

# Dentoalveolar anomalies and modern views on the mechanisms of local stress-modeling effect of orthodontic appliances on the periodontal tissues (a literature review)

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

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**The aim** of the study was to highlight the results of modern scientific developments in tracing the mechanisms of local stress-modeling effect of orthodontic appliances on the oral cavity and periodontal tissues during the active period of orthodontic treatment.

**Materials and methods.** The research methodology was implemented in the collection and analysis of scientific results on the stress-modeling effect of orthodontic appliances in patients with dentoalveolar anomalies obtained from the processed sources – published full-text articles of original and fundamental research by national and foreign authors based on the evidential databases MEDLINE / PubMed, PMC, Scopus, Web of Science, Cochrane, Google Scholar, ResearchGate and other scientific and practical resources.

**Results.** The main components of the stress-modeling effect of fixed orthodontic appliances on the oral cavity, and particularly on the periodontal tissues, were analyzed. The proportion of various complications is quite high and ranges from 32.7 % to 50.0 % of all cases. The development of oxidative stress during orthodontic treatment is potentiated by microcirculatory disorders and hypoxia of the periodontal tissues. The peculiarities of the periodontal cellular complex reaction, which has the ability to bear stress generated in the actin cytoskeleton by direct mechanical stimulation, to extracellular matrix proteins, affecting the three-dimensional organization of the extracellular matrix and its remodeling, have been traced. The role of lipid peroxidation, antioxidant system and enzymatic reaction of oral and crevicular fluids was also defined.

**Conclusions.** The development of oxidative stress during orthodontic treatment can be caused by local and systemic exposure to metals, corrosion processes in particular; by inflammation of periodontal tissues due to poor oral hygiene and activation of periodontal pathogenic microflora; by aseptic inflammation in the periodontal ligament due to the use of mechanical force. Certain enzymes of the oral fluid, in particular lactate dehydrogenase, can act as a sensitive marker of changes in the periodontal ligament metabolism during orthodontic teeth movement. The localization and nature of free radical pathology are largely caused by the nature of an exogenous inducer of lipid peroxidation and the genotypic characteristics of antioxidant system. It is this ratio that determines the initiation and further chain branching of free radical reactions. Without normalization of all pathogenetic links, successful treatment of inflammatory and dystrophic-inflammatory diseases of the periodontal tissues, in particular in orthodontic patients, is impossible.

## Ключові слова:

ортодонтичні аномалії, брекет-система, пародонт, оксидативний стрес, ремоделювання кістки, корозія, перекишене окиснення ліпідів, антиоксидантна система.

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## Зубощелепні аномалії та сучасні погляди на механізми місцевої стрес-моделювальної дії ортодонтичної апаратури на тканини пародонта (огляд літератури)

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**Мета роботи** – висвітлення результатів сучасних наукових досліджень щодо механізмів місцевого стрес-моделювального впливу ортодонтичної апаратури на порожнину рота і тканини пародонтального комплексу в процесі активного ортодонтичного лікування.

**Матеріали та методи.** Методологія дослідження реалізована у збиранні й аналізі наукових результатів про стрес-моделювальну дію ортодонтичної апаратури у пацієнтів зі зубощелепними аномаліями, що отримали з опрацьованих джерел фахової літератури, – повнотекстових статей оригінальних, фундаментальних досліджень вітчизняних і закордонних авторів, індексованих у доказових базах даних MEDLINE / PubMed, PMC, Scopus, Web of Science, Cochrane, Google Scholar, ResearchGate та інших науково-практичних ресурсах.

**Результати.** Здійснили аналіз основних компонентів стрес-моделювального впливу незнімної ортодонтичної техніки на порожнину рота та тканини пародонта зокрема. Питома вага різних ускладнень є доволі високою, становить від 32,7 % до 50,0 % усіх випадків. Порушення мікроциркуляції та гіпоксія тканин пародонта потенціюють розвиток оксидативного стресу під час ортодонтичного лікування. Визначили особливості реакції клітин пародонтального комплексу, що мають здатність переносити напруження, яка генерується в актиновому цитоскелеті шляхом прямої механічної стимуляції, на білки позаклітинного матриксу, впливаючи на тривимірну організацію позаклітинного матриксу та його ремоделювання. Встановлено роль перекишеного окиснення ліпідів, антиоксидантної системи та ферментної реакції ротової та кревікулярної рідин.

**Висновки.** Оксидативний стрес під час ортодонтичного лікування може бути спричинений місцевим і системним впливом металів, зокрема корозійними процесами; запаленням тканин пародонта через погану гігієну ротової порожнини й активацію пародонтопатогенної мікрофлори; асептичним запаленням у пародонтальній зв'язці через застосування механічної сили. Окремі ферменти ротової рідини, як-от лактатдегідрогеназа, можуть бути чутливим маркером змін метаболізму пародонтальної зв'язки під час ортодонтичного переміщення зубів. Локалізація та характер вільнорадикальної патології

значною мірою спричинені природою екзогенного індуктора перекисного окиснення ліпідів і генотиповими особливостями антиоксидантної системи. Саме від цього співвідношення залежить старт і наступне розгалуження ланцюгових вільнорадикальних реакцій. Без нормалізації всіх ланок патогенезу не можливе успішне лікування запальних і дистрофічно-запальних захворювань тканин пародонта, зокрема в ортодонтичних пацієнтів.

