Review

Association of interleukin-1 gene polymorphism and early crestal bone loss around submerged dental implants: A systematic review and meta-analysis

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Abstract

Aim: Early crestal bone loss (ECBL) has been observed regardless of the absence of possible etiologic factors for bone loss during the healing phase and before the second-stage implant surgery. The purpose of this systematic review and meta-analysis was to correlate the possible association of interleukin-1 (IL-1) gene polymorphisms and ECBL (bone loss before the second-stage surgery) around dental implants.

Settings and Design: Systematic review and meta-analysis following PRISMA guidelines.

Materials and Methods: Considering the inclusion criteria, an electronic search by using specific keywords of three databases PubMed [("Dental" OR "oral") AND ("Implants*") AND ("gene polymorphism" OR "genotype" AND ("IL-1" OR "interleukins")], Cochrane library [implant AND (biomarker or cytokine), interleukin-1 or IL-1 AND implants], and EMBASE [("gene polymorphisms"/de OR "interleukins"/cytokine exp OR "biomarker":ti,ab,kw) AND ("dental implantation"/de OR "oral implant")] and manual search from 1995 till March 2020 was made by 2 independently calibrated reviewers. ACROBAT-NRSI, Version 1.0.0 and Review Manager, Version 5.3, computer software were used for the risk of bias assessment and to conduct the meta-analysis respectively.

Statistical Analysis Used: Cochran's *Q* test and I^2 statistics.

Results: Of 38 articles which were found eligible for full-text screening, two articles fulfilled the inclusion criteria and hence were included in the meta-analysis. The I^2 statistic and *Q*-test values of the included studies revealed acceptable homogeneity for studied three IL-1 gene polymorphisms (IL-1A−889: $I^2 = 0\%$, IL-1B − 511: $I^2 = 0\%$, IL-1B+3954: $I^2 = 24\%$). Forest plot of association between IL-1B−511 gene and ECBL revealed a significant association between 2/2 genotype of IL-1B−511 gene and an increased risk of ECBL (OR = 0.23, 95% CI = 0.09–0.58, $P_{\text{heterogeneity}} = 0.68$, $I^2 = 0\%$, and $P = 0.002$). Results of the IL-1A−889 and IL-1B+3954 gene revealed no significant associations between any genotype of these genes with risk of ECBL.

Conclusions: There is an evidence of the association of IL-1B−511 (2/2) genetic polymorphisms and increased ECBL in the individuals of Asian ethnicity (OR = 0.23, $P = 0.002$).

Keywords: Dental implant, implant failure, marginal bone loss, single nucleotide polymorphism

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INTRODUCTION

Endosseous implants provide the most predictable and successful restoration technique for the aesthetic and functional replacement of missing teeth.[1] The longevity and success of these implants depend primarily on the phenomenon known as osseointegration which could be elaborated as a direct functional and structural union between synthetic implants and living bone tissues.[2] The crestal bone level encircling the dental implants plays a pivoted role for successful implant integration, as early breakdown or failure of implant-tissue junction instigate at the alveolar crest region.[1,2] The success and survival of implant rehabilitations have not attained 100%, failures do observed.[3,4] Bone loss around implants has been the leading reason for implant failure.[3-5] Factors contribute to peri-implant bone loss are infection, smoking, bone quality, mechanical overloading, surgical trauma, menopause, and metabolic diseases.[1,4-6] However, these factors play a role subsequent to the second-stage surgery. Majority of the researchers believe that in the absence of any underlying metabolic disease and other risk factors during the healing phase (4–6 months), bone loss should not occur.[3,7-10] Nonetheless, early crestal bone loss (ECBL) has been frequently observed during the healing period of submerged dental implants.[3,7-9] Probable etiologic factor behind this ECBL could be the genetic variations or polymorphisms of a particular gene as bone formation and resorption have been continuously under the control of cytokine production.[3,7,8,11] Evidence has suggested that peri-implant complications including bone loss and failures have been clustered in specific high-risk patients and in those patients if the failure of one implant occurs, there was the likelihood of further failures.[12,13] This prospective link has triggered a series of researches that attempted to categorize, both at the site and patient levels, distinct risk factors disrupting the host-parasite harmony and propagating to the development of implant complications.[14-16]

Interleukin (IL)-1 had been the frequently explored pro-inflammatory cytokine in several bone diseases and conditions as polymorphisms in the promoter region of this cytokine has been associated with the stimulated differentiation of osteoclast precursors leading to altered regulation of bone mineral density and accelerated bone loss.[3,7,17,18] These IL-1 gene polymorphisms have been illustrated in various studies to be linked with peri-implantitis,[19-24] periodontitis,[25-31] low bone mineral density,[32] and peri-implant bone loss[3,7,9,10,19,33,34] leading to implant failures and loosening of teeth as well. Most of the bone loss studies were related to the bone loss after second-stage surgery and in association with either peri-implantitis or periodontitis. Although there was an evidence for the association of the IL-1 gene with peri-implant bone loss, association studies related to IL-gene polymorphisms and ECBL (bone loss before second-stage implant surgery) are scarce. Thus, the aim of this systematic review and meta-analysis was to evaluate whether polymorphisms of the IL-1 gene (IL-1A−889, IL-1B−511, and IL-1B+3954) are associated with increased rates of crestal bone loss before the second-stage implant surgery (ECBL). The null hypothesis was that the IL-1 gene polymorphism might influence the crestal bone loss before the second stage surgery.

MATERIALS AND METHODS

The study design followed the criteria recommended by the Cochrane collaboration for reporting the systematic review and meta-analysis.[35] Preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines have been pursued to report the article.[36]

The patient, intervention, comparator, and outcome question index designed for the present study was as follows:

- Systemically healthy patients who received dental implant rehabilitation (P)
- Effects of IL-1 gene polymorphism on bone loss around the implants (I)
- Patient group that exhibited ECBL versus group that does not (C)
- Potential association between IL-1 gene polymorphism and ECBL/implant failure (O).

