CLINICAL ORAL IMPLANTS RESEARCH

Po-Chun Chang
Niklaus P. Lang
William V. Giannobile

Review

Evaluation of functional dynamics during osseointegration and regeneration associated with oral implants

Authors' affiliations:
Po-Chun Chang, William V. Giannobile, Department of Periodontics and Oral Medicine, School of Dentistry, University of Michigan, Ann Arbor, MI, USA
Po-Chun Chang, William V. Giannobile, Department of Biomedical Engineering, College of Engineering, University of Michigan, Ann Arbor, MI, USA
Po-Chun Chang, Department of Preventive Dentistry, Division of Periodontology, Faculty of Dentistry, National University of Singapore, Singapore
Niklaus P. Lang, Faculty of Dentistry, The University of Hong Kong, Hong Kong, China SAR
William V. Giannobile, Michigan Center for Oral Health Research, School of Dentistry, University of Michigan, Ann Arbor, MI, USA.

Correspondence to:
William Giannobile
University of Michigan
School of Dentistry
Michigan Center for Oral Health Research
1011 N. University Ave.
Rm. 3305 Dental Bldg.
Ann Arbor, MI 48109, USA
Tel.: +1 734 764 1562
Fax: +1 734 763-5503
e-mail: wgiannob@umich.edu

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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 biomimetric interface, or local delivery of growth-promoting factors. The current available pre-clinical 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.

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 & Jeffcoat 2001). While the structure and heterogeneity of mineralization affects the stiffness of bone (Hoffler et al. 2000), 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 pre-clinical use (Berzins et al. 1997). Therefore,

the clinical value of non-destructive measurements, such as resonance frequency analysis (RFA) or damping characteristics (Periotest® technique, Siemens, Bensheim, Germany), 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 pre-clinical 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 μm gap between the implant and host bone has been noted under microscopic investigations (Futami et al. 2000; Colnot et al. 2007), and depending on the extent of injury to the host bone, this gap may later extend to 100–500 μm (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 (Park & Davies 2000; Berglundh et al. 2003). 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 & 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 7 (Berglundh et al. 2003). Through continuous deposition, trabecular bone fills the initial gap and arranges in a three-dimensional (3D) network at day 14 (Franchi et al. 2005). The *de 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 8–12 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 & 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 & Albrektsson 2009).

Surface roughness

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

- Smooth surfaces: S_a value <0.5 μm (e.g. polished abutment surface).
- Minimally rough surfaces: S_a value $0.5-<1$ μm (e.g. turned implants).
- Moderately rough surfaces: S_a value $1-<2$ μm (e.g. most commonly used types).
- Rough surfaces: S_a value ≥ 2 μm (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 bone–implant contact (BIC) and removal torque force suggested enhanced secondary stability compared with 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 & Lemons 1994; Kim et al. 2008). Bowers et al. (1992) first demonstrated that the moderate roughness with sandblasted and acid-etching treatments significantly promoted cell attachment. Anselme & 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

Table 1. **The modes of growth factor delivery for promoting dental implant osseointegration**

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

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.

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 5–12 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 & 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 (Brett et al. 2004; Puckett et al. 2008; Misra et al. 2009). 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. 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 (Le Guehennec et al. 2007; Junker et al. 2009). Compared with 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 BIC 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 & 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 bone morphogenetic protein (BMP) and platelet-derived growth factor (PDGF), enhance osteogenesis and were suggested to regenerate the periodontal and dentoalveolar tissues (Taba et al. 2005; Ramseier et al. 2006), several of those biomolecules were also introduced to accelerate peri-implant wound healing and osseointegration (Table 1).

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* (Hak et al. 2006; Chang et al. 2007). 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 pre-clinical studies (Nevins et al. 1996; Cochran et al. 1999; Fiorellini et al. 2005; Nakashima & Reddi 2003; Barboza et al. 2004; Dunn et al. 2005). Some investigations have also reported that BMP exhibits

superior short- but not long-term effects over controls (Matin et al. 2001; Jones et al. 2006; Jovanovic et al. 2007). In clinical trials, BMP tended to accelerate extraction socket and alveolar ridge augmentation compared with collagen vehicle alone within the period of 4–6 months (Howell et al. 1997; Bianchi et al. 2004). However, no significant difference could be found between BMP application and bone grafting in the treatment of sinus floor and alveolar ridge augmentation (Jung et al. 2003; Boyne et al. 2005).

