes and snap-frozen on dry ice, while the biopsies for the fluorescence-

activated cell sorting (FACS) analysis were placed in tubes with RPMI (Roswell Park Memorial Institute) 1640 medium and placed on regular ice during transport.

To get an overview of the immune response in the tissues, they were examined histologically. Tissue samples from each group were embedded in optimal cutting temperature compound (OCT), frozen to -80 °C and then 7 µm sections were cut and stained with hematoxylin and eosin (H&E).

The characterization of the biomarkers in soft tissues were done by first lysing the tissue and homogenizing it. Then running a multiplex immunoassay of the same markers as for the crevicular fluids (Table 4). For both histology and multiplex analysis, the samples were stored in a -80 °C freezer between collection and analysis.

For the FACS analysis the biopsies were digested and filtered to a single cell suspension the same day as they were collected, without intermediate freezing. The suspensions were then stored in a liquid nitrogen freezer until staining and FACS analysis. The detailed staining procedure including antibodies used can be found in **study IV**, but broadly staining for live/dead cells, single/multiple cells, $CD45^+$, and then various other antigens. How the cell populations were defined can be seen in Table 4.

Table 4. Overview of how the $CD45^+$ cell types were defined in the FACS analysis.

Cell type	**Defining antigen(s)**
T cells	$CD3^+$
B cells	$CD19^+HLA\text{-}DR^+$
Neutrophils	$CD15^+$
APC (macrophages and DCs)	$CD64^+CD11c^+$ $CD64^-CD11c^+$ $CD64^+CD11c^-$

Abbreviations: CD, cluster of differentiation; FACS, fluorescence-activated cell sorting; HLA, human leukocyte antigens; APC, antigen precenting cells; DC, dendritic cell

4.8 Statistical analyses

Study I and **II** only included descriptive statistics and for that Microsoft Excel was used. Data analysis in **study III** was done with JASP (JASP Team, 2023) and IBM SPSS, whereas GraphPad Prism and IBM SPSS were used in **study IV**. In **study III** and **IV** level of significance was set at α = 5% (0.05). Two one-sided

tests (TOST) procedure, which compares the 100-2×α % CI of the difference between groups, was used to test for equivalence of the primary outcomes in **study III**, with a predefined zone of equivalence of ±1 (Lakens, 2017; Lakens et al., 2018). To test for differences between groups, in **study III**, among continuous variables Mann-Whitney U-test or independent samples Student's t-test were used and change within groups Wilcoxon signed-rank test or paired samples Student's t-test. In **Study IV** we used Mann-Whitney U-test for comparing two groups and Kruskal-Wallis test with a Dunn's post hoc-test for comparing multiple groups. For both **study III** and **IV**, Chi^2 test or Fischer's exact test was used for nominal data. Spearman rank correlation coefficient was used in **study IV** to correlate clinical and laboratory variables.

4.9 Ethical considerations

The four studies which this thesis is based upon are done in accordance with the Declaration of Helsinki (World Medical Association, 2013). Ethical approval was obtained for the three studies (**II**, **III**, and **IV**) in this thesis that involved human participants. For **study II** and **III** ethical review and approval was granted by the regional ethics committee in Stockholm (Dnr: 2015/822-31/2) and while for **study IV** it was the Swedish Ethical Review Authority (Dnr: 2019-01381) that reviewed and approved the ethics.

The participants gave their informed written consent after both verbal and written information about the respective study they were eligible to join. Of utmost importance was to stress that participating in either study was done voluntarily and that they were allowed to back out of either study if they did not want to continue for whichever reason. At the end of **study III**, those that had not responded to either treatment, were offered compensatory treatment in the form of the other treatment they had not received or re-treatment, depending on what was believed to be best for the individual patient.

For the three studies involving patients a challenge arose in the spring of 2020 in the form of the COVID-19 pandemic (J. Li et al., 2021), affecting both recruitment but also it required some ethical considerations. As Sweden did not completely lock down, we had a dialogue with each participant about if and how they wanted to proceed in the study. During the initial emergence of the pandemic in the spring of 2020 we postponed the scheduled visits until the summer when the first wave of spread had eased. We also made adaptations to in scheduling

so that the oldest participants could travel outside of rush hour, if they needed to travel by public transportation.

Transparency and standardized reporting are important parts of ethical research. **Study II** was performed and reported in accordance with the Standards of Reporting Qualitative Research (SRQR; O'Brien et al., 2014), by the Enhancing the quality and transparency of health research (EQUATOR) Network. **Study III**, as it was an RCT, was conducted and planned to be disseminated based on Consolidated Standards of Reporting Trials (CONSORT) guidelines (Schulz et al., 2010). For increased transparency, the study was also registered in the clinical trials registry ClinicalTrials.gov.

5 Results and discussion

5.1 Safety in using diode lasers on dental implants

There were some key differences as to the heat from the laser irradiation spread in the two models. In the PM model the heat spread quicker down to the midway point of the implant and the maximum temperature at the different measuring points were lower than in the GIC model. This is probably due to the larger mass and volume of the PM, so that the heat could spread out further acting as a more efficient heatsink to the dental implant and probably more in line with the real clinical situation in a patient's mouth. However, the GIC model provided insight in how the temperature could be controlled and affected by different settings and procedures.

5.1.1 Glass Ionomer Cement Model

Both the 445 nm and the 970 nm wavelengths yielded similar maximum temperatures and time to the thresholds of +10 °C and +20 °C in the static tests (test No. 1 in Table 1) in the GIC model.

In comparing using CW mode at 0.5 W with pulsed mode 3.0 W, 10 Hz, and 17% duty cycle i.e., similar average power of 0.51 W, the CW showed lower temperature increase at all measuring points except the apical. The higher peak power could probably be the cause of the higher temperature increases. Interestingly, the 445 nm used in contact with the implant resulted in a higher temperature than the 970 nm, although for the other distances (1.0, 2.0, and 3.0 mm) the wavelengths performed similarly. Using a sweeping motion and angle like the ones used in a real setting on patients resulted in a slightly higher increase in temperature at the midway and apical points, while the inside had a lower increase. This is expected as the laser fiber is angled apically and thus would reasonably increase the amount of energy in that direction. The temperatures also fluctuated at all sites, which is as anticipated when moving the handpiece as the energy is spread out over a larger area.

With continuous applying cooling water during irradiation, we were able to keep the temperature increase below 10 °C during irradiation with 1.0 W power in CW mode for all the surface measuring points, except the apical one for 970 nm. For 2.0 W power and both wavelengths only the midway measuring points were below the 10 °C limit. This indicates that 2.0 W is probably too high of a power

setting, which risks damaging the surrounding bone and soft tissues (Eriksson & Albrektsson, 1984). Irradiating in 30 s intervals with either 2.5 ml or 5.0 ml of cooling water between repetitions yielded a temperature reduction of between approximately 40-70% and 50-90% respectively, depending on the measuring point. The temperature increase for 15 s intervals were in general lower than the longer 30 s interval but had a clearer trend of a gradual increase between each irradiation interval. Based on this we noted that at least 5.0 ml of cooling water should be used if not applied continuously and preferably not more than 15 s irradiation interval in the GIC model.

