CHAPTER 2

LITERATURE REVIEW

The review is divided into six parts as follows:

2.1 Open bite

2.2 Molar intrusion

2.3 Clinical application of miniscrew implants for molar intrusion

2.4 Assessment of orthodontic molar intrusion

2.5 Assessment of miniscrew implant stability

2.6 Gingival crevicular fluid (GCF), peri-miniscrew implant crevicular fluid (PMICF), enzyme-linked immunosorbent assay (ELISA) and monoclonal antibody (mAb) WF6

2.1 Open bite

Open bite is defined as an absence of vertical overlap between opposing segments of teeth. It can occur between the anterior segments or between the posterior segments. The etiologies of open bite are multifactorial. Etiologic factors have been classified in three broad categories: 1) vertical growth pattern, 2) soft tissue aberration, such as abnormal size and function of tongue, weak elevator muscle function, and 3) digit-sucking habit. Other etiologies are developmental disturbances and disease processes, such as cleft lip, cleft lip and/or palate and Crouzon’s syndrome.

Open bite is classified into two types.
1. Dental open bite

Dental open bite is usually found in the anterior dento-alveolar region. It demonstrates normal craniofacial pattern, under-eruption of anterior teeth and normal or slightly excessive posterior dento-alveolar height. It is usually related to thumb- or finger-sucking. Dental open bite tends to be self-correcting, if the finger-sucking habit is terminated.

2. Open skeletal configuration

The open skeletal configuration is characterized by a greater than normal posterior dentoalveolar height in both maxilla and mandible, increased cranial base angle, increased gonial angle, long anterior facial height, anteriorly rotated palatal plane, retrognathic mandible and incisor extrusion. Open skeletal configuration cases are more difficult to treat than dental open bite cases.

Treatment options for open bite are 1) Orthodontic treatment 2) Surgical treatment or 3) a combination of 1) and 2). Orthodontic treatment alone is appropriate for dental open bite, but not for severe skeletal vertical discrepancies. Treatment modalities for closing anterior open bite include elimination of etiology, extrusion of anterior teeth, and molar intrusion. Surgical treatment always involves superior repositioning of the posterior part of the maxilla.

2.2 Orthodontic molar intrusion

Open skeletal configuration cases exhibit excessive maxillary and mandibular posterior dento-alveolar height. Molar intrusion is an option for correcting anterior open bite. The molar intrusion causes counter-clockwise mandibular rotation and anterior open bite closure.
Many techniques have been used to intrude maxillary and/or mandibular posterior teeth, for example, a passive posterior bite block, an active vertical corrector, a multiple edgewise arch wire (MEAW) technique, and a functional appliance or fixed appliance with high pull head gear. The multiloop edgewise arch wire (MEAW) technique provides treatment results similar to those of natural compensation, such as incisor extrusion and distally uprighting of posterior teeth. These are limitations to the use of the multiloop edgewise arch wire (MEAW) technique in patients with adequate or excessive anterior dento-alveolar height. Some of these techniques certainly require patient compliance.10

Anchorage control during molar intrusion is important for several reasons. Intra-oral anchorage, such as incorporation of many teeth in the anchorage unit, a transpalatal arch, a lingual arch, class II and/or class III elastic traction or a Nance appliance, may cause undesired tooth movement. Extra-oral anchorage, such as a headgear is used in order to reinforce intra-oral anchorage. High pull head gear is effective, but it requires patient compliance to get a successful result.7 Recently the miniscrew implant has been used to provide absolute anchorage in many orthodontic treatments including molar intrusion. The miniscrew implant is small, so it can be placed in any area. It is easily placed and removed. The miniscrew implant also requires less patient compliance.10,18 Moreover, miniscrew implants can be immediately loaded and can eliminate unwanted effects on the teeth that otherwise would have been used as anchorage.19
2.3 Clinical application of miniscrew implants for orthodontic molar intrusion