Eligibility criteria

Inclusion criteria:

1. Literature published in English
2. Prospective, cross-sectional, retrospective, and randomized control trial studies on peri-implantitis, dental implant loss, or peri-implant marginal bone loss before second-stage surgery in association with IL-1 gene polymorphism
3. Minimum follow-up period of 6 months and adult patients (≥18 years)
4. The included studies should report ECBL that is from the day of implant placement and before second-stage surgery during the bone healing period.

Exclusion criteria:

1. Studies reported in medically compromised patients such as uncontrolled/controlled diabetes mellitus, malignancy, and osteoporosis

2. Studies on immediate extraction and immediate loading
3. Case reports, review of literature, and studies on animals.

Information sources

An electronic search from inception to March 2020 was carried out in the following databases by two independently calibrated reviewers (C. G., M. A.): PubMed (Medline), Cochrane Library, and EMBASE.

Search strategy

Boolean operators based on Medical Subject Headings terms and PubMed included the following: ("Dental" OR "oral") AND ("Implants*") AND ("gene polymorphism" OR "genotype" AND ("IL-1" OR "ILs"). Search headings in the title, abstract, and keywords applied in the Cochrane Library were: implant AND (biomarker or cytokine), interleukin-1 or IL-1 AND implants. For EMBASE following keywords were used, ("gene polymorphisms"/de OR "interleukins"/cytokine exp OR "biomarker":ti,ab,kw) AND ("dental implantation"/de OR "oral implant").

In addition, manual searching of the reference lists of the following identified journals were carried out from 1995 up to March 2020: (*Clinical Implant Dentistry and Related Research, Oral Surgery Oral Medicine Oral Radiology Oral Pathology and Endodontics, Genes, Clinical Oral Implant Research, Implant Dentistry, European Journal of Oral Implantology, International Journal of Periodontics and Restorative Dentistry, International Journal of Oral and Maxillofacial Implants, Journal of Periodontal Research, Journal of Clinical Periodontology, Journal of Oral and Maxillofacial Surgery, Journal of Indian Prosthodontic Society, Journal of Dental Research, Journal of Periodontal and Implant Science,* and *the Journal of Periodontology*).

Validity assessment

Quality assessments of studies to be included were independently executed by two competent authors (P. C., K. K. A.) as a part of extraction process. Abstracts and titles of the search results were screened as per the selection criteria, and then full texts of selected articles were assessed and screened. Search methodology of databases involves a three-stage screening process by reviewers. First-stage screening involves screening of titles of searched articles. Second-stage involves the assessment of the abstract followed by full-text articles at the third stage. At each stage, a discussion was done to resolve discrepancies (if any) and if consensus was not reached, expert consultation was taken with an experienced third author (S. V. S). The k (kappa) statistics[37] was calculated for potentially relevant articles at the second and third stages of screening to assess the level of compliance between the authors concerning study inclusion.

Data collection

Data were extracted and analyzed from the eligible studies and the following predesigned and standardized information was obtained: publication year, authors, country of origin of study, participants characteristics (mean age, number, intervention received, etc.), sites and number of implants placed, follow-up period, study variables, and data of ECBL. Wherever possible, contacts with the corresponding authors were made, whenever data were found out to be missing, incomplete, or ambiguous. Studies with incomplete data (even after contacting corresponding authors and/or contacts not made) were excluded from the meta-analysis. The extracted data related to various characteristics were stratified and arranged in chronological order in the form of evidence tables, and finally, a descriptive summary was generated to facilitate the data synthesis process.

Risk of bias assessment

A Cochrane risk of bias assessment tool for nonrandomized studies of interventions (ACROBAT-NRSI), Version 1.0.0 (riskofbiastools. info), dated September 22, 2014, "ACROBAT-NRSI"[38] was used for assessment of risk of bias (ROB) for the observational studies of interventions.

A funnel plot was drawn to ensure asymmetry, if any, owing to ROB in the included studies. Any asymmetry observed in obtained funnel plot for included studies may point toward publication bias and other biases associated with sample size.[35]

Statistical analysis

Heterogeneity variations between included studies were determined by means of Cochran's Q-test (χ^2) and I^2 statistics. An I^2 value of >50% and $\alpha = 0.05$ for Q-test were considered statistically significant. Mantel–Haenszel method or fixed-effect model for meta-analysis was applied to draw the forest plot and to calculate the summary odd ratios (ORs) and 95% confidence intervals (CIs) ($\alpha = 0.05$). RevMan (Review Manager v5.3; Cochrane Collaboration) computer software, which is freely available on Cochran's site, was used to conduct the meta-analysis.

RESULTS

Figure 1 displays the study selection procedure through the PRISMA flowchart. Electronic search from various databases yielded 297 articles, while manual searching provided 21 articles. Two hundred and ten articles remained subsequent to the elimination of overlapping articles. One hundred seventy-two articles were eligible for screening of title and abstract. One hundred thirty-four articles were excluded after reading the "title and abstracts." Altogether, 38 articles were eligible for full-text screening. After initial full-text screening of 38 eligible articles, 33 articles[20-24,27-31,33,39-60] [Table 1]

were not included as they did not compare the IL-1 gene association with crestal bone loss, leaving five potentially eligible articles.[3,7,10,19,34] Full-text articles were obtained from these five articles, of them three articles[10,19,34] were further excluded following third-stage screening with reasons listed in Table 2. Thus, a total of two published articles[3,7] were included in the present meta-analysis.

