Universitatea
Transilvania
din Brasov

INTERDISCIPLINARY DOCTORAL SCHOOL
Faculty of Medicine

Dr. Codruța Elena CHIRA (CIURESCU)

COMPARATIVE STUDIES OF LASER THERAPY AND PHARMACOLOGICAL THERAPY IN INFLAMMATORY DISEASES OF THE ORAL CAVITY

SUMMARY

Scientific supervisor
Prof.univ.dr. Lorena DIMA

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INTRODUCTION

Periodontitis, the most provocative of inflammatory diseases of the oral cavity has a growing prevalence but on the other hand an important social impact. For this reason, the therapies of this condition are increasingly debated in the ranks of specialists in the field. Practice guides strongly recommend local mechanical treatment, non-surgical treatment as the main approach in the treatment of this condition.

Inflammatory diseases of the oral cavity are grouped into diseases of the oral mucosa, periodontitis conditions and diseases of the maxillary bones. Of these, periodontitis diseases stand out significantly due to the complexity, the frequency with which they are diagnosed among the population and social impact and not least due to the interconnection with a large number of systemic diseases: diabetes mellitus, metabolic diseases, autoimmune diseases – rheumatoid arthritis, premature birth, depression and anxiety disorders, atherosclerosis.

Favourite factors includes : altered immune response, age, smoking, stress and genetic predisposition (Eke P., et al., 2014) (Hajishengallis G., et al., 2014).

In Europe, the prevalence of periodontal disease is alarming, about 37% of the population is affected by various forms of this disease (Bruce A. D., et al., 2011). According to the "National Health and Nutrition Examination Survey (NHANES) 2009-2012" (Eke PI., et al. 2015), the prevalence of chronic periodontitis in the U. S. adult population is 46%, representing 64.7 million people.

Periodontal disease is a complex multifactorial disease, with an insidious onset arising from an imbalance between microbial species currently present in the oral cavity. This imbalance is favored by an altered immune response either by a minor IL-1 immune deficiency (genetic predisposition) (Lopez-Castejon G. et al, 2022), either by the presence of the general conditions listed above that alter the ability of the organism to cope with the aggression of pathogenic species present in sufficient quantity in the oral cavity. Inadequate oral hygiene results in the deposition of bacterial plaque on the tooth enamel and cement surfaces in the immediate proximity of the marginal periodontium. The construction of a placard from multiple layers of bacterial cells allows the organization of a microbial consortium in a protective environment and conducive to the development of pathogenic species at the expense of saprophytes, altering in this way the balance between the species present in the oral cavity.

Periodontitis is initiated by the accumulation of bacterial biofilm at and below the gingival margin, which activates the host's immune-inflammatory response. It is the installed oral dysbiosis that triggers a dysregulation of immune-inflammatory processes (Meyle J., et al., 2015) and ultimately competes in the destruction of periodontal tissue (Hajishengallis G., et al., 2021). It is basically the first stage of periodontal disease that can be diagnosed by classical methods, microbiological culture, and, but also by molecular methods represented by PCR (Real-time polymerase chain

reaction) analysis, which is distinguished by increased accuracy and reduced working time (4-5 days), or newer by clonal type 16SrDNA analysis using DNA extraction methods, as highlighted in the study (Akyiama T., et al., 2010, even before the lesions can be clinically highlighted by loss of peridental attachment.

In this context, periodontal disease should be addressed as a real public health problem, and periodontal therapy is crucial in the context of oral health policies and dentistry in general. In evolution, the disease leads to loss of attachment of support tissues: periodontium and alveolar bone at the root wall, resulting in sequential loss of affected teeth (Papapanou PN., et al., 2018).

Due to the increased prevalence and interconnection of this condition with a number of general conditions, there is an increase in the interest of specialists in the field for conservative therapeutic alternatives compared to the previous conventional ones, respectively, sanitizing and resection surgery, respectively the extraction of teeth affected by the disease.

Repopulation of dental plaque on root surfaces with pathogenic microorganisms is very fast and involves a recovery rate of at least 80% and a recovery time of no more than 12 weeks. That is why it is absolutely necessary to preserve the results obtained after treatment in the sense of selective removal of pathogenic species, and therefore to prevent local recurrences, aspect that can only be achieved with adjuvant treatments to reduce local bacterial load.

Of these, laser therapy is the most innovative periodontal therapy for the control of dysbiosis and the prevention of relapses, assuming sequences of therapeutic stages better tolerated by patients and non-aggressive for tissues, but at the same time with efficiency comparable to pharmacological preparations recommended as adjuvants in these diseases.

However, a variety of adjuvant treatments are proposed in order to augment the therapeutic results. Of these, laser treatments stand out as the newest and most promising adjunct treatment alternatives to mechanical therapy. In addition, a more recently developed condition, peri-implantar mucositis, with features very similar to periodontitis, also takes its amplitude as prevalence but also as social impact.

For these reasons, the prescription of antibiotics and antiseptics as adjuvant therapies in the treatment of these diseases has also grown. In the context of the escalation of antibiotic resistance, to antiseptics and the occurrence including cross-resistance between them, exploring therapies that could reduce local bacterial load and bring significant clinical improvements while avoiding the prescription of pharmacological preparations that may increase the risk of developing resistance is a necessary thing.

Therefore, the implications of lasers in the therapy of this condition are also investigated in order to provide information on the therapeutic options that exist in accordance with current knowledge in the field.

The theme was chosen from *the field of medicine* in order to cover informational gaps regarding this future therapeutic option. To date, studies on laser therapies versus pharmacological therapies, but especially variants of laser conjugations are extremely limited, and avoiding long-term and very long-term remission is the major goal of laser therapy.

THE THESIS STRUCTURE

The thesis is composed by a first third as theoretical research and 2 thirds personal contribution. It includes 8 chapters, of which the general part is made up of the first 4 chapters, followed by chapter 5 which includes the personal contributions highlighted by the 3 studies completed, then the chapter of general discussions, the one of general conclusions and the last news brought by the paper and the possibilities of further capitalization of the results.

CHAPTER 1 ANATOMICAL AND PHYSIOLOGICAL ASPECTS OF PERIODONTAL AND PERI-IMPLANTATION TISSUES

The similarities and differences between periodontal and peri-implant tissues concern research groups and practitioners, given that the interface between dental implants and soft tissues has the role of protecting the alveolar bone from the oral environment, so its quality depends on the success of implant-prosthetic therapy, and literature data shows that peri-implantation tissues are more susceptible to oral aggressions compared to periodontal tissues.

