OVIDIUS UNIVERSITY OF CONSTANTA
DOCTORAL SCHOOL OF MEDICINE
MEDICINE DOMAIN

DOCTORAL THESIS

STUDIES ON THE USE OF IL1-beta, OPG and TNF-alpha IN THE EVALUATION OF PATIENTS AFTER THE INSERTION OF DENTAL IMPLANTS

SUMMARY

Scientific coordinator: Professor Victoria Badea, PhD

PhD student: Dobrescu Marcel-Lucian

CONSTANȚA
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Content

GENERAL PART. GENERAL STUDY OF KNOWLEDGE

INTRODUCTION

According to the World Health Organization (WHO), oral health is defined as the absence of dental diseases and chronic facial pain, oropharyngeal cancer, oral inflammations, congenital defects such as labioschisis or palatoschisis, absence of gingival diseases, dental caries, loss teeth and other diseases affecting the mouth and oral cavity. [1]

IMPLANTOLOGY – SHORT HISTORY

Humanity has realized since ancient times the importance of good teeth; thus, teeth were also used as a weapon of attack and defense, and the effects of tooth loss on general health were felt even then. The earliest evidence of dental implants concerns an empirical form of endo-osseous implants, which appear to have been used since the Mayan civilization, more than 1,350 years ago. Data from the history of medicine shows, following the discoveries made, that these models of endo-osseous implants were originally made in Egypt, where the richest people replaced their lost teeth with those extracted from slaves or from poor people who sold their teeth; when no human teeth were found, even animal teeth were used (goat, monkey, dog). [2,3,4,5]

CHAPTER 1. MODERN IMPLANTOLOGY - Types of dental implants

We can classify the implants that can be purchased into three categories:

- Endo-osseous – implant placed transosseous, with two subtypes: cylindrical and blade.

1. *The cylindrical* implant has a diameter varying between 3.3-5 mm and a length between 7-13 mm, although some companies have introduced thin 2-2.8 mm implants for the horizontally resorbed ridge, with a diameter of 6 mm for cases of severe atrophy, or 30-52.5 mm for zygomatic implants.

2. *The blade* implant, which cannot be used for the independent replacement of a single missing tooth, as it is not stable.

- Subperiosteal – the implant built after imprinting the surgically exposed bone field (alveolar and basal); it is fixed intimately to the bone, under the periosteum, with transgingival abutments or bars and have the advantage of distributing the masticatory force over the entire alveolar ridge.

- Transosseous – with a submandibular stabilization plate, the implant crosses the mandibular bone from the base to the alveolar ridge.

It was considered that modern implants that insert into the bone (endo-osseous) are accepted, because in most of them no

delimitation is observed (radiologically and histologically) at the level of the bone-implant interface. [5]

CHAPTER 2. THE IMPACT OF IMPLANTOLOGY IN DENTAL AESTHETICS

2.1 Aesthetics in dentistry

After tooth loss, a considerable reduction in hard and soft tissue volume can be expected. In the anterior maxilla, tissue loss can make future dental implant restorations less predictable in achieving and maintaining favorable soft tissues. This is even more evident in esthetically challenging situations, such as patients with a high smile line. [19]

2.2 Dental implant in anterior maxillary oral rehabilitation

For planning implant treatment in the aesthetic area, it is important to look carefully at the soft tissues that will frame the restoration. Achieving a fully formed papilla between the implant restoration and the adjacent teeth in the end result can be challenging. If the interdental tissue and underlying bone have been completely lost prior to implant placement, ideal papillary contours may not be possible. [20]

2.3 Factors that influence the aesthetic result

The most important factors that influence the aesthetic result of restorations with implant insertion are: the smile line, the position of the tooth, the position of the root of the adjacent teeth, the particularities of the periodontium, the shape of the tooth, the position of the implant.

CHAPTER 3. OSTEOINTEGRATION OF THE DENTAL IMPLANT

3.1 The relationship of the dental implant to soft and hard tissues

Oral implantology has been successful due to the discovery of the biological and mechanical properties of titanium. Many studies have reported that several factors, including implant geometry, surface design (macro-, micro- and nano-), wettability/energy, hydrophilicity or hydrophobicity, appear to influence the inflammatory and regenerative phases that occur during osseointegration.