Study characteristics

The *k*-value (kappa) for inter-reviewer (P. C., K. K. A.) harmony for "titles and abstracts" was 0.82, whereas for "full text articles," its value was 0.72, indicating "nearly perfect" score for interobserver agreement as criteria established by Landis and Koch.[37] Cases and controls in both the included studies were dental implant patients. Studies were hospital based at separate geographical locations with the same ethnicity (Asian population). Detailed characteristics of included studies are revealed in Table 3.

Meta-analysis

The meta-analysis was carried out by pooled outcomes of included studies. The I^2 statistic and *Q*-test values of included studies revealed acceptable homogeneity for studied 3 IL-1 gene polymorphisms (IL-1A−889: I^2 = 0% and *Q*-test *P* = 0.99, IL-1B−511: I^2 = 0% and *Q*-test *P* = 0.68, IL-1B+3954: I^2=24% and *Q*-test *P* = 0.20) [Figures 2-4]. Therefore, a fixed-effect model was used to draw forest plots and to carry out the meta-analysis.

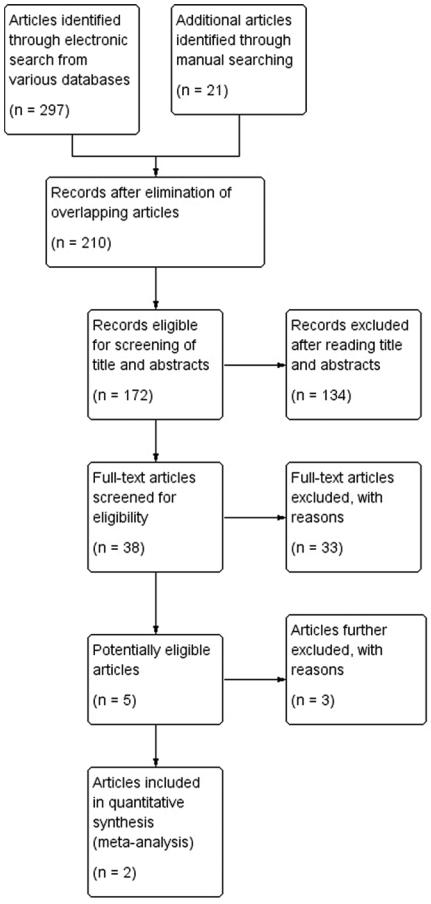

Figure 1: Preferred reporting items for systematic reviews and meta-analysis flowchart for meta-analysis

Association of IL-1 gene polymorphisms (IL-1A−889, IL-1B−511, and IL-1B+3954) and risk of ECBL using occurrences of dominant genotypes (1/1, 1/2, and 2/2) in a particular gene in each study are depicted by results of pooled fixed-model meta-analysis [Figures 2-4].

Forest plot of association between IL-1B−511 gene and ECBL [Figure 2] had revealed a significant association between 2/2 genotype of IL-1B−511 gene and an increased risk of ECBL (Pooled OR = 0.23, 95% CI = 0.09–0.58, $P_{heterogeneity}$ = 0.68, I^2 = 0%, and test for overall effect *P* = 0.002). The results of IL-1A−889 [Figure 3] and IL-1B+3954 [Figure 4] gene revealed no significant associations between any genotype of these genes with risk of ECBL (IL-1A−889 gene: Pooled OR = 0.96, 95% CI = 0.3–62.53, $P_{heterogeneity}$ = 0.99, I^2 = 0%, and test for overall effect *P* = 0.93; IL-1B+3954 gene: Pooled OR = 0.41, 95% CI = 0.11–1.46, $P_{heterogeneity}$ = 0.20, I^2 = 39%, and test for overall effect *P* = 0.17).

The possible risk of publication bias was carried out for included nonrandomized (case–control) studies, as illustrated in Table 4 and Figure 5. Both the included studies depict low ROB. A visual assessment of the shape of the funnel plots of the meta-analysis [Figure 5] revealed clear symmetry and none of the included studies extend beyond the limits of 95% CI, demonstrating the probable absence of bias related to publications.

DISCUSSION

Genetic polymorphism, which is primarily a result of mutations, is a term used to describe the co-existence of different variants of a gene in nature.[43] Variations of the IL-1 gene cluster, especially in the IL-α and IL-β genes, have been the most frequently investigated functional polymorphisms for implant loss.[58] Several

