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INTERLEUKIN 1 BETA – A MARKER OF APPRECIATION FOR THE FIXED PROSTHETIC RESTORATIONS EVOLUTION

Florin C. BADEA[1], Aureliana CARAIANE[1], Mircea GRIGORIAN[1]✉

[1] Faculty of Dental Medicine, Ovidius University of Constanta, Romania

ABSTRACT

Background. The purpose of modern dental medicine is to restore the patient's dental system in order to strengthen health, from a functional, comforting and aesthetic point of view.
Methods. The study group consisted of 30 patients to whom we inserted dental implants, which were then rehabilitated by overloading, as follows: 18 patients with fixed metal-ceramic prosthetic (12 women, 6 men) and 12 patients with zirconium-ceramic (5 women, 7 men). Interleukin 1 beta (IL1-β) was quantified in all patients after implant insertion at 7, 30 and 90 days, and after overloading at 0, 30 and 90 days.
Results. The IL1-β values correlate with the depth of the peri-implant pocket at all three moments of implant insertion ($r > 0.600$), with a high statistical significance between the 30- and 90-day determinations ($p < 0.001$). After overloading, it was demonstrated that there is a correlation between IL1-β values and the depth of the peri-implant pocket at all times of evaluation (metal-ceramic: r between *0.774-0.871*, zirconium ceramic: r between *0.679-0.895*).
Conclusion. The existence of high correlations between peri-implant pocket depth and IL1-β supports the utility of IL1-β quantification as a parameter for monitoring patients after insertion of dental implants. For both types of dental materials, the value of IL1-β is the expression of gingival tissue remodeling after fixed

RÉSUMÉ

L'interleukine1 beta- un marqueur de surveillance de l'evolution des reconstitutions prothetiques fixes

Introduction. Le but de la médecine dentaire moderne est la restauration du système bucco-dentaire du patient, en renforçant sa santé, des points de vue fonction, confort et esthétique.
Méthodes. Le groupe d'étude était composé de 30 patients chez lesquels ont été insérés des implants dentaires, et qui ensuite ont bénéficié de la réhabilitation orale par sur-prothèse comme suit: 18 patients avec prothèses fixes en métal-céramique (12 femmes, 6 hommes) et 12 patients avec prothèses en zirconium-céramique (5 femmes, 7 hommes). Chez tous les patients on a quantifié l'interleukine 1 bêta (IL-1β) après l'insertion de l'implant à 7, 30 et 90 jours, et après leur surcharge à 0, 30 et 90 jours.
Résultats. Les valeurs de l'IL-1β étaient corrélées avec la profondeur du sillon péri-implantaire dans tous les 3 moments de détermination après l'insertion de l'implant ($r > 0,600$), avec une signification statistique élevée entre les mensurations effectuées à 30 et 90 jours ($p < 0,001$). Après la surcharge il a été démontré qu'il existe une corrélation entre les quantités de IL-1β et la profondeur du sillon péri-implantaire dans tous les moments d'évaluation (métal-céramique: *r entre 0.774-0.871*; zirconium-céramique: *r entre 0.679-0.895*).

✉ Corresponding author: Mircea GRIGORIAN
Slt. Ion Ghiculescu Street no.1, Constanta, Romania
E-mail: mirceagrigorian@yahoo.com,
phone +40726310090

denture prosthesis. Values of IL1-β quantified in the peri-implant fluid show the superiority of the zirconium-ceramic material compared to the metal-ceramic material.

Keywords: Interleukin l-beta, fixed prosthetic restorations, dental materials, dental implant

Abbreviations

IL-1β = interleukin-1β
PICF = peri-implant crevicular fluid
ELISA = enzyme linked immunosorbent assay
Ag = antigen
Ac = antibody
PPD = Peri-implant pocket depth

Conclusion. L'existence d'une forte corrélation entre la profondeur du sillon péri-implantaire et de l' IL-1β, appuie à l'utilité de la quantification de l' IL1β en tant que paramètre pour la surveillance des patients après l'insertion des implants dentaires. Pour les deux types de matériaux dentaires la valeur de l'IL-1β est l'expression du remodelage du tissu gingival après la prothèse fixe unique. Les valeurs de l'IL-1β quantifiées dans le fluide péri-implantaire montrent la supérioritéqualitative du matériau en zirconium-céramiquepar rapport à celui en métal-céramique.

