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Reconstructive Materials and Bone Tissue Engineering in Implant Dentistry

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Periodontal function for natural teeth and dental implants depends strongly on the mechanical integrity of the bone in the maxilla and mandible. Ongoing healthy bone remodeling around a natural tooth or implant is critical for longevity. Chemical factors that influence bone remodeling have been explored with the goal of enhancing the growth and maintenance of good quality bone [1]. Less, but increasing, effort has been directed at understanding the mechanical signals and factors, including implant/prosthesis materials that transmit loads directly to the surrounding bone. This article reviews research on the effects of synthetic materials and resulting mechanical stimuli on bone tissue engineering in dentistry.

Effect of mechanical stresses on bone remodeling

Natural teeth and implants are subjected to loading conditions that can have a dramatic effect on the health of tissues, particularly in the case of bone. Although periodontal forces can be applied slowly or can be static under certain conditions, they are most often dynamic in situations in which mechanical stresses are repeated and relatively high loading rates are imposed. Dynamic forces can result from occlusion, such as chewing hard

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foods and parafunctional activity, and from traumatic impact by a foreign object. These forces are generated by muscular contraction and the kinetic energy associated with the impacting bodies. In contrast, static occlusal forces normally result from prolonged muscle contraction only. The additional kinetic energy associated with dynamic forces depends on the mass and relatively high velocity of the bodies involved. For occlusion, the kinetic energy is roughly equal to the mass of the mandible multiplied by the square of its velocity relative to the maxilla. Upon impact, this velocity decelerates to zero as the kinetic energy is converted to mechanical energy and heat by energy dissipative processes. The mechanical energy gives rise to dynamic forces that add to the quasi-static forces produced by muscle contraction. As a result of normal function and parafunctional activity, these dynamic loads are repeated many times over extended periods and can give rise to fatigue damage in a tooth, dental prosthesis, or supporting bone. Dynamic forces are generally more deleterious to a structure than static loads, even when they are of lower amplitude [2,3].

Dynamic forces can provide the necessary repeated mechanical stimulus for reinforcing tissue growth that reduces the risk of fatigue failure [4]. Wolff [5] is generally given credit for first recognizing that mechanical forces are responsible for the architecture of bone. His "law of bone transformation" implied a mathematical relationship between mechanical stress and the directions of bone formation. Building on this law, Fung [6] proposed a biomechanical stress–growth relationship, which asserted that stable bone growth occurs under an intermediate range of stresses (Fig. 1) and tissue resorption results at the low (atrophy) and high (damage) extremes. In deriving this relationship, it was recognized that (1) transport of matter depends on strain of the cell membranes, (2) actin-myosin cross-bridges in the cell membranes are sensitive to strain, and (3) chemical reaction rates within the cell depend on the stress level.

Fung proposed an optimal stress level that induces a maximum growth rate. This hypothesis implies that bone loss can result from either excessively low or high stress levels (see Fig. 1). Muscle and bone have been shown to atrophy during periods of immobility and relatively low skeletal loading

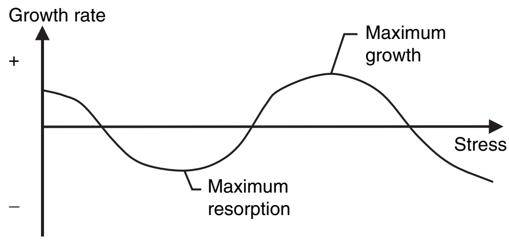

Fig. 1. Fung's stress-growth relationship. (*From* Fung YC. Biomechanics: motion, flow, stress, and growth. New York: Springer-Verlag; 1990. p. 530; with permission.)

[6,7]. On the other hand, simply overtightening a metal screw implanted in bone can result in resorption [6]. In addition to damage caused by an overload, functional dynamic forces could be biased and amplified by the static force of the screw, which could induce much greater fatigue damage in the bone.

Takakuda [8] proposed that mechanotransduction in bone is a complex cascade of events that involves fluid forces within the bone and extracellular matrix that ultimately trigger bone growth by osteoblasts. Takakuda's hypothesis accounts for remodeling under the relatively low levels of dynamic strain known to occur in human bone cells. Fluid forces also have been credited for triggering osteoblast activity through shear stresses that induce electric potentials or gene-regulated response elements [9–11]. Ogasawara and colleagues [12] demonstrated that the expression of one of these elements, cyclo-oxygenase 2, which results from fluid shear stress, is mediated by the binding of elements, such as cAMP response element-binding protein to the promoter region of the cyclo-oxygenase 2 gene in osteoblastic cells. It is important to note that fluid forces require repeated motion induced by dynamic loading to stimulate a significantly prolonged remodeling response. Under static loading, the fluid forces rapidly dissipate and remain near zero until the load is suddenly altered. This greater sensitivity to dynamic or fluctuating forces is important for avoiding fatigue damage.