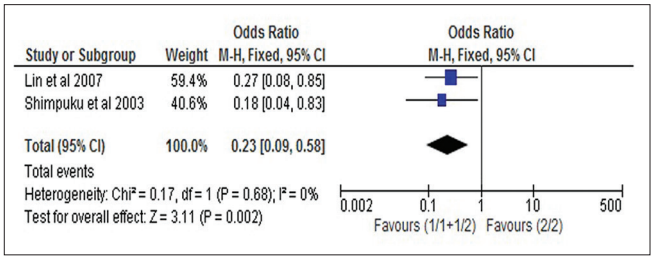

Figure 2: Forest plot of comparison: IL-1B−511 gene

Table 1: Full-text articles after second-stage screening

Selected study	Gene polymorphism studied	Complications
Petkovic-Curcin *et al*., 2017[33]	CD14, TNFα, IL-1, IL-6, IL-1ra	Delayed bone loss
Sampaio Fernandes *et al*., 2017[41]	IL1A, IL1B, IL1RN	Peri-implant success
Liao *et al*., 2014[42]	IL-1A (−889) and IL-1B (+3954)	Implant loss
Cosyn *et al*., 2016[43]	IL-1A (−889), IL-1B (−511), and IL-1B (+3954)	Early implant loss
Melo *et al*., 2012[20]	IL-1B, IL-6	Peri-implantitis
Rogers *et al*., 2002[44]	IL-1A (−889), IL-1B (+3953), IL-6, IFN γ	Implant loss
Campos *et al*., 2005[45]	IL-1 (−889) and IL-1B (+3953), IL-6	Early implant loss
Antoszewska *et al*., 2010[46]	IL-1B	Data on mini-implants
Andreiotelli *et al*., 2008[47]	IL-1	Peri-implantitis, Review article
Jacobi-Gresser *et al*., 2013[48]	IL1A (−889), IL1B (+3954), IL1RN (+2018), TNFA (−308)	*In vitro* study
Huynh-Ba G *et al*., 2008[49]	IL-1	Peri-implantitis-Review article
Wilson and Nunn, 1999[50]	IL-1	Implant loss
Hamdy and Ebrahem, 2011[51]	IL-1A (−889) and IL-1B (+3954)	Peri-implantitis
Hwang and Wang, 2007[52]	Il-1	Review article
Dereka *et al*., 2012[53]		Systemic review article
Bormann *et al*., 2010[21]		Review article
Laine *et al*., 2006[22]	IL-1A (−889), IL-1B (+3953), IL-1B (-511)	Peri-implantitis
Greenstein G *et al*., 2002[27]	IL1A+4845 and IL1B+3954	Periodontitis
Greenstein and Hart, 2002[28]	IL-1A+4845 and IL-IB+3954	Chronic periodontitis
Petkovic *et al*., 2010[23]	IL-1β, TNF-α, IL-8, MIP-1α	Peri-implantitis
Dirschnabel *et al*., 2011[39]	IL1B (C-511T)	Implant loss
Hao *et al*., 2013[29]	IL-1α, IL-1β and IL-1RN	Chronic periodontitis
Jansson *et al*., 2005[54]	IL-1	Early implant loss in patient under periodontal therapy
Rabel and Köhler, 2006[55]	IL-1	Implant loss in periodontally compromised patients
Montes CC *et al*., 2009[40]	IL1B (C+3954T) and IL1RN	Implant loss
De Boever and De Boever, 2006[30]	IL-1	Peri-implantitis, peri-mucocitis in patients with aggressive periodontitis
Lachmann *et al*., 2007[24]	IL-1 (−889), IL-1B (3954)	Peri-implantitis
Perala *et al*., 1992[56]	IL-1β, TNF-α	Implant loss
Baradaran-Rahimi *et al*., 2010[31]	IL-1	Periodontitis
Santiago Junior *et al*., 2018[57]	IL-1B, IL-1-, TNFα	Review article
Alvim-Pereira *et al*., 2008[58]	IL-1A, IL-1B, IL-2, IL-6, BMP, MMP, TNF-α	Review article
Ghassib *et al*., 2018[59]	IL-1β, IL-6, TNF-α, MMP-8	Review article
Schultze-Mosgau *et al*., 2006[60]	IL-1B, TGFβ1	Study on soft tissues

IL: Interleukin, MMP: Matrix metalloproteinase, BMP: Bone morphogenetic protein, TNF: Tumor necrosis factor, TGF: Transforming growth factor, MIP: Macrophage inflammatory protein, TNFA: Tumor necrosis factor-alpha

Table 2: Excluded studies and the reason of exclusion

Authors	Reasons for exclusion of full text articles
Grucia *et al*., 2004[34]	Bone loss was evaluated after 8-15 years and subjects were smokers
Feloutzis *et al*., 2003[10]	Bone loss was evaluated after the prosthetic rehabilitation and 5.6 years average thereafter
Al-Askar *et al*., 2018[19]	Study on diabetics, follow-up information missing

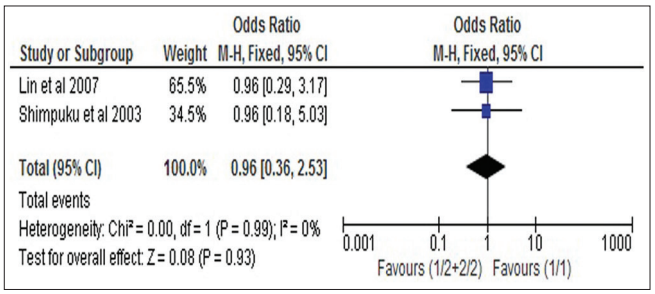

Figure 3: Forest plot of comparison: IL-1A−889 gene

studies[10,19,20,22-24,27-31,33,34,51,54-56] in the available literature reported that individuals carrying a particular genotype of IL-1 gene have been linked "directly or indirectly" to increased susceptibility to crestal bone loss around the natural teeth and/or dental implants. Most of the studies[20,22-24,27-31,51,54-56] were related to bone loss as a feature of the progression of periodontitis or peri-implantitis and hence were omitted from the present meta-analysis. Some studies[10,19,33,34] were excluded from the present review because of the chances of co-existence of multiple risks or confounding factors for bone loss, as in them, bone loss measurements were carried out after prosthetic loading. Only two studies,[3,7] fulfilling the eligibility criteria of the present review, which have had evaluated the association of IL-1 gene polymorphisms and ECBL were thereby included.

Included studies in the present analysis were observational studies with statistically homogenized ($P > 0.05$) samples for known risk factors for bone loss such as age, gender, and menopausal status as well as bone quality. Thus, these variables did not influence the outcome of the present meta-analysis. Heterogeneity was acceptable and a random effect model was followed for meta-analysis.