Mots-clés: interleukine 1-bêta, reconstitutions prothétiques fixes, matériaux dentaires, implants dentaires.

INTRODUCTION

The reunification of parts of the human body that have been lost or mutilated due to general disorders or accidents has been a preoccupation of physicians of all time; the achievement of this goal was different for each period, depending on how the findings in the field allowed the development of medical knowledge[1].

The evolution of dental medicine has been strictly dependent on the knowledge and the evolution of dental materials over time, and they are really the elements that have put a clear mark on the development of this important branch of medicine[2].

The purpose of modern dental medicine is to restore the patient's oro-dental system, strengthening its health, function, comfort and aesthetics. Currently, dental implants are the most important method of replacing one or more missing teeth in different clinical situations[2].

According to the Dental Prosthetics Guide, a dental prosthesis should improve functionality and occlusal ratios, minimizing negative load and promoting an optimal response of subjacent tissues. The choice of dental materials must satisfy the aesthetic aspects of the patient without requiring preparations that involve excessive removal of healthy dental tissue[3].

The vast majority of authors believe that in order to achieve successful oro-dental rehabilitation, the clinician should always consider the triad: health-functionality-aesthetic[4,5].

Progress in oro-dental rehabilitation was marked by the appearance of dental implantology, a field that significantly altered dental prosthesis, so that using dental implants made it possible to conserve the remaining teeth, adjacent to the edentation. The development and introduction of the concept of osteointegration of endo-osseous implants by Dr. Branemark was an important moment in the evolution of the

principles of treatment in dental medicine. Thus, the use of dental implants has increased over the past three decades, providing a solution for partial or complete edentation, with many benefits for patients[1].

Oral prosthetic restoration on implants is a method by which we follow on the first place the osteointegration, an element that guarantees the long-term survival of the dental implant, but also the realization of the aesthetic appearance and the restoration of the oro-maxillo-facial harmony[6-8].

The evaluation of the oro-dental clinical status after such interventions has explained the need of using biomarkers, the specialists in the field acknowledging that Interleukin 1 beta (IL1-β) has a remarkable value[9].

Deciphering the interleukins action mechanisms, of the mechanisms by which they intervene in the initiation and maintenance of the inflammatory process generated in the context of the instrumental manipulations associated with the stress generated by the foreign materials from which fixed dentures are made. Interleukin I-beta is a nodal element in the inflammatory process in the oro-dental cavity, its quantitative expression being related to the intensity of the inflammatory process[10].

Gingival crevicular fluid is a physiologically exudate infiltrate present in small amounts in the gingival pocket in clinically oro-dental healthy patients; its secretion may be abundant and containing IL1-β under conditions of an inflammatory process such as fixed restorations on natural teeth[11].

The peri-implant crevicular fluid (PICF) is in the place where gingival tissue comes into contact with the surface of the implant; it is an inflammatory exudate that originates in the blood vessels of the gingival plexus; it has a composition similar to that of crevicular gingival fluid, but with the presence of host enzymes, inflammatory cytokines and tissue metabolism products[12].

Qualitative and quantitative analysis of inflammatory mediators present in PICF can be used to assess the health of tissues around implants, with the premise that some cytokines, including IL1-β, may be used as potential markers in the oro-dental assessment of the patient after insertion of the dental implant[13].

Fixed prosthetic restorations are most commonly made with metal-ceramic materials that have compressive strength superior to the traction one, have special chemical stability and do not suffer changes in contact with saliva and other oral fluids; at the same time they are well tolerated by the marginal periodontium as well as the dental tissues, all of which are qualities that ensure good aesthetic and functional results[14,15].

With superior properties of metal-ceramic materials in terms of strength and biocompatibility, zirconium-ceramics are increasingly used; its mechanical properties are similar to those of the metal substrate, and the color is similar to that of the natural teeth, which makes it a choice material for oral aesthetic rehabilitation. The advantage of this material is related to mechanical properties similar to the metal substrate, which is why zirconium could be used successfully in oral rehabilitation for lateral teeth[16].

The study is based on the hypothesis that the composition and volume of peri-implant crevicular fluid in the context of the dental implant are different depending on the material used for the fixed prosthetic works.

In this regard, we followed the evaluation of the effects installed after fixed restorations made with metal-ceramic materials and zirconium-ceramic through IL1-β quantified in peri-implant fluid.

