Chapter 4

The Role of Cytokines in Orthodontic Tooth Movement

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Abstract

One of the most important breakthroughs in the understanding of biological features of bones is the explanation of the role of cytokine in reshaping of the bone (remodeling) including the alveolar tooth bone exposed to the effect of the mechanical force during the orthodontic treatment. Since remodeling of the bone initiated by orthodontic forces is connected during its early stage with the inflammation of the surrounding tissue, the assumption was presented about the role of the pro-inflammation cytokine in the process of remodeling of the bone, primarily *IL-1β, IL-6,* and *TNF*. These cytokines are mediators in the reactions of the acute stage of inflammation, as well as in the processes of metabolism, stimulation of resorption, and inhibition of bone creation. In this chapter, we aimed to review the existing knowledge about the roles and dynamics of the change in these three cytokines simultaneously during the early stage of the orthodontic tooth movement.

Keywords: orthodontic tooth movement, reshaping of bones, cytokines

1. Introduction

When more than 100 years ago the world knew about the theory about the regulation of the tooth movement, cytokines were unknown to science [1]. The first experimental evidence that supported the assumption about cytokines being the potential regulators of the reshaping process (remodeling) of bones during the orthodontic treatment was obtained approximately 20 years ago [2]. Since then, until today, the efforts of researchers last in order to clarify molecular events with cytokines as mediators, which follow the orthodontic tooth movement.

The role of cytokines in the orthodontic tooth movement is considered in the context of inflammation, which occurs at the very beginning of this process as a reaction to the mechanical pressure and represents necessary precondition for the realization of all its subsequent levels. In the conjunction of mechanical and biological mechanisms, which move the teeth during the orthodontic treatment, cytokines are given great importance for their feature of transmission of biochemical signals among numerous cells of various kinds reacting to orthodontic forces. Binding themselves to specific receptors at membranes of these cells, cytokines cause in them the biochemical changes responsible for the signal transmission to corresponding genes in these cells and, consequently, to the change of gene expression in them. This orthodontic tooth movement causes the features of unusually complex processes, whose different degrees—each individually and all together—are regulated by the network of positive and negative feedbacks, in which cytokine molecules act as mutual activators or inhibitors [3].

2. Orthodontic tooth movement and force effect

Orthodontic tooth movement is a biomechanical process initiated by the effect of mechanical forces, which overpower the bio-elasticity of the support tissue [4].

The process of orthodontic movement of teeth is based on the transformation (remodeling) of periodontal tissues and is initiated by external forces and differs from the processes that occur during normal jaw function (dentition, chewing) [5]. On the basis of remodeling of periodontium, there are mechanisms, which transform the physical effort into various cell responses within the periodontal system, which primarily leads to the disturbance and then to the establishment of the periodontal homeostasis on a different basis [6]. These mechanisms provide the adaptation of the biological system of periodontium to the changed conditions emerged as a result of the effect of orthodontic forces.

Biomechanical mechanisms of the orthodontic tooth movement, because of their complexity, have been explained by various, but not mutually exclusive theories. Orthodontic dogma is considered to be the one according to which the movement of the tooth in the periodontal space occurs by the effect of two dominant forces: pressure force (compression) and tensile strength (tension) [7]. As a result of the pressure, there is resorption (suction), whereas as a result of tension to apposition (addition) of alveolar bone, the movement of the tooth occurs as a direct outcome of the reshaping of the tissue around the tooth root caused by forces. On basis of this, processes are vascular, and consequently, cellular changes of the dental tissue are caused by chemical mediators, which are created and released under the influence of orthodontic forces. Even though, in the context of this, we must not neglect the theory, which emphasizes bending of the bones as the basis of the orthodontic tooth movement [8], as well as the theory of bioelectrical signals, which emphasizes the importance of electric potentials, which are created in the tissue as a response to the application of the mechanical force [9].

Orthodontic forces lead to the change of the structural features of dental tissues at the level of cells, molecules, and genes. Mutual activities of tooth cells, periodontal ligament, bone, and bioactive substances (cytokine, chemokine, hormone, growth factor, enzymes, neuropeptides, and ligands) are necessary because they provide that during these changes, the tooth and

periodontal ligament remain clinically intact and surrounding bone is reorganized. The final outcome of these activities (the speed of orthodontic movement of teeth) may be defined as a phenotypic expression of numerous gene-controlled mechanisms, which connects the orthodontic tooth movement with hereditary basis, i.e., hereditary variations of factors which participate in this process [10].

