REVIEW ARTICLE

Biomarkers in Orthodontics

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ABSTRACT

Orthodontic appliances stimulate cells within the periodontium to release biologically active substances. Such molecules evoke cellular responses in different cell types in and around teeth, which provides a favourable microenvironment for tissues to respond accordingly .The sequence of events following orthodontic tooth movement [OTM] can be characterized using such released molecules termed as biomarkers. The rate, amount and activity of the released substances/ biomarkers not only reflect the activity of individual cells but also indicate the metabolic activity in the involved tissues or organs.The knowledge of these biomarkers could be used in accelerating orthodontic treatment.

KEYWORDS: Biomarkers, Orthodontics, re-mineralization, OTM

INTRODUCTION

Orthodontic force application causes tooth movement which is characterised by remodeling changes in the dental and periodontal tissues.[1] The magnitude, direction and duration of applied force causes changes in periodontium.[2] Orthodontic force not only causes mechanical loading of dental tissues but also changes the vascularity of adnexal periodontal apparatus which in turn synthesizes and releases various molecules such as neurotransmitters, cytokines, growth factors, colony-stimulating factors (cytokines that are involved in maturing of various leucocyte, macrophage, and monocyte line), and arachidonic acid metabolites. These biologically active molecules provide a favourable environment for tissue resorption and deposition. Various cell-signalling pathways are activated which ultimately stimulate PDL turnover, as well as localised bone resorption and bone deposition.[3]

The sequence of events following OTM can be characterized using suitable biomarkers. The rate, amount, and activity of the released substances/ biomarkers not only reflect the activity of individual cells but also indicate the metabolic activity in the involved tissues or organs. Potential biological markers can be collected from different tissue samples, and suitable sampling is important to accurately reflect biological processes. Several possible biomarkers representing these biological changes during specific phenomenon, that is, bone remodeling (formation and resorption), inflammation, and root resorption have also been proposed. A biomarker can be used as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

Rate, amount and activity of biomarkers depict not just activity of individual cell but metabolic activity of tissue and organ together. So knowledge of these biomarkers may be clinically used in accelerating orthodontic treatment.

MATERIALS AND METHODS

Markers of Alveolar Bone Remodelling: Under normal conditions there occurs constant remodeling of tooth supporting tissues causing physiological tooth migration. The orthodontic intervention causes prolonged pressure on the teeth resulting in enhanced remodeling of periodontal structures, including supracrestal gingival and periodontal ligament (PDL) fibers, and alveolar bone.[4] The remodeling reactions involve differentiation of resident PDL cells into osteoblasts and fibroblasts.[5] Osteoblasts regulate osteoclasts recruitment and activity and control both the resorptive and formative phases of the bone remodeling cycle. Chemokines contribute in establishment of distinct microenvironments in compression and tension sites and cause differential bone remodeling in response to orthodontic force.[6] Matrix metalloproteinases[MMPs] break down the extracellular matrix and are important in bone remodeling. MMP-2 is an important marker for active tooth movement during very early stages of orthodontic treatment. Its level increases significantly in a time-dependent fashion, reaching a peak after 8 hours of force application.

Markers in bone formation: Procollagen type I C-terminal propeptide (PICP) and procollagen type I N-terminal propeptide (PINP) are two important bone

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formation markers. These are either osteoblastic enzymes or products of osteogenesis secreted by osteoblasts such as Type I procollagen . However, these are not specific bone markers. There are other important and more specific bone formation markers like Cbfa1 and Osterix which are transcription factors [TF] for early and late osteoblastic activity respectively while osteocalcin which is product of osterix acts as terminal osteoblast differentiation marker.

Osteogenesis may be promoted by growth factors [GFs] through their interaction with specific surface receptors on osteoblasts which in turn stimulates insulin-like GF-1which is a primary mediator of growth-promoting effects of growth hormone (GH) on bone and also regulates cell growth and development.

