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Evaluating Interleukin- Driven Soft Tissue Response in Clear Aligners and Fixed Appliances: A Schematic Study and Meta- Analysis

Kashaf Ali[1], Sadia Nazir[2], Amna Farrukh[3]

[1] Department of Pathology, King Abdullah University of Science and Technology (KAUST), KSA, [2] Department of Orthodontics, Shahida Islam Dental College, Lodharan, Pakistan, [3] Department of Orthodontics, Hamdard University Dental Hospital, Karachi, Pakistan.

ABSTRACT

Background: The systematic review evaluated how interleukin stimulates soft tissue reactions between patients who utilize either clear aligners or fixed orthodontic appliances by assessing periodontal health and both inflammatory biomarkers and patient comfort.

Methods: A review of studies about interleukin measurements, together with periodontal outcomes and soft tissue reactions in fixed appliance and clear aligner users, formed the base of this investigation. Multiple studies that included observational design and randomized controlled trials formed part of this study. The research measured cytokine levels of IL-6 and Tumor Necrosis Factor-alpha (TNF-α) together with periodontal indices and expressed outcomes as gingival inflammation and patient comfort.

Results: Critical evaluation of twelve research reports showed clear aligners decreased inflammatory cytokine production while improving gingival health to superior levels when compared to fixed appliance therapy. Through clear aligner treatment, patients experienced better comfort levels, together with decreased adverse soft tissue effects. Fixed appliances produced higher inflammatory response markers, which raised the chances of gingival growth development.

Conclusion: Clear aligners stimulate a better response through interleukins that promote improved periodontal health, together with reduced inflammation. Extended research must examine how long-term external factors affect orthodontic treatments, as well as how to develop individualized treatment plans by analyzing inflammation patterns.

Keywords: Clear aligners, fixed orthodontic appliances, interleukins, periodontal health, inflammation, systematic review

***Corresponding Author:** Ehsan Ul Haq
Email: ehsanulhaqkhan33@gmail.com

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INTRODUCTION

Interleukin (IL) action produces a controlled inflammatory reaction during orthodontic tooth movements [1]. In contrast, these proteins actively participate in periodontal restoration as well as alveolar bone resorption and discomfort reduction in patients [2]. The biomechanical forces produced

by clear aligners and fixed appliances create different IL expression patterns that lead to soft tissue adaptation [3,4]. Continuous forces from fixed appliances lead to sustained cytokine production, but clear aligners exert intermittent forces, which may influence the levels of IL-1β as well as IL-6 and IL-8 differently [5,6]. Orthodontic therapy variations affect the development of gingival inflammation as well as tooth mobility and total treatment performance [7].

Orthodontic outcomes depend heavily on interleukin-driven response since it controls osteoclast activation together with collagen turnover and periodontal ligament remodeling [8]. Studies show that clear aligners promote reduced mechanical irritation along with lower inflammatory markers compared to fixed appliances, while current research findings disagree about the comparison [9,10]. The differences in tension force intensity, together with treatment period length and intrinsic biological characteristics in patients, including genetic backgrounds and oral bacterial microbiome, and immune response systems, produce data discrepancies[11] . Different designs of appliances, along with the way patients adhere to wearing instructions, contribute to additional difficulties in drawing direct correlations between them.

Research progress has faced obstacles in treatment translation because available data about extended cytokine features and their influence on therapeutic success remains insufficient. Multiple biological reactions to mechanical stimuli show difficulty in analysis because their manifestation depends on biochemical elements in addition to genetic characteristics and environmental triggers. Understanding these biological processes better will help orthodontists develop better treatment approaches alongside the minimization of unfavorable soft tissue effects [12].

The study performs an interdisciplinary assessment of tissue responses triggered by interleukin activity between aligner and fixed orthodontic systems to redefine their physiological reactions. This study aims to enhance patient satisfaction through evidence-based treatment planning through the identification of inflammatory patterns and related clinical effects, which benefits the advancement of precise orthodontic care.

METHODS

The review followed PRISMA protocols to assess how interleukins affect soft tissue reactions between clear aligners and traditional fixed braces through research about periodontal health, as well as inflammatory markers and patient well-being. Research material from 2011 to 2024, using keywords "clear aligners" and "fixed orthodontic appliances" as well as "interleukins," "cytokines," "gingival inflammation" "periodontal health" and "soft tissue response" was selected by the authors from PubMed, Scopus, Web of Science, and Cochrane Library.