Dynamic loading effects have been investigated in several studies in the field of prosthetic dentistry [13–19]. Implant-borne dental prostheses are generally made of materials that undergo reversible elastic deformation under occlusal loading, storing and transmitting almost as much mechanical energy as is input to the system. By contrast, the periodontal ligament (PDL) in the natural tooth complex acts as a shock absorber, undergoing anelastic deformation that dissipates a significant amount of the available mechanical energy. A schematic comparison of energy conservative versus energy dissipative behaviors is illustrated in Fig. 2.

Energy dissipation is generally effective for reducing kinetic energy and the resulting dynamic forces. Sheets and Earthman [16] found that modifications of an implant-assisted prosthesis joined to natural teeth repeatedly led to the reversal of tooth intrusion [18]. In this work, percussion probe measurements were made to assess the change in energy dissipation, as indicated by the loss coefficient, associated with the modifications. Using a load cell, they also showed that increasing the loss coefficient by 10% results in a 60% reduction in a dynamic load transmitted through the model (Fig. 3). The loss coefficient, η, is given by

$$\eta = \frac{D}{2\pi U}$$

where D is the total energy dissipated per unit volume and U is the total strain energy per unit volume generated at the maximum displacement.

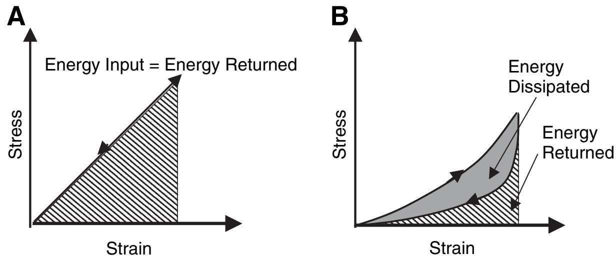

Fig. 2. Energy conservative elastic deformation (*A*) and energy dissipative anelastic deformation (*B*) plotted as stress versus strain. The amount of energy dissipated can be determined from the amount of potential energy—equal to the area under the curves—that is returned to the system upon unloading. For purely elastic deformation, loading and unloading follow the same path (reversible) so that the energy returned is equal to the energy input.

Pointing to the dichotomy in behaviors between implants and natural teeth, researchers have attributed the intrusion of natural tooth abutments to the inability of dental prostheses to provide a biocompatible level of energy dissipation [16]. The resulting excessive mechanical stimulus seems to be sensed by the nerves in the tooth root or PDL until the tooth abutment intrudes to a position that is sufficiently out of contact with the implant structure [18].

Fatigue data for bovine and human bone compiled by Taylor and Lee [20] are shown in Fig. 4 on a plot of stress amplitude versus number of loading cycles to failure. As indicated in this figure, a 60% reduction in stress (force/area) could result in an increase in fatigue life by more than two orders of magnitude. It follows that an increase in energy dissipation by as much as only 10% can reduce substantially the rate of fatigue damage in bone [18].

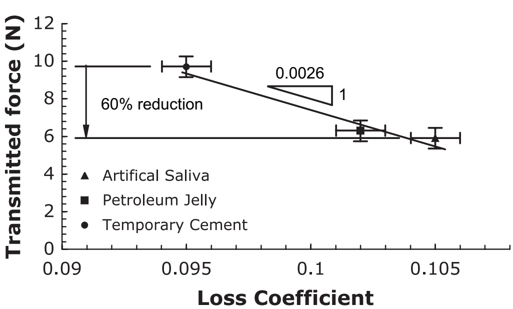

Fig. 3. Loss coefficient versus transmitted force for an in vitro implant support prosthesis model. The loss coefficient was increased by as much as 10% by substituting petroleum jelly for temporary cement in the structure. In a clinical study, this change resulted in the reversal of natural tooth intrusion. (*Data from* Sheets CG, Earthman JC. Tooth intrusion in implant-assisted prostheses. J Prosthet Dent 1997;77:39–45.)

