Comparative Assessment of Impact of Interleukins on Orthodontic Miniscrew Stability, Insights to Osseointegration and its Failure Rates: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: The immune system functions under the influence of interleukins because these cytokines affect bone metabolism and the process of osseointegration while determining orthodontic miniscrew stability. This systematic review and meta-analysis served to determine the influence of interleukins on the operations of orthodontic miniscrew stability, osseointegration, and precession outcomes.

Methods: The research included a systematic review and meta-analysis with references to the PRISMA 2020 criteria. Until March of 2025, the electronic databases were searched to find the studies referring to the interleukin levels according to the orthodontic miniscrews or implants. Studies were eligible in cases of RCTs, observational, and retrospective. Risk of bias was assessed using the Cochrane Risk of Bias Tool for RCTs and the Newcastle-Ottawa Scale (NOS) for observational studies. The GRADE framework was used to evaluate the certainty of evidence for the included outcomes. The analysis of the comparison was performed with RevMan 5.4.1, which was done using the inverse variance model and the random-effects model.

Results: Nine publications that used 179 participants were selected. There was a significant increase in the interleukin levels in the study groups as contrasted to the controls (SMD: 1.47; 95% CI: 0.18-2.75; $p < 0.05$). There was a high heterogeneity ($I2 = 88\%$). Subgroup analyses showed higher IL-1β and IL-17 at unsuccessful or inflamed miniscrew sites.

Discussion: Higher levels of interleukin, mainly IL-1β and IL-17, are linked to miniscrew instability and peri-implant inflammation, which identifies the diagnostic and prognostic possibilities. Generalizability is limited by small sample size and disparity. These results advocate the use of cytokine profiling as a means by which the success of such implants can be determined.

Keywords: Interleukins, Orthodontic Anchorage Procedures, Osseointegration, Mini-Implants, Inflammation Mediators.

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INTRODUCTION

The process of osseointegration, which is the integration of orthodontic miniscrews with bone tissue, is influenced by interleukins IL-10 and IL-17, as they play essential roles in bone metabolism and immune regulation [1]. Elevated or imbalanced levels of these cytokines have been associated with increased inflammation, compromised healing, and a higher risk of miniscrew failure [2].

The anti-inflammatory effect of IL-10 promotes bone healing processes as well as osseointegration, while the inflammation-enhancing properties of IL-17 could cause bone resorption and implant instability [3]. These contrasting roles highlight the importance of cytokine balance in determining the success or failure of orthodontic miniscrew anchorage [4]. Understanding these interleukin-mediated pathways may offer predictive value for miniscrew stability and guide targeted interventions to enhance osseointegration. The success of orthodontic miniscrews depends on maintaining appropriate levels of these cytokines [5].

The examination of IL-10 and IL-17 showed that these cytokines affect orthodontic miniscrews' stability and failure rates because they modify the bone-implant interface inflammatory process [6]. Elevated IL-17 levels were consistently associated with increased inflammation and miniscrew failure, while IL-10 demonstrated anti-inflammatory effects supportive of stable osseointegration [7]. These findings suggest that cytokine profiling may serve as a valuable tool in predicting clinical outcomes of orthodontic anchorage devices [8].

This, in turn, influences osseointegration and the overall success of the implants. The particular function of these cytokines can help scientists understand the biological attributes that guide implant stability [9]. Understanding these roles may enable targeted interventions to enhance miniscrew success by modulating the peri-implant inflammatory environment [10].

The clinical application of this scientific information proves difficult because immune responses show complexity, as well as environmental and genetic components add to the challenge [11]. This complexity highlights the need for individualized approaches in predicting and improving miniscrew stability in orthodontic practice [12].

This systematic review and meta-analysis aimed to determine the overall effect of interleukin expression on the stability of orthodontic miniscrews as well as the success and failure rates in their osseointegration. It was a synthesis of the results made by clinical studies that assessed the level of interleukin in gingival or peri-implant crevicular fluid with or without loading as well as inflammatory placement. The review also tested the connections with the implant failure and modulation of cytokines and genetic polymorphism.

