European Review for Medical and Pharmacological Sciences 2024; 28: 3566-3582

Relationship between interleukin 1 (IL-1) genetic polymorphism and periimplantitis: systematic literature review and meta-analysis

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Abstract. – OBJECTIVE: Periimplantitis (PI) is a complex multifactorial chronic disease caused by interactions between bacteria, host immune-inflammatory responses, and genetic or environmental factors that modify buccal eutrophism. In daily clinical practice, an increase in the prevalence of PI (8%) determined the need to establish the PI causes and set optimal therapeutic strategies. The interleukin family (IL-1), a group of cytokines, triggers and perpetuates peri-implantitis. Therefore, they could be used as biomarkers for diagnosis and treatment. This systematic review aimed to analyze the correlation between IL-1 allelic polymorphism (*IL-1A* –889, *IL-1β* –511, *IL-1β* +3954) and the PI disease.

MATERIALS AND METHODS: Selected databases were PubMed, Scopus, and Cochrane Library. The search strategy included the following terms: "dental implants"; "periimplantitis"; "interleukin-IL-1"; "polymorphism"; "perimplant bone loss". Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed. A meta-analysis was conducted on five of 40 review articles. *p*-values, confidence intervals (CI), and Odds ratios (OR) were assessed. In 4 articles, the p-value was lower than 0.05, confirming the statistical significance of the result.

RESULTS: The prevalence of the selected studies reported the existence of a causal association between polymorphisms of IL-1 and the onset of peri-implantitis, especially for *IL-1* allelic variants associated with further polymorphic genes encoding for IL-6, tumor necrosis factor-alpha (TNF-α), matrix metalloproteinases (MMP)-8, IL-1Na, IL-8, IL-18, osteopontin (OPN). In addition, the presence of the IL-1 polymorphism and PI is particularly higher in smokers, diabetes, and autoimmune disease patients.

CONCLUSIONS: The detection of salivary biomarkers is, therefore, a diagnostic tool with a high potential to intercept the PI early and act with appropriate and non-invasive treatment. Due to the continued technological innovation in biomarkers and diagnostic sciences, further studies are needed to investigate the role of these biochemical mediators. The results of studies and the recent technological innovation in biomarkers and diagnostic sciences will allow further research to investigate the role of these biochemical mediators.

Key Words:
Health, Dental implants, Periimplantitis, Interleukin-IL-1, Polymorphism, Perimplant bone loss.

Abbreviations

PI (periimplantitis), GCF (gingival crevicular fluid), MMPs (matrix metalloproteinases), TNF (tumor necrosis factor), OPN (osteopontin), CF (crevicular fluid).

Introduction

The long-term success of an implant depends on a careful and comprehensive design and planning, with an analysis of the predisposing factors for the failure of the procedure[1]. A growing number of studies[1-3] suggest that anaerobic plaque bacteria may have an adverse effect on the health of the periimplant tissue, leading to periimplantitis (PI). PI can also be directly related to the inadequate distribution of chewing pressure on the tissues surrounding the implant, resulting in the loosening of the prosthetic components, infection of the surrounding tissues, and consequent inflammatory processes[4]. Signs and symptoms of PI include redness and swelling, progressive bone loss, bleeding and/or suppuration on probing, and crater-shaped bone defect[5,6].

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Despite the prevalence and the diffusion of PI, the causes are still poorly understood. Therefore, decision-making for implant maintenance and treatment of PI should be a rational and evidence-based approach (EBM). Oral microflora components and the related biofilm appear to be a determining factor in the success or failure of a dental implant[7]. The main feature of oral biofilm is its capacity to cover every surface present in the oral cavity, including the implant neck and the related prosthetic components. The implant biofilm niche includes a protein with microorganisms living in a delicate balance with the host surrounding tissues[8]. Inflammation of the surrounding tissues and/or the changes of microflora can break this balance and lead to periimplantitis, with bone loss and eventual implant loss[9]. A dental implant is considered a failure if it is lost, mobile, or shows periimplant bone loss greater than 1.0 mm in the first year and greater than an additional 0.2 mm in the following year[3,10]. Therapeutic strategies proposed for the management of periimplant diseases seem to be largely based on the evidence available for the treatment of periodontitis or on empirical clinical values but not on particular scientific findings (Figure 1). Innovative technology and new findings in personalized medicine lead scientists and clinicians to adopt a different approach to PI, starting from an early diagnosis[11].

