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(REVIEW ARTICLE)

Biologic marker and periimplantitis: Literature review

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Abstract

Purpose: implant rehabilitation does not exclude failure risks and complications, as is the case of all treatments. Many are the way of diagnosis of implant failure, recourse to biomarkers has known lately its place in the domain of clinical research. A biomarker is a measurable characteristic that specifies a normal biological process or a pathological one. The aim of this literary review was to determine between the biomarkes and implant failure.

Material and methods: A literary research has been done on the basis of the following data : PubMed. The research has been limited to published documents in English and in French. out of 429 initially identified citations, 22 articles corresponded to our criteria of inclusion.

Results: Out of biomarkers identified in our review, Interleukin 1 is considered the most reliable factor in detecting peri implant disease. On the other hand, Interleukin 10 is considered the indicator of a healthy implant status, shows the succes of the implant and a good osteo integration. The clinical advantage of the study of these markers is based on their presence in implant sites even before clinical symptoms of inflammation, which leads to diagnosis by allowing to reveal early possible complications.

Keywords: Biologic Marker; Periimplantits; Osseointegration**;** Implant failure; Interleukines

1. Introduction

Methods of implantation have profoundly influenced dental practice. Dental implants have become the treatment of choice in many clinical situations requiring the replacement of lost teeth. However, this therapy is not without complications and problems, since implant osseointegration may not be achieved or maintained.

Peri-implantitis (PP) is the result of an interplay between a bacterial challenge to the implant-bearing tissues and the host immune response. It is speculated that the onset, severity, and extent of the disease depends on a variety of individual characteristics [1]. In addition to oral hygiene and smoking, systemic conditions, such as immunemediated diseases, diabetes, and obesity, are key factors for progressive peri-implant tissue breakdown. The expression of proinflammatory mediators, such as cytokines, chemokines, and matrix metalloproteinases, has been studied, but the intracellular signaling pathways associated with each of them is complex [2]. Proinflammatory cytokines,such as, interleukin (IL)-1b and tumor necrosis factor (TNF)-a, have been explored as biochemical markers of periimplant disease in clinical studies because of their noticeably elevated concentration in crevicular fluid from diseased sites.[3, 4]

As a result of clinical translational research, biomarkers are becoming increasingly available. They supplement clinical and radiographic information, allowing clinicians to make better decisions.

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The aim of this literature review is to assess the relationship between different biological markers and implant failure, and to what extent the polymorphism of the genes of these markers influences implant failure. What is the importance of these biomarkers when it comes to premature periimplant diagnosis before clinical signs appear.

2. Material and methods

2.1. Search strategy

An electronic search was conducted on the PubMed database. The search has been optimized by using keywords in English using the boolean operator AND:

- Biomarker AND dental implant failure
- Biologic factor AND dental implant failure
- Cytokine AND dental implant failure
- Biologic factor AND periimplantits

2.2. The study selection criteria

2.2.1. The inclusion criteria

- -Articles on biological markers and their relationship to implant failure
- -case series, cohorts, retrospective studies, prospective studies, and randomized controlled trials
- -the articles in French and English
    - articles relating to the study of at least 10 cases
- -studies on healthy patients

2.2.2. The exclusion criteria

    - case reports
- -Systematic reviews, literature reviews, and Meta-analysis
    - animal studies
- -studies on corpses
    - radiological studies
- -Studies that report the failure of preimplant grafts

2.3. Data Extractions

429 articles were identified after using the keywords and their combinations, from the PubMed database. After eliminating duplicate articles, 261 articles are retained for screening. Based on the exclusion criteria 23 articles were excluded from this study. Subsequently, the titles and abstracts of 238 articles were checked to identify full articles for full review. From two identified, the articles included in our study are determined.

The construction of a flow chart illustrates the process of research and selection of studies.

