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Evaluation of Functional Dynamics during Osseointegration and Regeneration Associated with Oral Implants: A Review

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Abstract

Objectives—The aim of this paper is to review current investigations on functional assessments of osseointegration and assess correlations to the peri-implant structure.

Material and methods—The literature was electronically searched for studies of promoting dental implant osseointegration, functional assessments of implant stability, and finite element (FE) analyses in the field of implant dentistry, and any references regarding biological events during osseointegration were also cited as background information.

Results—Osseointegration involves a cascade of protein and cell apposition, vascular invasion, *de novo* bone formation and maturation to achieve the primary and secondary dental implant stability. This process may be accelerated by alteration of the implant surface roughness, developing a biomimetic interface, or local delivery of growth-promoting factors. The current available preclinical and clinical biomechanical assessments demonstrated a variety of correlations to the peri-implant structural parameters, and functionally integrated peri-implant structure through FE optimization can offer strong correlation to the interfacial biomechanics.

Conclusions—The progression of osseointegration may be accelerated by alteration of the implant interface as well as growth factor applications, and functional integration of peri-implant structure may be feasible to predict the implant function during osseointegration. More research in this field is still needed.

Keywords

finite element analysis; growth factor; bone-implant interactions

Introduction

Osseointegration, which histologically is defined as “direct bone-to-implant contact”, is believed to provide rigid fixation of a dental implant within the alveolar bone and may promote the long-term success of dental implants (Franchi *et al.*, 2005, Joos *et al.*, 2006). The processes of osseointegration involve an initial interlocking between alveolar bone and

the implant body (primary implant stability), and later, biological fixation through continuous bone apposition (contact osteogenesis) and remodeling toward the implant (secondary implant stability) (Berglundh *et al.*, 2003).

Stiffness of the tissue-implant interface and implant-supporting tissues are considered as the main determinant factors in osseointegration (Ramp and Jeffcoat, 2001, Turkyilmaz *et al.*, 2008). While the structure and heterogeneity of mineralization affects the stiffness of bone (Hoffler *et al.*, 2000), Johansson *et al.* (Johansson *et al.*, 1998) demonstrated that biomechanical testing may be a more suitable indicator to evaluate the dynamic changes of osseointegration than any single structural parameter. However, biomechanical testing, such as push-out and pull-out measurements, is destructive and only available for preclinical use (Berzins *et al.*, 1997). Therefore, the clinical value of non-destructive measurements, such as resonance frequency analysis (RFA) or damping characteristics (Periotest® technique), are still limited due to the lower resolution and higher variability during examinations (Aparicio *et al.*, 2006). Thus, it is still of interest to develop effective approaches to functionally assess osseointegration for the evaluation of peri-implant wound healing and prognosis of implant therapy.

By reviewing the sequences of osseointegration and current efforts on promoting osseointegration, this paper is concentrated on the scientific significance of preclinical biomechanical testing and has characterized the state-of-the-art clinical functional assessments as well as the model analysis. According to the development of modern medical imaging techniques and mechanical modeling, the relationship between structural and biomechanical parameters were also described.

Timing of Osseointegration

While it has been demonstrated that excessive mobility may cause fibrous tissue formation and lead to failure of osseointegration (Huiskes *et al.*, 1997, Lioubavina-Hack *et al.*, 2006), in order to limit the micromotion and achieve primary stability of the implant, a slightly undersized osteotomy is usually prepared for press-fitting of the implant. However, a ~60 micrometer gap between the implant and host bone has been noted under microscopic investigations (Colnot *et al.*, 2007, Futami *et al.*, 2000), and depending on the extent of injury to the host bone, this gap may later extend to 100-500 micrometers (Eriksson *et al.*, 1984). Therefore, this gap is filled with blood and forms a water layer incorporated with hydrated ions on the implant surfaces immediately after implant placement (Berglundh *et al.*, 2003, Park and Davies, 2000). The small proteins adsorbed on the surface are subsequently replaced by larger proteins based on the 'Vroman effect'. Although different implant surface properties may affect the composition and conformational states of the binding proteins, the biological aggregates on the surface interact with the cell extensions, cell membrane, membrane-bound proteins or receptors, and initial cell attachment eventually establishes on the implant surface (Kasemo and Gold, 1999). The interface area is first occupied by red blood cells, inflammatory cells, and degenerating cellular elements, then is gradually replaced with spindle-shaped or flattened cells, concurrent with initiation of osteolysis on the host bone surface until day 3 (Futami *et al.*, 2000). Osteoblasts begin to attach and deposit collagen matrix at this stage (Meyer *et al.*, 2004).

Early bone formation is not evident until days 5-7 (Berglundh *et al.*, 2003, Colnot *et al.*, 2007) and is consistent with the sequence of appositional matrix deposition and calcification from the lamina limitans of host bone onto the implant surface (Marco *et al.*, 2005). Most of the interfacial zone is occupied by provisional matrix rich in collagen fibrils and vasculature, and woven bone can be observed around the vascular areas by day seven (Berglundh *et al.*, 2003). Through continuous deposition, trabecular bone fills the initial gap and arranges in a

three-dimensional network at day 14 (Franchi *et al.*, 2005). The *do novo* formation of primary bone spongiosa offers not only a biological fixation to ensure secondary implant stability (Ferguson *et al.*, 2006) but also a biological scaffold for cell attachment and bone deposition (Franchi *et al.*, 2005). After 28 days, delineated bone marrow space and thickened bone trabeculae with parallel-fibered and lamellar bone can be found within the interfacial area. After 8 to 12 weeks, the interfacial area appears histologically to be completely replaced by mature lamellar bone in direct contact with titanium (Berglundh *et al.*, 2003).

