Role of *IL-1β* Mutation in Peri-implantitis: Systematic Review and Meta-analysis

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Research Article

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Abstract

Background: To perform a systematic review and meta-analysis on the presence of *IL-1β* polymorphisms in patients with peri-implantitis (PI). PI is the main complication associated to dental implant therapy. Although its main risk factors are history of periodontitis, poor plaque control and lack of regular maintenance, genetic susceptibility could also be a determinant factor for its appearance. Single nucleotide polymorphisms (SNP) are small mutations of the DNA, that alter the osseointegration of implants. Interleukin 1β (IL-1β) is an inflammatory protein that participates in both destruction of the extracellular matrix and reabsorption of the alveolar bone.

Methods: A bibliographical research was made in PubMed, Scopus and Web of Science (keywords: "single nucleotide polymorphism", “polymorphism”, "periimplantitis", "SNP" and "implant failure").

Results: There is no significant relation between of *IL-1β* (+3953) SNP and PI, but there is a statistically significant association of peri-implant bone loss with the homozygotic model of *IL-1β* (-511) (I2=0%, p=0.555; OR: 2.255; IC: 1.040-4.889)

Conclusions: Absence of a strong link between of IL-1β polymorphisms and PI must be taken with caution due to the heterogeneous methodological design, sample size and diagnostic criteria of the studies. Thus, more well-designed studies are needed, that analyse the relationship between *IL-1β* polymorphism and PI.

1. Background

The combination of high numbers for partial and total edentulism[1], together with an average life expectancy of over 70 years for the world population[2], shows that treatment with dental implants is a major health advance[3]. However, the biological complications associated with this therapy, preferably peri-implantitis (PI), are frequent and must be prevented[4].

Peri-implantitis is an infectious and inflammatory multifactorial disease that is characterized by progressive loss of the supporting bone and that affects more than 45% of patients with dental implants, and [4]. History of periodontitis, poor plaque control and lack of regular maintenance are the main risk factors of this disorder[5]. However, not all individuals with these features end up developing PI[6]. Thus, genetic susceptibility has also been suggested as an important factor that would favour the development of PI[7–8].

Genetic variation is the basis of human diversity[9]. Genetic polymorphisms (GP) are individual variations at a given location in the DNA sequence, being single nucleotide polymorphisms (SNP) the most common[10]. SNP are distributed throughout the human genome by an average of approximately 1 SNP per 1000 base pairs[11]. The detection of this type of mutation can be used to identify altered genes or proteins in a specific disease[11].

The implication of a specific genetic susceptibility in periodontal disease has been widely studied[12–13]. It has been proven that several genotypes of interleukin-1 (IL-1) are strongly associated with chronic or aggressive periodontitis[14]. In the case of PI, different SNP involved in the inflammatory response have also been studied[8] and IL-1 has been the most frequent.

There are three forms of IL-1: IL-1α, IL-1β and IL-RN[15–16]. IL-1β is a low molecular weight protein, whose main biological functions are part of the innate immunity[17]. This molecule acts as a host defence mechanism for macrophages, monocytes and dendritic cells[18]. The most potent inducers of IL-1β are bacteria and their products[19]. The activity of IL-1β can be altered by different factors, such as the genetic mutation of *IL-1β* (long arm of chromosome 2)[20]. Since IL-1β is an inflammatory mediator, promoting both alveolar bone resorption and destruction of the extracellular matrix, and also promotes osteoclastogenesis through RANK signalling pathway, it plays an important role in bone physiopathology[21].

Thus, the mutation of *IL-1β* may trigger an abnormal inflammatory and resorptive response, which decreases the osseointegration capacity of dental implants[21–22]. For this reason, discovering the existence of a specific genotypic profile of *IL-1β* polymorphisms in patients with peri-implantitis would help us assess the level of individual risk and establish appropriate preventive measures.

The most frequent and studied *IL-1β* SNP is located at position 3953 [IL-1 (+ 3953)], only followed by 511 [IL-1 (-511)]. Nevertheless, the results have been highly variable, probably due to differences in the diagnostic assessment of the peri-implant disease[15,16,23,24].