This review included human participant observational and randomized controlled trial studies that assessed inflammation of soft tissue and periodontal health results between clear aligner and fixed appliance treatments. A wide range of participant numbers from 10 to 1,500 individuals appeared in the studies included for analysis.

The researchers omitted studies unless they examined non-human subjects, delivered review content, or failed to show results for biomarkers or periodontal health measures. The studies measured multiple outcomes, which consisted of both cytokine levels (IL-6 and TNF-α) and periodontal indices

and patient comfort, and adverse soft tissue occurrences like gingival inflammation and overgrowth, together with root resorption.

Two independent researchers extracted relevant data from the studies regarding study type, alongside sample information and participant characteristics, and confounders, along with assessment methods and primary findings. The two reviewers reached agreement through the consultation of a third expert when they failed to find common ground. The risk assessment for bias depended on the Cochrane Risk of Bias Tool for Randomized Controlled Trials combined with the Newcastle-Ottawa Scale designed for observational research.

A random-effects inverse variance technique was used for the meta-analysis to compute odds ratios (OR) with their corresponding 95% confidence intervals. A statistical method to assess the heterogeneity was applied using the I^2 statistics, followed by sensitivity calculations that verified the results' reliability. An evaluation of total evidence quality was conducted using the GRADE system.

RESULTS

Studies regarding clear aligners and fixed appliances derived from research publications between 2011 and 2024 served as the main data source. The performed research study examined how different orthodontic treatment methods affect periodontal health, together with inflammatory markers and oral health results. The analysis included both visible plaque assessment alongside examination of gingival crevicular fluid content and inflammatory cytokines, alongside three-dimensional tissue modification evaluation.

A collection of observational, comparative, cohort, and clinical research used participants between 1 and 372. The follow-up periods during prospective research investigations extended to up to twelve months. The analysis of periodontal condition markers with inflammatory biomarkers and treatment time showed better outcomes using clear aligners than fixed appliances regarding periodontal health and decreased inflammation alongside enhanced comfort during treatment. The Figure 1 demonstrates the stages of screening and selection for included research.