MATERIAL AND METHODS

Study group and criteria for patient selection:

The group consisted of 30 patients (17 women and 13 males) aged 24-35 years (mean age 26.4 years), selected from patients who had dental implants inserted in a private dental office.

The selection criteria for the study group were: absence of chronic diseases, no medication with 6 months prior to inclusion, women out of pregnancy, normal occlusion, presence of natural teeth near the dental implant and in the contralateral part, good oral hygiene; only patients with a single implant system were included in the group.

After 6 months oral rehabilitation by fixed prosthetic works with metal-ceramic materials (Cr-Ni-Mo) was performed in 18 patients (12 women, 6 men) and zirconium-ceramic in 12 patients (5 women, 7 males).

The assessment of osteointegration of dental implants during the 6 months was done by oro-dental clinical examination (plaque index, gingival index, bleeding index, depth of the peri-implant pocket)

and radiological examination. The assessment of post dental implant evolution over the 6 months period was also achieved by quantifying IL1-β in the peri-implant fluid.

Peri-implant crevicular fluid (PICF) sampling and markers analyzing:

The peri-implant crevicular fluid (PICF) acquisition was done in two steps, as follows: at 7, 30 and 90 days after insertion of the dental implant and then after the insertion of fixed prostheses: immediately after fixation, this being considered time 0, at 45 and 90 days. PICF sampling was performed according to the standard protocol, after the clinical examination and the registration of the clinical parameters, making the following steps: isolation of the implant with sterile wool roll; washing and drying the area with the air/water spray from the dental unit; removal of supragingival bacterial plaque; inserting in the peri-implant pocket a Periopaper Strip for 30 seconds; harvesting was resumed in the case of samples showing the presence of blood and also in samples contaminated with saliva; the cones were inserted into Eppendorf tubes in which 200 μL of phosphate buffer was previously dispensed; the samples were transported to the laboratory where they were centrifuged at 1000 rpm for 5 minutes. The supernatant was subsequently separated and stored in the freezer at –70°C until quantitative determination of IL1-β[17].

For determination of IL1-β, the kit manufactured by Salimetrics, which allows quantitative determination by ELISA (enzyme linked immunosorbent assay), with a high detection sensitivity of 0.6 pg/mL, was used. The enzyme-labelled reagent formed from Ag (or Ac) conjugated to an enzyme is active and reacts with either Ag (or Ac) from the probe immobilized on the solid support and also with the enzyme-linked substrate. Visualization of the reaction between the enzyme reagent and the initial Ag-Ac complex is accomplished by adding a substrate corresponding to the enzyme used. The formation of the complex is identified by a color reaction that occurs upon the addition of the specific substrate (disodium p-nitrophenylphosphate for alkaline phosphatase and tetramethylbenzidine for peroxidase). The presence of the color reaction signifies the presence of Ag, respectively of Ac in the sample; the color intensity is directly proportional to Ag, respectively to Ac, in the sample and is assessed spectrophotometrically[17].

Statistical analysis:

The results obtained were statistically analyzed using SPSS STATISTICS 19 and MedCalc Software. To verify the differences between the same variables taken in the study we chose as study method the Student t-TEST.

We used Pearson's correlation r coefficient to measure the degree of linkage between clinical and paraclinical parameters.

Ethical permission:

The study was conducted with the approval of the Research Ethics Commission of the „Ovidius" University in Constanta, and the inclusion in the study group was based on the written and informed agreement, freely expressed for each patient.

RESULTS

Clinical and paraclinical evaluation of patients was done 7, 30 and 90 days after insertion of the dental implants. Values obtained on IL1-β

quantification both after insertion of dental implants and after overloading show that there are differences in mean and standard deviation of values obtained after each evaluation. Values of IL1-β quantified in gingival crevicular fluid of natural teeth from the healthy hemisections, opposed to prosthetic works, were considered values for the control group.

Also, the results show that there are differences with high statistical significance between the 7/30 days and 7/90 days value series ($p<0.0001$) as it can be seen in Figure 1.

