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Research Article

Interleukin 17 (IL-17) and interleukin 23 (IL-23) levels are modulated by compressive orthodontic forces in humans

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ABSTRACT

Objective: The purpose of the investigation was to evaluate whether the application of compression forces exerted on the periodontal ligament during orthodontic movement is reflected at the level of interleukin (IL)-17 and IL-23.

Materials and methods: The gingival crevicular fluid (GCF) samples from the compression sites of 32 molars from 16 patients prescribed with modified Hyrax appliance were collected. The GCF were analyzed for IL-17, IL-23, and IL-1β (Control) at baseline and at 1, 7, and 14 days of active wear of the appliance.

Results: Orthodontic forces resulted in increased levels of IL-17 and IL-23 in the GCF, which were statistically significant at 7 days of force application at compression sites. At day 14, levels decreased to baseline; IL-1β levels (positive control) were more elevated at all times after force application. IL-17 and IL-23 levels were significantly lower than IL-1β, and undetectable in some samples.

Conclusion: Upregulation of IL-17 and IL-23 occurred in response to the force application in compression sites. Monitoring the levels of inflammatory mediators might be a clinically useful procedure, as they may help to define optimal forces to produce the most rapid tooth movement.

1. Introduction

Orthodontic tooth movement is based on forces that act on the periodontal ligament (PDL) and alveolar bone leading to its remodeling [1–3]. Mechanical stimuli applied to a tooth results in vascular changes that produce an aseptic and transient inflammatory response in periodontal tissues, where biological processes associated with alveolar bone resorption and new bone deposition occur [4]. Cytokines are key mediators of this complex process that leads to tooth movement under physiological conditions and during mechanical loading [5,6].

Of the cytokines implicated in inflammatory diseases, interleukin (IL)-17 and IL-23 have attracted great interest more recently. IL-17 has been associated with different pathologies and has been shown to modulate bone levels in the presence of inflammation [7]. Enhanced IL-17 expression is found in various inflammation models, such as rheumatoid arthritis, periodontitis, asthma, and organ rejection [8–10]. Recent reports suggest that IL-17 may play a role in processes that occur during tooth movement [11,12].

IL-23 is part of the IL-12 cytokine family [13]. This potent cytokine, produced by activated type 1 macrophages, monocytes, and dendritic cells [8,14,15], plays specific roles in the differentiation and expansion of memory T cells [16,17]. It has also been associated with a number of inflammatory diseases, such as rheumatoid arthritis and inflammatory bowel disease [10,18]. The IL-17–IL-23 axis seems to be a powerful mechanism by which cells of the innate immunity are recruited to an inflamed site [13], and has also been shown to be play a role in periodontal inflammation [8,16].

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This study examined the gingival crevicular fluid (GCF) of human teeth submitted to compressive orthodontic forces to determine the levels of IL-17 and IL-23.

2. Materials and methods

2.1. Participants

This study was approved by the Scientific and Ethics Committee of the School of Dentistry (protocol #38172) and the Institutional Review Board of Pontifícia Universidade Católica do Rio Grande do Sul. Before inclusion, participants and their guardians agreed to participate and signed an informed consent. The study sample included 16 study participants (ages 7–14 years; 10 boys, 6 girls) undergoing orthodontic treatment at the postdoctoral orthodontic clinic. All underwent opening of the palatal suture as the first phase of orthodontic treatment, rapid maxillary expansion (RME).

The inclusion criteria included the following: (1) malocclusion that required RME; (2) no use of anti-inflammatory, antibiotic, or immunosuppressive drugs in the previous 6 months and during the study course; (3) probing depth, measured as the distance from the gingival margin to the most apical portion of the sulcus; (4) no loss of periodontal attachment, defined as the distance between the bottom of the sulcus to the cementoenamel junction and no recessions; (5) no evidence of periodontal bone loss on periapical radiographs; (6) no syndromes or cleft lip and palate; (7) no bleeding on probing or suppuration in the target areas of analysis; and (8) nonsmokers.