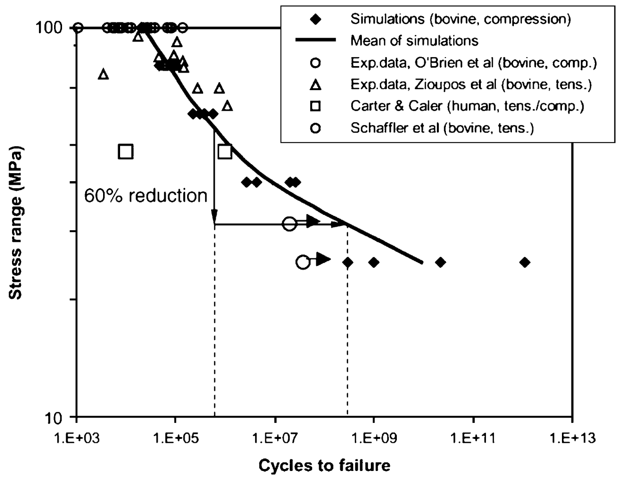

Fig. 4. Fatigue life as a function of stress amplitude for bovine and human bone. The two experimental data points with arrows to the right are for samples that did not fail as of the indicated number of cycles. comp., compression; tens., tension. (*Adapted from* Taylor D, Lee CT. A crack growth model for the simulation of fatigue in bone. Int J Fatigue 2003;25:391; with permission.)

Bone that neighbors an implant seems to remodel at different dynamic load levels compared with those for natural teeth based on a study in which implants were used as an orthodontic anchorage [21]. This difference is most likely caused by the effect of the PDL of the natural teeth on bone remodeling. Based on their study of orthodontic tooth movement in a rat model, Katona and colleagues [17] concluded that orthodontically induced bone growth processes were governed by tensile stresses in the PDL, whereas resorption was triggered by compression or shear stresses within the bone itself. They also proposed that the application of a static orthodontic force shifts the functional dynamic stresses, which then induce tooth movement in the desired direction. Fig. 5 depicts this shift in dynamic loading.

Movement of natural teeth by bone remodeling allows a healthy tooth to shed excessive dynamic loads relatively quickly to the other teeth, which makes the stress distribution more uniform. Alternately, a tooth under lower than normal loads emerges by growth of the underlying bone, which allows it to increase its share of the loading and leads to a more uniform stress distribution and an overall reduced susceptibility to fatigue damage.

These findings indicate that mechanical biocompatibility of dental prosthetics is an important factor for achieving optimum results. Mechanical biocompatibility refers to the evasion of unwanted physiologic changes and promotion of desired tissue growth and stability by optimizing the mechanical properties of synthetic materials in contact with the biologic structure. This biocompatibility not only depends on static mechanical properties, such as Young's modulus, but also is determined by the dynamic

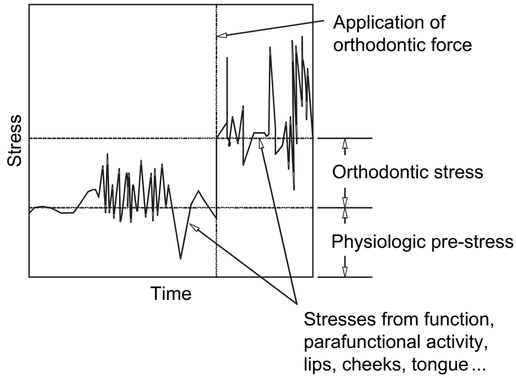

Fig. 5. Hypothetical history of the shift in dynamic stress state that occurs with the application of a static orthodontic load. Tooth movement results from the dynamic stresses that are biased in the desired direction by the orthodontic force. (*From* Katona TR, Paydar NH, Akay HU, et al. Stress analysis of bone modeling response to rat molar orthodontics. J Biomech 1995;28:36; with permission.)

properties of the material. It follows that energy dissipation must be addressed in prosthesis development for optimum tissue engineering during restoration.

Influence of dental materials in bone tissue engineering

The PDL plays an essential role in dissipating mechanical energy that, in turn, minimizes fatigue and trauma damage to the teeth and bone. It has been generally established for existing dental implant systems that the numbness and "clapping" of artificial teeth is primarily caused by the absence of a PDL [22]. The lack of energy dissipation in implant systems can be alleviated by introducing additional stress-absorbing elements in dental implants or changing the material to one with relatively high damping capacities in the existing implant structure. Barzin and colleagues [23] showed that superstructures made of either belle Glass (Kerr Manufacturing Co., Orange, California) or Gradia (GC America, Alsip, Illinois) composites resulted in significantly higher loss coefficient values compared with conventional restorative materials (Fig. 6). Extensive research efforts also have been made to explore dental implants that contain a PDL-like stress-absorbing element [14,19,22,24–27]. One of the challenges for these structures is providing sufficient damping without introducing a component that is susceptible to fatigue failure within a relatively short time period.

