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Interleukins 2, 6, and 8 levels in human gingival sulcus during orthodontic treatment

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Introduction: The aims of this study were to determine levels of interleukins 2, 6, and 8 during tooth movement, and test whether they differ from each other with leveling and distalization forces used in various treatment stages of standard orthodontic therapy. **Methods:** Fifteen patients (9 female, 6 male; ages, 15-19 years; mean age, 16.7 ± 2.3 years) participated in this study. Each underwent a session of professional oral hygiene and received oral hygiene instructions. Two months later, a fixed orthodontic appliance was placed. The patients were seen at baseline, at days 7 and 21, and as the teeth were leveled. Records of the baseline scores for the distalization forces were taken at the sixth month. Scores of days 7 and 21 after 6 months of the distalization treatment were also recorded. **Results:** Increases were seen in the volume of gingival crevicular fluid and the concentrations of interleukins 2, 6, and 8. **Conclusions:** Leveling and distalization of the teeth evoke increases in interleukins 2, 6, and 8 levels in the periodontal tissues that can be detected in gingival crevicular fluid. (Am J Orthod Dentofacial Orthop 2006;130:7.e1-7.e6)

Orthodontic tooth movement is based on force-induced periodontal ligament (PDL) and alveolar bone remodeling. Mechanical stimuli exerted on a tooth cause an inflammatory response in the periodontal tissues. Inflammatory mediators are released that trigger the biological processes associated with alveolar bone resorption and apposition.[1-3]

An important breakthrough in bone biology was the identification of the role of cytokines in bone remodeling. Cytokines are involved in initiating, amplifying, perpetuating, and resolving inflammatory responses. They are key mediators for tissue damage and play an important role in tooth movement. Cytokines are classified as proinflammatory and anti-inflammatory. Proinflammatory ones are tumor necrosis factor, interleukin 1, interleukin 2 (IL-2), interleukin 6 (IL-6), and interleukin 8 (IL-8). Anti-inflammatory cytokines are interleukins 4, 10, and 13. The proinflammatory ones are alarm cytokines, inducing vascular dilatation with increased permeability and enhancing inflammatory response.[4]

IL-2 is a proinflammatory cytokine derived from T-helper 1 cells. This cytokine is involved in B-cell activation and stimulates macrophages, natural killer cells, T-cell proliferation, and osteoclast activity. IL-2 has been also implicated in the stimulation of osteoclast activity in bone resorption, and it has been suggested that IL-2 plays an active role in the pathogenesis of periodontal diseases.[5]

IL-6 regulates immune responses in inflammation sites and has an autocrine/paracrine activity that stimulates osteoclast formation and bone resorbing activity of preformed osteoclasts.[6,7]

In the mononuclear phagotic system, several stages are required for local tissue cells to turn into full functional multinucleated cells.[8] IL-8 is a potent proinflammatory cytokine that has a key role in the recruitment and activation of neutrophils during inflammation. It is secreted mainly by monocytes and is important in regulating alveolar bone resorption during tooth movement by acting early in the inflammatory response.[9]

Various researchers demonstrated elevated levels of cytokines in tooth movement.[10-12] All studies to determine the levels of cytokines in gingival crevicular fluid (GCF) evaluated animal and human subjects for short times.[9-16] Also, these studies applied heavy distalization forces to the teeth and searched for early responses to the forces.

As a result of the great force that is exerted on the tooth, a hyalinized zone occurs in the compressed PDL. This hyaline zone has also been described as an area of focal aseptic necrosis. From the tension side, an indirect resorption process begins that regulates bone resorption. But orthodontic treatment does not always use heavy distalization forces to produce hyalinization, as

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in those studies, which applied heavy distalization forces on teeth.[9-16] As a result of this pressure on the periodontium, hyaline zones occurred, initiating indirect resorption and inducing changes of various cytokines. But in the first stages of orthodontic treatment, low leveling forces, which do not construct hyaline zones and therefore cause indirect resorption, are used. There might be different levels of cytokines in the leveling and distalization stages of the orthodontic treatment. The aims of this study were to determine IL-2, IL-6, and IL-8 levels in tooth movement, and test whether they differ from each other with leveling and distalization forces used in various treatment stages of standard orthodontic therapy.

MATERIAL AND METHODS

Fifteen patients (9 female, 6 male; ages, 15-19 years; mean age, 16.7 ± 2.3 years) at the Department of Orthodontics, School of Dentistry, Dicle University, Diyarbakir, Turkey, who were diagnosed for the extraction of first premolars participated in this study. The inclusion criteria were (1) a healthy systemic condition, (2) no use of anti-inflammatory drugs in the 6 months before the study, (3) the need for extraction treatment with fixed appliances involving distalization of at least 1 maxillary canine, (4) probing depth values (measured as the distance from the bottom of the sulcus to the most apical portion of the gingival margin) not exceeding 3 mm in the whole dentition, (5) no loss of periodontal attachment (measured as the distance from the bottom of the sulcus to the cementoenamel junction) exceeding 2 mm in any interproximal site, and (6) no radiographic evidence of periodontal bone loss after a full-mouth periapical radiograph examination. Informed consent was obtained from the patients and the parents of those under 18 years of age.