3. Orthodontic tooth movement and biological mechanisms of reshaping of the mechanic-sensitive dental tissue

The cells of alveolar bones and periodontal ligament, gingiva, and tooth pulp react to the effect of orthodontic forces after the remodeling of extracellular matrix (ECM), which surrounds them [11]. Dental and periodontal cell responses to the applied mechanical force comprise interactions of intracellular and extracellular structural elements and mutual influences of the effects of various biochemical structures. The nature of changes in the process of reshaping is determined by the combinatory of interactions, which is different at different levels of the tooth movement [12]. The scheme no. 1 presents the main events in dental tissues, which follow orthodontic movement of the tooth.

4. Orthodontic tooth movement and the change in the structure of cytoskeleton

The function of all cells in mechanic-sensitive dental tissues is closely related to the ECM, which surrounds them and makes the corresponding microenvironment for cell activities, which emerge after the application of orthodontic force. The orthodontic treatment leads primarily to ECM periodontium deflection, which results in the changes of cytoskeleton structure of cells anchored in ECM. ECM is multicomponent tissue, which enables the transmission of mechanical signals to the corresponding cells and thus the occurrence of changes in the structure and function of a certain tissue [11]. The structural components of ECM (collagen, fibronectin, laminin, elastin, proteoglycans, hyaluronic acid, etc.) bind with the adhesive receptors at cells called integrins, via which the mechanical stimuli are transmitted into the cell causing the changes of cytoskeleton structures. The application of mechanical force outside disturbs the integrin receptors at fiber areas of periodontal ligament and gingiva and bone cells (osteoblast, osteoclast, osteocytes), and their adaptive response may increase or decrease the creation of integral elements of ECM in them and thus influence the change of the mass and morphological appearance of the bone [13].

5. Orthodontic tooth movement and reorganization of blood vessels

Blood vessels in periodontal ligament actively participate in the remodeling of dental tissues, which is related to the orthodontic tooth movement. Under the influence of mechanical forces,

the reshaping of existing and creation of new blood vessels at periodontal ligament occur. These processes occur via numerous signal paths, which are activated after the deflection of ECM, which surrounds the cells of endothelia of blood vessels. They are mostly established via integrin of endothelial cells and ECM structures, which surround the blood vessels [14] and lead to the organization of endothelial cells unto multicellular pre-capillary network [11]. The response of blood vessels of periodontal ligament to the effect of mechanical forces is expressed by increased permeability, which, on its side, increases the fluid outpouring from capillary into the interstitial space [15]. These blood vessels play an essentially important role in aseptic inflammatory reaction caused by mechanical forces, acting as a source of inflammation mediators (cytokine and neurotransmitters), which mutually react with endothelial cells of periodontal capillary network encouraging them to bind circulating leukocytes and influence their relocation into periodontal ECM.

6. Orthodontic movement of teeth and inflammation

The mechanical stimulus stemming from the orthodontic forces causes aseptic inflammatory reaction within periodontal tissues, which initiates biological processes, which are connected to the reshaping of the bone [16]. Even though in normal conditions the movement of teeth is a sterile process, the early stage of orthodontic tooth movement is observed as a type of tissue injury and it is accompanied by the acute inflammatory response.

Generally speaking, the acute inflammation is an initial stage of defense reaction of the mechanism to the tissue injury (mechanical, physical, chemical, nutritive, biological). It occurs fast and does not last long and it emerges as the result of numerous, complex, and mutually related processes via which certain proteins and cells are transmitted from blood to the damaged tissue and whose final result is the recovery of the tissue. The acute phase of the inflammation is characterized by vascular changes (vasodilatation and increased permeability of blood vessels) and consequently, plasma leakage (exudation) and relocation of leukocytes (extravasation) from blood into the injured tissue.