This increased sensitivity of peri-implantation tissues is associated with decreased vascularity and increased proportion of collagen fibers, and, compared to periodontal tissues. There are numerous similar aspects between the soft tissues surrounding the implant and the soft tissues surrounding the natural teeth. In conditions where the dimensions of the junctional epithelium and connective tissue represent the biological wide of the peri-implantation soft tissues, the biological width at the level of dental implants is similar to the biological width at the level of natural teeth. Regarding the relationship between the epithelium and the crevicular ditch, the oral epithelium is well keratinized and continues the epithelium of the crevicular ditch both in the case of natural teeth and in the case of dental implants. The apical extension of the peri-implantar epithelium varies depending on the implantation technique.

Above the level of the crest bone, there is an area of connective tissue that includes dense circular fibers bounded by vascular lax connective tissue (Cochran D., 2000). While at the level of natural teeth, the connective tissue at their level is attached to the dental surface and, the collagen fibers that start from the crest bone have parallel trajectories with the surface of the dental implants towards the oral epithelium. The absence of cementum and the orientation of collagen fibers are responsible for the variability of „resistance to probing" of implant sites (Araujo MG., et al., 2018). The materials from which the prosthetic abutments are made influence the quality of the soft peri-implantation tissues (Abrahamsson I., et al., 1998).

CHAPTER 2. BACTERIAL PLAQUE. ORAL MICROBIOME IN PERIODONTITIS AND PERI-IMPLANTITIS

Periodontal bacterial biofilm is characterized by heterogeneous micromedias, determined by nutrient gradients, oxygen and metabolic residues, and, providing growth conditions for diverse bacterial species or bacteria with distinct phenotypic traits of the same species (Bernard CS., et al., 2012). Teles R., et al., (2013) draws attention to the fact that, although in recent years, special attention has been paid to the essential role of inflammation and other immune mechanisms in the pathogenesis of periodontal disease, new studies are needed on how interactions between the subgingival microbiota and the host's defensive mechanisms take place.
The authors believe that in recent years the field of knowledge has expanded in this field, due to the way in which the data obtained by molecular techniques have impacted on the knowledge of the etiology of periodontal disease, understanding the role of some viruses in the etiopathogenesis of periodontal disease, expanding the concepts of microbial ecology in the context of interactions between the host and periodontal pathogenic bacteria, understanding the role of inflammation in the pathogenesis of periodontal disease, the impact of these new concepts on preventive and therapeutic approaches in periodontal disease.
Studies that will extend over several decades are expected to identify all periodontal pathogens or combinations of periodontal pathogens involved in the pathogenesis of various types of periodontal disease. There are a number of difficulties in determining the role of specific subgingival periodontogenic microbiota components due to the following aspects (Teles R., et al., 2013): Diversity of subgingival microbial species, some of which are still non-cultivable by current techniques, difficulty obtaining representative samples during the collection of subgingival bacterial samples associated with, difficulties in identifying active sites where periodontal destruction processes take place, and last but not least, understand the concept of

mixed infection that includes numerous combinations of disease-associated pathogens, periodontitis.

In conclusion, the time of initiation of periodontal disease does not necessarily coincide with the detection or diagnosis of the disease, the time interval between the two is called „latent period". The latent period can be reduced by improving disease detection methods, namely by using paraclinical methods that can detect subclinical signs or markers associated with the initiation of periodontal disease (Teles R., et al., 2013).

CHAPTER 3. INTERCONNECTION OF PERIDENTAL AND PERI-IMPLANTATION INFLAMMATORY CONDITIONS WITH GENERAL CONDITIONS

According to the American Academy of Periodontology, numerous studies associate periodontal disease with various systemic diseases. Although evidence of a causal relationship is emerging, research suggests that periodontal disease may be related to the onset and progression of systemic conditions.

Patients whose glycemic values exceed physiological limits have the same increase in glycemic and crevicular fluid secreted at the gingival sulcus.

The treatment of periodontal disease and the reduction of the bacterial plaque load on the dental surfaces is beneficially reflected in the glycemic index control and vice versa.

Several studies have shown that periodontal disease can increase the risk of cardiovascular disease. Periodontal disease can also exacerbate existing heart conditions. Patients at risk of bacterial endocarditis require antibiotics prior to dental procedures.

Research has found that bacteria associated with periodontal disease can be sucked into the lungs and contribute to respiratory diseases such as pneumonia (Brock M., et. al., 2022).

Periodontal therapy is effective in reducing leukocytosis, but studies are limited in terms of red and platelet lines. In addition, patients with periodontitis suffering from white blood cell disorders seem to be more prone to severe periodontal destruction, given the pathophysiology of periodontitis and the immune role of leukocytes.

As research on the COVID-19 pandemic advances, more data is based on the potential relationship between periodontitis and COVID-19. However, the studies are far from complete.

The risk of developing rheumatoid arthritis increases in people with moderate to severe periodontitis, as found in studies. Although there may be differences in the etiology of both diseases, the underlying pathogenic mechanisms are strikingly similar, and it is found that people who have periodontitis and rheumatoid arthritis could be affected by a synchronous systemic rearrangement of the inflammatory response (Mercado FB.et.al, 2003).

Research has demonstrated a notable correlation between low birth weight premature birth and periodontitis, regardless of gender, race and maternal age (Sanchez AR.et al., 2004). Premature or spontaneous births are more likely in mothers with periodontal disease.

Recent studies have shown that high cholesterol can be among the leading causes of immune cell changes caused by diabetes. Recent studies on human subjects have associated high blood levels

of lipids and periodontitis. Some evidence supports the idea that periodontitis can cause higher levels of low-density lipoprotein (LDL) and triglycerides (TRG).

Although there is strong evidence between the presence of chronic kidney disease (CKD) and periodontal infection (PO), several studies are confirming a correlation between the two diseases. Studies have been conducted to highlight the possible strong link between chronic kidney disease and periodontal disease.

Periodontitis has been associated with an increased prevalence of various chronic non-communicable diseases, including gastrointestinal cancers. Indeed, the dysbiosis of the oral microbiome and the immune-inflammatory pathways related to periodontitis can affect the pathophysiology of the gastrointestinal tract and its accessory organs through the so-called "gum–gut axis".

Whereas periodontitis is an oral infectious disease associated with gram-negative anaerobic bacteria and can be considered a "-grade systemic disease by releasing proinflammatory cytokines into the systemic circulation and increasing C-reactive protein (CRP)". Inflammation plays an essential role both in the disease process and in the link between periodontitis and Alzheimer's disease.