2.2. Periodontal assessment

Patients were stringently screened for the presence of bleeding before and during the whole course of the assessment to avoid the interference of plaque-related inflammation in the composition of the GCF. Therefore, patients were preliminarily examined for the presence of inflammation - bleeding on probing (BOP) using a periodontal probe (PCP, UNC 15; Hu-Friedy, Chicago, IL) by gently scanning the gingival sulcus at a depth of approximately 2 mm. All participants received full mouth gentle scaling, as no major deposits were observed, and crown polishing with a soft rubber cup and prophylactic paste before appliance installation. Oral hygiene instructions were given to the guardians and study participants, which included the correct use of toothbrush, dental floss, and interdental brush when applicable. Patients who presented BOP at the preliminary assessment were enrolled in the study at least 2 weeks after the scaling and implementation of ideal oral hygiene parameters so as to enable enough time for resolution of the inflammation [19]. Also, periodontal conditions were assessed at each visit throughout the course of the study. At the time of GCF collection, no bleeding was observed in any of the participants at all timepoints.

2.3. Appliance

Orthodontic bands were placed on the patients' maxillary first molars for fabrication of a modified Hyrax appliance, as previously described [19]. The gingival band margins were trimmed to be placed supragingivally. After that, the bands were disinfected using alcohol and then dried. Transbond Plus glass ionomer cement (Multi-Cure Ionomer Orthodontic Band Cement; 3M Unitek, Monrovia, CA) was mixed according to the manufacturer's instructions. The bands were placed, and any excess cement was removed from the occlusal and cervical margins of the bands and the teeth. All band selections and cementations were performed by the same clinician (S.A.). The cement was light cured (QHL75 halogen curing light; Dentsply, Addlestone, Surrey, UK) for 30 seconds from the occlusal side [20]. One week after placement, the jackscrew was activated once (0.25 mm) by the operator (S.A.) and once by the patient or his or her guardian (total activation, 0.5 mm). The second activation occurred 24 hours later by the patient (or guardian) in the orthodontist's presence. Then the patient (or guardian) turned the jackscrew once in the morning and once in the evening (0.5 mm every 24 hours) until the planned expansion was achieved. For the patients in this sample, this occurred on the 19th day after initial activation. At this point, the screw was stabilized by tying it with a 0.010-inch-diameter metallic ligature. Patients were followed up every 7 days during the period of appliance activation and for a total of 14 days. A commonly used continuous heavy orthopedic force was reactivated daily. All clinical data were collected by a single investigator.

2.4. Collection of GCF

The patients were examined at baseline and at 1, 7, and 14 days of active appliance wear. Clinical data were collected from the buccal aspects of the maxillary right and left first molars, that is, pressure sites subjected to the orthodontic force. Briefly, the teeth included in the study were isolated with cotton rolls and gently dried with a brief air stream, and the surfaces were checked for absence of plaque; then a paper strip (Periopaper; ProFlow Inc., Amityville, NY) was gently introduced within 2 mm of the gingival sulcus of the target site and maintained in position for 20 seconds. The paper strips were transferred to two separate sterile 600 μL tubes containing 50 μL of sterile phosphate-buffered saline (pH 7.2) each. The tubes were maintained on ice throughout the whole process. Samples were further processed as previously described [21]. Briefly, the tubes containing the strips were gently vortexed and centrifuged at 4°C for 30 seconds at 1000 rpm on a tabletop centrifuge for post-elution and enrichment of the sample; then samples collected from the same individual were pooled in a separate 600-μL tube, bringing the final volume of the diluted sample to 100 μL. After processing, the samples were stocked at −80°C until total protein analysis and IL concentration determination. Although measurements of the periodontal parameters were not blinded, the examiner was not aware of previous scores. All laboratory analyses were performed by using a coding system, which was revealed to the examiner only after the completion of the analyses.

2.5. Measurement of IL levels

GCF samples of the mesiobuccal sites (pressure sites) were analyzed for IL-17, IL-23, and IL-1β (control) activity. Before analysis, a 1-μL sample was used to estimate total protein concentration using a fluorescence-based system according to the manufacturer's protocol (QuBit; Invitrogen, Carlsbad, CA) for better standardization of the total volume used in the analysis and to comply with the capabilities of the protein analysis system chosen. Levels of the target ILs were determined using a fluorescence-based multiplex quantitative array platform based on sandwich enzyme-linked immunosorbent assay technology (Quantibody Array; Raybiotech, Inc., Norcross, GA). Briefly, after bringing samples to room temperature, the entirety of the pooled sample, that is, 100 μL, was loaded into the array chips. The stock multiplex cytokine standard mix provided with the kit was serially diluted and loaded in the cytokine array. The chips were incubated overnight under constant agitation at 4°C and then washed. Detection antibody cocktail was added and incubated at room temperature for 2 hours and washed, followed by incubation with a Cy3-equivalent dye-conjugated streptavidin. The chips were protected from light and incubated