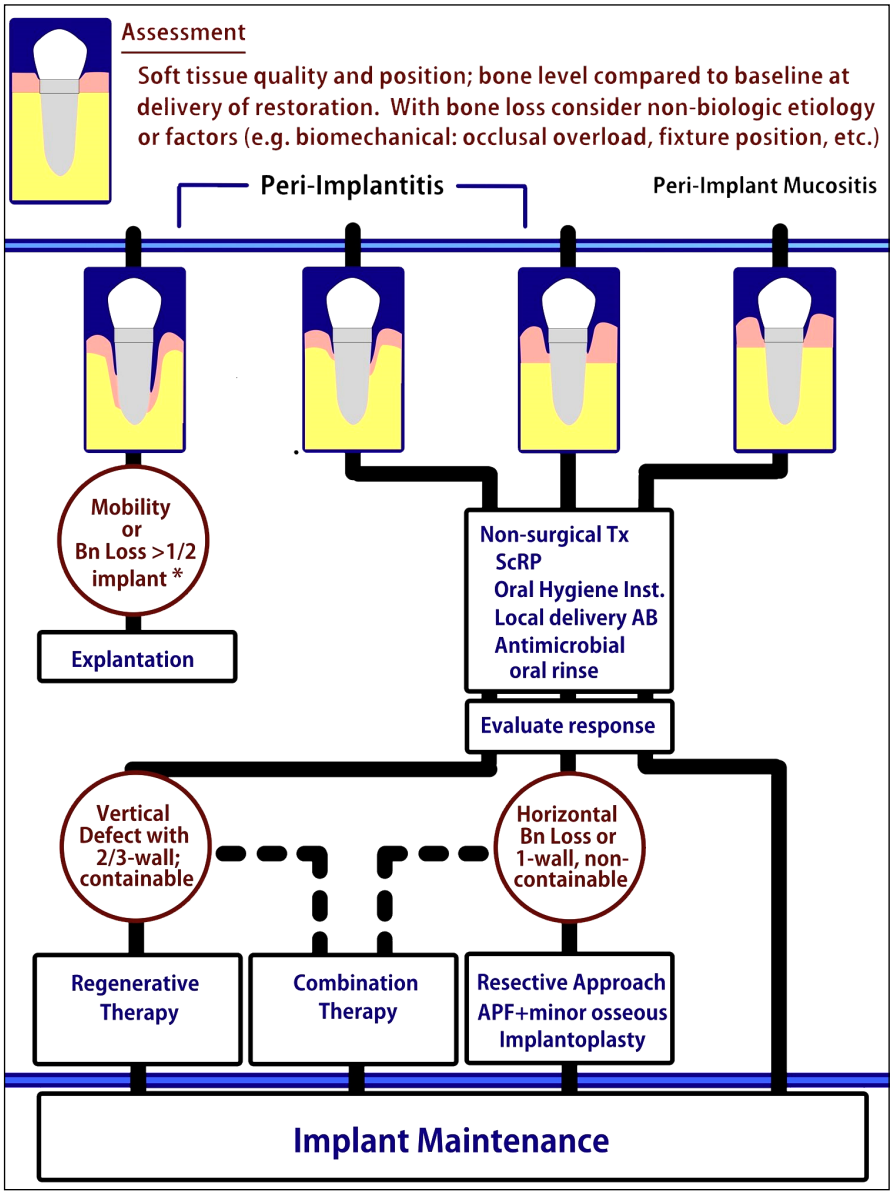

Figure 1. Figure reuse from Mishler et al[11]. A summary of the management for periimplant diseases. *The algorithm assumes a standard diameter 11.5 mm length implant.

This includes the detection of molecules involved in physiological and pathological processes, such as matrix metalloproteinases (MMPs) and cytokines used as biomarkers[12]. MMPs are proteases that serve to degrade the extracellular matrix. MMP-8 is a potent collagenase and plays a critical role in degrading host connective tissues at sites of inflammation and in bone resorption. Tumor necrosis factor (TNF) is a cytokine involved in systemic inflammation: TNF-α, in particular, is a stimulator of bone resorption[1]. Among cytokines, the interleukin (IL)-1 family triggers and perpetuates periodontal and periimplant inflammation[13]. Studies[14] on IL-1 family lead to discover 11 types of cytokines of which 7 with agonist activity (IL-1A, IL-1β, IL-18, IL-33, IL-36α, IL-36β, and IL-36γ), 2 with receptor antagonists (IL-1Ra, IL-36Ra), and 2 with antiinflammatory action (IL-37, IL-38). The IL-1 receptor antagonist (IL-1Ra) plays a key role in periodontitis. IL-33, instead, is a trigger for the production of Th2-associated cytokines and stimulates mast cells[13]. Patients with IL-1 allelic polymorphism have a higher production of IL-1, from 2.5 to 3.6 times more than the average population: this genetic pattern can be considered an early biomarker to be evaluated as a predictive index of a high risk of PI[15]. The increased concentration of cytokines locally produced in periimplantitis, as the IL-1A and IL-1β, can be used as indicators of disease progression and its activity; conversely, the increased concentration of other cytokines, such as IL-1Ra seems to have an antiinflammatory role[14]. Nicklin et al[16] found that 3 genes control interleukin production: *IL-1A*, *IL-1β* and *IL-1Ra*. The *IL-1A* gene synthesizes the IL-1A pro-inflammatory protein, just like the *IL-1β* gene encodes the IL-1β proinflammatory protein[15]. The *IL-1RN* gene controls the synthesis of the receptor antagonist, IL-1Ra, which inhibits the effect of IL-1A and IL-1β[17].

In polymorphisms of IL-1A and IL-1β, the long arm of chromosome 2 can present allele 1 (the most widespread form in the nitrogen sequences of the population) or allele 2, which is the minor variant (prevalence greater than 1%). The minor variants carry the substitution of cytosine (C) in their respective positions with thymine (T). If both genetic loci possess allele 2, i.e., the replacement of cytosine with thymine in both position 889 and position 3953 in the long arm of chromosome 2, the patient is described as a "positive genotype"[13,18]. These polymorphisms can increase the transcriptional activity of corresponding genes, with overexpression of the IL-1 family, and influence the host inflammatory response, breaking that delicate balance between biofilm, implant surface, and surrounding tissues[15]. The aim of this study is, therefore, to systematically review the literature on the possible correlation between IL-1 polymorphism and PI setting as the primary outcome of the detection of IL-1 cytokines in CF or in supragingival implant plaque and as a secondary outcome, the eventual association of periimplantitis with IL-1 positive genotype using a meta-analysis.

Materials and Methods

The current systematic review is registered on the Open Science Framework database, with registration DOI: 10.17605/OSF.IO/CHUPT accessed on 09/11/2022. The PECO method was used to develop this systematic review, defining the following parameters:

- P (Population): adult patients: population of patients affected by PI.
- E (Exposure): genotype including selected polymorphisms of interleukin-1.
- C (Control): genotype not including selected polymorphisms of interleukin-1.
- O (Outcomes/Outcome): development of periimplantitis and presence of polymorphisms in association with PI.

Therefore, the PECO question considered an adult population affected by PI, of which those affected by the polymorphism of *IL-1* were considered the exposed group, and those not affected by polymorphism of *IL-1* were considered the control group. The considered outcomes were the development and eventual association of PI and the presence of *IL-1* polymorphisms.

Search Strategy

This systematic review screened PubMed, Scopus, Embase, and Web of Science Library databases to select high-profile studies. The manuscript was drafted adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[19] (Figure 2).

Search Terms

An electronic search was conducted using the following search terms: "dental implants,";