CHAPTER 4. NON-INVASIVE THERAPEUTIC APPROACHES IN THE MANAGEMENT OF PERIODONTITIS AND PERI-IMPLANTITIS

The research groups focus on detecting and combating risk factors and on modern non-invasive approaches in periodontal disease therapy (Costa F.O, et al., 2018). Periodontal maintenance therapy in patients diagnosed with periodontitis in any of the stages, post periodontal treatment, provides for the reduction of indications of periodontal inflammation, alveolar lysis processes and the preservation of teeth on the arch for as long periods of time as possible (Martu S., et al., 2010). For stage 4 and specific in some cases in stage 3 , regenerative surgical therapies may be indicated (Nibali L.,et al.,2020)

CLASSES OF DRUGS USED IN CLASSICAL PERIODONTAL THERAPY

- Nonsteroidal antiinflamatory drogs

The immune response is a complex process that is triggered when specialized cells of the immune system recognize and respond to foreign agents or antigenic substances. This process can be initiated in the context of acute or chronic inflammation, involving the release of a series of bioactive molecules, such as eicosanoids, lipoxygenases, leukotrienes, cytokines and chemokines. These substances mediate complex interactions between different immune cells, including eosinophils, neutrophils, dendritic cells, lymphocytes, macrophages and their subtypes.
The main mechanism of action of NSAIDs results from the inhibition of cyclooxygenase, with the consequent reduction of prostaglandin biosynthesis underlying their anti-inflammatory, analgesic and antipyretic effects.

- **Antibiotics**

Antibiotics used to treat periodontal disease should be selected to cover the spectrum of pariopathogens involved in the disease, and the bactericidal or bacteriostatic effect should prove its effectiveness at therapeutic doses so that it has a proven clinical benefit in reducing the pathogenicity of the subgingival biofilm. A good tissue distribution would be an implicit requirement and also be well tolerated and not develop resistance (Luchian I., et al., 2021).
The most commonly accepted form of administration is generally administered, particularly by oral administration, however, forms of local administration in periodontal pockets are also taken as adjunctive therapy for several preparations.

- **Antiseptics**

Iodine (Povidone-iodine) and Chlorhexidine are the most well-known and used antiseptics in the adjuvant treatment of inflammatory diseases of the oral cavity. (Yuvashree M et al., 2023).

LASER TREATMENTS – ADJUVANT THERAPIES IN THE TREATMENT OF PERIODONTITIS AND PERI-IMPLANTAR INFLAMMATORY DISEASES (MUCOSITES AND PERI-IMPLANTITIS)

Laser therapy has benefits for the patient, by reducing psychological stress, discomfort and postoperative pain (in periodontal/peri-implantar surgery procedures) and increasing compliance with therapy (Coluzzi DJ., et al., 2016). In laser-assisted periodontal/peri-implantar surgery, ablation, disinfection and hemostasis of all involved tissues are easier to obtain compared to the classical technique (Aoki A., et al., 2015).

CHAPTER 5. PERSONAL CONTRIBUTIONS

Given the current state of knowledge in the international scientific literature, highlighted in the chapters of the general part, laser therapy adjunct to the mechanical treatment of periodontal diseases is a controversial and topical issue. Therefore, this doctoral thesis, through its 3 studies, aims to make a substantial contribution with concrete data in the field of the scientific community and oral health practitioners.

GENERAL METHODOLOGY

The 3 studies in this thesis are a two-year follow-up study following a randomized clinical trial and two randomized clinical trials.

The subjects included in the studies were patients diagnosed with inflammatory diseases of the oral cavity, respectively periodontitis and peri-implantar mucositis.

The age of inclusion of subjects was 30-75 years, except for the first study where the lower age limit for inclusion in the study was 25 years.

The inclusion criteria were the presence of specific disease lesions, periodontitis and peri-implantar mucositis, and the exclusion criteria involved the presence of general conditions that can change the course of the disease, and implicitly the research results, antibiotics received in the last 3 months or treatments of the condition for which subjects were included in the study treated in the last 12 months.

The studies were carried out according to and respecting the principles "Declaration of Helsinki", and each clinical protocol applied was approved by the Comitee of Ethics of "Transilvania University", Brașov by Decision no 01/14/2018 and of the Commission on Ethics of Medical Scientific Research, identification code 101E. All patients included in the studies signed Informed Consent.

For statistical data analysis, the statistical software program (MedCalc Statistical Software version 17.6, MedCalc Software) was used. Wilcoxon, U Mann-Whitney, t-test, was used, but Python 3.0 (Python Software Foundation, Wilmington, DE, USA)" was also used. The p-value < .05 was considered statistically significant.

The research was designed to evaluate the clinical results obtained by applying nonsurgical treatment for periimplantitis and peri-implantar mucositis by manual instrumentation according to the recommendations of the EEP and WWCP practice guidelines with laser adjuvant as follows: In the first study the clinical results of mechanical debridement with or without laser adjuvant (2780 nm + 940 nm) in the treatment of periodontitis was evaluated 2 years after, in the second study the clinical results of mechanical debridement with farmacological adjuvant and mechanical debridement with 2780 nm laser adjuvant in the treatment of periodontitis were

evaluated at 6, 12,24,48 months, and in the third study clinical results of mechanical treatment with farmacological adjuvant or laser adjuvant - 2 complementary lasers (2780 nm, 940nm) at 6 months from baseline were evaluated.

Er.Cr Laser:YSGG is known for its potential to reduce the bacterial load on the surface of the root and dental implant without damaging the titanium oxide coating on its surface due to the specific affinity for water molecules, he said, all resident organic deposits on the surface of the contaminated dental implant have water content , and restore wettabilitty

On the other hand, the InGaAsP Laser, which has melanin and hemoglobin as a chromophore, has recognized bactericidal properties on melanin-containing bacteria, the main pathogens involved in the onset and progression of periodontitis and peri-implantar inflammatory diseases, but also have a high intratisular penetration capacity, which may exceed 900 microns in certain conditions, this allows to obtain a considerable intratisular decontamination, but also at the level of surfaces that are hardly accessible by mechanical means due to topography or reduced working space.

The therapeutic doses used in this research have been carefully calculated to exceed the lower limit where clinical effects in soft tissues are highlighted (not to be subablative doses), also, its doses have therapeutic efficiency in soft tissues and bone tissue without inducing overheating, and it was also considered that the doses of energy administered also have a bactericidal effect and remove cellular debris, endo/exotoxins from the implant surface.

It was also considered the effect of conditioning and restoring the hydrophilia of the implant surface without damaging or modifying the surface porosity of the root surface or produce any damage on the titanium oxide layer that envelops the implant.

All subjects included in the study were subjected to clinical examination, anamnesis and radiographic examination. Valued variables, respectively the Periodontal probing depth (PPD), peri-implant depth (PID), the bleeding of probing (BOP) and the plaque index (PI) were initially evaluated by a calibrated assessor (AG).

Radiological examination of orthopantomography was performed for the purpose of correct classification in research. RBL – peri-implantar bone loss highlighted radiologically was noted in the last study.

Subjects were randomly assigned to 2 groups, following a computer randomization list. For further research and comparative statistical analysis between batches, in the third study the implants were subdivided into 2 other subgroups: implants less than or equal to 5 years old in the oral cavity and implants more than 5 years old in the oral cavity.

The topography of the affected implants was also noted in order to assess whether topography of the implants may be a factor that alters the response to therapy for the evaluated implants. The presence or absence of peri-implantar keratinised gum was also taken into account in the evaluation.