at room temperature for 1 hour and then washed copiously. The chips were then dried through a swinging-bucket centrifuge at 1000 rpm for 3 minutes and transferred to a digital scanner (Genepix 4000B, Molecular Devices, San Jose, CA). Chips were scanned at a wavelength of 532 nm (Cy3 dye channel) and photomultiplier and power levels set at 550 and 100, respectively. The images containing the chips' fluorescences were collected using the scanner proprietary software (GenePix Pro 6.0; Molecular Devices) and used to generate GAL files; final analysis against the multiplex standard array was carried out by plotting the GAL files data into a Excel spreadsheet (Quantibody Analysis Tool; Raybiotech, Inc.). Levels of the target cytokines were expressed as concentrations (ng/mL) within a cytokine-specific detection range that was variable for each cytokine (IL-1β = 3 pg/mL–2000 pg/mL; IL-17 = 11 pg/mL–8000 pg/mL; IL-23 = 14 pg/mL–10,000 pg/mL).

2.6. Statistical analysis

Descriptive statistics were calculated for all variables and the Levene test was used to check for distribution. The Friedman nonparametric test followed by Dunn's post hoc were used to assess differences among IL levels at a 5% confidence level. All statistical analyses were conducted using a statistical software (Prism 6 for Mac; GraphPad, La Jolla, CA) and differences were considered significant if $P < 0.05$.

3. Results

3.1. Clinical findings

The RME appliances were well tolerated and no adverse responses were observed. Throughout the course of the study, patients complied with oral hygiene and there were no changes in the position of the gingival margin or signs of inflammation (data not shown). Also, no significant changes in probing depths were observed.

3.2. Cytokine levels

Changes in the mean levels of IL-17, IL-23, and IL-1β are shown in Figures 1-3. At baseline, in most of the samples, there were basal levels of all the cytokines. Nevertheless, in some samples, levels were not detectable. Overall, orthodontic forces applied on target teeth resulted in increase of the detection levels of the three cytokines analyzed. For IL-17 and IL-23, a similar expression pattern was observed; at day 1, the values for the experimental sites had no significant differences from baseline values. The earlier changes in IL-17 and IL-23 levels that were detected in the model adopted herein appeared in the seventh day of force application ($P \leq 0.05$),

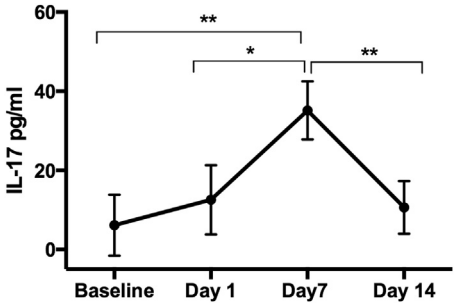

Fig. 2. Mean values and standard deviations (SD) of interleukin (IL)-17 (pg/mL) on compression sites at different time points.(*$P < 0.05$; **$P < 0.01$).

with a progressive decrease after that. At day 14, the levels of both cytokines resembled those of baseline. IL-1β, which was used as a positive control, presented a faster upregulation in response to the compression force, which was significant after 1 day of force application and remained significantly different from baseline until day 7, with a progressive decrease after that. Still, at all time points the mean levels of IL-1β were higher than IL-17 and IL-23 (Table 1).