Implant Surface Alteration to Accelerate Osseointegration

The chemical composition or charges of the implant interface on the implant surface were shown to affect initial cell attachment (Kasemo and Gold, 1999). This has aroused great interest on implant surface modification as a way to accelerate the rate of osseointegration (Junker *et al.*, 2009, Wennerberg and Albrektsson, 2009).

Surface Roughness

Depending on the scale of the features and based on the proposal of Wennerberg and Albrektsson (Wennerberg and Albrektsson, 2009), surface roughness can be divided into four categories (Lang and Jepsen, 2009):

- Smooth surfaces: Sa value < 0.5 μm (e.g. polished abutment surface)
- Minimally rough surfaces: Sa value 0.5 to < 1.0 μm (e.g. turned implants)
- Moderately rough surfaces: Sa value 1.0 to < 2.0 μm (e.g. most commonly used types)
- Rough surfaces: Sa value $\geq 2.0 \mu\text{m}$ (e.g. plasma sprayed surfaces).

Moderate roughness and roughness is associated with implant geometry, such as screw structure, and macroporous surface treatments. Previous studies demonstrated that this type of roughness allowed for bone ongrowth and provided mechanical interlocking shortly after implant placement (Berglundh *et al.*, 2003, Franchi *et al.*, 2005). Higher BIC and removal torque force suggested enhanced secondary stability compared to smooth and minimally rough implants (Buser *et al.*, 1991, Wennerberg *et al.*, 1996).

There are two main theories regarding the influence of implant surface microtopography on peri-implant tissue formation – 1) the surface energy and 2) the distortional strain. The smaller grain size on the surface results in higher surface energy, which is more favorable for cell adherence (Kilpadi and Lemons, 1994, Kim *et al.*, 2008). Bowers and colleagues (Bowers *et al.*, 1992) first demonstrated that the moderate roughness with sandblasted and acid-etching treatments significantly promoted cell attachment. Anselme and Bigerelle (Anselme and Bigerelle, 2005) later investigated long-term osteoblast adherence and behavior *in vitro* and demonstrated that a low amplitude of the surface roughness induced cell spreading more intimately than the rougher one. Therefore, the microtopography of the implant surface also influences differentiation events by providing the distortional signals. While osteoblastic cells show a cuboidal shape with polarized nuclei, the inactive bone-lining cells tended to have a flattened morphology without polarization (Kieswetter *et al.*, 1996). Later studies further demonstrated that minor distortional strain and low compressive hydrostatic stress on mesenchymal stem cells were most likely for promoting osteogenic differentiation, whereas excessive distortional strain resulted in fibrogenesis as well as chondrogenesis, due to significant hydrostatic pressure (Andreykiv *et al.*, 2008). Based on the mesenchymal cell size of about 5 to 12 μm in length, surface microtopographic pits with a 4 μm diameter and 1.5 μm depth are thought to be optimal for cells to attach and

subsequently differentiate on the implant surface (Hansson and Norton, 1999, Schwartz *et al.*, 1999).

Based on the large proportion of grain boundaries increasing surface energy, significant enhancement of cell attachment, proliferation, viability, spreading, and early osteogenic differentiation on these nano-/ultrafine-grained structures has been demonstrated in several investigations (Misra *et al.*, 2009, Puckett *et al.*, 2008, Brett *et al.*, 2004). However, reproducible surface roughness on a nanoscale level is difficult to achieve, thus optimal surface nanotopography for rapid osseointegration is still not achievable (Le Guehennec *et al.*, 2007).

Surface Coating and Biomimetic Approaches

Another category of implant surface modification is to coat the implant with layers of bioactive materials. One approach is to coat the titanium surface of implants with calcium phosphates, mainly composed of hydroxyapatite (HA), by plasma-spraying. The calcium phosphates are released to the peri-implant area after implantation and precipitated biological apatites, which serve as matrices for subsequent osteogenic cell attachment and growth (Junker *et al.*, 2009, Le Guehennec *et al.*, 2007). Compared to a titanium surface without coating, osteogenic cells attach, proliferate, and differentiate on the HA-coated surface (Knabe *et al.*, 2004), and result in superior initial rates of osseointegration *in vivo* (Geurs *et al.*, 2002). However, the delamination of the coating and particle release from the implant surface causes long-term failure in some studies (Chang *et al.*, 1999, Lee *et al.*, 2000a). To prevent this, recent investigations have focused on depositing HA onto the implant surface through biomimetic approaches, such as electrodeposition or immersion in SBF (Le Guehennec *et al.*, 2007).