The IL1-β values correlate positively with the depth of the peri-implant pocket at all 3 moments of determination after the insertion of dental implants, as shown in Figure 2.
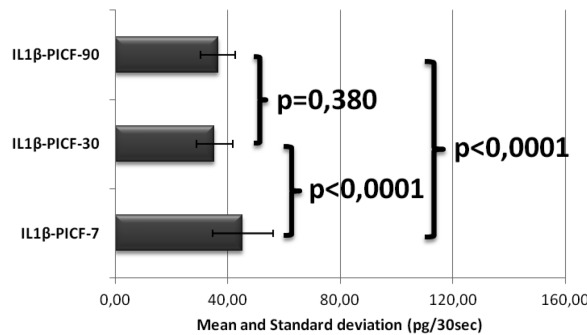

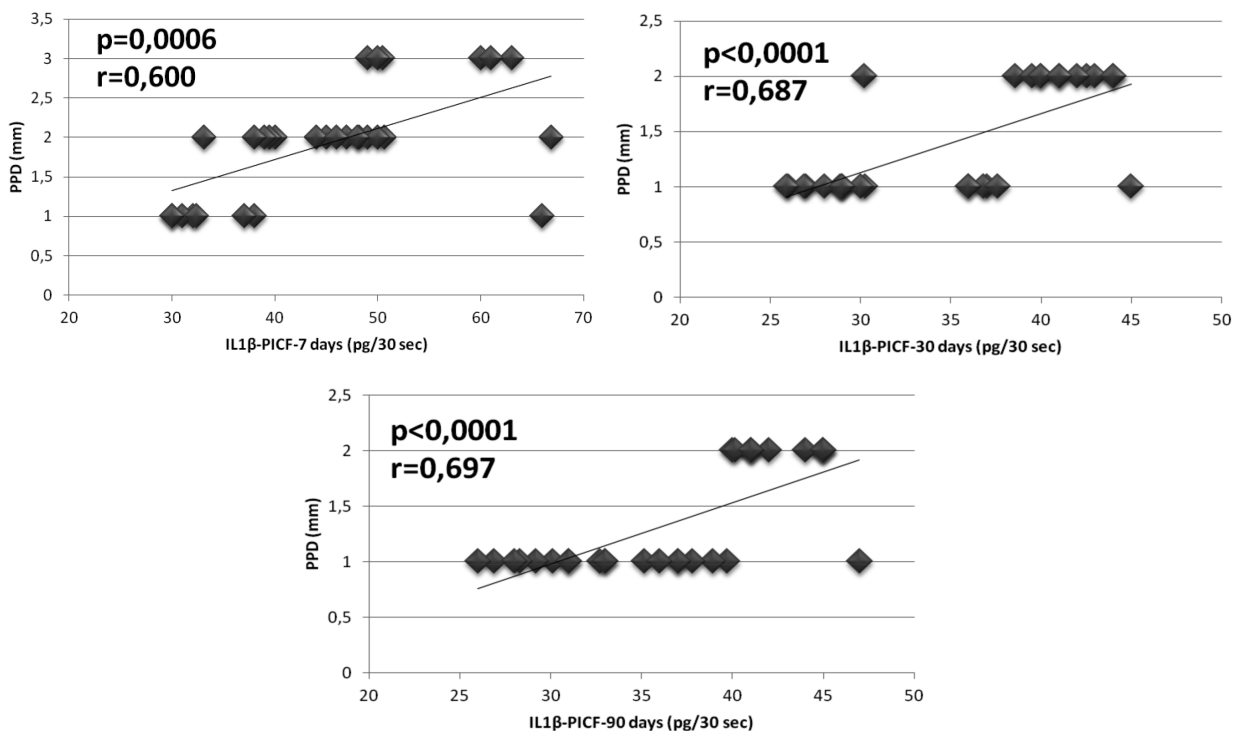**Figure 1.** Distribution of IL1-β values at 7, 30 and 90 days after insertion of the implants

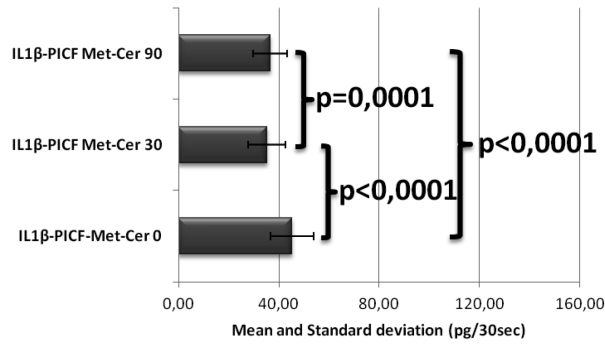**Figure 2.** Correlation between IL1-β and peri-implant pocket depth at 7, 30 and 90 days

