CHAPER II

REVIEW OF LITERATURE

The literature review comprises six topics, including

2.1 Treatment of skeletal open bite

2.2 Assessment of molar intrusion

2.3 Assessment of miniscrew implant stability

2.4 Gingival crevicular fluid and peri-miniscrew implant crevicular fluid

2.5 Biomarkers in gingival crevicular fluid

2.6 Alkaline phosphatase

2.1 Treatment of skeletal open bite

Treatment of skeletal open bite is a challenging procedure. In adult patients with severe open configuration, surgical maxillary impaction is required to achieve counterclockwise rotation of the mandible and subsequent reduction of anterior facial height. Nonetheless, complexity, risks and cost are limitations of orthognathic surgery. Dental compensation can be optional for borderline cases and for those who are reluctant to undergo orthognathic surgery.

Orthodontic molar intrusion procedure can be performed to decrease the posterior dentoalveolar height, which causes mandibular rotation simultaneously. This brings significant alteration of skeletal pattern and soft tissue profile. Recently,

several reports showed the success of molar intrusion using miniscrew implants with different techniques and placement sites.[1-2, 15-16]

2.2 Assessment of molar intrusion

Conventionally, observation of orthodontic molar intrusion is conducted by clinical and radiographic evaluations. Biochemical test can be carried out to assess treatment result. To explain the biological responses *in vivo*, various biomarkers in gingival crevicular fluid have been monitored. A number of gingival crevicular fluid constituents have been shown to be diagnostic markers in periodontal status[17] and tissue response to orthodontic force.[18] Isik *et al*. observed the changes in several bone turnover markers during the experimental orthodontic intrusion of maxillary premolar teeth. The results showed that deoxypyridinoline, osteocalcin, and bone alkaline phosphatase values were decreased with force application.[18]

2.3 Assessment of miniscrew implant stability

The assessment of dental implant stability could be used for miniscrew implant. Inflammation of the peri-miniscrew implant tissue is related to the mobility of miniscrew implant. Radiographic assessment can be used to assess the miniscrew implant stability. Radiographs were used to identify peri-miniscrew implant radiolucencies and to assess the stationary of the miniscrew.[19]

The miniscrew implants could be evaluated for their mobility on close inspection. Presumably, special devices, developed for dental implant, may be applied to assess the miniscrew implant stability, such as Periotest® (Siemens AG, Bensheim, Germany) and Dental Fine Tester® (Kyocera, Kyoto, Japan). In addition,

the resonance frequency analysis has also been used. Nonetheless, miniscrew implant loosening can be only observed when the bone around the implant was extensively destructed. Thus biochemical assessment may be an alternative.

Researchers have monitored components in peri-implant crevicular fluid for several years.[20] Constituents of this fluid could reveal peri-implant tissue health and disease. Analysis of peri-implant crevicular fluid constituents may offer important information around implants for inflammatory or immune responses.

So far, few studies pertaining to monitoring alkaline phosphatase levels from peri-implant crevicular fluid have been conducted.[12-13] Alkaline phosphatase level was higher in peri-implant crevicular fluid from peri-implantitis patients than that from clinically healthy implant patients.[12-13] Sari and Ucar[14] monitored levels of interleukin-1ß around miniscrew implants, used as orthodontic anchorage for canine retraction. The result showed that the miniscrew implants did not demonstrate increased interleukin-1ß levels during tooth movement. The authors concluded that miniscrew implants might be useful as absolute anchorage devices. Nevertheless, the relationship between other directions of tooth movement, intrusion in particular, and other biochemical markers collected from peri-miniscrew implant crevicular fluid, should also be investigated.

2.4 Gingival crevicular fluid, peri-implant crevicular fluid and peri-miniscrew implant crevicular fluid

Gingival crevicular fluid is a fluid that emerges between tooth surface and the gingival lining epithelium. It plays a protective role around sulcular region, due to the flushing effect and transportation of antibacterial substances, either of host origin or

of those introduced into the circulation such as antibiotics, to the crevicular space. Some irritation, chemical or mechanical stimulation, and chronically inflamed gingivae could induce the production of gingival crevicular fluid as an exudate by increase in vascular permeability underlying junctional and sulcular epithelium.[21-22] Alfano suggested that the initial product could simply represent interstitial fluid which appears in the crevice as a result of an osmotic gradient.[23] This pre-inflammatory fluid was considered to be a transudate, and, on stimulation, this was changed to inflammatory exudate.