The treatment was carried out by a qualified operator (CC) other than the one who performed the clinical and radiological (AG) measurements. The two operators were instructed not to communicate any aspect of current research to each other.

The first study is a follow-up study, the continuation of a randomized clinical trial, which aimed to evaluate the potential benefits of laser adjuvant therapy of classical non-surgical periodontal treatment in improving clinical parameters in periodontal disease. The objectives of the study were to evaluate the comparative long-term evolution of clinical parameters and the periodontal probing depth (PPD), respectively, the level of clinical attachment (CAL) and the bleeding at probing (BOP) to monitor the results obtained and possible remissions of subjects treated by periodontitis by supragingival and subgingival debridement with laser adjuvant treatment or without the latter a year and two years after the initial treatment. The working hypothesis of this study was that laser treatment associated with non-surgical periodontal treatment brings improvements in the resolution of the disease and in the prevention of remissions.

To date, there are no data from randomised controlled trials assessing the potential clinical and microbiological effects of an Er, Cr laser combination: YSGG and InGaAsP diode laser used in combination with mechanical debridement for the treatment of patients with periodontitis. Therefore, the purpose of this study was to clinically and microbiologically evaluate the results obtained after the combined application of InGaAsP laser and Er,Cr:YSGG laser for the non-surgical treatment of chronic periodontitis.

The combination of erbium lasers with diode lasers is based on the fact that Er:YAG lasers are effective in removing plaque/calculus deposits , while diode lasers are effective in reducing bacteria and deepening the walls of the periodontal pockets.

The purpose of this study was to investigate the role of laser adjuvant therapy of classical nonsurgical periodontal treatment at improving clinical parameters in long-term periodontal disease. The objective of this study was to benchmark the long-term clinical development of maintaining the results achieved, and/or highlighting the possible remissions of the subjects treated by periodontitis by supra and subgingival debridement with adjuvant laser treatment or without, by assessing the clinical parameters and the PPD survey depth, the CAL clinical attachment level, and bleeding on probing BOP one year and 2 years after initial treatment. The working hypothesis of the study was that laser treatment associated with non-surgical periodontal treatment brings improvements in disease resolution and in preventing remissions.

The present study was designed as a follow-up study of clinical results obtained 1 year and 2 years after therapy of a previously published randomised, controlled clinical trial.

Patients were initially randomized into two groups according to a computer-generated list in two research groups, mechanical debridement with adjuvant laser treatment or without, randomisation that was also maintained in the present longitudinal study.

The two lots of subjects participants were evaluated by recording the variables previously investigated and noted respectively the depth of PPD periodontal pockets, respectively, the level of CAL clinical attachment and bleeding at BOP probing 1 year and 2 years after treatment and variables were compared between groups and within the group to assess maintenance of the results obtained and/or possible relapses following treatment.

Results: At 6 months both treatment groups showed statistically significant microbiological reductions for all periodontal pathogens evaluated. With the exception of E nodatum, which was present in significantly higher numbers in the laser group, all other bacteria showed no initial differences between the groups.

"P gingivalis, T denticola, T forsythia, P intermedia, P. micros, F. nucleatum and E. nodatum" were statistically significantly reduced in the test group compared to the control group at 6 months. The statistical analysis did not reveal statistically differential differences between batches for A actinomycetemcomitans at any time, qualitative analyses showed that A actinomycetemcomitans was detectable prior to treatment only in one subject in the control group and five in the test group, respectively, while at 6 months there were no patients in the test group and two control group subjects were positive for this bacterium.

Similar to the quantitative analysis, qualitative microbiological results showed statistically significantly higher reductions in the number/percentage of positive patients for" P gingivalis, T forsythia, T denticola, P intermedia, etc, P micros and F nucleatum".

The results of this study indicate that in patients with stage III and IV periodontitis, grade B, the use of InGaAsP laser and Er,Cr laser:YSGG in a protocol that combines these two complementary wavelengths as an adjunct to subgingival debridement can significantly improve clinical outcomes compared to mechanical debridement over a 24-month period representing thus a valuable approach in non-surgical periodontal therapy.

The results obtained, respectively the significant improvement of the clinical parameters following the applied therapy, were maintained in a higher proportion than those obtained in comparison with the parameters obtained in the absence of adjuvant treatment at 24 months.

The second study is a randomized controlled clinical trial aimed at assessing the role of adjuvant laser treatment Er, Cr YSGG in the long-term progression of periodontitis, compared to adjuvant pharmacological treatment with chlorhexidine antiseptic, currently considered the standard of good practice according to expert guidelines, both associated with nonsurgical periodontal treatment. The objectives of the study were to evaluate in comparison over a period of 4 years the evolution of the clinical parameters and the periodontal survey depth (PDP), clinical attachment level (CAL), and, bleeding on probing (PDO) and number of residual pockets (PDP above 4 mm post treatment) in treated subjects with mechanically debridement and pharmacologically adjuvant therapy, and those treated with mechanical debridement treatment and laser adjuvant treatment Er,Cr:YSGG. The working hypothesis was that adjuvant laser treatment to mechanical therapy may bring comparable clinical results to mechanical therapy

with pharmacological adjuvant therapy in improving clinical parameters and reducing the number of residual pockets.

The aim of the study was to assess the therapeutic potential of Er,Cr:YSGG laser treatment, in the long-term evolution of clinical parameters of patients treated with periodontitis compared to those treated with pharmacological treatment with chlorhexidine antiseptic, in, currently considered "standard of care" according to expert practice guidelines, both used as adjuvants in nonsurgical periodontal treatment. The present study was designed as a controlled, randomized clinical trial spanning a 4-year period.

The specific objective of this randomized clinical trial was to prospectively evaluate over 4 years the evolution of periodontal survey depths (PPD), clinical attachment level (CAL), and, of the probing bleeding (BOP) and the number of residual pockets in 5 time points: initially at 6 months, at 12 months, at 24 months and 48 months after the initial assessment. We started from the hypothesis that the non-chirugal periodontal treatment with laser adjuvant brings results at least equal to the non-surgical periodontal treatment in the treatment of periodontitis, and it also reduces the number of residual pockets remaining after treatment to an equal or greater extent.

The study was designed as a randomized clinical trial in which 2 batches of patients received non-surgical periodontal treatment with adjuvant laser or pharmacological treatment according to group allocation and were followed up on duration of 4 years. Patients were instructed to follow a strict hygiene protocol so that the dental plaque index reaches a value below 0.3 acceptable for starting therapy and maintain it during the research.