Implant surfaces may be also coated with biomolecules, such as bio-adhesive motifs or growth factors, to enhance osseointegration. The RGD sequence from fibronectin is the most commonly used bio-adhesive motif, which binds adhesion receptors and promotes cell adhesion (Shakesheff *et al.*, 1998). RGD-functionalized, tissue-engineered constructs have shown improvement during early bone ingrowth and matrix mineralization *in vivo* (Alsberg *et al.*, 2001, Lütolf *et al.*, 2003). However, RGD immobilization on titanium implant surfaces has not improved bone-implant contact nor osteoblast differentiation (Schliephake *et al.*, 2002, Tosatti *et al.*, 2004), presumably due to neglecting the conformation-dependent effects and absence of crucial modulatory domains from the native fibronectin, thus diminishing the RGD signals through non-specific adsorption of plasma protein and interactions with inflammatory components (Garcia and Reyes, 2005).

Growth Factor Delivery to Accelerate Osseointegration

The rate of osseointegration is dependent on the commitment, replication, and differentiation of osteoprogenitor cells, and on interfacial tissue maturation (Brunski *et al.*, 2000, Marie, 2003). Since growth factors, such as BMP and platelet-derived growth factor (PDGF), enhance osteogenesis and were suggested to regenerate the periodontal and dentoalveolar tissues (Ramseier *et al.*, 2006, Taba *et al.*, 2005), several of those biomolecules were also introduced to accelerate peri-implant wound healing and osseointegration (Table 1).

Bone Morphogenetic Proteins (BMPs)

Belonging to the transforming growth factor-beta (TGF- β) superfamily, BMPs have been proven to drive the multipotent cells into an osteogenic lineage and promote extracellular matrix formation through the Smad signaling pathway (Chen *et al.*, 2004). Among all of the BMPs isoforms, BMP-2 and BMP-7 are the most commonly investigated. BMP can induce ectopic and periosteal bone formation *in vivo* (Chang *et al.*, 2007, Hak *et al.*, 2006). Within

the dental field, BMP has been shown to promote tooth extraction socket healing, peri-implant wound healing, and sinus floor and alveolar ridge augmentation in preclinical studies (Barboza *et al.*, 2004, Brandao *et al.*, 2002, Cochran *et al.*, 1999, Nevins *et al.*, 1996, Dunn *et al.*, 2005, Nakashima and Reddi, 2003). Some investigations have also reported that BMP exhibits superior short- but not long-term effects over controls (Jones *et al.*, 2006, Jovanovic *et al.*, 2007, Matin *et al.*, 2001). In clinical trials, BMP tended to accelerate extraction socket and alveolar ridge augmentation compared to collagen vehicle alone within the period of 4-6 months (Bianchi *et al.*, 2004, Howell *et al.*, 1997). However, no significant difference could be found between BMP application and bone grafting in the treatment of sinus floor and alveolar ridge augmentation (Boyne *et al.*, 2005, Jung *et al.*, 2003).

Platelet-Derived Growth Factors (PDGFs)

PDGF is a potent mitogen and chemotactic factor for cells of mesenchymal origin, including periodontal ligament (PDL) cells and osteoblasts (Graves *et al.*, 1994). PDGF can also regulate the expression of vascular endothelial growth factor (VEGF) to promote angiogenesis and is reported as an essential hormone in the healing process of soft tissue and bone (Hollinger *et al.*, 2008). PDGF exists as a dimer form (-AA, -AB, -BB, -CC, and -DD) and signals through binding to tyrosine kinase receptors, termed PDGF receptors alpha and beta (Seifert *et al.*, 1989), with PDGF-BB the most widely used isoform of PDGF based on its capability to bind to all known PDGF receptor isotypes (Hollinger *et al.*, 2008).

PDGF plays an indirect role in osteogenesis by recruiting and expanding the osteogenic cell populations, and subsequent differentiation of those cells is achieved by BMPs (Chaudhary and Hruska, 2001, Cho *et al.*, 2002). *In vivo* investigations also indicate that applying PDGF to denuded tooth root surfaces increase proliferation of PDL cells, osteoblasts, and perivascular cells, and accelerate alveolar bone regeneration (Giannobile *et al.*, 1996, Park *et al.*, 1995, Wang *et al.*, 1994). A multicenter clinical trial validated PDGF-BB is capable of promoting periodontal defect regeneration (Nevins *et al.*, 2005). Furthermore, a significant amount of *in vivo* bone regeneration was also noted in a 'pure' orthopaedic environment such as the calvarial or femoral critical-sized osteotomy using a combination of calcium phosphate graft and PDGF (Lee *et al.*, 2000b, Nash *et al.*, 1994). Combination of PDGF and insulin-like growth factor-1 (IGF-1) had shown to stimulate bone regeneration around the press-fit titanium implants (Becker *et al.*, 1992, Lynch *et al.*, 1991). Recently Chang et al. demonstrated the PDGF protein or gene delivery was capable of accelerating oral implant osseointegration *in vivo* as well as improving biomechanical properties (Chang *et al.*, 2009a).

On the other hand, the possible inhibitory effects to osteogenesis have also been documented. Kono and colleague reported that PDGF treatment negatively regulates osteogenic differentiation (Kono *et al.*, 2007), and Tokunaga et al demonstrated that specifically the PDGF receptor beta had a determinable effect on mesenchymal cell differentiation (Tokunaga *et al.*, 2008). Therefore, the bidirectional effect on osteogenesis is associated with the expression profile of PDGF, with pulse PDGF application stimulating osteogenesis while continuous PDGF exposure elicits an inhibitory effect (Hsieh and Graves, 1998).