Table 1 Results of Data Extractions

Author	Biologic marker	study period	Total subjects	Implant number	Method	Cilinical parameter	Results
BASEGMEZ ET AL ; 2012 [5]	MMP-8 PGE2	3-18months	277 unrelated patients, including 185 individuals presenting at least one osseointegrated, and 92 individuals presenting at least one implant loss.	28 (n=72)	Sampling of crevicular fluid	- Plaque index -probing depth - gingival index	-Periimplantitis is associated with an elevated level of PGE2 and MMP-8. -Strong correlation between gum index and MMP-8 level.
RAKIC ET AL ; 2014 [9]	RANK OPG SCLEROTIN	2 years	164 participants (72 women and 92 males)	(52 patients with peri-implantitis, 54 with mucositis and 58 with healthy peri-implant tissues)	Sampling of crevicular fluid	- probing depth - Bleeding on probing	-RANK, OPG and sclerotin levels increase in periimplantitis. -Correlation between clinical signs and RANK level -The RANK concentrations were approximately 3-fold higher in peri-implantitis compared to healthy implants (p=0.002), and also significantly increased when compared to mucositis (p=0.021). -Sclerostin was detected in a small number of specimens including 10 samples from the peri-implantitis group, but the differences were clearly higher in peri-implantitis group when compared to mucositis and healthy implants (p<0.001).
CASADO ET AL ; 2013 [6]	IL-1B IL-10	1year	H: 10 (7/3); MU: 10 (5/5); PP: 10 (6/4), 130 implants	30(n=130)	Sampling of crevicular fluid	-probing depth -plaque index	-High level of IL-10 in case of osseointegration implants. Periimplantitis is associated with a high level of IL-1B. -IL-1b levels werelower in Hcompared to MU and PP; -IL-10 levels were significantly higher in H than MU and

							PP; and -MU had higher concentration of IL-10 compared with PP -No information on smoking patients. -PICF/C: 1 mL with calibrated, volumetric microcapillary pipettes; sites that did not express any volume of fluid were discarded
COSTA-JUNIOR ET AL ; 2012 [23]	MMP-8	-	Control group: 100 patients with one or more healthy implants. Test group: 80 patients that had suffered one or more early implant failures.	180	ADN collection	-	-Implant failure is associated with polymorphism of MMP-8 -significant difference in the presence of the different alleles between the control group and test group for the MMP-8 gene (p00.0011).
GRUICA.B ET AL ; 2004 [11]	IL-1	-	180(53 smokers. 127 non smokers)	292 implants. From these, 51 implants in 34 patients showed late (infectious) biologic complications, and 241 implants had survived without any	ADN collection	-	- Lack of correlation between the IL 1 genotype and implant failure in non-smoking patients unlike in smoking patients -The results for the non-smoking group indicated no significant correlation between implant complications and a positive IL-1 genotype. However, there was a clear association for heavy smokers between a positive IL-1 genotype and implant complications

				biologic complications at all			
PETKOVIC ET AL ; 2010 [10]	IL1B TNF-alpha IL 8	12-36mois After delivering suprastructures in function for 12 to 36 months.	H: 49; MU: 30; PP: 11; no information on implants	90	Sampling of crevicular fluid	-plaque index -probing depth -Bleeding on probing	- Low levels of IL1B, IL8, TNF-alpha in patients with peri-implantation disease. -Correlation between gingival index and the rate of IL1b, TNF-alpha, IL8. -H present lower concentrations of IL-1b, TNF-a, IL- 8, and MIP-1a in PICF compared with MU and PP; -positive correlation between IL-1b and TNF-a in H; -positive correlation between MIP-1a and IL-8 in the MU group
TATLI ET AL ; 2013 [20]	IL 1B TNF-alpha	1an	A total of 60 dental implants placed in 60 patients (27 patients were smoker and 33 were nonsmoker) Patients age ranged from 29 to 62 years, with a mean age of 44.9 6 10.46 years.		Sampling of crevicular fluid	-Plaque index -probing depth -ginigval index	- Smoking increases the risk of developing peri-implantitis, -The level of IL1B and TNF-alpha increases in patients who smoke, -Correlation between clinical parameters and IL1B and TNF-alpha.
DURATE ET AL ; 2009 [21]	IL4 IL12 IL10 OPG TNF-ALPHA RANKL	-1 week	H: 10 (6/4), 10 implants; MU: 10 (6/4), 10 implants; PP: 15 (8/7), 20 implants	48	Biopsy	- Plaque index -probing depth -ginigval index	- Both IL12 and TNF-alpha increase with increasing plaque index. -The level of OPG and RANKL decrease with increasing plaque index. -Level of TNF-a was significantly higher in PP and MU than H; -levels of TNF-a of diseased implants