4. Discussion

Tooth movement is a complex process that mobilizes a myriad of cell subpopulations and soluble proinflammatory molecules that act to effect bone resorption. Regulatory mediators aid in the process of orchestrating the events that lead to bone remodeling, whereas effector molecules directly play a role in the degradation and renovation of the extracellular matrix. Several biomarkers of this inflammatory process, produced by the periodontal ligament cells, diffuse into the GCF [20]. The identification of the degree of remodeling in periodontal tissues during orthodontic treatment through monitoring the levels of biochemical mediators may be a clinically useful procedure because these mediators play important roles in tooth movement, as well as in tissue damage. A number of studies have reported that cytokines are promptly regulated in the periodontium during orthodontic movement [6]. The present study showed that rapid expansion orthodontic movement can lead to changes in the levels of IL-17 and IL-23, which were more significant at 7 days within the conditions and forces used in this study. It has been reported that compression of the PDL vascular complex leads to ischemia that results in tissue necrosis [2]. So, the presence of immune cells in an environment devoid of bacteria is likely related to the presence of damaged host cells and the need to recruit inflammatory cells. IL-17 is part of a relatively newly identified group of cytokines that play key roles in bone remodeling and intermediating a switch in the cell-mediated immune response. It

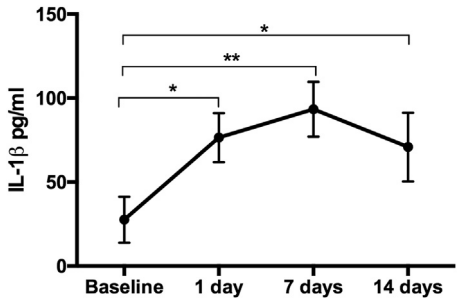

Fig. 1. Mean values and standard deviations (SD) for interleukin (IL)-1β (pg/mL) throughout the course of the study at different time points (*$P < 0.05$; **$P < 0.01$).

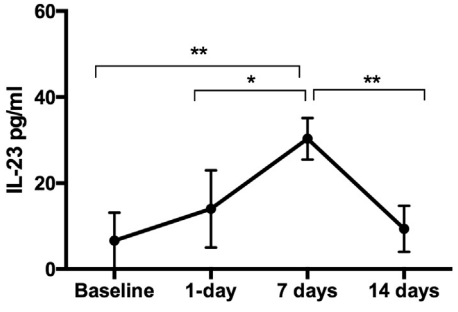

Fig. 3. Mean values and standard deviations (SD) of interleukin (IL)-23 (pg/mL) on compression sites at different time points (*$P < 0.05$; **$P < 0.01$).

Table 1
Mean IL-1β fold-change relative to IL-17 and IL-23

Cytokine	Baseline	1 day	7 days	14 days
IL-17	1.91	3.70[a]	1.23[b]	4.27[a]
IL-23	2.14[b]	3.15[b]	1.30[b]	2.43[b]

IL, interleukin.
[a] $P < 0.01$.
[b] $P < 0.05$.

intermediates the transition toward appropriate antigen-specific effector mechanisms [13]. Therefore, even though it involves a subset of T-helper cells (i.e., T_H17), these mediators are predominantly related to the inflammation by recruiting neutrophils and setting the stage later for the Th1/Th2 response when applicable [10,13]. IL-23 is secreted by macrophages and drives a T-cell population that produces IL-17; however, more recent reports show that other signals are necessary that are related to the presence of IL-6 and IL-1β, which are also upregulated during orthodontic movement [6]. Interestingly, other cytokines that are related to immune processes have been shown to be expressed in the periodontium in response to orthodontic forces as well [22–24]. Although there was a progressive increase in the levels of the cytokines, the mean levels of IL-17 and IL-23 were not as high as those for IL-1β, and in some samples neither one (i.e., IL-17 or IL-23) was detected. In point of fact, IL-1β seems to be promptly upregulated during orthodontic movement in fairly elevated levels [19], which is why it was picked as a positive control. Results from others suggest that cytokine expression and time-related changes are related to factors such as the side from which samples are being collected, that is, if compressive or tension sides [6], and even the age of the subjects [25]. Our findings seem to be supported by studies in rats showing that after application of an orthodontic force there is an increase the number of IL-17–positive cells [11]. These alterations coincide with the increase in TRAP-positive multinucleated cells and formation of resorption lacunae. The magnitude of the force may have an implication in the local response, as IL-17 and the influx of T_H17 cells increases with higher forces [11], and have been claimed to be a potential cause of root resorption.

IL-23 has been shown to be an important modulator of Th17 cell differentiation and IL-17 production [16]. Participation of the IL-17–IL-23 axis in the pathogenesis of inflammation and autoimmune alterations has been reported [10], including periodontal disease [26] and endodontic lesions [27].