Over the past decades, the results of studies have shown a consistently high incidence of dentoalveolar anomalies (DA) in patients of different ages (from 23 % to 85 %), wide variability of data in the world and in Ukraine in particular, which leads to the consideration of this problem not only from the standpoint of medical but also social significance [1,2,3,4]. The multitietologic nature of DA and untimely diagnosis at the stages of temporary and variable occlusion lead to the development of more severe forms in the permanent occlusion [4].

DA is one of the causes of the masticatory apparatus dysfunction accompanied by impaired coordinated work of the masticatory muscles and changes in the symmetry of the mandible movements with the possible development of a number of pathological changes in the temporomandibular joint [5]. Impaired chewing and functional loads lead to deterioration of metabolism in the periodontal tissues with the development of gingival recession, atrophy of the alveolar bone, or the formation of periodontal pockets and the prevalence of destructive processes [6]. The consequences of undiagnosed and untreated periodontal disease are the possible development of regional vasoconstriction and tissue hypoxia, and a decrease in the intensity of metabolic processes [7].

According to current data, periodontal tissue diseases are diagnosed in 30–50 % of 12-year-old patients and 55–96 % of cases in 15-year-olds. At the same time, chronic catarrhal gingivitis is most common in this age range (up to 90 % of cases). It has been found that the most common is Engle class I, which is diagnosed in about 45–70 % of people, Engle class II – 19–25 % and dental crowding – in 58 % of cases [8]. According to various sources, the prevalence of chronic catarrhal gingivitis in the pediatric population of Ukraine is 70–80 % of cases, forming a risk group for the development of more severe destructive forms of periodontal tissue diseases in the process of growing up [8].

To date, it has been revealed that orthodontic treatment in adolescence does not have a significant negative impact on the subsequent condition of the periodontal tissues. However, the situation remains complicated for adult patients. According to the American Association of Orthodontists, one in four orthodontic patients is an adult. At the same time, some studies show that almost 40 % of patients with DA requiring orthodontic treatment are adults [9]. Periodontal diseases in the presence of DA lead to critical loss of bone tissue of the alveolar ridge of the jaws, which, in turn, becomes the basis for the occurrence of dentoalveolar deformities due to tooth migration [10]. Therefore, the effect of orthodontic appliances on the periodontal tissues of adult patients with even a minor inflammatory or dystrophic-inflammatory pathological process can be unpredictable.

## Aim

The aim of the study was to highlight the results of modern scientific developments in tracing the mechanisms of local stress-modeling effect of orthodontic appliances on the oral

cavity and periodontal tissues during the active period of orthodontic treatment.

## Materials and methods

The research methodology is implemented in the collection and analysis of scientific results on the stress-modeling effect of orthodontic appliances in patients with dentoalveolar anomalies, obtained from the processed sources – published full-text articles of original and fundamental research by national and foreign authors based on the evidential databases MEDLINE / PubMed, PMC, Scopus, Web of Science, Cochrane, Google Scholar, ResearchGate and other scientific and practical resources.

## Results

According to modern concepts, the human body responds to any adverse effect with a multilevel reaction, which leads to the development of a local or general stressful situation, resulting in adaptation or its disruption – maladaptation with the transition into a disease. According to classical concepts, the initial action of a stressor on an organism or a separate organ triggers a stress response, the so-called “urgent (emergency) adaptation”, which ensures the maintenance of homeostasis in new conditions. The basis of this stress reaction is the activation of a complex, united in the concept of “stress system”, which implements this reaction and the activation of “stress-limiting” systems that limit the intensity of the stress reaction. Only an optimal ratio of the activity of these two systems ensures an adequate response of the body to stressors and leads to the development of a general adaptation syndrome, in which the autonomic nervous system plays a leading role [11].

**Local manifestations of stress-modeling effect of orthodontic appliances on periodontal tissues.** Despite the widespread use of fixed orthodontic appliances in the active period of orthodontic treatment and a significant improvement in its effectiveness, the proportion of various complications, including changes in the tissues of the periodontal complex, is quite high and ranges from 32.7 % to 50.0 % of all cases [12,13].