							decreased from baseline to 3 months after therapies; and -no differences among groups for IL-4, IL- 10, and IL-12
PIGOSSI ET AL ; 2014 [12]	IL 4	-	186 individuals presenting at least 1 Osseo integrated implant and (2) study group (S) composed of 94 individuals presenting at least 1 implant loss.	278(n=1 367)	ADN collection	-	-A correlation between the level of IL 4 and implant failure. the C allele of the +33 (C/T) (rs2070874) polymorphism in the IL4 gene was significantly associated with susceptibility to dental implant loss in the Brazilian population studied.
FERNANDES ET AL ; 2017 [13]	IL 1B	2 ans	58 edentulous Caucasian patients rehabilitated with implant overdentures.	(n=229)	ADN collection	-mobility -Gingival index -Bone loss	-a significant association between IL1B polymorphism and implant failure. -Of the 58 subjects, 32 (55.2%) were classified as Group A (presence of biological complications) and the remaining 26 (44.8%) as Group B (successful). -The sample distribution according to the presence or absence of biological complication in implant-supported overdentures occurred in the same way in both sexes. In men, 9 had biological complications (28.1%), and 5 had successful overdentures (19.2%), while in women, 23 had biological complications (71.9%) and 21 had successful overdentures (80.8%). The average age was

							68.4 years for Group A and 69.3 years for Group B. The result of the t-student test (t=0.425, df=56, p=0.672) confirmed that there were no significant differences in mean age between subjects with and without biological complications.
SEVERINO ET AL ; 2011 [7]	IL 6 IL 8 IL10 IL 17	-	H: 11 (10/1), 20 implants; PP: 14 (8/6), 20 implants	25(n=40)	Sampling of crevicular fluid	-	- IL17 level increases in patients with periimplantitis, - IL10 levels increase in patients with well-osseointegrated implants -For IL 6 IL8 no significant difference between the two groups. -IL-17 shows higher levels in PP than H; -IL-6, IL-8, and IL-10 without differences between groups; -positive correlation between IL-6 and IL-8 in PP group In the PP group we found higher expression of IL-17 when compared to HP, with significant difference ($p < 0.05$) -Patients from the HP group had higher levels of IL-10 compared to patients from the PP group, but also no significant difference between groups was observed -There was significant positive correlation between levels of IL-6 and IL-8 in the PP group
PIGOSSI ET AL ; 2012 [14]	IL 10	-	From those 126 individuals that presented implant loss, 92 were evaluated (34 subjects	92	ADN collection	-	-Lack of significant correlation between IL10 polymorphism and implant failure

			were not evaluated because of death or address change). Thus, the dental implant failure group (DIF) was composed by 92 individuals presenting at least one implant loss. The control group was matched by gender, age and smoking, and was composed by 185 patients treated with osseointegrated implants, with at least one implant in function for more than 6 months and without any loss				
VAZ ET AL ; 2011 [15]	IL 1	-	A total of 155 Caucasian Portuguese subjects were divided into two groups: 100 with successful dental implants and 55 with unsuccessful dental implants89 (57.50%) women and 66 (42.58%) men,		ADN collection	-	-Implant failure is associated with the expression of alleles 2 of ILA1 and ILB1 -Success of dental implants was mainly associated with a negative TGP Genetic Test for Periodontitis result, whereas no success was found to be related to a positive result.
LACHMANN ET AL ; 2007 [22]	IL1B PGE2 PAI 2	-	29		Sampling of crevicular fluid + ADN collection	-	- The level of PAL2 is relatively linked to the level of IL1B and PGE2 in the case of perimplantitis. -An elevated level of IL1 in the crevicular fluid in patients with peri-implant disease. -PAI-2 levels were positively related to IL-1b and PGE2 levels in