3.2 Osseointegration of dental implants

To achieve an optimal osseointegration process, it is necessary to minimize bacterial adhesion by all means, while promoting and stimulating the differentiation of osteogenic and fibroblastic cells to achieve perfect integration of the implant in hard and soft tissues. The goal of future research is to design multipurpose implant models with properties aimed at biocompatibility and osseointegration on the one hand and prevention of peri-implantitis on the other. [38]

3.3 Proinflammatory cytokines-Interleukin 1-beta (Il1-beta), Tumor necrosis factor (TNF-alpha), Osteoprotegerin (OPG) and their impact on osseointegration

Cytokines are defined as important components in the inflammatory response and which, from a chemical point of

view, are immunomodulatory peptides or proteins produced by a large number of cells, such as T or B lymphocytes (LT, LB), monocytes and neutrophils, but and periodontal cells, such as fibroblasts and epithelial cells.

3.4 Biomarkers in predicting the status of patients after dental implant

Biomarkers can be defined as objectively measurable substances that assess normal biological processes, pathological processes and pharmacological responses following a therapeutic intervention. Therefore, biomarkers are substances produced in the body of healthy individuals or by patients who present a condition, they are used in monitoring the clinical status, in identifying the moment of onset of the disease or the response obtained following a treatment.

CHAPTER 4. COMPLICATIONS AFTER DENTAL IMPLANT INSERTION – PERIIMPLANTITIS

Peri-implantitis has been mainly defined as an inflammatory response of the mucosa around the implant with marginal bone loss, while mucositis is an inflammation of the soft tissues. [49]

4.1 Clasification

A recent classification, accepted by specialists in the field, made by Ata-Ali et al. according to the most relevant clinical signs for mucositis and peri-implantitis is presented in the tables below. [53]

Table 3. Classification of mucositis [53]

STAGING	**DEFINITION**
Stage 0A	PD ≤ 4 mm and IS and/or SUP, without signs of bone loss followed by bone remodeling during healing
Stage 0B	PD > 4 mm and IS and/or SUP, without signs of bone loss followed by bone remodeling during healing

PD = peri-implant ditch; IS = bleeding index; SUB = suppuration

Table 4. Classification of peri-implantitis *[53]*

Stages	**DEFINITION**
Stage I	IS and/or SUP and bone loss ≤ 3 mm beyond bone remodeling
Stage II	IS and/or SUP and bone loss > 3 mm and < 5 mm beyond bone remodeling
Stage III	IS and/or SUP and bone loss ≥ 5 mm beyond bone remodeling
Stage IV	IS and/or SUP and bone loss ≥ 50% of implant length* beyond bone modelling

IS= Bleeding Index; SUP = suppuration

4.2 Etiopathogenesis of peri-implantitis

Bacteriological studies carried out over time have suggested that the bacterial species involved in these infections are common to those that largely generate periodontitis, and from here the hypothesis, which has been verified otherwise, that the teeth affected by periodontal disease are the source of implant infection, and are therefore responsible for the appearance of peri-implantitis. The bacterial species involved in the production of mucositis are mainly cocci and gram-positive, immobile, aerobic bacilli, while in peri-implantitis mainly anaerobic gram-negative bacilli are identified alongside spirochetes.

4.3 Pathophysiology of peri-implantitis

From a physiopathogenic point of view, the vast majority of specialists in the field appreciate that bacteria represent the starting point in the appearance and development of the local inflammatory process, with all the clinical harm it entails for the patient. [56, 57, 58, 59, 60]

CHAPTER 5. GENERAL METHODOLOGY

5.1 Types of implants used - Dental implant insertion protocol

In my personal study and research I used Dentium implants produced in South Korea - the company Dentium Co LTD. [63]

5.2 Peri-implant fluid collection technique

Peri-implant crevicular fluid (FCPI) - is a tissue exudate in which plasma proteins, antimicrobial peptides, cytokines and

immunoglobulins are present, components that support, among others, the antibacterial potential of this fluid.