The principle of orthodontic appliance operation is continuous, intermittent or alternating pressure on the teeth, bone tissue of the alveolar processes and jaws with the help of mechanical devices activated by spring wire, sliding screws, rubber rings, ligatures. The efforts of the masticatory and facial muscles are applied (in case of a disjointed bite), and the stereotypical movements of the lower jaw are changed. A continuously acting force presses on a tooth without a resting phase for a long period of time and, as a result, probably complicates the necessary tissue reorganization. In the periodontal tissues, an inflammatory process usually begins with disorders in the hemomicrocirculation system, manifested by congestion due to venous outflow disorders, perivascular edema, and diffuse perivascular hemorrhages. Moreover, the occurrence of a

local inflammation causes a violation of the entire microcirculatory system in the area involved in the pathological process, including the microcirculatory system of the tooth pulp, alveolar processes of the jaws and soft tissues [14].

During the active period of orthodontic treatment, about 90 % of patients report pain as one of the main discomforts. Separate studies have found that 39 % of patients experience pain or significant discomfort after each visit to the orthodontist for orthodontic appliance maintenance. This type of pain is usually mild/moderate (56–69 %), short-term (45 % lasted less than two days), during chewing (82 %), and not spontaneous (associated with chewing function, clenching or brushing) [15].

During orthodontic treatment, various forces act through braces and arches, causing the tooth to move in the alveolar bone of the jaws. In this regard, patients report two types of pain: immediate pain associated with periodontal compression and delayed pain associated with an inflammatory response. At the beginning of treatment, the pain peak occurs mostly 24 hours after the placement of elastic and/or fixed multibraces. Then the pain response decreases until it reaches a minimum level in about 7 days [16]. General discomfort, according to various studies, occurs in 65.7 % of cases, and in 34.3 % of cases the situation is limited to localized discomfort [15]. In terms of gender, most studies show no statistically significant differences among users of orthodontic appliances [17,18].

An analysis of the risk factors for periodontal disease in the use of braces has shown that orthodontic treatment with fixed orthodontic appliances leads to a significant decrease in the level of individual oral hygiene. As a result, the aggressiveness of periodontal pathogenic microflora increases, which causes the deepening of the inflammatory process in the periodontal complex tissues [19,20,21]. It was found that signs of inflammation in the gingival tissues significantly decreased after the removal of braces. Therefore, the improvement of periodontal tissue condition approximately 30 days after removal of braces from the oral cavity was accompanied by a decrease in the level of cultured *A. actinomycetemcomitans* and *B. forsythus*. However, such studies did not take into account the initial state of the periodontal pocket microbiota before orthodontic treatment [19,20,21].

The negative impact of fixed orthotics primarily affects the gingival soft tissues in the form of papillary hyperplasia and edema [22]. Most often it is a hypertrophic form of gingivitis [23]. The exact mechanism of gingival edema development is not yet fully understood, but it may be associated with increased production of amorphous basic substance with high levels of glycosaminoglycans by fibroblasts against the background of a reduced level of individual oral hygiene. Increased expression of collagen type I mRNA and increased keratinocyte growth factor receptor play an important role in the excessive proliferation of epithelial cells and the development of hypertrophic gingivitis [13].

The oral mucosa, in particular the buccal epithelium, which is part of the mucosal system, is an indicator of local and general homeostasis disorders. A comparative analysis of buccal epithelial cytograms in adolescents with DA revealed that before orthodontic treatment with a bracket system due to the existing inflammatory process in the gingival mucosa, 30 % of patients showed rejuvenation of the

epithelial cell layer: the appearance of parabasal epithelial cells, an increase in the number of cells in the III stage of differentiation and a decrease in the percentage of cells in the V stage. In the initial period of the active phase of orthodontic treatment, the incidence of catarrhal gingivitis and local periodontitis reached 76 % of cases. At the same time, the index of epithelial cell differentiation decreased, loosening of the epithelial layer, disruption of intercellular connections and desquamation of epithelial cells were observed. The index of alveolar bone destruction and the inflammatory-destructive index increased [24].

**Influence of orthodontic treatment on the processes of maxillary bone remodeling.** In response to the applied orthodontic forces, mechanical stimulation of cells and the associated extracellular matrix has the ability to directly regulate integrin expression, focal adhesion proteins, cytoskeleton organization, cell morphology, cell adhesion to the extracellular matrix, cell proliferation, and cell differentiation, thus affecting bone modeling [25]. In cases where the extracellular matrix is subjected to stress, isometric stress develops in the cells within the matrix. This isometric stress is equal in magnitude to the mechanical tensile force acting on the cells from the extracellular matrix and leading to changes in their cellular cytoskeleton and structure with activation of cellular transcription factors. In turn, this has an impact on how genes involved in cell adhesion, proliferation, differentiation, and death are expressed. Additionally, by applying direct mechanical stimulation to extracellular matrix proteins, cells can transfer the stress created in the actin cytoskeleton, affecting the three-dimensional organization of the extracellular matrix and its remodeling [26,27].