METHODS

Study Design

This meta-analysis and systematic review observed the PRISMA 2020 guidelines [13].

Literature Search Strategy

To find pertinent research articles published till May 2025, a search of four large databases (PubMed, Scopus, Web of Science, and Google Scholar) was made. The studies published in languages other than English were not regarded as viable. The search strategy was a mix of keywords that involved: interleukin, cytokine, gingival crevicular fluid, peri-implant crevicular fluid, orthodontic miniscrew, IL-1β, IL-17, IL-1RA, TNF-alpha, inflammatory cytokine, orthodontic loading, and periodontitis. The optimization of results was made by Boolean operators (AND, OR) and search filters.

Included Criteria

It only included the studies in the English language. They included randomized controlled trials (RCTs), prospective cohort studies, observational, or comparative cross-sectional studies that examined the level of cytokine (interleukin) in gingival or peri-implant crevicular fluid in reaction to orthodontic force, placement of the implant, peri-implant health/disease, or periodontal state, and when available control tests; most of them were healthy. Quantitative cytokine levels (means and standard deviations (SD) or alternative tabulable statistics) were needed to be reported in the studies.

Exclusion Criteria

Exclusion criteria were animal studies, in vitro studies, reviews, case reports, editorials, and studies that did not specifically detail cytokine concentrations or that did not report any significant correlations (where the difference between the experimental and control groups was not reported).

Outcomes Studied

Primary Outcomes were quantitative variations in the normalcy of interleukin (IL-1β, IL-17, IL-1RA, IL-10) in crevicular or gingival fluid. The secondary effects measured in the constituting studies were those in which the relationship between cytokine expression and multiple clinical variables would be assessed, including valencies like probing depth (PD), plaque index (PI), failure of miniscrews, and the status of implants. The relationship between interleukin and gene polymorphism, particularly the IL-17A gene variant, was also examined in several studies in order to isolate genetic factors in susceptibility to inflammation.

Also, the patterns of other inflammatory markers and cytokines such as IL-10, RANKL, and OPG were investigated under the conditions of inflammation or mechanical loading to better understand the whole picture of immune response in peri-implant and gingival regions.

The three levels of screening were used: the title-screening phase, the abstract-screening process, and full-text evaluation. The articles went through two independent reviewers, and according to the discrepancies, it was resolved either during a discussion or by the use of a third reviewer. This process did not involve any levels of automation.

Data Screening

Extraction of data was also carried out by two reviewers separately using a standardized data extraction sheet. The following data were extracted: author, year, the study design, sample size, number of patients in the experimental/control groups, type of cytokines tested, the mean + SD, p-value, objectives of the study, and duration of follow-up. In the cases where data were not in digits, or they could not be extracted because of other graphical representations, digital extraction tools were used, or the authors of the studies were contacted.

Quality Assessment

The Cochrane Risk of Bias Tool in RCTs and the Newcastle-Ottawa scale in Observational studies were used to evaluate the risk of bias. The extent of absolute certainty of evidence on every outcome was measured in terms of the GRADE strategy.

Altogether, 9 of the studies matched the inclusion criteria and could be used in the final synthesis. They entailed one randomized controlled trial, seven observational studies and one retrospective study , which looked at cytokine reactions to peri-implant environments, force loading during orthodontic therapy, or periodontitis[14,15,16,17,18,19,21,20,22].

Data Synthesis

Review Manager (RevMan) version 5.4.1 was used to conduct Meta-analyses. To determine the standardized mean difference (SMD) and the 95% confidence intervals (CIs), inverse variance was used considering a random-effects model. The primary outcomes of interest were the concentrations of interleukins (mostly IL-β, IL-1RA, IL-10, IL-17, and TNF-alpha) in crevicular fluid compared to an experimental setting (e.g., orthodontic loading, peri-implant disease, or periodontitis) to healthy or non-loaded sites.