The maxillary first premolars were extracted from each participant, and, during the next 2 months, all subjects received repeated oral hygiene instructions that included the correct use of a toothbrush and an interdental brush. After this period, before orthodontic treatment with full brackets (Omni Roth, GAC International, Bohemia, NY) began, GCF was collected (baseline) from the mesial and distal aspects of the maxillary canines. At this appointment, orthodontic treatment was begun with 0.014-in Nitinol archwires (GAC International). A second GCF sample was collected 7 days later, at the next appointment. Patients were instructed to brush their teeth and then not eat anything for 3 hours before the second sampling. The forces that were applied on the tooth were still active. Twenty-one days later, the third sampling was performed with the same procedures.

In the first 6 months of treatment, only leveling forces were applied on the canines. Leveling forces were established by replacing the Nitinol archwire with a thicker one when it was deactivated. Any forces that would tip the tooth to produce hyaline zones were eliminated. It is difficult to design an appliance that delivers specific forces in vivo because of the irregularity of root surfaces. This is a limitation of in-vivo studies, but we aimed to use light leveling forces that would not produce hyaline zones, initiating indirect resorption, in the first 6 months of treatment. After the sixth month, heavy forces that would produce hyaline zones to initiate indirect resorption were used.

In the sixth month, before we proceeded with the distalization of the canines with rectangular stainless steel archwires, the fourth GCF sample was collected; it served as a baseline score for distalization because it was done before the application of retraction forces on the canines. A 7-mm Sentalloy closed coil spring (GAC International) applied 150 g of force to retract the canines. Seven days after starting the distalization, the same sampling procedure was followed. The last sample was taken on the 21st day of retraction.

Distalization forces were achieved by Sentalloy closed-coil springs stretched between the canines and the molars, applying 150 g of force. Sentalloy coil springs deliver constant force levels when they are activated. A full-bracketed 0.016 × 0.022-in stainless steel archwire was used to distalize the teeth.

GCF was obtained with paper strips (Periopaper, Pro Flow, Amityville, NY) by using the method described by Rudin et al.[17] Samples were taken only on the vestibular sides of the tooth to prevent salivary contamination.

The 7th and 21st days were used for GCF sampling because the 7th day is the turnover day for enzymes, and the indirect resorption process starts on the 21st day.

Samples were collected early in the day. Sample sites were isolated with cotton rolls, plaque was removed, and the tooth surfaces were air dried. Paper strips were placed into the sulcus, and, after waiting 30 seconds, an apparatus (Periotron 8000, Ora Flow, Plainview, NY) was used for determining the GCF volume. Paper strips were stored in sterile tubes at −20°C until experimentation. Samples contaminated with blood or saliva were excluded from the study. GCF sampling was done before any other clinical examinations were performed to prevent increases in fluid volume. Before examination of the GCF, 1000 μL of sterile sodium chloride solution (9 mg/mL) was

Table I. Concentrations of IL-2, IL-6, and IL-8 (pg/mL)

	Statistic	*Baseline*	*7th day*	*21st day*	*6th month*	*6th month + 7th day*	*6th month + 21st day*
IL-2	Mean	89.707	90.553	91.000	84.387	87.920	92.600
	SD	49.789	49.529	47.604	41.893	41.874	43.398
	SE	12.780	12.788	12.921	10.817	10.812	11.205
	Maximum	190	198	187	170	174	181
	Minimum	46.4	49.6	47.5	41.9	41.9	44
	Significance	—	.814	.986	.725	.877	.998
	F	—	.056	.001	.127	–.231	.060
IL-6	Mean	2.447	2.373	2.327	2.320	2.387	2.433
	SD	1.317	.711	.576	.528	.472	.399
	SE	.340	.183	.149	.136	.122	.103
	Maximum	6.1	3.7	3.3	3.4	3.7	3.3
	Minimum	1.3	1.3	1.5	1.4	1.6	2.0
	Significance	—	.083	.159	.535	.594	.996
	F	—	3.231	2.901	.395	.291	.077
IL-8	Mean	75.733	67.307	71.467	72.800	102.433	65.627
	SD	82.716	44.068	41.433	71.011	110.336	46.373
	SE	21.357	11.378	10.698	18.335	28.471	11.973
	Maximum	261	193	180	260	456	165
	Minimum	6.4	17.8	19	15	19.7	16
	Significance	—	.023*	.958	.128	.389	.738
	F	—	5.744	.003	2.456	.767	.550

*$P < .05$.

added to the paper strips, and the GCF was diluted at 3000 g at + 5°C for 20 minutes.[18] The kit and the machine used for measuring IL-2, IL-6, and IL-8 concentrations were the immunoassay system (Immulite, Diagnostic Products, Los Angeles, Calif). For the manual dilution of patient samples, IL-2, IL-6, and IL-8 free nonhuman buffer matrix was used.