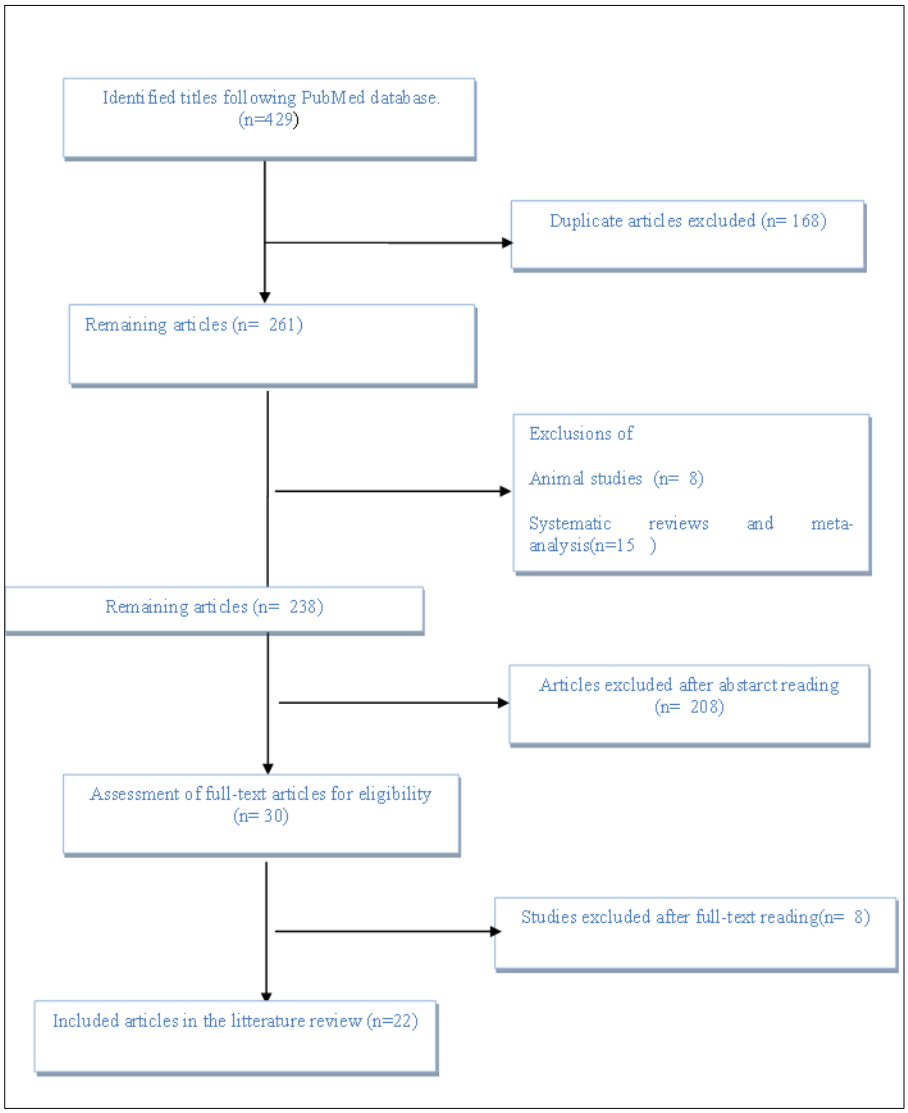
							Patients with PI
CORNELINI ET AL ; 2003 [16]	TGF-B	-	20	10 biopsy healthhy keratinized mucosa 10 biopsy from periimplant soft tissues surrondi ng failing implants	Biopsy	-	The level of TGF-B is high in the epithelium in the event of implant failure unlike well osseointegrated sites -The differnece between TGF-B expression in the epitheluim around failing and healthy implant were statisticlly signifiant (p<0.0001). the difference between TGF-B expression in the blood vessels in the soft tissus around healthy and failing implants were also statisaclly signifant (p<0.0001).
LAINE ET AL ; 2006 [17]	IL1	-	71		ADN collection	-	The IL1 alleles were detected with a percentage of: 47.8% in patients with peri-implantitis 44.7% in patients with mucositis 8.3% in patients with well-osseointegrated implants Significant differences were found in the carriage rate of allele 2 in the IL-1RN gene between peri-implantitis patients and controls (56.5% vs. 33.3%, respectively; odds ratios (OR) 2.6; 95% confidence interval (CI) 1.2–5.6; P¼0.015). Logistic regression analysis taking smoking, gender and age into account confirmed the association between the