In the initial stage of over and subgingival descaling followed by curettage with manual curettage in all periodontal pockets with depths above the measured value of 4 mm was carried out in both research groups followed immediately adjuvant treatment according to group allocation. After 6 months a new supragingival descaling was performed followed by manual curettage and adjuvant treatment for all survey depths greater than 4 mm highlighted by periodontometry at this time point repeated in the same manner at 1 year and 2 years. Clinical parameter assessments were carried out at 5 time points: initially, at 6 months, at 12 months, at 24 months and 48 months after the initial assessment. The variables assessed are PPD (PPD>=5mm), CAL, BOP and the number of residual pockets. Orthopantomography X-rays were performed as part of the initial examination.

Results: All estimated coefficients provide new empirical evidence that PPD, CAL, BOP and PI are positive indicators that ensure periodontal health in laser therapy for periodontitis.

Of these, PPD has the strongest estimates, followed by CAL and BOP, while PI has the least influence power, the most, being used as a marker to evaluate the quality of oral hygiene, its follow-up is important because poor oral hygiene has a negative influence on treatment results.

Both treatment protocols, SRP+CHX and SRP+Er,Cr:YSGG laser, have been confirmed to be effective. Periodontal treatment SRP+Er,Cr:YSGG laser demonstrated significant clinical

improvements and provided a better clinical result compared to SRP+CHX after 4 years. In addition, significant differences between groups were observed when tracking T2, T3, T4. PPD, CAL, BOP and PI prove to be essential indicators for the success of periodontal therapy, as shown by GGMs and SEM.

Treatment of periodontal pockets remaining after the primary stage of periodontal treatment represents a sensitive element in maintaining the results and preventing relapses. ErCr:YSGG laser due to the therapeutic impact it has not only on soft tissues, but also on soft tissues, the mucosal wall of the supra-crestal periodontal pockets and also on the root wall turns out to be a valuable adjunct in non-chirugal periodontal therapy.

The third study is a controlled clinical trial aimed at assessing the role of adjuvant laser treatment compared to pharmacological adjuvant treatment in patients with peri-implary mucositis. The objectives of the treatment were to evaluate the evolution of clinical parameters and peri-implantar sounding depth (PID) and 6-month probing bleeding (PDO) in patients treated with mechanical debridement pharmacologically adjuvant or treated by mechanical and adjuvant laser debridement therapy, respectively two lasers with complementary therapeutic actions Er.Cr:YSGG and InGaAsP. The working hypothesis was that adjuvant laser treatment to mechanical therapy brings clinically comparable results to mechanical therapy with adjuvant pharmacological treatment.

The aim of this research is to evaluate the potential of 2 complementary lasers in reducing the bacterial charge with pathogenic potential at the peri-implantation space level and subsequently, in reducing the signs of inflammation around the implants diagnosed with mucositis and compare their effectiveness with a widely accepted treatment, using abrasive powder with compressed air and chlorhexidine solution, the, as pharmacological adjuvant treatment.

The specific objective of this randomized clinical trial was to prospectively evaluate over 6 months the evolution of peri-implantation survey depths (PPD), and, a bleeding at probing (BOP) and peri-implantar bone (assessed) radiological level (RBL) in two batches of subjects carrying dental implants affected by mucositis treated with mechanical therapy and pharmacological adjuvant (chlorhexidine) and mechanical and adjuvant laser therapy in two previously randomised treatment groups. The probing depth below 5mm associated with the negation of the bleeding index is considered therapeutic success parameters.

In this research we start from the hypothesis that adjuvant laser treatment to mechanical therapy in the treatment of peri-implantar mucositis would bring clinical benefits at least equal to adjuvant pharmacological treatment to mechanical therapy in the treatment of peri-implantar mucositis this is the most popular treatment among clinicians and the most documented and supported by existing publications: local treatment with glycine powder and chlorhexidine solution 0.2%.

The results of this research indicate that laser treatment with 2 complementary wavelengths in order to reduce local bacterial load and manage dysbiosis in the peri-implantation space is a

treatment that can be considered an alternative therapeutically viable and the results proven by this study can be considered encouraging.

Therapeutic intervention on the peri-implantation soft tissues of lasers is beneficial and with clear clinical effects.

The use of an adjuvant treatment with two lasers with synergistic tissue interactions from some perspectives but complementary from others may be considered a timely alternative in the treatment of inflammatory conditions of peri-implantation fabrics.

The results of the study reveal a higher potential for resolution of perimplantar mucositis if two complementary lasers are additionally used.

In the situation of a disease with increasing prevalence, the confirmation of new therapeutic techniques that can increase the possibilities of resolution of the disease is more than gratifying.

CHAPTER 6. FINAL DISCUSSIONS

This paper aimed to evaluate the therapeutic potential of lasers in inflammatory diseases of the oral cavity, especially periodontitis and peri-implantar mucositis, conditions with high prevalence between dental diseases of the population.

With the increase in quality of life, the greater interest of the current population compared to previous generations in oral health, but also the increase in the life expectancy of the population, the number of periodontal diseases diagnosed is increasing.

Periodontal diseases are frequently diagnosed in subjects who have a multitude of other organic diseases and not only. Very often the subjects affected by the disease are looking for therapeutic solutions as current and as potent as possible as a therapeutic result, but there is also a category of subjects who reject the idea of accepting medicinal treatments, for example adjuvant drug treatments in periodontal and peri-implantation conditions, have various allergies or contraindications. In addition, the high number of antibiotic resistances reported by world health associations and disease control centers further limits the possibilities of using pharmacological adjuvant therapy in support of mechanical therapy basic, this is because adjuvant therapies are an extremely important component of non-surgical therapies for periodontal and peri-implantation diseases treatments and it is recognized that they bring important improvements in the resolution of these diseases.

This entails a greater focus of clinicians to find innovative therapeutic solutions that can cover the needs of periodontal treatment, but at the same time adjuvant treatments that improve the results of treatments already accepted or that cannot be replaced.

In this context, adjuvant laser treatments come to bring solutions for clinical cases that are difficult to manage for medical reasons and can be considered an alternative to consider in periodontal or peri-implantation treatments non-surgical in order to augment and prolong the clinical results obtained.

Since the introduction of antibiotics into medicine, they have been assigned a special role in the treatment of infectious diseases.

Antibiotics are an important component of health therapies because they allowed survival and healing for conditions that in the past led to the death of patients.

On the other hand, the mechanisms by which they act both from the perspective of the human subject and the microorganisms involved have many critical aspects.

The spectrum of diseases caused by microorganisms is growing worrying, but also the emergence of resistance to their use. Concerning resistance arising after administration of antibiotics, in the

United States in 2019, the Centers for Disease Control reported more than 2.8 million illnesses with resistant microorganisms and more than 3,500 deaths due to them. (Shrestha J., et al, 2023).

For the administration of antibiotics, in dental medicine as in general medicine, more caution would be desirable, and a simple and clear set of measures to prevent incorrect administration and prevent the risk of developing resistance.

All health practitioners should become more aware of the risks and consequences of abusive or inappropriate antibiotic administration.