PDGFs

PDGF is a potent mitogen and chemotactic factor for cells of mesenchymal origin, including periodontal ligament (PDL) cells, and osteoblasts (Oates et al. 1993). 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 dimeric 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 & 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 (Wang et al. 1994; Park et al. 1995; Giannobile et al. 1996). 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' orthopedic environment such as the calvarial or femoral critical-sized osteomtomy using a combination of calcium phosphate graft and PDGF (Nash et al. 1994; Lee et al. 2000b). Combination of PDGF and insulin-like growth factor-1 (IGF-1) had shown to stimulate bone regeneration around the press-fit titanium implants (Lynch et al. 1991; Becker et al. 1992). Recently Chang et al. (2009a) demonstrated the PDGF protein or gene delivery was capable of accelerating oral implant osseointegration *in vivo* as well as improving biomechanical properties.

On the other hand, the possible inhibitory effects to osteogenesis have also been documented. Kono et al. (2007) reported that PDGF treatment negatively regulates osteogenic differentiation, and Tokunaga et al. (2008) demonstrated that specifically the PDGF receptor beta had a determinable effect on mesenchymal cell differentiation. 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 & Graves 1998).

Other growth factors and combinations

Besides BMP and PDGF, there are several growth factors being investigated for accelerating osteogenesis, such as TGF-β, IGF, and fibroblast growth factor (FGF) (Andrades et al. 1999; Mukherjee & 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 (Lynch et al. 1989b; Giannobile et al. 1996), and promoted initial dental implant osseointegration in later investigations (Lynch et al. 1991; Becker et al. 1992; Stefani et al. 2000). The combination of angiogenic (i.e., VEGF) and osteogenic growth factors (i.e., 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).

Pre-clinical 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 at 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 intramedullarly 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

Table 2. **Current biomechanical assessments for dental implant osseointegration**

Methodology	Destructive	Clinical use	Property investigated	Parameters	References
Tensional test	Yes	No	Lateral resistance	Maximal lateral load	Brånemark et al. (1998), Kitsugi et al. (1996)
Push-out/pull-out	Yes	No	Interfacial shear	Maximal force Interfacial stiffness	Berzins et al. (1997), Brunski et al. (2000)
Removal torque	Yes	No	Interfacial shear	Loosening torque Torque load	Johansson et al. (1998), Meredith et al. (1997)
Cutting resistance/ Insertional torque	No	Yes	Interfacial shear	Peak insertional torque Torque load	Friberg et al. (1995), O'Sullivan et al. (2000)
Periotest	No	Yes	Damping	Periostest value (PTV)	Aparicio et al. (2006), Schulte & Lukas (1993)
Resonance frequency analysis	No	Yes	Vibration/damping	Implant stability quotient (ISQ)	Friberg et al. (1999), Meredith et al. (1997), Turkyilmaz et al. (2009)

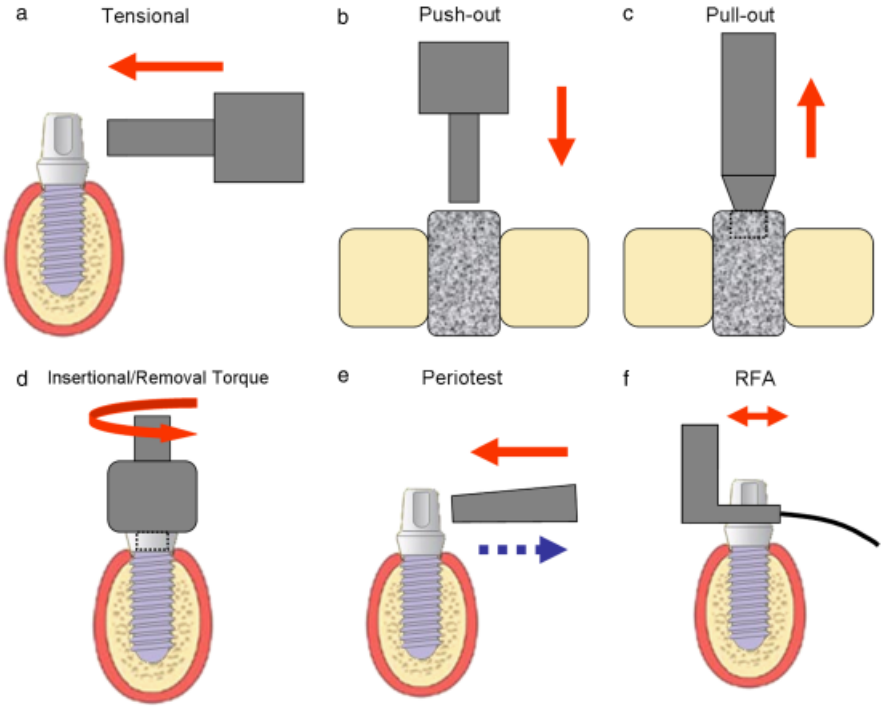

Fig. 1. Biomechanical assessments for oral implant osseointegration (a) tensional test, (b) push-out test, (c) pull-out test, (d) insertional/removal torque test, (e) Periotest, and (e) resonance frequency analysis (RFA).