A finite element study conducted by van Rossen and colleagues [14] was aimed at determining stress distributions in bone around implants with and without stress-absorbing elements. In this investigation, two different models were constructed to simulate a freestanding single implant and an implant connected with a natural tooth. The stress-absorbing element,

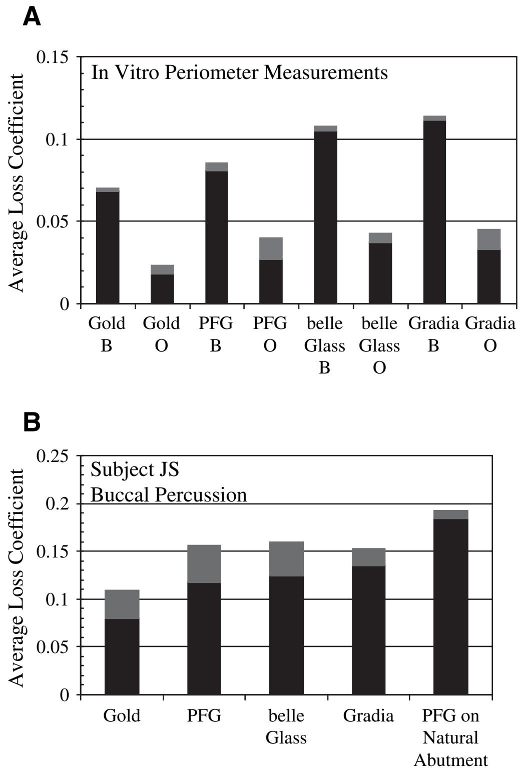

Fig. 6. Average loss coefficient for different superstructure materials and percussion directions for an in vitro implant model (*A*) and human subject (*B*). The shaded portions of the columns represent the standard deviations, and the height of the black columns indicates the average values of the loss coefficient. Columns designated with a "B" correspond to percussion in the buccal direction, and columns designated with on "O" correspond to percussion in the occlusal direction. PFG, porcelain fused to gold. (*From* Barzin A, Sheets CG, Earthman JC. Mechanical biocompatibility of dental implant materials. In: Proceedings of the 4th Pacific Rim International Conference on Advanced Materials and Processing (PRICM4). Sendai (Japan): The Japan Institute of Metals; 2001. p. 2952; with permission.)

which was positioned between the post and the submucosal part of the implant, was characterized as two linear elastic materials with two different values of Young's modulus. For the freestanding implant, their results show that the static stress distribution does not change significantly during static loading when the elastic modulus of the stress-absorbing element was increased from 150 to 110,000 MPa (ie, from a soft material to a rigid material). This result implied that the primary effect that a stress-absorbing element has on bone is not related to its elastic modulus but rather to its viscous damping properties. In the case of a tooth-connected implant, the influence of the stress-absorbing element on the loading of the natural tooth was signified by a decrease of 20% to 45% in the height of the peak stresses (ie, the stress distribution becomes more uniform when stress-absorbing elements are used) [14]. A principal conclusion is that a stress-absorbing element should not be modeled simply by a linear elastic material. Rather, a realistic model should include a damping capacity term for this element that characterizes dissipation of mechanical energy during dynamic loading.

More recently, Genna and colleagues [26] studied the behavior of a PDL-like layer using three-dimensional finite element analysis. In their paper, nonlinear hyperelastic deformation was assumed for the PDL-like layer, and they found that such an implant can be effective in terms of stress redistribution and stress absorption even in the case of a freestanding implant. They also noted that the PDL layer helps to reduce significantly the axial stress in the connecting screw caused by its tightening and the self-stresses induced by geometric misfits. It is evident from the results of van Rossen and colleagues [14] and Genna and colleagues [26] that the damping capacity of the PDL plays a crucial role in redistributing and absorbing dynamic stresses transmitted through teeth into bone. An implant material that mimics the damping capacity provided by the PDL would be of interest to enhance the longevity and reliability of the implant structures.

