

Review

The Interaction of Cytokines in Orthodontics: A Systematic Review

Francesco Inchingolo ^{1,*}, Angelo Michele Inchingolo ^{1,†}, Giuseppina Malcangi ^{1,*}, Laura Ferrante ¹, Irma Trilli ¹, Angela Di Noia ¹, Fabio Piras ¹, Antonio Mancini ¹, Andrea Palermo ², Alessio Danilo Inchingolo ^{1,‡} and Gianna Dipalma ^{1,‡}

- ¹ Department of Interdisciplinary Medicine, University of Bari “Aldo Moro”, 70124 Bari, Italy; angeloinchingolo@gmail.com or a.inchingolo3@studenti.uniba.it (A.M.I.); laura ferrante79@virgilio.it or laura.ferrante@uniba.it (L.F.); irmatrilli@hotmail.com or irma.trilli@uniba.it (I.T.); angeladinoia@libero.it or angela.dinoia@uniba.it (A.D.N.); dott.fabio.piras@gmail.com or fabio.piras@uniba.it (F.P.); dr.antonio.mancini@gmail.com or antonio.mancini@uniba.it (A.M.); ad.inchingolo@libero.it or a.inchingolo1@studenti.uniba.it (A.D.I.); giannadipalma@fiscali.it or gianna.dipalma@uniba.it (G.D.)
- ² Implant Dentistry College of Medicine and Dentistry Birmingham, University of Birmingham, Birmingham B4 6BN, UK; andrea.palermo2004@libero.it
- * Correspondence: francesco.inchingolo@uniba.it (F.I.); giuseppinamalcangi@libero.it or giuseppina.malcangi@uniba.it (G.M.); Tel.: +39-331-211-1104 (F.I.); +39-3403348500 (G.M.)
- † These authors contributed equally to this work as first authors.
- ‡ These authors also contributed equally to this work as last authors.

Abstract: Aim: Cytokines are crucial low-molecular-weight proteins involved in immune responses. This systematic review highlights the need for in-depth studies on cytokines’ biological mechanisms, providing insights into disease onset and potential therapeutic strategies. Materials and methods: A comprehensive literature search identified 18 relevant articles, emphasizing the multifaceted role of cytokines in orthodontic treatment (OT). The quality assessment using the ROBINS-I tool ensures a rigorous evaluation of the included studies, contributing to the overall reliability of the findings. Results and Conclusions: This systematic review explores the intricate relationship between cytokines and OT. Cytokines exhibit different properties, influencing cellular activities through autocrine, paracrine, and endocrine activities. OT, aimed at achieving stable occlusion, induces tension and compression in the periodontal ligament (PDL), triggering cytokine release. Proinflammatory cytokines play a role in inflammation, influencing bone and soft tissue metabolism. Studies show elevated cytokine levels in gingival crevicular fluid (GCF) after orthodontic force application. The choice of orthodontic devices, such as self-ligating brackets, influences cytokine concentrations, indicating the importance of attachment design. Further research promises to enhance orthodontic practices, and optimize patient care.

Keywords: cytokine; orthodontic therapy; inflammation; interleukin; health care



Citation: Inchingolo, F.; Inchingolo, A.M.; Malcangi, G.; Ferrante, L.; Trilli, I.; Di Noia, A.; Piras, F.; Mancini, A.; Palermo, A.; Inchingolo, A.D.; et al. The Interaction of Cytokines in Orthodontics: A Systematic Review. *Appl. Sci.* **2024**, *14*, 5133. <https://doi.org/10.3390/app14125133>

Academic Editor: Vittorio Checchi

Received: 26 April 2024

Revised: 4 June 2024

Accepted: 5 June 2024

Published: 13 June 2024



Copyright: © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Cytokines (cyto-, cell and -kinos, movement), also called “molecular words”, are low-molecular-weight proteins. Via specific membrane receptors, they function to induce and/or stimulate reactions in the same cell that produces them (autocrine activity), in neighboring cells (paracrine activity) or at a distance, and through the bloodstream (endocrine activity) (Figure 1) [1,2].

They are also referred to as “immunomodulatory agents”, since they play a very important role in both innate (by activating macrophages and natural killer cells) and acquired immune responses, both humoral and cellular (by activating T-lymphocytes and B-lymphocytes). They are produced and released by cells as soon as the immune system detects the presence of a pathogen and other stimuli, such as the orthodontic force [3–5].

Cytokines can have the following properties: redundant (amplified effect by action of multiple cytokines on the same cell); pleiotropic (action on multiple cell types); synergistic (associated with other cytokines); or antagonistic (on the impact of another cytokine) [6,7]. To date, 36 cytokines have been isolated in humans. There is no definitive classification because different cell types can produce the same cytokine, and a single cytokine can have multiple functions [8]. However, they could be classified according to the producing cells, lymphokines (from lymphocytes) or monokines (from monocytes), or according to their activities:

- (1) Proinflammatory cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8) and tumor necrosis factor (TNF), deputed to control inflammation, fever, sleep rhythm, hematopoiesis and reabsorption [9,10];
- (2) Immunoregulatory cytokines: IL2, IL3, IL4, IL5, IL7, IL10, IL12. These ILs, in fact, control the immune system response by stimulating differentiation into natural killer cells and B lymphocytes for antibody production [11];
- (3) Effector cytokines: interferons, chemokines, and stimulating factors (CSFs) that modulate defense processes toward infectious agents and neoplastic processes [9].

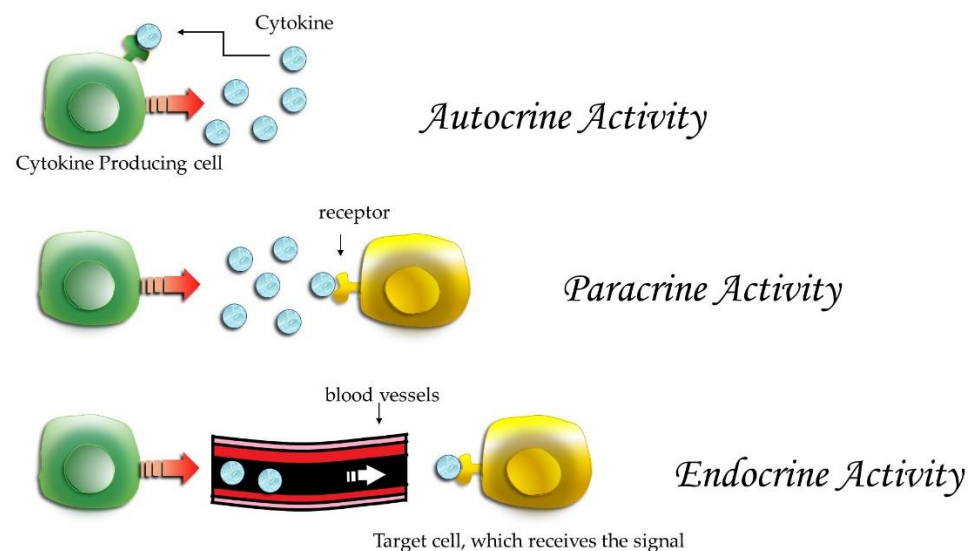


Figure 1. Cytokines act primarily in local form, affecting both the producing cell itself (autocrine activity) and adjacent cells (paracrine activity), rather than exerting significant effects on cells and tissues distant from the site of production (endocrine activity).

Studies show how the occurrence of various disease states (organ failure, fibrosis, and chronic inflammation) are related to insufficient cytokine production or secretion [6,12]. An interesting correlation was found between OT and the presence of cytokines [13,14]. OT, whatever the method, aims to achieve a stable, functional and balanced occlusion. This requires the need to make modifications of both the bony bases and the dental elements. The forces applied for orthodontic movement generate areas of tension and compression at the level of the PDL, resulting in remodeling of the entire periodontium (PDL, alveolar bone and gums). The PDL immediately undergoes blood flow changes through the release of cytokines, growth factors, and bacterial flora growth factors, following signals emitted by other molecules such as eicosanoids, substance P and calcitonin gene-related peptide, and cyclic adenosine monophosphate (cAMP) [15–17]. Cytokine production and migration affects bone and soft tissue metabolism by acting on NF kappa B ligand receptors (RANKL), osteoprotegerin (OPG), matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs (TIMPs) [18,19]. Study findings revealed elevated concentrations of proinflammatory cytokines and markers of tissue and bone metabolism in gingival crevicular fluid (GCF) following the application of orthodontic forces [20,21]. Increased levels were observed after 4 h and persisted for up to 6 weeks. At the site of compression, an increase in IL-1beta and

IL-8 was recorded after 4 h, MMP-9 after 7 and 42 days, and RANKL after 42 days [18,22]. Vasodilatation and leukocyte invasion, signs of the onset of the inflammatory state, occur due to the action of proinflammatory cytokines, such as IL-1 β , IL-2, IL-5, IL-6, IL-8, TNF α , interferon- γ and Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF). In contrast, anti-inflammatory cytokines such as IL-4 and IL-10 intervene in the healing process [23–27]. IL-1 β , produced predominantly by activated monocytes, induces osteoclastic activity as a consequence of the acute phase [28]. Notable elevations in IL-1 β , IL-8, TNF α , MMP-9, and TIMP 1 and 2 were found at the tension sites adjacent to the dental elements in all time spaces following force application [18,19]. IL-1, TNF- α , and IL-6 increase bone resorption by modulating the binding of RANKL, stimulating osteoclast maturation, also caused by a reduction in the osteoblastic production of OPG, receptor of RANKL, inhibiting its differentiation [29,30]. Orthodontic movement also results in soft-tissue remodeling, which has been studied on the concentrations of metabolites released in GCF. Enzymes such as MMPs and tissue inhibitors of matrix MMPs (TIMPs) metabolize soft tissue [31,32]. Collagen fibers are degraded by collagenases, specifically MMP-1 and MMP-8, while denatured collagen is degraded by gelatinases, such as MMP-2 and MMP-9. In the GCF at compression and tension sites, an increase in the concentration of MMP-1, MMP-8, MMP-2, MMP-9, and TIMP-1 was found, varying in amounts according to the interval of force application (e.g., MMP-1 shows very high levels already after the first hour of force application, while MMP-2 reaches higher basal levels after 8 h) [33,34]. Alterations in the orthodontic patient's physiometabolic status also modifies the periodontal complex's inflammatory response during treatment. Chronic pathological conditions, such as type 2 diabetes mellitus (DMT2), manifested increased concentrations of advanced glycation metabolite levels and GCF proinflammatory chemokines [35–41]. In obese adolescent patients, there is already a pre-existing situation of periodontal tissue inflammation, recorded by increased levels of adipokines, leptin, and resistin in GCF [42,43]. With regard to chronic diseases, research shows that a cytokine response can also occur in temporary, acute-phase diseases, such as in SARS-CoV-2 infection [44,45]. The correlation between COVID-19 patients and cytokine release is a topic of great interest in scientific research, as it is recognized that COVID-19 elicits an inflammatory immune response involving various types of cytokines [46,47]. In this situation, numerous pro-inflammatory cytokines, including TNF, interferon- γ , IL-1, IL-6, IL-18, and IL-33, are released uncontrollably, giving rise to a cytokine storm. The entire pathological process, triggered by defects in the cytolytic activity of lymphocytes, continues with increased macrophage activity and hyperactivation of the immune system, culminating in cytokine storm. In patients who contracted COVID-19 during OT, increased cytokines were found in periodontal tissues [48–51]. The increased cytokine response occurs in the more acute stages, and the control of the periodontal situation could be more difficult and, during OT, could affect the final outcome. The acute phase, in this type of infection, is also quite long, encompassing the entire convalescence period. In some patients, this immune response may become excessive, leading to an overproduction of cytokines and resulting in a state of systemic inflammation.

