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Submission date: 17-Sep-2020 01:33PM (UTC+0800)
Submission ID: 1389244866
File name: gingival_crevicular_fluid_during_orthodontic_tooth_movement.pdf (65.62K)
Word count: 2870
Character count: 15452

DOI : 10.35124/bca.2020.20.S1.2903

Biochem. Cell. Arch. Vol. 20, Supplement 1, pp. 2903-2906, 2020 | www.connectjournals.com/bca | *ISSN 0972-5075*

CYTOKINES AND CHEMOKINES IN THE GINGIVAL CREVICULAR FLUID DURING ORTHODONTIC TOOTH MOVEMENT : A REVIEW

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Received 6 March 2020, Revised 5 May 2020, Accepted 11 May 2020)

ABSTRACT : Chemokine and cytokine that recognized in gingival crevicular fluid (GCF) during orthodontic tooth movement (OTM) is critical to anticipate or distinguish the inflammation in the bone remodeling. Chemokine and cytokine during OTM which happens toward in the initial of this procedure as a response to mechanical force. Chemokine and cytokine can be recognized in GCF were secreted consecutively in different phase of OTM. The purpose of this study is to describe that there are cytokines and chemokine that stimulate the osteoclast or osteoblast activity during OTM, for instance, Interleukin (IL)-1, IL-6 and Tumor Necrosis Factor Alpha (TNF-α). This study method with precise audit utilizes one database, PubMed as a database and as indicated by the pursuit utilizes the free content term, in particular cytokines and chemokine during OTM. The consequences of the study show that there were some cytokine and chemokine play important role during OTM. Osteoprotegerin (OPG) expression was found in 24 hours and an expansion in Receptor activator of nuclear factor κB (RANK) and Transforming Growth Factor-Beta (TGF-β) expression following 7 days was detected. Others inflammatory mediators for example, IL-1b, which increment most quickly 1 minute or following 4 hours, Receptor activator of nuclear factor κB Ligand (RANKL) following 42 days or following 24 hours and 24 hours, IL-8 following 4 hours or 10 days was detected.

Key word : Cytokines, chemokines, orthodontic technique, gingival crevicular fluid.

INTRODUCTION

Orthodontic Tooth Movement (OTM) can be done through the application of orthodontic force by means of orthodontic appliance (Narmada *et al*, 2019). The application of orthodontic force can stimulate the inflammatory response in the periodontal tissue (Sitasari *et al*, 2020). The surrounding cells in the tooth will be stressed and induce the signaling of cellular and molecular cascade of inflammatory response (Hermawan *et al*, 2020). The sterile inflammatory response will be occurred due to orthodontic force (Nugraha *et al*, 2020). The initial phase of OTM is the enhancement permeability of vascular and leukocyte infiltration (Nareswari *et al*, 2019). The homing or migration of immune cell may secrete the inflammatory cytokine and chemokine (Krishnan and Davidovitch, 2006).

The biomolecular and biochemical inflammatory mediator are secreted eventually inthe different stage of OTM. It can be detected in thegingival crevicular fluid (GCF) (Suparwitri *et al*, 2019). GCF is a biology fluid that can be found in the gingival, which is a suitable fluid for investigation or study for the inflammatory mediators during OTM with high sensitivity (Masella and Richard, 2006). GCF can be obtained easily and noninvasively within several times of OTM (Alhasyimi *et al*, 2018). In addition, the cryopreserved of GCF is possible (Uitto, 2003). Cytokines are proteins with small molecular weights (mW 25kDA) released autocrine and paracrine in response to local stress cell signals (Roberts *et al*, 2004). The inflammatory cytokines such as Interleukin (IL)-1, IL-2, IL-3, IL-6, IL-8, Tumor Necrosis Factor-α, and Interferon γ (IFN-γ) can be detected in the GCF during OTM (Ren *et al*, 2007).

The secretion of various mediators is produced by cells activated by orthodontic forces. The OTM rate depend on the alveolar bone remodeling (Nugraha *et al*, 2019). The alveolar bone remodeling is the homeostasis of bone formation in the tension side and bone resorption in the compression side (Hisham *et al*, 2019). The osteoclast and osteoblast are the cell which have the important role in the alveolar bone remodeling (Roberts *et al*, 2004; Rezkita *et al*, 2020). Previous studies have shown that cytokines and some inflammatory markers can activate alveolar remodeling (Saito *et al*, 1990; Yao

et al, 2008). There are cytokines that enhance the differentiation and activation of osteoclast such as IL-1b and TNF-α (Ba°aran *et al*, 2006). The aim of this study is to describe the cytokine and chemokine that can be detected in the GCF during the OTM.

METHODS

This was narrative review used a single database, PubMed as a database and according to the search uses the free text term that is the OTM cytokine. The words are then entered into PubMed. The inclusion criteria for the data found were researched with a randomized control test. Interventions and exposures to cytokines include IL, TNF-α, growth factor (GF), macrophage colony-stimulating factor (M-CSF), Interferon (IFN), chemokines, RANK, RANKL, OPG with specific specifications in OTM biomolecular mechanisms, orthodontic force applications, and GCF sample collections. Exclusion criteria are studies other than cytokines, chemokines and receptors in periodontal tissue inflammation without OTM.