With this background, we planned to carry out a systematic review and meta-analysis, with the aim of understanding the relationship between the presence of *IL-1β* polymorphisms and the development of peri-implantitis in patients with dental implants.

2. Methods

2.1. Information sources and search strategy

The design of this study matches the PRISMA criteria[25]. A systematic bibliographical research was performed in PubMed (US National Gallery of Medicine), Web of Science/ Knowledge and Scopus, with the keywords “single nucleotide polymorphism”, SNP, “peri implantitis”, and “implant failure”: (“single nucleotide polymorphism” AND “peri implantitis”; “single nucleotide polymorphism” AND “implant failure”; SNP AND “peri implantitis”: SNP AND peri-implantitis; SNP AND “implant failure”). A manual search of the referenced studies, as well as of prominent journals of the field, was carried out aiming to include additional papers.

PECOS question was: patients with dental implants (population), with *IL-1β* polymorphisms (exposure), in contrast to patients with dental implants who don’t have *IL-1β* polymorphisms (comparison), to study the

effect of *IL-1β* polymorphisms in the onset of peri-implantitis (outcome). Only longitudinal observational studies were included (type of study).

2.2. Eligibility criteria

The articles selected for this work met the following inclusion criteria: 1) being published until April 2020, 2) being written in English or Spanish (guarantee of full comprehension of content), 3) human studies. Exclusion criteria were: 1) studies that didn't analyse *IL-1β* polymorphisms and/or didn't show the genotype frequencies, 2) studies on peri-implant disease that didn't report the peri-implant bones loss, 3) previous meta-analysis or reviews, and 4) case reports, conferences or chapter of books. The information extracted from each study was: author and year of publication, type of study, number of patients (with and without PI) and genotype frequency of the polymorphisms.

2.3. Selection process

Two independent reviewers made a duplicate bibliographical research (ILIM, ASO). Title and abstract of all registers were evaluated, and then, these were analysed taking into account the inclusion and exclusion criteria. Any disagreement between the them was resolved by a third reviewer (XMM) to minimize risk of bias. Data about the included studies was gathered by two reviewers (ILIM, ASO) and double-checked by another three (XMM, AMGF, JMAU), to guarantee the integrity of the contents.

2.4. Quality analysis

We used modified Newcastle-Ottawa Scale (NOS) to assess the methodological quality of the studies (Wells et al., 2015). NOS system is used to analyse the risk of bias of longitudinal observational studies, considering three domains (selection, comparability and outcome). Total maximum score is 9: a study with score from 7–9 has high quality, 4–6 high risk of bias and 0–3 very high risk of bias.

2.5. Statistical analysis

To analyse the heterogeneity of the studies, I2 test was applied. Fixed-effect model was used when $I2 < 50\%$. To evaluate the correlation of PI with the susceptibility to different genotypes, the following genotypic models were carried out: heterozygous model (T/C vs T/T) and homozygous model (C/C vs T/T). For each model the odds ratio (OR) and 95% confidence interval (CI95%) were obtained. Statistical analysis was performed with the OpenMeta tool (Analyst).

3. Results

3.1. Results of the search

We obtained a total of 193 records in the initial research, out of which 103 were eliminated because they were duplicates. Additionally, 3 articles were included by manual search. After the initial screening, 47 articles were excluded: 43 for not investigating the presence of SNP in PI and 4 for not being available in full-text. Thus, 46 registers were analysed for their suitability, but 13 were eliminated: 11 because they

were previous meta-analyses or literature reviews and another 2 because they were conference texts or book chapters. Also, we excluded 19 registers that did not analyse *IL-1β* polymorphisms and 5 that did not indicate the parameters used for the diagnosis of peri-implant disease. Finally, 7 studies were selected for the systematic review, whose data are shown in Table 1[15,16,26–30].