In these patients, greater orofacial pain, after 24 h of OT, was also related to higher levels of the proinflammatory cytokine IL-1 β before and during tooth movement, and a higher concentration of TNF- α was found compared with non-obese adolescents. No difference was found in the speed of tooth movement during the initial week of orthodontic therapy between obese and non-obese patients [52,53]. Studies on failures in the stability of mini implants, increasingly used as skeletal anchors in OT in both adults and adolescents, have evaluated genetic, biomolecular and inflammatory aspects [54,55].

The single-nucleotide polymorphism (SNP) of IL-1 (IL-1 α and IL-1 β) and IL-6 can recognize the same receptor on the same target cell, resulting in the same biological responses and amplifying them. Tissue trauma, derived from the same mini-implant insertion, the presence of plaque around peri-implant tissues and crevicular fluid, the application of forces, and smoking determine the release of pro-inflammatory cytokines (IL-1 β , IL-2, IL-6, and IL-8) around the device [56,57]. This results in an activation of lymphocytes,

macrophages, endothelial cells, neutrophils, and prostaglandins with the appearance of fibrinolytic and osteoclastic activity and mobilization and failure of the miniscrew [58,59]. Higher concentrations of IL-1 β , IL-6, and IL-8 were recorded after at 8 h implantation, remaining elevated during the first 24 h. This is likely related to tissue trauma following implant placement and the immediate application of forces. These findings imply that by controlling orthodontic pressure, cytokine concentrations and implant detachment could be reduced [56,60,61]. Studies have been carried out on the different inflammatory response between self-ligating brackets and conventional brackets. Data report a more amplified response and a higher concentration of cytokines and bacteria in self-ligating brackets [61,62]. Therefore, in patients at risk of periodontal disease and root resorption, the design of the attachment has great relevance. While evaluating the biocompatibility and possible toxicity of resin surface sealants, there were no different concentrations between IL-6 and IL-8 levels among the different resins used [63,64]. Instead, a diversity of individual anti-inflammatory response was found. Therefore, OT today must involve careful evaluation of each individual patient to tailor the treatment accordingly. This approach is fundamental to improving clinical outcome and preserving patients' periodontal health [65,66]. The overlapping cellular response to OT in premenopausal and postmenopausal women, given that, at the start, the latter have increased bone turn markers in GCF, more specifically in RANKL and osteopontin (OPN) levels, indicates the safety of OT in postmenopausal women as well [67,68]. In male patients undergoing fixed OT, the more pronounced inflammatory response (IL-17 A and RANKL), greater cytokine presence, and faster orthodontic tooth movement (OTM) would appear to be determined by lower estrogen levels, manifesting, thus, a correlation between sex and hormone levels [69,70]. OT with lingual braces induces a distinct inflammatory response, as evidenced by altered levels of cytokines and cellular composition in saliva. In fact, higher levels of chemokine ligand 2, IL-17A and IL-6 (two to four times higher) were found in patients with lingual braces than in those with fixed labial braces, as well as lower levels, detected by enzyme-linked immunosorbent assay (ELISA) tests, of defensins in the saliva of patients with lingual OT [71–73]. In the comparison of inflammatory reactivity between aligners and lingual devices, analyzing GCF biomarkers revealed that higher levels of TNF- α were also shown in situations where aligners were used compared to lingual fixed appliances. However, significant levels of interleukins (IL-1 α , IL-1 β , IL-2, IL-6, and IL-8) and TNF- α were recorded in GCF in both treatments [74]. Salivary chemokine secretion between the lingual and labial braces groups showed higher secretion of C motif chemokine ligand 2 (CCL2), CCL11, CCL2, CCL5 and C-X-C motif chemokine ligand 8 (CXCL8) in subjects with labial braces.

In the saliva of patients treated with conventional lingual braces, the percentage of CD45+ (a marker for leukocytes) and CD326+ (a marker for epithelial cells) cells was higher, while the value of C-X-C motif chemokine ligand 9 (CXCL9) showed slightly higher secretion. These changes in chemokine secretion affect inflammatory actions and long-term oral health [71,72]. Photodynamic therapy (PDT), with the application of diode lasers at low-level wavelengths (LLLTs) from 660 and 830 nm, resulted in an improvement in the tooth element's rate displacement due to a higher concentration of IL-1 β , RANKL, and OPG present and a consequent increased osteoclastic activity [75,76]. The average increase in orthodontic movement speed with the application of PDT, found in the various studies, is around 20%; calculated as a percentage of the control group in nine studies, it is 24% [77,78]. PDT activates adenosine triphosphate (ATP) production, increases blood flow at the site, inhibits the secretion of inflammatory substances, and stimulates that of neurotransmitters, interfering with the conduction and stimulation of peripheral nerves, stimulating the release of endorphins [79]. Controlling the inflammatory state and pain of PDT, therefore, contributes, overall, to periodontal health in orthodontic patients [80,81].

Cytokines are important biomarkers for health; they are small proteins released by different cells that influence the behavior of other cells by acting as messengers in the immune system. Cell signaling is crucial to the immune response, and dysfunction in this process is often associated with diseases such as cancer and autoimmune disorders.

Cytokines are classified according to their properties and immune response. There are proinflammatory cytokines, which amplify inflammatory responses; growth factors, which promote cell survival and cause structural changes; and anti-inflammatory cytokines, which control the proinflammatory cytokine reaction. Several categories of cytokines perform specific functions in the immune system [82]. For example, chemokines are involved in the migration of immune system cells, interferons defend the body against viral and tumor diseases, and ILs mediate interactions between immune system cells [83]. Cytokines play crucial roles in modulating the immune response, inducing the inflammatory response, regulating hematopoiesis, and wound-healing. They are produced by various cells, including those of the immune system such as macrophages, B and T lymphocytes, and mast cells (Figure 2) [19].

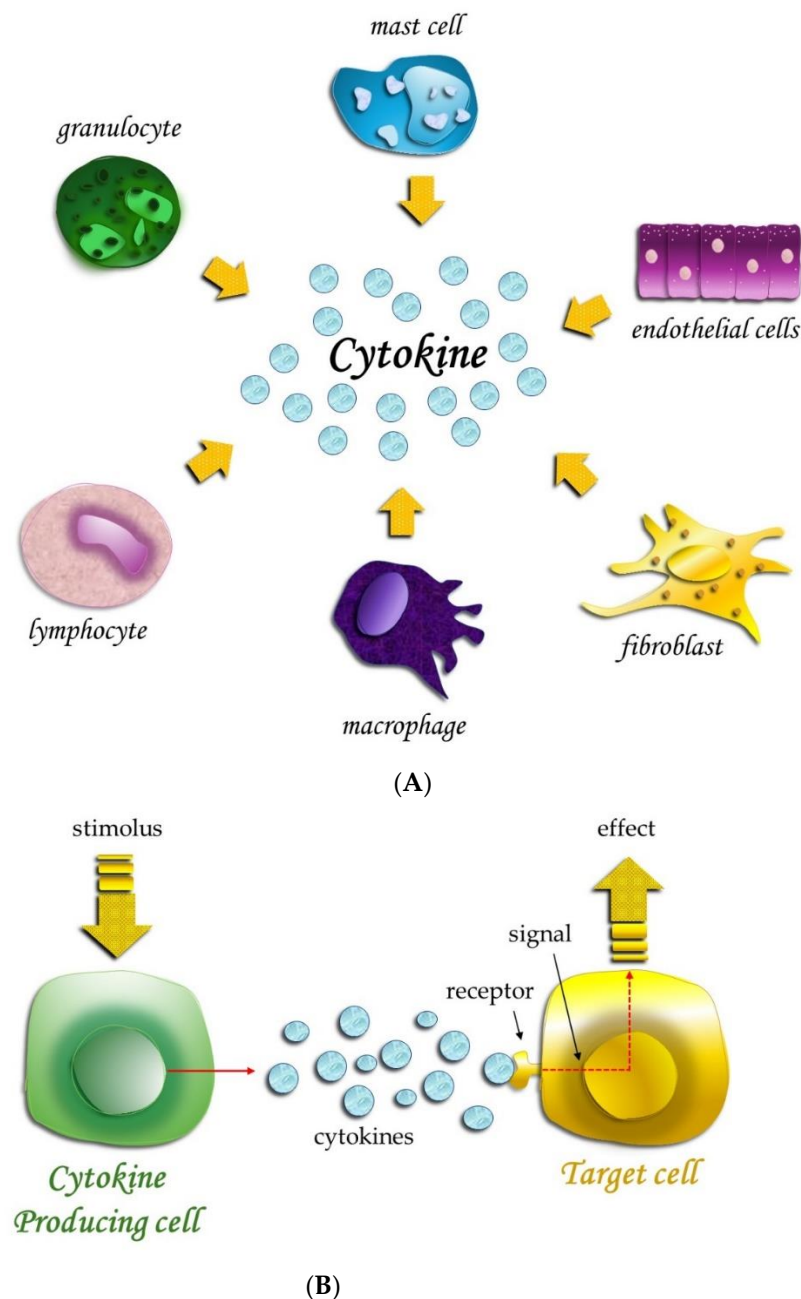


Figure 2. Cytokines, mainly produced by cells of the immune system, but also by epithelial cells and fibroblasts (A), induce a biological response in other cells by activating membrane receptors and signal transduction mechanisms (B).

Their short half-life in blood and extracellular fluids limits their range of action. The importance of cytokines in health and disease is evident in the processes of defense against infection, immune cell differentiation and responses, inflammation, sepsis, reproduction, viral pathogenesis, angiogenesis, and tumorigenesis [51]. Cytokines are also used in therapies, as natural immunostimulants to combat immunodeficiencies such as in AIDS, or to reduce the side effects of chemotherapy in cancer treatment [84,85].

It is, therefore, well understood that cytokines play a crucial role in orthodontic treatment, particularly in fixed orthodontics. They are fundamental in the regulation of inflammatory responses and bone remodeling, which are key processes during tooth movement. In-depth studies on the biological mechanisms of cytokines can improve the understanding of the initial phases of orthodontic treatment and any complications. Detailed knowledge of cytokines with more in-depth studies on biological mechanisms can lead to the identification of new therapeutic strategies, thus optimizing clinical outcomes and reducing treatment times. Therefore, the importance of cytokines in the orthodontic context cannot be underestimated.

2. Materials and Methods

2.1. Protocol and Registration

This review was carried out in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, and it was registered under the number CDR509520 on PROSPERO (The International Prospective Register of Systematic Reviews).

2.2. Search Processing

We limited our search to English-language papers published between 1 January 2013 and 7 January 2024 in PubMed, Scopus and ScienceDirect that were relevant to our topic. In the search approach, the Boolean keywords “cytokines AND OT” and “cytokines” AND “orthodontic therapy” were used. We selected these phrases because they most accurately reflected our investigation’s aim, which was to gain additional insight into the interaction between cytokines and orthodontic therapy (Table 1).

Table 1. Indicators for database searches.

Articles screening strategy	KEYWORDS: “A”: cytokines; “B”: OT; “C”: orthodontic therapy
	Boolean Indicators: “A” AND “B”; “A” AND “C”
	Timespan: 1 January 2013 to 7 January 2024
	Electronic databases: Pubmed; Scopus; ScienceDirect.

2.3. Inclusion Criteria

Three reviewers evaluated all relevant papers based on the following chosen criteria: (1) solely human subject studies; (2) complete text; and (3) scientific studies assessing changes in cytokine levels prior to, during, and following OT. The following process was used to construct the PICO model:

- Criteria: Application in the present study;
- Population: Human subjects;
- Intervention: Fixed OT;
- Comparison: Groups with differing fixed OT;
- Outcome: Evaluation of cytokines levels variations before during and after fixed OT;
- Study design: Clinical trials.

2.4. Exclusion Criteria

Articles written in languages other than English, ineligible study designs, ineligible outcome measures, ineligible populations, case studies, reviews, and animal studies were among the exclusion criteria.