Orthodontic tooth movement determines the biological response of all supporting tissues to which the force is applied. Orthodontic force at the biological level has the ability to cause an acute inflammatory reaction in the periodontal tissues. Drastic changes can occur in the periodontal ligament and alveolar bone as a result of a biochemical adaptation reaction, which leads to the reorganization of the intracellular and extracellular matrix. There is a modification of local vascularization, which stimulates the cascade production, synthesis and release of arachidonic acid, metabolites, proteins, cytokines and growth factors [28,29].

Bone remodeling or remodeling is a physiological process that involves osteoclast-mediated bone resorption combined with osteoblastic bone formation. The ratio of bone production to resorption determines the bone mass. Following resorption, physiologically active substances such as bone morphogenetic proteins (BMPs), fibroblast growth factor (FGF), and transforming growth factor (TGF) are released from the organic matrix of the resorbed bone and enter the local microenvironment, where they stimulate osteoblast-mediated bone production. The bone marrow monocyte / macrophage lineage of hematopoietic stem cells gives rise to osteoclasts that break down a bone. The multiple cytokines, hormones, and growth factors that are involved in osteoclast differentiation. In turn, osteoclast function is mediated by complex interactions between several agents, including parathyroid hormone, calcitonin, vitamin D, macrophage colony-stimulating factor (M-CSF), tumor necrosis factor (TNF), estrogen, and several interleukins (ILs) [30].

The deformation of the bone matrix caused by orthodontic pressure creates a complex, heterogeneous biophysical environment in bone tissue consisting of fluid flow, direct mechanical stress, and electrokinetic effects. The latter are localized electric fields ( $\approx 6$  mV/cm) that arise endogenously as a result of piezoelectric effects and/or flow potentials. These biophysical signals trigger osteocytes' intracellular signaling pathways, which in turn excite mechanosensors and increase bone cells' sensitivity. Stretching deformations in the periodontal ligament and alveolar bone have the ability to stimulate the activation of osteogenic gene expression with the differentiation of osteogenic progenitor cells into mature osteoblasts that deposit osteoid, which subsequently undergoes mineralization. It has been established that bone formation caused by tensile stress is not associated with osteoblast proliferation, but with an increase in the rate of differentiation and maturation of osteoblast progenitor cells [27,31].

When studying the changes that occur during orthodontic tooth movement, it should be noted that the periodontal ligament is a fibrous structure of high tensile strength and relatively low elasticity that connects the tooth to the alveolar bone. When the interstitial fluid is displaced by a load, the ligament fibers become electrically charged, which causes these fibers to repel each other, simulating an elastic effect. The colloidal substances in the interstitial fluid act as dampers for the pseudoelastic fibers of the periodontal ligament: the fibers, fluids and colloids form a viscoelastic system. The thixotropic colloids of the periodontal matrix change from a "sol" state (solid in liquid) to a gel-like state depending on the amount of stress they are subjected to. This transition transforms the colloidal solution into an integral polymer network. Thus, the rate of fluid flow through the interstitial spaces of the periodontal ligament is regulated [32].

During the initial phase of orthodontic tooth movement, when a tooth is displaced within the space of the periodontal ligament, the latter becomes hyperemic, swollen and infiltrated with cells of the acute inflammatory process. The increase in inflammatory fluid and cellular infiltrate in the periodontal ligament and the adjacent alveolar bone affects the viscoelastic properties of both the bone and the ligament itself. There is a progressive decrease in the tensile strength of collagen bundles as a result of the release of matrix metalloproteinases and other catabolic agents that disrupt the cross-links and molecular integrity of the extracellular matrix. Accordingly, the hydrodynamic damping effect of the periodontal ligament decreases, and the elasticity of the bone increases [27,33,34].

The theoretical model that formalizes the induction of tooth movement following the application of an external force has multiple stages: first, stretching in the matrix of the periodontal ligament and alveolar bone leads to changes in fluid flow in both tissues. This causes cellular deformation and activates fibroblasts and osteoblasts in the periodontal ligament and osteocytes in the bone. The combination of ligament remodeling and alveolar bone remodeling allows the tooth to move [35]. Collagen fibers in periodontal ligament gaps are compressed, stretched, or twisted as a result of applied orthodontic stresses, thus disrupting the configuration of extracellular matrix proteins, integrating integrins and focal adhesion domains to reveal compounds that can activate fibroblasts [36]. Some of these

newly identified activating molecules and mechanically induced signals generated by orthodontic force induce the expression of genes encoding several proteins and enzymes necessary for remodeling the extracellular matrix of the periodontal ligament. Matrix metalloproteinases, serine proteases, aspartate proteases, and cysteine proteases are the enzymes that modify and breakdown collagen and other macromolecules. These proteins include fibronectin and collagen [34,37]. Cells in the periodontal ligament respond differently to tensile and compressive deformations, mediating predominantly catabolic tissue changes in areas of compression and predominantly anabolic activity in areas under tension. This coordinated ligament remodeling is important for orthodontic tooth movement [27].