5.3 Technique for identifying pro-inflammatory cytokines - ELISA technique

METHODS FOR QUANTIFICATION OF IL1-beta, OPG and TNF-alpha - ELISA METHODTo determine these biomarkers, we used kits produced by the company Salimetrics for IL1-beta, Affymetrix eBioscience for OPG and ABCAM for TNF-alpha, kits that allow the quantitative determination of these parameters through the ELISA (enzyme linked immunosorbent assay) technique.

5.4 Methods for identifying bacterial species in peri-implant fluid and crevicular fluid

Due to the need to identify as accurately as possible the bacterial species involved in these conditions, a modern method of identification - the API system - was created and perfected. [65]

5.5 Presentation of the study group. Inclusion and exclusion criteria

In the delimitation of the study group, the inclusion and exclusion criteria, as well as in the choice of the clinical and paraclinical parameters used, we took into account the data from the specialized literature accessed. As we stated in Chapter 4 of the Current State of Knowledge, J. Ata Ali made an updated classification in 2015, in which he uses clinical parameters for mucositis (the depth of the peri-implant trench, the bleeding index and the presence of suppuration), while for peri-implantitis only uses the index of bleeding, suppuration

along with the radiological examination [53], a classification followed in the studies carried out by other authors as well. [66, 67, 68]

5.6 Study design - Presentation of the study group

The study group was made up of a group of 320 patients presented in the private dental practice and in the department of Implantology of the Faculty of Dental Medicine, "Ovidius" University of Constanța. A total of 1223 dental implants were inserted in them, between January 2020 and January 2022. We mention that 286 (89.38%) patients had a favorable evolution after dental implant insertion and 34 (10.62%) had an unfavorable evolution.

From the group of patients with a favorable evolution, we randomly selected 20 patients who constituted the control group. To these we added the 34 patients with unfavorable evolution of the dental implant, thus forming the study group of 54 patients.

Following the periodontal clinical and radiological examination, the patients in the study group were classified into 3 categories as follows in table 9.

Table 9. The proportion of patient samples in the study group

Healthy	20	37.04%
Mucositis	24	44.44%
Peri-implantitis	10	18.52%
Total	54	100%

CHAPTER 6. STUDY I - IL1-beta, TNF-alpha, OPG AND CORRELATION WITH CLINICAL PARAMETERS SEVEN DAYS AFTER DENTAL IMPLANTS INSERTION

6.1 Introduction

I chose to follow the dynamics of TNF-alpha and IL1-beta from the first category, and from the second category, OPG, in my personal research. This is the motivation for which I chose in my doctoral thesis to study these markers in the complex context of peri-implantitis, in the hope that the results obtained can constitute a small step forward regarding the optimization of patient monitoring after the insertion of dental implants and, at the same time, to be able brings new elements related to the development of knowledge on this topic.

6.2 Working hypothesis

Interleukin 1-beta, TNF-alpha and OPG are markers that can be used to assess the evolution of patients after the insertion of dental implants.

6.3 Purpose and objectives

Correct clinical and paraclinical assessment using biomarkers aims to establish and apply the most correct monitoring and treatment scheme, so that the risk of implant loss is as low as possible. The objectives of this study are to quantify the

following biomarkers seven days after the insertion of dental implants:

- IL1-beta;
- TNF-alfa;
- OPG ;
- Evaluation of these biological parameters in relation to the radiological aspect.

6.4 Obtained results

6.5Discussions

IL1-beta, OPG and TNF-alpha values were higher around implants that generated mucositis and peri-implantitis compared to implants with a favorable evolution; the most significant differences between the three groups were recorded for IL1-beta. The special predictive value of IL1-beta is also demonstrated by the highly statistically significant correlation with the depth of the peri-implant groove and with the bleeding index for both mucositis and peri-implantitis patients, results also cited by other authors. Osteoprotegerin and TNF-alpha correlate very highly with the bleeding index in patients with mucositis and those with peri-implantitis, results also cited by Hasan Gündoğar and A. B. Petkovic. [45, 76]

From the evaluation of the obtained results, the differences with the highest statistical significance were observed for TNF-alpha in FCPI between patients with mucositis and those with

peri-implantitis, which is very useful for the practitioner. Similar results have been cited in other studies looking at the quantification of TNF-alpha along with other biomarkers in patients with favorable implant outcomes and in patients with short-term peri-implantitis. [82]

