Peri-Implant Disease

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Contributor: Masoud Sadeghi

Despite the high survival rate and success of dental implants, it has long been known that osseointegrated implants may suffer from biological complications, collectively referred to as peri-implant disease (PID).

Keywords: peri-implant disease ; implant failure ; peri-implantitis ; bone loss ; cytokine

1. Introduction

Despite the high survival rate and success of dental implants, it has long been known that osseointegrated implants may suffer from biological complications, collectively referred to as peri-implant disease (PID) [1]. PIDs are defined as inflammatory lesions of the tissue around the implant and include mucositis around the implant (inflammatory lesion confined to the mucosa around the implant) and peri-implantitis (an inflammatory lesion of the mucosa that affects the supporting bone with bone loss) [2]. A recent meta-analysis included peri-implantitis, implant failure, and marginal bone loss as PIDs [3]. A review study showed peri-implantitis in 28% and ≥56% of cases and in 12% and 43% of implant sites [4]. A systematic review suggested that the prevalence of peri-implantitis was approximately 22% (range: 1–47%) [5]. Another study found the prevalence of dental implant failures to be 11% in males and 9% in females; this prevalence was dependent on implant length, implant diameter, and bone quality [6]. Marginal bone loss (>0.5 mm) at implants was also recognized in 30% of cases and 16% of implant sites [7]. Evidence suggests that those who are aged more than 60 years, smokers, receiving head and neck radiation, postmenopausal, suffering from diabetes, and receiving hormone replacement therapy experienced significantly elevated implant failure in comparison with healthy patients [8].

Genetic susceptibility has been shown to be a significant risk factor for peri-implantitis, and there are numerous studies assessing this in different populations [9][10][11]. Gene polymorphisms refer to changes in DNA sequencing, such as the regulation of inflammatory mediators, primarily the gene promoter region, which can affect gene function and the progression of inflammatory diseases [12][13]. Polymorphisms of cytokines associated with the risk of PID, such as *interleukin (IL)-1A* [14], *IL-1B* [14][15], *IL-6* [16][17], tumor necrosis factor-alpha (*TNF-α*) [17], and *IL-10* [15][18] as an anti-inflammatory cytokine, could inhibit the production of proinflammatory cytokines and the induction of B lymphocyte proliferation as well as prevent the proliferation and activation of natural killer cells [19]. TNF-α is another anti-inflammatory cytokine that plays an important role in inflammatory processes [17]. The role of TNF-α in the destruction of bone around the implant has been suggested by researchers [20]. A meta-analysis [21] assessed the association of *TNF-α (−308 G > A)* and *IL-10 (−1082 A > G)* polymorphisms with the risk of implant failure by including two and three studies, respectively. Another meta-analysis [3] investigated the role of *TNF-α (−308 G > A)* polymorphism in PID using the data from six studies.

2. Design

The preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines were used to report this study [22]. The PICO (patient/population, intervention, comparison, and outcomes) question was as follows: Is there an association between *IL-10* and *TNF-α* polymorphisms and the risk of PID in patients with dental implants?

3. Literature Search Strategy

The Web of Science, Cochrane Library, Scopus, and PubMed/Medline databases were searched for studies published until 12 April 2021 without any restrictions. The searched terms were (“dental implant*” or “oral implant*” or “peri-implant disease*” or “implant loss” or “implant failure” or “peri-implantitis” or “periimplant” or “implant bone loss” or “failing implant”) and (“interleukin-10” or “IL-10” or “IL10” or “TNFA” or “TNF-α” or “TNF-alpha” or “TNFalpha” or “tumor necrosis factor-alpha” or “tumor necrosis factor alpha” or “TNFα” or “tumor necrosis factor-α”) and (“polymorphism*” or “allele” or

"genotype*" or "variant*" or "SNP"). In addition, we manually checked the references of seminal articles related to the subject area to ensure that no potential articles were missed.

4. Eligibility Criteria

The studies were retrieved from the databases by one author (M.S.), and the duplicates and irrelevant studies were then excluded. The studies were considered relevant if they met the following eligibility criteria: (I) case–control design; (II) PID as the outcome of interest; (III) reporting *TNF-α (−308 G > A)*, *IL-10 (−1082 A > G)*, *IL-10 (−819 C > T)*, or *IL-10 (−592 A > C)* polymorphisms with any genetic models; and (IV) having the required data to calculate the odds ratios (ORs) with 95% confidence intervals (CIs) for the genetic models. The studies were removed if they did not have the required data regarding genotype distributions or were animal studies, meta-analyses, review articles, letters to the editor, reported secondary data, and reported genotype distributions after treatment. The second author (L.J.) rechecked the relevant articles based on the eligibility criteria. Any disagreement between the two authors was resolved by discussion.

5. Data Extraction

One author (M.S.) independently extracted the data from each study and another author (J.T) rechecked them. The information retrieved from the studies included the first author's name, publication year, ethnic group, control source, mean/median age and male/female ratio in the two groups (patients and controls), genotyping method, form of disease, number of patients or controls, the *p*-value of Hardy–Weinberg equilibrium (HWE) in controls, the quality score, and the distribution of genotypes in the two groups. If there was a disagreement between the authors, the problem was resolved by a short discussion.

