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.

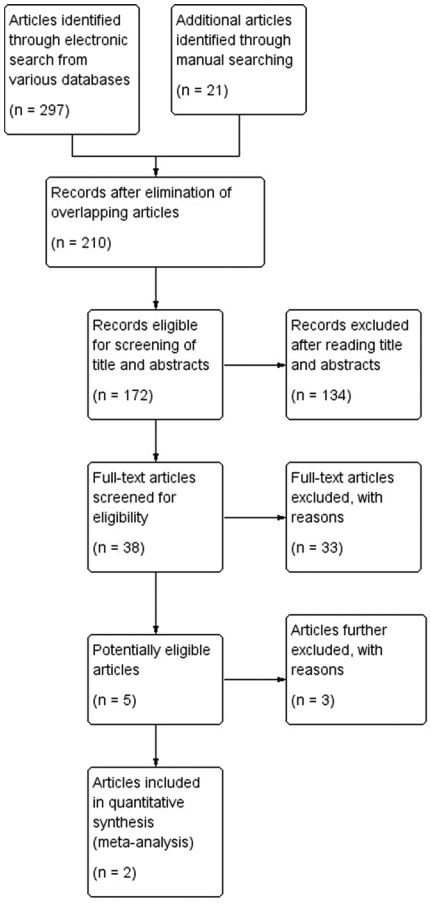

Figure 1: Preferred reporting items for systematic reviews and meta-analysis flowchart for meta-analysis

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

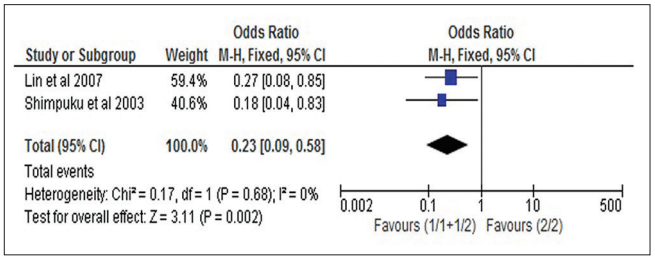

Figure 2: Forest plot of comparison: IL-1B−511 gene

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

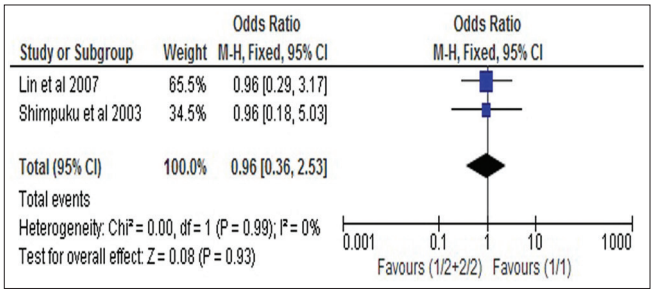

Figure 3: Forest plot of comparison: IL-1A−889 gene

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

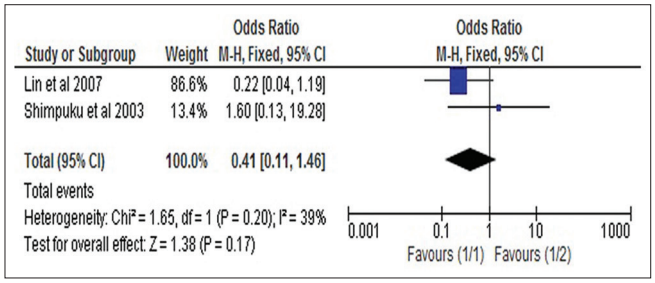

Figure 4: Forest plot of comparison: IL-1B+3954 gene

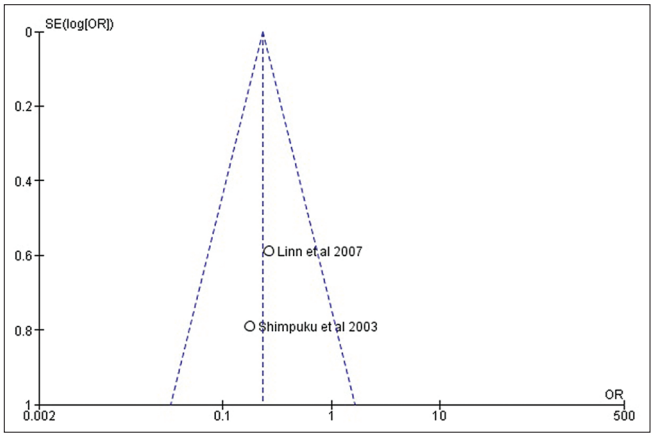

Figure 5: Funnel plot for risk of bias assessment

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.

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