Coverage of the biological processes occurring in the alveolar bone of the jaws during orthodontic movement of teeth is a crucial task of modern orthodontics. This is due to the fact that in cases when compressive deformations created by orthodontic forces exceed the elastic limit of the bone, either microfractures or degenerative changes can occur. As a result, local osteocytes in their lacunae and their cytoplasmic processes in the tubules connecting the lacunae in the bone tissue are disrupted. Within this three-dimensional tubular lacuna network, osteocytes communicate with each other and with osteoblasts through gap junctions at the tops of their cytoplasmic processes. The gap junction is a channel that connects the cytoplasm of two neighboring cells and allows the passage of ions, metabolites, and small signaling molecules such as adenosine triphosphoric acid (ATP) and  $Ca^{2+}$  [7]. This channel consists of two half-channels, each of which belongs to one of the adjacent cells. Each half-channel is called a gap junction and has six gap junction proteins. These gap junctions mediate direct intercellular communication between neighboring osteocytes and osteocytes with other cells on the bone surface, such as osteoblasts, osteoclasts, and cells of the vascular system [10].

Among the various proteins that form gap junctions, the most abundant protein present in bone cells is connexin 43 (Cx43) [38]. When two connexins, one of which belongs to the cell membrane of each neighboring cells, oppose and attach in the intercellular space, they form a functional gap junction channel. Electrical, chemical and mechanical factors affect the opening or closing of the gap junction opening. Integrins ( $\alpha 5\beta 1$ ) are activated mechanically by orthodontic pressures, which mediate the opening of Cx43 half-channels in osteocytes with the release of prostaglandin  $E_2$  and ATP into the microenvironment. The same orthodontic pressures that result from periodontal tissues being compressed and stretched also cause fluid flow shear stress with the expression of cyclooxygenase-2 (COX-2) and prostaglandin  $E_2$  receptor  $EP_2$  in osteocytes. As a result of activation of the  $EP_2$  receptor by prostaglandin  $E_2$ , there is an increase in the expression of Cx43, which leads to the creation of additional functional gap junction channels with improved passage of signal molecules and increased communication between bone cells. In the middle of the lacunocanalicular network, osteocytes and their cytoplasmic processes are washed by a fluid that transports signaling molecules, nutrients, and waste products and has a significantly different ion content than the extravascular interstitial fluid [9,28,39].

All bone cells experience changes in their microenvironment and fluid pressure as a result of orthodontic loading or overloading, which results in fluctuations in the inflow and outflow of this lacunocanalicular fluid, but especially on osteocytes confined to their own bone localization [36]. The fluid's viscosity and biochemical makeup, the type of organic membrane, and the physical traits of the lacunocanalicular system walls are all significant factors because osteocytes respond to the physical stimulus of the fluid flow by generating, amplifying, and transmitting signals through the gap junctions. It is this cross-talk between osteocytes that drives bone remodeling. Orthodontic loading causes microdamages to bone tissue, and, accordingly, the associated changes in fluid flow in the lacunocanalicular network can also damage osteocytes and induce their apoptosis. Osteoclasts can be attracted to the microdamage zone by signals from osteocytes that are undergoing apoptosis, where they, together with other bone cells, participate in bone remodeling [36]. As a result of bone damage, the local release of inflammatory mediators, cytokines, and growth factors such as NO, endothelin, prostaglandin E<sub>2</sub>, vascular endothelial growth factor (VEGF), and TGF- $\beta$  further promote bone remodeling, facilitating orthodontic tooth movement [7,10].

The inflammatory cascade is not critical for orthodontic tooth movement, but unregulated or excessive inflammation is problematic and leads to the destruction of the periodontal complex and tooth tissues in particular. Orthodontically induced root resorption (OIRR) and tissue remodeling should be limited to periodontal tissues, excluding root cementum and the tooth itself [40]. However, 1–5 % of orthodontic patients experience excessive root resorption with a loss of more than 4 mm or one-third of the original root length. Reducing the root length decreases the crown-to-root ratio of damaged teeth, which is of great clinical importance. The cellular mechanism of OIRR is similar to osteoclastic bone resorption and correlates with increased receptor activator of nuclear factor-kappa B ligand (RANKL) concentrations and decreased osteoprotegerin (OPG) levels in the periodontal ligament [41]. Orthodontic treatment of patients with a predisposition to gingivitis and periodontitis is particularly dangerous, as the combination of aseptic inflammation and inflammation associated with the activation of periodontopathogenic microflora causes accelerated loss of attachment and progression of the pathological process in the periodontal tissues [27].

Orthodontic forces in some cases can cause compression of the periodontal tissues with reduced blood flow and potential ischemic necrosis of the alveolar bone. A mild degree of ischemia and hypoxia cause the cells of the local microenvironment to express specific genes that regulate metabolic processes, allowing them to adapt to the changed microenvironment [7,42]. Under these conditions, growth factors and other biological agents are released from the bone matrix and from the compressed blood vessels, involving local bone progenitor cells and further bone remodeling.