2.5. Data Processing

Two independent reviewers (F.P. and L.F.) assessed the quality of the included studies according to pre-defined criteria, including criteria for selection, methods of outcome assessment, and data analysis. Also, the quality criteria concerned in this modified 'Risk of Bias' tool included selection, performance, detection, reporting, and other bias. Full texts were retrieved for any potentially relevant studies and then were identified according to the inclusion criteria. Any disagreements were resolved by discussion or consulting with a third researcher (F.I.).

2.6. Article Identification Procedure

An appropriateness evaluation was performed independently by two reviewers, F.I. and F.P. An additional manual search was conducted to increase the number of articles available for full-text analysis. English-language articles that met the inclusion criteria were taken into consideration, and duplicates and items that did not qualify were marked with the reason they were not included.

2.7. Study Evaluation

The article data were independently evaluated by the reviewers using a special electronic form designed according to the following categories: authors, year of study, aim of the study, materials and methods, and results.

2.8. Quality Assessment

Two reviewers, F.P. and I.T., evaluated the included papers' quality using the ROBINS-I tool. In order to evaluate the possibility of bias in the outcomes of non-randomized trials comparing the health impacts of two or more therapies, ROBINS-I was created. Each of the seven evaluated points was given a bias degree. F.I., the third reviewer, was consulted in the event of disagreement, and discussions were held until a consensus was reached. The reviewers were instructed on how to use the ROBINS-I tool and adhered to the guidelines in order to assess the potential for bias in seven different domains: confounding, participant selection, intervention classification, deviations from intended interventions, missing data, outcome measurement, and choice of reported results. Discussion and consensus were used to settle any differences or conflicts amongst reviewers in order to improve the assessments' objectivity and uniformity. In situations when agreement could not be reached, the final decision was made by a third reviewer. An extensive assessment of potential biases in the non-randomized studies included in this study was made possible by the use of ROBINS-E for bias assessment. It contributed to the overall evaluation of the caliber and dependability of the results by pointing out the evidence base's advantages and disadvantages. The writers of this review were able to reach more informed interpretations and conclusions based on the facts at hand by taking the risk of bias into account.

3. Results

After eliminating duplicates (480), a total of 1478 papers were obtained from the databases ScienceDirect (652), PubMed (701), and Scopus (125). This resulted in 998 articles. A total of 846 entries were eliminated after their titles and abstracts were examined. The writers were able to successfully obtain the remaining 152 papers and confirm their eligibility. A total of 111 items were eliminated in this process because they were off-topic. The qualitative analysis of the 18 final articles is included in this study (Figure 3). Each study's findings are presented in Table 2.

Table 2. A descriptive item selection summary.

Authors (Year)	Type of the Study	Aim of the Study	Materials	Results
Nunes L. et al. (2017) [85]	Controlled Longitudinal study	To detect and quantify cytokine levels in GCF during initial OT	The study sample included 15 healthy patients, undergoing OT at the Orthodontic Clinic of the Faculty of Dentistry of the State University of Rio de Janeiro. Periodontal monitoring was performed at each stage of the OT, with assessments of visible plaque and of bleeding on palpation. Furthermore, GCF samples were collected from specific teeth at different stages of OT, using Luminex technology for cytokine quantification.	The results showed that total cytokine levels in the GCF remained constant in teeth subjected to orthodontic forces, suggesting a constant response to the light mechanical stimulus exerted by the NiTi brace inserted for alignment and leveling. In the control group, the levels of many cytokines in the GCF decreased significantly over time.
Grant M. et al. (2012) [18]	Controlled longitudinal intervention study	This study investigates on changes in cytokines and biomarkers of bone and tissue metabolism within GCF from patients undergoing OT.	GCF was collected from 20 volunteers during different stages of OT using Periopaper™ strips. The samples were obtained at baseline, before appliance placement, and 10 weeks after the first appliance placement, with additional collection at specific intervals following the application of distalizing forces. Analysis included assessing various cytokines (GM-CSF, interferon-gamma, IL-1beta, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, and TNFalpha), tissue biomarkers (MMP-9, TIMP-1 and 2), and bone metabolism indicators (RANKL and OPG).	Orthodontic force application increased pro-inflammatory markers in GCF, including IL-1beta, IL-8, TNFalpha, MMP-9, TIMPs 1 and 2 at tension sites near canines. Compression sites also exhibited elevated levels of IL-1beta, IL-8 (after 4 h), MMP-9 (after 7 and 42 days), and RANKL (after 42 days).
Mohamed A. et al. (2019) [86]	Prospective study	The text addresses orthodontic tooth movement as a result of cellular elements and periodontal ligament fluid, which plays a crucial role in the normal functioning of the periodontal ligament that surrounds all teeth in the oral cavity.	The article reports the results of a study conducted on 30 patients undergoing premolar extractions, analyzing changes in IL-6 levels in the periodontal ligament during OT.	This study suggests that IL-6 could play a key role in bone remodeling during orthodontic movement and could be considered as a potential biomarker to improve efficacy and management.
Lin T. et al. (2021) [31]	Prospective study	This study aimed to investigate the regulation of Th17 on MMPs expression during OTM.	Eighteen children in OT provided GCF samples at different time points: application day (T0), one hour (T1), 24 h (T2), one week (T3), 4 weeks (T4), and 12 weeks (T5) post-orthodontic force application. Cytokines and MMPs in GCF were measured using a Multiplex Luminex analyzer, and PDL tissues were stimulated by IL-17.	It was found that the expression of IL-17 was correlated with MMPs. After rhIL-17 treatment, the expression of MMP-1, MMP-2, and MMP-9 were up-regulated significantly.
Chelărescu S. et al. (2021) [87]	Randomized clinical trial	This study aims to analyze inflammatory mediators, particularly cytokines such as IL1β and IL6, in healthy adolescents and young adults during the acute phase of OT.	The research involved 20 patients, aged between 11 and 16 and between 17 and 28 undergoing OT. Crevicular fluid was collected before and 24 h after orthodontic activation. Fluid volume was measured with Periotron 8000, and cytokines were analyzed by immunoenzymatic methods.	The study uses bone remodeling biomarker analysis in crevicular fluid to monitor orthodontic treatment efficiency. Results show increased crevicular fluid volume and IL1β levels 24 h after treatment, with adolescents experiencing faster tooth movement compared to young adults.

Table 2. Cont.

Authors (Year)	Type of the Study	Aim of the Study	Materials	Results
Şahin E. et al. (2022) [88]	Controlled clinical trial	The aim of this study was to compare the effectiveness of oral irrigators with interdental brushes in patients with fixed OT. Furthermore, biochemical data, particularly on IL-1 β concentrations in GCF, are presented, showing results favorable to the oral irrigator group.	There were two groups of patients with fixed OT. One of these used oral irrigator for oral hygiene, and the other interdental brushes.	The text suggests that the use of oral irrigators can have a positive impact on gum health, offering an effective alternative to interdental brushes, especially during fixed OT.
Madureira D.F. et al. (2015) [19]	Retrospective study	To analyze the expression of cytokines in GCF and PDL after mechanical stress.	Twenty-three healthy patients were included. The experimental group underwent a 0.980 N force for 1–28 days, while contralateral teeth served as controls. GCF and PDL samples were collected concurrently to analyze cytokines using cytometric bead array.	IL-6 production in the PDL significantly increased on day 1 after force application. Strong positive correlations between GCF and PDL in the experimental group were observed on days 3 (interferon-gamma), 7 (IL-10), 14 (IL-17A), and 28 (IL-17A, tumor necrosis factor-alpha), with strong negative correlations on days 14 (interferon-gamma) and 21 (IL-2, IL-10).
Nur Ozel et al. (2018) [89]	Prospective clinical study	To evaluate the impact of Rapid Maxillary Expansion (RME) on periodontal health, focusing on markers of oxidative stress and IL-1 β levels in GCF.	GCF samples collected and analyzed for oxidative stress markers (TAC, TOS, OSI), IL-1 β levels, and NO activity.	IL-1 β levels insignificantly increased. NO levels increased during RME, associated with force loading and sutural relapse. TAC and TOS levels varied between buccal and palatal sides, with higher palatal levels.
Gabriel Antônio dos Anjos Tou et al. (2022) [90]	Prospective clinical study	To explore the molecular and clinical complexities of passive OT in 20 patients with indications for interceptive OT, anterior open bite, and good oral hygiene.	Measurement of cytokine levels (IL-8, IL-1 β , IL-6, IL-10, TNF- α , and IL-12p70) in GCF. GCF samples collected at baseline, 24 h, and 7 days after bonding.	Increase in GCF cytokines observed 1 min to 1 h after bonding, peaking at 24 h, with a secondary peak at day 7. Insight into molecular dynamics of ILs during passive OT in children. Influence of lip pressure and perioral musculature on tooth movement and open-bite correction.
Sandra Sagar (2023) [91]	Prospective longitudinal study	To assess salivary levels of vitamin D3 and the pro-inflammatory cytokine IL-17A in OT patients.	Saliva samples collected from 97 patients aged 13 to 18 years with Class I malocclusion, analyzed by ELISA.	Significant decrease in mean salivary vitamin D3 levels from early to late phase, followed by stabilization in the log phase. Salivary levels of IL-17A decreased from early to late phase and further in the log phase. No significant gender-based differences in vitamin D3 levels.

Table 2. Cont.

Authors (Year)	Type of the Study	Aim of the Study	Materials	Results
Marzieh Karimi-Afshar et al. (2021) [92]	Descriptive–analytical study	To investigate the dynamics of IL-8 levels in GCF during OT.	GCF samples collected at different times: before OT, 24 h, 7 days, and 28 days after treatment. IL-8 levels measured using ELISA.	IL-8 concentration significantly decreased one day after treatment, followed by an increase at one and four weeks but did not reach baseline. Age groups (adolescents and adults) showed a significant difference in IL-8 concentration on the first day of treatment, with adults having lower IL-8 levels. No significant difference between sexes during the treatment period.
J. Amanda et al. (2018) [93]	Prospective clinical study	To investigate the dynamics of RANKL concentrations in GCF during early OT.	Patients aged 15 to 35 years divided into two experimental groups and a control group. RANKL concentrations analyzed by ELISA.	Passive slot bracket system showed higher RANKL concentrations at 168 h than the straight wire system.
Hosam Ali Baeshen et al. (2021) [72]	Cross-sectional comparative study	Investigate chemokines in saliva samples from patients treated with conventional lingual and labial fixed orthodontic appliances.	Forty saliva samples from subjects with lingual and labial braces.	CXCL8, CCL11, CCL2, and CCL5 showed higher secretion in subjects with labial braces. CXCL9 showed slightly higher secretion in subjects with lingual braces.
Hosam Ali Baeshen et al. (2021) [71]	Prospective comparative study	To analyze the impact of OT with lingual and labial fixed appliances.	Saliva samples from 20 patients with lingual appliances and 20 with labial fixed appliances.	Higher levels of CCL2, IL-17A, and IL-6 in patients with lingual braces compared to fixed labial braces. ELISA tests demonstrated lower levels of defensins (HNP-1, HNP-2, HBD-1, and HBD-2) in saliva of patients with lingual braces.
Abhilasha Khanal et al. (2015) [69]	Prospective comparative study	To analyze levels of IL-17A and RANKL in the GCF during OT in adolescents and young adults.	GCF samples collected from mesial, medial, and distal sides of the right maxillary canine. IL-17A and RANKL levels measured by ELISA.	Significant increase in IL-17A and RANKL levels in the treatment group compared with controls. Gender-specific differences observed, with males showing higher cytokine expression than females. Correlation between IL-17A and RANKL suggested a synergistic effect.
Agita Pramustika et al. (2018) [94]	Prospective experimental study	To examine the GCF of 18 patients before and after OT with passive self-ligating brackets and pre-ligated brackets.	Measure tumor necrosis factor- α (TNF- α) concentrations using ELISA kits.	TNF- α levels increased at 24 h in both experimental groups, decreasing significantly after 168 h in the passive elastomeric ligature group.