Related to OPG, other studies similar to those in this doctoral thesis are cited in the specialized literature; thus, Rakic M. et al. which concludes that also in the present study, that OPG correlates with clinical parameters and can be used for the diagnosis and monitoring of peri-implantitis, with statistically significant differences between the groups of patients with peri-implantitis and those with implants with favorable evolution. [66, 89]

CHAPTER 7. STUDY II - Particularities of the bacterial flora in patients with dental implants

7.1 Introduction

The importance that bacteria have in the etiopathogenesis of mucositis and peri-implantitis is undeniable; numerous studies carried out so far have demonstrated the existence of multiple valences of the cause-effect relationship related to the presence of peri-implant bacterial biofilm with the inflammatory reaction of soft tissues in the case of mucositis, respectively soft and hard tissues in the case of peri-implantitis. The overwhelming role of pathogenic bacterial species in the occurrence of mucositis is demonstrated by the reversibility of this condition after three weeks of complex treatment, which implicitly also aims to destroy pathogenic bacteria. [67]

7.2 Working hypothesis

In the context of the above, the working hypothesis in this research pillar is that bacteria generate and maintain changes in peri-implant tissues, in the clinical context of mucositis and peri-implantitis.

7.3 Purpose and Objectives

The purpose of the study is to optimize the diagnosis of mucositis and peri-implantitis through the bacterial prism, in order to institute the most effective treatment scheme as early as possible**.**

The objectives of the study are:

1. Identification of the bacterial species that correlate best with the clinical status of mucositis and peri-implantitis.

2. Evaluation of the possibility of a causal relationship between the presence of bacteria and infections after dental implant insertion (mucositis and peri-implantitis) - calculation by Odds Ratio.

3. Establishing the extent to which bacterial species can contribute to the unfavorable evolution of peri-implantitis, the risk of disease progression - calculation by Risk Ratio.

7.4 Results obtained

Bacterial Species	FCPI	Subgingival Plaque
Porphyromonas spp.	20	20
Prevotella spp.	16	16
Peptostreptococcus	8	8
Fusobacterium spp.	8	8
Actinomyces odontolyticus	15	15
Staphylococcus aureus	8	6
Veillonella parvula	12	10
Streptococcus intermedius	19	22
Streptococcus constellatus	19	26
Streptococcus sanguis	18	17
Streptococcus gordonii	15	9

Streptococcus vestibularis	**11**	**9**
Total	**169**	**196**

Depending on the presence/absence and the number of pathogenic bacterial species identified alongside the saprophytic species, a bacterial score was created that we further used in the research in this chapter.

Table 33. Distribution of bacterial scores on the three lots taken in the studio

Score	**1**	**2**	**3**	**4**	**5**
Favorable Evolution	10	9	1	0	0
Mucositis	2	2	19	0	1
Peri-implantitis		1	1	3	5
Total	12	13	20	3	6

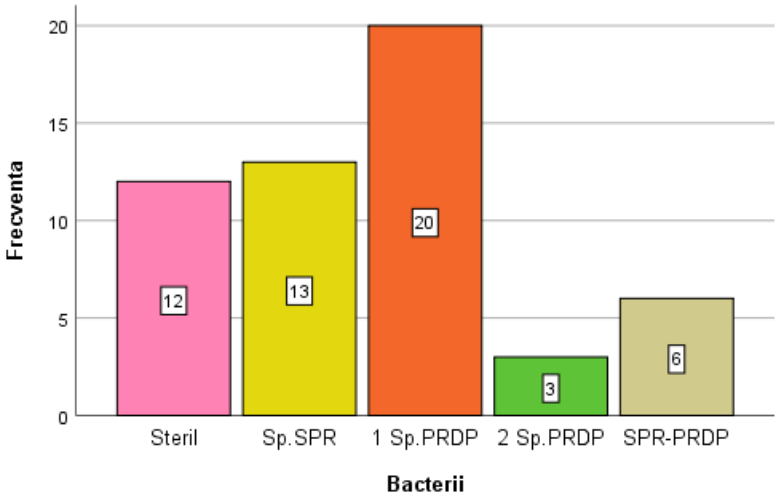

Figure 48. Distribution of bacterial scores on the three studied lots

7.5 Discussions

Given the fact that in the specialized literature we did not find data related to mathematical calculation, in order to provide objective evidence regarding the causal relationship between bacteria and infections following the insertion of the dental implant, in the present study we assessed this relationship by calculating the Odds Ratio (Room R); we also considered that it is useful and relevant at the same time for the evaluation of the patient after the insertion of dental implants, to be able to correctly assess the risk of disease progression - Risk Ratio (Rr), risk related to the presence of bacteria.