Immediately upon the application of orthodontic force, the disturbance of the microcirculation of periodontal ligament occurs, which results in the ischemia of local tissue, periodontal vasodilatation, and migration of leukocytes via capillaries of periodontal ligament. The changes are temporary and, by the rule, do not have pathological effects.

Even though inflammatory changes occurred during the orthodontic tooth movement are mostly the consequence of reactive processes in the support tissue, mechanical stimuli may be transmitted also to the tooth pulp and may initiate the inflammatory response within this dental tissue [17].

6.1. Orthodontic movement of teeth and inflammation mediators

Inflammatory response in orthodontic tooth movement is followed by the increased creation of inflammatory mediators (cytokines, prostaglandins, leukotrienes), enzymes (matrix metalloproteinase, lactate-dehydrogenase, alkaline phosphatase, aspartate-aminotransferase),

growth factor (epidermal growth factor—EGF), and neuropeptides (P-SP substance, calcitonin gene-related peptide—CGRP), which indicates the participation and mutual communication of cells of immune, endocrine, and nervous system in the regulation of the bone remodeling [16, 18–22].

The primary role in the initiation of a series of biochemical processes that stimulate or inhibit cellular activities during the inflammatory changes, initiated by the effect of orthodontic

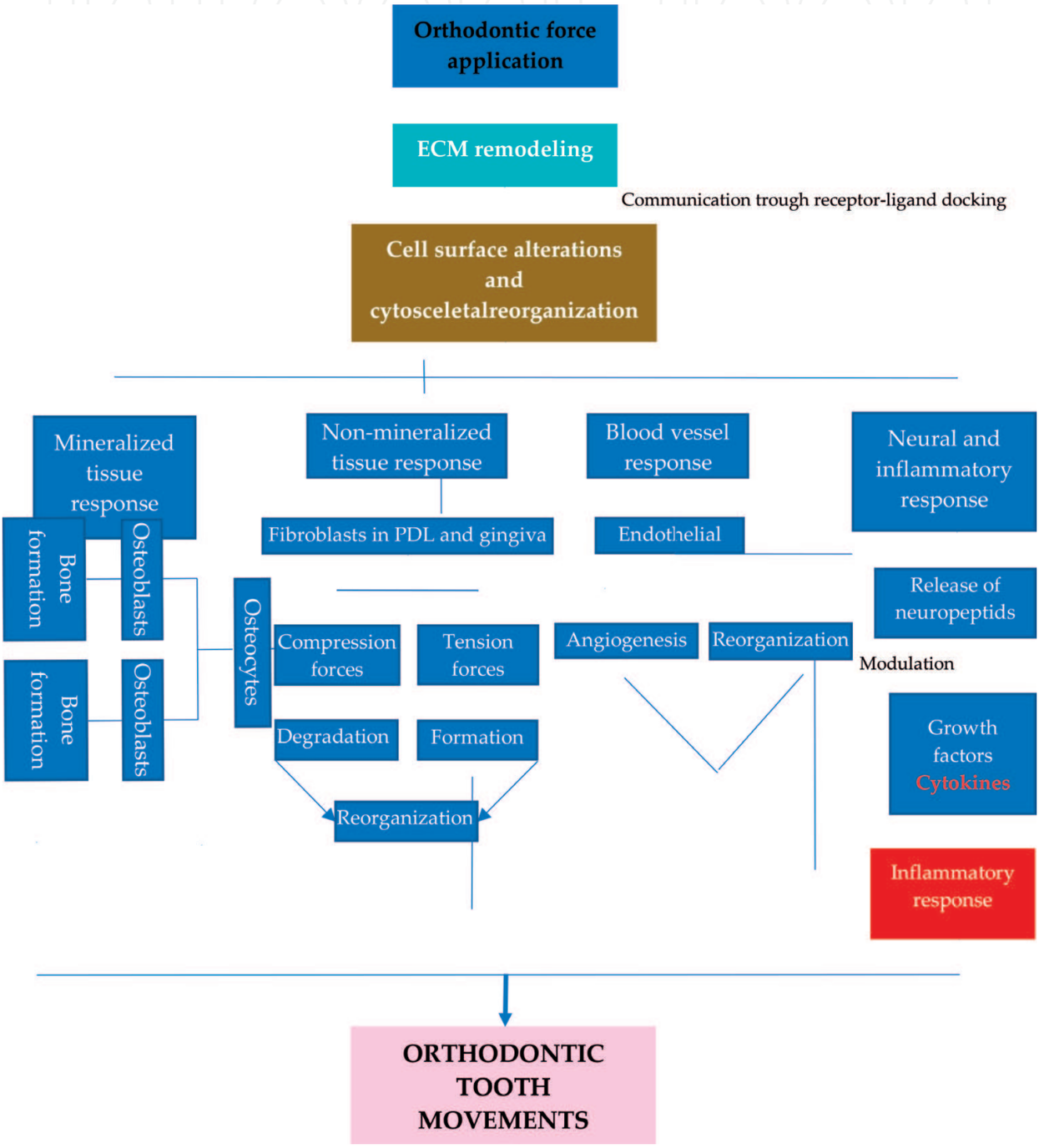

Figure 1. The sequence of events in dental tissues during orthodontic tooth movement. ECM—extracellular matrix; PDL—periodontal ligament.

forces, is attributed to cytokines [6]. Cytokines are small protein molecules, which transmit signals among cells. They are excreted by various cells as a response to external stimuli, and most frequently, they have a local effect. The effect of cytokines may be autocrine (to the cell which excretes it), paracrine (to other, adjacent cells), and endocrine (to distant cells). Cytokines express their effects by binding themselves to specific receptors at the cell membrane, which are affected by cytokines causing the biochemical changes responsible for the transmission of the signal to the corresponding genes in these cells and, consequently, to the change of the gene expression in them.

During the orthodontic tooth movement, cytokines are created by the inflammatory cells, which after the mechanical stimulus came outside widened capillaries of periodontal ligament [6, 18]. As the main regulators of the bone remodeling process during the orthodontic treatment, three cytokines are mentioned: interleukin 1 beta (IL-1β), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF-α) [6, 18, 23]. All three cytokines cause many local and systemic changes, which are the features of the acute stage of inflammation (**Figure 1**).