The U. S. Centers for Disease Control reports 20%-50% incorrect or unnecessary antibiotic administrations in treatment centers, respectively 40-75% incorrect or unnecessary administration of antibiotics in care centers. The percentages are worrying.

The Antimicrobial Resistance Surveillance Center (AMS) programs follow the following strategy through which they aim to achieve better management of antibiotic administration and reduce the risks of developing bacterial resistance with all the inconvenience that arises from this, a strategy that is primarily addressed to medical teams, but also has in mind the awareness of patients to avoid self-administration.

Clinicians should be prepared to make the right antibiotic prescription, the right dose, the most appropriate method of administration, optimal duration of therapy and including reduction of time to evidence of therapeutic antibacterial efficacy following administration. (Shrestha J. et al.,2023).

Bacterial resistance developed to antibiotics is a complex mechanism. This type of bacterial resistance is genetically mediated by specific fragments or even genes that encode these specific transmembrane proteins. Sometimes these genes that confer microbial resistance phenotype are mobile from bacteria to bacteria, giving resistance by horizontal gene transfer.

Moreover, according to several studies, the oral cavity is a very rich environment for antibiotic resistance genes (Abhood H M., et al., 2023; Alekshun M N., et al., 2007).

Still not fully explored, however, is the correlation between bacteria's resistance to antiseptics and that of antibiotics. For these reasons, it is very important to manage the prevention of antibiotic and antiseptic resistance by reducing the use of antibiotics and chlorhexidine, and by using ozone, lasers, etc, hydrogen peroxide and natural substances as adjuvant treatment alternatives in the management of periodontal and peri-implantation infections. (Sevi S., et al., 2024).

The resistance of different bacterial species to CHX has been reported in studies over the past few decades, but at concentrations well below those used in the clinical context. Compliance with standard laboratory procedures for biocide susceptibility testing prevents the synthesis of these findings. Meanwhile, studies of bacteria adapted to CHX in vitro have reported cross-resistance between CHX and other antimicrobials.

This may be related to the common resistance mechanisms of CHX and other antimicrobials, as well as the selective pressure created by the intensive use of CHX. While clinical studies supporting the CHX cross-resistance hypothesis with antibiotics are currently lacking, it is important to highlight the potentially negative impact of the unhindered use of CHX on combating antimicrobial resistance. (Abbood Hm., et al., 2023).

The effect of chlorhexidine on the damage to the bacterial cytoplasmic membrane is followed by the leakage of cytoplasmic material. Thus, the mechanisms that confer resistance to CHX include multidrug efflux pumps and cell membrane changes. Recent studies have identified changes in outer membrane proteins and lipopolysaccharide profiles involved in resistance to CHX and cross-resistance to antibiotics (Cieplik F., et al., 2019).

In view of these aspects, we have researched alternative methods of antibiotics and local antiseptics administration to reduce bacterial load and pathogenicity of the flora from the periodontal and peri-implantation space as potential treatment alternatives adjuvant in periodontitis and peri-implantar mucositis. The study reveals the capacity of diode and erbium lasers in synergistic effect in certain aspects and complementary in other aspects of removal of periodontal pockets.

Correcting dysbiosis is an extremely important element in healing periodontitis and preventing relationships, the results of the research come to light the ability of lasers to effectively modulate the proportion of pathogenic and non-pathogenic species in periodontal pockets immediate after treatment and also their ability to bring therapeutic results which are stable and durable over time.

Also, the clinical parameters obtained post treatment are superior in the laser group compared to the control group, the gain of attachment being significantly higher. An essential element in this treatment is the quality of the new clinical attachment obtained post therapy.

Its quality is clearly superior, the new clinical attachment obtained by adjuvant laser treatment being of conjunctive type, histologically close to the authentic attachment before the onset of the disease, unlike the long junction epithelium attachment obtained with known periodontal treatments, respectively the mechanical treatment without adjuvant treatments or with pharmacological adjuvant. The clinical attachment obtained post therapy is in fact the most important vector of long-term success.

The reduction in the depth of periodontal pockets is the main clinical element assessed in the counting of disease progression, and the benefits of adjuvant laser treatment are definitely confirmed as superior compared to the adjuvant pharmacological treatment.

Much diminished sampling depths following nonsurgical laser adjuvant mechanical treatment have been achieved, but especially significant reduction in the number of residual pockets, this is an important factor of relapse in periodontal disease due to the maintenance of a territory where

periopathogens can multiply and subsequently recolonize the previously treated and healed periodontal spaces.

Correcting dysbiosis is also an extremely important element in maintaining long-term results. Dysbiosis cannot be corrected by mechanical therapy alone, and the results obtained by using a pharmacological adjuvant are not sufficient.

Topically administered pharmacological preparations have low-term effects, and generally administered antibiotics modify local dysbiosis induced by periodontal disease to other forms of dysbiosis according to the spectrum of action of the antibiotic used. Preparations containing specific probiotics for the oral cavity are of interest for therapy, but the long-term benefits of these preparations are still not fully supported by clinical trials on large batches of subjects.

The results of these 3 studies come to prove the therapeutic potential that the combination of lasers in fact 2 wavelengths with complementary clinical effects can bring in the treatment of periodontal and peri-implantar inflammatory conditions.

The present studies aimed to inform the scientific community on the interactions that these two lasers have with periodontal and peri-implantation tissues, the tissue therapeutic impact and the effects on periopathogens by correcting dysbiosis, the study said, but also objectifying the therapeutic effects obtained by using them. Extension of research with follow-up to 2 years, at 4 years in study 2, respectively, it once again confirms the stability of the superior clinical results obtained in the laser group compared to the control group and the absence of remissions.

It is a very comfortable therapy, easy to tolerate, without contraindications (except for patients with malignant diseases, where local biostimulation is avoided). This is a minor aspect, but it comes to be important given that the treatment of patients suffering from periodontitis or peri-implantar mucositis consists of repeated therapy sessions, and the pain experienced during treatment, or later, it can cause patients to stop treatment.

The 2 InGaAsP and Er,Cr YSGG lasers have a complementary tissue impact: the most important benefits in periodontal treatment come from the water-absorbing laser and hydroxylapatite, and in a smaller proportion from the diode, for this reason, we have separately evaluated in a 4-year research the contribution that this laser brings in improving the results obtained by non-surgical periodontal treatment compared to the classical treatment only by debridement non-surgical treatment and manual curettage.

The results are statistically significantly better in the laser group at 6 months, at 1 year, at 2 years and at 4 years. There are very few post-periodontal treatment evaluation studies that span such a long period. From this perspective, the research also brings important information on the dynamics of periodontal survey depths if the subjects are treated with mechanical and pharmacological adjuvant treatment, but even more so on the long-term benefits of adjuvant laser therapy.

In this research, it was revealed that the number of residual pockets remains significantly lower in the laser group throughout the entire research period. These studies confirm that the erbium laser is an extremely important adjuvant in incrementing the final therapeutic results of non-surgical mechanical periodontal treatments, regardless of the topography of the lesions.