Apse *et al.* found that the peri-implant gingival sulcus appeared to be similar to gingival sulcus with respect to gingival crevicular fluid and microflora.[11] The volume of crevicular fluid did not differ between implant sites and natural teeth. The features of inflammation seemed to be similar around teeth and implants. In addition, the histologic arrangement of peri-implant soft tissue resembles that observed around natural teeth.[24] Although there was a lack of the biologic and biochemical information of comparison between peri-implant and peri-miniscrew implant tissues, one may indicate that both tissues have similar components of sulcular fluid.

2.5 Biomarkers in gingival crevicular fluid

A number of constituents of gingival crevicular fluid are value as potential diagnostic or prognostic biomarkers of the periodontium in health and disease. Biomolecular markers from gingival crevicular fluid include:

1. Biomarkers from microbial plaque

Factors derived from certain bacteria in dental plaque, which are recognized as the principal etiological agents, may be useful indicators of their presence and metabolic activity, such as endotoxin, bacterial enzymes, and metabolic end-products. Gram-negative bacteria has lipopolysaccharides or endotoxin in the outer membrane of the cell wall, which has been positively correlated with gingival inflammation.[25] Some of the suspected periodontopathogens, such as *Porphyromonas gingivalis* and *Treponema denticola* produce broad-spectrum neutral proteinases as part of their virulent factors.[26] End-products of metabolism of carbohydrates, lipids, and proteins, including H_2S, butyrate, proprionate, and various polyamines, have been found the association with developing gingivitis and periodontitis.[27]

2. Tissue degradation products

Breakdown of the extracellular matrix is a natural consequence of the disease and results from the catabolic response of bacterial and host challenge. Generally the identification of specific tissue components of the periodontium in gingival crevicular fluid represents the tissue metabolism and destruction. The detection of proteoglycan metabolites in gingival crevicular fluid, such as chondroitin sulfate, has proved to be a potentially strong biomarker for assessing bone resorption and remodeling during orthodontic tooth movement.[28]

3. Biomarkers from immune response, neuropeptides and associated inflammatory mediators

Immunoglobulins, neuropeptides and cytokines are closely related to the inflammatory response. In recent years, the expression of regulatory proteins in the gingival crevicular fluid has been recognized as a promising diagnostic tool for

monitoring orthodontic treatment outcome. Cytokines, such as interleukins and prostaglandins, in gingival crevicular fluid reflect the local microenvironment of periodontal tissues, the area whereupon the effect of orthodontic forces is exerted.[29]

4. Host-derived enzymes

Stromal cells, epithelial cells and cells of the hemopoietic lineage in periodontal tissues release a variety of hydrolyse enzymes to the tissues, regarding to the inflammatory stimuli. Many enzymes originate from the azurophilic granules of polymorphonuclear leukocytes. The amount of these cells in the gingival sulcus represents a potential marker of inflammation, since they account for the majority of the total white cells present.[28] Host-derived enzymes in gingival crevicular fluid have been studied as biomarkers for periodontal metabolisms, including acid and alkaline phosphatases, glycoprotein-degrading enzymes, proteinases, and enzymes associated with tissue destruction.[28, 30]

The result of searching the entire human studies, from Pubmed data base in September 2008, showed that 95 potentially relevant studies about biochemical markers in gingival crevicular fluid during orthodontic tooth movement were presented. The majority (52.63%) focused on the group of biomarkers from immune response, neuropeptides and associated inflammatory mediators. The rest of these studies were investigated on tissue degradation products and host enzymes in the similar proportion (23.16% and 24.2%, respectively). Four articles were researched the gingival crevicular alkaline phosphatase around orthodontically treated teeth.[6, 9, 18, 31] However, only the study of Isik *et al.*[18] was done in orthodontic intruding teeth.

2.6 Alkaline phosphatase

Formation and roles of alkaline phosphatase

Alkaline phosphatase is a membrane-bound glycoprotein located on the outer cell surface, anchored to the plasma membrane via a glysosyl-phosphatidylinositol linkage. This hydrolytic enzyme is produced by many cells, such as polymorphonuclear leukocytes, osteoblasts, macrophages, and fibroblasts within the area of the periodontium and gingival crevice.

The precise function of alkaline phosphatase is yet unknown, but alkaline phosphatase obviously plays an important role in osteoid formation and mineralization. It promotes minieralization by hydrolyzing inorganic pyrophosphate, a potent inhibitor of hydroxyapatite crystal formation and dissolution within the extracellular calcifying matrix vesicles. Interestingly, alkaline phosphatase, which is expressed in gingival crevivular fluid, is involved in inflammation and regeneration of periodontium.