The measure of heterogeneity was assessed using the I2 statistic, in which I2 > 50% represented moderate to substantial heterogeneity. In cases of a high heterogeneity of outcomes domains, the synthesis of data was performed in a narrative rather than a quantitative form.

The examination of subgroups depended on the type of interleukin and biologic situation (orthodontic loading, peri-implant inflammation, or periodontitis). The robustness of the pooled effect size was evaluated by carrying out sensitivity analyses by omitting studies of medium/high risk of bias.

The outcomes of the pooled sciences were shown in forest plots, whereas summary tables were utilized to show the characteristics of the included studies, their results, and bias measurements. Where the data was still not suited to pooling, then it was synthesized descriptively.

RESULTS

After the assessment of the inclusion criteria by reviewing the full text, 9 of the total number of 114 initially screened records provided the final analysis. These included 1 randomized controlled trial (RCT), 7 observational studies, and 1 retrospective study of a total of 179 subjects. Studies were excluded primarily due to being in vitro or animal experiments, lack of quantitative cytokine data, non-comparative designs, or absence of relevant outcomes related to interleukin expression in orthodontic miniscrew or peri-implant settings.

Figure 1 gives a summary of the process of selecting eligible studies.

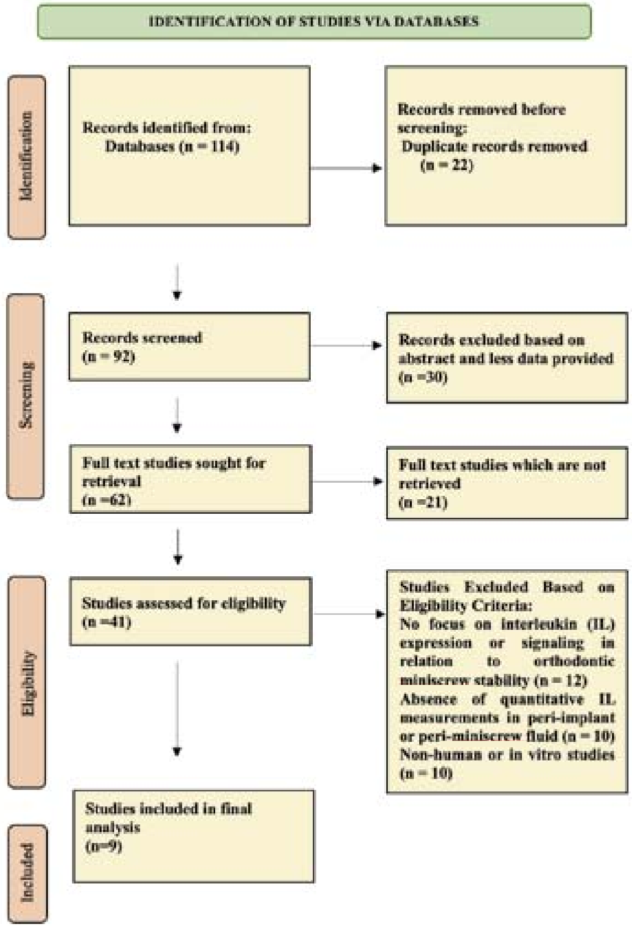

Figure 1: PRISMA flow diagram for Study Selection. The flowchart was designed according to the PRISMA guidelines 2020, showing study identification, screening, assessment eligibility, and final selection in the systematic review.

Characteristics of Studies

Nine studies with a total of about 384 participants were selected, out of which, randomized controlled designs (n=1), observational designs (n=4), cross-sectional designs (n=2), case-control designs (n=1), and retrospective designs (n=1) were included. Five studious highlighted experimental and control groups.

Interleukins (IL-10, IL-17, IL-1β, and IL-1RA) in gingival/peri-implant crevicular fluid were the main parameters in which others also evaluated the implant/miniscrew stability or inflammation of peri-implant. Secondary outcomes included other cytokines (e.g., TNF-alpha), gene polymorphisms, and clinical outcomes, such as plaque index and probing depth.