It is difficult to pinpoint the exact roles these cytokines are playing in orthodontic movement, but it is feasible to consider that a direct role in bone resorption and/or root resorption takes place as previously suggested [11]. The higher levels of the cytokines and significant differences between values at baseline and 7 days after activation of the HYRAX appliance may explain the fact that in inflammatory environment, IL-23–IL-17 axis may promote additional inflammatory cascades by stimulating the production of chemokines that recruit and activate granulocytes. Upregulated IL-17 induces local inflammation, produces inflammatory and osteoclastogenic mediators, such as tumor necrosis factor-α, and promotes the expression of receptor activator of nuclear factor kB ligand (RANKL) [28,29]. IL-17 also has potential angiogenic effects, promoting migration of endothelial cells [9]. Along with its effects activating T_H17 cells, IL-23 also seems to have a broader function and modulate bone resorption by inducing expression of RANKL in some cell types [30]. The decrease of IL-17 and IL-23 levels after 7 days is explained by the decrease in osteoclastic activity after tooth movement.

ILs may be found in the absence of clinical inflammation of the tissues [8,23], something that was also observed in our results. The fact that ILs play an essential role in the innate immune mechanisms that maintain homeostasis may explain the presence of IL-17 and IL-23 at baseline in our study. Also, low production of IL-23 and IL-17 in steady state might primarily act to fortify the epithelial barrier and inhibit bacterial colonization [15,31]. Classically, IL-23 is capable of differentiating and expanding memory T cells, promoting differentiation of the Th17 cell and increasing the production of IL-17, which is indicative of the importance of the IL-23-IL-17 axis [13,18,32]. Noteworthy, the array technology, which used multiplex analysis with lower sample working volumes, enabled a reduction in the dilution of the GCF samples and more efficient detection even in relatively low concentrations. However, even with a relatively wide detection range of the system, some of our samples presented nondetectable levels of IL-17 and IL-23, which may suggest that tissue responses to the applied forces may be dependent on other factors as well. Data from others [11] showed that the number of T_H17-positive cells during orthodontic movement in rats depends on the magnitude of the force applied, suggesting that more cell damage caused by excessive forces can lead to the generation of biochemical signals, which will lead to more cells assuming a T_H17 phenotype. Thus, there could be some individual variation in the tissue response to the force applied, affecting the changes in cytokine levels. More recently it has been shown that IL-17 upregulates the expression of IL-6 and MMP-1 in human periodontal ligament cells, leading to collagen degradation associated with orthodontic tooth movement [33].

The overall concentrations of IL-17 and IL-23 were fairly lower that those of IL-1β throughout the course of study, and although the levels of IL-17 increased 1 day after force application, levels at the experimental sites were not significantly different from baseline values. Later on, after the initial signal caused by cell damage and vascular changes has been processed, the initial inflammatory response has been replaced with the appropriate inflammatory/immune effector functions, which included an influx of activated T cells [7,15,34] and the signal to differentiate into T_H17.

Effective immune responses are essential for the eventual eradication of the aggressive agent [13,32], which in our case was the force-associated damaged structures/cells produced by the expansion appliance. It is interesting to note that, at least based on clinical parameters, no plaque-induced inflammation was present. In the periodontal milieu, it is not feasible to obtain a surface that is totally devoid of bacteria, but oral hygiene measures can reduce the numbers of pathogenic species that lead to subclinical changes. Nevertheless, some impact of bacteria-induced inflammation in the results presented cannot be ruled out. Therefore, within the limitations imposed by the clinical parameters of inflammation, all alterations in the cytokine levels are assumed to be related to the orthodontic compressive forces.

5. Conclusion

Within the conditions of the present investigation, IL-23 and IL-17 are upregulated in orthodontic compressive sites, although at levels significantly lower and sometimes below detection. There was a peak in the levels of both that occurred at 7 days, with a progressive decrease afterward. The exact role of the IL-17–IL-23 axis in orthodontic treatment has yet to be determined; it may be part of the protective physiological cascade of events that leads to bone remodeling in response to forces or it may be related to responses to forces that are detrimental to the tissues and a more effective way of clearing damaged cells. The levels of biochemical mediators in GCF might be ultimately used as parameters to improve the effectiveness of orthodontic treatment, as they may help to define optimal forces to produce the most rapid tooth movement with the fewest undesirable side effects.

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