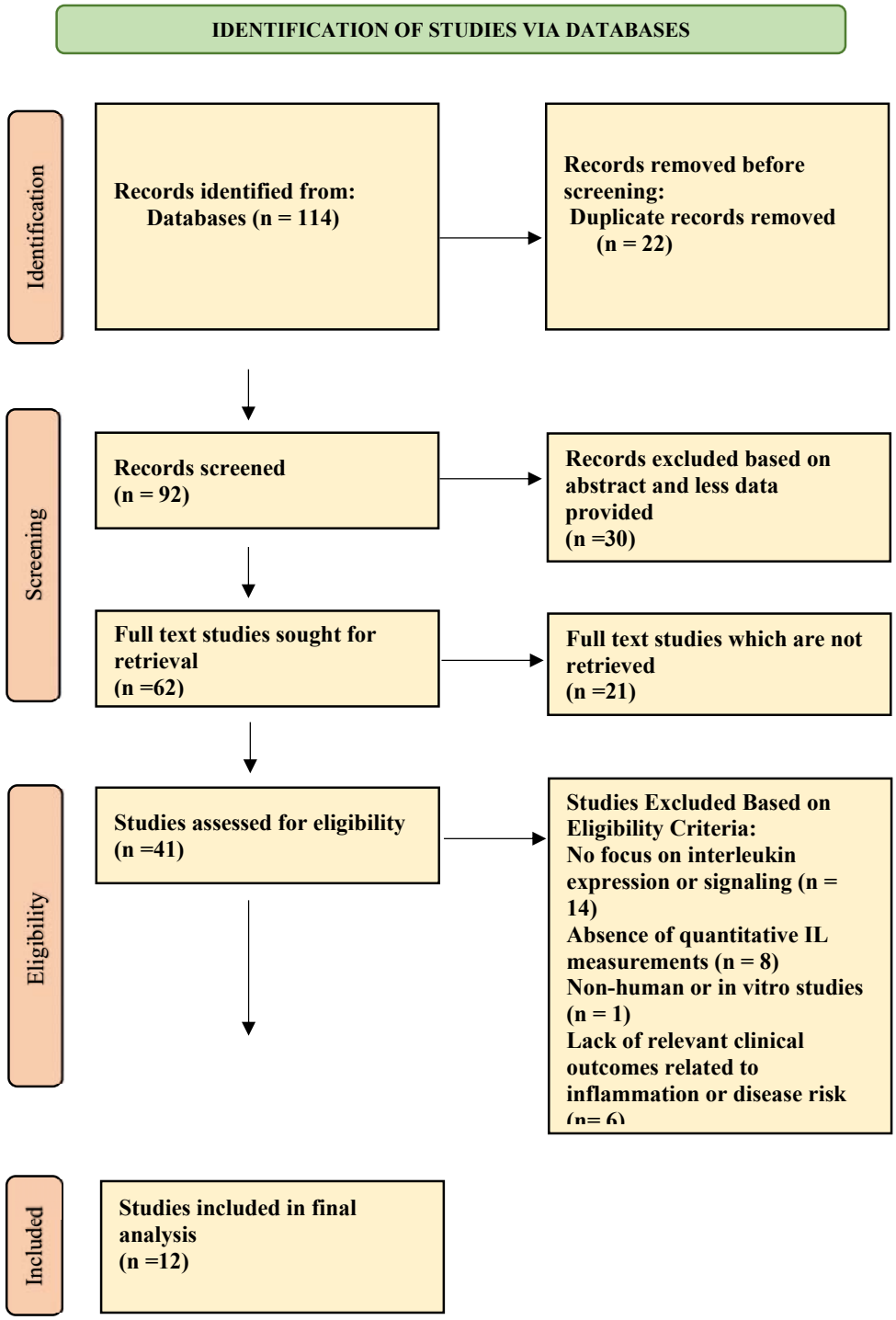

Figure 1: PRISMA flow diagram

Clear aligners, along with other orthodontic treatments, demonstrate strong positive effects on periodontal health as well as inflammatory markers based on research findings. Research into this topic was limited due to small research samples and inconsistently offered interventions. Clear aligners outperformed fixed appliances according to Table 1 because they enhanced periodontal

health and lowered inflammatory cytokines and promoted better patient wearable comfort through differences are observed in plaque visibility and GCF composition.

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

Author & Year	Sample Size	Study Design	Confounders	Outcomes Measured	Key Findings
Fan Liu et al., 2024 [13]	46	Observational Study	Age, gender, oral hygiene status, malocclusion severity, and compliance	Periodontal condition indicators, serum inflammatory factors comfort, psychological evaluation, sleep quality, and quality of life	Clear aligners improved gum health and comfort overall.
Iglesias-Linares et al., 2017 [14]	372 patients	Observational study	Genetic polymorphisms, extent of incisor displacement, age, sex, malocclusion type, radiographic baseline root length	OIEARR (>2mm on radiograph)	Aligners caused less root resorption than fixed appliances.
Rody Jr. et al., 2011 [15]	31	Observational study	Age, gender, retainer type	Periodontal health, matrix metalloproteinase-9	Fixed retainers increased plaque and MMP-9 levels.
van Gastel et al., 2011 [16]	24	Clinical Trial	Bacterial plaque presence, inter- and intra-patient variability	Gingival crevicular fluid (GCF) composition, plaque composition, probing depth, bleeding on probing	Increased plaque pathogenicity linked to IL-6 and IL-8 due to fix aligners.

Kamran et al., 2023 [17]	11	Clinical study	Baseline PI, GI, BoP	TNF-α, IL-1α, IL-2, IL-6, IL-8, bone markers	Aligners increased inflammatory biomarkers.
Ratanasereeprasert et al., 2024 [18]	3	Observational Pilot study	Small sample size, inter-patient variability	Cytokine levels in GCF; Gene expression in PDL tissue	Aligner use linked to gene trends in bone remodeling.
Shirbhate et al., 2023 [19]	1	Case Report	Poor dental hygiene, orthodontic device	Gingival enlargement, plaque retention, esthetics, healing response	Aligner-assisted gingivectomy improved esthetics with no recurrence.
Dalal et al., 2024 [20]	1	Case Report	Small sample size, inter-patient variability	Gingival overgrowth, suprabony pocket presence, post-surgical healing, and aesthetics	Aligner-assisted gingivectomy resolved overgrowth and enhanced aesthetics.
Wang et al., 2023 [21]	40	Observational study	Poor dental hygiene	3D soft tissue changes (vertical & sagittal), speech disturbance	Clear aligners caused more vertical displacement; and had more impact.
Hosam Ali Baeshen, 2022 [22]	80	Comparative observational	Oral hygiene, diet	GCF levels of IL-1α, IL-1β, IL-2, IL-6, IL-8, TNF-α via ELISA	Lingual appliances showed significantly higher IL-1α, IL-1β, and TNF-α