5.1.2 Pig Mandible Model

As for the GIC model the two wavelengths behaved similarly in the static tests in the PM model as well. The 445 nm wavelength were quicker to reach the 20 °C threshold and for the outside measuring points and reached higher temperatures for these points after 30s of continuous irradiation and continuing being higher through the rest of the 120 s irradiation session.

Based on the GIC tests and the static tests in the PM we did a clinical simulation test for both wavelengths, 1.0 W power, 30 s irradiation intervals, sweeping manual motion of the laser fiber, and with applying 5.0 ml of cooling water between intervals. This treatment protocol was able to keep the temperature in check (Figure 6) after 4 repeated intervals. There was a tendency towards a gradual increase in temperature between each repeat so as a clinical recommendation this should be seen as an upper limit of how long one can use a laser with these wavelengths on a dental implant. Bach et al. (2000) showed that there were no adverse outcomes in patients with dental implants up to 5 years after using a 810 nm diode laser in CW mode at 1.0 W power with a maximum of 20 s irradiation time. Another kind of laser, the Er:YAG, has also been used in treating peri-implantitis without reported adverse effects at similar average power 1.0 W (100mJ/pulse, 10Hz), with continuous water irrigation (Schwarz et al., 2011). Rios et al. (2016) suggested using 968 nm diode laser for implant decontamination and could *in* vitro show temperatures below 10 °C threshold for 1.65 W and 1.98 W in CW mode when used for a maximum of 10 s and with air cooling. Kong et al. (2023) tested 810 nm and 1064 nm lasers in pulsed mode and reported that with an average power of 1.0 W the time to reach +10 °C were above 30 s. Our findings are in line with the overall evidence in this research field

that demonstrate the importance of short intervals of continuous irradiation and rigorous cooling to ensure a safe treatment for the patient.

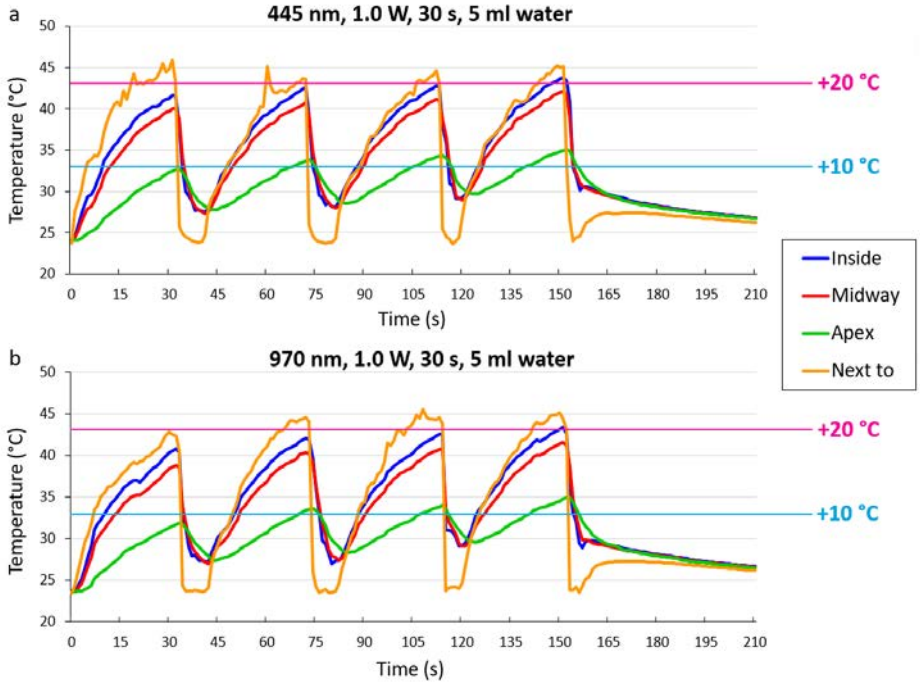


Figure 6. Clinical simulation tests with both wavelengths and thresholds marked in blue for +10 °C and pink for +20 °C. The temperature was measured every second, by thermocouples connected to a multimeter, at four points on the dental implant: inside, midway down the implant, apex and next to the irradiation site. *Figure from **study I**: Malmqvist et al. 2019, CC-BY.*

5.1.3 Surface Alterations

Neither machined surfaced nor sandblasted and acid-etched showed any signs of surface alterations after 4 min of irradiation with the 445 nm wavelength at 2.0 W power setting in CW mode (Figure 7 and 8). In contrast, Pergolini et al. (2023) showed what they claim to be thermal damage to a dental implant with sandblasted surface when using 445 nm at 2.0 W both in contact with the surface an non-contact. As they used different magnifications and sites for the control SEM pictures and after irradiation, an outsider reviewing their work cannot make an adequate comparison. They instead highlighted their suggested setting of 0.5 W pulsed mode with 50% duty cycle (average power 0.25 W). It would have been interesting to see 0.25 W in CW mode to compare but also a

stepwise and even increase of power to cover the gap between 0.25 W and 2.0 W to get an idea where the limit for developing alterations is.

Romanos et al. (2000) stated that a Nd:YAG (1064 nm) laser at 2.0 and 4.0 W in CW mode caused melting and damage to titanium discs, while a 980 nm diode laser in CW mode at 5.0, 10.0, and 15.0 W did not show any signs of alterations, both wavelengths use in contact. Both Deppe et al. (2021) and Giannelli et al. (2015) noted for 445 nm and 810 nm, respectively, that using the lasers in contact with the titanium surface caused scratches on the surface and residue of the laser fiber, which could potentially explain the variances between studies on which wavelengths that causes alterations.