Both lasers "InGaAsP" and "Er,Cr:YSGG" also have a secondary benefit, namely local perilezional biostimulation. Perilesionally dissipated energy following the action of the laser in the affected territory causes stimulation of local circulation, modulates local immune response, normalizes membrane potential, reduces post therapeutic discomfort, it increases mitochondrial activity and the synthesis of alkaline phosphatase and calcitonin, both of which are useful for local bone healing.

The research has also been extended to peri-implantar mucositis, a newer class of conditions with the increase in the number of implants applied, hence its more recent awareness as an inflammatory condition of the oral cavity.

The onset forms clinically classified as mucositis benefit from successful nonsurgical treatment in disease resolution. There is still no single generally accepted and recommended treatment, various adjuvant treatment methods are tried in addition to mechanical treatment.

The results of this study come to validate the presumed benefits that laser treatment with 2 wavelengths, the, previously checked as an effective adjuvant treatment in the resolution of periodontitis brings the same results in the treatment of mucositis (the form of onset of peri-implantar inflammatory diseases). If two successful vectors were evaluated for this condition, combined, namely reducing the sounding depth below a clinical value of 6 mm and negating the local bleeding index, respectively, in this study, 34 out of 48 implants achieved healing in the adjuvant laser treatment group, compared to only 14 out of 42 implants where healing was achieved in the adjuvant pharmacological group, which is confirmed in detail by the statistical results.

The laser parameters chosen seems to be at least for now the most suitable to achieve clinical results without damaging the root surface or the implant surface. Further research would be appropriate in order to assess whether these studied parameters are optimal or whether there are other more appropriate energy doses that could bring superior clinical results to those obtained in this research.

No tissue damage has been shown to overheat the marginal bone neither in the treatment of periodontitis nor in the treatment of mucositis, although this was a serious reason to worry and limit the energy dose used, but also the working time, in this research.

Diode, the laser most likely to cause local temperature rise in tissues during treatment benefited from a clear limitation of working time to 60 seconds per treatment session for monoradicular teeth and 120 seconds per treatment session for pluriradicular teeth having a larger diameter. For implants, the working time was also limited to 60 seconds, and in the first and last study in which

this laser was used, the, it was supplemented with water jet during the time the laser was in action to keep the local temperature within security parameters.

No evidence of any damage to the implant surface was found to prevent reattachment of human tissues, respectively bone tissue, conjunctive, root surface to the titanium oxide coating on the implant surface, no thermal damage to the level of these tissues by increasing the local temperature determined by the diodes, neither was the ablation of cementum on the root surface or of the titanium oxide layer on the implant surface by the erbium laser that would have been a risk again highlighted. These aspects come to confirm that the working parameters were correctly chosen, the handling of the two machines was also correct and the working protocol was rationally chosen.

The limitations of these studies come primarily from the investigation of small batches of patients. Another limitation would be that the group of subjects included come from a social group that addressed the services medical a private clinic, and from this perspective we can not appreciate whether the group of subjects is entirely representative of the general population.

CHAPTER 7. CONCLUSIONS

The results of these comparative studies confirmed the ability of adjuvant laser treatment to bring a significant improvement in the clinical results of mechanical treatment in both periodontitis and peri-implantar mucositis. The confirmation of laser treatments as a therapeutic alternative of adjuvant treatment with results at least comparable to other pharmacological adjuvant therapies described in the literature is supported due to the results of these studies.

Reduction of the prescription of antiseptic, especially chlorhexidine, widely used in the treatment of periodontitis and peri-implantar mucositis, and the same is true of the antibiotic prescription in the treatment of these two conditions with high prevalence is more than necessary and can only be obtained by replacing them with alternative therapies that can bring results comparable clinics.

Confirmation of maintaining the results of parodotitis or peri-implantar mucositis treatments with the support of these adjuvant treatments over time is also proven by the research results.

Although there are a wide variety of adjunctive treatments in the treatment of periodontitis and mucositis, laser treatments can be considered a valid alternative for improving and supporting therapeutic results.

Laser treatments are much more comfortable per-patient compared to other treatments in the same field.

Also postoperative the discomfort of patients is significantly reduced. Biostimulation provided by perilesionally dissipated energy significantly speeds local healing compared to current methods.

CHAPTER 8. ORGINAL CONTRIBUTIONS AND THEIR APPLICABILITY

The administration of antibiotics and antiseptics in dentistry is already a current practice. The scale of their use, however, brings serious problems related to the resistance developed to antibiotics and antiseptics that have far broader medical implications. In this respect, the research that is part of the present thesis explored therapeutic alternatives to reduce the prescription of antibiotics and the consumption of antiseptics in dentistry in order to reduce the risk of developing resistance bacterial to antibiotics and antiseptics, but also cross-allergies between them.

Some lasers have the ability to selectively reduce the amount of pathogens in the contaminated periodontal and peri-implant space and in this way can be a therapeutic alternative to consider as adjunctive therapy in the treatment of periodontitis and peri-implantitis for the resolution of common forms of the disease, but also for special clinical situations that do not find their solution with already known therapeutic strategies.

The theme approached: the usefulness of lasers in inflammatory diseases of the oral cavity comes to open new therapeutic perspectives in the treatment of periodontitis and peri-implantitis.

Although there are mechanic-antiseptic, pharmacological treatments confirmed by numerous publications that bring therapeutic success and healing, the impact/the benefit that lasers can bring to the treatment of these two conditions with high prevalence among the population is an important one, but knowledge in this area is still limited.

The confirmation obtained by the present research on the specific indications of lasers in the treatment of these diseases, the right wavelengths, the correct doses and parameters to be applied in the treatment of these conditions is considerable, and last but not least, the working protocols chosen in order to obtain optimal clinical results are solutions that can have wide applicability in ascestor treatment two conditions with such high prevalence.

This research provides the medical community with information about the clinical use of lasers in the treatment of periodontitis and peri-implantar mucositis in order to broaden the range of therapeutic options available to practitioners for treatment of these conditions.

These studies open many directions of further research on the parameter range, the energy dose or doses, and the protocols that can be used in laser treatment of inflammatory diseases of the oral cavity.

In addition, given that the increase in the prescription of antibiotics and antiseptics has led to the emergence of resistances, including cross between them, difficult to manage, exploring and studying alternative therapies that could bring comparable results has become necessary. Reducing the prescription of chlorhexidine in the treatment of periodontal and peri-implantation

conditions would be useful in conditions where chlorhexidine is widely used in the treatment of these conditions, and the reduction of its prescription can only be made if it is replaced by other alternative therapies that bring comparable clinical results, reducing local bacterial load and correcting local dysbiosis is an essential factor in achieving disease resolution and maintaining clinical results over a long period of time.