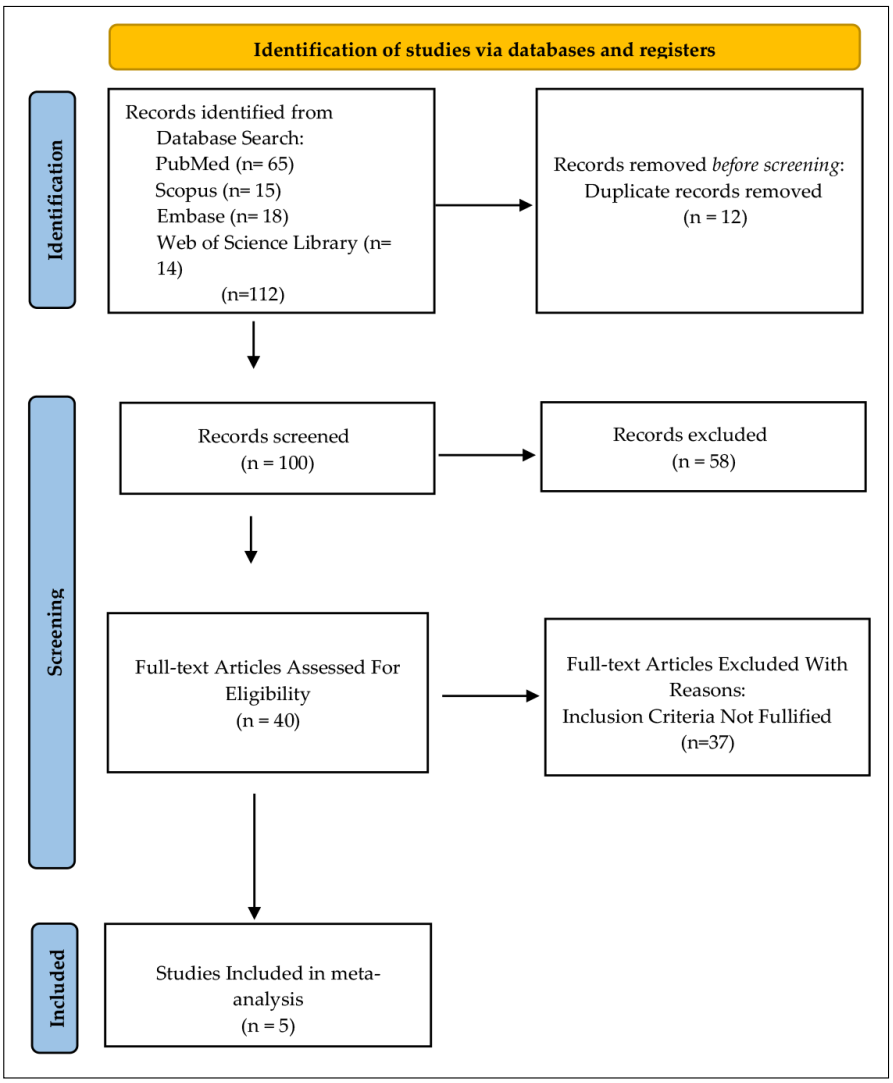

Figure 2. PRISMA flowchart illustrating the experimental study search and selection process. The screening process initially excluded 58 items from the initial title and abstract assessment. The remaining 42 items were assessed using the inclusion criteria. Finally, 5 studies were considered eligible for meta-analysis.

"periimplantitis,"; "interleukin-IL-1,"; "polymorphism,"; "peri-implant bone loss."

Inclusion Criteria

Articles were included if they met the following inclusion criteria: randomized controlled trials (RCT), controlled clinical trials (CCT), retrospective and prospective, with comparison test and control groups; publications years from 1992 to 2022; *in vivo* human studies; coexistence of post-treatment clinical, radiographic and immune chemical results, and studies in English.

Exclusion Criteria

Articles were excluded if they met the following exclusion criteria: *in vivo* and *in vitro* animal studies; lack of results; studies involving patients with systemic contraindications; unclear follow-up of the control group; no time of implant loss referred; medically compromised patients (e.g., antibiotics assumption); several implants rough surface exposure; patients declined to take part in the study.

Study Selection

Two independent authors (N.S. and D.G.) dealt with the primary literature research. The same researchers conducted a second reevaluation of the selected titles, in which the studies that were not adapting to the established eligibility and inclusion criteria were deleted. Therefore, the remaining reports were intensely screened, considering the full-text articles for compatibility. In case of disagreements between the authors after independent evaluation, a consensus was reached by reevaluation and discussion. In the event of discrepancies in the data, the corresponding authors were contacted by email for further explanation

when possible. The remaining studies were finally revised for qualitative synthesis.

Data Collection

Data were extracted, including the year of publication, type of study, duration of follow-up, number of patients, comparison groups, post-healing, radiological, clinical, and histological results. The main collected results are percentage data, clinical data, percentages of IL-1 levels in crevicular fluid, and radiographic data.

Bias Assessment

The bias of the present systematic review was assessed according to the study quality assessment tool for systematic reviews (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). The study conducted is both qualitative and quantitative as it combines the results of different studies into a single "pooled estimate of effect," in our case, given by the odds ratio (Table I).

Meta-Analysis

The meta-analysis was performed through the MedCalc software Ltd (Version 19.1.7, Ostend, Belgium, available at: https://www.medcalc.org/). The meta-analysis was conducted on the articles investigating allelic polymorphism, the data of which were analyzed quantitatively and qualitatively and were comparable for uniformity.

The selection process, through digital research on the above-mentioned databases, identified 40 of 50 articles found congruent and consonant with the study's objective. The title and abstract were evaluated to identify any further studies to be excluded, and then inclusion and exclusion criteria were applied, leading to the selection and inclusion of the 40 eligible studies[17,20-58], two[25,46] of which were eligible for further analysis.

Afterward, the meta-analysis was performed on 5 articles[23,44,47,48,58] that investigated allelic polymorphism and had comparable data ana-

Table I. Bias assessment: the table is constituted of 8 questions and provided guidelines to evaluating the research question, study population, exposure, outcomes, follow-up.

TOOLS	YES	NO	CD*
Is the analysis based on an adequately formulated and described question?	Yes, the question examined is the correlation between interleukin IL-1 polymorphism and peri-implantitis	/	/
Have the eligibility criteria for including or excluding studies in the meta-analysis been clearly specified and defined?	Yes, in fact, only 5 out of 42 articles were considered	/	/
Does the literature search strategy use a comprehensive and systematic approach?	Yes, the bibliography draws on various databases such as Pubmed, Scopus, Embase, and Web of Science	/	/
Are the title, the abstract and the body of the text of the articles considered relevant both independently and in relation to the others chosen?	Yes, the review was conducted by several independent reviewers belonging to different application domains	/	/
Was the quality of each individual study independently assessed by multiple reviewers using standard methods?	Yes, the quality of the assessment was guaranteed, with a clear description of the parameters used	/	/
Did the list of selected studies possess important shared characteristics and results?	Yes, in fact, articles that did not adequately respond to the shared eligibility characteristics were excluded from the meta-analysis	/	/
Was publication bias assessed?	Yes, in order to minimize potential publication bias, the researchers included research strategies.	/	/
Has heterogeneity been assessed?	Yes, in two different modes: Cohran's Q and I^2 statics.	/	/

*CD = cannot be determined.

lyzed (quantitatively and qualitatively) to reduce bias (publication, heterogeneity of studies, enrollment).

Statistical Analysis

In detail, the effect size was estimated using an Odds Ratio (OR) with the 95% Confidence Interval (CI) test with a random effects model. The pooled effect was considered significant if the *p*-value was <0.05. Forest plots were drawn to present the data. Heterogeneity was assessed by χ^2-based Q-statistic method and I^2 measurement, with significance indicated by $p<0.1$. Publication bias was assessed using Egger's and Begg's tests. The statistical analysis was performed using the MedCalc software Ltd (Version 19.1.7, Ostend, Belgium, available at: https://www.medcalc.org/).

Results

According to the presence or absence of a genetic correlation, the 40 studies[17,20-58] were divided into 3 groups:

1. the IL-1 polymorphism is not associated with PI[20-27];
2. the influence of the IL-1 polymorphism on PI is not defined[28-34];
3. there is an association between IL-1 polymorphism and PI[17,25,35-58].