Figure 3. Distribution of IL1-β values in patients with metal-ceramic prostheses after 0' 30 and 90 days
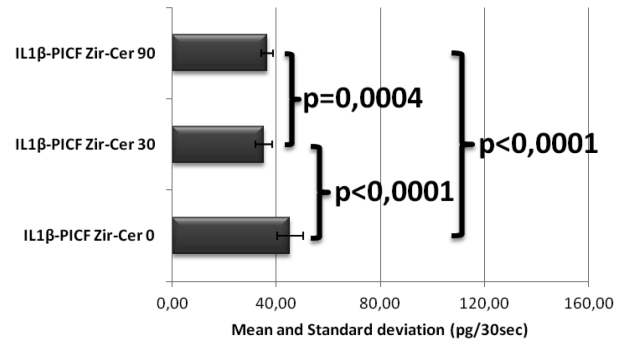
Figure 4. Distribution of IL1-β values in patients with zirconium-ceramic prostheses after 0, 30 and 90 days
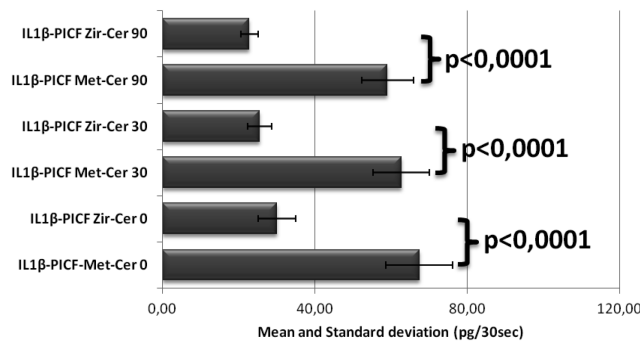

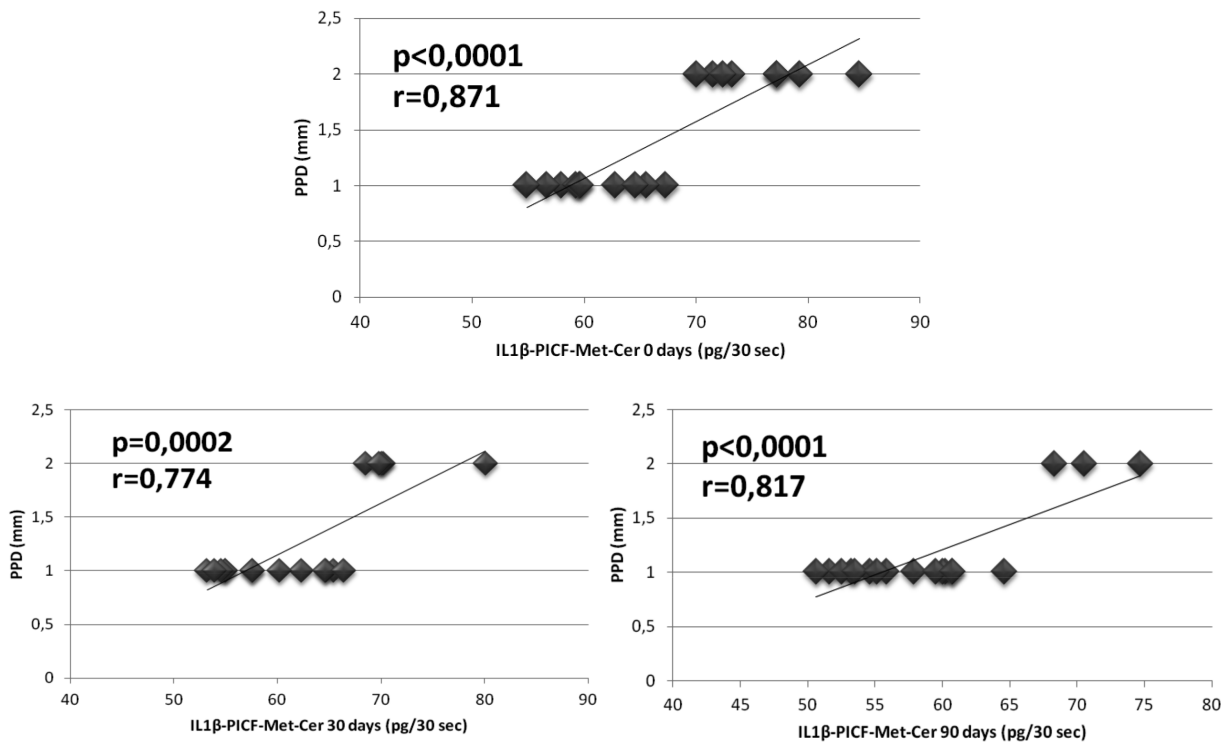**Figure 5.** Distribution of IL1-β values in the two groups of over-prosthetics patients