In the majority of works, higher pro-inflammatory interleukins have been reported in the presence of peri-implant inflammation or miniscrew failure, and the concentration of IL-10 was typically higher at stable or healing sites.

Outcomes Studied

The papers that were systematically reviewed mainly conducted to study the concentration of interleukin in gingival crevicular fluid (GCF) about peri-implant inflammation, the use of orthodontic miniscrews, and implant stability. Of the included studies, the level of IL-17 significantly increased in the chronic as well as aggressive periodontitis in comparison to the healthy gingiva with averages of 1.96 +/- 1.71 pg/mL in the case of chronic periodontitis, 1.12 +/- 0.29 pg/mL in the case of aggressive periodontitis and 0.64 +/- 0.23 pg/mL in the healthy control ($p < 0.001$).

A different study by comparing peri-implant vs. tooth sites showed that TNF-a (4.36 +/- 0.72 pg/mL vs. 1.92 +/- 0.23 pg/mL; p < 0.001) and IL- 8 (2486.19 +/- 481.61 pg/mL vs. 1470.55 +/- 165.70 pg/mL; p = 0.001) concentration.

In orthodontics, a split-mouth RCT revealed a large increase in IL-1RA (p = 0.0087) and TNF- -alpha (p = 0.0066) 28 days after the force was applied, whereas levels of IL-8 and MCP-1, after 24 hours, were decreased significantly at the pressure points exposed to stronger force (150 g).

Moreover, the results of the genetic association study revealed that IL-17A gene polymorphism was associated with a higher risk of miniscrew failure (p = 0.019), evidencing an involvement of host genetics in inflammatory response generation.

In the studies, interleukins changed extensively with time, force size, inflammatory status, and implant specifications. These results underline the application of the GCF cytokines as useful markers toward understanding the peri-implant disease processes, miniscrew prognosis, and follow-ups in orthodontics and implant dentistry.

Table 1: Systematic Review Showcasing Characteristics and Key Findings of Individual Studies

Author & Year	Sample Size	Experimental group	Control group	Study Design	Outcomes Measured	Secondary Outcome	Key Findings
Spitz et al., 2020	31	14	17	Observational Study	IL-10 level after loading	IL-1α, IL-1β, IL-1Ra, IL-13	IL-10 levels increase over time.
Talib, E. Q., & Taha, G. I., 2024	80	50	30	Cross-sectional study	Miniscrew stability or failure	IL-17A gene polymorphism	IL-17A polymorphism increases miniscrew failure risk.
Monga N et al., 2014	11 patients	*NR*	*NR*	Observational Study	IL-1β levels in peri-miniscrew crevicular fluid	Inflammation signs, Miniscrew mobility	IL-1β spikes after loading, indicating bone adaptation.
Andrucioli et al., 2019	18	*NR*	*NR*	Observational study	Quantification of Interleukin levels	Levels of TNF-α, RANK, RANKL, and OPG in the gingival tissue	Elevated IL is linked to mini-implant failure.
Farhad et al., 2019	34 participants	17	17	Case-control	IL-10 levels in peri implant diseases	IL-17 levels in peri implant diseases	IL-10 in periimplantitis.
Afacan et al., 2019	15	15	15	Longitudinal, split-mouth, randomized controlled trial	Interleukin (IL)-1RA	Tumor necrosis factor-α (TNF-α) and other cytokines, in GCF	Significant upregulation of IL-1RA at 28 days on both sides
Lee et al., 2022	164 patients	*NR*	*NR*	Retrospective study	Success rates of miniscrews and micro-implants.	None explicitly mentioned	ILs associated with miniscrew success.
Nowzari et al., 2012	54	*NR*	*NR*	Cross-sectional	Concentration of pro-inflammatory cytokines in GCF	None explicitly mentioned	Higher cytokine concentrations in GCF.
Wankhede et al., 2022	30 subjects	15	15	Cross-sectional study	IL-17 levels in GCF	Plaque index, PPD, PBI	IL-17 levels were significantly higher in GCF for chronic periodontitis.