The most commonly used technique in most of the studies for the detection of interleukins in CF included the following procedure: after having marked the supramucosal plaque levels and removed the bacterial biofilm, periimplant crevicular gingival fluid was collected in each of the study subjects with PI (test group) and in each of the study subjects with healthy implants (control group), short (patients who developed PI within six months) and long term (patients who developed PI after more than a year). After insulation with cotton rolls and gentle air drying, a strip of absorbent filter paper (from different brands, e.g., PerioPaper, or Harco Electronics, Winnipeg, Manitoba, Canada) was first gently inserted on the buccal surface of each implant abutment selected in the submucosal area for 30 seconds, and then placed in a plastic tube to be subjected to microcentrifuge and finally stored at -80°C until the examination was performed into the laboratory.

Levels of IL-1, isolated or associated with other interleukins and cytokines, were measured in crevicular fluid samples collected using a commercially available ELISA kit (example: Cistron). The multiple detection of IL-1β, MIP-1α, MMP-8, and other immune mediators, etc., was performed using Luminex IS 100 instruments with the kits available from R&D Systems and EMD Millipore (Billerica, MA, USA). The most frequently evaluated clinical parameters are:

- the depth of the pocket on probing;
- bleeding on probing;
- the percentage of plaque;
- the percentage of bone loss on radiographic examination (where present);
- the clinical signs and the laboratory examination of the samples taken.

As regards the evaluation of allelic variation, different types of commercial genetic kits were used (such as the PST, which identifies polymorphisms by exploiting the PCR) in De Boever and De Boever[20] and Garcia-Delaney et al[21] studies.

The IL-1 Polymorphism is not Associated with PI

The authors of the first group[20-27] did not identify an association between IL-1 polymorphism and PI. Unfortunately, the small number of patients considered valid for enrolment in the "cross-sectional" study by Melo et al[22] was not sufficient to determine a statistically significant differential value between the 2 groups. Also, in the 68 implants of the De Boever and De Boever[20] study, there were no statistically significant differences. As in 2015, Garcia-Delaney et al[21] compared the IL-1β polymorphism in heavy smokers, 27 patients with PI and 27 healthy: the incidence of PI was significantly higher in patients with a previous history of periodontitis (p=0.024; OR=10.9). Both groups were similar in *IL-1A* –C889T, *IL-1β* +C3953T, and *IL-1RN* *+T2018C* genotypes. No increased risk was found in heavy smokers with IL-1 + polymorphism. The same applies to the study by Campos et al[23], which investigated the association between IL-1 + polymorphism and early implant failure due to lack of osseointegration in a Brazilian non-smoking population; it appears that there was no statistically significant difference between the control group of 34 healthy patients and the test group of 28 PI affected subjects in the genetic examination of the allelic polymorphism of *IL-1A* –889, *IL-1β* +3954, *IL-1β* –511 and *IL-RN*, even if they showed a fair difference between the two groups. All the authors of the 1st group consider,

at the end of their investigation, it is necessary to continue the search for a correlation between the polymorphism of IL-1 and the high risk of developing periimplantitis, starting from a wider selection of the population to be examined and more homogeneous in the recruitment criteria.

The Influence of the IL-1 Polymorphism on PI is not Excluded

In the second study group[28-34], a correlation between the polymorphism of IL-1 and PI was not excluded. Further research on this topic was thought to be needed (also according to the study by Huynh-Ba et al[30]).

The cross-sectional study by Lachmann et al[29] showed that the IL-1 polymorphism has only a slight influence on the immune response at the sulcular level. However, these authors explicitly note that their findings may have been influenced by the study design. Also, the small number of patients (11 patients with PI and 18 with healthy implants), the different types of prosthetic and implant restorations, and the patient's age heterogeneity may have influenced the results. Quantitative-quality comparisons and concentration measurements of inflammatory and immunological parameters do not always coincide with the literature. Researchers[29] use different biochemical materials, and the acquired data are often grouped or reported as concentration per implant site rather than volume of crevicular and periimplant gingival fluid.

Although Lin et al[28] consider a positive IL-1 genotype, along with other factors, such as smoking, age, sex, and menopause, as a contraindication for implant placement, the authors caution that currently available evidence is insufficient to establish a connection between early marginal bone loss around the implant and IL-1 positive genotype.

Association Between IL-1 Polymorphism and Periimplantitis

The articles of the third group (27) are divided into 2 subgroups in which:

-3a - it is highlighted that there is an association between IL-1 polymorphism and PI only when combined with polymorphism of other cytokines[17,25,35-47].

-3b - it is clear that there is an association between IL-1 polymorphism and PI given some risk factors [e.g., heavy smoking; systemic autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus (SLE), Sjogren's Syndrome; or chronic metabolic diseases such as diabetes][17,46,48-58].

The 3rd group of articles allowed us to extract quantitative data and perform a meta-analysis.

Meta-Analysis

The studies selected in the period 2003-2020, according to the aforementioned metanalysis, were 5: Campos et al[23], He et al[44], Laine et al[47], Cosyn et al[56], Shimpuku et al[58]. Those articles belonging to the 3rd group confirm the correlation between polymorphism and periimplantitis, while the study of Campos et al[23], belonging to the 1st group, did not find it. Data from these 5 articles[23,44,47,56,58], even though belonging to different groups, allowed an adequate weight for a comparative analysis. The main characteristics are summarized in Table II. The results of the different studies, with 95% CI, and the overall effect (under the fixed and random effects model) with 95% CI are illustrated in the forest plot. All articles included in the metanalysis, except for Campos et al[23], presented a *p*-value lower than 0.05, confirming the statistical significance of the result. In particular, the article of Cosyn et al[56], considering allele *IL-1β* +3954 (*p*-value=0.003) and the article by Shimpuku et al[58] (*p*-value=0.013), presented a

Table II. Data of the case and control groups. Samples are the number of total implants. The number indicates the number of implants affected by PI in the case group and the number of healthy implants in the control group.

		Cases group			Control group		
	Samples	Number	Mean age	Smoking	Number	Mean age	Smoking
Campos et al[23] (2005)	62	28	52.7	No	34	43.3	No
He et al[44] (2020)	318	144	44.7	No	174	44.7	No
Laine et al[47] (2020)	120	71	68	78%	49	66	45%
Cosyn et al[56] (2016)	461	14	67	71%	14	64	71%
Shimpuku et al[58] (2003)	39	17	55	29%	22	55	41%

greater weight of significance. According to the different considered variants, the CI (the reliability of the estimation method) for *IL-1A* –889 was from 1.23 to 2.5, for *IL-1β* –511 from 0.39 to 1.2; finally, for *IL-1β* +3954, it was between 1.2 and 2.5; the OR, as shown in Table III, is respectively 0.69 for *IL-1β* –511 and 1.77 *IL-1A* –899 allele. The average OR for *IL-1β* +3954 was 1.75, with the highest value found in Cosyn et al[56] (17.33). These results, shown in Table IV, confirm a more evident correlation of the phenomenon analyzed.

Finally, the effect size resulted in 3.1 for *IL-1A* –889, 1.27 for *IL-1β* –511, and 3.05 for *IL-1β* +3954 (Tables III, V, VI).