If the orthodontic forces are within an acceptable therapeutic range, then compression ischemic necrosis of the bone will be negligible. This results in resorptive remodeling and controlled tooth movement [36]. On the other hand, if excessive orthodontic forces exceed the adaptive capacity of the damaged tissues, compressive forces can cause cell

death, hyalinization of tissue in the periodontal ligament, a zone of alveolar bone necrosis, and external root resorption. Subsequently, neovascularization and regeneration of the damaged periodontal ligament and alveolar bone occur [43,44].

According to other data, the reaction of periodontal tissues to "light" orthodontic forces, i. e. forces that are less than capillary blood pressure, leads to ischemia of the periodontal ligament with simultaneous bone resorption and formation. This results in more continuous tooth movement. A "moderate" force, i. e. a force that exceeds capillary blood pressure, leads to strangulation (clamping, pinching) of the periodontal ligament, which in turn delays the processes of bone resorption. "Strong / heavy" forces, i. e., forces that significantly exceed capillary blood pressure, lead to ischemia and degeneration of the periodontal ligament, which leads to hyalinization with a greater delay in tooth movement [36,45].

Thus, the applied orthodontic forces are transmitted through the tense tissue matrix to the local cells of the periodontal ligament and alveolar bone, stimulating the cells to release pro-inflammatory, angiogenic and osteogenic agents. They trigger the process of remodeling the periodontal ligament and the adjacent alveolar bone of the jaws. In bone tissue, tension in cells and their extracellular matrix caused by mechanical stress, as well as fluid flow stress, can mediate changes in cell gene expression. This results in the initiation of osteoclastogenesis and differentiation of osteogenic cells with subsequent production of nitric oxide, prostaglandins, osteocalcin, osteopontin, alkaline phosphatase, and type 1 collagen, thus contributing to bone formation and remodeling [35].

**Oxidative stress.** One of the biological reactions to orthodontic treatment and the subsequent development of the inflammatory process in the oral cavity is oxidative stress (OS). During orthodontic treatment, various inflammatory mediators (cytokines) that cause aseptic inflammation in the periodontal ligament are released after mechanical action on the teeth, causing a cascade of reactions in the periodontium, leading to tissue remodeling and tooth movement. Since there is strong evidence that periodontal inflammation is one of the main sources of reactive oxygen species (ROS) in the oral cavity, it can be assumed that aseptic inflammation may be associated with OS-related damage [46,47].

OS is defined as an imbalance between the production of free radicals and the body's ability to stop or minimize their harmful effects by neutralizing them with antioxidants. From a physiological point of view, there is a dynamic balance between the set of free radicals that have the ability to cause oxidative damage by ROS and the antioxidant defense capacity. The defense mechanisms of normal cells destroy most of these ROS and free radicals [47,48].

OS occurs when intracellular concentrations of ROS exceed physiological values. The cytotoxic effect of free radicals on cells is harmful and leads to cellular damage by affecting the peroxidation of double bonds of fatty acids, proteins and DNA. OS is defined as a change in the balance between the production of ROS and the antioxidant defense system that counteracts them. Free radicals, as well as ROS, are any chemical species with unpaired electrons that are produced from many sources, including

the environment (from ozone and nitrogen dioxide) and many different biological and biochemical processes [49].

Free radicals are neutralized by the antioxidant system. This system functions at the cellular, membrane and extracellular levels to protect against free radical attack. The components that make up this system include members of the catalase, peroxidase, and dismutase families, as well as the glutathione system, including superoxide dismutase (SOD) (converts superoxide to hydrogen peroxide), catalase, and glutathione peroxidase. During orthodontic treatment, two different situations coexist that can cause OS: on the one hand, the appliance itself, and on the other hand, the biomechanics of tooth movement. At the same time, the use of an orthodontic appliance often creates a complicated situation that provokes the development of OS due to an inflammatory reaction around the teeth that move [50].

**Corrosion processes in the oral cavity.** The oral cavity is exposed to a variety of external factors, including dental materials that have a significant oxidizing potential and the ability to generate ROS. Orthodontic appliances are made of ceramic, plastic (organic-polymer), and metal materials, which can release metals or other elements through the phenomenon of corrosion. This can increase ROS levels through various reactions with free radicals catalyzed by metals. Orthodontic materials affect the oral environment and enter into complex reactions with various components. Their influence on the parameters of saliva and oral mucosa is not fully understood, despite innovations in the development of orthodontic appliances and the nature of their interaction with tissues [51].