Origin of alkaline phosphatase in gingival crevicular fluid

Since gingival crevicular fluid presents both an exudates and transudate, alkaline phosphatase in which expresses in gingival crevicular fluid derives from two sources: serum and adjacent tissues. Nevertheless, several reports demonstrated that gingival crevicular fluid alkaline phosphatase is mainly produced locally.[28, 32-34] In serum, the enzyme is associated with bone disease, and its elevation in gingival crevicular fluid could well reflect changes of alveolar bone in localized areas.[28] Chapple *et al*.[33] found that the level of gingival crevicular fluid alkaline phosphatase is not related to the fluid volume. This statement indicated that the difference in enzyme levels is due to a difference in the amount of enzyme being produced locally

within the periodontal tissues rather than an increase in serum exudation. The authors also provided the supporting data that the alkaline phosphatase concentration in gingival crevicular fluid was 12-times higher than in serum for clinically healthy periodontal tissues.[34] Binder *et al*., however, presented that the mean alkaline phosphatase activity in gingival crevicular fluid was 20-times higher than that of plasma.[32]

Alkaline phosphatase in gingival crevicular fluid is primarily originated from host cells, possibly from polymorphonuclear leukocytes, osteoblasts, periodontal ligament cells, and fibroblasts. The principal source is, however, polymorphonuclear leukocytes or neutrophils, through secondary granule release. Neutrophil-alkaline phosphatase is both membrane bound and presented in intracellular compartments. It is thought to play a role in superoxide generation and as a general player in the first line of defense, which is dominated by neutroplils. Numbers of polymorhponuclear leukocytes within gingival crevicular fluid have been shown to weakly correlate with gingival inflammation,[35] although enzymes released by polymorphonuclear leukocytes demonstrated a stronger relationship.[33] By comparison with other connective tissue cells, periodontal ligament cells show higher alkaline phosphatase activity.[36]

Alkaline phosphatase is also expressed in gingival fibroblast but not a specific cell marker in chronic inflammatory periodontal lesions. In a ultrahistochemical investigation of chronically inflamed human gingiva by Abe *et al.*[37], it indicated that differential expression of membrane alkaline phosphatase activity by gingival fibroblasts depends on their tissue location. The results showed that the majority of

fibroblasts located in the inflammatory gingival connective tissue exhibited intense membrane alkaline phosphatase activity. However, the majority of fibroblasts in the adjacent non-inflammatory gingival connective tissue showed little or no membrane alkaline phosphatase activity.

Bacteria presented in the gingival sulcus also produce alkaline phosphatase, and contribute to alkaline phosphatase levels in gingival crevicular fluid. A histological study by Lo Storto *et al*.[38] demonstrated the presence of alkaline phosphatase in the periplasmic spaces of gram negative bacteria and also in the extracellular plaque matrix. The extracellular enzyme was found attached to the membranes around small microbial vesicles and also non-complexed in the intermicrobial ground space, without any association to specific structures. The latter enzyme have probably been derived from the host gingival crevicular fluid.[33] Several potential periodontal pathogens, including *P. gingivalis, P. intermedia*, *C. ochracea*, *F. nucleatum fusiformis* and *P. negrescens* produce detectable alkaline phosphatase in vitro and the activity is presented in washed plaque suspensions.[39] Nonetheless, there is a lack of significant difference in gingival crevicular fluid alkaline phosphatase levels for the different plaque indices.[33] Chapple *et al*.[39] indicated that the majority of the enzyme is host derived, since bacterial alkaline phosphatase contributes less than 20% to total gingival crevicular fluid alkaline phosphatase activity. At present alkaline phosphatase from polymorphonuclear leukocytes would appear to be the most likely source of the enzyme.

<u>Expression of alkaline phosphatase in gingivitis and periodontitis</u>

In the periodontium, alkaline phosphatase is a very important enzyme as it is part of the normal turnover of periodontal ligament, root cement formation and maintenance, and bone homeostasis. Gingival crevicular fluid alkaline phosphatase has been suggested as a potential diagnostic marker for gingivitis and periodontitis.

Chapple *et al.*[39] found that increased gingival crevicular fluid alkaline phosphatase in early gingivitis is largely of neutrophil origin. However, the associated pathogenic flora, osteoblast and fibroblast activities may contribute more to overall gingival crevicular fluid alkaline phosphatase levels in more advanced stages.[39] In addition, there is a site-specific pattern of alkaline phosphatase distribution in the mouths of adults demonstrating periodontal health, with concentrations being higher anteriorly than posteriorly and the lower anterior region providing the highest concentration.[34]