Other Growth Factors and Combinations

Besides BMP and PDGF, there are several growth factors being investigated for accelerating osteogenesis, such as transforming growth factor-beta (TGF- β), insulin-like growth factor (IGF), and fibroblast growth factor (FGF) (Andrades *et al.*, 1999, Mukherjee and Rotwein, 2009). TGF- β has been proposed as an osteoinductive factor based on its ability to promote proliferation of osteoblasts (Macdonald *et al.*, 2007). However, studies also demonstrate that

TGF- β enhances chondrogenesis rather than osteogenesis in MSCs (Ng *et al.*, 2008, Xu *et al.*, 2008). IGF-1 and IGF-2 regulate the bone formation process through increasing type I collagen synthesis, decreasing collagen degradation, modestly enhancing mitogenesis, and stabilizing α -catenin, a key regulator in Wnt pathway of osteogenic differentiation (Giustina *et al.*, 2008). FGF-2 promotes mitogenesis and reduces apoptosis of osteoprogenitor cells, which increases the population of functional osteoblasts, but induces apoptosis in more differentiated osteoblasts, thus limiting the early increase of mature cells in the osteoblast pool (Marie, 2003). A recent clinical investigation demonstrated that FGF-2 significantly increased the alveolar bone height after 36 weeks in patients with periodontitis suggesting that FGF-2 could be a potential stimulator for bone regeneration (Kitamura *et al.*, 2008).

The process of osteogenesis is regulated through several growth factors, and cross-talk most likely exists among them (Marie, 2003, Singhatanadgit *et al.*, 2006). Thus, combination of growth factors is a viable approach to amplify osteogenesis. The first approach was proposed based on the synergistic effects on wound healing using a combination of PDGF-BB and IGF-1 (Lynch *et al.*, 1989a). This combination exhibited greater alveolar bone and cementum regeneration than single growth factor application (Giannobile *et al.*, 1996, Lynch *et al.*, 1989b), and promoted initial dental implant osseointegration in later investigations (Becker *et al.*, 1992, Lynch *et al.*, 1991, Stefani *et al.*, 2000). The combination of angiogenic (ie., VEGF) and osteogenic growth factors (ie., BMP) promoted bone regeneration (Huang *et al.*, 2005, Patel *et al.*, 2008), and dual delivery of BMP/TGF- β or BMP/FGF also enhanced osseointegration *in vivo* (Lan *et al.*, 2006, Sumner *et al.*, 2006). However, application should be controlled by sequential release profile of the growth factors in order to maximize the beneficial effects of combinatorial delivery (Kempen *et al.*, 2009).

Preclinical Biomechanical Assessments for Osseointegration

Tensional Test

The interfacial tensile strength was originally measured by detaching the implant plate from the supporting bone (Kitsugi *et al.*, 1996) (Table 2). Brånemark later modified this technique by applying the lateral load to the cylindrical fixture (Brånemark *et al.*, 1998) (Fig 1a). However, they also addressed the difficulties of translating the test results to any area-independent mechanical properties.

Push-out/Pull-out Test

The 'push-out' or 'pull-out' test is the most commonly used approach to investigate the healing capabilities within the bone-implant interface (Brunski *et al.*, 2000, Kempen *et al.*, 2009). In the typical push-out or pull-out test, a cylinder-type implant is placed transcortically or intramedullarily in bone structures and then removed by applying a force parallel to the interface (Fig 1b-c). The maximum load capability (or failure load) is defined as the maximum force on the force-displacement plot, and the interfacial stiffness is visualized as the slope of a tangent approximately at the linear region of the force-displacement curve prior to breakpoint (Brunski *et al.*, 2000, Lütolf *et al.*, 2003) (Table 2). Therefore, the general loading capacity of the interface (or interfacial shear strength) can be measured by dividing the maximum force by the area of implant in contact with the host bone (Berzins *et al.*, 1997). However, the push-out and pull-out tests are only applicable for non-threaded cylinder type implants, whereas most of clinically available fixtures are of threaded design, and their interfacial failures are solely dependent on shear stress without any consideration for either tensile or compressive stresses (Brunski *et al.*, 2000).

Removal Torque

The removal torque refers to the torsional force necessary for unscrewing the fixture (Fig 1d) and was first investigated by Johansson and coworkers (Johansson *et al.*, 1998). The removal torque value was recorded using a torque manometer calibrated in Newton-centimeters (Ncm). This technique primarily focuses on interfacial shear properties (Table 2). However, the results may be affected by implant geometry and topography (Meredith *et al.*, 1997, Yeo *et al.*, 2008).

Combination of Push-out/pull-out and Removal Torque

This combinational trial was introduced by Brånemark and colleagues by applying torsional force until reaching the maximum torque and then pulling the implant out (Brånemark *et al.*, 1998). In this investigation, the removal torque was related to the interfacial bonding capability, and the pull-out strength was related to the shear properties from the implant-supporting structure.