Table 3: Characteristics of the included studies

Characteristics	Lin *et al*.[7]	Shimpuku *et al*.[3]
Publication year	2007	2003
Study design	Prospective	Prospective
Country of origin	China	Japan
Ethnicity	Asian	Asian
Age range (years)	18-67	29-74
Mean age (years) (cases/controls)	44.24±12.114/41.30±13.376	54.2±12.2/55.9±6.6
Gender distribution (male/female) (cases/controls)	(19/10)/(13/17)	(5/12)/(10/12)
Postmenopausal women (yes/no) (cases/controls)	(3/7)/(11/6)	(8/4)/(8/4)
Bone quality (Type 3/Type 2) (cases/controls)	(17/12)/(15/15)	(4/13)/(6/16)
Number of patients at the beginning of the study	59	39
Drop out	0	0
Number of implants placed	143	251
Mean healing period (maxillary/mandibular)	Not reported	6.8/4.1 months
Implant failed	0	0
Outcome	Marginal bone loss	Marginal bone loss
Implants with bone loss	32	36
Patients with/without bone loss (cases/controls)	29/30	17/22
Baseline radiograph	After implant placement	After implant placement
Follow-up radiograph	Before second-stage surgery	Before second-stage surgery
Standardized radiograph	Panoramic	Unclear
Gene polymorphism studied	IL-1A-889, IL-1B-511, IL-1B+3954	IL-1A-889, IL-1B-511, IL-1B+3954
Examiner blinding for genotypes	Yes	Yes
Calibration of examiners	Not reported	Not reported
Result-gene polymorphism associated with bone loss	Significant association of IL-1B-511 (2/2)	Significant association of IL-1B-511 (2/2)

IL: Interleukin

Table 4: A Cochrane risk of bias assessment tool for nonrandomized studies of interventions

Study	Bias due to confounding	Bias in selection of participants	Bias in intervention measurements	Bias due to intervention departures	Missing data bias	Bias in measuring outcomes	Reported results bias	Other bias	Pooled bias
Shimpuku H *et al*.	Moderate risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Linn YH *et al*.	Moderate risk	Low risk	Moderate risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk

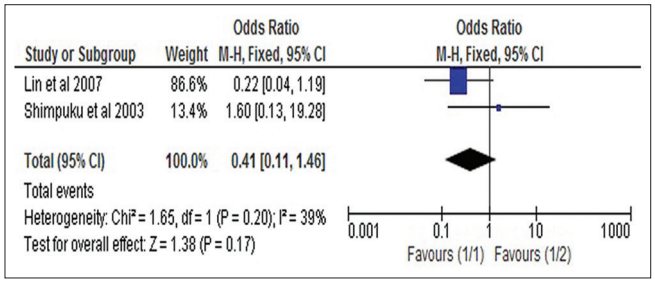

Figure 4: Forest plot of comparison: IL-1B+3954 gene

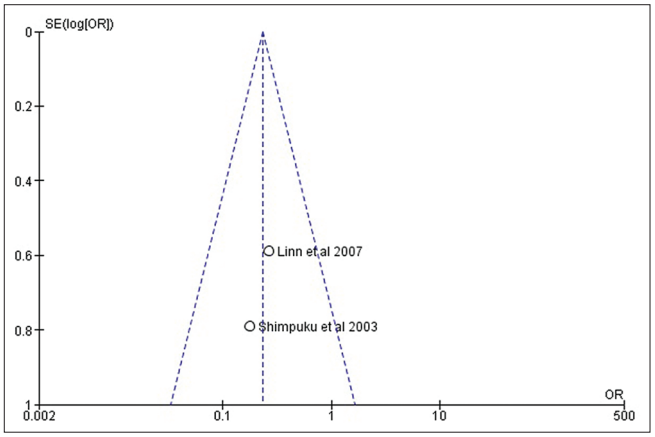

Figure 5: Funnel plot for risk of bias assessment

The null hypothesis was accepted since forest plots of an association indicate that there has been a significant association of IL-1 gene and ECBL as evident through pooled results of the included studies. The presence of IL-1B−511 (2/2) genotype has been identified as a risk factor independent of age, gender, menopausal status, and bone quality for the occurrence of marginal bone loss around dental implants before stage-two surgery (OR = 0.23, 95% CI = 0.09–0.58, *P* = 0.002).

There was no significant association found among other (IL-1A−889 and IL-1B+3954) genetic variations of the IL-1 gene (IL-1A−889 gene: OR = 0.96, 95% CI = 0.36–2.53, *P* = 0.93; IL-1B+3954 gene: OR = 0.41, 95% CI = 0.11–1.46, *P* = 0.17). In fact IL-1A−889 (2/2) and IL-1B+3954 (2/2) genotype was not detected in any participant of both the included studies.

Kornman *et al*.[17] suggested for the first time the genetic susceptibility of the composite genotype of IL-1A−889 and IL-1B+3954 as a genetic vulnerability marker linked with an elevated risk for severe chronic periodontitis. Thereafter, studies on the association of

IL-1 gene biomarker and crestal bone loss have come into existence.[3,7,10,19,34] Three systematic reviews and two meta-analyses studies assessed the possible involvement of the genotypic variations of IL-1 gene in various peri-implant diseases.[21,42,47,49,53] Contrasting opinion exists among these reviews regarding inclusion criteria, search strategies, and focused questionnaires. A systematic review by Dereka *et al*.[53] was focused on the genetic predisposition of the implant biological complications including peri-implantitis and implant failures. They concluded that there was no significant association between genetic polymorphisms and implant loss mediated through biological complications; perhaps, they reported some link toward occurrences of peri-implantitis and IL-1 genotype. Other reviews by Andreiotelli *et al*.[47] and Bormann *et al*.[21] and meta-analysis by Huynh-Ba *et al*.[49] and Liao *et al*.[42] were based on genetic associations with peri-implantitis only. Two systematic reviews[21,47] on peri-implantitis only found insufficient evidence regarding these associations with IL-1 gene polymorphisms. Huynh-Ba *et al*.[49] included two observational studies in their meta-analysis and found an insignificant association between annual crestal bone loss (a surrogate biomarker of peri-implantitis) and the IL-1 composite genotypes (IL-1A−889 and IL-1B+3954). Included studies (Gruica *et al*.[34] and Feloutzis *et al*.[10]) in the above-mentioned review were confounded by factors such as sex distribution, follow-up period, smoking status, blinding procedure, lack of a control group for comparison, and had measured bone loss after second-stage implant surgery and hence were excluded from the present meta-analysis. The meta-analysis results by Liao *et al*.[42] were similar to the present meta-analysis results. However, their study was related to the association of IL-1 composite genotypes with peri-implant disease. They found a significant association of IL-1B−511 allele T carrier with peri-implant disease in Asian descents, while no significant association was identified for other composite genotypes of IL-1 gene (IL-1A−889 and IL-1B+3954) in Asian as well as European descents.