6. Quality of Assessment

One author (L.J) distinguished the quality of each included article using the modified Newcastle–Ottawa Quality Assessment Scale questionnaire, which was used in a similar meta-analysis involving gene polymorphisms. It involves assigning scores ranging from 0–2 and 0–1 on five (representativeness of cases, ascertainment of case outcomes, ascertainment of controls, H–W equilibrium in controls, and association assessment) and two (description of follow-up and genotyping examination) criteria, respectively. A maximum total score of 12 was possible for each study [3].

7. Statistical Analyses

The Review Manager 5.3 (RevMan 5.3; the Cochrane Collaboration, the Nordic Cochrane Centre, Copenhagen, Denmark) was used to calculate crude odds ratio (OR) and 95% confidence interval (CI) showing the association between *IL-10* and *TNF-α* polymorphisms and dental PID risk in the five genetic models. To evaluate the pooled OR significance, the Z test was applied with a $p < 0.05$. The Cochrane Q test and I^2 statistic showed the heterogeneity (inconsistency in the polymorphism effect across primary studies). If there was a statistically significant heterogeneity ($p < 0.1$ or $I^2 > 50\%$), we used a random-effect model (DerSimonian and Laird method) [23], and if there was no significant heterogeneity, a fixed-effect model (Mantel–Haenszel method) [24] was used.

The chi-square test was used to calculate the *p*-value of HWE in the control group of each study, with $p < 0.05$ indicating a deviation from the HWE.

Subgroup, sensitivity, and meta-regression analyses were performed where possible depending on the number of studies available. The subgroup analysis for explanation of heterogeneity based on a priori hypothesis was done for *TNF-α (−308 G > A)* polymorphism according to the ethnicity, control source, disease form, and number of individuals.

The funnel plots were analyzed by the Egger's and Begg's tests (with *p*-values < 0.05 indicating statistically significant existence of the publication bias). To evaluate the stability of the pooled results, we used sensitivity analyses ("one study removed" and "cumulative analysis") for *TNF-α (−308 G > A)* and *IL-10 (−819 C > T)* polymorphisms. The Comprehensive Meta-Analysis version 2.0 (CMA 2.0; Biostat Inc., Englewood, NJ, USA) was used for sensitivity analyses and assessing publication bias. A meta-regression was performed to check the effect of publication year and number of individuals on the pooled results of *TNF-α (−308 G > A*) polymorphism. SPSS version 22.0 software (IBM Corp. Release 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp) was used to calculate the results of meta-regression.

Each meta-analysis may create a false-positive or -negative conclusion [25]. Hence, TSA was conducted using TSA software (version 0.9.5.10 beta) (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet,

Copenhagen, Denmark) to reduce these statistical errors [26]. Additionally, a threshold of futility was tested by TSA to earn a conclusion of no effect before reaching the information size. The required information size (RIS) based on an alpha risk of 5%, a beta risk of 20%, and a two-sided boundary type was computed. For those analyses where the Z-curve reached the RIS line or monitored the boundary line or futility area, it was considered that the studies had adequate sample size and their results were valid. Otherwise, it was assumed that the available information was inadequate and more evidence was needed.