We were only able to use 5 studies to perform the meta-analysis (2.6% of the initial search), due to lack of genotype data[15, 26–28,30]. The summary of the selection process is shown in Fig. 1.

3.2. Characteristics of included studies

In total, the included studies investigated 375 patients, of which 80 were from China and the rest from other countries (Austria, Brazil, Egypt, Spain, the Netherlands). Most authors used radiographic alveolar bone loss (ABL) to diagnose PI[15,16,26,28,29], and the rest probing depth analysis[27,30].

- *IL-1β (+ 3953)*

All the articles included in this review analyse the possible relationship between the presence of *SNP IL-1β* (+ 3953) and the development of PI, however, none of them recognizes a significant association. For García-Delaney et al.[16], peri-implantitis was only related to history of periodontitis. The studies by Shimpuku et al.[26] and Lin et al.[28] did not find the existence of a specific genotype of *IL-1β* (+ 3953) in patients with peri-implant disease. Nor did Lachmann et al.[27] and Melo et al.[30], who excluded smoker patients.

Only two studies[15,29] observed a statistically significant association between the composite genotype *IL-1β* (+ 3945) and *IL-1α* (-889), and patients with PI.

- *IL-1β (-511)*

The link of SNP *IL-1β* (-511) and peri-implantitis has been analysed in 4 studies[15,26,28,30], but only two conducted in Japan[26,28] recognized a direct relation to peri-implant bone loss.

3.3. Meta-analysis

Our study showed that there are no statistically significant differences between the presence of *IL-1β* (+ 3953) polymorphism and the appearance of peri-implantitis (T/C vs T/T: I2: 19.8%, p = 0.395; OR: 1.484; IC95%: 0.991–2.223 and C/C vs T/T: I2:0%, p = 0.775; OR: 0.770; IC95%: 0.316–1.873) (Fig. 2). However, we did observe a risk association between the presence of the CC genotype of the *SNP IL-1β* (-511) and peri-implantitis (T/C vs T/T: I2 = 0%, p = 0.921; OR:0.902; IC95%: 0.510–1.595 and C/C vs T/T: I2 = 0%, p = 0.555; OR: 2.255; IC95%: 1.040–4.889) (Fig. 3).

3.4. Quality of studies

After applying modified NOS assessment, 71.4% of the studies revealed 8 stars and 28.6% of them 6 (Supplementary Table 1). Overall risk of bias was low.

4. Discussion

The first cases of peri-implantitis were described as "*inflammatory reactions with loss of supporting bone in the tissues surrounding a functioning implant*"[31]. Later, it was demonstrated that this pathology was physiopathologically different to periodontitis[32]; and it is currently considered as an inflammatory disorder ("Peri-implant Conditions and Diseases")[33].

Inflammation is a physiological response that participates in many acute and chronic diseases in humans[34]. The term interleukin-1 was firstly used in the International Lymphokine Workshop in Ermatingen in 1979[35], to define "*a macrophagic product that stimulates T and B cells, with non-immunological properties*"[17]. It was later discovered that genetic variations of this cytokine are relevant for the pathogenesis of many inflammatory and malignant disorders (pancreatitis, lupus erythematosus, etc.)[36–37]. Because there is strong evidence of the role of *IL-1β* in the physiopathology of periodontitis[14], recent research is trying to unveil its link to peri-implantitis.

After conducting a systematic review, we found that only two authors (Egypt and the Netherlands) demonstrated a significant association between the composite genotype of *IL-1β* (+ 3945) and *IL-1α* (-889) and the presence of peri-implantitis[15,29]. This genotype has already been associated to patients with chronic periodontitis, but not with aggressive periodontitis[14]. We believe that there may be a specific group of patients with peri-implantitis who present this genotypic profile.

Myeloid differentiation factor-88 (MyD88) is responsible for the activation of pro-inflammatory cytokines IL1β and IL-1α, inducing an intracellular cascade system that secretes both proteins to the extracellular matrix[38]. Unlike IL-1β, IL-1α also has a silent nuclear expression under normal homeostasis, that changes under pathological conditions to initiate the inflammatory response[39]. Thus, in the recent years it has been postulated that IL-1α would be a dual-function cytokine[39]. This may explain why *IL-1α* polymorphism, located at position 889 [IL-1α (-899)], is not independently and significantly associated with the development of PI[15,16,26–29].