7. Orthodontic tooth movement and *IL-1β*, *IL–6*, and *TNF-α* effects

7.1. *IL-1β*, *IL–6*, and *TNF-α* and remodeling (resorption and apposition) of bones

The effects of *IL-1β*, *IL–6,* and *TNF-α* during the orthodontic tooth movement are going in a few connected directions and occur within the physiological process of remodeling of periodontal tissue after the application of mechanical forces. Judging by their concentration in gingival fluid, the creation of all three interleukins is already increased at the beginning stage of this process (12th and 24th hour) when leukocytes and fibroblasts of gingiva, periodontal ligament and alveolar bone make them as mediators of inflammation due to forces [6, 18, 23]. The maximum level is reached on the third day after the application of these forces [23].

IL-1β, *IL–6*, and *TNF-α* are osteotropic cytokines. They are released at the inflammatory spot and directly or indirectly (via substances whose synthesis and excretion they influenced) react with bone cells initiating the process of bone resorption [16]. Generally, it is believed that the bone resorption caused by inflammation is caused by local stimulation of osteoclast initiated by the effects of cytokines released from the infiltrated inflammatory cells [24, 25]. The process occurs in a complex signal manner via receptors of *TNF–α* (*TNF–R1*) at osteoblasts [24]. This receptor is activated by nuclear transcription factor *NF-κB*, so it is therefore called receptor activator of *NF-κB* ligand (*RANKL*) [26]. *RANKL* binds itself for the receptor at mature osteoclasts called *RANK*. Binding itself for *RANK*, *RANKL* may activate mature osteoclast and their precursors in the direction of oclastogenesis. It is prevented from doing so by natural antagonist osteoprotegerin (OPG), soluble receptor bait for RANKL, which prevents its binding for *RANK*, acting as a natural inhibitor of maturation and activation of osteoclast [27, 28]. For *TNF–α* and IL-*1β*, it is shown that together or independently from one another, *IL-1β* via *IL-1RI* receptors at osteoblasts may regulate the balance between *RANKL* and *OPG* in microenvironment of bones and mesenchymal tissue along the bone [29], not only

intensifying the expression of *RANKL* and contributing to the resorption of bones, but also that they may activate osteoclasts at RANKL independently [30]. There is evidence that *IL-1β* and *IL-6* released by osteoclasts themselves may cooperate with pro-inflammatory *IL-1β* and IL-6 in osteoclastogenesis [31].