plot, and the interfacial stiffness is visualized as the slope of a tangent approximately at the linear region of the force–displacement curve before 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 et al. (1998). The removal torque value was recorded using a torque manometer calibrated in Newton-centimeters (N cm). 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 et al. (1998) by applying torsional force until reaching the maximum torque and then pulling the implant out. 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 non-invasive assessment of osseointegration (Aparicio et al. 2006). A Periotest® (Siemens) was originally designed to assess the damping characteristics of the PDL by calculating the contact time between the

test subject and the percussion rod (Fig. 1e) and are reported as Periotest value (PTV) (Schulte & 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 & 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 with 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 & Lukas 1992).

RFA

RFA was first introduced by 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 0–100 (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), and because of the non-invasive nature of the measurement, RFA has been widely used for clinically assessing osseointegration, as well as for prognostic evaluation (Meredith et al. 1997; Aparicio et al. 2006; 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 (Brunski 1992; Bischof et al. 2004), 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 (Brunski et al. 2000; Bischof et al. 2004), 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 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 3D computed tomography (CT) images (Homolka et al. 2002; Turkyilmaz et al. 2009), and is strongly correlated with increasing implant diameter. Akça et al. (2006) also found significant correlation between the trabecular bone structure and the insertional torque value. 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 pre-clinical study demonstrated a similar tendency of change in removal torque value and BIC 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 & 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 et al. (1998) demonstrated that the total bone thickness (TBT) 50 μm from the interface and BIC area were significantly correlated to the maximal and breakpoint torque, and the TBT also strongly correlated to the subsequent pull-out force. 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 (i.e., 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 & 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 (i.e., 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).

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 et al. (2008)
IT	Human cadaver	CT (3D)	BMD	$r = 0.690^*$	Turkyilmaz et al. (2009)
RFA	Human cadaver	CT (3D)	BMD	$r = 0.557^*$	Turkyilmaz et al. (2009)
IT	Human cadaver	Micro-CT (3D)	Tb.Th	$r = 0.825^*$	Akça et al. (2006)
			Tb.N	$r = 0.718^*$	
			Tb.Sp	$r = -0.795^*$	
RFA	Human cadaver	Micro-CT (3D)	Tb.Th	NS for any parameter	Akça et al. (2006)
			Tb.N		
			Tb.Sp		
IT	Human cadaver	CT (3D)	BMD	$r^2 = 0.81^*$	Homolka et al. (2002)
IT	Human	CT (3D)	BMD	$r = 0.1$–0.83^*	Turkyilmaz et al. (2007)
RFA	Human	CT (3D)	BMD	$r = 0.34$–0.91^*	Turkyilmaz et al. (2007)
IT	Human cadaver	CT (3D)	BMD	$r = 0.86^*$	Beer et al. (2003)
IT	Human	CT (3D)	BMD (ID < 4 mm)	$r = 0.33$–0.59^*	Turkyilmaz et al. (2006)
			BMD (ID > 4 mm)	$r = 0.05$–0.29	
RT	Human cadaver	Calipers	CBT	$P < 0.05^*$	Niimi et al. (1997)
			TBT	NS	

$^*P < 0.05$.

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; NS, no significant difference ($P > 0.05$).