During the eligibility analysis, several studies were excluded because they did not indicate the diagnostic criteria of PI. Interestingly, Feloutzis et al.[40] and Gruica et al.[41] found a significant association between *SNP IL-1β* (+ 3953) and peri-implant bone loss, only in heavy smokers (> 20 cigarettes/day). However, they did not indicate whether the patients had peri-implantitis[42–43]. Furthermore, our analysis didn't find a significant association between *IL-1β* (+ 3953) polymorphism, tobacco use and of PI[15,16,26,28].

In contrast, two study groups from Japan did report the link between *IL-1β* (-511) and PI[26,28]. After performing the meta-analysis with the rest of the studies, this relationship remain statistically significant. We believe this positive result is because the authors used ABL > 0.5 mm as diagnostic criteria for PI[26,28]. Although the first sign of peri-implantitis can be the presence of a bone loss (0.5 mm)[44], diagnosis of PI is based on: 1) presence of bleeding and/or suppuration on gentle probing, 2) probing depths of ≥ 6 mm,

or bigger than previous examinations, and 3) bone levels ≥ 3 mm apical of the most coronal portion of the intraosseous part of the implant, or greater than initial bone remodelling[33]. Therefore, dental implants with diagnosis of peri-implantitis in some studies[15,26,28], could currently be reclassified as peri-implant health.

In addition, the diagnostic criteria of peri-implanitis have been in constant change thought the years[32,45], and it is not possible to ensure that all the patients were correctly classified as either healthy or sick, with respect to PI. Since these variations are very important in risk assessment studies, the application of the latest classification of periodontal diseases may reduce this bias, allowing the homogeneity of future investigations[46].

5. Conclusions

In summary, after performing this systematic review and meta-analysis, we conclude that there is currently no evidence that patients carrying the *IL-1β* (+ 3945) SNP have a higher risk of developing peri-implantitis, nor do those with *IL-1β* (-511) SNP. However, individuals with composite genotype *IL1β* (+ 3945) and *IL-1α* (-889) may be at greater risk for developing peri-implantitis. Also, patients who smoke more than 20 cigarettes a day and have *IL-1β* (+ 3953) polymorphism would have a higher risk of peri-implant bone loss.

It is necessary to plan well-designed studies with larger samples, to analyse the involvement of genetic polymorphisms of more inflammatory molecules involved in peri-implant processes.

6. Declarations

Ethics approval and consent to participate:

Not applicable.

Consent for publication:

Not applicable.

Availability of data and material:

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

IL contributed with the design, data extraction, data collection and the writing of the manuscript; AS contributed with data extraction and data collection; AMG: contributed with the editing of the manuscript; JMA: contributed with the writing and editing of the manuscript; XM: performed the statistical analysis and helped with the editing of the manuscript. All authors read and approved the final manuscript.

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Table

Table 1.

Main data of the included studies.

Authors, year	Patients			Diagnostic criteria for diagnosis of peri-implantitis
	Ethnicity	Case	Control	
Shimpuku et al. 2003	Japan	17	22	ABL > 0,5 mm
Laine et al. 2006	Belgium	71	44	ABL (3 implant threads), BOP, pus
Lachmann et al. 2007	Germany	11	18	PD > 4 mm
Lin et al. 2007	Japan	29	30	ABL > 0,5 mm
Hamdy et al. 2007	Egipt	25	25	PD > 4 mm, ABL, BOP
Melo et al. 2012	Italy	16	31	PD > 4mm, BOP, pus
García-Delaney et al. 2015	Spain	27	27	ABL > 2 mm, PD > 4mm, BOP, pus

Case: Patients with peri-implantitis. Control: Patients without peri-implantitis. ABL: Alveolar bone loss; BOP: Bleeding on probing; PD: Probing depth