The miniscrew implant is used to provide anchorage for many orthodontic tooth movements such as distal movement of canines, en masse retraction of anterior teeth and molar intrusion. In addition, the miniscrew implant encourages tooth movement in many directions.\textsuperscript{18,20}

The sites for miniscrew implant placement in the maxilla are palatal and buccal surfaces of the alveolar process, paramedian area, midpalatal area and zygomatico-alveolar crest. The areas in the maxilla where implantation should be avoided are the maxillary anterior region because of lip irritation, and the area palatal to the upper central incisors because of the location of the incisive foramen and thick mucosa. In the mandible, the miniscrew implant is usually placed at the buccal cortical plate of the alveolar process between the second premolar and first permanent molar. In the mandible implantation should be avoided on the lingual side because of tongue irritation.\textsuperscript{20}

Many authors have reported successful treatment of anterior open bite by molar intrusion using miniscrew implant anchorage. The recommended miniscrew implant placement sites used in those studies were the buccal, lingual or both sides of the alveolar bone, the midpalatal area, and the paramedian area. A transpalatal arch and/or lingual holding arch should be used to prevent tipping of the teeth, especially in cases where the miniscrew implant placement is only on one side. The miniscrew implant diameter ranged from 1.2 to 2.0 mm and the length ranged from 7.0 to 15.0 mm. The molar intrusion force ranged from 100 to 200 g.\textsuperscript{3,7-8,11,18}

Techniques for force application to intrude molars by using miniscrew implant anchorage vary. In the maxilla, Xun et al.\textsuperscript{5} generated intrusion force by using a
Nickel-Titanium coil spring (150 g) connected from the miniscrew implant head to a soldered hook on a transpalatal arch. Park et al.\textsuperscript{3} used an elastic thread (100 g) to engage the miniscrew implant head and a soldered hook on a transpalatal arch. Yao et al.\textsuperscript{7} applied force by connecting an elastic chain (150-200 g) between the miniscrew implant head and an attachment on a molar band. In the mandible, intrusion force was applied by a power chain connected from the main arch wire to the miniscrew implant head,\textsuperscript{8} or from a buccal tube on the first molar band to the miniscrew implant head.\textsuperscript{3} All those studies assessed treatment results by using clinical appearance and radiographic superimposition, and reported successful outcomes.\textsuperscript{3-5, 7-9, 21}

2.4. Assessments of orthodontic molar intrusion

1. Clinical assessment

Tooth movement under orthodontic force can be clinically assessed by comparison between pre- and post-treatment photographs and between pre- and post-treatment dental casts.\textsuperscript{22} Many authors have reported that the anterior open bite was reduced after molar intrusion.\textsuperscript{3,6,8} Yao et al.\textsuperscript{7} compared the relocation of the specific cusp tip on pre- and post-treatment dental casts using a mechanical desktop three-dimensional (3D) digitizer. In summary, the surface topology of the cusp tips and incisal edges of the dental cast were recorded. Then the three-dimensional pre- and post-treatment dental casts were traced and the captured points of the cusp tips and incisal edges were superimposed for comparison. The investigators reported that the maxillary molars were intruded an average of 3-4 mm by using mini-implant anchorage for five months.
2. Radiographic assessment

2.1) Lateral cephalometric radiograph superimposition is widely used for assessing sagittal and vertical tooth movements. The lateral cephalometric radiograph is performed with the Frankfort horizontal plane parallel to the floor and with the teeth in centric occlusion. The lateral cephalometric radiograph should be taken by using the same cephalostat for all patients, with standardized settings. The tracing of the radiograph is performed with a sharp pencil, and the bilateral landmarks are averaged to reduce error from head position. The pre- and post-treatment lateral cephalometric radiographs are superimposed by using reference planes such as the cranial base, palatal plane and mandibular plane. Previous studies of Xun et al. and Liou et al. used a line drawn seven degrees from the sella-nasion line, registered at sella as the horizontal reference plane, and a line drawn perpendicular through sella served as the vertical reference plane. The dental change was evaluated by measuring the distance between two reference points, such as an upper first molar to the point on the palatal plane intersected by a perpendicular from the first point. The radiographic image of the miniscrew implant head and palatal or mandibular plane were used to establish the coordinate system. Xun et al. reported that the first maxillary and mandibular molars were intruded an average of 1.8 mm and 1.2 mm, respectively and the anterior open bite was closed by counter-clock-wise rotation of the mandible. Gurton et al. assessed the molar intrusion from the distance between the maxillary first molar to the Frankfort horizontal plane and between the mandibular first molar to the mandibular plane. The overall skeletal change after molar intrusion is usually assessed by angular and linear parameters such as SNA, SNB, ANB, SN-PP, SN-MP, and anterior and posterior facial heights. Park et al. reported the counter-clockwise
rotation of the mandible, after molar intrusion, which was represented by the reduction of FMA.