Clinical Biomechanical Assessments for Osseointegration

Cutting Resistance/Insertional Torque

The cutting resistance refers to the energy required in cutting of a unit volume of bone (Friberg *et al.*, 1995) while the insertional torque occurs during the fixture tightening procedure (Ueda *et al.*, 1991). Both of these measurements consider the lateral compression force and friction at the interface during implant insertion and are mainly influenced by the tolerance of the fixture thread design (O'Sullivan *et al.*, 2000). Many researchers also used the peak insertional torque value, which is generated during the last fixture tightening step, as an indicator of primary implant stability (Table 2). A positive correlation between insertional and removal torque is evident however, any relationship between the cutting resistance and the peak insertional torque is still unclear (Molly, 2006).

Periotest®

Significant deformation of the bone-implant unit is not measurable for most clinical situations. To overcome this limitation, damping characteristics, or the dynamic tissue recovery processes after loading, have been recommended for noninvasive assessment of osseointegration (Aparicio *et al.*, 2006). A Periotest® (Siemens, Bensheim, Germany) was originally designed to assess the damping characteristics of the periodontal ligament (PDL) by calculating the contact time between the test subject and the percussion rod (Figure 1e) and are reported as Periotest value (PTV) (Schulte and Lukas, 1993) (Table 2).

The main limitation of the Periotest® is a lack of sensitivity in evaluating osseointegration, whereby the range of PTV in osseointegrated implants falls to a narrow zone (−5 to +5) within a wide scale (−8 to +50) (Olive and Aparicio, 1990). This could be accounted for by physical differences between periodontium and the bone-implant interface, because bone is much stiffer and does not allow for significant deformation as compared to the soft tissue of the periodontium (Meredith *et al.*, 1997). Moreover, results may also be influenced by the position and direction of the percussion rod (Schulte and Lukas, 1992).

Resonance Frequency Analysis (RFA)

RFA was first introduced by Meredith and co-workers (Meredith *et al.*, 1997). An L-shaped transducer connected to the implant was utilized to provide a high frequency mechanical vibration and record the frequency and amplitude of the signal received (Fig 1f). The resonance frequency was thus defined as the peak of the frequency-amplitude plot and converted to a value representing stiffness of the bone-implant interface. Currently, Osstell®

(Integration Diagnostic AB, Goteborg, Sweden), a commercialized product utilizing the concept of RFA, has translated the resonance frequency ranging from 3000 to 8500 Hz as the implant stability quotient (ISQ) of 0 to 100 (Atsumi *et al.*, 2007) (Table 2).

While moderate to strong correlation is found between cutting resonance and ISQ value upon implant placement (Friberg *et al.*, 1999, Turkyilmaz *et al.*, 2008), and because of the noninvasive nature of the measurement, RFA has been widely used for clinically assessing osseointegration, as well as for prognostic evaluation (Aparicio *et al.*, 2006, Meredith *et al.*, 1997, Oates *et al.*, 2009). However, the latter aspect still has to be questioned (Aparicio *et al.*, 2006).

Relevance of the Peri-Implant Structure to Interfacial Biomechanics

Considering that intrinsic properties of the peri-implant bone may affect the stiffness of bone-implant interface (Bischof *et al.*, 2004, Brunski, 1992), a number of studies have been initiated to provide insights of correlation between peri-implant structure and implant stability (Tables 3 and 4).

Correlations between Primary Implant Stability and Peri-Implant Structures

Considering that intrinsic properties of the peri-implant bone may affect the stiffness of bone-implant interface (Bischof *et al.*, 2004, Brunski *et al.*, 2000), a number of studies have undertaken to provide insight into the correlation between peri-implant structure and implant stability (Tables 3 and 4).

Correlations between Primary Implant Stability and Peri-Implant Structures

The relationship between the primary implant stability and peri-implant structures was first reported by Niimi and colleagues (Niimi *et al.*, 1997). These authors applied torque to implants within the fibulae, iliac crest, and scapula of human cadavers and found that the removal torque value was significantly correlated to cortical bone thickness but was not associated with the trabecular bone area based on histological sections. This same correlation was also observed in a later investigation using implant pull out methods from dog mandibulae (Salmoria *et al.*, 2008).

Primary implant stability may also be correlated to the bone mineral density (BMD) by analyzing and interpreting three-dimensional (3D) computed tomography (CT) images (Homolka *et al.*, 2002, Turkyilmaz *et al.*, 2008), and is strongly correlated with increasing implant diameter (Turkyilmaz *et al.*, 2008). Akça and coworkers also found significant correlation between the trabecular bone structure and the insertional torque value (Akça *et al.*, 2006). However, most of these investigations also revealed that the insertional torque value tended to be more sensitive to the peri-implant structure than the ISQ value (Table 3).

Correlations between Secondary Implant Stability and Peri-Implant Structures

An early preclinical study demonstrated a similar tendency of change in removal torque value and bone-implant contact over a period of time (Johansson *et al.*, 1998), demonstrating that results could be influenced by implant topography or metal biocompatibility (Johansson *et al.*, 1998, Wennerberg and Albrektsson, 2009). However, a relationship between the amount of bone within the threaded area and the removal torque value was not made clear from these approaches (Wennerberg *et al.*, 1996). Because of the inability to perform biomechanical testing and structural analysis on the same specimens due to, at that time, a lack of reliable clinical biomechanical assessments or more definitive imaging techniques, careful review of those results appears to be necessary.