Figures

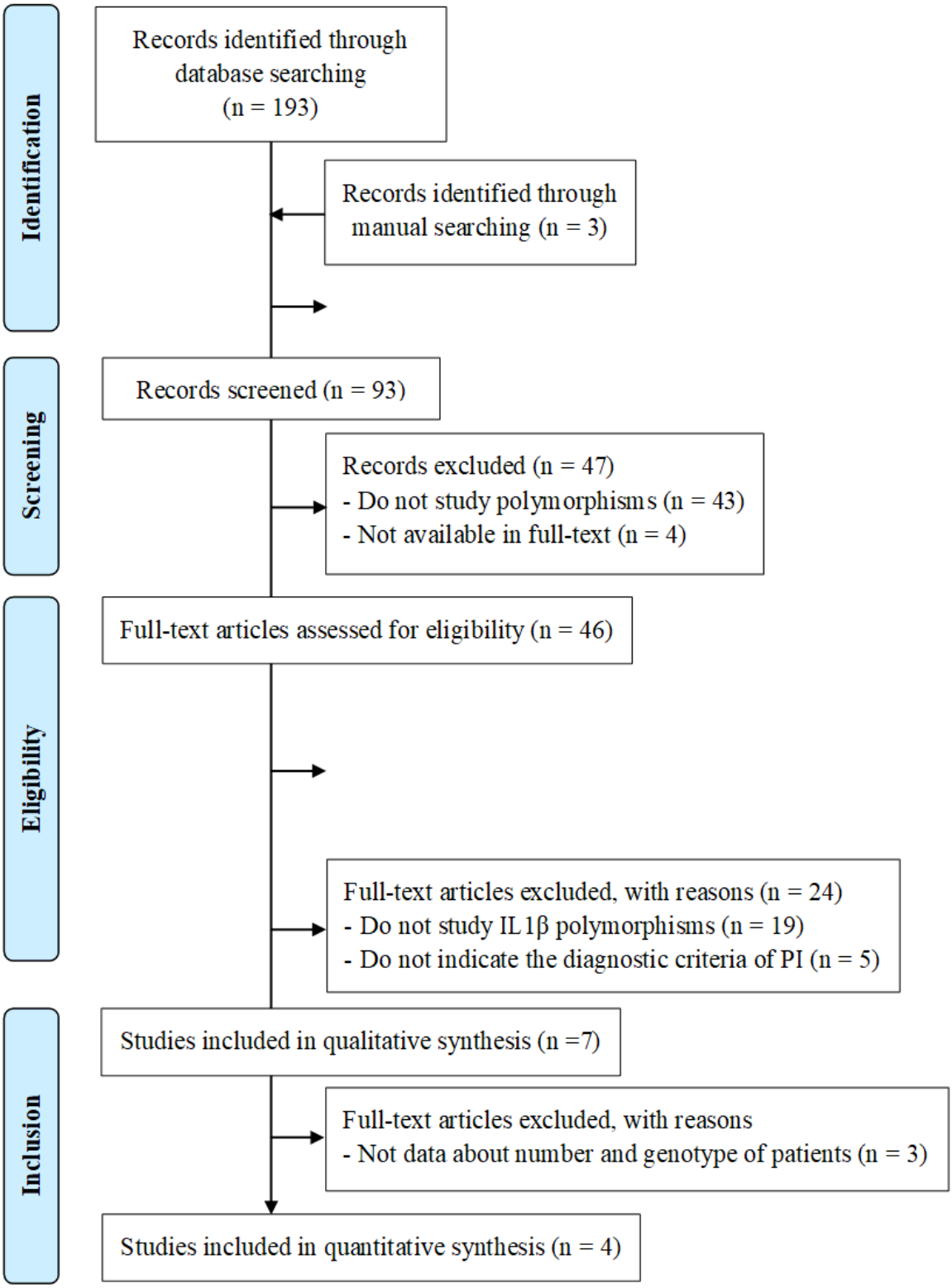

Figure 1

PRISMA Flow diagram. Synthesis of the selection process of the included articles in the review.