2.2) Panoramic radiographs provide no overlap of the images of the right and left sides but usually contain distortion. Sherwood et al. investigated molar intrusion by using panoramic radiographs. They measured the distance between a band point and a miniplate reference point to assess molar intrusion by using miniplate anchorage.

2.3) Periapical radiographs were used to assess side effects of molar intrusion, especially root resorption.

3. Biochemical assessment

A biomarker is a substance used as an indicator of a biologic state. Monitoring of biomarker levels can elucidate physiological or pathological conditions or the response to treatment. Biomarkers can be found in blood, tissue or other body fluids, such as urine.

Gingival crevicular fluid, a periodontal tissue exudate derived from serum, can be collected from the gingival crevice around the teeth. It can represent the constituents of serum and the cellular response in the periodontium. The components of gingival crevicular fluid, which are used as biomarkers for periodontal disease and periodontal tissue response under orthodontic forces, are divided into four categories as follows:

1. Products derived from subgingival microbial plaque

2. Inflammatory mediators

The inflammatory mediators include interleukin-1β, prostaglandin E₂, serum antibody, total protein concentration and acute-phase protein.
3. Host-derived enzymes

Host-derived enzymes include alkaline phosphatase, β-galactosidase, collagenase, neutral proteolytic enzyme, elastase and gelatinase.

4. Tissue-breakdown products

Tissue-breakdown products include glycosaminoglycans (GAGs), fibronectin, hydroxyapatite, osteopontin, osteonectin, procollagen, laminin and hemoglobin β-chain peptides.

The response of periodontal ligament and alveolar bone under orthodontic force causes degradation of extracellular matrix into gingival crevicular fluid (GCF). One element of the extracellular matrix is proteoglycans. Proteoglycans are comprised of a protein core, to which one or more glycosaminoglycan (GAG) chains are covalently attached. Chondroitin sulphate is the predominant glycosaminoglycan (GAG) in alveolar bone. It can represent the degenerative change of the deeper periodontal tissue of alveolar bone. The relation of chondroitin sulphate (CS) levels to compressive force during orthodontic tooth movement has been reported. Last et al. investigating glycosaminoglycan (GAG) in gingival crevicular fluid during orthodontic tooth movement, showed a significant rise of chondroitin sulphate levels in the gingival crevicular fluid of teeth undergoing orthodontic tooth movement. Jaito et al. used a newly synthesized WF6 monoclonal antibody (which represented the degenerative epitope of chondroitin sulphate) and an enzyme-linked immunosorbent assay (ELISA) method to monitor the chondroitin sulphate levels in gingival crevicular fluid as biomarkers for alveolar bone remodeling, and reported that the detectable chondroitin sulphate levels were associated with the applied orthodontic forces.
2.5 Assessments of miniscrew implant stability

The criteria for successful orthodontic miniscrew implant use are: 1) absence of infection or inflammation, 2) absence of pain or any subjective discomfort, 3) no clinical detectable mobility, and 4) miniscrew implant stability throughout the treatment. The stability of miniscrew implants depends on bone density, thickness of the peri-implant soft tissue, miniscrew implant design, surgical procedure, force load and diameter of the miniscrew implants. The stability assessments of miniscrew implants (as well as dental implants) are as follows:

1. Clinical assessments

1.1) Clinical feature assessment can indicate early signs of implant failure. Pain, discomfort and inflammation of peri-implant tissues are associated with peri-implant bone loss, implant mobility and implant failure. Mucosal conditions, such as color changes in keratinized gingival tissue or in oral mucosa, plaque accumulation, bleeding on probing, increased probing depth of implant pockets, redness and swelling of marginal tissue and suppuration, have been reported to be clinical signs and symptoms of peri-implant tissue inflammation.