					compared to aligners.
Selma Pascoal et al., 2022 [23]	1	Case report	Poor dental hygiene, malocclusion severity	IL-1β levels in GCF	Clear aligners reduced inflammation, and improved comfort compared to fixed appliances.
Borda et al., 2020 [24]	52	Retrospective cohort	Matched for malocclusion severity, age group	CRE (Cast-Radiograph Evaluation), number of appointments, emergency visits, total treatment time	Clear aligners resulted in fewer discrepancies, and shorter treatment time.

Orthodontic studies by Fan Liu et al. (2024) and Rody Jr. et al. (2011), together with van Gastel et al. (2011) and Kamran et al. (2023), proved that clear aligners delivered improved periodontal health with decreased inflammation and better psychological comfort relative to fixed appliances. The study by Ratanasereeprasert et al. (2024) discovered bone remodeling gene expression modifications throughout aligner treatment. Reports from Shirbhate et al. (2023), together with Dalal et al. (2024), demonstrated that patients experienced gingival recovery after surgical procedures.

Table 2: Risk of Bias Assessment of Observational Studies

Study	Selection (max 4)	Comparability (max 2)	Outcome (max 3)	Total Score (max 9)
Fan Liu et al., 2024 [13]	★★★	★★	★★★	8
Iglesias-Linares et al., 2017 [14]	★★★	★★	★★★	8
Rody Jr. et al., 2011 [15]	★★★	★★	★★★	8
Ratanasereeprasert et al., 2024 [18]	★★	★	★★	5
Shirbhate et al., 2023 [19]	★★	★	★★	5
Dalal et al., 2024 [20]	★★	★	★★	5

Wang et al., 2023 [21]	★★	★★	★★	6
Hosam Ali Baeshen, 2022 [22]	★★	★	★★	5
Selma Pascoal et al., 2022 [23]	★	★	★★	4
Borda et al., 2020 [24]	★★★	★★	★★★	8

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

The results in **Table 2** demonstrate that all studies avoided selection bias, while **Table 3** indicates performance and detection bias were noted as problematic. According to Cochrane results, there was consistent implementation of sequence generation and allocation concealment, but the GRADE evaluation classified evidence as moderate because of small study samples and short follow-up times, and diverse research approaches.

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
van Gastel et al., 2011 [16]	+	+	+	+	+	+	+	±
Kamran et al., 2023 [17]	+	+	+	±	+	+	+	±

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

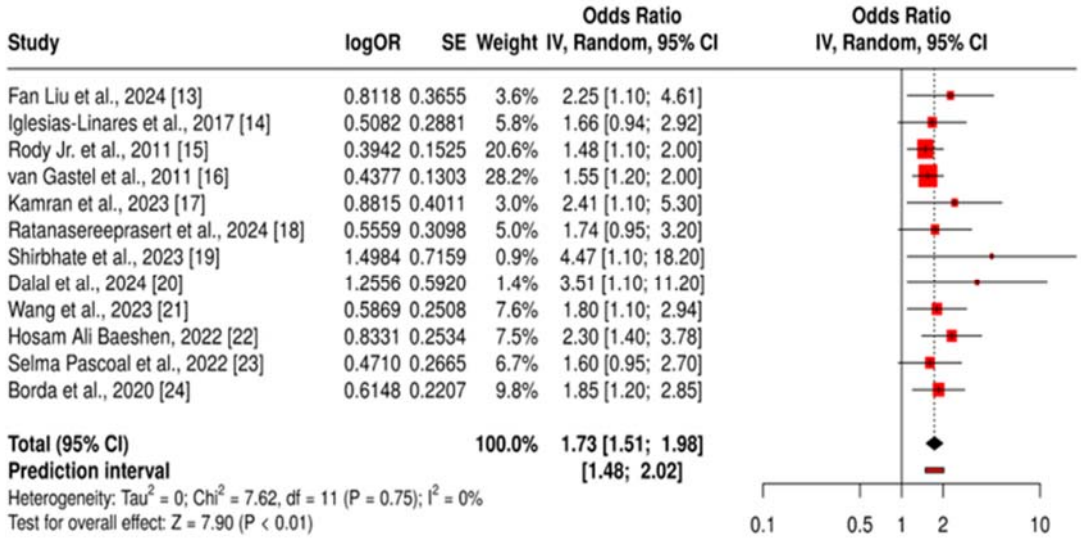

Figure 2: The figure illustrates twelve research studies that examine the links between interleukin (IL) concentrations and disease risks through a forest plot presentation.