The termination of the resorption of bones and initiation of its reformation comprises inhibition of the osteoclast function and stimulation of the activity of osteoblasts. The termination of resorption cycle includes the inhibition factors, which are created not only by surrounding cells but also by the osteoclasts themselves. They regulate negatively the activity of these cells causing their apoptosis and preventing their creation and simultaneously increasing the function of osteoblasts. This stage of normal bone remodeling is followed by lowering of the level of pro-inflammatory cytokines. The number of cells of inflammation, which are created by *IL-1β*, *IL–6*, and *TNF–α*, as well as the level of these cytokines in gingival fluid is decreased after 7–10 days since the beginning of the effect of mechanical forces [18, 23], which overlaps with the initial phase of reparation of periodontal tissue, which lasts for approximately 9 days [31]. During this stage, blood vessels are no longer excessively permeable [32]. In this stage the creation of transforming growth factor beta is intensified (TFG-β), insulin-like growth factor (IFG I and II), fibroblast growth factor (FGF), IL-10, etc. [33], which modulate the reactivity of osteoblasts and prevent the bone resorption [31]. Complicated interactions among these factors, with many of them still not being explained entirely, create the basis of the coordinated formation of a new bone at the resorption location.

7.2. *IL-1β*, *IL-6*, and *TNF-α* and orthodontic forces

Although the causal relationship of cytokine expression and orthodontic force is not entirely explained, it is believed that the direction and the nature of these forces affect the level of changes in the blood flow and thus the relationship of inflammatory mediators, which are expressed in periodontal tissues and gingival sulcus. The blood flow is decreased at the spot of compression (ligament compression) and increased at the spot of tension (ligament stretching); therefore, the response of the tissue at this location is greatly determined by the opposing forces that affect them. The inflammatory reaction occurs in both spots and the content of *IL-1β*, *IL–6*, and *TNF-α* is increased both in the zone of compression and in the zone of tension (in comparison with the control teeth), but the level of some of them in either of these zones is different [34, 35]. It is believed that these differences are the reflection of specificity of the process, which occurs at the location of effect of certain force during the orthodontic treatment [34]. Even though they are not completely harmonized, the data so far show that the level of pro-inflammatory cytokines in comparison with control teeth is generally higher in the compression zone than in the tension zone, which is connected to the role of these cytokines in the regulation of osteoclastogenesis mediated by RANKL (vide supra) and the process of bone resorption at the compression spot [34, 35]. Simultaneously, it is shown that the expression of anti-inflammatory cytokine *TGF-β* is greater at the tension spot than at the compression spot, which is attributed to its role in the process of inhibition of osteoclastogenesis and bone formation at the tension spot [35]. However, the balance between pro-inflammatory and anti-inflammatory mediators at the spots of compression and tension is still not studied enough.

The effects of cytokine in the response of the tissue to orthodontic forces are connected to the creation of nitrogen oxide (NO), which is known to be one of the important regulators of bone remodeling. For the creation of NO, the activity of two enzymes is necessary: inducible nitrogen-oxide synthesis (iNOS) and endothelial nitrogen-oxide synthesis (eNOS). The gene expression of these two enzymes is activated by pro-inflammatory (*IL-1β*, *TNF-α*) and anti-inflammatory (*IL-4, IL-10, TGF-β*) cytokines, which are created during the resorption and reparation of bones [36]. At the experimental model (rat), it was noticed that after the application of the orthodontic force iONS is the mediator in the bone resorption caused by the inflammation at the compression zone and eNOS in the bone creation at the tension zone [37].

Orthodontic forces express their effect to the dental pulp initiating the responses of fibroblast in it. Even though it is considered that the reactions of the pulp to the orthodontic treatment are very small, they still bring about changes in the blood flow and releasing of *IL-1β, IL-6,* and *TNF-α* from the pulp fibroblast, which results in its inflammation [17]. The process is specifically related to the pulp innervations and neurogenic mechanisms [38], and in the case of more expressed effect of mechanical forces may lead to the resorption of the tooth root [39].