							IL-1RN allele 2 carriers and peri-implantitis (OR 3; 95% CI 1.2–7.6; P¼0.02).
COSYUN ET AL ; 2014 [19]	IL1	3 years	461 461 groupe control	1180 implants	ADN collection	-	The level of IL1A is associated with implant failure. No significant relationship between IL1B level and implant failure.
RIBEIRO ET AL ; 2017 [18]	RANK IL 10	-	A total of 150 patients were called to participate in the study, and 126 attended the tests; 15 patients were excluded from the study; and 21 were lost due to the lack of appropriate genetic material. The final sample consisted of 90 individuals with a total of 245 implants.	n=245	ADN collection	-bleeding on probing -Probing depth	- Lack of significant correlation between polymorphism of IL10 genes and implant failure. -Absence of a significant correlation between the polmorphism of the RANKL genes and implant failure. -We found no significant association (p > 0.05) between the frequencies of genotypes in the *RANKL* gene region (-438 A/G) and implant failure. Taking into account the distribution of allele frequencies, it was also not possible to verify significant difference between A and G (p > 0.05) -No significant association (p > 0.05) between genotypic frequencies in the region of the *IL-10* gene (-1082 A/G) and implant failure. Regarding the distribution of allele frequencies, it was also not possible to verify significant differences between A and G (p > 0.05) (Table 2).

FERNANDES ET AL ; 2017 [13]	IL1B	2ans		58(n=229)	ADN collection	-mobility	Biological complications are related to the expression of the allele 2 of the IL1B gene (+3953)
LISKMEN ET AL ; 2006 [24]	IL6 IL8 IL10	-	24 subjects, 15 men and 9 women,	30 Implants with inflammatory lesions PPD, pocket probing depth. _ 4mm GI, gingival index 1 BOP, bleeding on probing 1 Healthy implants PPD, pocket probing depth. _ 3mm GI, gingival index 0 BOP, bleeding on	Sampling of crevicular fluid	-gingival index Probing depth	High level of IL8, IL10 in the crévicular fluid around non-osseointegrated implants

				probing 0			
ARAKAWA ET AL ; 2012 [25]	MMP-8	6- 12 months	64 (male/female: 31/33; mean age: 68.5 _ 6.7 years;	-162 implants	Sampling of crevicular fluid	-	-Significant correlation between MMP-8 level and peri-implant disease. This study showed that MMP-8 is the major collagenase present in PISF of active peri-implantitis sites Among the total of 64 patients (male/female: 31/33; mean age: 68.5 _ 6.7 years; 162 implants) that fulfilled the selection criteria, only 4 subjects (male/female: 2/2; mean age: 68.5 _ 6.7 years; 9 implants) presented baseline AVBL(vertical bone losss) higher than 0.6 mm and were included in the severe peri-implantitis group. The healthy group comprised a total of 60 patients, among which 4 subjects (male/female: 2/2, mean age: 66.0 _ 5.8 years, 8 implants) were randomly selected and matched to the peri-implantitis group by age, gender and implantation site. Despite of sample matching, mean functional duration was significantly (p = 0.029) longer in the peri-implantitis group (5.0 _ 2.3 years) compared to control group (2.7 _ 1.4 years). Additionally, mean amount of collected protein from the periimplantitis group (357.11 _ 90.2) was also significantly (p = 0.001) higher than the control group (204.75 _ 37.83)Based on these results, the incidence of peri-implantitis was of 6.25% of patients and 3.7% of implants.