7.6 Preliminar conclusions

1. The pathogenic bacterial species identified with the highest weight were species of the genera Prevotella and Porphyromonas, species with predictive value in defining peri-implantitis.

2. The close causal relationship between bacteria and infections following the insertion of dental implants is demonstrated by the very high values calculated by the Odds ratio.

3. The definite involvement of bacteria in these infections is proven by the increased risk of evolution towards mucositis in patients with a favorable evolution in the conditions of the association of a single pathogenic bacterial species.

4. The presence of pathogenic bacterial species correlates with the depth of the peri-implant groove both in the case of mucositis and in the case of peri-implantitis; the highest level of correlation being in the context of peri-implantitis.

5. The presence of pathogenic bacteria correlates with the bleeding index in patients with mucositis and those with peri-implantitis.

6. Bacteriological examination of the peri-implant fluid is extremely useful in monitoring the patient after the insertion of dental implants.

7. The identification of pathogenic bacterial species allows treatment according to the antibiogram in order to block the peri-implant inflammatory process.

8. Understanding the factors underlying the bacterial etiopathogenesis of peri-implantitis is essential in developing strategies for the prevention, diagnosis and treatment of peri-implantitis.

CHAPTER 8. THE THIRD STUDY IL1-BETA, TNF-ALFA, OPG THREE AND SIX MONTHS AFTER DENTAL IMPLANTS INSERTION

8.1 Introduction

The studies on the dynamics of pro-inflammatory cytokines in the context of this condition focused on the analysis of Il-1beta and TNF-alpha, given their known role in the development of the inflammatory process, the reduction of the regeneration capacity of peri-implant tissues and the occurrence of bone resorption; the manner of increasing the expression of the receptor of nuclear factor K (RANKL) under the influence of TNF-alpha was also studied. [76, 114]

Similarly, data related to OPG, as a key factor in the regulation of bone metabolism and a valuable biomarker in the assessment of alveolar bone destruction and bone loss, are extremely valuable. For these reasons, I considered it useful to continue to clinically and paraclinically evaluate the patients included in the study, after three and six months after the insertion of the dental implants, with the idea of capturing as accurately as possible the dynamics of the biomarkers for a more objective

assessment of the favorable evolution or unfavorable of the patients.

8.2 Working hypothesis

Taking into account the above, study III starts from the assumption that there is an initial increase in pro-inflammatory cytokines, most likely, in the context of surgical trauma; subsequently, under the conditions of maintenance of the inflammatory process by bacteria, there would be an excess synthesis of the three biomarkers with the consequent destruction of the maxillary bone in severe forms of peri-implantitis.

8.3 Purpose and Objectives

- The aim of the study is the clinical and paraclinical evaluation of patients using biomarkers, so that it is possible to diagnose and apply a treatment scheme as early as possible, so that as many patients with mucositis and peri-implantitis as possible can be recovered, and finally, the risk of implant loss to be as low as possible.
- The objectives of this study are to evaluate the dynamics of IL1-beta, TNF-alpha and OPG three and six months after the insertion of dental implants.

8.4 Results

After the evaluation carried out three months after the insertion of the dental implants, ten patients with mucositis passed into the group of those with a favorable evolution and four patients with peri-implantitis passed into the group of those with mucositis, resulting in a rearrangement of the patients into study groups looks like see Table 56.