Measuring specimens during and after implant removal, Brånemark and co-workers demonstrated that the total bone thickness (TBT) 50 µm from the interface and bone implant contact area (BIC) were significantly correlated to the maximal and breakpoint torque, and the TBT also strongly correlated to the subsequent pull-out force (Brånemark *et al.*, 1998). The correlation between insertional torque value and cortical bone thickness was recently reported (Motoyoshi *et al.*, 2007). However, the opposite result was found from a study on dog mandibles, where the pull-out force was correlated to primary implant stability, but this correlation became non-significant in the latter healing stages (Salmoria *et al.*, 2008).

Using non-destructive biomechanical assessments (ie., Periotest®, RFA) on dog mandibles, a high correlation was found between the mechanical impedance from the Periotest® and BIC as well as bone density from histology and radiography at 3 months post-implantation (Ramp and Jeffcoat, 2001). Significant correlations between PTV and BIC based on histology were also found (Sykaras *et al.*, 2004). However, using a different treatment modality such as the pull-out test, the PTV was not sensitive to the osseous wound repair (Sykaras *et al.*, 2004). Significant, but weak correlations between ISQ values and BIC were shown in some reports (Itoh *et al.*, 2003, Scarano *et al.*, 2006), whereas others failed to demonstrate such correlations (Schliephake *et al.*, 2002). Moreover, recent investigations utilizing micro-CT technology also demonstrated a variety of moderate to strong correlations between the structural parameters (ie, BIC, bone volume, trabecular bone thickness, trabecular number, and connectivity density) and pull-out results, and different treatment strategies resulted in similar a correlation between the biomechanical and structural properties (Gabet *et al.*, 2006).

Model Analysis for Osseointegration

Finite Element (FE) Analysis

FE analysis had been extensively used as a tool of functional assessments in the field of implant density over the past 2 decades (Geng *et al.*, 2001). The FE model was built based on the pre-determined geometry of tissue and implant, material properties, and boundary conditions. Through applying the loading situation and numerical iteration, the functional performance of dental implant system could be expressed as specific values or gradient distribution of stress and strain in the model (Van Staden *et al.*, 2006). Thus, FE analysis had been utilized to investigate the functional influence the implant geometry (Himmlova *et al.*, 2004), material properties of implant (Yang and Xiang, 2007), quality of implant-supporting tissue (Petrie and Williams, 2007, Sevimey *et al.*, 2005), fixture-prosthesis connection (Akça *et al.*, 2003), and the loading condition (Mellal *et al.*, 2004, Natali *et al.*, 2006).

The bone-implant interface was considered as the boundary condition, and usually assigned as the pre-determined situation in FE model. Thus, the interfacial biomechanics have not been directly assessed from FE analysis (Van Staden *et al.*, 2006). Therefore, in most of the FE model, the assignment of material properties was based on the theoretical value or references, and a simplified model following reasonable assumptions was usually suggested to reduce the complexity of iteration and assure the numerical convergence. The numerical artifacts may somewhat influence the accuracy of evaluations (Ladd and Kinney, 1998). Thus, the results from FE analyses should be carefully interpreted, and the experimental validation should be necessary if possible.

Functional Apparent Moduli

Homogenization of the mechanical properties to calculate the effective stiffness of bone was first introduced by Hollister and colleagues (Hollister *et al.*, 1994). They acquired three-dimensional trabecular bone architecture from micro-CT imaging and investigated the stress

and strain distribution of the elements under simulated loading conditions to calculate the effective Young's modulus of the bulk specimen. The effective modulus revealed significant agreement with experimental results. Utilizing the concept of homogenization, later investigations by heterogeneous micro-elastic properties assignments demonstrated that the non-uniform mineral density and trabecular architecture could influence the effective tissue modulus (Morgan *et al.*, 2004, Renders *et al.*, 2008, van der Linden *et al.*, 2001).

According to the unavailability of functionally evaluating peri-implant tissue, our group utilized the homogenization theory to calculate the effective stiffness of peri-implant tissue under loading from dental implant (Fig 2), whereas the functional bone apparent modulus (FBAM) represented the effective modulus of bone architecture, and functional composite tissue modulus (FCAM) for effective modulus of whole tissue within the wound (Chang *et al.*, 2009b). Compared with individual structural parameters, the results indicated that the bone repair in early stage was to provide significant resistance to support the dental implant rather than fill the wound space or maturation. A much stronger correlation to interfacial biomechanics than all the other structural parameters was also noted (Table 4).

Conclusions

Although several approaches are available to assess implant stability (at the implant or surrounding host bone regions), limitations still exist to date, and no definite link between the function and peri-implant structure can be established. Functional apparent modulus through FE optimization is feasible to evaluate peri-implant osseous wound repair as well as interfacial biomechanics. Hence, integration of peri-implant structure may be necessary to predict the interfacial properties. However, further confirmation through preclinical and clinical models is still needed for investigating the mechanism involved in osseointegration and bone regeneration associated with oral implants.

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Figure 1. Biomechanical assessments for oral implant osseointegration
(a) tensional test, (b) push-out test, (c) pull-out test, (d) insertional/removal torque test, (e) Periotest, and (f) resonance frequency analysis (RFA).