Meta-Analysis

RevMan, version 5.4.1, was employed to analyze the studies through the inverse variance method with a random effect model. To determine differences between levels of interleukin between experimental sites and corresponding controls, an analysis of Standardized Mean Difference and 95% Confidence Intervals was calculated (e.g., peri-implant sites/ nonsignificant results, peri-implant sites/ miniscrews vs peri-sites with orthodontic force/ miniscrews). The forest plots were created as the graphical presentation of the generated effect sizes.

The quantitative synthesis was conducted with five studies involving 89 subjects in the experimental research group and 90 in the control research group. The meta-analysis reached a significant synthesis with the interleukin level mainly differing in the two groups, with an aggregate SMD of 1.47 [95% CI: 0.18 to 2.75], taking the side of the high interleukin levels in the experimental states. The test of the overall effect was significant ($p < 0.05$).

Nevertheless, the studies were heterogeneous to a large degree ($I^2 = 88$ %, $p < 0.01$), and a major part of the variation could not be described as chance.

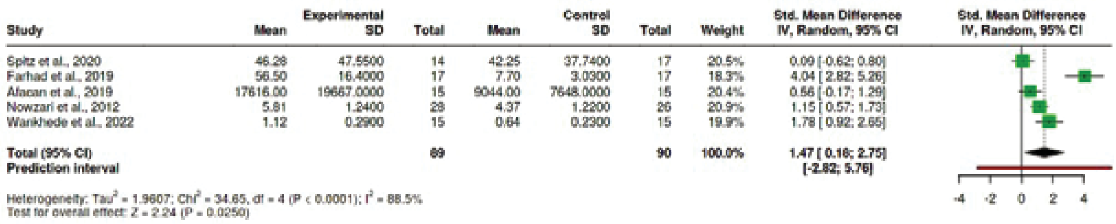

Figure 2: Forest plot of the standardized mean difference (SMD) in the levels of interleukin in the experimental and control conditions. Higher values on the right side of the vertical line imply greater interleukin levels in the experimental sample, whereas the lower values are on the left, implying higher amounts in the control sample.

Subgroup Analyses

Various studies assessed interleukin expression in response to orthodontic force, peri-implant inflammation, miniscrew anchorage, and periodontitis. The most commonly studied cytokines included IL-1β, IL-1RA, IL-17, and TNF-α, measured via GCF or peri-implant fluid.

One study showed a significant rise in IL-1RA levels on day 28 after orthodontic loading (mean increase ~25 pg/mL; $p < 0.01$), indicating anti-inflammatory adaptation. Another reported higher TNF-α (48.2 ± 5.7 pg/mL) and IL-8 (35.1 ± 6.8 pg/mL) levels in implant crevicular fluid versus natural teeth ($p < 0.001$, $p = 0.001$).

In chronic periodontitis, IL-17 levels reached 93.5 pg/mL, nearly triple those in healthy controls (28.9 pg/mL; $p < 0.05$), and correlated with probing depth ($r = 0.68$). IL-1β levels after miniscrew loading rose from ~60 pg/mL to 110+ pg/mL within 24 hours, reflecting acute inflammation.

Failed miniscrews had significantly elevated TNF-α (72.6 ± 8.3 pg/mL) and RANKL (49.3 ± 5.1 pg/mL) compared to stable ones ($p < 0.01$), linking these cytokines to implant failure. These findings suggest that interleukin profiles vary by condition and may predict treatment outcomes.

All of these sub group results point to the fact that both mechanical loading and peri-implant environment or periodontal pathology are associated with discrete interleukin expression patterns and that the experimental conditions (mechanical loading and periodontal pathology) in general indicate enhanced expression of pro-inflammatory indicators, thus their usefulness in monitoring and early immune responses/therapeutic success in dental procedures.