7.3. *IL-1β, IL-6,* and *TNF-α* and "neurogenic inflammation"

The orthodontic tooth movement is accompanied by releasing neuropeptides from peripheral endings of sensor nerves, which permeate the dental pulp and periodontium, as well as from the inflammatory cells localized in the periodontal tissue. Released neuropeptides regulate the microcirculation of the pulp and mediate in inflammatory processes during remodeling of bones, characteristic for orthodontic tooth movement [19]. Such neural effect, which is generally called "neurogenic inflammation," is connected to the pain, which partially occurs during stretching and pressing of the tissue under the influence of mechanical forces and partially because of the interaction of numerous inflammatory mediators with local pain receptors [38, 40].

The main mediators of neutrogenic inflammation are neuropeptides, SP and CGRP, which are proven to have vasodilatation effect, increase vascular permeability and participate in the inflammatory processes related to the damage, and recovery of the tissue [41]. The increase of the level of these neuropeptides is recorded in gingival fluid immediately after the effect of orthodontic forces, which occurs simultaneously with the increase of the level of pro-inflammatory cytokines *IL-1β*, *IL-6*, *TNF-α* in this liquid [42]. Although the ratio of neuropeptides and cytokines included in the process of inflammation, which occurs during the orthodontic tooth movement, is still not entirely clear, the data show that SP and CGRP stimulate the excretion of *IL-1β*, *IL-6*, and *TNF-α* from fibroblast of human dental pulp, but they do not work synergistically [16, 42]. The neuropeptide SP is included in the resorption phase of the reshaping of the bone during the orthodontic tooth movement by stimulating the creation of RANKL in the cells of human dental pulp similar to fibroblasts [43]. The SP expression may be prevented by *TGF-β* [44], whose excretion overlaps with the initial stage of reparation of periodontal tissue.

The effects of neuropeptides to cytokines are not unidirectional [19, 38]. *IL-1β* and *TNF-α* secreted from inflammatory cells after the stimulation with SP lead to the creation of nerve

growth factor (NFG), which then leads to the increased production of SP and CGRP, which establishes the mechanisms of positive feedback during the inflammatory response [41].

7.4. *IL-1β, IL-6,* and *TNF-α* and other inflammatory mediators in periodontium

Apart from mutual interactive effects in the processes of inflammatory responses and bone remodeling during the orthodontic tooth movement, *IL-1β, IL-6*, and *TNF-α* frequently have effects in the combination with various other bioactive structures included in these processes.

After the primary inflow to the inflammation location and the initiation of an early stage of periodontal remodeling, these cytokines start the second tide of cytokine regulation of this process by "introducing" other relevant cytokines. It is shown that an early but not initial phase of the orthodontic tooth movement is followed by the increase of the level of *IL-8* in gingival fluid [6, 45], which is known to regulate inflammatory responses in periodontium in combination with other cytokines [46]. *IL-1β, IL-6,* and *TNF-α* stimulate the creation of *IL-8* in monocytes, macrophages, epithelial cells, and fibroblasts of periodontium, so that the IL-8 mechanism of feedback could initiate the creation of *IL-1β, IL-6*, and *TNF-α* [6], when periodontal system moves from resorptive to formative stage of bone remodeling. With IL-8 during the orthodontic treatment, the level of IL-2 also increases and it is considered to be the indicator of inflammatory activities in periodontium [47].

The increased expression of pro-inflammatory cytokines in human periodontium, due to orthodontic forces, is followed by prominent increase in the level of prostaglandin E_2 (PGE_2). This prostaglandin, which is created in various cells of mammals as one of the intermediary products of metabolism and arachidonic acid, is the mediator in the sustaining of local homeostasis, modulating numerous physiological processes including the inflammation. During the resorptive phase of bone remodeling caused by mechanical stress and initiated by acute inflammatory response, PGE_2 is created in cells of periodontal ligament (mechanically deformed osteoblasts and gingival fibroblasts), stimulating the creation of osteoclasts, which intensifies the bone resorption [16]. In this process, *IL-1β* and *TNF-α* express synergistic effects to the creation of PGE_2 stimulating the fibroblasts to the synthesis of this prostaglandin. The increased level of PGE_2 in the reaction results in the decrease of the expression of pro-inflammatory cytokines [48] and, consequently, the inhibition of the inflammatory response and stimulation of the bone formation. This dual role of PGE_2 (resorption on the one hand and bone formation on the other) is interpreted by the possibility of prostaglandin directing in different manners the bone cells: for resorption those in bone marrow and for the bone formation those at their surface.