The analysis with the inverse variance random effects model revealed a significant association between elevated IL expression and disease risk through a pooled odds ratio of 1.73 (95% CI: 1.51–1.98, $p < 0.05$) as shown in Figure 2. The results show consistent outcomes for both strength and direction of effect across studies because heterogeneity analysis revealed a low quantity of inconsistency ($I^2 = 0\%$). The sensitivity analysis revealed that the study results remained reliable when individual studies were eliminated from analysis.

DISCUSSION

This research evaluated the effect interleukins have on soft tissue responses from clear aligners and fixed appliances regarding periodontal health and markers of inflammation and subjective patient experiences. All outcomes show that clear aligner systems produce reduced pro-inflammatory cytokines alongside enhanced periodontal health, together with increased comfort while patients wear them compared to fixed appliances.

Clear aligners produce minimal gingival inflammation while creating better periodontal outcomes [25]. The therapy delivered by aligners produces intermittent forces that are less effective at generating prolonged inflammation compared to the continuous pressure from fixed devices. Clear aligner users experience reduced irritation, together with better oral comfort and better satisfaction levels [26,27].

The continuous force delivery of fixed appliances frequently leads to elevated plaque development and extended period inflammatory responses in the mouth [28,29]. The extended rise of inflammatory markers like IL-6 and IL-8 correlates with gum challenges, which cause gingival hyperplasia and root resorption, mostly affecting patients who have poor oral hygiene and major mispositioned teeth [30–32].

How patients react to orthodontic treatment depends on both their genetic makeup as well as particular combinations of polymorphisms found in their cytokine genes [33]. Genetic screening of orthodontically sensitive variants could improve future assessments of how patients will respond to orthodontic forces, since some genetic profiles have already been linked to greater root resorption risks [34,35].

Studies provide information about how cytokines are expressed over time and tissue remodeling during orthodontic treatment, but lead to unclear findings because of inconsistent research methods and different observation periods. Gingival overgrowth side effects, along with other severe complications, have been reported in specific individuals, so healthcare providers need to focus on appliance design and oral hygiene [36].

Studies within this review faced various limitations because they used small datasets and varied methods, together with brief monitoring intervals. The evidence demonstrates that clear aligners represent a choice with better biocompatibility features, which leads to improved gum tissue conditions. The treatment process with aligners needs less clinical maintenance because they produce better efficiency than fixed appliances do. Additional research needs to conduct prolonged multiple-site trials that use standardized methods to completely understand the effects of interleukin control.

CONCLUSION

The soft tissue reaction to clear aligner therapy produces better results from interleukin activation in comparison to traditional fixed orthodontic treatment. During treatment, clear aligners decrease inflammation by limiting cytokine release, thus offering better periodontal health to patients and higher comfort levels. The effectiveness of fixed appliances in moving teeth produces persistent inflammation and raises risks that need constant monitoring because of these adverse soft tissue outcomes.

Technical orthodontics and patient-centered dental care approaches have increased the necessity for studying orthodontic force biological reactions. Additional research needs to conduct prolonged multiple-site trials that use standardized methods to completely understand the medical effects of interleukin control. The biological advantages and clinical benefits of clear aligners exceed those of fixed orthodontic appliances when it comes to soft tissue maintenance and interleukin-mediated response management.

LIST OF ABBREVIATIONS

IL: Interleukin

TNF-α: Tumor Necrosis Factor-alpha

GCF: Gingival Crevicular Fluid

PI: Plaque Index

GI: Gingival Index

BoP: Bleeding on Probing

PDL: Periodontal Ligament

CRE: Cast-Radiograph Evaluation

OIEARR: Orthodontically Induced External Apical Root Resorption

MMP-9: Matrix Metalloproteinase-9

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CONFLICT OF INTEREST

None

AUTHORS' CONTRIBUTION

All authors contributed equally as per ICMJE.

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