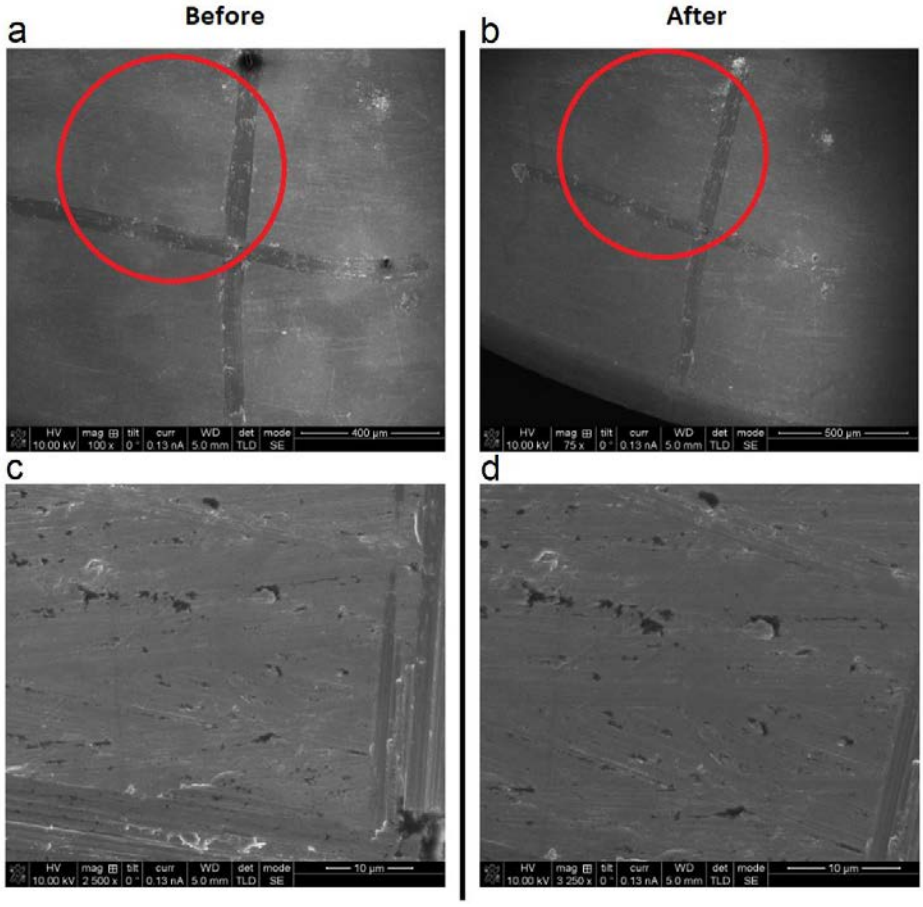


Figure 7. Machined surfaced titanium discs before (a & c) and after (b & d) 4 min of 2.0 W 445 nm laser in CW mode. Each row has comparable level of magnification in their SEM pictures. The red circle indicates area that has been magnified in the lower row (c & d) and the spot where the laser was used. *Figure from* ***study I****: Malmqvist et al. 2019, CC-BY.*

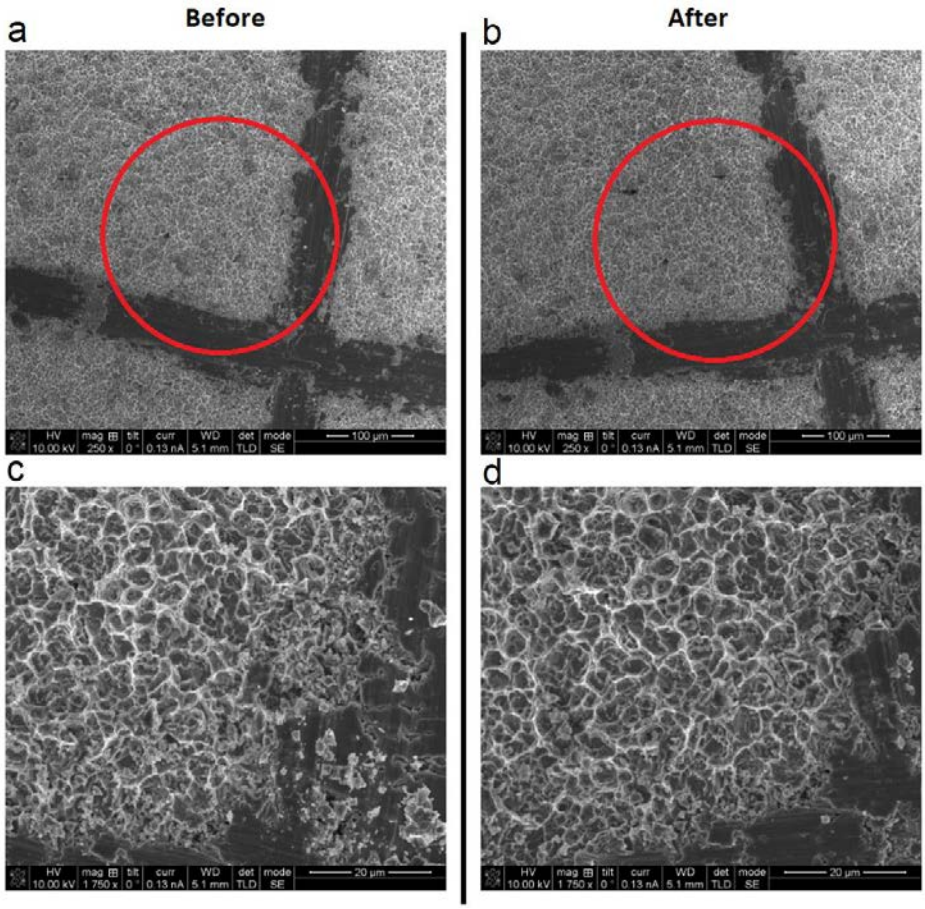


Figure 8. Sandblasted and acid-etched titanium discs before (a & c) and after (b & d) 4 min of 2.0 W 445 nm laser in CW mode. Each row has comparable level of magnification in their SEM pictures. The red circle indicates area that has been magnified in the lower row (c & d) and the spot where the laser was used. *Figure from **study I**: Malmqvist et al. 2019, CC-BY.*

An important aspect in assessing the potential surface alterations of different wavelengths remains unknown – how these altered surfaces affect the clinical situation *in vivo* in terms of possible re-osseointegration and recolonization of pathogenic bacteria. An altered chemical composition (increased concentration of oxygen) and a rougher surface topography has been noted after use of Er,Cr:YSGG (2780 nm) and 940 nm diode laser (Fahlstedt et al., 2023) with water cooling during irradiation with both. In theory, an increased oxide layer on the dental implant could lead to a more hydrophilic surface and together with an increased surface roughness might promote osseointegration (Kilpadi & Lemons,

1994; Wennerberg & Albrektsson, 2010). Kong et al. (2023) demonstrated that surface alterations after use of Nd:YAG (1064 nm) laser promoted cell growth and adhesion of human gingival fibroblasts, however they stress the fact that a lot more research is needed to draw conclusions of the surface alterations role in a clinical setting. A potential downside of promoted cell growth could be increased bacterial growth, but it remains to be seen.

5.2 Recruited study populations

In the time span of September 2019 to November 2021, 33 potential participants were screened to receive treatment for peri-implantitis with either 970 nm diode laser or mucosal flap surgery for **study II** and **III**. 29 patients received treatment (15 laser and 14 surgery), 18 (9 laser and 9 surgery) out of those were interviewed in **study II**, and 26 (14 laser and 12 surgery) completed the 6 months follow-up. Between June 2019 to March 2022 patients undergoing surgeries, specified in section **4.7.1** and **4.7.2**, were asked to participate in **study IV** and 62 patients consented to give biopsies and PICF or GCF.

