BIOMARKERS OF ORTHODONTIC TOOTH MOVEMENT

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Objectives

Orthodontic tooth movement (OTM) leads to remodeling of periodontal ligament, alveolar bone, and gingiva (Fig. 1). Tooth movement is characterized by bone deposition at sites of tension and bone resorption at pressure sites (Fig. 2). Due to a sterile inflammatory process in the PDL space, a flow rate of gingival crevicular fluid (GCF) is increased and its composition is modified (Fig. 3). Various cell-signaling pathways are activated, which ultimately stimulate PDL turnover, as well as localized bone resorption and bone deposition (Fig. 4). Biochemical and cellular processes associated with orthodontic tooth movement may be better understood if we study changes of specific biomarkers in GCF during orthodontic therapy. Such information can be used clinically to choose a proper mechanical loading, to shorten a period of treatment, and to avoid adverse consequences, such as root resorption.

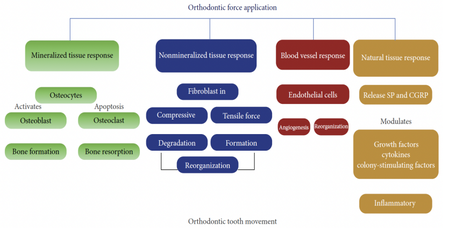
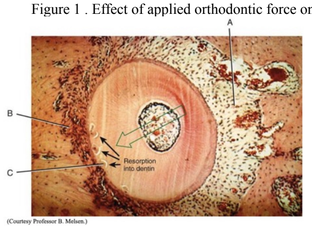


Figure 1 . Effect of applied orthodontic force on mineralized and non mineralized tissues (Fabrizia et al., 2013)



(Courtesy Professor B. Melsen.)

Figure 2. Coronal section through the root of a premolar being moved to the left (arrow). The histological picture shows reactions of tissues in PDL space to application of force on a tooth. The tension zone is wide, strings of osteoblasts are visible reflecting proliferation and migration of osteoblasts, blood vessels are enlarged (A), the compression zone is narrow, with packed cells and hardly visible blood vessels meaning a limited blood flow, lacunae formed by osteoclasts are visible in the alveolar bone (B), even lacunae in the root surface (areas of external root resorption by osteoclasts) are seen (C). *(Proffit et al. 2007)*

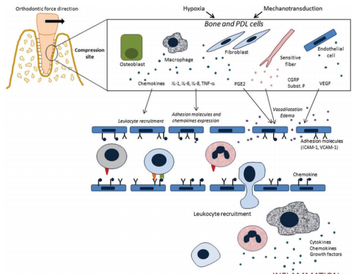


Figure 3 . Inflammatory innate immune response of PDL to movement of a tooth. (Andrade et al., 2012)

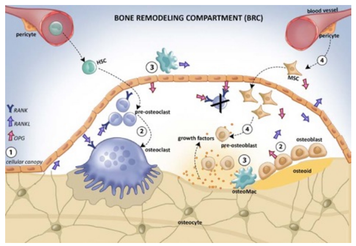


Figure 4. Diagram of bone remodeling. (1) bone that is not remodeled, (2 on the left side) monocytes are attracted into the active remodeling zone and differentiate into osteoclasts, (3) local macrophages digest bone osteoid and release growth factors that were embedded in it, (4) pericytes are the source of new osteoblasts that are triggered by growth factors to proliferate, differentiate and form a new osteoid (2 on the right side). *(Matsumoto et al, 2016).*

Methods

Various systematic reviews and original articles were studied and analyzed to identify the changes in GCF biomarkers and their roles during orthodontic treatment. GCF has been extensively studied due to simple, quick, and noninvasive nature of its collection and ease of repetitive sampling from the same site with the help of platinum loops, periopaper strips (Oraflow) (Fig. 5), gingival washings, or micropipettes. GCF is then analyzed for content of various biochemical markers.