Table 2. Cont.

Authors (Year)	Type of the Study	Aim of the Study	Materials	Results
Bergamo et al. (2018) [62]	Randomized clinical trial	To investigate the correlation between bracket design and the ratio of five proinflammatory cytokines in GCF while exploring bacterial adhesion in the absence of tooth movement influence.	The study enrolled 20 participants aged 11 to 15 years. Conventional metallic brackets and two self-ligating brackets were affixed to maxillary incisors and canines. GCF samples were collected before and 60 days after bonding using standard filter paper strips. Cytokine levels (IL-12, IL-1 α , IL-1 β , IL-6, and TNF- α) were assessed through the LUMINEX assay. Checkerboard DNA–DNA hybridization analyzed the levels of red and orange bacterial complexes. Non-parametric tests were employed for data analysis at a 5% significance level.	Bracket design demonstrated an impact on cytokine levels and bacterial adhesion. This underscores the importance of considering bracket design in patients at risk of periodontal disease and root resorption.
Sinan Şen et al. (2019) [95]	Randomized clinical trial	To assess potential adverse biological effects of three commonly used surface sealants and a bonding primer on gingival tissues by analyzing cytokines in crevicular fluid following their application in orthodontic patients.	A single-center parallel trial with a split-mouth design was executed. Quadrants of 15 patients requiring OT with fixed appliances were randomly assigned to one of three surface sealants or a bonding primer. IL-8 and IL-10 levels in crevicular fluid were evaluated at four time points (before application, and at 30, 60, and 90 min after application).	The commonly used pre-bonding surface sealants did not exhibit a significant impact on inflammatory cytokine levels in crevicular fluid. Moreover, they did not seem to contribute to sensitization or hypersensitivity events, indicating their relatively benign biocompatibility in this study.

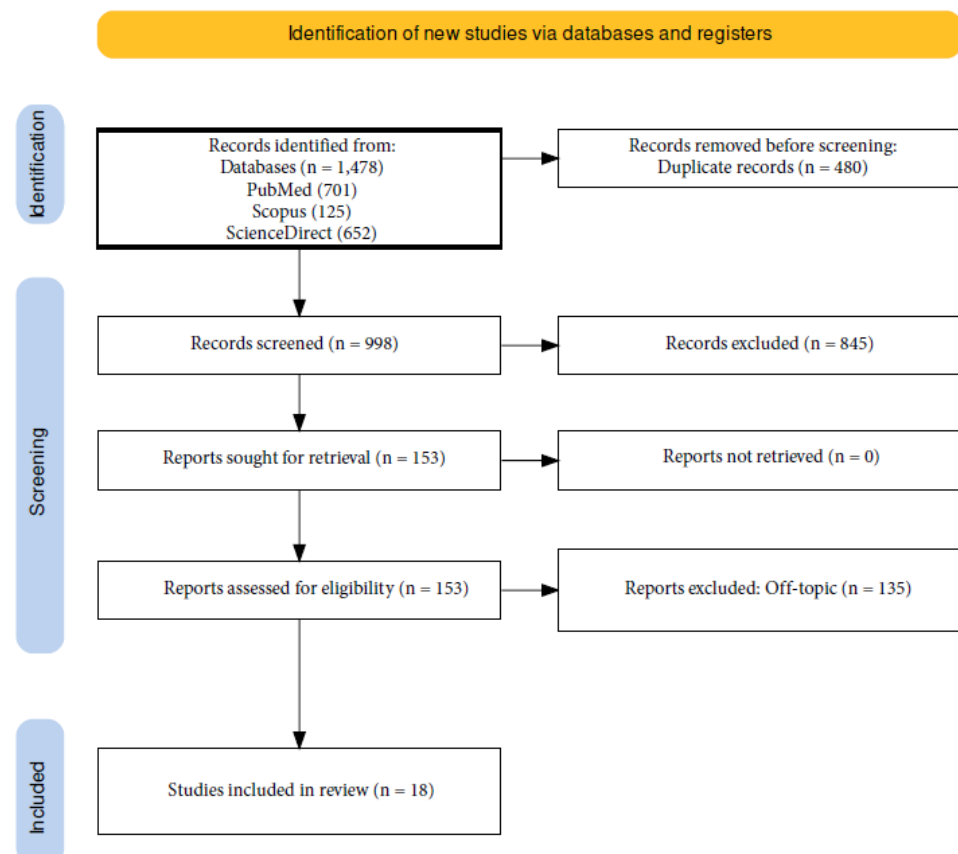


Figure 3. PRISMA flowchart of the literature search and article inclusion process.

Quality Assessment and Risk of Bias of Included Articles

The risk of bias in the included studies is reported in Figure 4. Regarding the bias due to confounding, most studies had a high risk. The bias arising from measurement is a parameter with low risk of bias. Many studies had low risk of bias due to bias in selection of participants. Bias due to post exposure could not be calculated due to high heterogeneity. The bias due to missing data was low in many studies. Bias arising from measurement of the outcome was low. Bias in the selection of the reported results was high in most studies. The final results show that 14 studies had a high risk of bias, 2 had a very high risk of bias, and 16 had a low risk of bias.

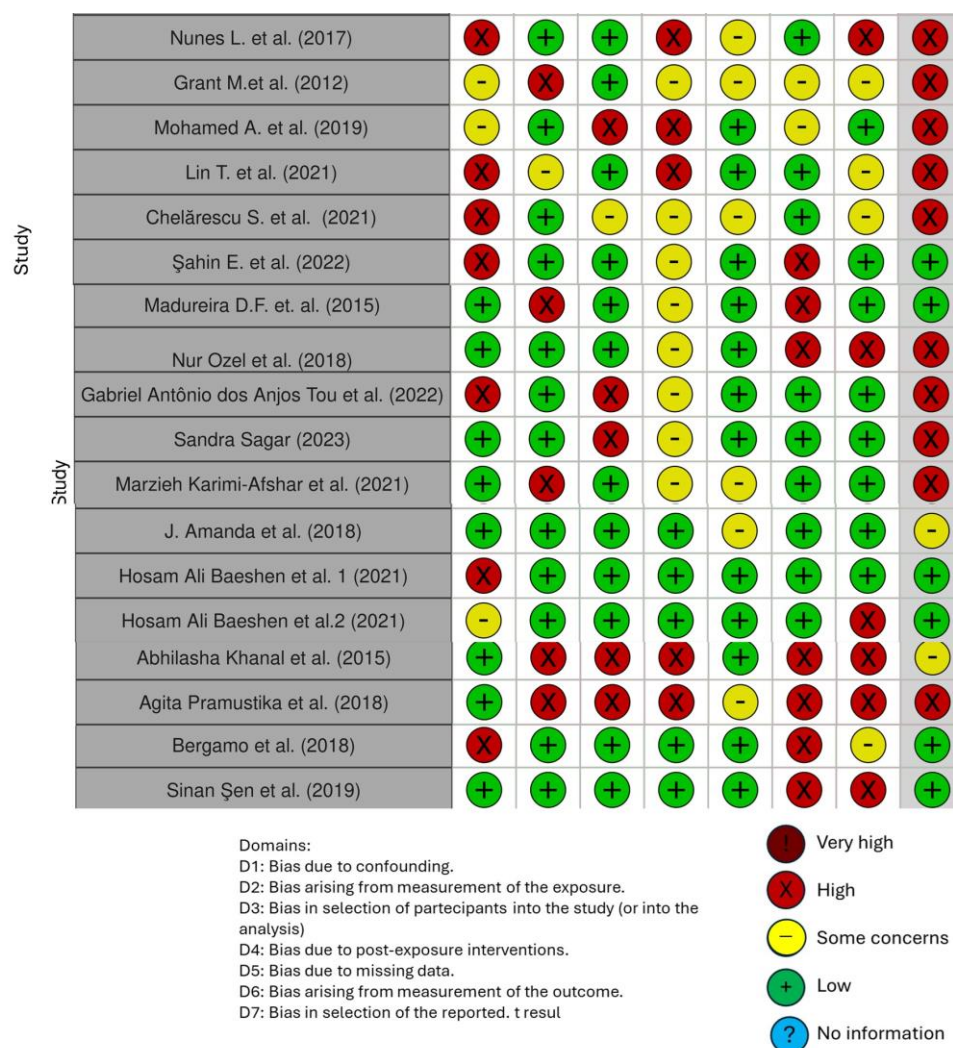


Figure 4. Bias assessment by Robins tool. Nunes L. et al. (2017) [85], Grant M. et al. (2012) [18], Mohamed A. et al. (2019) [86], Lin T. et al. (2021) [31], Chelărescu S. et al. (2021) [87], Şahin E. et al. (2022) [88], Madureira D.F. et al. (2015) [19], Nur Ozel et al. (2018) [89], Gabriel Antônio dos Anjos Tou et al. (2022) [90], Sandra Sagar (2023) [91], Marzieh Karimi-Afshar et al. (2021) [92], J. Amanda et al. (2018) [93], Hosam Ali Baeshen et al. (2021) [72], Hosam Ali Baeshen et al. (2021) [71], Abhilasha Khanal et al. (2015) [69], Agita Pramustika et al. (2018) [94], Bergamo et al. (2018) [62], Sinan Şen et al. (2019) [95].

4. Discussion

The production of specific cytokines in the laboratory is an area of active research. Applying a force of a certain magnitude, frequency, and duration to the teeth enables orthodontic tooth movement to the periodontal ligament, causing alveolar bone and pe-

riodontal ligament remodeling. Orthodontic tooth movement is preceded by an acute inflammatory response, characterized by vascular dilatation and increased vascular permeability. It is not only interesting to understand which and how many proinflammatory cytokines are activated and released, but also to understand the various types of braces used and the various orthodontic movements sought [96]. In order to do so, Nur Ozel et al. evaluated the impact of RME on periodontal health, specifically examining markers of oxidative stress and IL-1 β levels in GCF. A modified hyrax appliance was used for OT, and patients were monitored at various times, including activation and maintenance periods. Clinical parameters, including probing depth, gingival index, plaque index and bleeding on probing, were recorded throughout the duration of the study [89]. GCF samples were collected, and markers of oxidative stress (total antioxidant capacity (TAC), total oxidant state (TOS), oxidative stress index (OSI)) and IL-1 β levels were measured. In addition, nitric oxide (NO) activity was evaluated. The results indicated that RME had no adverse effects on periodontal tissues. The probing depth increased during the early stages but remained stable thereafter. GCF volume increased significantly during RME, attributed to mechanical trauma during device activation. IL-1 β levels showed an insignificant increase during RME, probably due to the minimal orthodontic forces applied. NO levels increased during RME, with higher values associated with force loading and sutural relapse in the retention period. TAC and TOS levels in GCF varied between the buccal and palatal sides, with higher palatal levels. The study concludes that RME had no adverse effects on periodontal tissues, and that the observed changes in oxidative status and IL-1 β levels can be explained by the orthopedic effect of applied forces [89]. Meanwhile, Gabriel Antônio dos Anjos Tou et al. explored the molecular and clinical complexities of passive OT by focusing on 20 patients who presented with indications for interceptive OT, had an anterior open bite, and maintained good oral hygiene and periodontal health. Exclusion criteria included systemic diseases, recent use of antibiotics or anti-inflammatory drugs, bleeding during GCF sampling, and presence of orthodontic accessories. The levels of cytokines—IL-8, IL-1 β , IL-6, IL-10, TNF- α and IL-12p70—in the GCF were measured. Spurs were bonded to the lingual surface of mandibular incisors, and GCF samples were collected from maxillary and mandibular central incisors at baseline, 24 h and 7 days after bonding. Notably, an increase in GCF cytokines was observed as early as between 1 min and 1 h after bonding, reaching a peak at 24 h, followed by a secondary peak at day 7. The study offers a unique insight into the molecular dynamics of ILs during passive OT in children, highlighting the influence of lip pressure and perioral musculature on tooth movement and open-bite correction [90]. Sandra Sagar's study aimed to assess salivary levels of vitamin D3 and the pro-inflammatory cytokine IL-17A in patients receiving fixed orthodontic therapy. The study included 97 patients aged 13 to 18 years with Class I malocclusion. The collected saliva samples were analyzed by ELISA for vitamin D3 and IL-17A levels. The results revealed a significant decrease in mean salivary vitamin D3 levels from early to late phase and a subsequent stabilization in the log phase. At the same time, salivary levels of IL-17A showed a decrease from early to late phase and a further decrease in the log phase. A comparison of vitamin D3 levels between genders showed no significant differences, contrary to some previous studies potentially influenced by demographic variations [91]. The descriptive-analytical study by Marzieh Karimi-Afshar et al. investigates the dynamics of IL-8 levels in GCF during OT. The research involved 20 orthodontic patients, including 10 adolescents (under 19 years old) and 10 adults (19 years and older). Inclusion criteria ensured good general health, no recent antibiotic or anti-inflammatory use, no periodontal disease, Class I malocclusion, permanent dentition, and no planned dental extraction. GCF samples were collected at different times: before OT and 24 h, 7 days, and 28 days after the start of treatment. IL-8 levels were measured by an ELISA method. The study revealed that IL-8 concentration significantly decreased one day after treatment compared to baseline, followed by an increase at one and four weeks after treatment, but did not reach baseline. Interestingly, the age groups (adolescents and adults) showed a significant difference in IL-8 concentration on the first day of treatment, with adults showing lower IL-8 levels. No