Studies published so far in the field of laser use in periodontal and peri-implantation therapy are few compared to other therapeutic methods. Optimal energy doses are still the subject of debate among the clinicians. The use of two laser wavelengths is a novelty.

The research contained in this thesis comes to bring new information on the therapeutic possibilities in the field and to open new research possibilities on the different combinations of lasers possible in order to achieve therapeutic results superior to those obtained so far. From another point of view, the use of lasers as adjuvants in periodontal therapy opens new research opportunities on therapeutic protocols that could be tested in maintenance therapy and in the treatment of residual pockets, an important factor of relapse in periodontal disease.

The few published studies on laser treatments in inflammatory diseases of peri-implantation tissues justify investigating and exploring the possibility of using these laser therapeutic protocols confirmed and validated by previous clinical research in periodontal treatments and for other conditions with increasing prevalence, for example, peri-implantatitis.

In light of the known similarity between periodontal and peri-implant conditions, research in this area is overwhelmingly in vitro studies. However, they bring important information on the interaction of lasers with bone, epithelial and conjunctive cells at the laser doses chosen and also the interaction of laser energy with the implant surface.

The ablative doses and thermal impact on the titanium oxide surface on the implant surface have been highlighted. In this context, conducting clinical research on the potential benefits of two-month complementary wave laser therapy in the treatment of peri-implantar inflammatory conditions came naturally. The results of the research come to confirm the initial hypothesis and open new clinical perspectives of treatment for peri-implantar inflammatory conditions and future clinical research in this field.

The current research is a unique study from the perspective of the research originality, the laser treatment protocol, the proposed laser treatment stages and how to include them in the nonsurgical periodontal therapy. The energy doses delivered were chosen based on in vitro research in the previously published literature confirming the correct interaction and no side effects between lasers and tissues at the doses administered and in context of proposed treatment.

Also, the extension of the follow-up of the subjects for 4 years in the second study brings confirmations of the clinical results that are found in few specialized papers. The treatment protocol of mucositis with two lasers with complementary effect is a new approach, and in this

case, the delivered energy doses and the administration protocol are completely new and are calculated in the context of a good knowledge of the interaction between each laser and human tissues, previously confirmed and standardised intreaction from laboratory studies previously published in literature.

This paper aims to provide the academic environment and clinicians with information about the therapeutic potential of lasers in the treatment of these two conditions as well as details of current practice in the use of these lasers in hope dissemination of these treatments.

During the research, we performed syntheses on the stage of knowledge in inflammatory diseases of the oral cavity, especially in periodontal and peri-implantation diseases. We have also performed syntheses on the use of lasers in the treatment of oral diseases.

The research focused on the laser variants that can be used, respectively, different wavelengths with specific tissue interactions in accordance with the specific chromophores of each laser, clinical implications, therapeutic protocols used, and, variations in protocols and doses of energy administered. Also possible contraindications, risks for various lasers have been studied.

Dissemination of informations in the medical world on the therapeutic possibilities of lasers in the treatment of diseases present in the oral cavity and on the ways of using lasers in this field is carried out by the publication of the three studies the first of which brings long-term evaluated clinical results of a therapeutic protocol designed and exposed to the previous scientific environment.

So far, very few scientific papers have been published on this topic and none of them evaluate the results after a longer period of time (2 years, 4 years). The latest study brings the results of a new treatment protocol in which two lasers are used simultaneously as adjuvants in the treatment of peri-implantar mucositis.

Developing a treatment protocol with mechanical therapy and laser adjuvant of early peri-implantar inflammatory diseases (mucosites) starting from the similarity with the incipient forms of periodontitis for which there is already a validated protocol of previous studies that I have participated in and that have been published previously and others.

Validation of the results obtained by periodontal laser treatment of a study on the adjuvant use of lasers in the treatment of long-term prodontitis 2 years and 4 years, respectively.

Identification of optimal parameters for the use of the optimal laser energy dose in interaction with epithelial, connective tissues, bone, root surface and contaminated surface of dental implants and confirmation of efficient energy doses at tissue level as proposed therapeutic action, without causing any tissue damage.

FUTURE RESEARCH DIRECTIONS

- Starting from the results I propose in the future:
- The study of other laser treatment protocols with other doses in order to define the most effective laser treatment and the most efficient wavelength respectively doses of energy applied in order to maximize clinical results.
- Other research to define a standard reference treatment in the treatment of peri-implantar inflammatory conditions.
- Disseminating laser treatment protocols among clinicians in order to help them broaden their therapeutic possibilities.
- Prospecting a laser treatment protocol in the treatment of peri-implantitis.
- Research on decontamination of implant surfaces contaminated with pharmacological means and lasers.
- Investigation of other adjunctive therapies in the treatment of inflammatory diseases of the oral cavity that could reduce the use of antibiotics and antiseptics and implicitly the risk of resistance developed to them.

ARTICLES ON THE TOPIC OF DOCTORAL THESIS

1. **Ciurescu CE**, Dima L, Ciurescu VA, Noja GG, Istodor AV, Moga MA, Ardelean LC, Rusu LC, Leretter MT. Laser Therapy Effects on Periodontal Status: A Randomized Study Using Gaussian Network Analysis and Structural Equation Modeling Approach. Medicina (Kaunas). 2024;60(3):437. doi: 10.3390/medicina60030437. PMID: 38541163; PMCID: PMC10971936. **Impact Factor 2,4** https://www.mdpi.com/1648-9144/60/3/437

2. **Ciurescu CE**, Dima L, Ciurescu V A, Moga M A, Leretter M T, Rusu LC, Tigmeanu CV NEW APPROACHES TO LASER TREATMENT FOR ORAL PERIIMPLANT MUCOSITIS **Romanian Journal of Oral Rehabilitation**; 2024;16(1) DOI: 10.6261/RJOR.2024.1.16.1. **Impact Factor 0,7** https://rjor.ro/new-approaches-to-laser-treatment-for-oral-peri-implant-mucositis/

3. **Ciurescu CE**, Gutknecht N, Ciurescu VA, Gheorghiu A, Franzen R, Arweiler NB, Sculean A, Cosgarea R. Two-year outcomes following the adjunctive use of InGaAsP and Er,Cr:YSGG lasers in nonsurgical periodontal therapy in patients with stages III and IV periodontitis. **Impact Factor 2,175** Quintessence Int. 2021 Oct 19;52(10):848-857. doi: 10.3290/j.qi.b1702285. PMID: 34235909.

4. **Ciurescu CE**, Cosgarea R, Ciurescu D, Gheorghiu A, Popa D, Franzen R, Arweiler NB, Sculean A, Gutknecht N. Adjunctive use of InGaAsP and Er,Cr:YSGG lasers in nonsurgical periodontal therapy: a randomized controlled clinical study. **Quintessence Int.** 2019;50(6):436-447. doi: 10.3290/j.qi.a42508. PMID: 31111123,.**Impact Factor 1,460**

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