A recent meta-analysis on the use of IL-1B, IL-6, tumor necrosis factor-α, and MMP-8 gene polymorphisms to differentiate healthy implants, peri-implant mucositis, and peri-implantitis by Ghassib *et al*.[59] observed that the mucositis group exhibited a significantly greater IL-1B level than the healthy implant group (standardized mean difference = 1.94, 95% CI = 0.87–3.35 and $P < 0.001$). They also found that in meta-analysis of four included studies, IL-1B level in mucositis site was comparable to that in peri-implantitis site (standardized mean difference = 1.52, 95% CI =−0.03–3.07 and $P = 0.055$). They concluded that in addition to other cytokines, IL-1B cytokines could be used to differentiate healthy implants, peri-implant mucositis, and peri-implantitis.

Findings of the present review may help in the identification of individuals (through preoperative genetic screening) with greater risk for the ECBL and subsequently the implant failure, thereby assisting the health-care workers in developing customized treatment plans and prevention strategies so as to improve the success and survival rates of implants.

Limitations

The limitations of the study are following:

1. Included studies in the present review had a case–control design, meaning a particular characteristic was observed in two groups of subjects at one point in time
2. Although funnel plot and ACROBAT-NRSI tool showed low publication bias, there has been possibility of study biases because of the presence of confounding factors. For example, in the included studies, exact location (anterior or posterior) and length of edentulous span (single tooth gap or multiple tooth gaps) for implant placements were not specified, both maxillary and mandibular implants were included, minimum required available bone height and width for implant placement were not clear, and torque value range of inserted implants was not described in inclusion criteria. These are confounding factors for bone loss
3. The number of included studies in the meta-analysis is limited which contributes to the low power of the statistical test for publication bias
4. Lack of sample size and/or statistical power calculation. Small sample sizes and limited number of included studies, limits the author's ability to perform definitive stratification analysis to explore the multiple sources of heterogeneity. As reported by Ioannidis *et al*.,[61] at least a couple thousand participants would have been needed in any study to draw a definite conclusion regarding involvement of the genetic risk factors for a particular characteristic or a disease
5. Since bone formation and resorption have been under the control of multiple factors, it is desirable to investigate, in subsequent studies, other genetic factors involved in bone metabolism
6. Finally, selection bias in the English language literature cannot be excluded.

CONCLUSIONS

Within the limitations of the present meta-analysis, the following conclusions were drawn:

1. There was an evidence of association of IL-1B−511 (2/2) genetic polymorphisms and increased ECBL in individuals of Asian ethnicity
2. No significant influences of other genetic polymorphisms of IL-1 gene (IL-1A−889, IL-1B+3954) were found with ECBL
3. The limited number of included studies and the presence of confounding factors restrict the author's ability to draw any definite conclusion
4. Well-designed observational studies based on the following parameters: adequately powered sample sizes, the inclusion of patients with different ethnicities, avoidance of potential sources of bias, and consideration of all possible confounding factors and its adjustment in the final analysis is required to support our findings.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Albrektsson T, Zarb G, Worthington P, Eriksson AR. The long-term efficacy of currently used dental implants: A review and proposed criteria of success. Int J Oral Maxillofac Implants 1986;1:11-25.
2. Swami V, Vijayaraghavan V, Swami V. Current trends to measure implant stability. J Indian Prosthodont Soc 2016;16:124-30.
3. Shimpuku H, Nosaka Y, Kawamura T, Tachi Y, Shinohara M, Ohura K. Genetic polymorphisms of the interleukin-1 gene and early marginal bone loss around endosseous dental implants. Clin Oral Implants Res 2003;14:423-9.
4. Bhargava D, Thomas S, Pandey A, Deshpande A, Mishra SK. Comparative study to evaluate bone loss during osteotomy using standard drill, bone trephine, and alveolar expanders for implant placement. J Indian Prosthodont Soc 2018;18:226-30.
5. Singh P, Garge HG, Parmar VS, Viswambaran M, Goswami MM. Evaluation of implant stability and crestal bone loss around the implant prior to prosthetic loading: A six month study J Indian Prosthodont Soc 2006;6:33-7.
6. Mahajan N. Current evidences on various systemic problems in patients undergoing dental implant therapy. J Indian Prosthodont Soc 2018;18:S89.
7. Lin YH, Huang P, Lu X, Guan DH, Man Y, Wei N, *et al*. The relationship between IL-1 gene polymorphism and marginal bone loss around dental implants. J Oral Maxillofac Surg 2007;65:2340-4.
8. Nosaka Y, Tachi Y, Shimpuku H, Kawamura T, Ohura K. Association of calcitonin receptor gene polymorphism with early marginal bone loss around endosseous implants. Int J Oral Maxillofac Implants 2002;17:38-43.
9. Toljanic JA, Banakis ML, Willes LA, Graham L. Soft tissue exposure of endosseous implants between stage I and stage II surgery as a potential indicator of early crestal bone loss. Int J Oral Maxillofac Implants 1999;14:436-41.
10. Feloutzis A, Lang NP, Tonetti MS, Bürgin W, Brägger U, Buser D, *et al*. IL-1 gene polymorphism and smoking as risk factors for peri-implant bone loss in a well-maintained population. Clin Oral Implants Res 2003;14:10-7.
11. Malhotra P. Epigenetics: An unexplored frontier of implant dentistry – A review. J Indian Prosthodont Soc 2018;18:S81.
12. Weyant RJ, Burt BA. An assessment of survival rates and within-patient clustering of failures for endosseous oral implants. J Dent Res 1993;72:2-8.
13. Fransson C, Lekholm U, Jemt T, Berglundh T. Prevalence of subjects with progressive bone loss at implants. Clin Oral Implants Res 2005;16:440-6.
14. Tonetti MS. Risk factors for osseo-disintegration. Periodontol 2000;17:55-62.
15. Panagakos FS, Aboyoussef H, Dondero R, Jandinski JJ. Detection and measurement of inflammatory cytokines in implant crevicular fluid: A pilot study. Int J Oral Maxillofac Implants 1996;11:794-9.
16. Salcetti JM, Moriarty JD, Cooper LF, Smith FW, Collins JG, Socransky SS, *et al*. The clinical, microbial, and host response characteristics of the failing implant. Int J Oral Maxillofac Implants 1997;12:32-42.
17. Kornman KS, Crane A, Wang HY, di Giovine FS, Newman MG, Pirk FW, *et al*. The interleukin-1 genotype as a severity factor in adult periodontal disease. J Clin Periodontol 1997;24:72-7.
18. Shimpuku H, Ohura K. Association of Interleukin-1 gene polymorphism with adult periodontitis in Japanese. J Osaka Dent Univ 2001;35:99-104.
19. Al-Askar M, Ajlan S, Alomar N, Al-Daghri NM. Clinical and radiographic peri-implant parameters and whole salivary interleukin-1β and Interleukin-6 Levels among Type-2 Diabetic and Nondiabetic Patients with and without Peri-Implantitis. Med Princ Pract 2018;27:133-8.
20. Melo RF, Lopes BM, Shibli JA, Marcantonio E Jr., Marcantonio RA, Galli GM. Interleukin-1β and interleukin-6 expression and gene polymorphisms in subjects with peri-implant disease. Clin Implant Dent Relat Res 2012;14:905-14.
21. Bormann KH, Stühmer C, Z'Graggen M, Kokemöller H, Rücker M, Gellrich NC. IL-1 polymorphism and periimplantitis. A literature review. Schweiz Monatsschr Zahnmed 2010;120:510-15.
22. Laine ML, Leonhardt A, Roos-Jansåker AM, Peña AS, van Winkelhoff AJ, Winkel EG, *et al*. IL-1RN gene polymorphism is associated with peri-implantitis. Clin Oral Implants Res 2006;17:380-5.
23. Petković AB, Matić SM, Stamatović NV, Vojvodić DV, Todorović TM, Lazić ZR, *et al*. Proinflammatory cytokines (IL-1beta and TNF-alpha) and chemokines (IL-8 and MIP-1alpha) as markers of peri-implant tissue condition. Int J Oral Maxillofac Surg 2010;39:478-85.
24. Lachmann S, Kimmerle-Muller E, Axmann D, Scheideler L, Weber H, Haas R. Associations between peri-implant crevicular fluid volume, concentrations of crevicular inflammatory mediators, and composite IL-1A -889 and IL-1B+3954 genotype. A cross-sectional study on implant recalls patients with and without clinical signs of periimplantitis. Clin Oral Implants Res 2007;18:212-23.
25. Engebretson SP, Lamster IB, Herrera-Abreu M, Celenti RS, Timms JM, Chaudhary AG, *et al*. The influence of interleukin gene polymorphism on expression of interleukin-1beta and tumor necrosis factor-alpha