Biomarker	Abbreviation
MMP-8	Matrix Metalloproteinase-8
PGE-2	La prostaglandine E2
RANK	receptor activator of nuclear factor ligand
OPG	Osteoprotegerin
SCLEROTIN	Sclerotin
IL-1B	Interleukine-1- beta
Il-10	Interleukine 10
IL-1	Interleukine-1
IL-8	Interleukine 8
TNF-alpha	Tumor Necrosis Factor,
IL4	Interleukine 4
IL12	Interleukine 12
TGF-B	transforming growth factor beta
PAI2	Plasminogen activator inhibitor-2
IL17	Interleukine 17



Evaluation of Full Text Articles for Eligibility (n=30)

Figure 1 Process of research and selection of studies

3. Discussion

The placement of dental implants is characterized by successive physiological stages of bone trauma, bone debris formation, bone hemostasis, blood clot formation and tissue hypoxia. These steps can be influenced by the activity and involvement of the immune system activated during implant recognition.

The cytokine network, activated in diseased periimplant tissue, is complex because of the overlapping role of many cytokines and is subject to shifts depending on disease activity. Considering this complexity, Interleukins ILs are a group of cytokines produced by a wide variety of cells, important for proper function of the immune system by promoting the development and differentiation of B and T cells. They also have a major function in inflammatory reactions, such as periodontitis and peri-implantitis.

A few Ils (IL-6, IL-8, IL-10, and IL-12) have been proposed as possible biomarkers for periimplant diseases. It is important to comprehend the signaling pathways involved in cytokine expression in periimplant diseases to design new approaches to modulate the host response affecting the whole cytokine profile [24]

Several studies have been carried out with the aim of demonstrating the relationship between biological markers and implant failure, some have been carried out on the crevicular fluid by taking a sample from the peri-implant sulcus, and others by referring to the analysis of DNA in order to determine the influence of the genetic polymorphism of these markers on the state and fate of the implant.

Some studies concerned implant failure by demonstrating an increase in both on prostaglandin E2 (PGE2) and matrix metalloproteinase-8 (MMP-8).

Matrix Metalloproteinases MMPs are endopeptidases capable of degrading various extracellular matrix proteins and play a role in cell proliferation, differentiation, migration, and apoptosis. Peri-implantitis has been shown to demonstrate a similar pattern of destruction as periodontitis, and MMP upregulation has been associated with irreversible periimplant connective tissue destruction. [27 28 3031]

The rate of prostaglandin E2 (PGE2) and matrix metalloproteinase-8 (MMP-8) is high in the periimplant crevicular fluid, Many authors have confirmed this increase based on a sample of the crevicular fluid. BASEGMEZ ET AL (2012) [5], ARAKAWA et al (2012) [25] and other authors [22, 20] carried out studies confirming downstream this association.

Another group concluded that MMP-8 levels in clevicular fluid may be useful for monitoring the progression of periimplant disease, as an increase of MMP-8 levels may be an early sign of inflammation.[29] 25 A systematic review carried out by YUANJUN (2014) [26] reported the same result.

Some authors have focused their studies on the correlation of PGE2 and smoking, this is what constituted the work of TATLI (2013) [20] which confirmed this correlation.

Other factors have always been studied following the sampling of the crevicular fluid, it is the plaque index and the probing depth which lead to an increase in MMP-8, BASEGMEZ (2012)[5] reported the same result.

Studies concerning biomarkers showed also interest in the DNA. this is the case of COSTA JUNIOR (2012) [23] who found a significant correlation between the polymorphism of MMP-8 and implant failure.

Another IL important for inflammatory responses and alveolar bone resorption is IL-1b. A study looking at IL-1b concentrations showed it to be significantly higher in peri-implantitis sites compared with both periimplant mucositis and healthy sites.21 The same results were demonstrated by other groups [30.31] 13,29 and support the idea that IL-1b is responsible for the stimulation of bone loss.

A systematic review carried out by CANDEL MARTI (2011) [92] reports similar inflammatory responses, on the other hand, CASADO (2013) [6] PETKOVIC (2010) and other authors [10, 20, 22]have also shown a significant link between IL1B and implant failure, others have been based on the study of the relationship between IL1B polymorphism and loss of osseointegration, including FERNANDES (2017) [13], VAZ (2011) [15] and other authors [19] have reported a significant correlation between the two.