Few efforts have been made to identify and develop high damping materials to serve the purpose of dental implantation. Among those materials, commercially available polymers, such as polymethyl methacrylate and polyoxymethylene, have been used because they have higher damping capacities than almost all metals. Ironically, polymer elements that reduce damage to the bone and other components of the implant structure tend to fail by fatigue after relatively short periods, which results in frequent replacement. Consequently, the limited fatigue resistance of these materials has hindered their widespread use as PDL-like elements [27]. New designs are being developed that attempt to address this problem. For example, Gaggl and Schultes [28] proposed an implant structure that they claim is maintenance free and contains silicone rings. It remains to be seen whether the longevity of the polymer elements in this and other new designs is comparable to the metallic materials in use.

Commercially pure titanium has been considered one of the most chemically biocompatible materials [29]. These materials generally have much better fatigue properties than those of polymers but also have high elastic moduli and low damping capacities compared with bone. A mismatch in elastic modulus is often cited as the mechanical factor that results in poor biocompatibility because of a nonuniform stress distribution [30]. The lack of energy dissipation on the part of metallic materials can give rise to more severe problems, however, such as fatigue failure and tooth intrusion [3,15,18].

Superelastic Ti-Ni alloys have drawn considerable attention for dental applications because of their excellent corrosion resistance, superelasticity, and shape memory characteristics [31–35]. Superelasticity results from the stress-induced phase transformation that is characterized by a plateau in the stress versus strain response (Fig. 7). Orthodontic Ti-Ni wires stressed

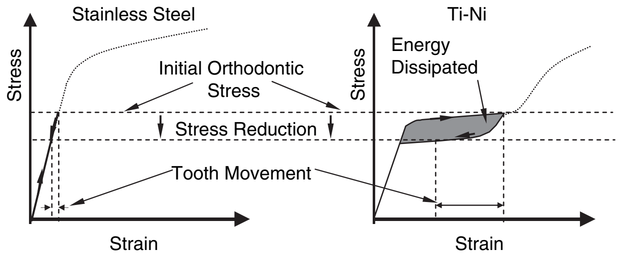

Fig. 7. Comparison of stress strain curves for stainless steel and a superelastic Ti-Ni alloy that exhibits a plateau resulting from stress-induced phase transformation. After an applied orthodontic stress, more tooth movement can be accommodated by a Ti-Ni wire compared with a stainless steel wire for a given decrease in applied stress. This schematic also illustrates the energy dissipation that is achieved by the Ti-Ni alloy when deforming in the superelastic plateau region.

into the plateau region can accommodate large tooth movement (strain) with relatively little reduction in stress. Ti-Ni wires offer the advantage of fewer retightening procedures compared with stainless steel wires for a given amount of tooth movement.

Iramaneerat and colleagues [34] investigated dynamic force transmission during orthodontic archwire application using dynamic finite element analysis. Their results showed that the superelastic Ti-Ni alloy wire has a damping capacity that is more than twice that of a stainless steel wire counterpart. This additional damping on the part of Ti-Ni caused by irreversible phase transformation is also shown schematically in Fig. 7. More quantitatively, De Santis and colleagues [36] reported a damping coefficient of approximately 0.004 for a Ti-Ni alloy at a high frequency of approximately 300 Hz. When used in orthodontic archwire applications, it has been shown that superelastic Ti-Ni wire has the ability to buffer a significant amount of the dynamic occlusal force transmitted to the PDL [37]. This finding is consistent with the results in Fig. 3, which show the sizable reduction in transmitted occlusal loads that can be accomplished with a modest increase in the damping capacity of the structure.

The cytotoxicity of Ni has been a concern for Ti-Ni alloys used for implants [27], and extensive efforts in surface modification are still being made to address the issue [38]. Accordingly, the use of Ti-Ni in its current compositions is generally not recommended for dental implants. Its use in abutments and superstructures above the tissue level, as in the case of orthodontic wires, should be acceptable, however. The ultimate goal is to achieve a combination of longevity, energy dissipation, and aesthetics that has so far eluded many researchers and clinicians.

Immediate loading of implants and bone remodeling

Immediate loading refers to the fixation of a prosthesis to an implant in or out of direct occlusal function within 48 hours of surgical placement.

There are several categories of immediately loaded implants. First, an implant can be placed into healed bone where the initial stability depends predominately on the surgical technique, bone density, bone height, and implant geometry. Second, an implant can be placed immediately into a fresh extraction site, which adds further complications to establishing initial stability. The complicating factors include the size of the extracted tooth versus the size of the implant replacement, density of the surrounding bone, potential need for grafting, presence of micro- or macrofractures of the bone complex from the extraction process itself, and the potential presence of infection associated with the extracted tooth that could jeopardize the osseointegration process. For successful osseointegration, both situations depend highly on being protected from excess forces during the initial healing process. It is believed that the most damaging forces on the immediately placed implant are from excessive postsurgical loading from parafunctional habit patterns and unmonitored mastication [39].