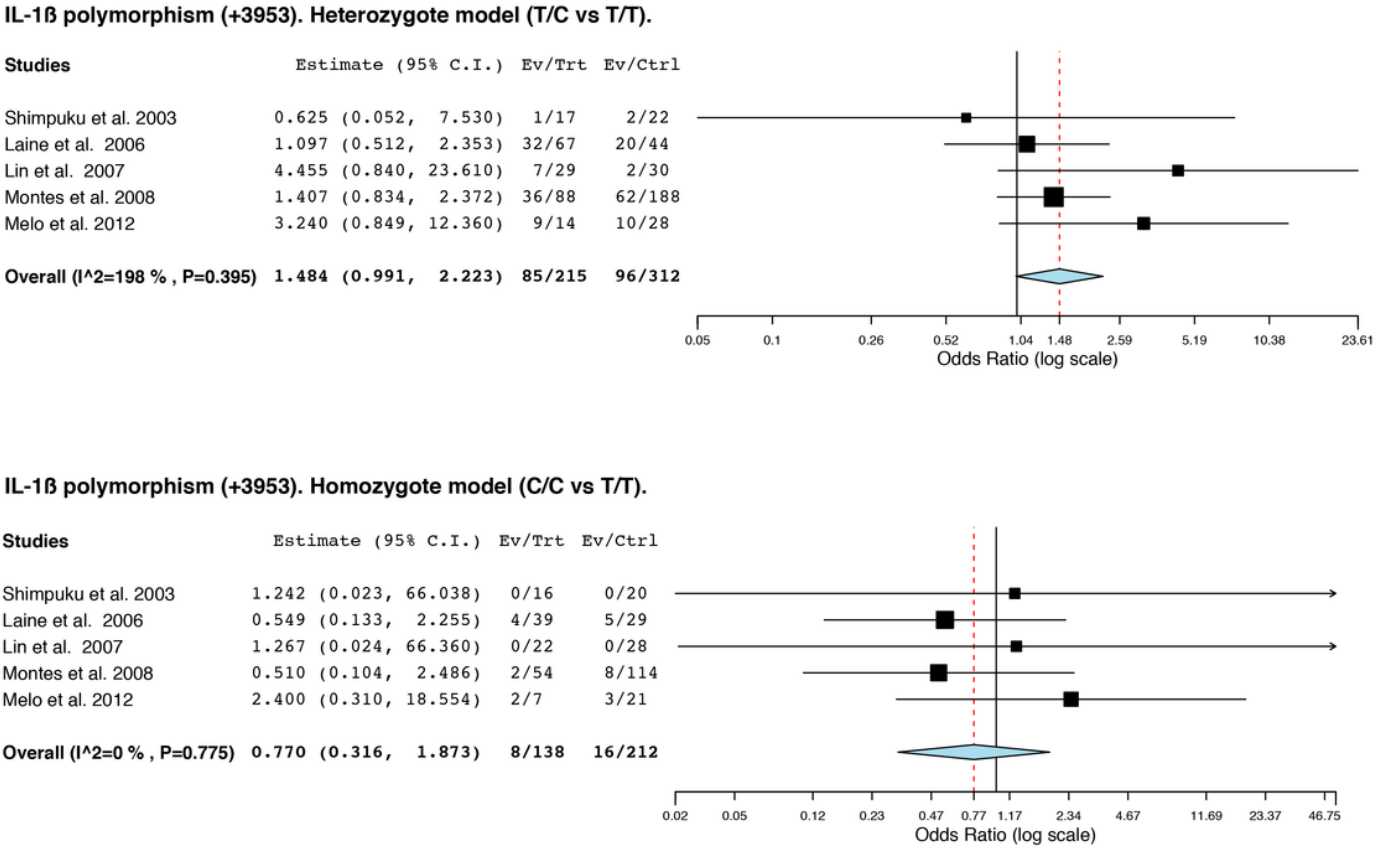

Figure 2

Association between IL-1β (+3953) polymorphism and peri-implantitis in the heterozygote and homozygote model.