significant difference was observed between the sexes during the treatment period [92]. The prospective clinical study by J. Amanda et al. investigates the dynamics of RANKL concentrations in GCF during the initial stages of OT, specifically comparing the effects of Passive SL (Damon Q; Ormco) and PEA (MBT; Ormco) bracket systems. Patients, aged 15 to 35 years, were divided into two experimental groups and a control group. RANKL concentrations were analyzed by ELISA. The results revealed statistically significant differences in RANKL concentrations within the experimental groups, particularly in the passive SL group. Additionally, the study explored the impact of bracket systems on tooth movement and RANKL expression [18]. The passive SL bracket system showed higher RANKL concentrations at 168 h than the PEA system, attributed to different force systems and mechanotherapeutic aspects. This suggests a potential association between bracket systems, force application, and RANKL production during the early stages of OT. Understanding the nuanced responses of RANKL concentrations in the GCF to different bracket systems improves our understanding of orthodontic mechanotherapy, guiding clinicians in choosing bracket systems that are appropriate for patients' needs. Further investigations with extended follow-up periods and diverse patient populations are needed to corroborate and generalize these findings [93]. Hosam Ali Baeshen et al. aimed to investigate the chemokine levels in 40 saliva samples from patients treated with conventional lingual and labial fixed orthodontic appliances. Specifically, salivary chemokine secretion showed uniqueness between the lingual and labial appliance groups. CXCL8, CCL11, CCL2 and CCL5 showed higher secretion in subjects with labial braces, while CXCL9 showed slightly higher secretion in subjects with lingual braces. These variations in chemokine secretion suggest different impacts on the oral microenvironment, influencing inflammatory actions and long-term oral health [72]. The study by Hosam Ali Baeshen et al. analyzed the impact of OT with lingual and labial fixed appliances on salivary cytokine levels in a cohort of 40 patients. The saliva samples comprised 20 from patients with traditional lingual appliances and 20 from those with labial fixed appliances. The analysis focused on a panel of 13 cytokines, including IL-4, IL-2, CXCL10, IL-1 β , IL-17A, IL-6, IL-10, TNF- α , CCL2, IFN- γ , IL-12p70, CXCL8, and TGF- β 1 [72,97]. The results revealed significantly higher levels of CCL2, IL-17A, and IL-6 in patients with lingual braces compared with those with fixed labial braces. In addition, ELISA tests demonstrated lower levels of defensins (HNP-1, HNP-2, HBD-1, and HBD-2) in the saliva of patients with lingual braces. The results suggest that OT with lingual braces induces a distinct inflammatory response, as evidenced by the altered levels of cytokines and cellular composition in saliva. Despite the limitations of the study, including the relatively small sample size, these results provide valuable insights into the potential long-term effects of orthodontic appliances on oral health and tissue homeostasis. Further research is needed to elucidate the underlying signaling pathways and optimize orthodontic appliances to improve patient outcomes [71]. A study by Abhilasha Khanal et al. analyzed the levels of IL-17A and RANKL in the GCF of adolescents and young adults undergoing OT. The study aimed to analyze the impact of treatment duration on cytokine expression and to assess changes by gender.

Participants were divided into two groups: Group A (treatment group) with fixed braces and Group B (control group) without braces. GCF samples were collected from the mesial, medial and distal sides of the right maxillary canine, and IL-17A and RANKL levels were measured by an ELISA. The results indicated a significant increase in IL-17A and RANKL levels in the treatment group compared with controls. In addition, gender-specific differences were observed, with males showing higher cytokine expression than females. The correlation between IL-17A and RANKL suggested a synergistic effect. The results underscore the impact of OT on inflammatory processes, osteoclastogenesis, and OTM. The study emphasizes the importance of considering patients' sex and hormone levels in treatment planning, as women with higher estrogen levels showed lower cytokine expression and potentially slower OTM [69]. In a study by Agita Pramustika et al., the GCF of 18 patients, before and after OT with passive self-ligating brackets and pre-ligated brackets, was examined. Tumor necrosis factor- α (TNF- α) concentrations were measured at different

time points using ELISA kits. The results showed significant differences in TNF- α values between the experimental groups (self-ligating brackets and passive elastomeric ligature) and control groups after orthodontic force application. TNF- α levels increased at 24 h in both experimental groups, decreasing significantly after 168 h in the passive elastomeric ligature group. In contrast, levels remained elevated in the self-bonded bracket group, suggesting different inflammatory responses. The study provides insights into the dynamic changes in TNF- α during early orthodontic tooth movements and highlights the potential implications of bracket systems on inflammatory responses. These findings contribute to the understanding of cytokine involvement in bone remodeling during OT [94]. In a retrospective clinical study by Qian Liu et al., the correlation between inflammatory cytokine levels in saliva and the development of white spot lesions (WSL) following invisible orthodontic correction was explored. Saliva samples were collected at three distinct time intervals: before the placement of orthodontic appliances (T0), 6 months after placement (T1), and during follow-up evaluations. Analysis revealed significant differences in the transcript levels of various inflammation-related cytokines, including CXCL1, CXCL2, CXCL8, IL-1 β , IL-2, CCL3, and CCL4, between patients with WSL (WLG) and those without (nWLG). Further investigation showed that after treatment, the levels of CXCL8, CCL3, CCL4, IL-1 β and IL-2 in saliva increased significantly in both groups. Importantly, the WLG group showed significantly higher levels of these inflammatory cytokines than the nWLG group. These results underscore the significant role of inflammatory cytokines, particularly CXCL8, in the development of white spot lesions after OT with clear aligners in adolescents. The study suggests that monitoring and understanding the levels of these cytokines could serve as a valuable indicator to predict and prevent WSLs, helping to improve post-treatment outcomes in orthodontic patients [98]. Xiao Cen et al. studied the efficacy of glucosamine sulfate (GS) and hyaluronic acid (HA) in the treatment of osteoarthritis of the temporomandibular joint (OA). The GS + HA intervention involved intra-articular injection of sodium HA and GS hydrochloride tablets, while the control group received a placebo. Clinical outcomes, such as TMJ pain and maximum mouth opening, as well as laboratory results measuring proinflammatory cytokines in TMJ synovial fluid, were evaluated. The results of short- and long-term efficacy analysis indicated that both GS and HA injections alone were effective in relieving TMJ OA symptoms. The GS group showed significant improvements in pain relief, mouth opening, and reduction in proinflammatory cytokines compared with the placebo group, especially in the long term. Age-related differences were observed: younger patients had better short-term results, while both age groups showed similar long-term improvements. The study suggests that GS, in addition to HA injection, may have an impact on inflammation-associated cytokines, providing a potential therapeutic approach for TMJ OA patients [99].

This research underscores the importance of employing multiple approaches to managing orthodontic pain. While medications, like naproxen, can effectively control pain, it is also essential to consider psychological factors, such as anxiety and catastrophizing, that influence pain perception. In addition, the comparison between drugs and nonpharmacological therapies, such as LLLT, highlights the need for a personalized approach to optimize orthodontic pain management. Further research should explore more specific biological markers and deepen understanding of the underlying mechanisms of orthodontic pain to improve treatment strategies.

A study conducted by Ana Zilda Nazar Bergamo et al. extensively examined the impact of orthodontic brackets, focusing on the difference between self-ligating brackets and conventional brackets. The interesting finding concerns changes in cytokine levels and bacterial accumulation in GCF. The identification of increased TNF- α levels and increased bacterial presence in self-ligating brackets is a remarkable finding. These findings suggest that the choice of bracket type could influence the inflammatory response and the risk of bacterial accumulation. However, it is crucial to note that further research on larger samples and a focus on various orthodontic movements is needed to confirm and further investigate these findings [62]. Sinan Şen et al. addressed issues related to the application

of surface sealants, which are common during OT with fixed appliances. The main concern was the possible toxicity of monomers in resin-based sealants and their ability to cause inflammatory and immune responses [95].

A study by Nunes et al., 2017, aimed to detect and quantify cytokine levels in GCF during OT [85]. The study sample included 15 healthy patients who underwent OT. Periodontal monitoring was performed at each stage of OT, with assessments of visible plaque and bleeding on palpation. In addition, GCF samples were collected from specific teeth at different stages of OT using Luminex technology. Cytokine levels remained constant during orthodontic movement, suggesting a constant response to mechanical stimulus. Cytokines, proteins involved in inflammation, play a crucial role in biological processes associated with orthodontic tooth movement. However, the lack of uniformity in research methodologies makes it difficult to fully understand the molecular mechanisms of orthodontic movement. A text by Grant M. et al., from 2012, focuses the discussion on the effects of orthodontic force on periodontal tissues, focusing on the periodontal ligament, alveolar bone, and gums [18]. After force application, tension and compression occur in the periodontal ligament, triggering a cascade of molecular signals. Signal molecules include arachidonic acid metabolites, neurotransmitters such as substance P and calcitonin gene-related peptide, and second-type messengers such as cyclic cAMP, phosphoinositides, and diacylglycerol. These signals lead to the release of cytokines and growth factors that influence bone and tissue modulation. Cytokines, such as IL-1 β , IL-2, IL-5, IL-6, IL-8, TNF- α , and interferon-gamma. In particular, IL-1 β is associated with the acute inflammatory response and induction of bone resorption [100].

5. Conclusions

Comprehending the molecular mechanisms behind tooth movement requires an understanding of the release of cytokines during fixed orthodontic treatments. Tumor necrosis factors (TNFs), growth factors, and interleukins are examples of cytokines that are important for controlling the inflammatory response and bone remodeling, two processes that are necessary for healthy tooth movement.

According to recent research, the application of orthodontic forces results in the timely and localized release of several cytokines, which work in concert to start and continue the remodeling processes of bone and periodontal tissue. Elevated concentrations of pro-inflammatory cytokines, including IL-1 β , TNF- α , and IL-6, have been associated with the stimulation of osteoclasts, which are vital cells required for bone resorption during tooth movement. Moreover, the variation in cytokine response between patients implies that orthodontic treatments should be customized to account for individual biological variances in addition to biomechanical features. Expanding our understanding of molecular mediators and investigating pharmacological therapies that could regulate cytokine release could result in novel therapeutic approaches that maximize treatment efficacy and timing while reducing side effects and patient discomfort.