Markers of bone resorption: Osteoclasts are responsible for bone resorption and the earliest marker of this process is Interleukin- 1 beta (IL-1*β*).[7]

The potential sources of IL-1β during tooth movement include cells such as fibroblasts, macrophages, cementoblasts, cementoclasts, osteoblasts, and osteoclasts.[8] IL-1β is secreted by osteoclasts in initial stage of OTM as an immediate response to mechanical stress and by macrophages which accumulate in compressed areas in later stages. It is a powerful inducer of yet another chemokine Interleukin-6 (IL-6) . Even biological actions of IL-1β overlap with those of IL-6 and Tumor Necrosis Factor-α (TNF-α).[9]

All these proteins regulate osteoclastic activity by activation of the nuclear factor kappa B (RANK) and nuclear factor kappa B ligand (RANKL). Osteoblasts synthesise RANKL, which also controls this process by promoting more osteoclast differentiation.[10]

Bone metabolism is regulated by Osteoprotegerin (OPG) and RANK-RANKL; the TNF-related ligand and its decoy receptor. Many hormones and cytokines produce their anti-resorptive effect through RANKL which is a downstream regulator of osteoclast formation and activation.[11] RANKL is present on osteoblasts while RANK receptor on osteoclast and their binding produces the resultant biological effects. Oshiro et al.[12] in their study found that during OTM there are changes in RANK, RANKL, and osteoprotegerin (OPG) in the tooth-supporting tissues. Actually compressive forces upregulate PGE2 and RANKL while OPG is inhibited, all this together leads to osteoclastogenesis.[13,14] During severe orthodontic root resorption also increase in RANKL and decrease in OPG has been observed.[15,16] Therefore, root resorptive processes need specific biomarkers other than RANKL or OPG in order to apply optimum force during OTM.

Bone remodeling is controlled by a balance between RANK-RANKL binding and OPG production . In a recent study by Kanzaki et al.[17] it was found that OPG gene transfer inhibits RANKL- mediated osteoclasto-genesis in periodontal tissues and also experimental tooth movement in animal models. So it is hypothesized that the inhibition of the osteoclast differentiation promoting activity of RANKL may be helpful in preventing movement of anchor teeth during OTM and also prevent relapse post –treatment.

Markers of Inflammatory Processes: Neuroimmune interactions may be of primary importance in the initial inflammatory response during experimental tooth movement.[18] Interleukin-1β (IL-1β) is one of the most potent cytokines in periodontal environment in initial stage of OTM. Another proinflammatory cytokine that is involved in acute or chronic inflammation is TNF-α. In presence of macrophage- colony – stimulating factor [M-CSF] osteoclast progenitors are directly differentiated into osteoclasts which stimulates bone resorption.[19] M-CSF has an important implication in OTM. It causes an increased early osteoclastic recruitment and differentiation.[20] Various clinical and animal studies have also identified the role of prostaglandins E (PGE_1 and PGE_2) in mediating inflammatory responses and stimulating bone resorption by activating osteoclasts.[21]

Markers of Root Resorption: An unwanted iatrogenic outcome of orthodontic tooth movement is root resorption. Pre- existing root conditions, type of tooth movement, amount and type of force, treatment duration and racial predilection are important risk factors associated with root resorption.[22, 23, 24]

Kereshanan et al reported the potential for measuring dentine sialoprotein (DSP) in GCF as a biomarker to monitor root resorption.[25] DSP is one of the non-collagenous proteins found in dentin. Others being DMP1 (dentine matrix protein 1), dentinephosphoprotein (DPP). DPP and DSP are products of mRNA transcription and are portions of one expressed protein known as dentine sialophosphoprotein (DSPP).

CONCLUSION AND CLINICAL RELEVANCE

Suitable biomarkers may be used to characterize the sequence of events following OTM. Evaluation of amount and rate of synthesis of biomarkers in periodontium may help to assess the biological mechanisms which control shift of stimulus from continuous force application to reaction and displacement of tooth in periodontal space. This knowledge of the ongoing process occurring in periodontal tissues during orthodontic and orthopedic therapies in turn may help us to make proper choice of mechanical loading and may shorten the period of treatment. It may also help to avoid adverse consequences such as root resorption or bone loss associated with orthodontic treatment.

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