5.2.1 Treatment cohort

The mean age of the 26 participants that completed **study III** were 65.8 ± 13.5 years (range 30-84 years). There were no statistically significant differences between the treatment groups in age, number of implants and teeth, gender, smoking, as well as implant brand and position. A majority of the treated implant (62.1%) were different types of Straumann implants, and all included implants had a modified rough surface with screw-retained prosthesis. There were, however, some numerical differences of note such as that the laser group had on average fewer teeth (14.6 ± 8.7) and more dental implants (4.4 ± 2.2) than the surgery group (20.8 ± 6.1 teeth and 3.4 ± 2.4 dental implants). This could potentially be due to a more extensive history of periodontitis in the laser group, which is a risk factor for peri-implantitis (Ferreira et al., 2018). Non-smokers were 5 in each group, but smokers and former smokers differed, with 7 (50%) former smokers and 2 (14.3%) current smokers in the laser group whereas the numbers were reversed in the surgery group with 2 (16.7%) former and 5 (41.7%) current smokers. As smoking has been reported to worsen both periodontitis and peri-implantitis and the healing after treatment of them (Apatzidou, 2022).

5.2.2 Interview cohort

Out of the 29 patients that received treatment, 18 was interviewed, with 9 from each treatment group. They were between 33 and 84 years old and there were 14 women and 4 men. The participants reported that their dental implants had been in use from 3 to more than 20 years and the implant placement surgery were done in Sweden, Italy, Lithuania, and Spain.

5.2.3 Immune profile cohort

In total 62 patients, 43 women and 19 men, were recruited for **study IV** and they had a mean age of 66.1 ± 11.3 years. The distribution of participants between the groups were 15 in the peri-implantitis group, 23 in periodontitis group, and 24 in the control group. Naturally the peri-implantitis group had more dental implants 4.8 (±2.6) and fewer teeth 13.7 (±9.3) than the other two groups, the periodontitis group having 0.7 (±1.6) implants and 21.8 (±6.8) teeth, while the controls had 1.1 (±1.6) implants and 23.3 (±3.6) teeth. The periodontitis group had more smokers 47.8% compared to 26.7% for the peri-implantitis group and 8.3% for the controls. The peri-implantitis patients did, however, have a significantly deeper mean PPD of 8.75 (±1.49) mm while the periodontitis patients had 7.56 (±1.09) mm (p=0.025). The different analysis had varying numbers of participants (Table 6).

Table 6. Number of sampled sites for each analysis and divided per group.

Group	Histology	Soft tissue multiplex	PICF/GCF multiplex	FACS
Peri-implantitis	3	5	12	8
Periodontitis	3	9	16	8
Controls	3	6	16	7

Abbreviations: PICF, peri-implant crevicular fluid; GCF, gingival crevicular fluid; FACS, fluorescence-activated cell sorting.

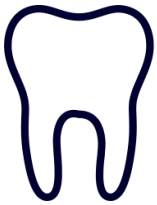
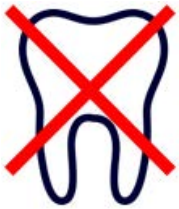
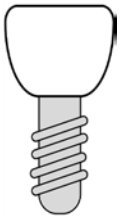
5.3 The patient's experiences

5.3.1 Losing teeth & living with dental implants

There were a broad range of experiences surrounding going through loss of a tooth and then receiving a dental implant (Table 7). Overall, keeping one's own teeth were preferable and they were tied to psychosocial well-being. The

participants expressed positive associations with having a fixed replacement of teeth in the form of dental implants, especially compared to removeable dentures. However, there were also negative experiences, which is important to take into consideration and to address when planning for dental implant therapy.

Table 7. Overview of the categories and subcategories of how the participants experienced the process of needing and receiving a dental implant.

	**Having your own teeth**	*Esthetics* *Well-being* *Healthy feeling* *Facilitates chewing* *Fresh feeling* *Nice smell* *Self-esteem* *Social life*
	**Loosing teeth**	*Psychologically tough* *Sadness* *Avoiding opening the mouth* *Losing a part of yourself* *Removeable prosthetic – unnatural & affected taste*
	**Dental implants**	*Regained chewing ability* *Looks like teeth* *Stable solution* *Feels like teeth*
		No difference *Another feeling* *Numb* *Different surface* *Extensive journey* *Stiff, cold feeling in the winter*
		Prefer teeth *Avoiding more implants* *Harder to clean* *Food impaction* *Increased bite force, negative for the teeth* *Costly*

Note: Pictures used in this table are created by the author or licensed with Creative Commons CC0.

The negative feelings of amputation and shame in losing teeth, and the positives of receiving dental implants, are in line with previous qualitative research on this topic (Johannsen et al., 2012). Losing teeth regardless of the underlying cause is associated with reduced quality of life (Saintrain & de Souza, 2012), mainly through psychosocial effect. Receiving dental implants can have a positive impact on chewing ability and overall esthetic satisfaction, which has been seen quantitatively as well by Derks et al. (2015). It should be noted when interpreting the negative associations found in **study II** that the participants had already received a diagnosis of peri-implantitis i.e., had developed complications in need of specialist care with at least one dental implant.

5.3.2 Peri-implantitis

Regarding potential perception of the disease peri-implantitis, there were two sides – those that felt symptoms and those that did not. The symptoms described were classical signs of inflammation such as swelling, bleeding, soreness, and pulsating feeling. There were those that in retrospect could acknowledge that they had symptoms but ignored them to avoid having to visit the dental care. While others mentioned that they felt greater symptoms from other conditions like temporomandibular pain and fractured neighboring tooth, which potentially masked the peri-implant sensations. For the patients lacking subjective symptoms, the diagnosis came out of nowhere as a shock. They expressed the desire to know more about the disease beforehand as they had not even considered that the dental implant could develop disease.

When presented with the diagnosis and its consequences, the participants described either a positive mental approach or a negative one. Some reasoned rationally around the situation and put their trust in the specialist care, some were even inspired to improve their oral hygiene procedure to contribute in whichever way they could increase the chance for a successful treatment outcome. The negative feelings described were that of unease, worry, fear, and frustration. After years of treatments with invested time and money, for there to arise another oral problem, one can understand the frustration of the patients. Some blamed themselves while others blamed their previous dental caregivers, which is in line with the findings by Abrahamsson et al. (2017). They also confirmed that there seems to be some that notice their peri-implant disease before their dental caregivers do. Few quantitative studies have explored the patients' perceived symptoms of peri-implantitis. Alqahtani et al. (2019)

compared the self-perceived oral symptoms of peri-implantitis among 100 smokers (cigarettes and waterpipe) and nonsmokers, in a questionnaire. Disregarding group, their participants reported the following symptoms: 66% felt that the gums around their implant hurt, 34% noticed bleeding around the implant, and 11% thought that their implant felt loose. This is an area in need of more research and importantly with a methodology to capture and/or follow dental implant patients before they receive a peri-implantitis diagnosis, as this introduces bias which probably affects the respondents' answers.