Author Contributions: Conceptualization, F.P., G.M., A.D.I., A.M.I., F.I., A.P., I.T., L.F., A.D.N., A.M. and A.D.I.; methodology, A.M. and G.M.; software, F.P. and A.D.I.; validation, F.I., G.D. and G.M.; formal analysis, A.P.; investigation, A.P., I.T. and F.I.; resources, A.D.N., G.M. and A.M.I.; data curation, F.P., A.M.I., G.M., L.F., A.D.I., G.D., A.M., A.P. and F.I.; writing—original draft preparation, L.F., G.M., A.D.I. and A.M.; writing—review and editing, F.P., L.F., I.T., A.D.I. and A.P.; visualization, G.M.; supervision, L.F., G.M., F.I. and G.D.; project administration, F.I. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

AGEs	advanced glycation end products
ATP	adenosine triphosphate
BMI	body mass index
cAMP	cyclic adenosine monophosphate
CD326	marker for epithelial cells
CD45+	marker for leukocytes
DMT2	type 2 diabetes mellitus
ELISA	enzyme-linked immuno-sorbent assay
ESP	elastomeric separator placement
GCF	gingival crevicular fluid
GM-CSF	granulocyte-macrophage colony-stimulating factor
GS	glucosamine sulfate
CXCL8	motif chemokine ligand 8
CXCL9	motif chemokine ligand 9
HA	hyaluronic acid
IL	interleukin
LLLT	low-level laser therapy
MI	mini-implants
MMPs	matrix metalloproteinases
NiTi	nickel titanium
NO	nitric oxide
OSI	oxidative stress index
OT	orthodontic treatment
OTM	orthodontic tooth movement
OA	osteoarthritis
OPG	osteopontin
OPN	osteopontin
OSI	oxidative stress index
Passive SL	passive self-ligating
PDL	periodontal ligament
PDT	photodynamic therapy
PEA	preadjusted edgewise appliance
PMICF	peri-miniscrew implant crevicular fluid
RME	rapid maxillary expansion
RANKL	receptor activator of nuclear factor κ -B ligand
SNPs	single-nucleotide polymorphism
SP	substance P
TAC	total antioxidant capacity
TGF	transforming growth factor
TGK- β 1	transforming growth factor-beta one
TIMPs	tissue inhibitors of MMPs
TMJ	temporomandibular joint
TNF	tumor necrosis factor
TOS	total oxidant state
VAS	visual analog scale
WSL	white spot lesions

References

1. Cytokine Storm and Sepsis Disease Pathogenesis. Available online: <https://pubmed.ncbi.nlm.nih.gov/28555385/> (accessed on 28 January 2024).
2. Kennedy, R.H.; Silver, R. Neuroimmune Signaling: Cytokines and the Central Nervous System. In *Neuroscience in the 21st Century*; Pfaff, D.W., Volkow, N.D., Rubenstein, J.L., Eds.; Springer International Publishing: Cham, Switzerland, 2022; pp. 883–922. [CrossRef]
3. Striz, I.; Brabcova, E.; Kolesar, L.; Sekerkova, A. Cytokine Networking of Innate Immunity Cells: A Potential Target of Therapy. *Clin. Sci.* **2014**, *126*, 593–612. [CrossRef]

4. Tamayo, E.; Fernández, A.; Almansa, R.; Carrasco, E.; Heredia, M.; Lajo, C.; Goncalves, L.; Gómez-Herreras, J.I.; de Lejarazu, R.O.; Bermejo-Martin, J.F. Pro- and Anti-Inflammatory Responses Are Regulated Simultaneously from the First Moments of Septic Shock. *Eur. Cytokine Netw.* **2011**, *22*, 82–87. [CrossRef] [PubMed]
5. Netea, M.G. Training Innate Immunity: The Changing Concept of Immunological Memory in Innate Host Defence. *Eur. J. Clin. Investig.* **2013**, *43*, 881–884. [CrossRef]
6. Silk, A.W.; Margolin, K. Cytokine Therapy. *Hematol. Oncol. Clin. N. Am.* **2019**, *33*, 261–274. [CrossRef] [PubMed]
7. Cui, A.; Huang, T.; Li, S.; Ma, A.; Pérez, J.L.; Sander, C.; Keskin, D.B.; Wu, C.J.; Fraenkel, E.; Hacohen, N. Dictionary of Immune Responses to Cytokines at Single-Cell Resolution. *Nature* **2024**, *625*, 377–384. [CrossRef]
8. Jarczak, D.; Nierhaus, A. Cytokine Storm-Definition, Causes, and Implications. *Int. J. Mol. Sci.* **2022**, *23*, 11740. [CrossRef] [PubMed]
9. Structural Biology of Shared Cytokine Receptors. Available online: <https://pubmed.ncbi.nlm.nih.gov/18817510/> (accessed on 28 January 2024).
10. Thomson, A.W.; Lotze, M.T.; Thomson, A.W.; Lotze, M.T. *The Cytokine Handbook, Two-Volume Set*, 4th ed.; Academic Press: Cambridge, MA, USA, 2003; ISBN 978-0-08-051879-4.
11. Balzanelli, M.G.; Distratis, P.; Aityan, S.K.; Amatulli, F.; Catucci, O.; Cefalo, A.; De Michele, A.; Dipalma, G.; Inchingolo, F.; Lazzaro, R.; et al. An Alternative “Trojan Horse” Hypothesis for COVID-19: Immune Deficiency of IL-10 and SARS-CoV-2 Biology. *Endocr. Metab. Immune Disord. Drug Targets* **2022**, *22*, 1–5. [CrossRef]
12. Liao, W.; Lin, J.-X.; Leonard, W.J. Interleukin-2 at the Crossroads of Effector Responses, Tolerance, and Immunotherapy. *Immunity* **2013**, *38*, 13–25. [CrossRef]
13. Ergoren, M.C.; Paolacci, S.; Manara, E.; Dautaj, A.; Dhuli, K.; Anpilogov, K.; Camilleri, G.; Suer, H.K.; Sayan, M.; Tuncel, G.; et al. A Pilot Study on the Preventative Potential of Alpha-Cyclodextrin and Hydroxytyrosol against SARS-CoV-2 Transmission. *Acta Bio Medica Atenei Parm.* **2020**, *91*, e2020022. [CrossRef]
14. Inchingolo, A.D.; Dipalma, G.; Inchingolo, A.M.; Malcangi, G.; Santacroce, L.; D’Oria, M.T.; Isacco, C.G.; Bordea, I.R.; Candrea, S.; Scarano, A.; et al. The 15-Months Clinical Experience of SARS-CoV-2: A Literature Review of Therapies and Adjuvants. *Antioxidants* **2021**, *10*, 881. [CrossRef]
15. Ballini, A.; Cantore, S.; Farronato, D.; Cirulli, N.; Inchingolo, F.; Papa, F.; Malcangi, G.; Inchingolo, A.D.; Dipalma, G.; Sardaro, N.; et al. Periodontal Disease and Bone Pathogenesis: The Crosstalk between Cytokines and Porphyromonas Gingivalis. *J. Biol. Regul. Homeost. Agents* **2015**, *29*, 273–281.
16. Ballini, A.; Gnoni, A.; Vito, D.D.; Dipalma, G.; Cantore, S.; Isacco, C.G.; Saini, R.; Santacroce, L.; Topi, S.; Scarano, A.; et al. Effect of Probiotics on the Occurrence of Nutrition Absorption Capacities in Healthy Children: A Randomized Double-Blinded Placebo-Controlled Pilot Study. *Eur. Rev. Med. Pharmacol. Sci.* **2019**, *23*, 8645–8657.
17. Inchingolo, A.D.; Carpentiere, V.; Piras, F.; Netti, A.; Ferrara, I.; Campanelli, M.; Latini, G.; Viapiano, F.; Costa, S.; Malcangi, G.; et al. Orthodontic Surgical Treatment of Impacted Mandibular Canines: Systematic Review and Case Report. *Appl. Sci.* **2022**, *12*, 8008. [CrossRef]
18. Grant, M.; Wilson, J.; Rock, P.; Chapple, I. Induction of Cytokines, MMP9, TIMPs, RANKL and OPG during Orthodontic Tooth Movement. *Eur. J. Orthod.* **2013**, *35*, 644–651. [CrossRef]
19. Madureira, D.F.; da Silva, J.M.; Teixeira, A.L.; Abreu, M.H.N.G.; Pretti, H.; Lages, E.M.B.; da Silva, T.A. Cytokine Measurements in Gingival Crevicular Fluid and Periodontal Ligament: Are They Correlated? *Am. J. Orthod. Dentofac. Orthop.* **2015**, *148*, 293–301. [CrossRef]
20. Vidmar Šimic, M.; Maver, A.; Zimani, A.N.; Hočevan, K.; Peterlin, B.; Kovanda, A.; Premru-Sršen, T. Oral Microbiome and Preterm Birth. *Front. Med.* **2023**, *10*, 1177990. [CrossRef]
21. Inchingolo, F.; Inchingolo, A.D.; Palumbo, I.; Trilli, I.; Guglielmo, M.; Mancini, A.; Palermo, A.; Inchingolo, A.M.; Dipalma, G. The Impact of Cesarean Section Delivery on Intestinal Microbiota: Mechanisms, Consequences, and Perspectives-A Systematic Review. *Int. J. Mol. Sci.* **2024**, *25*, 1055. [CrossRef]
22. Inchingolo, F.; Martelli, F.S.; Gargiulo Isacco, C.; Borsani, E.; Cantore, S.; Corcioli, F.; Boddi, A.; Nguyễn, K.C.D.; De Vito, D.; Aityan, S.K.; et al. Chronic Periodontitis and Immunity, Towards the Implementation of a Personalized Medicine: A Translational Research on Gene Single Nucleotide Polymorphisms (SNPs) Linked to Chronic Oral Dysbiosis in 96 Caucasian Patients. *Biomedicines* **2020**, *8*, 115. [CrossRef]
23. Di Francesco, F.; Lanza, A.; Di Blasio, M.; Vaienti, B.; Cafferata, E.A.; Cervino, G.; Cicciù, M.; Minervini, G. Application of Botulinum Toxin in Temporomandibular Disorders: A Systematic Review of Randomized Controlled Trials (RCTs). *Appl. Sci.* **2022**, *12*, 12409. [CrossRef]
24. Crescente, G.; Minervini, G.; Spagnuolo, C.; Moccia, S. Cannabis Bioactive Compound-Based Formulations: New Perspectives for the Management of Orofacial Pain. *Molecules* **2022**, *28*, 106. [CrossRef]
25. Pramstraller, M.; Simonelli, A.; Farina, R.; Trombelli, L. Biologically-Oriented Alveolar Ridge Preservation. *Minerva Dent. Oral Sci.* **2023**, *72*, 176–184. [CrossRef]