1.2) Radiographic assessment is a widely used method to assess implant stability. The absence of radiolucent areas around implants indicate implant success, and the presence of radiolucency around implants indicates implant failure. Lateral cephalometric radiographic superimposition has been used to investigate miniscrew implant displacement. Liou et al. reported that the miniscrew implants were stable, but not absolutely stationary, under orthodontic loading. Miniscrew implant stability depended on several factors, such as miniscrew size, bone quality and quantity, orthodontic force magnitude and the depth of the miniscrew inside the implant site.
However, radiographic assessment provides insufficient information about peri-implant bone loss in the early stages and cannot predict future peri-implant failure. Moreover, conventional plain film radiographs are unreliable for diagnosing implant stability.\textsuperscript{35-36}

1.3) Clinical implant mobility can be assessed by various means, such as finger pressure, Periotest®, and resonance frequency analysis (RFA). The Periotest® is an electronic instrument which was originally developed to evaluate periodontal status. It has also been used to detect low degrees of implant mobility. Resonance frequency analysis (RFA) has been used to measure primary and long term implant stability. A small transducer is attached to the implant surface. Stability of the implant is measured by determining the resonance frequency of the implant-bone complex stiffness or implant stability quotient (ISQ). The higher the implant stability quotient, the higher the implant stability.\textsuperscript{31} Cheng et al.\textsuperscript{34} assessed implant mobility by firmly grasping the miniscrew implant head with cotton pliers and trying to displace it, and concluded that mobility of an implant represented implant failure. Liou et al.\textsuperscript{24} evaluated miniscrew implant mobility by using an orthodontic tension gauge, and concluded that the miniscrew implant was a stable anchorage, but was not an absolute anchorage. The displacement of a miniscrew can be attributed to several factors, such as miniscrew size, orthodontic force magnitude, bone quality and quantity at the implant site, and the length of the healing period before loading. Monitoring of clinical implant mobility is not a sensitive method, or one that can be used to assess early failure because it represents implant failure at a rather late stage.
2. Histological assessments

Histological assessment of miniscrew implant stability involves investigating the percentage of bone contact to the miniscrew implant, which represents the degree of osseointegration after immediate load. This method is certainly reliable, but not practical in the clinical situation.\(^{37}\) Kim et al.\(^{38}\) reported that the drill-free miniscrew implant produced more bone contact area and offered greater primary stability under orthodontic force than did the miniscrew that required drilling.

3. Mechanical assessments.

Miniscrew implants attach to bone by means of mechanical retention. An important factor in miniscrew implant success is the manner in which stresses are transferred to the surrounding bone. Finite element analysis (FEA) is a method for predicting stress distribution in the contact area of the miniscrew implant and surrounding bone. Finite element analysis consists of a computer model of a material or subject that is used to analyze specific results and also to simulate the interaction phenomena between implants and the surrounding bone.\(^{39}\) From the principle of finite element analysis, Costa et al.\(^{40}\) developed a cone-shaped miniscrew, which provided better strength and mechanical stability than did cylindrical miniscrews. Motoyoshi et al.\(^{41}\) investigated the biomechanical effects of miniscrew implant design (abutment and thread pitches) on stress distribution and stability by using finite element analysis, and reported that miniscrew implants could tolerate orthodontic force.