The results of the different studies, with 95% CI, and the overall effect (under the fixed and random effects model) with 95% CI are illustrated in the forest plots (Figures 3-5) to graphically display the estimated results.

The Q values detected were respectively: 4.7039 for *IL-1A* –889 (Table VII); 0.8624 for *IL-1β* –511 (Table VIII); 7.1436 for *IL-1β* +3954 (Table IX). Hence, the heterogeneity was not statistically significant. Therefore, studies considered are homogeneous.

The I^2 values detected were respectively: 14.96% for *IL-1A* –889 (Table VII); 0.00% for *IL-1β* –511 (Table VIII); 44.01% for *IL-1β* +3954 (Table IX). Despite these high values for *IL-1A* –889 and *IL-1β* +3954, the heterogeneity was not statistically significant because the *p*-values for the heterogeneity test were greater than 0.05.

Table III. Effect size of *IL-1A* –889.

Study	Intervention	Controls	Odds ratio	95% CI	z	p	Weight (%) Fixed	Weight (%) Random
Campos et al[23]	13/28	16/34	0.975	0.358 to 2.657			13.27	15.77
He et al[44]	54/144	35/174	2.383	1.444 to 3.933			53.10	45.67
Laine et al[47]	47/71	30/49	1.240	0.582 to 2.642			23.32	25.28
Cosyn et al[56]	8/14	4/14	3.333	0.693 to 16.023			5.41	6.96
Shimpuku et al[58]	3/17	4/22	0.964	0.185 to 5.031			4.89	6.32
Total (fixed effects)	125/274	89/293	1.770	1.234 to 2.539	3.100	0.002	100.00	100.00
Total (random effects)	125/274	89/293	1.696	1.108 to 2.598	2.430	0.015	100.00	100.00

Table IV. The table collects the *p*-values, the confidence intervals (CI), and the odds ratios (OR). However, due to insufficient starting data in the articles, OR and CI were not calculated for the IL-1R polymorphism only. *IL-IA* –889 (μ), *IL-Iβ* +3954 (π), I*L-IRN* (∞), *IL-Iβ* –511 (∂), *IL-1-RN/B-511/Bþ3953/A-889* (●).

	p-value	CI	OR
Cosyn et al[56]	0.039 (μ)	X (μ)	3.9 (μ)
He et al[44]	0.021 (μ)	1.2-4.64 (μ)	2.37 (μ)
Murata et al[55]	0.003 (π)	X (π)	15.0 (π)
He et al[44]	0.035 (π)	1.4-3.68 (π)	1.9 (π)
Laine et al[47]	0.02 (∞)	1.2-7.6 (∞)	3 (∞)
Shimpuku et al[58]	0.013 (∂)	1.64-71.9 (∂)	10.86 (∂)
Campos et al[23]	0.8348 (●)	X (●)	X (●)

Table V. Effect size of *IL-1β* –511.

Study	Intervention	Controls	Odds ratio	95% CI	z	p	Weight (%) Fixed	Weight (%) Random
Cosyn et al[56]	11/14	12/14	0.611	0.0854 to 4.371			8.15	8.15
Laine et al[47]	41/71	30/49	0.866	0.412 to 1.820			57.14	57.14
Shimpuku et al[58]	1/17	2/22	0.625	0.0519 to 7.530			5.09	5.09
Campos et al[23]	14/28	23/34	0.478	0.170 to 1.342			29.62	29.62
Total (fixed effects)	67/130	67/119	0.694	0.397 to 1.215	-1.278	0.201	100.00	100.00
Total (random effects)	67/130	67/119	0.694	0.396 to 1.217	-1.274	0.203	100.00	100.00

Table VI. Effect size of *IL-1β* +3954.

Study	Intervention	Controls	Odds ratio	95% CI	z	p	Weight (%) Fixed	Weight (%) Random
Campos et al[23]	13/28	10/34	2.080	0.730 to 5.925			12.12	20.25
He et al[44]	57/144	44/174	1.936	1.200 to 3.122			58.15	38.85
Laine et al[47]	36/71	25/49	0.987	0.477 to 2.045			25.05	29.44
Cosyn et al[56]	8/14	1/14	17.333	1.750 to 171.67			2.53	6.14
Shimpuku et al[58]	1/17	2/22	0.625	0.0519 to 7.530			2.14	5.31
Total (fixed effects)	115/274	82/293	1.745	1.222 to 2.493	3.059	0.002	100.00	100.00
Total (random effects)	115/274	82/293	1.736	0.947 to 3.181	1.784	0.074	100.00	100.00

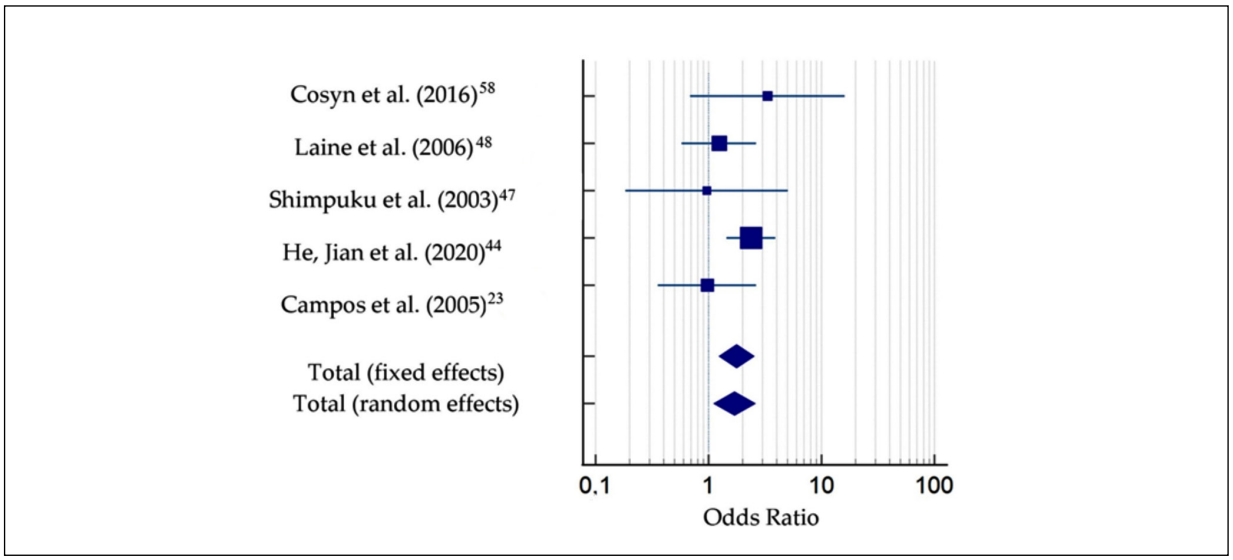

Figure 3. Forest plot for odds ratio *IL-1A* –889.