5.3.3 Treatment of peri-implantitis

Expectations before either treatment were to keep the implant and become free from infection. There were also some concerns about the esthetics i.e., if the implant would become more visible.

Perceptions and sensations of the treatments had some likenesses to each other. Anesthesia was described as the worst part of both treatments. This is in line with findings in quantitative research as well, that the participants rated the localized anesthesia as most discomfortable part of periodontal treatment (Fardal et al., 2002). Many did not feel or perceive anything special during either treatment. Afterward no or some soreness were reported from the respondents. Some laser-specific experiences were a slight burnt smell, unsettling sound from the laser machine, and a prickling feeling, during the treatment. For the surgery the main unique complaint from the patients were the sutures. That the sutures were a source of discomfort for the participants in the surgery group could also be seen in **study III**, as they rated their discomfort significantly higher during the first week of healing, at 24.9 ± 12.8 mm on the VAS compared to the laser group's 12.0 ± 12.6mm (p=0.010) (Figure 8). The participants rating of pain for the FWH followed the same pattern, as the discomfort, with surgery reporting 28.5 ± 25.7 mm and laser 15.7 ± 17.7 mm on the VAS (p=0.068) (Figure 9). Within the surgery group the rating of pain increased significantly when comparing directly after treatment (still under localized anesthesia) and rating of the FWH (p=0.026) The perception of discomfort varied more between the participants than the pain, except for rating the first week of healing, which can be seen in Figure 9 & 10. Level of satisfaction remained stable in the laser group, while in the surgery group it decreased statistically significantly from 96.6 ± 5.2 mm to 87.7 ± 17.4 mm after the FWH (p=0.022). This is likely also due to the sutures and is in general a quite minor reduction.

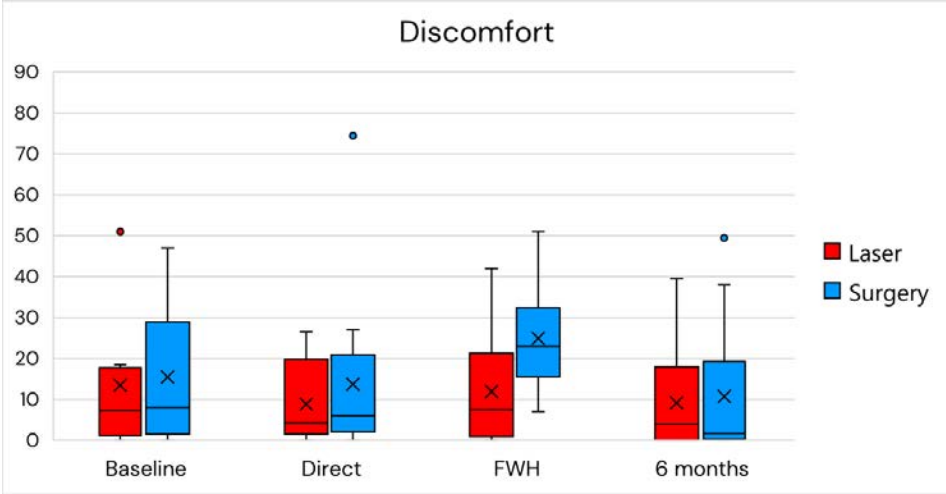


Figure 9. Box plots of the participants' ratings of their discomfort on a VAS at various timepoints in **study III**. Outliers are circles outside the whiskers and X marks the mean for each rating. *Figure by Sebastian Malmqvist.*

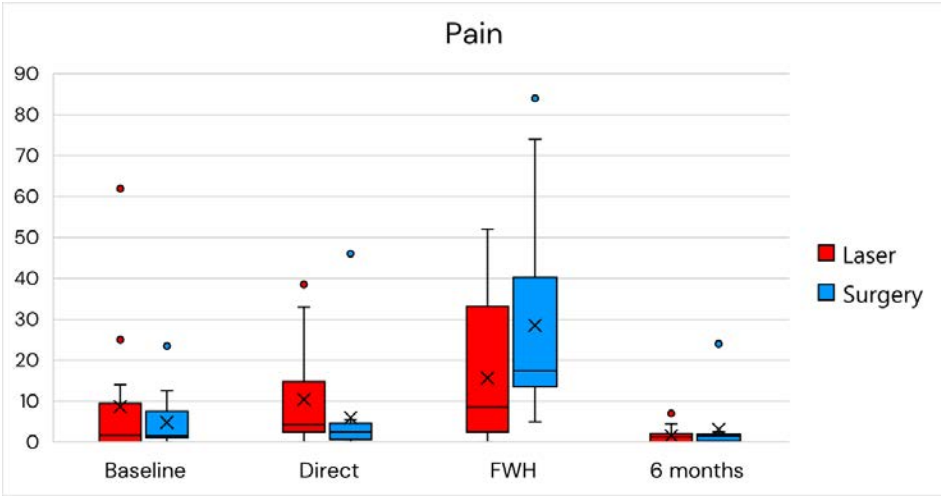


Figure 10. Box plots of the participants' ratings of their pain on a VAS at various timepoints in **study III**. Outliers are circles outside the whiskers and X marks the mean for each rating. *Figure by Sebastian Malmqvist.*

5.4 Effectiveness of the diode laser treatment

In **study III** we could not determine statistical equivalence between the 970 nm diode laser treatment and mucosal flap surgery (Figure 11). The TOST for PPD failed for the upper bound of the 90% CI (p=0.280), while for RBL it barely failed on the lower bound (p=0.081).

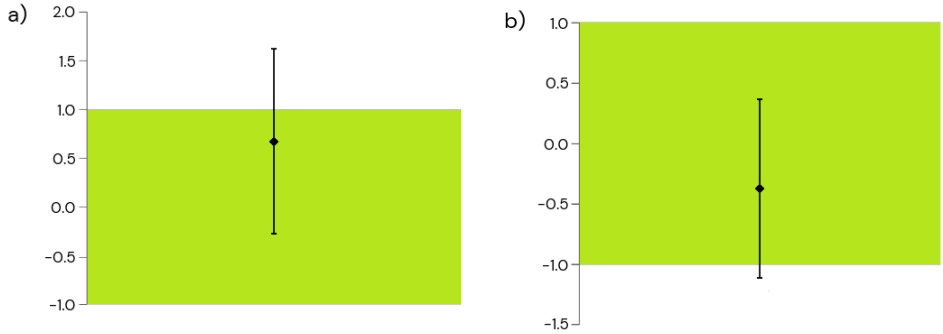


Figure 11. The mean and 90% CI of the differences between treatment groups in change of a) PPD and b) RBL to follow-up compared to the zone of equivalence (-1, 1) in green. *Figure by Sebastian Malmqvist.*

The mean change in PPD for the laser group was -0.22 ± 0.91 mm and for the surgery group -0.90 ± 1.84 mm, which was not significantly different (p=0.238). However, comparing the subgroups of those that improved their PPD, which were 8 in the laser group and 9 in the surgery group, the surgery had significantly greater reduction of PPD 1.81 ± 0.94 mm compared to 0.83 ± 0.40 mm of the laser group (p=0.016).