The amounts of IL-2, IL-6, and IL-8 in each sample were compared with standard curves for IL-2, IL-6, and IL-8 that show a direct relationship between optical dentistry and cytokine concentration. The total amounts of IL-2, IL-6, and IL-8 were determined in picograms.

Statistical evaluation

A 1-way paired *t* test was used to determine differences between the amounts of IL-2, IL-6, and IL-8 (Table I). The Mann-Whitney U test was used to understand the significant differences between the groups at a time interval, by taking the differences between 2 adjacent points for IL-2, IL-6, and IL-8 concentrations (Table II). Descriptive measurements of GCF volume are given in Table III All statistical evaluations were made with SPSS 10.0 software (SPSS, Chicago, Ill).

RESULTS

The concentrations of IL-2, IL-6, and IL-8 are given in Tables I and II. There were no statistical differences between the observations except at the 7th day of leveling for IL-8 ($P < .05$). Although there were no statistical differences in IL-2 levels, it increased at the 7th and 21st days of leveling and distalization. IL-6 showed no significant fluctuations either statistically or mathematically. IL-8 showed a statistically significant decrease on the 7th day of leveling. Again on the 7th and 21st days of the distalization, it increased to some extent. The 2 adjacent observations were not statistically different from each other ($P > .05$).

GCF volumes are given in Table III. GCF volumes were greater on the 7th and 21st days of leveling and distalization, and returned to baseline levels after leveling. No statistically significant results were found between the groups ($P > .05$).

DISCUSSION

Orthodontic tooth movement occurs by the remodeling of the alveolar bone as a result of the force exerted on the periodontium. When a force, greater than capillary blood pressure, is directed on the tooth; a hyaline zone occurs in the direction of force. On the opposite side, a tension site occurs. This hyaline zone, free of cells, is necrosed by osteoclasts that originate from the tension site. On the tension side, osteoblasts occur in the bone-apposition process.[19] These are well-known histological signs. Preinflammatory cytokines play important roles in bone and root resorption.

Determining the levels of various cytokines during various phases of orthodontic treatment undoubtedly

Table II. Comparison of 2 adjacent concentrations of IL-2R, IL-6, and IL-8

	Statistic	*7th-21st day*	*21st day-3rd month*	*3rd month-6th month*	*6th month-6th month + 7 days*	*6th month + 7 days-6th month + 21 days*
IL-2	Mean	90.130	84.387	87.157	90.486	95.143
	SD	48.665	41.893	42.014	42.213	43.861
	SE	8.883	10.817	11.231	11.282	11.722
	Maximum	198	198	187	174	181
	Minimum	46.4	47.5	41.9	41.9	40.9
	Significance	.846	.974	.658	.859	.841
IL-6	Mean	2.400	2.450	2.330	2.390	2.410
	SD	.730	1.32	.580	.472	.430
	SE	.194	.34	.150	.122	.132
	Maximum	6.1	3.5	3.4	3.4	3.3
	Minimum	1.3	1.4	1.5	1.6	1.7
	Significance	.109	.159	.587	.654	.786
IL-8	Mean	71.521	69.390	72.130	87.620	84.03
	SD	65.264	42.080	57.130	92.390	85.220
	SE	14.073	14.570	16.700	17.200	14.030
	Maximum	261	193	260	456	456
	Minimum	6.4	17.8	14	14	6
	Significance	.373	.561	.455	.290	.361

Table III. Volumes of GCF (mg)

Statistic	*Baseline*	*7th day*	*21st day*	*6th month*	*6th month + 7th day*	*6th month + 21st day*
Mean	0.0014	0.0016	0.0025	0.0012	0.0018	0.0026
SD	0.0009	0.0008	0.0012	0.0009	0.0014	0.0009
Median	0.0012	0.0012	0.0026	0.0010	0.0013	0.0023
Minimum	0.0007	0.0009	0.0017	0.0006	0.0006	0.0010
Maximum	0.0034	0.0036	0.0030	0.0026	0.0036	0.0034

contributes to our understanding of the underlying mechanisms of tooth movement. Biologic aspects of tooth movements should be clearly determined. This consideration would help us to use suitable force types in clinical orthodontics.