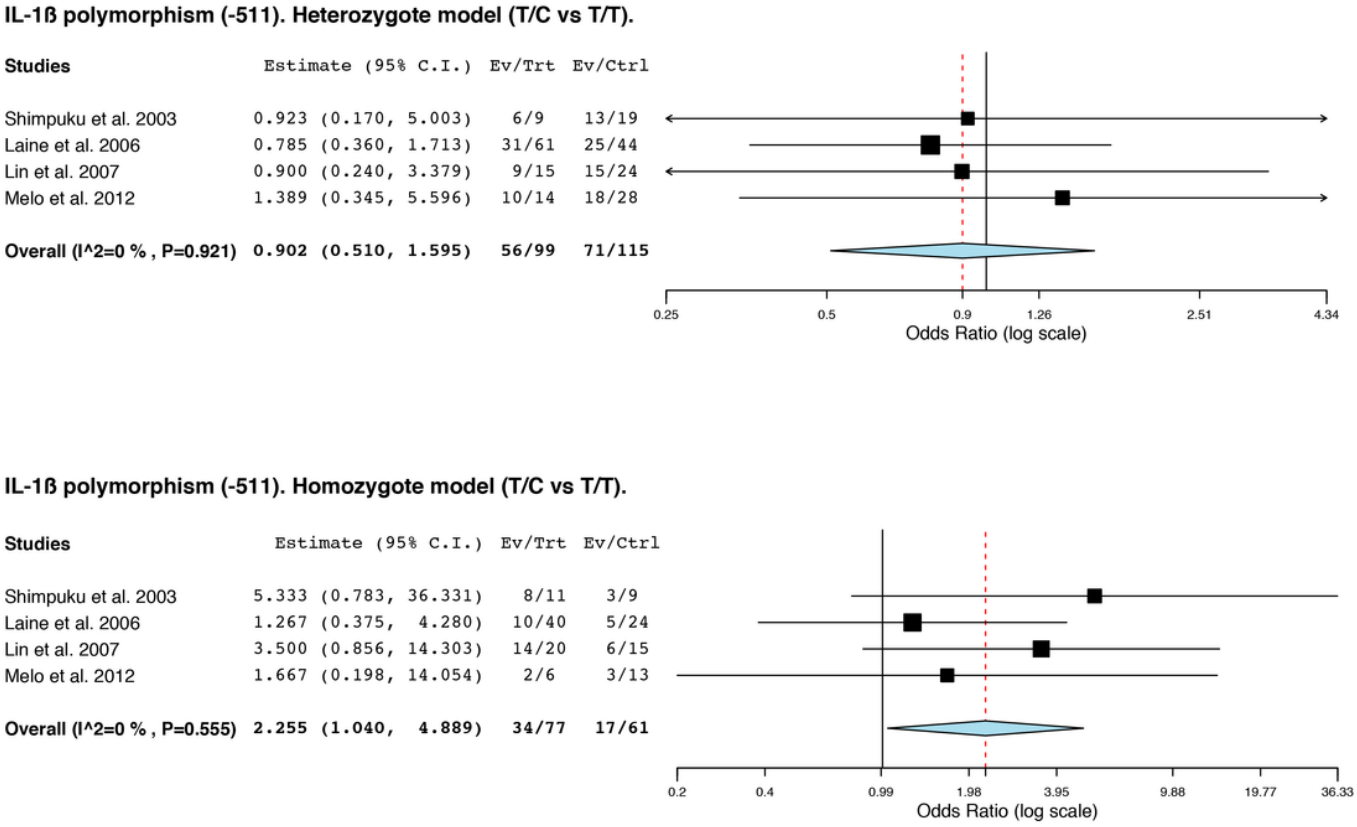

Figure 3

Association between IL-1β (+3953) polymorphism and peri-implantitis in the heterozygote and homozygote model.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Complementarytable.docx