Ishikawa and Cimasoni[40] and Binder *et al.*[32] longitudinally monitored patients and demonstrated a strong positive relationship between the levels of alkaline phosphatase in gingival crevicular fluid and previous disease activity. Nakashima *et al.*[41] found that total amounts and concentrations of alkaline phosphatase were significantly higher in periodontitis as compared to healthy and gingivitis sites, and were significantly and positively correlated with probing depth and gingival index. These changes occurred prior to significant attachment loss[5], thus total gingival crevicular fluid alkaline phosphatase has potential for diagnosing currently progressing of recently active attachment loss.[4] A longitudinal study which related gingival crevicular fluid alkaline phosphatase levels to periodontal attachment loss of

more than 2 mm showed that active sites yielded 2-times the activity found in serum.[32]

On the other hand, gingival crevicular fluid alkaline phosphatase activity may be used as a diagnostic tool for monitoring periodontal regeneration. In clinical study, alkaline phosphatase levels were significantly increased in regenerating human periodontal cells 5 to 7 weeks after the surgical placement of membranes.[42] Perinetti et al.[43] demonstrated that decreases in gingival crevicular fluid alkaline phosphatase activity after scaling and root planning in chronic periodontitis patients reinforced the potential for gingival crevicular fluid alkaline phosphatase activity to be used as a tissue-monitoring parameter.

Expression of alkaline phosphatase in peri-implantitis

Monitoring of peri-implant status may also be carried out by analysis of alkaline phosphatase activity. Plagnat *et al.*[12] and Paknejad *et al.*[13] determined the presence of alkaline phosphatase in sulcular fluid collected from dental implant with and without clinical and radiographic signs of peri-implantitis. These studies showed that increased alkaline phosphatase activity was observed for peri-implantitis dental implants in comparision with healthy ones. The authors indicated that the inflammatory response in peri-implant mucosa did not differ from that of the gingiva. Nonetheless, no investigation of alkaline phosphatase has been conducted in peri-miniscrew implant tissue yet.

Expression of alkaline phosphatase in periodontium of orthodontically treated teeth

In orthodontic tooth movement, the bone remodeling process is more complex with resorptive activity initially (3-5 days) and is followed by its reversal (5-7 days). Subsequently, a late phase of bone deposition (7-14 days) occurs in both tension and pressure sites of the alveolar wall. The osteoblast is now perceived as the cell that regulates both the formative and resorptive phases of the bone remodeling cycle in response to hormonal and mechanical stimuli. In the early phases, bone resorption is greater than bone deposition, but in the later phase, resorption and deposition become synchronous. This might be due to the high acid phosphatase activity that has been observed in the early period of tooth movement; high levels of alkaline phosphatase activity have been described after 7 days, when bone deposition begins.[7] Nevertheless, early elevation in gingival crevicular fluid alkaline phosphatase activity during a time when little tooth movement could occurs.[8] Since alkaline phosphatase activity increases with inflammation, this finding suggests that early inflammatory processed known to occur during the early stages of orthodontic tooth movement may be detected in the gingival crevicular fluid as an increased alkaline phosphatase activity.

Batra *et al.*[9] investigated alkaline phosphatase activity in gingival crevicular fluid during canine retraction. At compression side of distalized canines, the enzyme activity increased during first three weeks and then slightly dropped after that, compared with control teeth. At the tension side, the enzyme activity showed the higher increase from the start, compared with the compression side of the treated teeth and control teeth, and the sharp fall after three weeks. On the compression side, bone resorption would occur and osteoclastic activity was high with little or no osteoblastic activity; however, alkaline phosphatase activity followed a similar trend as on the

tension side. These indicated that gingival crevicular fluid alkaline phosphatase activity increased in compression side, even though no bone formation was presented.

There has been only one study that observed the changes of gingival crevicular fluid constituents during orthodontic intrusion. Isik *et al*.[18] observed the changes in several bone turnover markers during the experimental orthodontic intrusion of maxillary premolar teeth. The results showed that alkaline phosphatase activity began to decrease with force application.

Effect of mechanical stress to alkaline phosphatase expression in periodontal ligament cells

Since periodontal ligament has the highest alkaline phosphatase activity, compared with other connective tissues,[36] several studies have investigated if periodontal ligament cells showed increase or decrease of alkaline phosphatase activity after force application. Both increase and decrease in the enzyme activity in animal periodontal ligament cells were performed. This depended on whether compressive forces were intermittent or continuous.[44-47] These conflicting results may be caused by nature of mechanical stress. Application of compressive force continuously decreases expression of alkaline phosphatase in the periodontal ligament cells[45] and osteoblast-like cells.[47] On the other hand, intermittent compressive force increases the alkaline phosphatase activity in many cell-types.[44, 46-47]

However, tension stress decreased alkaline phosphatase activity of periodontal ligament cells in many studies.[48-50] Reduction of enzyme activity might depend on both relatively high magnitudes of tensional forces[48, 50] and time.[50]