Other than the difference in PI on implant level between the laser group's -10.7 ± 31.7 % and surgery group's 22.9 ± 39.1 % (p=0.023), no other clinical or radiographic variable differed significantly, neither on patient level nor on implant level.

Difference in PI between groups could potentially be explained by increased motivation in the intervention group, as the laser felt like a modern and a bit exciting treatment option, as found in **study II**. There has been reports of context effects that influences the outcomes in a study e.g., patients positive expectations affecting the plaque levels and gingival inflammation (Pastagia et al., 2006). This is a downside of **study III** not being blinded for the participants; however, it would be hard to mask which treatment they received as they are distinctly different and obvious to the patient.

Few RCTs have investigated diode lasers in treating peri-implantitis and as far as we know none have been done on the 970 nm laser before **study III** (Herrera et al., 2023). Roccuzzo et al. (2022) evaluated an 810 nm diode laser had the same inclusion criteria as **study III** but their laser treatment protocol differed in magnitude and aim. They used it mainly to disinfect the peri-implant pocket i.e.,

for its antimicrobial effect, with a low power setting and 3 times 30 s irradiation intervals. Whereas, we had a longer total irradiation time and strived to remove granulation tissue around the dental implant, sort of like a less intrusive semi-surgical approach. Roccuzzo et al. (2022) did not demonstrate any significant differences in clinical, radiographical, immunological, or microbiological outcomes, basically similar to us but they used nonsurgical mechanical debridement as control whereas we used mucosal flap surgery. Conversely, Tenore et al. (2020) yielded favorable results for a 980 nm diode laser compared to nonsurgical mechanical debridement in PPD and BOP at 3 months after treatment with what they call "soft tissue laser curettage". Their description of their treatment protocol sounds similar in scope as our, although they used different power settings. Unfortunately for comparison's sake, they included both peri-implant mucositis and peri-implantitis in their study.

4 patients in each group were assessed to need re-treatment at the 6 months follow-up. 7 participants in the laser group needed an extra visit post-study, to further evaluate the healing as a part of their continued care within conventional specialist care, whereas only 1 in the surgery group needed that. Possible explanations could be either that the laser treatment needs longer follow-up time for resolution or simply that the severity of peri-implantitis treated were too far gone for the laser to have effect. That both groups had peri-implant lesions that did not positively respond to treatment is in line with the findings by Carcuac et al. (2020), who reported a disease recurrence of 43.8% and implant loss of 20.8% 5 years after surgical treatment. Tentatively one could suggest that the 970 nm laser protocol, tested in **study III**, could be used on initial stages of peri-implantitis or in re-treating a nonresponsive peri-implantitis lesion that has been surgically treated, as the laser treatment is not as extensive. Nevertheless, the treatment protocol must be more extensively tested and optimized before such a recommendation can be made in general, but there are some promising aspects which warrants further research.

Overall, we found no significant differences in the 3 selected biomarkers or PICF volume between the groups. Roccuzzo et al. (2022) reported similarly that IL-1β did not significantly change. One might need to include a longer follow-up time than 6 months to detect a meaningful change in the markers as there probably still is an inflammation process ongoing, which might resolve more noticeably later. The significance of a regular supportive maintenance plan has been demonstrated previously (Herrera et al., 2023; Renvert & Polyzois, 2018).

While Roccuzzo et al. (2022) demonstrated intra-group improvements in selected pathogenic bacteria species, in both groups, we did not find any significant changes in bacterial counts. Possible explanations for our lack of microbial change, in either group, could be that at 6 months there might already have occurred a recolonization by extra-pocket pathogens or that neither treatment succeeded in bringing on an ecological shift in the submucosal flora (Mombelli, 2018).

5.5 Immune profile of peri-implantitis

Overall, we found no significant differences in inflammatory profile or immune cell composition between peri-implantitis and periodontitis, in **study IV**. This could potentially support the notion that the diseases are similar in nature, a comparable pathogenesis, although with different anatomical and structural aspects leading to a greater area of inflammation in peri-implantitis (Carcuac & Berglundh, 2014; Schwarz et al., 2018). Also, we do show some interesting patterns and tendencies for further investigations which could facilitate a differentiation of the diseases or characterize their degree of inflammatory activity.

In PICF and GCF, a significantly higher total amount of IL-1β, TNF-α, IL-23, and BAFF were found in in both disease groups compared to controls ($p<0.05$). In the peri-implantitis group IL-4 was significantly increased ($p=0.03$) and with a tendency of an increase in the periodontitis group ($p=0.07$). For G-CSF the periodontitis group had a significant increase compared to the controls ($p=0.01$), while this could not be seen in the peri-implantitis group.

Histological examination of the three groups' biopsies revealed a similarly extensive inflammatory infiltrate in peri-implantitis and periodontitis lesions (Figure 12).

Figure 12. Representative histological samples for each group, stained with H&E. *Figure modified from the material of* ***study IV****: Malmqvist et al. Manuscript 2023.*

In homogenized soft tissue, the levels of IL-1β, TNF-α, IL-4 IL-17A, IL-23, G-CSF, and BAFF were significantly higher in peri-implantitis tissue compared to controls, while only IL-1β, IL-4, and G-CSF were elevated in periodontitis tissue (p<0.05). The only significant correlations between PICF/GCF and soft tissue biopsies were IL-4 (r=0.685; p=0.03) and TNF-α (r=0.711; p=0.02).

The immune cell profile of peri-implant and periodontal soft tissues primarily consisted of lymphocytes (75.4%). T cells constituted 57.6% (±11.2) of immune cells, while the proportions for B cells were 17.8% (±7.8), neutrophils 4.6% (±3.5), and APCs 4.1% (±1.8). Peri-implantitis and periodontitis lesions did not differ significantly in proportions of immune cells characterized in **study IV**. However, a tendency for stepwise increase in B cells were seen from controls to periodontitis and from periodontitis to peri-implantitis. There were significant lower portion of neutrophils and higher portion of B cells in peri-implantitis tissues than in controls (p<0.01). In periodontitis only proportion of neutrophils were significant different from controls (p=0.04).