26. Hexiang, Z.; Ziyan, C.; Jing, W.; Zhenlin, G. Biomechanical Characteristics of Orthodontic Tooth Movement before and after Increasing Alveolar Bone Mass with Periodontally Accelerated Osteogenic Orthodontics. *Chin. J. Tissue Eng. Res.* **2024**, *28*, 2133–2139. [CrossRef]
27. Ramadanov, N.; Marinova-Kichikova, P.; Hable, R.; Dimitrov, D.; Becker, R. Comparison of Postoperative Serum Biomarkers after Total Hip Arthroplasty through Minimally Invasive versus Conventional Approaches: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Prosthesis* **2023**, *5*, 694–710. [CrossRef]
28. Osteoclast Activating Factor Is Now Interleukin-1 Beta: Historical Perspective and Biological Implications. Available online: <https://pubmed.ncbi.nlm.nih.gov/3139850/> (accessed on 28 January 2024).
29. Effects of Aging on RANKL and OPG Levels in Gingival Crevicular Fluid during Orthodontic Tooth Movement. Available online: <https://pubmed.ncbi.nlm.nih.gov/16918678/> (accessed on 28 January 2024).
30. Boyle, W.J.; Simonet, W.S.; Lacey, D.L. Osteoclast Differentiation and Activation. *Nature* **2003**, *423*, 337–342. [CrossRef]
31. Lin, T.; Yang, L.; Zheng, W.; Zhang, B. Matrix Metalloproteinases and Th17 Cytokines in the Gingival Crevicular Fluid during Orthodontic Tooth Movement. *Eur. J. Paediatr. Dent.* **2021**, *22*, 135–138. [CrossRef]
32. Cantarella, G.; Cantarella, R.; Caltabiano, M.; Risuglia, N.; Bernardini, R.; Leonardi, R. Levels of Matrix Metalloproteinases 1 and 2 in Human Gingival Crevicular Fluid during Initial Tooth Movement. *Am. J. Orthod. Dentofac. Orthop.* **2006**, *130*, 568.e11–568.e16. [CrossRef]
33. Expression of Genes for Gelatinases and Tissue Inhibitors of Metalloproteinases in Periodontal Tissues during Orthodontic Tooth Movement. Available online: <https://pubmed.ncbi.nlm.nih.gov/17043917/> (accessed on 28 January 2024).
34. Uematsu, S.; Mogi, M.; Deguchi, T. Interleukin (IL)-1 Beta, IL-6, Tumor Necrosis Factor-Alpha, Epidermal Growth Factor, and Beta 2-Microglobulin Levels Are Elevated in Gingival Crevicular Fluid during Human Orthodontic Tooth Movement. *J. Dent. Res.* **1996**, *75*, 562–567. [CrossRef]
35. Gentile, C.; Gruppioni, E. A Perspective on Prosthetic Hands Control: From the Brain to the Hand. *Prosthesis* **2023**, *5*, 1184–1205. [CrossRef]
36. Toti, Ç.; Kaçani, G.; Meto, A.; Droboniku, E.; Gurakuqi, A.; Tanellari, O.; Hysi, D.; Fiorillo, L. Early Treatment of Class II Division 1 Malocclusions with Prefabricated Myofunctional Appliances: A Case Report. *Prosthesis* **2023**, *5*, 1049–1059. [CrossRef]
37. Sammartino, G.; Gasparro, R.; Marenzi, G.; Trosino, O.; Mariniello, M.; Riccitello, F. Extraction of Mandibular Third Molars: Proposal of a New Scale of Difficulty. *Br. J. Oral Maxillofac. Surg.* **2017**, *55*, 952–957. [CrossRef]
38. Lombardo, G.; Signoriello, A.; Marincola, M.; Bonfante, E.A.; Díaz-Caballero, A.; Tomizioli, N.; Pardo, A.; Zangani, A. Five-Year Follow-Up of 8 and 6 Mm Locking-Taper Implants Treated with a Reconstructive Surgical Protocol for Peri-Implantitis: A Retrospective Evaluation. *Prosthesis* **2023**, *5*, 1322–1342. [CrossRef]
39. Vale, F.; Nunes, C.; Reis, J.; Travassos, R.; Ribeiro, M.; Marques, F.; Pedrosa, A.; Marto, C.M.; Paula, A.B.; Francisco, I. Pharyngeal Obturator Prosthesis Ideal for Orthodontic Appliances: A Case Series. *Prosthesis* **2023**, *5*, 1129–1138. [CrossRef]
40. Romeo, E.; Scaringi, R.; Lops, D.; Palazzolo, A. Single Crown Restorations Supported by One-Piece Zirconia Dental Implants: Case Series with a Mean Follow-Up of 58 Months. *Prosthesis* **2023**, *5*, 1060–1074. [CrossRef]
41. Scandurra, C.; Gasparro, R.; Dolce, P.; Bochicchio, V.; Muzii, B.; Sammartino, G.; Marenzi, G.; Maldonato, N.M. The Role of Cognitive and Non-cognitive Factors in Dental Anxiety: A Mediation Model. *Eur. J. Oral Sci.* **2021**, *129*, e12793. [CrossRef] [PubMed]
42. Soares Bonato, R.C.; Abel Mapengo, M.A.; de Azevedo-Silva, L.J.; Janson, G.; de Carvalho Sales-Peres, S.H. Tooth Movement, Orofacial Pain, and Leptin, Interleukin-1 β , and Tumor Necrosis Factor- α Levels in Obese Adolescents. *Angle Orthod.* **2022**, *92*, 95–100. [CrossRef] [PubMed]
43. Cantore, S.; Mirgaldi, R.; Ballini, A.; Coscia, M.F.; Scacco, S.; Papa, F.; Inchingolo, F.; Dipalma, G.; De Vito, D. Cytokine Gene Polymorphisms Associate with Microbiological Agents in Periodontal Disease: Our Experience. *Int. J. Med. Sci.* **2014**, *11*, 674–679. [CrossRef] [PubMed]
44. Balzanelli, M.G.; Distratis, P.; Lazzaro, R.; Pham, V.H.; Tran, T.C.; Dipalma, G.; Bianco, A.; Serlenga, E.M.; Aityan, S.K.; Pierangeli, V.; et al. Analysis of Gene Single Nucleotide Polymorphisms in COVID-19 Disease Highlighting the Susceptibility and the Severity towards the Infection. *Diagnostics* **2022**, *12*, 2824. [CrossRef] [PubMed]
45. Montemurro, N.; Perrini, P.; Marani, W.; Chaurasia, B.; Corsalini, M.; Scarano, A.; Rapone, B. Multiple Brain Abscesses of Odontogenic Origin. May Oral Microbiota Affect Their Development? A Review of the Current Literature. *Appl. Sci.* **2021**, *11*, 3316. [CrossRef]
46. Inchingolo, A.D.; Inchingolo, A.M.; Bordea, I.R.; Malcangi, G.; Xhajanka, E.; Scarano, A.; Lorusso, F.; Farronato, M.; Tartaglia, G.M.; Isacco, C.G.; et al. SARS-CoV-2 Disease through Viral Genomic and Receptor Implications: An Overview of Diagnostic and Immunology Breakthroughs. *Microorganisms* **2021**, *9*, 793. [CrossRef]
47. Inchingolo, A.D.; Gargiulo, C.I.; Malcangi, G.; Ciocia, A.M.; Patano, A.; Azzollini, D.; Piras, F.; Barile, G.; Settanni, V.; Mancini, A.; et al. Diagnosis of SARS-CoV-2 during the Pandemic by Multiplex RT-rPCR hCoV Test: Future Perspectives. *Pathogens* **2022**, *11*, 1378. [CrossRef]
48. SARS-CoV-2 Disease Adjuvant Therapies and Supplements Breakthrough for the Infection Prevention. Available online: <https://pubmed.ncbi.nlm.nih.gov/33806624/> (accessed on 1 February 2024).

49. Marrapodi, M.M.; Mascolo, A.; di Mauro, G.; Mondillo, G.; Pota, E.; Rossi, F. The Safety of Blinatumomab in Pediatric Patients with Acute Lymphoblastic Leukemia: A Systematic Review and Meta-Analysis. *Front. Pediatr.* **2022**, *10*, 929122. [CrossRef] [PubMed]
50. Di Paola, A.; Tortora, C.; Argenziano, M.; Marrapodi, M.M.; Rossi, F. Emerging Roles of the Iron Chelators in Inflammation. *Int. J. Mol. Sci.* **2022**, *23*, 7977. [CrossRef] [PubMed]
51. Crincoli, V.; Ballini, A.; Fatone, L.; Di Bisceglie, M.B.; Nardi, G.M.; Grassi, F.R. Cytokine Genotype Distribution in Patients with Periodontal Disease and Rheumatoid Arthritis or Diabetes Mellitus. *J. Biol. Regul. Homeost. Agents* **2016**, *30*, 863–866. [PubMed]
52. Saloom, H.F.; Papageorgiou, S.N.; Carpenter, G.H.; Cobourne, M.T. The Effect of Obesity on Orofacial Pain during Early Orthodontic Treatment with Fixed Appliances: A Prospective Cohort Study. *Eur. J. Orthod.* **2018**, *40*, 343–349. [CrossRef] [PubMed]
53. Do Prado, W.L.; Lofrano, M.C.; Oyama, L.M.; Dâmaso, A.R. Obesidade e adipocinas inflamatórias: Implicações práticas para a prescrição de exercício. *Rev. Bras. Med. Esporte* **2009**, *15*, 378–383. [CrossRef]
54. Malcangi, G.; Patano, A.; Ciocia, A.M.; Netti, A.; Viapiano, F.; Palumbo, I.; Trilli, I.; Guglielmo, M.; Inchingolo, A.D.; Dipalma, G.; et al. Benefits of Natural Antioxidants on Oral Health. *Antioxidants* **2023**, *12*, 1309. [CrossRef] [PubMed]
55. Inchingolo, F.; Inchingolo, A.M.; Latini, G.; Ferrante, L.; Trilli, I.; Del Vecchio, G.; Palmieri, G.; Malcangi, G.; Inchingolo, A.D.; Dipalma, G. Oxidative Stress and Natural Products in Orthodontic Treatment: A Systematic Review. *Nutrients* **2023**, *16*, 113. [CrossRef] [PubMed]
56. Profiles of Inflammation Factors and Inflammatory Pathways around the Peri-Miniscrew Implant. Available online: <https://pubmed.ncbi.nlm.nih.gov/33834451/> (accessed on 27 January 2024).
57. Interleukin-17, RANKL, and Osteoprotegerin Levels in Gingival Crevicular Fluid from Smoking and Non-Smoking Patients with Chronic Periodontitis during Initial Periodontal Treatment. Available online: <https://pubmed.ncbi.nlm.nih.gov/19656027/> (accessed on 28 January 2024).
58. LOX-1 Is Involved in IL-1 β Production and Extracellular Matrix Breakdown in Dental Peri-Implantitis. Available online: <https://pubmed.ncbi.nlm.nih.gov/28898769/> (accessed on 28 January 2024).
59. Che, C.; Liu, J.; Yang, J.; Ma, L.; Bai, N.; Zhang, Q. Osteopontin Is Essential for IL-1 β Production and Apoptosis in Peri-Implantitis. *Clin. Implant Dent. Relat. Res.* **2018**, *20*, 384–392. [CrossRef]
60. Andrucio, M.C.D.; Matsumoto, M.A.N.; Fukada, S.Y.; Saraiva, M.C.P.; Bergamo, A.Z.N.; Romano, F.L.; da Silva, R.A.B.; da Silva, L.A.B.; Nelson-Filho, P. Quantification of Pro-Inflammatory Cytokines and Osteoclastogenesis Markers in Successful and Failed Orthodontic Mini-Implants. *J. Appl. Oral Sci.* **2019**, *27*, e20180476. [CrossRef]
61. Kaur, A.; Kharbanda, O.P.; Kapoor, P.; Kalyanasundaram, D. A Review of Biomarkers in Peri-Miniscrew Implant Crevicular Fluid (PMICF). *Prog. Orthod.* **2017**, *18*, 42. [CrossRef]
62. Cytokine Profile Changes in Gingival Crevicular Fluid after Placement Different Brackets Types. Available online: <https://pubmed.ncbi.nlm.nih.gov/29032048/> (accessed on 27 January 2024).
63. Enhos, S.; Veli, I.; Cakmak, O.; Ucar, F.I.; Alkan, A.; Uysal, T. OPG and RANKL Levels around Miniscrew Implants during Orthodontic Tooth Movement. *Am. J. Orthod. Dentofac. Orthop.* **2013**, *144*, 203–209. [CrossRef] [PubMed]
64. Brambilla, E.; Locarno, S.; Gallo, S.; Orsini, F.; Pini, C.; Farronato, M.; Thomaz, D.V.; Lenardi, C.; Piazzoni, M.; Tartaglia, G. Poloxamer-Based Hydrogel as Drug Delivery System: How Polymeric Excipients Influence the Chemical-Physical Properties. *Polymers* **2022**, *14*, 3624. [CrossRef] [PubMed]
65. Gingival Crevicular Fluid Volume and Periodontal Parameters Alterations after Use of Conventional and Self-Ligating Brackets. Available online: <https://pubmed.ncbi.nlm.nih.gov/27607519/> (accessed on 28 January 2024).
66. Alterations in Plaque Accumulation and Gingival Inflammation Promoted by Treatment with Self-Ligating and Conventional Orthodontic Brackets. Available online: <https://pubmed.ncbi.nlm.nih.gov/25992985/> (accessed on 28 January 2024).
67. Gingival Crevicular Fluid Bone Turnover Biomarkers: How Postmenopausal Women Respond to Orthodontic Activation. Available online: <https://pubmed.ncbi.nlm.nih.gov/28651765/> (accessed on 27 January 2024).
68. Receptor Activator of NF(Kappa)B Ligand/Osteoprotegerin (RANKL/OPG) System and Osteopontin (OPN) Serum Levels in a Population of Apulian Postmenopausal Women. Available online: <https://pubmed.ncbi.nlm.nih.gov/17215793/> (accessed on 28 January 2024).
69. Khanal, A.; Hu, L.; Chen, L. Comparison of Expression Levels of RANKL and Interleukin-17A in Male and Female Orthodontic Patients with and without Appliances. *Int. J. Periodontics Restor. Dent.* **2015**, *35*, e28–e34. [CrossRef] [PubMed]
70. Pacifici, L.; Santacroce, L.; Dipalma, G.; Haxhiresha, K.; Topi, S.; Cantore, S.; Altini, V.; Pacifici, A.; De Vito, D.; Pettini, F.; et al. Gender Medicine: The Impact of Probiotics on Male Patients. *Clin. Ter.* **2021**, *171*, e8–e15. [CrossRef] [PubMed]
71. Baeshen, H.A. Assessment of Salivary pro Inflammatory Cytokines Profile Level in Patients Treated with Labial and Lingual Fixed Orthodontic Appliances. *PLoS ONE* **2021**, *16*, e0249999. [CrossRef] [PubMed]
72. Baeshen, H.A. Comparative Analysis of Growth Factors and Chemokine Secretions between Conventional Lingual and Labial Fixed Orthodontic Appliances. *Niger. J. Clin. Pract.* **2021**, *24*, 1438–1441. [CrossRef] [PubMed]
73. Ata-Ali, F.; Plasencia, E.; Lanuza-Garcia, A.; Ferrer-Molina, M.; Melo, M.; Ata-Ali, J. Effectiveness of Lingual versus Labial Fixed Appliances in Adults According to the Peer Assessment Rating Index. *Am. J. Orthod. Dentofac. Orthop.* **2019**, *155*, 819–825. [CrossRef] [PubMed]