To date, according to various studies, no specific correlation has been definitively determined between the placement of an orthodontic appliance in the oral cavity and the exact biological and clinical consequences of this action [47]. During orthodontic treatment with fixed appliances, studies have been conducted on the local effects of heavy metals released from corroded areas. In particular, there are reports that metal ions, such as chromium, undergo a redox cycle, thus directly producing ROS through metal-catalyzed free radical reactions (Fenton reactions). *In vitro* studies have shown that ions of metals such as nickel, cobalt and chromium released from corrosive orthodontic braces and arches cause OS. Despite the lower corrosivity of titanium alloys, due to the protective layer of titanium oxide, mechanical friction in the contact between the bracket and the arch during orthodontic treatment leads to the destruction of the protective layer of titanium oxide, causing corrosion and the release of titanium ions, which can also produce ROS [51].

Thus, in the study conducted by V. Kovac et al. [50], the systemic level of OS during orthodontic treatment with fixed appliances in patients with clinically healthy periodontium, determined by capillary blood samples by the spectrophotometric method, was evaluated. Fixed orthodontic appliances consisted of stainless steel brackets (Gemini, 3M Unitek; USA) attached to the upper and lower teeth and two nickel-titanium arches (3M Unitek; USA) inserted into the bracket slots. Capillary blood was collected before the placement of the fixed orthodontic appliance and after 6 hours, 24 hours, and 7 days. The tested hypothesis was that the selected parameters of OS in capillary blood changed

significantly in the first week of orthodontic treatment with fixed appliances.

In assessing the risks of OS caused by metal ions released from fixed orthodontic appliances during orthodontic treatment, J. Primožič et al. found [52] that due to the simultaneous effects of corrosion, deformation, friction and mechanical action on fixed orthodontic appliances, braces and arches degrade, which causes higher concentrations of metal ions in the oral cavity. The authors provide an assessment of the health risk due to the amount of released heavy metals and the level of selected parameters of OS formed during treatment with fixed orthodontic appliances.

**Lipid peroxidation-antioxidant system.** The study at the modern level on the peculiarities of the pathogenesis of periodontal tissue diseases in orthodontic patients is impossible without a deep understanding of the metabolic mechanism role, in particular in the lipid peroxidation-antioxidant defense system, which form the basis of many pathological reactions of the human body. Under physiological conditions, the intensity of lipid peroxidation (LPO) is regulated by the antioxidant system (AOS), which is represented in the body by enzymatic and non-enzymatic components. The AOS protects cells and the body as a whole from the toxic effects of oxygen radicals and lipid peroxides and neutralizes toxic products that cause membrane-destructive effects [53]. Violation of the oxidation-antioxidant balance leads to OS, characterized by a significant increase in the processes of LPO, accumulation of free radicals against the background of reduced activity of antioxidant defense (AOD) [54].

A common pattern in all types of inflammatory processes is an increase in LPO against the background of a decrease in the activity of the physiological AOS of the body. One of the main reasons for the activation of LPO in various pathological processes is tissue hypoxia, which occurs due to impaired tissue ability to absorb oxygen from the blood or due to a decrease in the efficiency of enzymatic oxidation. Oxygen utilization by tissues can be impeded as a result of inhibition of biological oxidation by various inhibitors, impaired enzyme synthesis, or damage to cell structures [7]. A number of reasons cause the activation of ROS in periodontal tissues: a decrease in the intake of such alimentary antioxidants as tocopherol, ascorbate, bioflavonoids, etc.; stress of various genesis (under the influence of catecholamines and corticosteroids, excess fatty acids and oxygen enter the bloodstream); external chemical oxidants (pesticides, drug oxidants, alcohol, etc.); physical factors (increased radioactive background, electromagnetic field, ultraviolet and laser irradiation, etc.); excessive and unbalanced intake of fats and carbohydrates against the background of insufficient consumption; hypokinesia with low levels of biological oxidation of enzymes (reduced level of pyridine nucleotide reduction); congenital enzymopathies of antioxidant enzymes (catalase, glutathione reductase, glutathione peroxidase, glucose-6-phosphate dehydrogenase; a decrease in the activity of antioxidant enzymes with age [55].

The stress-modeling effect of orthodontic appliances leads to changes in the activity of antioxidant enzymes in the oral fluid and the concentration of LPO products. In the oral cavity, free radicals catalyze the oxidative modification of proteins and lipids of the mucous membrane. There is

evidence of changes in the levels of beta-interleukin-1 (IL-1 $\beta$ ), TNF- $\alpha$ , malondialdehyde (MDA), nitric oxide (NO), and 8-hydroxydeoxyguanosine (8-OHdG) in oral fluid and in samples of gingival sulcus fluid (crevicular fluid) by spectrophotometric method in patients without periodontal disease with fixed orthodontic appliances [34]. Against the background of measurements of clinical periodontal parameters, samples were taken from all patients before orthodontic treatment, and then at 1 and 6 months of treatment. While the level of IL-1 $\beta$  detected in the crevicular fluid at the 6th month of orthodontic treatment was statistically significant compared to the baseline, all other biochemical parameters in the samples did not show significant changes in any measurement period. The authors found that orthodontic tooth movement and orthodontic materials used in the active period of treatment in patients without periodontal pathology did not lead to changes above physiological limits. This indicates the absence of oxidative damage to both gingival and oral fluids.