Il-4 and BAFF levels correlated to the proportion of B cells, which is as expected as they affect the function and survival of B cells. In an animal model of peri-implant mucosa, it has been shown that $RANKL^+$ B cells are increased in peri-implantitis, which could be one of the mechanisms behind peri-implant bone loss (Heyman et al., 2022). This is in line with our findings of increased amount and activity of B cells in disease and if our finding of a stepwise increase in proportion of B cells holds true, which have been confirmed in other studies (Berglundh & Donati, 2005; Carcuac & Berglundh, 2014; Heyman et al., 2022), it might at least partly explain the faster progression of bone loss around dental implants than teeth (Heitz-Mayfield & Lang, 2010). However, we found a positive

correlation between proportions of B cells and the PPD of the sampled site and as the peri-implantitis group had statistically significantly deeper PPD, which might account for the tendency of a step between peri-implantitis and periodontitis. Although the PPD at a single site does not portray the full scope of the disease picture and a more detailed characterization of the lesions would have been desired. This correlation in our observational study should also be confirmed in experimental models to more reliably examine the mechanisms involved in peri-implant bone degeneration.

Our finding of a lower proportion of neutrophils in both disease tissues compared to controls are at odds with findings by Berglundh et al. (2011), Dutzan et al. (2016) and Heyman et al. (2022). Then again, it has also been shown that neutrophils are a main component of the immune response during early phases of disease, to gradually decrease as the severity increases (Berglundh et al., 2011; Nussbaum & Shapira, 2011). The lower proportion could in part be due to the disease lesions being quite severe and established enough to warrant a referral to specialist care. However, we did see an increase in neutrophil related inflammatory markers, IL-1β, TNF-α, and G-CSF, in both tissue and PICF/GCF in disease compared to controls. Possibly the choice of analysis or transportation affected the ability to detect the neutrophils, but it could also be due to increased migration out into the peri-implant or periodontal pocket in severe disease.

5.6 Methodological considerations

The findings in **study I** should be interpreted with caution as they are based on *in vitro* models. However, the tests were mostly designed as worst-case scenarios with the laser angled 90° to the implant or disc surfaces. Noteworthy is that we used a single PM for repeated tests whereas Kong et al. (2023) used 7, to try to account for potential variations between different PMs. For both studies it should be noted that the tests took place in non-living tissue and neither of us measures the temperature in the bone, but the surface temperature of the implant is of interest as it is in direct contact with the surrounding bone.

For the surface alterations, flat discs were used in our study and has been by others (Kong et al., 2023; Romanos et al., 2000). Using actual dental implants, as done by Lee et al. (2011) could potentially affect the alterations of the surfaces as the structure could potentially reflect the laser beam differently. Comparing

discs with implants in the same study would be interesting to evaluate the applications of the findings from studies on discs. A study methodology that could lead to interesting results would be if one uses different wavelengths of lasers on dental implants slated for extraction and then evaluated them in SEM after removal. Using parameters of the laser that are safe in terms of temperature would be key here to not damage the surrounding tissue in an actual patient.

In the qualitative study (**II**) we strived to improve the overall trustworthiness of the findings through certain methodological adaptations (Lincoln & Guba, 1985). We recruited participants to interview to get a broad range of backgrounds such as age, employment, and single or multiple implants, to increase the richness of the material which affects the credibility. Credibility, i.e., the amount of truth, in the results of qualitative research can also be improved by triangulation techniques (Farmer et al., 2006). We used investigator triangulation by having three of the authors of **study II** analyze the interviews separately, to then come together and discuss the categories and subcategories, until consensus was reached. There are other ways to improve the credibility of qualitative research, which we did not utilize e.g., member checking, where the analysis and categories are presented to the participants to give feedback on (Morse, 2015).

Dependability, another aspect of trustworthiness relating to consistency and repeatability of the results, were improved by having researchers with different experiences analyzing the material and discussing it amongst themselves (Graneheim et al., 2017). The different pre-understandings and experiences in the research group, of qualitative research and patients with peri-implantitis, hopefully led to increased richness of the analysis due to complementing perspectives on these issues. Many of the findings were also in line with other quantitative and qualitative studies (Abrahamsson et al., 2017; F. Alqahtani et al., 2019; Fardal et al., 2002), which can be a sign of dependability in the results.

Accounting for one's own pre-understanding in qualitative research is an important part, not only for dependability, but also for confirmability. Confirmability relates to the degree that the respondents' answers affect the outcome of the analysis rather than the researcher's opinions (Hamberg et al., 1994). Member checking would have strengthened this aspect of trustworthiness as well and would have been desired. One of research group members were not

involved in the initial analysis and came in after a first draft of the analysis was done, not exactly an external audit of the analysis, more of a semi-external.

Transferability, being the qualitative equivalent of the quantitative concept of generalizability, can in **study II** be shaped by that the participants had already received a diagnosis of peri-implantitis, with its accompanying information of what the disease is (Hamberg et al., 1994). This probably affected the answers within the themes of living with dental implants and sensations of peri-implantitis. A way to handle this is to address it in the analysis and strive for a thick or rich description of the phenomenon, to give it context which makes it easier to correctly apply in part or as a whole to other situations (Hamberg et al., 1994; Lincoln & Guba, 1985).

One of the main limitations in **study III** was the lower number of participants than intended, resulting in lower statistical power (Hefti & Preshaw, 2012). Statistically we concluded that the laser is neither equal nor different from the surgical treatment, but in subgroup analysis we try to give perspective to our findings. Although, the reason for the decreased number were out of our control as it was due to the COVID-19 pandemic (J. Li et al., 2021). From a research and periodontal care perspective, the pandemic has had a significant negative impact on the patients, in terms of oral health and receiving needed treatments and follow-ups, as well as for the caregivers and academia (Rocha-Gomes et al., 2021).

There were of course other limitations in **study III** such as the partial blinding of variables. Achieving blinding of the participants would have been exceedingly difficult to do in a reliable and credible way, as the treatments are so fundamentally different in procedure and to give sham-surgery with sutures only to mask group allocation would be unethical. A strength of the study was the intra-examiner agreement of PPD which had a correlation of 0.989 between baseline measurement and a repeated measurement 2-4 weeks after in four patients. Assessing the examiner is an important step in determining the reliability of the results, but unfortunately it is rarely adequately reported as 72.3% of articles in top periodontal journals failed to do so (Hefti & Preshaw, 2012).

Selection of the participants were an unrandomized one of convenience, as the eligible patients with peri-implantitis being referred to a specialist clinic within the timespan for the study were included. The participants were however,

randomized to their respective treatment, with the use of block randomization stratified for mean initial PPD of worst affected dental implant. The stratification was below, within or above the PPD interval 4.5-6.5 mm. Only one participant was in the below category which might suggest that the range of the three categories could be adjusted. However, in one of the few previous RCTs of diode laser treatment of peri-implantitis by Alpaslan Yayli et al. (2022), they had mean baseline PPDs between 4.14 and 4.48 mm in their three treatment groups. Meaning that roughly half, disregarding possible skewness of their data, would be in the below strata in our study. This could partly justify having the lowest strata and it was created with initial peri-implantitis and localized deep peri-implant pockets in mind.