74. Aziz, S.B.; Singh, G. Cytokine Levels in Gingival Crevicular Fluid Samples of Patients Wearing Clear Aligners. *J. Oral Biol. Craniofacial Res.* **2020**, *10*, 199–202. [CrossRef] [PubMed]
75. Yang, H.; Liu, J.; Yang, K. Comparative Study of 660 and 830 Nm Photobiomodulation in Promoting Orthodontic Tooth Movement. *Photobiomodul. Photomed. Laser Surg.* **2019**, *37*, 349–355. [CrossRef]
76. Photobiomodulation Impacts the Levels of Inflammatory Mediators during Orthodontic Tooth Movement? A Systematic Review with Meta-Analysis. Available online: <https://pubmed.ncbi.nlm.nih.gov/34599400/> (accessed on 28 January 2024).
77. Domínguez Camacho, A.; Montoya Guzmán, D.; Velásquez Cujar, S.A. Effective Wavelength Range in Photobiomodulation for Tooth Movement Acceleration in Orthodontics: A Systematic Review. *Photobiomodul. Photomed. Laser Surg.* **2020**, *38*, 581–590. [CrossRef]
78. Fernandes, M.R.U.; Suzuki, S.S.; Suzuki, H.; Martinez, E.F.; Garcez, A.S. Photobiomodulation Increases Intrusion Tooth Movement and Modulates IL-6, IL-8 and IL-1 β Expression during Orthodontically Bone Remodeling. *J. Biophotonics* **2019**, *12*, e201800311. [CrossRef] [PubMed]
79. Cronshaw, M.; Parker, S.; Anagnostaki, E.; Lynch, E. Systematic Review of Orthodontic Treatment Management with Photobiomodulation Therapy. *Photobiomodulation Photomed. Laser Surg.* **2019**, *37*, 862–868. [CrossRef] [PubMed]
80. Current Protocol to Achieve Dental Movement Acceleration and Pain Control with Photo-Biomodulation. Available online: <https://pubmed.ncbi.nlm.nih.gov/38229945/> (accessed on 28 January 2024).
81. Inchingolo, A.M.; Malcangi, G.; Inchingolo, A.D.; Mancini, A.; Palmieri, G.; Di Pede, C.; Piras, F.; Inchingolo, F.; Dipalma, G.; Patano, A. Potential of Graphene-Functionalized Titanium Surfaces for Dental Implantology: Systematic Review. *Coatings* **2023**, *13*, 725. [CrossRef]
82. Zhang, J.-M.; An, J. Cytokines, Inflammation and Pain. *Int. Anesthesiol. Clin.* **2007**, *45*, 27–37. [CrossRef] [PubMed]
83. Megha, K.B.; Joseph, X.; Akhil, V.; Mohanan, P.V. Cascade of Immune Mechanism and Consequences of Inflammatory Disorders. *Phytomedicine* **2021**, *91*, 153712. [CrossRef] [PubMed]
84. Conlon, K.C.; Miljkovic, M.D.; Waldmann, T.A. Cytokines in the Treatment of Cancer. *J. Interferon Cytokine Res.* **2019**, *39*, 6–21. [CrossRef] [PubMed]
85. Nunes, L.; Quintanilha, L.; Perinetti, G.; Capelli, J. Effect of Orthodontic Force on Expression Levels of Ten Cytokines in Gingival Crevicular Fluid. *Arch. Oral Biol.* **2017**, *76*, 70–75. [CrossRef] [PubMed]
86. Ozel, N.; Aksoy, A.; Kirzioglu, F.Y.; Doguc, D.K.; Aksoy, T.A. Evaluation of Interleukin-1 β Level and Oxidative Status in Gingival Crevicular Fluid during Rapid Maxillary Expansion. *Arch. Oral Biol.* **2018**, *90*, 74–79. [CrossRef] [PubMed]
87. Tou, G.A.D.A.; Diniz, I.M.A.; Ferreira, M.V.L.; de Mesquita, R.A.; Yamauti, M.; Silva, T.A.; Macari, S. Evaluation of Periodontal Parameters and Gingival Crevicular Fluid Cytokines in Children with Anterior Open Bite Receiving Passive Orthodontic Treatment with a Spur. *Korean J. Orthod.* **2022**, *52*, 142–149. [CrossRef]
88. Correlation of Salivary Cytokine IL-17a and 1,25 Dihydroxycholecalciferol in Patients Undergoing Orthodontic Treatment. Available online: https://www.researchgate.net/publication/371320269_Correlation_of_Salivary_Cytokine_IL-17a_and_125_Dihydroxycholecalciferol_in_Patients_Undergoing_Orthodontic_Treatment (accessed on 26 January 2024).
89. Karimi-Afshar, M.; Torabi, M.; Abdollahi, S.; Safarian, M.S.; Farsinejad, A. A Comparative Study on the IL-8 Expression in Gingival Crevicular Fluid during Early Alignment Stage of Orthodontic Treatment in Adults and Adolescents. *J. Kerman Univ. Med. Sci.* **2021**, *28*, 367–373. [CrossRef]
90. Amanda, J.; Widayati, R.; Soedarsono, N.; Purwanegara, M.K. RANKL Concentrations in Early Orthodontic Treatment Using Passive Self-Ligating and Preadjusted Edgewise Appliance Bracket Systems. *J. Phys. Conf. Ser.* **2018**, *1073*, 042002. [CrossRef]
91. Gujar, A.N.; Baeshen, H.A.; Alhazmi, A.; Bhandi, S.; Raj, A.T.; Patil, S.; Birkhed, D. Cytokine Levels in Gingival Crevicular Fluid during Orthodontic Treatment with Aligners Compared to Conventional Labial Fixed Appliances: A 3-Week Clinical Study. *Acta Odontol. Scand.* **2019**, *77*, 474–481. [CrossRef] [PubMed]
92. Comparison of Tumor Necrosis Factor- α Concentrations in Gingival Crevicular Fluid between Self-Ligating and Preadjusted Edgewise Appliances in the Early Leveling Stage of Orthodontic Treatment. Available online: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5863418/> (accessed on 26 January 2024).
93. Liu, Q.; Guo, T.; Dang, W.; Song, Z.; Wen, Y.; Luo, H.; Wang, A. Correlation between Salivary Cytokine Profiles and White Spot Lesions in Adolescent Patients Receiving Clear Aligner Orthodontic Treatment. *BMC Oral Health* **2023**, *23*, 857. [CrossRef] [PubMed]
94. Cen, X.; Liu, Y.; Wang, S.; Yang, X.; Shi, Z.; Liang, X. Glucosamine Oral Administration as an Adjunct to Hyaluronic Acid Injection in Treating Temporomandibular Joint Osteoarthritis. *Oral Dis.* **2018**, *24*, 404–411. [CrossRef] [PubMed]
95. Şen, S.; Orhan, G.; Zingler, S.; Katsikogianni, E.; Lux, C.J.; Erber, R. Comparison of Crevicular Fluid Cytokine Levels after the Application of Surface Sealants: A Randomized Trial. *J. Orofac. Orthop. Fortschritte Kieferorthopadie* **2019**, *80*, 242–253. [CrossRef]
96. Teixeira, C.C.; Khoo, E.; Tran, J.; Chartres, I.; Liu, Y.; Thant, L.M.; Khabensky, I.; Gart, L.P.; Cisneros, G.; Alikhani, M. Cytokine Expression and Accelerated Tooth Movement. *J. Dent. Res.* **2010**, *89*, 1135–1141. [CrossRef] [PubMed]
97. Mohammed, A.; Saidath, K.; Mohindroo, A.; Shetty, A.; Shetty, V.; Rao, S.; Shetty, P. Assessment and Measurement of Interleukin 6 in Periodontal Ligament Tissues during Orthodontic Tooth Movement. *World J. Dent.* **2019**, *10*, 88–92. [CrossRef]
98. Chelărescu, S.; Şurlin, P.; Decusară, M.; Oprică, M.; Bud, E.; Teodorescu, E.; Elsaafin, M.N.; Păcurar, M. Evaluation of IL1 β and IL6 Gingival Crevicular Fluid Levels during the Early Phase of Orthodontic Tooth Movement in Adolescents and Young Adults. *Appl. Sci.* **2021**, *11*, 521. [CrossRef]

99. Şahin, E.; Cetinkaya, B.O.; Avci, B.; Kurt-Bayrakdar, S.; Elekdag-Turk, S. Human Randomized Controlled Trail Clinical and Biochemical Evaluation Oral Irrigator Effectiveness in Patients Under Orthodontic Treatment. *preprint*, 2022. [[CrossRef](#)]
100. Santos, L.L.D.; Conti, A.C.C.F.; Fernandes, T.M.F.; Garlet, G.P.; Almeida, M.R.; Oltramari, P.V.P. Influence of Anxiety and Catastrophizing on Pain Perception in Orthodontic Treatment and Its Association with Inflammatory Cytokines. *Braz. Oral Res.* **2023**, *37*, e010. [[CrossRef](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.