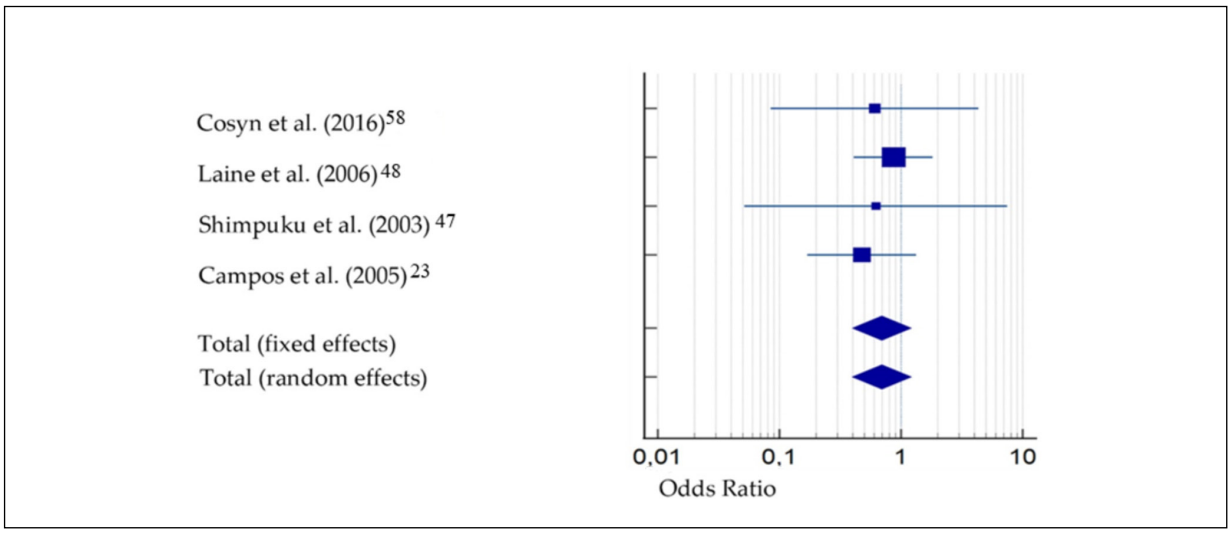

Figure 4. Forest plot for odds ratio *IL-1β* –511.

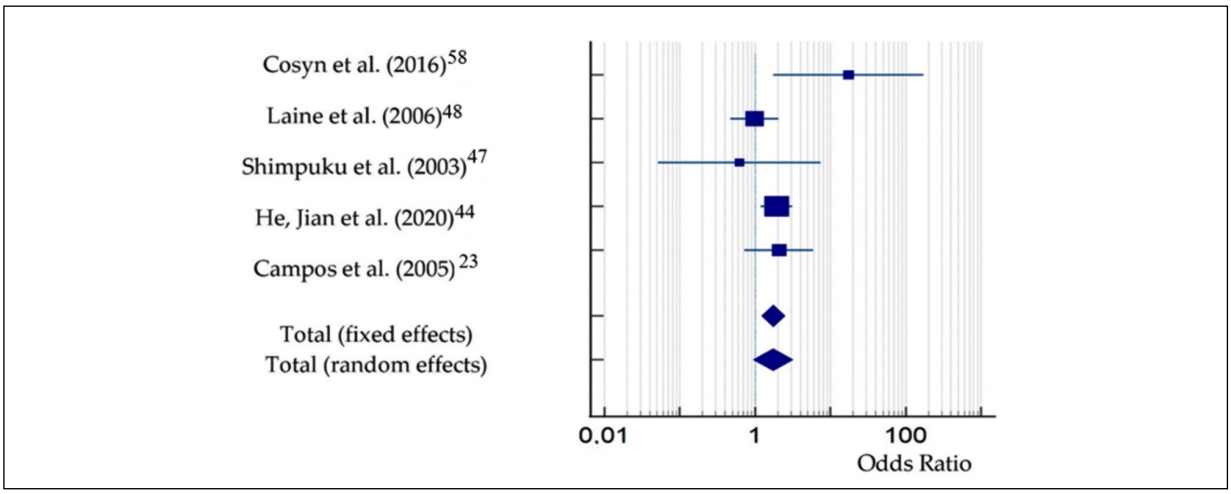

Figure 5. Forest plot for odds ratio *IL-1B* +3954.

Table VII. Heterogeneity test of *IL-1A* –889.

Q	4.7039
DF	4
Significance level	p=0.3191
I^2 (inconsistency)	14.96%
95% CI for I^2	0.00 to 83.35

Table VIII. Heterogeneity test of *IL-1β* –511.

Q	0.8624
DF	3
Significance level	p=0.8345
I^2 (inconsistency)	0.00%
95% CI for I^2	0.00 to 55.09

Table IX. Heterogeneity test of *IL-1β* +3954.

Q	7.1436
DF	4
Significance level	p=0.1285
I^2 (inconsistency)	44.01%
95% CI for I^2	0.00 to 79.45

The publication bias, including the Egger's test and the Begg's test, is reported to complete the meta-analysis (Tables X, XI, XII).

Discussion

This systematic review focused on verifying a clear and definite relationship between IL-1 and

Table X. Publication bias of *IL-1A* –889.

Egger's test	
Intercept	-0.9760
95% CI	-4.8264 to 2.8743
Significance level	p=0.4788
Begg's test	
Kendall's Tau	-0.2000
Significance level	p=1.0000

Table XI. Publication bias of *IL-1β* –511.

Egger's test	
Intercept	-0.4660
95% CI	-3.4806 to 2.5486
Significance level	p=0.5744
Begg's test	
Kendall's Tau	0.0000
Significance level	p=1.0000

Table XII. Publication bias of *IL-1β* +3954.

Egger's test	
Intercept	0.4778
95% CI	-3.6894 to 4.6449
Significance level	p=0.7394
Begg's test	
Kendall's Tau	0.0000
Significance level	p=1.0000

the onset of PI. The inclusion of a wide window of research (from the first studies in 1992 to the most recent one in 2022) allowed us to identify all the relevant works produced on the subject (as many as 50 publications) with comprehensive and multi-source research. Finally, the 40 included studies showed three general trends, categorized into 3 groups, of which the third required the formation of two subgroups. Regarding the demographic data, how gender affects PI was not fully investigated, nor was there a hypothetical correlation between gender and PI with IL-1 polymorphism.

Studies in the literature have shown that the concentration of IL-1 in the gingival crevicular fluid (GCF) of teeth affected by periodontitis was higher than that of healthy teeth[13,18]. Likewise, Panagakos et al[54] and Curtis et al[54] reported an increase in IL-1 concentration around implants with PI, contradicting the results of Hultin et al[27] in 2002.

In 2017, Petkovic-Curcin et al[14] examined the cytokine gene polymorphism with the risk of PI and, in particular, examined the *IL-1Ra* gene polymorphism. Indeed, IL-1Ra has an anti-inflammatory role, and a variation in the alleles in the *IL-1Ra* might influence the severity of PI.