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 et al. (2007)
PO	Canine	Histology	CBT	NS	Salmoria et al. (2008)
RFA	Human	Histology	BIC	$P = 0.016$	Scarano et al. (2006)
RFA	Canine	Histology	BIC	$r = 0.128$, $P = 0.264$	Schliephake et al. (2002)
			BVD	$r = 0.206$, $P = 0.072$	
Periotest	Canine	Radiography	BIC	$r = 0.38^*$	Sykaras et al. (2004)
Periotest	Canine	Histology and radiography	BIC (His)	$r^2 = 0.72^*$	Ramp & Jeffcoat (2001)
			BIC (Rad)	$r^2 = 0.88^*$	
			BVD (His)	$r^2 = 0.8^*$	
RFA	Porcine	Histology	BIC	$r = 0.221^*$	Ito et al. (2008)
RT	Rodent	Histology	BIC	$r = 0.78$–0.84^*	Brånemark et al. (1997)
			TBT	$r = 0.68$–0.76^*	
PO	Rodent	Histology	TBT	$r = 0.87^*$	Brånemark et al. (1997)
PO	Rodent	Micro-CT (3D)	BIC	$r^2 = 0.52$ (FL)* 0.24 (IS)*	Gabet et al. (2006)
			BV/TV	$r^2 = 0.72$ (FL)* 0.43 (IS)*	
			Tb.Th	$r^2 = 0.6$ (FL)* 0.31 (IS)*	
			Tb.N	$r^2 = 0.47$ (FL)* 0.32 (IS)*	
			Conn.D	$r^2 = 0.37$ (FL)* 0.28 (IS)*	
PS	Rodent	Micro-CT (3D) and FE optimization	BV	$r = 0.67$ (OA)* 0.34 (OS)*	P.C. Chang et al., 2009b, unpublished data
			BMC	$r = 0.7$ (OA)* 0.71 (OS)*	
			BMD	$r = 0.61$ (OA)* 0.62 (OS)*	
			FBAM	$r = 0.96$ (OA)* 0.84 (OS)*	
			FCAM	$r = 0.74$ (OA)* 0.95 (OS)*	

$^*P < 0.05$.

**Highest correlation coefficient for each parameter.

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 (0.6 × 1 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; NS, no significant difference ($P > 0.05$).

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 two 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 systems could be expressed as specific values or gradient distribution of stress and strain in the model (Van Staden et al. 2006). Thus, FE analysis has been utilized to investigate the functional

influence the implant geometry (Himmlova et al. 2004), material properties of implant (Yang & Xiang 2007), quality of implant-supporting tissue (Sevimay et al. 2005; Petrie & Williams 2007), 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 models, 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 & Kinney 1998). Thus, the results from FE analyses should be carefully interpreted, and the experimental validation should be performed if possible.

Functional apparent moduli

Homogenization of the mechanical properties to calculate the effective stiffness of bone was first introduced by 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 property assignments demonstrated that the non-uniform mineral density and trabecular architecture could influence the effective tissue modulus (van der Linden et al. 2001; Morgan et al. 2004; Renders et al. 2008).

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 represented the effective modulus of bone architecture, and functional composite tissue modulus for effective modulus of whole tissue within the wound (P.C. Chang et al., 2009b, unpublished data). 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).

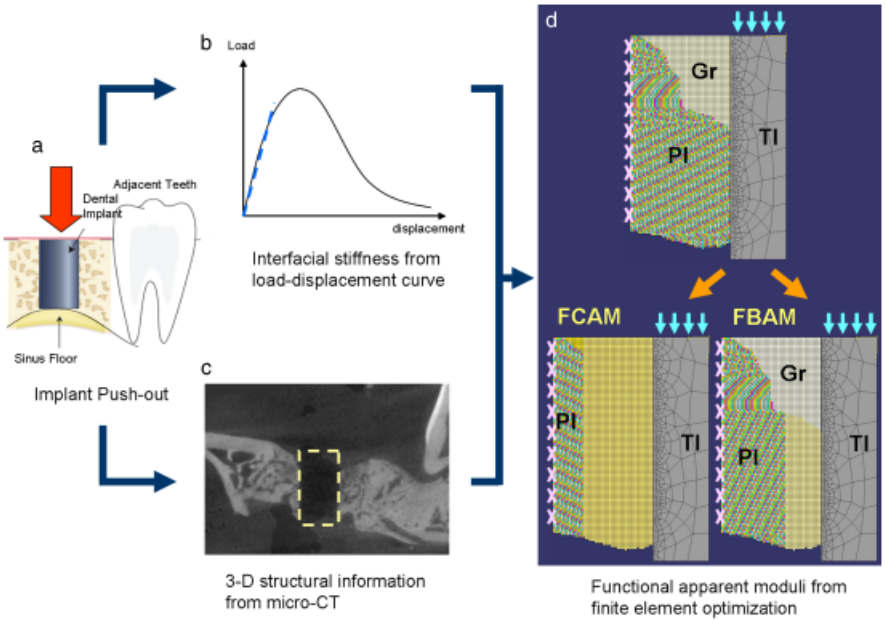

Fig. 2. The *in vivo* finite element homogenization procedures for functional apparent moduli (a) The cylinder implant was pushed out (following the direction of the red arrow) from the jaw bone, and (b) the load-displacement relationship was recorded for calculating the interfacial stiffness (dash line, 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). 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

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 pre-clinical and clinical models is still needed for investigating the mechanism involved in osseointegration and bone regeneration associated with oral implants.

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