According to another report, C. Menéndez López-Mateos et al. studied the level of salivary markers of OS in groups of young patients undergoing orthodontic treatment with clear aligners and fixed self-ligating braces using "light forces" [56]. At the initial stages of orthodontic treatment, the use of both types of equipment did not cause changes in the indicators of total antioxidant capacity (TAC) and myeloperoxidase activity (MPO). An increase in the levels of products of deep oxidation of proteins (AOPP) was observed only after the first 30 days of treatment. At the same time, there were no differences in AOPP levels between treatment with clear aligners and self-ligating braces during the first 90 days of treatment. The antioxidant capacity of the oral fluid at the initial stages of orthodontic treatment in patients with clinically intact periodontium when using both types of orthodontic appliances did not undergo significant changes.

Reports on the analysis of enzyme activity using biochemical methods, which can be used to more accurately assess the degree of damage to the periodontal tissues and fully monitor the treatment process, concerned the level of lactate dehydrogenase (LDH) in the crevicular fluid, which is released from the cytoplasm into the extracellular space after programmed cell death in gingivitis or periodontitis, including during orthodontic treatment [57,58]. Changes in LDH levels were recorded depending on the type, magnitude, and direction of orthodontic force application. The time of increase in LDH levels varied depending on the applied force level. Moreover, when applying "heavy" forces (250 g), an increase in enzyme levels occurred in 2 weeks, and when used for molar distalization compared to an increase in force by 125 g – in 3 weeks [6].

In similar studies, the ratio of activity, enzymatic reaction rate and changes in the value of the Michaelis constant for the enzymes lactate dehydrogenase (LDH)/amylase and alkaline phosphatase (ALP)/amylase were used to diagnose the degree of inflammation in the periodontal complex tissues. *In vitro*, a decrease in the activity of amylase was found against the background of an increase in the activity of LDH and ALP enzymes. Therefore, an increase in the index of the speed of the biochemical reaction ALP/amylase for periodontitis of the third degree of severity was noted in comparison with the index of intact periodontium by four times. Thus, the use of enzyme indices in the diagnosis

of different degrees of periodontitis allows to predict the development of the pathological process more accurately and to start treatment measures in a timely manner [57,59].

## Conclusions

1. The local stress-modeling effect of orthodontic appliances on the periodontal tissues is an urgent problem of modern dentistry.

2. The development of oxidative stress during orthodontic treatment can be caused by various factors: local and systemic exposure to metals, corrosion processes in particular; inflammation of the periodontal tissues due to poor oral hygiene and activation of periodontal pathogenic microflora; aseptic inflammation in the periodontal ligament due to the use of mechanical force.

3. About 90 % of patients report experiencing various types of pain during the active period of orthodontic treatment.

4. During the active period of orthodontic treatment, cells in the periodontal ligament react differently to tensile and compressive deformations, mediating mainly catabolic tissue changes in areas of compression and mostly anabolic activity in areas under tension. Orthodontic forces are transmitted through the stressed tissue matrix, stimulating the cells of the periodontal ligament and alveolar bone to release pro-inflammatory, angiogenic and osteogenic agents. They trigger the process of periodontal ligament and the adjacent alveolar bone of the jaws remodeling.

5. Numerous studies have shown the absence of oxidative damage to samples of oral and crevicular fluids in young patients during active orthodontic treatment under the influence of orthodontic appliances against the background of clinically healthy periodontium.

6. *In vitro* and *in vivo* studies on changes in biomarkers of oxidative stress in the local environment due to the influence of orthodontic fixed appliances insufficiently cover the problem of oxidative stress induction at the systemic level in patients with a predisposition to the periodontal pathology development.

7. Oral fluid lactate dehydrogenase can act as a sensitive marker of changes in the periodontal ligament metabolism during orthodontic tooth movement.

8. The localization and nature of free radical pathology are largely caused by the nature of the exogenous inducer of lipid peroxidation and the genotypic characteristics of the antioxidant system. It is this ratio that determines the initiation and further branching of chain free radical reactions. Without normalization of all pathogenetic links, successful treatment of inflammatory and dystrophic-inflammatory diseases of periodontal tissues, in particular in orthodontic patients, is impossible.

**Prospects for further research.** It is necessary to deepen methodologically sound research and develop effective therapeutic and preventive measures on their basis to eliminate the local stress-modeling effect of orthodontic fixed appliances on periodontal tissues. The data on the brace effect on the chemical composition of mixed saliva during active orthodontic treatment are not sufficiently covered in the literature. In view of this, research in this area will be relevant not only for theoretical but also for clinical use. It is promising to discuss approaches to avoiding oxi-

dative stress and recommendations for the prophylactic use of antioxidants during orthodontic treatment.

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