The inflammatory response, which occurs during the orthodontic tooth movement, is followed by the increase of β_2 expression, microglobulin (β_2-*MG*), glycoproteins, which together with the pro-inflammatory cytokines initiate the process of bone remodeling [18]. β_2-*MG* occurs in soluble form in different bodily fluids of organisms including the gingival fluid and also is in the composition of the main histocompatible locus of I class (MHC class I), which is expressed at the surface of various cells, mostly lymphocytes and monocytes. In the process

of bone remodeling, after a mechanical stress, β_2-*MG* is included as a regulatory factor of the bone metabolism, with the function of a stimulator of the osteoclast activity in the resorption stage and the function of the increase of the binding for bone cells *IGF-I* in the stage of bone formation [49].

Apart from pro-inflammatory cytokines and other pro-inflammatory substances, during the orthodontic tooth movement to gingival fluid, various metabolites are released, too. For lactate-dehydrogenase (*LDH*) [21] and metalloproteinase 8 [20], it is shown that they increase their level or the activity simultaneously with pro-inflammatory cytokines, in approximately the same time, so it is considered that their existence reflects the increased periodontal remodeling caused by orthodontic forces primarily at early stages of this process. *LDH* is intracellular, cytoplasmic enzyme, which is released outside the cell under conditions of cellular necrosis or tissue degradation. It is believed that the increase of the *LDH* level at gingival fluid during the orthodontic tooth movement follows the process of bone resorption [21]; metalloproteinase 8 is the isoform of the enzyme of collagenase, which is released from periodontal fibroblasts due to the effects of mechanical forces. In the increased level in gingival fluid, it emerges during the initial stage of the orthodontic tooth movement, expressing the increased periodontal remodeling caused by these forces [20].

The damage of dental tissues caused by inflammation and its reparation are based on many elements and their coordination inside and outside cells. Even though there are differences between pathological inflammatory changes and those which accompany mechanically caused reshaping of tissues, the basic cellular responses to stimuli, regardless of their nature, express essentially the same properties [50]. Our researches of changes of individual integral parts of the immune system and ECM in normal and inflammatory gingiva [51–53] were the basis for the examination of the expression of IL-*1β*, *IL-6*, and *TNF-α* and their mutual relation in gingival fluid and tissue of gingiva of children and adults who underwent the orthodontic treatment. Analyzing the causes of gingival fluid and tissue of free gingiva of orthodontically treated teeth (experimental teeth) and their nontreated antagonists (control teeth) in four different moments in time ("zero" hour, 24th hour, 72nd hour, and 168th hour after the application of the separator), we have reached the knowledge about the dynamics of the change in the local cytokine network during the initial stage of orthodontic tooth movement and differences existing in the amplitude of these changes between children and adult examinees [54]. The results led us to assume that in the first moments of orthodontic treatment, the constitutive creation of pro-inflammatory cytokines is created and then it is overcome in the following time intervals by more expressive reaction of cells to the effects of mechanical force. The time coincidence of quantitative changes of *IL-1β*, *IL-6*, and *TNF-α* in gingival fluid and tissue expression of orthodontically treated teeth indicate that these three cytokines could be in specific interdependence during the early stage of the orthodontic tooth movement. Put into the context of the concept about the pharmacological modulation of the tooth movement, especially the aspect which leads the acceleration of the process of tooth movement in the connection with the local application of cytokine, the results could be very useful.

8. Conclusion

The early stage of the tooth movement is followed by the inflammatory response of the tissue to the effects of the mechanical force, which are conducted and regulated by pro-inflammatory cytokines *IL-1β*, *IL-6*, and *TNF-α*, acting as mutual activators and inhibitors.

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