in periodontal tissue and gingival crevicular fluid. J Periodontol 1999;70:567-73.
26. McDevitt MJ, Wang HY, Knobelman C, Newman MG, di Giovine FS, Timms J, *et al*. Interleukin-1 genetic association with periodontitis in clinical practice. J Periodontol 2000;71:156-63.
27. Greenstein G, Hart TC. A critical assessment of interleukin-1 (IL-1) genotyping when used in a genetic susceptibility test for severe chronic periodontitis. J Periodontol 2002;73:231-47.
28. Greenstein G, Hart TC. Clinical utility of a genetic susceptibility test for severe chronic periodontitis: A critical evaluation. J Am Dent Assoc 2002;133:452-9.
29. Hao L, Li JL, Yue Y, Tian Y, Wang M, Loo WT, *et al*. Application of interleukin-1 genes and proteins to monitor the status of chronic periodontitis. Int J Biol Markers 2013;28:92-9.
30. De Boever AL, De Boever JA. Early colonization of non-submerged dental implants in patients with a history of advanced aggressive periodontitis. Clin Oral Implants Res 2006;17:8-17.
31. Baradaran-Rahimi H, Radvar M, Arab HR, Tavakol-Afshari J, Ebadian AR. Association of interleukin-1 receptor antagonist gene polymorphisms with generalized aggressive periodontitis in an Iranian population. J Periodontol 2010;81:1342-6.
32. Bajnok E, Takács I, Vargha P, Speer G, Nagy Z, Lakatos P. Lack of association between interleukin-1 receptor antagonist protein gene polymorphism and bone mineral density in Hungarian postmenopausal women. Bone 2000;27:559-62.
33. 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 Implants 2017;32:e241-8.
34. Gruica B, Wang HY, Lang NP, Buser D. Impact of IL-1 genotype and smoking status on the prognosis of osseointegrated implants. Clin Oral Implants Res 2004;15:393-400.
35. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0; London, UK: The Cochrane Collaboration; 2011. Available from: https://www.cochrane-handbook.org or. Available from: http://handbook.cochrane.org. [Last accessed on 2020 Mar 03].
36. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. BMJ 2009;339:b2700.
37. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159-74.
38. Sterne JA, Higgins JPT, Reeves BC on Behalf of the Development Group for ACROBAT-NRSI. Cochrane Risk of Bias Assessment Tool: For Non-Randomized Studies of Interventions (ACROBAT-NRSI). Version 1.0.0; 24 September, 2014. Available from: http://www.riskofbias.info. [Last accessed on 2020 May 22].
39. Dirschnabel AJ, Alvim-Pereira F, Alvim-Pereira CC, Bernardino JF, Rosa EA, Trevilatto PC. Analysis of the association of IL1B (C-511T) polymorphism with dental implant loss and the clusterization phenomenon. Clin Oral Implants Res 2011;22:1235-41.
40. Montes CC, Alvim-Pereira F, de Castilhos BB, Sakurai ML, Olandoski M, Trevilatto PC. Analysis of the association of IL1B (C+3954T) and IL1RN (intron 2) polymorphisms with dental implant loss in a Brazilian population. Clin Oral Implants Res 2009;20:208-17.
41. Sampaio Fernandes M, Vaz P, Braga AC, Sampaio Fernandes JC, Figueiral MH. The role of IL-1 gene polymorphisms (IL1A, IL1B, and IL1RN) as a risk factor in unsuccessful implants retaining overdentures. J Prosthodont Res 2017;61:439-49.
42. Liao J, Li C, Wang Y, Ten M, Sun X, Tian A, *et al*. Meta-analysis of the association between common interleukin-1 polymorphisms and dental implant failure. Mol Biol Rep 2014;41:2789-98.
43. Cosyn J, Christiaens V, Koningsveld V, Coucke PJ, De Coster P, De Paepe A, *et al*. An exploratory case-control study on the impact of IL-1 gene polymorphisms on early implant failure. Clin Implant Dent Relat Res 2016;18:234-40.
44. Rogers MA, Figliomeni L, Baluchova K, Tan AE, Davies G, Henry PJ, *et al*. Do interleukin-1 polymorphisms predict the development of periodontitis or the success of dental implants? J Periodontal Res 2002;37:37-41.
45. Campos MI, Santos MC, Trevilatto PC, Scarel-Caminaga RM, Bezerra FJ, Line SR. Evaluation of the relationship between interleukin-1 gene cluster polymorphisms and early implant failure in non-smoking patients. Clin Oral Implants Res 2005;16:194-201.
46. Antoszewska J, Raftowicz-Wójcik K, Kawala B, Matthews-Brzozowska T. Biological factors involved in implant-anchored orthodontics and in prosthetic-implant therapy: A literature review. Arch Immunol Ther Exp (Warsz) 2010;58:379-83.
47. Andreiotelli M, Koutayas SO, Madianos PN, Strub JR. Relationship between interleukin-1 genotype and peri-implantitis: A literature review. Quintessence Int 2008;39:289-98.
48. Jacobi-Gresser E, Huesker K, Schütt S. Genetic and immunological markers predict titanium implant failure: A retrospective study. Int J Oral Maxillofac Surg 2013;42:537-43.
49. Huynh-Ba G, Lang NP, Tonetti MS, Zwahlen M, Salvi GE. Association of the composite IL-1 genotype with peri-implantitis: A systematic review. Clin Oral Implants Res 2008;19:1154-62.
50. Wilson TG Jr., Nunn M. The relationship between the interleukin-1 periodontal genotype and implant loss. Initial data. J Periodontol 1999;70:724-9.
51. Hamdy AA, Ebrahem MA. The effect of interleukin-1 allele 2 genotype (IL-1a(-889) and IL-1b(+3954)) on the individual's susceptibility to peri-implantitis: Case-control study. J Oral Implantol 2011;37:325-34.
52. Hwang D, Wang HL. Medical contraindications to implant therapy: Part II: Relative contraindications. Implant Dent 2007;16:13-23.
53. Dereka X, Mardas N, Chin S, Petrie A, Donos N. A systematic review on the association between genetic predisposition and dental implant biological complications. Clin Oral Implants Res 2012;23:775-88.
54. Jansson H, Hamberg K, De Bruyn H, Bratthall G. Clinical consequences of IL-1 genotype on early implant failures in patients under periodontal maintenance. Clin Implant Dent Relat Res 2005;7:51-9.
55. Rabel A, Köhler SG. Microbiological study on the prognosis of immediate implant and periodontal disease. Mund Kiefer Gesichtschir 2006;10:7-13.
56. Perala DG, Chapman RJ, Gelfand JA, Callahan MV, Adams DF, Lie T. Relative production of IL-1 beta and TNF alpha by mononuclear cells after exposure to dental implants. J Periodontol 1992;63:426-30.
57. Santiago Junior JF, Biguetti CC, Matsumoto MA, Abu Halawa Kudo G, Parra da Silva RB, Pinto Saraiva P, *et al*. Can genetic factors compromise the success of dental implants? A systematic review and meta-analysis. Genes (Basel) 2018;9:444.
58. Alvim-Pereira F, Montes CC, Mira MT, Trevilatto PC. Genetic susceptibility to dental implant failure: A critical review. Int J Oral Maxillofac Implants 2008;23:409-16.
59. Ghassib I, Chen Z, Zhu J, Wang HL. Use of IL-1 β, IL-6, TNF-α, and MMP-8 biomarkers to distinguish peri-implant diseases: A systematic review and meta-analysis. Clin Implant Dent Relat Res 2019;21:190-207.
60. Schultze-Mosgau S, Wehrhan F, Wichmann M, Schlegel KA, Holst S, Thorwarth M. Expression of interleukin 1-beta, transforming growth factor beta-1, and vascular endothelial growth factor in soft tissue over the implant before uncovering. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;101:565-71.
61. Ioannidis JP, Trikalinos TA, Ntzani EE, Contopoulos-Ioannidis DG. Genetic associations in large versus small studies: An empirical assessment. Lancet 2003;361:567-71.