Figure 6. Correlation between IL1-β and depth of peri-implant pocket in patients over-dentured with metal-ceramic at 0, 30 and 90 days
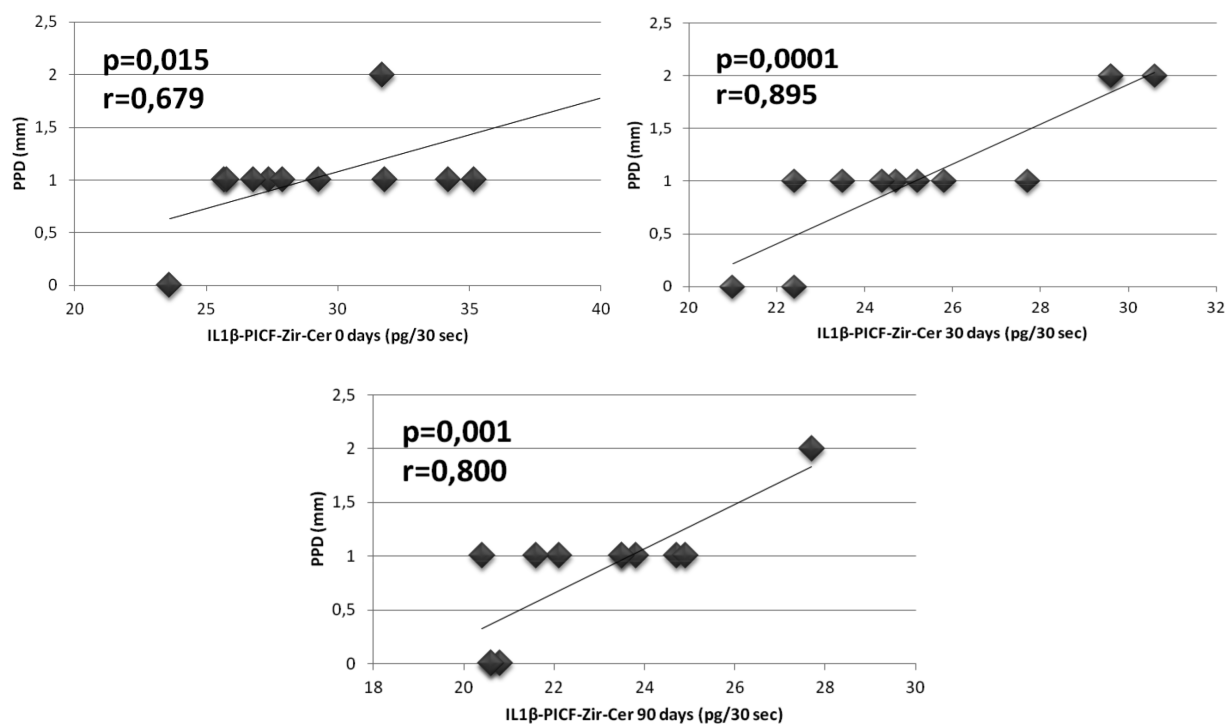
Figure 7. Correlation between the IL1-β and the depth of the peri-implant pocket in patients over-dentured with zirconium-ceramic at 0, 30 and 90 days.

Six months after the insertion of the dental implants, in the conditions where the oro-dental and radiological examination revealed their osteointegration, we performed the over-prosthetics of dental implants.

Quantification of IL1-β in patients with fixed-localized metal-ceramic prostheses shows that there are differences with high statistical significance ($p \leq 0.0001$) in all three determinations (0, 30 and 90 days) as shown in Figure 3.

Similar results were obtained for IL1-β in patients with zirconium-ceramic prostheses, being differences with high statistical significance ($p \leq 0.0004$) in all 3 determinations (0, 30 and 90 days) as seen in Figure 4.

Also, following the IL1-β series in patients with prosthetics from the two types of materials, there were significant statistically differences ($p < 0.0001$) in all three determinations (Figure 5).

Regarding the association between IL1-β values and peri-implant pocket depth, it can be concluded that there is a good correlation between the two parameters in patients overloaded with metal-ceramic dental materials (r=*between* 0.774-0.871) as one can be seen in Figure 6.