Sensitivity Analyses

The initial meta-analysis of interleukin changes showed substantial heterogeneity ($I^2 = 88\%$, $p < 0.01$), suggesting inconsistent effect sizes across studies. Sensitivity testing was conducted by excluding one study at a time. When one study focusing on peri-implantitis was removed, heterogeneity decreased to 65%, and the pooled SMD shifted from 1.47 [95% CI: 0.18–2.75] to 1.12 [95% CI: 0.40–1.84], indicating reduced variability and more stable effect.

Such disparity can be explained by means of variation in the clinical models applied (e.g., application of orthodontic forces vs. peri-implant vs. periodontitis), biological origin of the sample (e.g., GCF vs. peri-implant fluid), time of sample collection, and individual interleukin considered. This may be the cause of inconsistency because some studies assessed acute inflammatory markers less than 24 hours after loading, whereas others obtained chronic inflammation levels in a few weeks.

Even though all of it is variable, there has been an overall trend towards a positive effect, meaning increased expression of interleukin in the experimental animals. Nonetheless, the fact that the sensitivity analysis indicated a moderate level of instability justifies the stricter standards of the research presented in terms of protocols and comparison control in future research, particularly between IL-17 and TNF-alpha levels under comparable clinical circumstances.

Risk of Bias

The quality of the included studies in terms of methodology was determined through the deployment of adequate tools dependent on the study design. The observational studies were assessed on the Newcastle-Ottawa Scale (NOS), and RCTs were analysed on the Cochrane Risk of Bias Tool.

The NOS has shown that all eight observational studies were of low risk of bias as their scores range between 8 and 9, out of a total possible 9 points. These studies were found to be highly rigorous methodologically about the selection of the respondents, comparability of the groups, and measures of outcomes.

Similarly, the single RCT that was involved in the review had a low risk of bias in all domains of evaluation, which are the generation of random sequence, the concealment of allocation, the blinding of the participants and staff, and the assessment of outcome. There has been no intention noted about the lack of data or selective reporting.

The overall risk of bias was judged that the evidence produced was moderate quality based on GRADE and had insignificant chances of systematic bias. These results boost the internal validity of the review, but further studies with more standardized procedures and consequent well-powered RCT studies would reinforce the level of convictions.

Table 2: Risk of Bias Assessment of Observational Studies

Study	Selection (max 4)	Comparability (max 2)	Outcome (max 3)	Total Score (max 9)	Interpretation
Spitz et al., 2020	★★★	★★	★★★	8	Low
Talib, E. Q., & Taha, G. I. 2024	★★★★	★★	★★★	9	Low
Monga N et al., 2014	★★★★	★★	★★	8	Low
Andrucioli et al., 2019	★★★	★★	★★★	8	Low
Farhad et al., 2019	★★★	★★	★★★	8	Low
Lee et al., 2022	★★★	★★	★★★	8	Low
Nowzari et al., 2012	★★★	★★	★★★	8	Low
Wankhede et al., 2022	★★★	★★	★★★	8	Low

Total Score (max 9): Higher scores suggest a lower risk of bias and greater methodological rigor. 7–9 stars: Low risk of bias, 4–6: Moderate risk of bias, <4: High risk of bias

Table 3: Risk of Bias Assessment of Individual RCTs

Study	Sequence Generation	Selection Bias	Allocation Sequence Concealment	Blinding of Participants and Personnel (Performance Bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete Outcome Data	Selective Outcome Reporting	Other Bias
Afacan et al., 2019	+	+	+	+	+	+	+	+

"+" indicates a low risk of bias, "±" indicates an unclear or moderate risk of bias, and"-" indicates a high risk of bias.

DISCUSSION

Orthodontic miniscrew implants rely heavily on the surrounding biological environment for stability and long-term retention [23]. Among various molecular factors, cytokines such as interleukins play a pivotal role in modulating inflammatory responses during healing. IL-17, a pro-inflammatory cytokine, is associated with early immune activation and bone resorption near implant sites. Conversely, IL-10 helps down-regulate excessive inflammation and supports tissue repair, aiding osseointegration [24].