IL-1b levels around peri-implantitis lesions were also shown to be positively correlated with the amount of gingival inflammation, indicating it may be a good marker to detect periimplant mucositis lesions before they progress to periimplantitis. [32] 22

Among the markers that were studied, tumor necrosis factor alpha (TNF-alpha) was also highlighted following a sample of the crevicular fluid and which showed a high rate at the periimplantitis sites. In this sense, PETKOVIC (2010) [10], TATLI (2013), [21 20], have reported the same results.

On the other hand DURATE (2009) [21] was interested in the study of TNF-alpha and the increase in plaque index and gingival index, and showed a significant correlation between the high level of marker in question and these.

With regard to pro-inflammatory cytokines, interleukins 8 and interleukins 4 have been the subject of studies carried out from a sample of the crevicular fluid, and the results of which have shown a high rate in the event of peri-implantitis, PETKOVIC (2010) [10], LIKSMANN (2006)[24], PIGOSSI (2014) [14] reported similar results.

In the same sense, a systematic review carried out by CANDELL MARTI (2011) [92] confirmed this increase.

However, this opinion was not shared by SEVERINO (2011) [7] who indicates that the level of interleukins 8 remains identical to the level of the crevicular fluid both around well osseointegrated implants and implants with peri-implant disease.

Another factor has been studied by PETKOVIC (2010) [10], it is the plaque index which leads to an increase in interleukins 8.

IL-6 increased in concentration in patients with periimplant disease and was also positively correlated with clinical parameters such as BOP and pocket depth.10 Konttinen et al14 also found the same increase in IL-6 concentration, with the difference being statistically significant, and even suggested treatment with cytokine modulators. In several other studies, this correlation between increasing IL-6 concentration in patients with periimplant disease was not supported.[30 32] 13,17

As for interleukins 17, the studies carried out after sampling revealed their increase in the level of the crevicular fluid in the event of periimplantitis, PETKOVIC (2010)[10] confirmed this increase and in the same direction a systematic review carried out by FAOT et al (2015) shows a similar result.

Studies have focused on Receptor activator nuclear factor (RANK), osteoprotegerin (OPG) and sclerotin which have clearly shown their level increased in patients with peri-implant disease, RAKIC (2014)[9] confirmed this increase, in this meaning a systematic review by YUANJUN (2014) showed a similar result.

Furthermore, a decrease in the levels of RANK, OPG was correlated with a significant increase in the plaque index in a study carried out by DURATE et al (2009) [21]

Among the markers which have been demonstrated, osteopontine, Plasminogen activator inhibitor (PAI2) and Transformation growth factor-B1 have not been the subject of several studies, and therefore clinical data remain limited, we cite among others CHENGYE (2017) [8] who showed that the level of osteopontin is increased in the crevicular fluid around non-osseointegrated implants, LACHMANN (2007) [22] who indicates that the level of Plasminogen activator inhibitor (PAI2) in the event of peri-implantitis, and on the other hand CORNELINI (2003) [16] showed that the rate of Transformation growth factor-B1 is increased in the presence of peri-implant disease.

Interleukins 10 are an important element in determining the state of peri-implant health, their presence in the crevicular fluid indicates good osseointegration and determines the success of the implant. CASADO (2013) [6], SEVERINO (2011) [7] have shown that the level of interleukin 10 is high in the level of the crevicular fluid around well osseointegrated implants. on the other hand PIGOSSI (2012)[14] performed a DNA study and showed a lack of significant correlation between implant failure and polymorphism of interleukin 10 genes.

In addition LIKSMANN (2006) [24] has shown a significant correlation between the rate of IL-10 and implant failure, but this could be related to the limited number of the sample which did not exceed 30 cases.

4. Conclusion

The placement of dental implants should be considered a delicate surgical act with the possibility of risks and complications, but which certainly has a relatively high success rate.

Implant failure is a major concern for the practitioner, whose risk factors are multiple and sometimes unknown.

The literature review carried out in this work focused on the relationship between implant failure and biological markers as well as their polymorphisms, the results highlight an association between biological markers and peri-implant health: the studies show a higher biomarkers in peri-implantitis sites.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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