The testing site in this study was the gingival sulcus, because its access in the oral cavity is easy and it has a continuity with the PDL. Tissue samples of the PDL or the bone undergoing resorption would provide a more direct site for measuring changes in cytokines, but they cannot be obtained from human subjects. Thus, cytokine values in the sulcus provide an indirect measurement of changes in the PDL. Localization of cytokines in the PDLs of animals can be accomplished by histologic techniques. In humans, a noninvasive method is needed. The prediction that compression of the PDL in humans could result in the migration of biochemical products into the gingival sulcus is the basis of our experimental design. Previous in-situ techniques for biochemical analysis of the gingival crevice involved sampling crevicular fluid with paper strips.[13] The paper-strip method was used in this study.

The maxillary canines of all patients were monitored because these teeth are accessible and easily cleaned. It has also been reported that plaque accumulation depends on the site; more plaque accumulates in the anterior area than in the posterior area.[20]

It has been shown that levels of biochemical markers in the GCF might depend on different collection sites.[21] For this reason, the canines were used as both test and control teeth. The control data, collected at the baselines, were obtained before any force was applied. Serra et al[22] stated that age and sex did not increase enzymatic activity, so age and sex differences were not considered in our study.

Gingival modifications incident to tooth movement were reported in both histologic and ultrastructural analyses, and clinically evident changes were also detected.[23] Researchers reported that GCF volumes increase during orthodontic treatment.[24,25] In our study, GCF volumes also increased, especially when orthodontic force was exerted on the tooth.

The increased mean concentrations of IL-2 and IL-8 were significantly higher compared with the baseline, but this was not statistically significant because of the large variation. This finding was the same as was

shown in previous studies.[24,26] In the first 6 months of our experiment, 3 samples were collected. The first was the baseline score, and the others were taken at the 7th and 21st days of our study.

IL-2 is a cytokine produced by T-helper 1 cells. This cytokine stimulates macrophages, natural killer cells, and T-cell proliferation, which mediate the cellular immune response, being regarded as a proinflammatory cytokine.[27,28] IL-2 has been also implicated in the stimulation of osteoclast activity in bone resorption.[29] The levels of IL-2 in the sera of periodontitis patients are elevated when compared with those of normal subjects.[30] Due to its biologic properties, IL-2 has been suggested as a useful marker of inflammatory activities.[31] To our knowledge, there are no earlier reports on the role of IL-2 in orthodontic tooth movement, which is basically PDL and alveolar bone remodeling, so similar mechanisms with periodontal bone loss must be responsible. The elevated levels of IL-2 with leveling and distalization forces in this study demonstrated this relationship.

In preceding studies, it was shown that IL-6 plays important roles in osteoclast formation and bone resorbing activity.[6,7] Researchers demonstrated that the increased levels of cytokines were lower at 7 and 10 days after application of orthodontic force.[12,13] Also, Lee et al[26] demonstrated that the mean concentrations of cytokines increased in the first 24 hours, and then an equilibrium was reached. Saito et al[32] remarked on the possible synergistic additive, subtractive, or suppressive effects of cytokines on each other. These researchers observed IL-6 levels in the early stages of tooth movement, but the levels of IL-6 at the 7th and 21st days of this study showed no apparent increases. This kind of a periodicity can possibly explain the slight fluctuations, instead of increases, of IL-6 levels in our study.

Sfakianakis et al[33] reported the precise localization of IL-8 receptors in periodontitis and noninflamed human gingivae, and suggested that IL-8 plays a multifunctional role in the pathogenesis of periodontal disease. In a previous study, it was demonstrated that orthodontic forces evoked changes in the levels of IL-8.[24]

Researchers reported that cytokine levels fluctuated with a 28-day cycle when a continuous orthodontic force was applied.[24,34] The increased mean levels of IL-8 with continuous forces, exerted in the leveling stages of our study, seem to be related to this kind of periodicity. Distalization forces increased IL-8 levels at the 7th day and decreased them the 21st day. In our study, the intermittent force affected the level of IL-8 that was determined in a previous study.[26]

This in-vivo study provides information about the levels of IL-2, IL-6, and IL-8 in normal orthodontic treatment. Both leveling and distalization forces evoked changes in these proinflammatory cytokines. These mediators initiate and achieve continuity of tooth movement by cylic relations when mechanically activated. But cytokines have some synergistic reactions on each other. This synergism prevents these mediators from increasing excessively.

CONCLUSIONS

This phenomenon in the periodontium is important during orthodontic treatment, because various leveling and distalization forces cause direct and indirect resorption, respectively. Proinflammatory cytokines (IL-2, IL-6, and IL-8) play important roles in bone resorption. This study demonstrated similar levels of these cytokines in direct and indirect bone resorption. Further in-vivo and in-vitro studies are needed to determine cytokine levels for leveling and distalization forces at relatively short times (1 and 24 hours).

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