There is association between IL1-β values and the peri-implant pocket depth in patients overloaded with zirconium-ceramic (r=*between* 0.679-0.895) as shown in Figure 7.

DISCUSSION

All methods of oral rehabilitation, both classical on the natural teeth and those made by over-denturing a dental implant, contribute to the overall achievement of the health state through the special benefits offered from aesthetic and functional point of view.

As it is presented in the literature, the development of a variety of dental materials has shaped the final success in oral rehabilitation[1,2,14].

It has been shown that there is a toxic and allergic potential related to some components of the materials used in prosthetics such as nickel, cobalt, cadmium[18].

That's why, with the desire to overcome these deficiencies, over the time dental medicine has seen an upward trend in the quality of the dental materials used, starting from the old surgical alloys (vitalium) to the present time, when the use of zirconium as a skeleton brings a plus value for biocompatibility, while also ensuring dento-facial aesthetics[14].

The results obtained in this study regarding the IL1-β values in peri-implant fluid show that its levels are highest in the first week after insertion of the dental implant and subsequently decrease to different degrees after 30 and 90 days, respectively.

It has been very difficult to compare the results of this study with similar ones in the literature, given

that there are a wide variety of techniques used for quantification of IL1-β and also a wide variety of quantitative expressions of the interleukin 1 beta volume, as also noted by Javier Ata-Ali et al[19].

Similar results to those presented in this study were obtained by Siamak Y. et al, who studied the IL1-β value in crevicular fluid around healthy teeth and peri-implant crevicular fluid in patients with favorable developmental implant[20].

Other very similar results were also quoted by Panagakos F. et al and Javier Ata-Ali et al, in studies showing quantified IL1-β values in patients with favorable progression after insertion of dental implants[11,19].

It is to be emphasized that IL1-β correlates best with the depth of the peri-implant pocket, the results being similar to those of other studies published by Siamak Y. et al[20].

Physiologically, gingival tissue is remodeling along the contour of the unidirectional fixed prosthesis, which explains in a first step the installation of a mild inflammatory process expressed by increasing the volume of peri-implant fluid and the amount of IL1-β contained.

The results of the present study show that IL1-β can be used as a biomarker for monitoring after the over-prosthetics, as demonstrated by the existence of statistically significant differences in IL1-β values quantified at 0, 30 and 90 days after over-prosthetics by using the materials taken into study.

There is a correlation between the clinical status assessed by the depth of the peri-implant pocket and IL1-β in patients with the two types of materials used in over-prosthetics, which demonstrates the usefulness of IL1-β as a biomarker in assessing the patient's evolution after over-prosthetics. The results obtained are similar to the ones cited by J. Ozen, mentioning that it included in study groups only patients over-dentured with metal-ceramics[18].

We have searched the literature and have not found data related to the involvement of IL1-β in the evolution of zirconium-ceramic treated patients. Therefore, by extrapolation, considering same properties of the zirconium-ceramic in the present study, with the whole ceramic material quoted in J. Ozen's studies, we compared the IL1-β values obtained in PICF and we found that there are minimal differences in the mean and standard deviation IL1-β[18].

Interest in the use of biomarkers in monitoring patients after over-prosthetics is also demonstrated by other studies that quantify the intensity of the inflammatory process using other biomarkers; thus Shu-Juan Yu uses Osteoprotegerin (OPG) and the nuclear factor activator K (RANKL), ultimately

demonstrating that zirconium-ceramic is clearly superior to metal-ceramics[16].

In the same way, we can assume that IL1-β values quantified in PICF demonstrate the superior net tolerance of zirconium-ceramic material compared to metal-ceramic materials, the inflammatory process expressed by IL1-β being lower for fixed prosthetics made with zirconium-ceramics.

Conclusions

1. The existence of high correlations between peri-implant pocket depth and IL1-β supports the utility of IL1-β quantification as a biomarker to monitor patients after insertion of dental implants.

2. For both types of dental materials studied, the IL1-β value is the expression of gingival tissue remodeling after the fixed denture prosthesis.

3. Values of the IL1-β biomarker quantified in the peri-implant crevicular fluid show the superiority of the zirconium-ceramic material compared to the metal-ceramic material.

Compliance with Ethics Requirements:

„The authors declare no conflict of interest regarding this article"

„The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law."

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