In a recent systematic review, Cardoso et al[59] concluded in their meta-analysis that the literature lacks studies whose sample sizes are adequate to draft a conclusion on the influence or/and association of IL-1 and IL-1 receptor antagonist polymorphisms on the development of PI. Regarding the Cardoso et al[59] meta-analysis, the authors reported that the population with polymorphism in the *IL-1β* +3954 gene presented a higher risk for the development of periimplantitis[59]. Indeed, the quality of the data's validity showed that the IL-1 allelic subgroup variants are involved in PI etiology. A recent meta-analysis associated the T allele and CT genotype of IL-1β +3954 polymorphism with an elevated risk of PI[60]. The last two points of this meta-analysis are in agreement with the results of our systematic analysis.

The studies[20-27] included in the first group did not identify an association between IL-1 polymorphism and PI, and no increased risk was found in heavy smokers with IL-1 + polymorphism. A review performed by Andreiotelli et al[61] disagrees with our data: indeed, the authors assumed a synergistic effect of the IL-1 positive genotype and smoking habit in implant failure. However, the authors highlighted the smoking habit might hide the effect of the IL-1 genotype and recommend further research in this field.

The studies[28-34] classified in the second group found that a correlation between the IL-1 polymorphism and PI is not excluded. The influence of gene polymorphism can affect implant failure, probably due to the small sample size in the considered articles. Even though differences are reported, the data are not enough to establish the correlation between the IL-1 polymorphism and PI. Further research on this topic was estimated to be necessary[30].

The qualitative synthesis of the third group of studies leads to the conclusion of the presence of an association between PI and IL-1 polymorphism. The group gathered the largest number of articles[17,25,35-58], 27, even published in recent years, often consisting of more recent works[23,44,47,55,58] by the same authors who, after years of preliminary data, only recently succeeded in obtaining proper and solid results.

Similar data on mean bone loss were also found in the study by Hultin et al[27], which identified similar percentages, although a direct comparison with the articles of this group is difficult due to the different duration of the studies and the different types of implants.

The results obtained by the studies[17,25,35-58] included in the third group showed a correlation between the immune response and clinical inflammatory parameters, which is in agreement with the results of Panagakos et al[53] but in disagreement with Hultin et al[27].

Polymorphisms in the interleukin gene cluster are often associated with periodontitis[58]. Laine et al[47] examined *IL-1* cluster gene polymorphism related to PI in 120 Caucasian patients (including 71 with PI and 49 healthy) and discovered a mutation in the *IL-1-RN* gene cluster. This alteration of the IL-1Ra weakens the natural IL-1 antagonist; consequently, IL-1 can freely unfold its pro-inflammatory effect. If both gene mutations occur simultaneously, the overproduction and decreased inhibition of *IL-1RN* will be amplified to produce an even greater risk of periodontitis and PI[47]. The authors[47] described a significant influence on the progression of periimplant disease due to this gene alteration on the receptor antagonist, regardless of other risk factors such as bacterial load or smoking. However, other studies[49,50], in disagreement with these results, described a microbial load associated with smoking habit as a major risk factor for PI. This is due to the sampling bias in the work of Laine et al[47]: in the control group with healthy implants, the proportion of smokers (45%) was significantly lower than in the PI test group, of which 76% were smokers.

The results of Murata et al[55], which identified the concentration of IL-1 in the GCF as an indicator of periimplant inflammation, agree with the results of Curtis et al[54] and Panagakos et al[53], but disagree with the results obtained by Hultin et al[27] and Lachmann et al[29].

Shimpuku et al[58], through their case-control studies on the Japanese population, examined 251 implants in 39 patients and analyzed the periimplant marginal bone loss that occurred in 36 implants. Patients with the *IL-1β* –511 2/2 genotype showed a significantly higher incidence of bone loss than those with negative polymorphism. The study results lead to the conclusion that genetic variants can be considered a risk factor for bone loss and the quality of osseointegration as age, smoking, and menopause, with an odds ratio between 0.44 and 6.20. These data were highly suggestive of a significant association in early rather than late periimplant bone loss.

Similarly, Che et al[45] showed that early bone loss is apparently not caused by bacterial toxins. The authors argued that this bone loss is due to "bone resorption not strictly related to infection" since this resorption had already begun before the implant abutment was connected and evolved differently between positive and negative genotypes for IL-1 polymorphism; furthermore, the authors demonstrated that the relationship between *IL-1β* –511 2/2 polymorphism and bone loss around the implant. In conclusion, the presence of *IL-1β* –511 may be a genetic marker for early bone loss around implants, not directly associated with toxins. Periimplant bone loss after abutment connection may be related to the polymorphism of *IL-1A* –889 and *IL-1β* -3954.

The results of Curtis et al[54] found that the amount of IL-1β and TNF-α is directly related to the release of toxins by plaque bacteria and the intensity of the mechanical load.

Laine et al[47] documented an increased presence of the periodontal pathogens *Prevotella nigrescens*, *Peptostreptococcus micros*, *Fusobacterium nucleatum* in PI. *Peptostreptococcus micros* was considered a pathogenic marker for the diagnosis of periodontitis and PI.

Papathanasiou et al[13] found numerous pathogens in periodontal pockets and consequently reported that teeth affected by periodontal disease represent a reservoir of microorganisms potentially harmful to implants.

The findings of Laine et al[47] showed the inflammatory mediators' prostaglandin E2 (PGE2) and IL-1 were significantly increased in GCF, resulting in profuse bleeding of the periimplant mucosa. This confirms that PGE2 and IL-1 modulate the inflammatory process and play an important role in the destruction of bone and connective tissue.

Panagakos et al[53] demonstrated that cytokine measurement could be a useful tool for diagnosing early periimplant diseases and monitoring treatment success in PI with a risk of advanced bone loss. Indeed, PI with early bone loss has higher IL-1 concentration (associated IL-1β and TNF-α) than PI with advanced and later bone loss, probably due to the different states of inflammation (acute and chronic).

In the 3b subgroup, there was a correlation between the IL-1 polymorphism and PI in the presence of some risk factors, such as smoking habit, diabetes, and chronic dysmetabolic and/or autoimmune diseases (Sjogren's syndrome, rheumatoid arthritis, Les, etc.). This is in agreement with Jansson et al[57] and Feloutzis et al[49].

The prevalence of IL-1-positive genotypes in the presence of smoke habits is debated in the literature. Jansson et al[57] observed that although smokers had a higher rate of implantation loss than non-smokers, the difference was not significant. Abduljabbar et al[48], on the other hand, confirmed the synergistic effect of smoking and a positive IL-1 genotype, which leads to a significantly higher implant loss rate. This latest study on a population of 66 patients, 33 smokers and 33 non-smokers, analyzed the concentration of IL-1β and IL-6, TNF-α in the periimplant sulcus fluid, resulting in a statistically significant result with an increase in the group of smokers.