Figure 2. The *in vivo* finite element homogenization procedures for functional apparent moduli (a) The cylinder implant was pushed out (following the direction of the red arrow) from the jaw bone, and (b) the load-displacement relationship was recorded for calculating the interfacial stiffness (dash line, referred to the slope of the curve before the yielding point). (c) The three-dimensional (3-D) peri-implant structure was identified after removing the implant. (d) The finite element model was developed from projecting the peri-implant structure and interfacial information (microscopic model, upper panel) with the suspension boundary condition (pink marks on the peri-implant tissue border). In the optimizing model (lower panels), the peri-implant layer of interest was homogenized (yellow peri-implant regions), and the effective stiffness was calculated from the numerical approximation (to the microscopic model) under the implant loading condition (light blue arrows). Abbreviations: TI: titanium implant; PI: peri-implant tissue; Gr: granulation tissue in peri-implant area; FBAM: functional bone apparent modulus; FCAM: functional composite tissue apparent modulus

Table 1**The Modes of Growth Factor Delivery for Promoting Dental Implant Osseointegration**

Growth Factor	Mechanisms	Delivery Mode	Reference
BMPs (-2 & -7)	Osteogenic lineage differentiation	Recombinant protein	(Barboza <i>et al.</i> , 2004, Bianchi <i>et al.</i> , 2004, Brandao <i>et al.</i> , 2002, Cochran <i>et al.</i> , 1999, Nevins <i>et al.</i> , 1996)
		Gene delivery	(Dunn <i>et al.</i> , 2005)
PDGF-BB	Mitogenesis and chemotaxis of mesenchymal and osteogenic cells populations	Recombinant protein	(Lee <i>et al.</i> , 2000b, Nevins <i>et al.</i> , 2005)
		Gene delivery	(Jin <i>et al.</i> , 2004, Chang <i>et al.</i> , 2009a)
TGF- β	Mitogenesis of osteoblasts	Recombinant protein	(Ng <i>et al.</i> , 2008, Xu <i>et al.</i> , 2008)
IGFs (-1 & -2)	Collagen matrix production and stabilization, mitogenesis	Recombinant protein	(Giustina <i>et al.</i> , 2008)
FGF-2	Mitogenesis and anti-apoptosis of osteoprogenitor cells	Recombinant protein	(Kitamura <i>et al.</i> , 2008, Marie, 2003)
PDGF-BB/IGF-1	Combinational effects of dual growth factors	Recombinant protein	(Becker <i>et al.</i> , 1992, Stefani <i>et al.</i> , 2000)
BMP-2/VEGF	Combinational effects of dual growth factors	Recombinant protein	(Huang <i>et al.</i> , 2005, Patel <i>et al.</i> , 2008)
BMP-2/FGF-2	Combinational effects of dual growth factors	Recombinant protein	(Lan <i>et al.</i> , 2006)
BMP-2/TGF- β	Combinational effects of dual growth factors	Recombinant protein	(Sumner <i>et al.</i> , 2006)

Abbreviations: BMP: bone morphogenetic protein; PDGF: platelet-derived growth factor; TGF: transforming growth factor; IGF: insulin-like growth factor, FGF: fibroblast growth factor; VEGF: vascular-endothelial growth factor

Table 2

Current Biomechanical Assessments for Dental Implant Osseointegration

Methodology	Destructive	Clinical use	Property Investigated	Parameters	Reference
Tensional test	Yes	No	Lateral resistance	Maximal lateral load	(Brånemark <i>et al.</i> , 1998, Kitisugi <i>et al.</i> , 1996)
Push-out/Pull-out	Yes	No	Interfacial shear	Maximal force Interfacial stiffness	(Berzins <i>et al.</i> , 1997, Brunski <i>et al.</i> , 2000)
Removal Torque	Yes	No	Interfacial shear	Loosening torque Torque load	(Johansson <i>et al.</i> , 1998, Meredith <i>et al.</i> , 1997)
Cutting Resistance/Insertional Torque	No	Yes	Interfacial shear	Peak insertional torque Torque load	(Friberg <i>et al.</i> , 1995, O'Sullivan <i>et al.</i> , 2000)
Periotest	No	Yes	Damping	Periotest value (PTV)	(Aparicio <i>et al.</i> , 2006, Schulte and Lukas, 1993)
Resonance Frequency Analysis	No	Yes	Vibration/Damping	Implant stability quotient (ISQ)	(Friberg <i>et al.</i> , 1999, Meredith <i>et al.</i> , 1997, Turkyilmaz <i>et al.</i> , 2009)

Table 3
Correlation between Biomechanical Testing and Peri-Implant Structures (Primary Stability)