Table 56. Study groups after three months after the insertion of dental implants

Healthy-7 days	Mucositis -7 days	Peri-implantitis - 7 days	Healthy-3 months	Mucositis-3 months	Peri-implantitis - 3 months
20	24	10	30	14	10
Total 54			Total 54		

Healthy-3 months	Mucositis - 3 months	Peri-implantitis-3 months	Healthy-6 months	Mucositis -6 months	Peri-implantitis- 6 months
30	14	10	40	5	9
Total 54			Total 54		

Table 60. Study groups after six months after the insertion of dental implants

8.5 Discussions

As seen in Table 60, the application of the treatment protocols allowed the number of patients with a favorable evolution to increase and those with mucositis and peri-implantitis to decrease at the end of the six-month evaluation. I emphasize that the evolution of cases of mucositis to peri-implantitis six months after the insertion of dental implants was possible in the conditions where the patients did not follow all the recommendations related to oral cavity hygiene and were not present at the scheduled consecutive consultations; the progression of the bleeding index and the depth of the peri-implant groove were the most important changes in the clinical parameters recorded in these patients, in parallel with the increase of IL1-beta, OPG and aTNF-alpha, results similar to those published by Costa F.o.et al. on a group of 80 patients, evaluated over a period of five years. [115]

8.6. Preliminary conclusions

1.Evaluation of clinical and paraclinical parameters by quantification of biomarkers alongside the data provided by radiological images reflects an accumulation of clinical and paraclinical events with important significance for the time at which these evaluations are made.

2. The evaluation of biomarkers three months after the insertion of dental implants shows in a few cases an important increase in values, the change in clinical and radiological parameters suggestive of peri-implantitis being registered only at the evaluation after 6 months.

3. These results suggest that the three biomarkers are very sensitive and could be used in the early diagnosis of peri-implant infection.

4. The statistical study of the obtained results shows that there are highly significant differences ($p \leq 0.0001$) regarding the values of the three biomarkers between the three study groups, evaluated after three and six months, respectively, after the insertion of the dental implants.

5. The highly significant statistical differences of these values demonstrate the utility of the three biomarkers in the diagnosis of mucositis and peri-implantitis, the institution of treatment and the preservation of inserted implants.

6. Diagnostic accuracy using TNF-alpha, Il1-beta and OPG can have a significant positive impact in the monitoring of patients with peri-implantitis in conditions where the prevalence of this condition could increase.

7. In this vein, the identification and validation of a set of useful biomarkers in the early diagnosis of peri-implantitis could represent an important step in implantology.

8. I believe that, understanding the roles of quantified biomarkers in the peri-implant crevicular fluid, will in the near future create the premises for the early identification of the inflammatory processes preceding this condition.

CHAPTER 9. VALUE ESTIMATION OF BIOMARKERS REGARDING THE CAPACITY TO PERFORM THE DIAGNOSIS OF MUCOSITIS AND PERI-IMPLANTITIS

9.1 VALUE ESTIMATION OF BIOMARKERS REGARDING THE CAPACITY TO PERFORM THE DIAGNOSIS OF MUCOSITIS

9.2 VALUE ESTIMATION OF BIOMARKERS REGARDING THE CAPACITY TO PERFORM PERI-IMPLANT DIAGNOSIS

IL-1-beta

I considered it useful from a practical point of view to make an analysis of the capacity of the performed tests, to make the diagnosis of mucositis, respectively peri-implantitis as correctly as possible based on the analyzed biomarkers, respectively: Il1-beta, OPG, TNF-alpha, as well as according to the most important clinical parameters evaluated during the personal research, respectively: the depth of the peri-implant groove, the presence of bleeding, the presence of pathogenic bacteria.

For each biomarker, we determined the sensitivity, specificity, positive predictive value, negative predictive value (using the data obtained in the study as the prevalence of the disease), the positive probability rate and the negative probability rate, respectively the area under the ROC curve. The Youden J index was also calculated for the threshold value determined from the statistical analysis.

9.3 Discussions. Conclusions

1. IL1-beta has the highest ability to correctly classify patients for the diagnosis of mucositis and peri-implantitis (value of the area under the ROC curve-0.990).

2. The presence of a single pathogenic bacterial species is an important factor that can change the status of a patient with a favorable evolution after the insertion of dental implants.

3. The depth of the peri-implant groove is a sufficiently revealing parameter for the diagnosis of mucositis only in combination with IL1-beta.

4. Since the depth of the peri-implant groove has 100% sensitivity and 100% specificity, it is a clinical parameter of overwhelming value in the diagnosis of peri-implantitis.

5. In the event of bleeding, in order to diagnose peri-implantitis, it is sufficient to quantify one of the two biomarkers with an area under the ROC curve of 1 (IL1-beta or OPG).