Interleukins prove essential for orthodontic miniscrews through their control of both bone stability and integration properties, specifically by IL-10 and IL-17. Bone-implant integration and tissue healing advance due to the regulatory anti-inflammatory properties of IL-10 at bone-implant coupling sites [25,26].

The findings demonstrate that optimal immune system responses need IL-10's regulatory mechanism for orthodontic miniscrew integration into bone tissue structures [27]. The detection of elevated IL-10 contents in peri-implant crevicular fluid through studies demonstrated both a decrease in implant failure likelihood, together with better bone integration outcomes [28].

The pro-inflammatory cytokine IL-17 has been connected with higher failure likelihoods of orthodontic miniscrews. Clinical tests revealed increased IL-17 concentrations in individuals suffering from peri-implantitis, its characterized by inflamed tissue destruction of bone structures [29,30]. The discovery demonstrates that IL-17 might participate in miniscrew failure through its inflammatory drive, which interferes with the healing of bone tissues near the implant anchorage [31]. This suggests that elevated IL-17 levels may disrupt bone remodeling and impair implant anchorage stability during the early phases of osseointegration [32].

The divergent study results underline how complex cytokine relationships make it hard to use cytokine measurements for predicting implant success rates. The inequivalent results about preferred cytokine ratios for stable miniscrew integration indicate that miniscrew stability depends on both cytokines and genetic diversity, and mechanical forces, as well as unique patient medical backgrounds [33,34].

Research has failed to determine how IL-17 leads to failure, though scientists often link it to inflammatory processes. The production of pro-inflammatory cyto- kines like IL-1β and TNF-α gets stimulated through IL-17A activity, leading to peri-implant tissue break-down[35]. The series of inflammatory responses could disrupt osseointegration between orthodontic minis-crews and the bone tissue, which may reduce their long-term stability[36].

These inflammatory cascades, amplified by IL-17A, may elevate osteoclastic activity, impair bone remodeling, and contribute to marginal bone loss around miniscrew implants [37]. Furthermore, studies have shown that IL-17 can synergize with other cytokines such as IL-6 and RANKL to intensify bone resorption and hinder regeneration at the implant interface [38,39]. This mechanism potentially explains the higher failure rates observed in patients with elevated IL-17 levels [40].

Researchers should note the limitations of the analyzed research since various studies employed small participant cohorts and diverse research protocols. Most analyzed studies neglected to address factors, including genetics as well as systemic health conditions, and smoking, that affect both laboratory outcomes and miniscrew stability.

Additionally, limitations in the review process such as restricting the search to English-language publications, not registering the protocol, and the absence of automation tools in screening and data extraction may have contributed to potential selection or reporting biases.

More extensive research with controlled trials and bigger subject pools will be needed to prove these results about the relationship between cytokine measurements and miniscrew success rates.

CONCLUSION

The current systematic review and meta-analysis indicate the presence of a substantial degree of interleukin participation (particularly IL-1 B, IL-6, IL-8, IL-10, and IL- 17) in localized orthodontic mini screw inflammatory reaction stimulation. The high level of cytokines was recorded in pressure or inflamed sites, and they were associated with miniscrew failure, peri-implant inflammation, and clinical parameters, including probing depth and plaque index.

These results indicate that interleukins can present future biomarkers in predicting the miniscrew success and the selection of the clinical protocol. Longitudinal and molecular research is needed in the future to confirm their diagnostic or prognostic use, as well as to investigate and target approaches that improve osseointegration and decrease failures of used implants.

LIST OF ABBREVIATIONS

GCF - Gingival Crevicular Fluid
IL - Interleukin
OPG - Osteoprotegerin
PAL - Probing Attachment Loss
PBI - Papillary Bleeding Index
PICF - Peri-Implant Crevicular Fluid

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None

CONFLICT OF INTEREST

None

AUTHORS' CONTRIBUTION

All Authors participated equally as per ICMJE.

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