In terms of generalizability, it could be argued that the results of **study III** are mainly applicable for moderate to severe peri-implantitis patients, as recruitment took place in a specialist clinic. However, they are probably relevant for peri-implantitis in general as the lesions are greater in size than its periodontitis counterpart and the limited effect of nonsurgical mechanical debridement warrants a more extensive treatment regime (Heitz-Mayfield & Lang, 2010). Another aspect of the generalizability of the study cohort is that only dental implants with modified rough surfaces were included. As it has been shown that the modified surface tends to increase the rate of progression and risk for recurrence of the disease (Carcuac et al., 2017), it would be of interest to also evaluate the effect of the treatment on smooth machined implant surfaces. If the healing after treatment would differ between the surface types, then it could be seen as a strength that only one kind was included in **study III**.

In previous studies on diode lasers, they compared the intervention to nonsurgical mechanical debridement (Alpaslan Yayli et al., 2022; Roccuzzo et al., 2022) or used the laser adjunctively during mucosal flap surgery (Papadopoulos et al., 2015). Our control group received the current gold standard treatment for peri-implantitis of such severity. We also use the laser more extensively than other protocols to remove some of the infected tissue in a manner what could be described as "soft tissue laser curettage" (Tenore et al., 2020). Gold standard comparison and the laser protocol tested are the reasons why we chose mucosal flap surgery as control treatment, but to gain clarity it would be good to use three groups, adding a nonsurgical debridement one to elucidate the diode laser's role more precisely.

In **study IV** we characterized the immune profile with FACS by staining with LIVE/DEAD fixable cell stain and 7 different fluorochrome-conjugated antibodies. This panel identified different major cell groups such as T cells, B cells, neutrophils, and different APCs. It would have been interesting to have a larger panel either by dividing the samples in two aliquots after digestion into a single cell suspension and running different panels or the more costly way of using a flow cytometer with more fluorescent detectors to be able in one run differentiate the subgrouping of immune cells (McKinnon, 2018).

The sample size in **study IV** could also have been larger as we noted a broad inter-individual variation in both cell composition and cytokine profile. Other than sample size, an adaptation in the methodology would possibly reduce this variation by sampling individuals with both peri-implantitis and periodontitis. This would have required a longer sampling time as participants with both diseases and lesions of them that require surgical treatment are fewer than those having one or the other. We only identified two such patients in our sampling period, but there might have been more as it was not a specific aim of our study. Regardless of approach with both disease diagnoses in one patient or with single diagnosis patients, a limiting factor in the comparison is the difference in severity and expression of the diseases. Matching samples of similar RBL could potentially compensate in some way for this, but as the peri-implantitis lesion tends to extend further out in the surrounding tissues (Carcuac & Berglundh, 2014), it will be hard to fully match samples of these two diseases. Another limiting factor in **study IV** was that there was no healthy peri-implant mucosa as control. Although, as there are exceptionally few indications to perform surgery around or near healthy dental implants, it would be difficult to gather such material and potentially ethically questionable to harvest biopsies just for research purposes. Especially since that has been done previously, which has showed that healthy peri-implant mucosa and gingiva are similar in size of infiltrate and immune cell proportions (Zitzmann et al., 2001).

6 Conclusions

This thesis includes unique findings regarding treatment of peri-implantitis, to remove infected peri-implant tissue, with a 970 nm diode laser. To the best of our knowledge, no other RCTs or clinical studies have evaluated this laser treatment protocol previously.

Main findings of this thesis:

- A rigorous amount of cooling water is essential when using diode lasers on dental implants. If continued water irrigation is not possible then a maximum continuous interval of radiation should not extend 15-20 seconds, depending of course on the power settings.
- There were no meaningful i.e., clinically relevant, or statistically significant, differences in temperature in using 445 nm or 970 nm diode laser on dental implants and no surface alterations were seen in SEM.
- Among individuals with peri-implantitis there were a variety of positive and negative sensations and experiences of having dental implants, which highlights the importance of systematic information regarding risk of disease.
- As some patients felt symptoms of peri-implantitis, it might be feasible to involve the patient in the monitoring of their peri-implant health, through increased knowledge of the signs of disease.
- Treatment of peri-implantitis, whether with laser or mucosal flap surgery, created only slight discomfort and the main advantage in patient experience of the laser seems to be the lack of sutures.
- Although equivalence could not be established between 970 nm diode laser treatment and mucosal flap surgery, a potential role of the laser could be in treating early stages of peri-implantitis where extensive pocket elimination is not needed and where surgery might be regarded as a too extensive intervention.
- The inflammatory and immune cell profiles of peri-implantitis and periodontitis did not significantly differ from each other. However, both in proportion of B cells and levels of associated biomarkers, a significant increase was noted for peri-implantitis, with a tendency to a stepwise increase from controls to periodontitis and from periodontitis to peri-implantitis.

7 Points of perspective

Both the findings in this thesis and the current evidence show that there is a need for more studies on diode lasers in treating peri-implantitis and to gain further knowledge of the characteristics of peri-implantitis.

In terms of safety, there seems to be little, if any, consensus nor homogenous findings about which is the most appropriate wavelength of laser. Future studies should include more than two wavelengths of laser and further compare the different settings such as CW and pulsed mode. Which wavelength and what setting that causes surface alterations on dental implant also needs further inquiry, but also the surface alterations impact in a clinical setting. Kong et al. (2023) suggested that there seems to be improved cell growth on the altered titanium surfaces and whether that helps, in terms of fibroblast activity, or hinders, with bacterial growth, remains to be seen.

Our suggested laser protocol for the 970 nm diode laser is also in need of further studies, not only to optimize its laser settings but also to solidify its potential role as early stages option to surgical intervention. Ideally such study should include two control groups, one with nonsurgical and one with surgical mechanical debridement of the dental implant. Future clinical studies should be examiner blinded and with an RCT design, as there are few such studies on lasers in treating peri-implantitis (Herrera et al., 2023).

There is also a need for studies looking into early detection of peri-implantitis. Both to include the patient in the monitoring of their peri-implant healthy through education (Holtzman et al., 2017), and through further characterization of the immune response to potentially find appropriate biomarkers for easy-to-use chairside detection kits (Sorsa et al., 2020). A deeper understanding of the immunological response in peri-implantitis and periodontitis could in the future perhaps lead to targeted immune modulating treatment modalities (Heyman et al., 2022). An increased understanding of the mechanisms of peri-implantitis could also better guide the optimization of the laser treatment e.g., if a more thorough elimination of bacteria is needed then perhaps a blue wavelength would be more effective (Leanse et al., 2022). Incidentally, a higher cutting efficiency has been noted when using a 445 nm diode laser, making it a prospective wavelength to evaluate (Braun et al., 2018).

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