6. In the presence of pathogenic bacterial species, the parallel quantification of any of the three biomarkers is sufficient to validate the diagnosis of peri-implantitis.

CHAPTER 10. ORIGINALITY AND INNOVATIVE CONTRIBUTIONS OF THE THESIS

The ORIGINAL elements of the thesis are the following:

1. Demonstration of the causal relationship between IL1-beta, OPG, TNF-alpha and peri-implantitis.

2. Demonstration of the causal relationship between bacteria and peri-implantitis.

3. Mathematical assessment of disease progression risk related to IL1-beta, OPG, TNF-alpha and clinical parameters.

4. Identification of threshold values of IL1-beta, OPG, and TNF-alpha according to which the subsequent clinical evolution of patients after the insertion of dental implants can be estimated.

5. Identification of combinations of bacterial species that can predict the subsequent clinical evolution of patients after the insertion of dental implants.

6. Mathematical assessment of the risk of disease progression related to pathogenic bacterial species.

7. The value ranking of clinical parameters according to the possibility of the most correct assessment of patients after the insertion of dental implants.

INNOVATIVE CONTRIBUTIONS in the field of Implantology of the thesis results

1. Estimation of the possible evolution from the clinical status of implant with favorable evolution-mucositis and mucositis-peri-implantitis by identifying the bacterial score.

2. Estimation of the possible evolution from the clinical status of implant with favorable evolution-mucositis and mucositis-

peri-implantitis by identifying the combinations between the three biomarkers and pathogenic bacterial species.

3. Identification of PRAG values of the three biomarkers above which the risk of unfavorable evolution is high.

4. The obtained results create the premises for the optimization of the peri-implantitis diagnostic scheme by quantifying the three biomarkers and the bacterial score.

CHAPTER 11. GENERAL CONCLUSIONS

1. Cytokine quantification in peri-implant fluid is a non-invasive method that can be used in the prediction of peri-implantitis as well as for monitoring the patient with peri-implantitis.

2. Interleukin 1-beta correlates highly with the depth of the peri-implant groove in all study groups having the highest capacity to delimit the three types of clinical status after the insertion of dental implants.

3. Osteoprotegerin has a good ability to differentiate between the groups of patients with favorable evolution and mucositis.

4. Tumor necrosis factor-alpha allows high-sensitivity differentiation between patients with mucositis and peri-implantitis.

5.Osteoprotegerin and TNF-alpha correlate highly with the depth of the peri-implant groove in the group of patients with mucositis, being configured as extremely useful parameters in the diagnosis of mucositis.

6. A single pathogenic bacterial species identified creates a highly statistically significant difference between the status of patients with a favorable evolution and that with mucositis, demonstrating the important role of bacteria in the unfavorable evolution of patients after the insertion of dental implants.

7. The bacteriological examination of the peri-implant fluid is extremely useful in monitoring the patient after the insertion of dental implants.

8. The close causal relationship between bacteria and infections is demonstrated by the very high values calculated by the Odds ratio as well as the relative risk of unfavorable progression of mucositis in the context of the association of pathogenic bacterial species.

9. The identification of pathogenic bacterial species allows treatment according to the antibiogram in order to block the evolution of the peri-implant inflammatory process.

10. The evaluation of biomarkers three months after the insertion of dental implants shows in a few cases an important increase in values, the change in clinical and radiological parameters suggestive of peri-implantitis being registered only at the evaluation after 6 months.

11. These results suggest that the three biomarkers are very sensitive and could be used in the early diagnosis of peri-implantation infection.

12. Diagnostic accuracy using TNF-alpha, Il 1-beta and OPG can have a significant positive impact in the monitoring of patients with peri-implantitis.

13. The identification and validation of a set of biomarkers useful in the early diagnosis of peri-implantitis would be an important step in patient monitoring after the insertion of dental implants.

14. Understanding the factors underlying the bacterial etiopathogenesis of peri-implantitis is essential in developing strategies for the prevention, diagnosis and treatment of peri-implantitis.

15. Identifying the molecular and cellular mechanisms that control the bone-dental implant relationship and knowing the dynamics of osseointegration will be elements that will ensure the key to success in Implantology.

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