References

1. Van Steenberghe, D.; Klinge, B.; Lindén, U.; Quirynen, M.; Herrmann, I.; Garpland, C. Periodontal indices around natural and titanium abutments: A longitudinal multicenter study. J. Periodontol. 1993, 64, 538–541.
2. Figuero, E.; Graziani, F.; Sanz, I.; Herrera, D.; Sanz, M. Management of peri-implant mucositis and peri-implantitis. Periodontology 2000 2014, 66, 255–273.
3. Mo, Y.-Y.; Zeng, X.-T.; Weng, H.; Cen, Y.; Zhao, Q.; Wen, X. Association between tumor necrosis factor-alpha G-308A polymorphism and dental peri-implant disease risk: A meta-analysis. Medicine 2016, 95, e4425.
4. Zitzmann, N.U.; Berglundh, T. Definition and prevalence of peri-implant diseases. J. Clin. Periodontol. 2008, 35, 286–291.
5. Jepsen, S.; Berglundh, T.; Genco, R.; Aass, A.M.; Demirel, K.; Derks, J.; Figuero, E.; Giovannoli, J.L.; Goldstein, M.; Lambert, F. Primary prevention of peri-implantitis: Managing peri-implant mucositis. J. Clin. Periodontol. 2015, 42, S152–S157.
6. Singh, R.; Parihar, A.S.; Vaibhav, V.; Kumar, K.; Singh, R.; Jerry, J.J. A 10 years retrospective study of assessment of prevalence and risk factors of dental implants failures. J. Fam. Med. Prim. Care 2020, 9, 1617.
7. Cecchinato, D.; Parpaiola, A.; Lindhe, J. A cross-sectional study on the prevalence of marginal bone loss among implant patients. Clin. Oral Implant. Res. 2013, 24, 87–90.
8. Moy, P.K.; Medina, D.; Shetty, V.; Aghaloo, T.L. Dental implant failure rates and associated risk factors. Int. J. Oral Maxillofac. Implant. 2005, 20, 569–577.
9. Kadkhodazadeh, M.; Tabari, Z.A.; Pourseyediyan, T.; Najafi, K.; Amid, R. Relationship between Genetic Polymorphisms with Periodontitis and Peri-Implantitis in the Iranian Population: A Literature Review. J. Long-Term Eff. Med Implant. 2016, 26, 183–190.
10. Lee, S.; Kim, J.-Y.; Hwang, J.; Kim, S.; Lee, J.-H.; Han, D.-H. Investigation of pathogenic genes in peri-implantitis from implant clustering failure patients: A whole-exome sequencing pilot study. PLoS ONE 2014, 9, e99360.
11. Van Dyke, T.E. The impact of genotypes and immune reactivity on peri-implant inflammation: Identification and therapeutic use of anti-inflammatory drugs and immunomodulators. Eur J Oral Implant. 2012, 5, S51–S60.
12. Cullinan, M.; Westerman, B.; Hamlet, S.; Palmer, J.; Faddy, M.; Seymour, G.; Middleton, P.; Taylor, J. Progression of periodontal disease and interleukin-10 gene polymorphism. J. Periodontal Res. 2008, 43, 328–333.
13. Ding, C.; Ji, X.; Chen, X.; Xu, Y.; Zhong, L. TNF-α gene promoter polymorphisms contribute to periodontitis susceptibility: Evidence from 46 studies. J. Clin. Periodontol. 2014, 41, 748–759.
14. He, K.; Jian, F.; He, T.; Tang, H.; Huang, B.; Wei, N. Analysis of the association of TNF-α, IL-1A, and IL-1B polymorphisms with peri-implantitis in a Chinese non-smoking population. Clin. Oral Investig. 2020, 24, 693–699.
15. Saremi, L.; Shafizadeh, M.; Esmaeilzadeh, E.; Ghaffari, M.E.; hosein Mahdavi, M.; Amid, R.; Kadkhodazadeh, M. Assessment of IL-10, IL-1ß and TNF-α gene polymorphisms in patients with peri-implantitis and healthy controls. Mol. Biol. Rep. 2021, 48, 2285–2290.
16. Ladeira Casado, P.; Villas-Boas, R.; de Mello, W.; Leite Duarte, M.E.; Mauro Granjeiro, J. Peri-implant disease and chronic periodontitis: Is interleukin-6 gene promoter polymorphism the common risk factor in a Brazilian population? Int. J. Oral Maxillofac. Implant. 2013, 28, 35–43.
17. Petkovic-Curcin, A.; Zeljic, K.; Cikota-Aleksic, B.; Dakovic, D.; Tatic, Z.; Magic, Z. Association of Cytokine Gene Polymorphism with Peri-implantitis, Risk. Int. J. Oral Maxillofac. Implant. 2017, 32, e241–e248.
18. Pigossi, S.C.; Alvim-Pereira, F.; Montes, C.C.; Finoti, L.S.; Secolin, R.; Trevilatto, P.C.; Scarel-Caminaga, R.M. Genetic association study between Interleukin 10 gene and dental implant loss. Arch. Oral Biol. 2012, 57, 1256–1263.
19. Moore, K.W.; de Waal Malefyt, R.; Coffman, R.L.; O'Garra, A. Interleukin-10 and the interleukin-10 receptor. Annu. Rev. Immunol. 2001, 19, 683–765.

20. Duarte, P.M.; De Mendonça, A.C.; Máximo, M.B.B.; Santos, V.R.; Bastos, M.F.; Nociti Júnior, F.H. Differential cytokine expressions affect the severity of peri-implant disease. Clin. Oral Implant. Res. 2009, 20, 514–520.
21. Santiago Junior, J.F.; Biguetti, C.C.; Matsumoto, M.A.; Abu Halawa Kudo, G.; Parra da Silva, R.B.; Pinto Saraiva, P.; Fakhouri, W.D. Can genetic factors compromise the success of dental implants? A systematic review and meta-analysis. Genes 2018, 9, 444.
22. Moher, D.; Liberati, A.; Tetzlaff, J.; Altman, D.G. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Int. J. Surg 2010, 8, 336–341.
23. DerSimonian, R.; Laird, N. Meta-analysis in clinical trials. Control. Clin. Trials 1986, 7, 177–188.
24. Mantel, N.; Haenszel, W. Statistical aspects of the analysis of data from retrospective studies of disease. J. Natl. Cancer Inst. 1959, 22, 719–748.
25. Imberger, G.; Thorlund, K.; Gluud, C.; Wetterslev, J. False-positive findings in Cochrane meta-analyses with and without application of trial sequential analysis: An empirical review. BMJ Open 2016, 6, e011890.
26. Wetterslev, J.; Jakobsen, J.C.; Gluud, C. Trial sequential analysis in systematic reviews with meta-analysis. BMC Med. Res. Methodol. 2017, 17, 1–18.