Another mechanical assessment of miniscrew implant stability is torque testing. Rupture of the miniscrew implant thread interface and of the bone interface is required during torque testing.\(^{42}\) The pull-out strength test is a method for testing
mechanical competency, or holding power of miniscrew implants. For the pull-out test, the miniscrew implant must be aligned with the axis of the testing machine. The pull-out strength is related to the thickness of cortical bone where the miniscrew implant is placed.43

4. Biochemical assessments

It has been reported that the composition of the peri-implant crevicular fluid (PICF) is similar to that of the gingival crevicular fluid (GCF) around the natural teeth.44 Numerous investigators reported the association between the stability of implant and the levels of extracellular component in peri-implant crevicular fluid (PICF). The potential biomarkers for assessing implant condition are neutral proteolytic enzyme,36 collagenase, protease, prostaglandin E2, neutrophil elastase, alkaline phosphatase and glycosaminoglycans.44-45 In almost all studies, biochemical assessments were used to assess only dental implant stability but not miniscrew implant stability. The peri-implant sulcular fluid from successful dental implant sites is composed of low levels of chondroitin sulphate and hyaluronan. Chondroitin sulphate in peri-implant sulcular fluid may primarily originate from the metabolism of alveolar bone. The assessment of chondroitin sulphate levels is useful for monitoring the peri-implant tissue condition.44

Sari and Ucar14 evaluated the levels of interleukin-1β (IL-1β), an inflammatory mediator, in peri-microscrew implant crevicular fluid, and reported no significant interleukin-1β (IL-1β) level change around healthy microscrew implants. Intachai et al.15 concluded that the chondroitin sulphate (WF6 epitope) can be detected in peri-miniscrew implant crevicular fluid, and chondroitin sulphate (WF6 epitope) levels of
one failed miniscrew implant were remarkably elevated 14 days prior to miniscrew implant failure, and that further investigation should be conducted.17

2.6 Gingival crevicular fluid (GCF), peri-miniscrew implant crevicular fluid (PMICF), enzyme-link immunosorbant assay (ELISA) and monoclonal antibody (mAb) WF6

Gingival crevicular fluid is a periodontal tissue exudate. The main source of gingival crevicular fluid is the serum from the capillary vessels within the gingival tissues passing through the gingival crevice. The general composition of gingival crevicular fluid includes cells, immunoglobulins, micro-organisms, toxins, lysosomal enzymes and glycoprotiens.

Gingival crevicular fluid flow rate and components have been used as indicators for assessing gingival and periodontal status. Pander et al.46 found that the gingival crevicular fluid volumes collected from sites of the greater gingival inflammation are higher than those collected from sites of less inflammation. Brecx et al.47 reported the correlation between gingival crevicular fluid flow rate and histological changes during gingivitis. During orthodontic tooth movement, Last et al.30 and Baldwin et al.48 reported significant increases in the gingival crevicular fluid volume during orthodontic tooth movement.

Application of orthodontic force to a tooth induces fluid movement and strain in cells and in extracellular matrix in the periodontal tissues, followed by local damage to the periodontal ligament, and by tissue remodeling. Gingival crevicular fluid components are also changed.28 Many gingival crevicular fluid components, such as interleukin-1β, prostaglandin E2, substance P, tumor necrosis factor -α (TNF-α),
sulphate glycosaminoglycans and chondroitin sulphate have been used to evaluate cellular response under orthodontic force.\textsuperscript{12-13, 28, 30}

Gingival crevicular fluid assessment is a non-invasive investigation. The methods for collecting gingival crevicular fluid are as follows:\textsuperscript{28}

1. Placing a micro capillary tube into the gingival crevice for 10 to 15 minutes. This technique may disrupt the crevicular epithelium and causes the contamination of gingival crevicular fluid by blood and serum.

2. Using a prewashed absorbent string in the same manner. This method also causes irritation of crevicular epithelium.

3. Placement of filter paper strips in the gingival crevice. This method is a common method to collect gingival crevicular fluid. This method causes less disruption to crevicular epithelium, and decreases the contamination of gingival crevicular fluid by serum.