RESULTS

Based on this review results with related methods obtained forty studies which were then included. Fifteen studies meet the inclusion criteria. Two studies discuss biomarkers in OTM, one study discusses chemokine ligands in OTM, one study discusses the saturation of biological responses in orthodontic forces, and the other one discusses OTM effect in the cytokine level detected in GCF.

Gingival Crevicular Fluid

The gingival crevicular fluid is a liquid that can be collected from the gingival sulcus, which is one of the samples and is a source of factors related to cellular or molecular changes that occur in the periodontium during OTM. The GCF is useful due to it can be collected non-invasive and easy to re-examine in the same area (Suparwitri *et al*, 2019).

Mediator of OTM

Cytokine and mediator of orthodontic tooth movement areIL-1B, TNF-a, IL-8, IL-6, IL-2, IL-4, IL-10, IL-1, IL-5, IL-1a and RANKL (Kapoor *et al*, 2014). The receptors OPG, Interleukin-1a Receptor (IL-1aR) and RANK were found during OTM. Chemokines are chemokine ligand 5 (CCL5) and monocyte chemoattractant protein (MCP-1) can be found in the GCF (Alikhani *et al*, 2013). Growth factors such as Vascular Endothelial Growth Factor and Fibroblast Growth Factor can be detected during OTM (Inayati *et al*, 2020). Increased mediators such as cytokines and prostaglandins were found in the GCF of OTM, which were marked as biomarkers in these phases. Post orthodontic force applications in 24-hour, Real Time-Polymerase Chain Reaction (RT-PCR) can be used to analyze chemokines, receptors and 92 cytokine mRNA level. Biomolecular analysis showed an increase in cytokine levels within 24 hours in course of OTM. Chemokine levels increased significantly after 24 hours after OTM. It was known that the levels of CCL-2, CCL-3, CCL-5 and IL-8 increased during OTM. CCL2, CCL5, IL1 and TNF-α activities increased significantly with each orthodontic strength (Capelli *et al*, 2011).

DISCUSSION

This narrative review describes the cytokines, chemokines, receptors and antagonists during OTM. The initial biomolecular bone marker that increase are IL-1b, IL-8, RANKL and TNF-α. Those markers are the earliest marker that increase from 1 minute to 1 hour and it reaches the peak at 24 hours due to OTM. In 48 hours, 168 hours, 14 days and 21 days, thoseinflammatory mediators slowly decreased (Kapoor *et al*, 2014). In contrast, biomolecular mediators of bone formation such as OPG showed a decreased expression or level of 1 hour and 24 hours after OTM. During osteoclastogenesis, the role of RANK, RANKL and OPG has been seen studied in the animal model and *in vitro* studies (Oshiro *et al*, 2002; Kanzaki *et al*, 2006). After orthodontic force was applied, RANKL expression upregulation occurs which stimulates the Prostaglandin E2 (PGE2) pathway and osteoclast activity begins which results in bone resorption (Kanzaki *et al*, 2001; Wise *et al*, 2008). OPG formed by osteoblasts and periodontal ligament cells will bind to RANKL and will inhibit RANK/RANKL interactions and osteoclastogenesis (Boyce *et al*, 2008).

Apart from receptors, several factors that influence osteoclast differentiation, maturity and activity are cytokines such as TNF-a, IL-1b, IL-6 and chemokines such as CCL9, CCL7, CCL5, CCL2, CCL3 (Yano *et al*, 2005; Yu *et al*, 2004). There was an increased in this mediator in GCF in the application of orthodontic strength. The evidence suggests that mechanical stress induces acute inflammation that affects the microvascular environment, which will support the release of IL-1b, TNF-α and local chemokine expression, which increases the adhesion and migration of leukocytes. In IL-1b, PGE2 and TNF-α levels show an initial increase (Karacay *et al*, 2007; Ren *et al*, 2002). The latest technique for accelerating orthodontics, namely micro-osteoperforation, is also known to cause an increase in cytokine levels in GCF such as IL-1a, IL-1b, IL-6 and TNF-α and chemokine at 24 hours, which shows that the inflammatory process is associated with induction of

cortical bone perforation. Previous study showed that the release of pro-inflammatory cytokines by micro perforation is known to recruit osteoclast precursors and increase OTM by affecting the process of bone remodeling (Teixeira *et al*, 2010).

Previous study mentioned that, there was a decrease in OPG within 24 hours and an increase in RANK and TGF-B1 after 7 days. In addition, IL-1b level increase as quickly as 1 minute or after 4 hours, RANKL after 42 days or after 24 hours and 24 hours, IL-8 after 4 hours or 10 days. In contrast, TNF-α and various other mediators such as IL-1b, PGE2 and IL-8 show an increase in tension areas during OTM (Nishijima *et al*, 2006).

This study summarizes that growth status and age are factors that influence cytokine levels in the GCF and affect the rate and number of tooth movements, as well as variations between growth status in young and adult individuals.

CONCLUSION

There are some cytokine and chemokine important to OTM that can be detected in GCF such as OPG, RANK, RANKL, TNF-α, IL-1b and IL-8. Those cytokines and chemokine can be useful for further study to predict or detect the inflammatory response during OTM.

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