Methodology	Model	Structure Assessment	Structural Parameters	Correlation	Reference (s)
PO	Canine	Histology	CBT	$r=0.44^*$	(Salmoria <i>et al.</i> , 2008)
IT	Human cadaver	CT (3D)	BMD	$r=0.690^*$	(Turkylilmaz <i>et al.</i> , 2009)
RFA	Human cadaver	CT (3D)	BMD	$r=0.557^*$	(Turkylilmaz <i>et al.</i> , 2009)
IT	Human cadaver	Micro-CT (3D)	Tb.Th Tb.N Tb.Sp	$r=0.825^*$ $r=0.718^*$ $r=-0.795^*$	(Akça <i>et al.</i> , 2006)
RFA	Human cadaver	Micro-CT (3D)	Tb.Th Tb.N Tb.Sp	N.S. for any of parameter	(Akça <i>et al.</i> , 2006)
IT	Human cadaver	CT (3D)	BMD	$r^2=0.81^*$	(Homolka <i>et al.</i> , 2002)
IT	Human	CT (3D)	BMD	$r=0.10-0.83^*$	(Turkylilmaz <i>et al.</i> , 2007)
RFA	Human	CT (3D)	BMD	$r=0.34-0.91^*$	(Turkylilmaz <i>et al.</i> , 2007)
IT	Human cadaver	CT (3D)	BMD	$r=0.86^*$	(Beer <i>et al.</i> , 2003)
IT	Human	CT (3D)	BMD (ID<4 mm) BMD (ID>4 mm)	$r=0.33-0.59^*$ $r=0.05-0.29$	(Turkylilmaz <i>et al.</i> , 2006)
RT	Human cadaver	Calipers	CBT TBT	$p<0.05^*$ N.S.	(Niimi <i>et al.</i> , 1997)

Abbreviations: IT: insertional torque; PO: pull-out; PS: push-out; RFA: resonance frequency analysis; CT: computed tomography; CBT: cortical bone thickness; BIC: bone-implant contact; BVD: bone-volume density; BMD: bone mineral density; BV/TV: bone volume/total volume; ID: implant diameter; TBT: total bone thickness; Tb.Th: trabecular thickness; Tb.N: trabecular number; Tb.Sp: trabecular separation; Conn.D: connectivity density; N.S.: no significant difference ($p>0.05$)

* $p<0.05$

Table 4
Correlation between Biomechanical Testing and Peri-Implant Structures (Secondary Stability)

Methodology	Model	Structure Assessment	Structural Parameters	Correlation	Reference (s)
IT	Human	CT (2D)	CBT	$r=0.320^*$	(Motoyoshi <i>et al.</i> , 2007)
PO	Canine	Histology	CBT	N.S.	(Salmoria <i>et al.</i> , 2008)
RFA	Human	Histology	BIC	$p=0.016^*$	(Scarano <i>et al.</i> , 2006)
RFA	Canine	Histology	BIC BVD	$r=0.128, p=0.264$ $r=0.206, p=0.072$	(Schliephake <i>et al.</i> , 2002)
Periotest	Canine	Radiography	BIC	$r=0.38^*$	(Sykaras <i>et al.</i> , 2004)
Periotest	Canine	Histology & radiography	BIC (His) BIC (Rad) BVD (His)	$r^2=0.72^*$ $r^2=0.88^*$ $r^2=0.80^*$	(Ramp and Jeffcoat, 2001)
RFA	Porcine	Histology	BIC	$r=0.221^*$	(Ito <i>et al.</i> , 2008)
RT	Rodent	Histology	BIC TBT	$r=0.78-0.84^*$ $r=0.68-0.76^*$	(Brånemark <i>et al.</i> , 1997)
PO	Rodent	Histology	TBT	$r=0.87^*$	(Brånemark <i>et al.</i> , 1997)
PO	Rodent	Micro-CT (3D)	BIC BV/TV Tb.Th Tb.N Conn.D	$r^2=0.52$ (FL) $^* 0.24$ (IS) * $r^2=0.72$ (FL) $^* 0.43$ (IS) * $r^2=0.60$ (FL) $^* 0.31$ (IS) * $r^2=0.47$ (FL) $^* 0.32$ (IS) * $r^2=0.37$ (FL) $^* 0.28$ (IS) *	(Gabet <i>et al.</i> , 2006)
PS	Rodent	Micro-CT (3D) & FE optimization	BV BMC BMD FBAM FCAM	$r=0.67$ (OA) $^* 0.34$ (OS) * $r=0.70$ (OA) $^* 0.71$ (OS) * $r=0.61$ (OA) $^* 0.62$ (OS) * $r=0.96$ (OA) $^* 0.84$ (OS) * $r=0.74$ (OA) $^* 0.95$ (OS) *	(Chang <i>et al.</i> , 2009b)

Abbreviations: IT: insertional torque; PO: pull-out; PS: push-out; RFA: resonance frequency analysis; CT: computed tomography; CBT: cortical bone thickness; BIC: bone-implant contact; BV: bone volume; BVD: bone-volume density; BMC: bone mineral content; BMD: bone mineral density; BV/TV: bone volume/total volume; FBAM: functional bone apparent modulus; FCAM: functional composite tissue apparent modulus; ID: implant diameter; FL: failure load; IS: interfacial stiffness; OS: implant placing in osteotomy hole with osseous defect situation (0.6x1 mm circumferential); OA: implant placing in osteotomy-alone without any surrounding defect situation; TBT: total bone thickness; Tb.Th: trabecular thickness; Tb.N: trabecular number; Tb.Sp: trabecular separation; Conn.D: connectivity density; N.S.: no significant difference ($p>0.05$)

* $p<0.05$

** highest correlation coefficient for each parameter