4. The para-magnetic bead method.

The gingival crevicular fluid is not removed from the crevice but para-magnetic beads are covered with monoclonal antibodies and placed in the sulcus and gingival crevicular fluid is analyzed by a special magnetic harvester. This method is especially used for detecting tumor necrosis factor (TNF).

Peri-implant crevicular fluid (PICF) has been investigated to assess the status of dental implants. Kao \textit{et al.}\textsuperscript{49} found significantly greater elevation of interleukin1-β levels in failing implants than in healthy implants. Okazaki \textit{et al.}\textsuperscript{44} reported that the contents of peri-implant crevicular fluid (PICF) were similar to those in the gingival crevicular fluid around the natural teeth, and that chondroitin sulphate can be detected
in peri-implant crevicular fluid (PICF). They suggested that chondroitin sulphate in peri-implant crevicular fluid (PICF) might be primarily released from the breakdown or metabolism of alveolar bone. Peri-miniscrew implant crevicular fluid (PMICF) components have been used for assessing the stability of miniscrew implants during tooth movement.  

The methods for analysis of gingival crevicular fluid and peri-miniscrew implant crevicular fluid include electrophoresis, immunohistochemistry and enzyme-linked immunosorbent assay (ELISA).  

Enzyme-linked Immunosorbent Assay (ELISA) is a widely used biochemical technique for measuring the concentration of a particular molecule in fluids, such as serum or urine, by using antibodies which are specific to a particular antigen. This method can analyze constituents in gingival crevicular fluid, even in trace amounts. In summary, ELISA is performed by using two different antibodies. The antibodies react with the antigen whose concentration is to be measured. A fixed quantity of one antibody is attached to a series of replicate solid supports, such as plastic microtiter wells. A test solution containing antigen at an unknown concentration, or a series of standard solutions with known concentrations of antigen, are added to the wells and allowed to bind. Unbound antigen is removed by washing, and the second antibody, which is enzyme-linked or radiolabeled, is allowed to bind. The antigen serves as a bridge, so the more antigens in the test or standard solutions, the more enzyme-linked or radiolabeled second antibody will bind. The enzyme converts the substrate to the detectable signal (chromogenic or fluorogenic or electrochemical signal) that can be quantified by a spectrophotometer, spectrofluorometer or other electrochemical device. The results from the standards are used to construct a binding curve for the
second antibody as a function of antigen concentration, from which quantities of antigen in the test solutions may be inferred. When this test is performed with two monoclonal antibodies, it is essential that these antibodies recognize non-overlapping determinants on the antigen; otherwise, the second antibody cannot bind (Figure 1).

**Figure 2.1** Competitive ELISA and monoclonal antibody in detecting antigen.

For detecting chondroitin sulphate by ELISA, monoclonal antibody 3B3 and WF6 have been used.\(^{13,15,52}\) Monoclonal antibody WF6 has been transduced and characterized at the Thailand Excellent Center for Tissue Engineering, Faculty of Medicine, Chiang Mai University. This monoclonal antibody recognizes an epitope on a native chondroitin sulphate and a competitive ELISA method was then developed to detect the WF6 epitopes in human serum, using aggrecan as a standard
(A1D1 fraction). The synthesis of the mAb WF6 has been described in previous studies.\textsuperscript{52-54} Pothacharoen\textsuperscript{52} reported that the levels of this epitope were higher in the serum of patients with osteoarthritis than in the serum of normal patients, and were also significantly higher in the serum of patients with rheumatoid arthritis. Therefore, Pothacharoen\textsuperscript{52} suggested that the levels of WF6 epitope reflect the degradation of cartilage similar to the way that increased levels of 3B3 epitope do so in degenerative joint disease. However, the detection of WF6 epitope levels by using mAb WF6 does not need the step of chondroitinase digestion, unlike detection by using mAb 3B3, because the mAb WF6 detects the native state of CS. This monoclonal antibody acts against the chondroitin sulphate and the detectable chondroitin sulphate represents a metabolic change of alveolar bone during orthodontic tooth movement.\textsuperscript{13}