In the study by Gruica et al[50], 36% of patients had an *IL-1* positive genotype, which is similar to previous studies[42,55,49] on the Caucasian population. The mean percentage of smokers – 29% of patients – was comparable across studies and agreed in particular with Feloutzis et al[49]. Indeed, Feloutzis et al[49] examined the influence of smoking on periimplant bone loss following the application of prosthetic reconstructions and after an observation phase of 5.6 years on average. The implants were exposed to bacterial inflammatory processes for an adequate period of time. In the maintenance phase, only one patient lost numerous implants. The annual bone loss around the implants was considered as variable. *IL-1* genotype status did not cause bone loss in non-smokers. *IL-1* polymorphism alone probably cannot be considered a risk factor for periimplant bone loss, but it becomes one when associated with other

risk factors, such as smoking. This agrees with the findings of Huynh-Ba et al[30].

He et al[44] found that the IL-1 level in the periimplant crevicular fluid (PICF) of inflamed periimplant gingiva increased in non-smokers. The Chinese population was constituted of 144 patients affected by PI and 174 with healthy implants, and the genetic variation of immunoregulatory proteins was associated with PI risk. In other studies[57,62,64], smokers showed significantly lower levels of IL-1β in PICFs and achieved similar results. It was hypothesized that neutrophil granulocytes, instead of migrating into the periimplant sulcus, presumably remain in the periimplant tissues. This process is comparable to leukocyte dysfunction in smokers. They produce and secrete cytokines, which subsequently lead to the accelerated destruction of connective tissue and alveolar bone[57,62,64].

In the study by Cosyn et al[56], 416 patients with an average of 1.18 implants for each patient were considered. A 31/33 of implants were lost in the first year, and 14 of these were early implants lost (within the first 6 months). Rapid implant loss can be seen rather as a biological response of the bone to implant placement or attributed to other traumatic/mechanical factors, such as the release of metal particles from the surgical burs[65], rather than as inflammation mainly related to bacteria. In the study of Cosyn et al[56], the examined population was Caucasian, and the IL-1 polymorphism was statistically relevant and consequently influenced the implant osseointegration process.

Garcia-Delaey et al[21] considered smoking as a determinant risk factor for early implant loss, hiding the influence of IL-1 polymorphism. In the Wilson and Nunn study[51], with 36 implant failures, 27 of the 62 patients (44%) were smokers. However, the number of patients examined was too low; only 2 implant systems and 2 different implant surfaces were involved.

In terms of different implant surfaces, the studies by Murata et al[55] analyzing 34 titanium implants and by Monga et al[43] on titanium mini-screws provided valuable information. The significant increase in the concentration of IL-1β in the periimplant tissue four months after implant placement in the PI group rather than in the healthy ones or in the group of patients with mucositis could be caused by the absorption of lipopolysaccharides on the surface of the titanium.

Pettersson et al[63] found that the amount of IL-1 varies by implant type, bringing a new concept to the discussion of interleukin. They reported *in vitro* that inflammation is activated by Ti ions, causing an increase in the production of IL-1β in culture cells as well as in PISF.

Che et al[46] identified an increase in osteopontin (OPN) concentration on the periimplant gingival surface in response to the presence of pathogens such as *P. gingivalis*. OPN is an osteo-immuno-inflammatory marker and is involved in the nosogenesis of PI. Another molecule, lectin-like oxidized low-density lipoprotein receptor 1 (LOX-1), which is a multi-ligand receptor of the oxidized low-density lipoprotein (ox-LDL) but which also binds to activate platelets, apoptotic cells, bacteria, and C-reactive protein, is responsible for the downregulation of OPN and *vice versa*. The reduction of LOX-1 leads to the increase of OPN, determining an increase in the production of IL-1β[46]. IL-6 and IL-8 increase significantly in the first hours in response to inflammation since the release of other cytokines is less specific than IL-1. IL-1 also comes from osteoblast-like cells (precursors); monocytes and/or macrophages are, therefore, not the only producers of interleukin[46]. IL-1 is involved in the activation of osteoclasts. IL-6 is often associated with bone diseases such as Paget's disease, rheumatoid arthritis and postmenopausal osteoporosis (IL-1 and IL-6 induce osteoclast activity, while IL-18 inhibits it)[46]. Not only monocytes and macrophages but also neutrophilic granulocytes and fibroblasts are involved in the release of the cytokines IL-6 and IL-8. Since no stimulation with bacterial toxins can yet occur within 24 hours, this may be why the IL-1 concentration did not show a significant increase one day after surgery[46].

The meta-analysis was conducted on 4 studies[23,48,49,56] (which present a greater uniformity of the data considered) of the 3rd group: it is evident that the *p*-value was statistically significant (see Table II for the alleles *IL-1A* –889, *IL-1β* –511 and *IL-1β* +3954) and in particular it was seen that for the polymorphism *IL-1β* +3954, the *p*-value was 0.003 (highly significant). An average odds ratio (i.e., the probability that the association occurs) of 1.75 confirms a more evident relationship of the phenomenon. Clinical parameters to diagnose PI are periodontal probing and/or radiographic examinations. However, high probing depths can be noticed relatively late during follow-up and maintenance treatment appointments[66]. As regards imaging, bone loss is observable after significant demineralization and loss of the cortical lamina[67]. An early diagnosis enables fast and timely intervention to minimize tissue damage

and improve treatment outcome[67]. Therefore, the concentration of IL-1 as a marker of early inflammation might be useful for an early interception of the disease onset[18,56].

Conclusions

The final result of the subjective response in the periimplant process comes from the interaction of a large number of genetic variations (allelic) that regulate the action of pro-inflammatory proteins such as: IL-1, IL 1-Na, IL-6, IL- 8, IL-10, IL-18, TNF-α, MMP-8 and OPN. The articles pooled in the present study confirm the trend of researching and improving the technologies for the efficacy of genotype tests to foresee the susceptibility of a patient to PI.

Since PI is a complex and multifactorial disease, the results of our study confirm the need to investigate further the synergistic action of IL-1 (especially the +3954 *C/T* mutated) with other interleukins (such as IL-17, IL-33, IL-36, IL-38, etc, already examined for periodontitis) and with other environmental factors, such as smoking habit. Further review studies, also associated with prospective studies and meta-analysis, will help to better understand the role of these biochemical mediators, particularly IL-1, in association with other cytokines in the genesis of periimplantitis.

Authors' Contributions

Conceptualization, G.V., and S.B.; methodology, N.S., D.G.; validation, S.B., F.R.; investigation, N.S., and D.G.; resources, M.P.; data curation, I.B.; writing-original draft preparation, S.B.; writing-review and editing, G.V and V.P.

Funding

This research received no external funding.

Ethics Approval and Informed Consent

Not applicable due to the design of the study.

Data Availability

Data will be available upon reasonable request to the corresponding author.

Conflicts of Interest

The authors declare no conflict of interest.

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