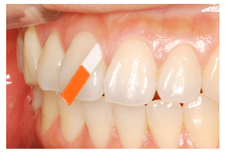


Figure 5 Periopaper strips

Results

Biomarkers of orthodontic tooth movement quantified in GCF can be classified into categories corresponding to specific biochemical pathways altered by application of orthodontic force. The main pro-inflammatory mediators released are interleukins (IL) IL-1α, IL-1β, IL-2, IL-6, IL-8 and tumor necrosis factor alpha (TNF-α), which act on PDL surfaces undergoing compression. Chemokines released during tooth movement are monocyte chemoattractant protein-1 (MCP-1) and CCL3, which up-regulate osteoclastic differentiation, as well as CCL5, which down-regulates bone resorption. Additional inflammatory mediators, such as prostaglandins (PGs) and neuropeptides, act as local and systemic factors to stimulate bone remodeling. The expression patterns of macrophage colony-stimulating factor (M-CSF), receptor activator of nuclear factor kappa B ligand (RANKL) and osteoprotegerin (OPG) by osteoblasts play key roles in tooth movement. Significance of biomarkers specific for consecutive stages of orthodontic tooth movement is shown in the Table 1.

Table 1 . Biomarkers and their role in orthodontic tooth movement (Kumar et al., 2015)

Inflammatory biomarkers	Role
Prostaglandin E2	Stimulate octeoclasts, bone resorption
Substance P (neuropeptide)	Bone resorption, induction of osteoclast differentiation
Epidermal growth factor	Bone formation
Transforming growth factor beta	Bone remodeling
RANKL	Stimulation of osteoclastic differentiation and function
Osteoprotegerin (OPG)	Inhibition of osteoclastic differentiation and function
Granulocyte macrophage colony stimulating factor	Bone turnover
α2 microglobulin	Enhancer of IGF-1
Interleukin 1β, 2, 6, 8	Bone remodeling
Myeloperoxidase	Enzyme in PMN, inflammation
Tumor necrosis factor alpha (TNF-α)	Stimulates octeoclasts, bone resorption

Metabolic products of paradental remodeling	Role
Hyaluronic acid	Indicator of breakdown of gingival tissue
Chondroitin sulfate	Indicator of breakdown of bone and PDL
Pentraxin-3	Marker of innate inflammation
Osteocalcin	Bone turnover
Insulin-like growth factor 1 (IGF1)	Regulator of cell differentiation vs apoptosis
Pyridinoline, deoxypyridinoline	Collagen I metabolism, bone resorption
N-telopeptide	Collagen I metabolism, bone resorption
Dentin matrix protein	Root resorption

Enzymes and chemoattractants	Role
Acid phosphatase	Bone resorption
Alkaline phosphatase	Bone formation
Aspartate amino transferase	Indicator of cell death
Cathepsin B	Extracellular matrix degradation
Matrix metalloproteinases (1, 2 and 8)	Breakdown of denatured collagen
β glucuronidase	Marker of granule release from PMN
Lactate dehydrogenase	Indicator of cell death
Monocyte chemoattractant protein 1,2 (MCP 1,2)	Recruiting monocytes that turn into osteoclasts
CCL 3	Up regulates osteoclast differentiation
CCL 5	Down-regulator of alveolar bone resorption

Conclusions

Study and knowledge of ongoing processes in periodontal tissues during orthodontic treatment can lead to a proper choice of mechanical loading, shortening of treatment, better planning and minimizing adverse consequences (Fig. 6). However, majority of the studies were focused on individual biomarkers, which are representative of only a single biochemical pathway. Future research needs to assess groups of GCF biomarkers, thus providing a more complete understanding of the overall response of periodontal tissues to application of orthodontic force.

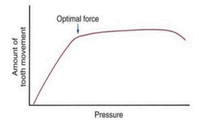


Figure 6. Tooth movement increases as pressure increases up to a saturation point and then plateaus. It is important to understand dynamics of biomarkers along this curve as well as in saturation point. Increasing pressure further may have detrimental effects (root resorption). (Proffit et al., 2007)

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