Convention has established that traditional methods of determining implant stability, such as the tapping of an implant fixture with the end of a mouth mirror and radiographs, are sufficient indicators of implant health. Certainly high success rates for implants in both arches are documented in the literature. A growing number of scientists and clinicians are starting to call for systems that provide a more definitive measurement of osseointegration, however [40–50].

The ability to quantify levels of osseointegration is important because of two current trends in implant dentistry. First, the traditional Brånemark two-stage placement protocol has been modified toward immediate or early loading of implants. An increase in the number of osseointegration failures is anticipated as more high-risk immediate load surgeries are performed. Several authors are reporting early indications of this disturbing possibility [51–53]. Second, there is an increasing trend to train nonspecialists to place and restore implants [54]. Although there are many good reasons to expand the number of clinicians who provide implant services, it does place less experienced clinicians in the roles that formerly have been held by trained specialists.

The intersection of these two trends has the potential of creating an environment of increasing implant failures. Quantitative methods of assessing osseointegration and fixture structural integrity must be introduced into accepted protocols. Quantitative monitoring of implants allows therapeutic measures to be instituted when implants become vulnerable to disintegration [39]. Currently, therapeutic measures are not instituted until bone loss can be identified by radiographs or clinical mobility, which is often too late in the failure process to establish implant health.

Ideally, a clinician should be able to obtain sensitive biomechanical information critical to implant health and longevity in a nondestructive, cost-effective, and noninvasive manner. A system also should be able to provide information throughout all stages of implant life—information that would allow early effective therapeutic intervention when indicated.

Biomechanical approaches for assessing implant and bone stability

The most commonly used method for assessing implant stability is the use of manual percussion and the subsequent evaluation of the auditory sound. Numerous authors have described the lack of discernment that this method provides [55]. Although gross levels of osseointegration can be assessed in this way, there is no ability to determine levels of osseointegration or bone quality. Numerous experimental models have been noted in the literature, few of which have become commercially viable and have been relegated to limited research use at best. Two exceptions are a unit that measures percussion time (Periotest [MedizinTechnik Gulden, Lautertal, Germany]) and a unit that measures resonance frequency (Osstell Mentor [Integration Diagnostics AB, Göteborg, Sweden]).

The Periotest unit was designed to measure periodontal stability of natural teeth. The instrument measures percussion time on an arbitrary scale and is expressed in Periotest values. The Periotest has provided some information for evaluation of the osseointegration process in the literature but has not received widespread acceptance for several reasons [56]. The most damaging criticism is that the Periotest gives inconsistent results. The inconsistency has been related to several factors: the probe must be held steady in a horizontal position so that the tip is 2 mm from the surface of the implant, the unit is not shielded from external electromagnetic noise, and the resolution of the Periotest values scale is limited in the range corresponding to implants [43,44,55,57].

The Osstell Mentor uses the measurement of resonance frequency as an indicator of implant stability. The new version of this technology recently was released in Europe. The Osstell system provides a more quantitative and reliable measurement of implant stability compared with the Periotest. The Osstell also has limitations, however: a specialized measuring device (‘‘smart peg’’) must be attached directly to the implant at the fixture level, each implant design requires a different smart peg geometry for testing, it is inconvenient to disassemble the implant for each testing session, the act of disassembly can compromise the mucosal barrier and result in the loss of connective tissue and bone during the early stages of implant healing, and the measurements are subject to some variability because of differences in bone quality [58,59]. Accordingly, this system has not realized widespread acceptance in the United States.

A more recently developed system that measures the structural stability and integrity for dental implants and natural teeth is the Periometer (Perimetrics, LLC, Newport Beach, California). This device provides two pieces of diagnostic information: the loss coefficient of the structure (described previously) and an energy return time profile that indicates localized defects, such as cracks and loose fixtures. The analysis of these two results gives a wealth of information regarding the attachment of an implant to the bone and the structural stability of the entire implant complex being tested.

The features of this device are a handheld probe, a disposable stabilization tip, a horizontal level scale, a computer interface, data analysis software, statistical validity indicators, automatic abnormal analysis and alerts, and a medical grade power supply and shielding. The Periometer is able to gather diagnostic data at every stage of implant life using clinically relevant mechanical energy. It does not induce an artificial strain rate and provides two related categories of diagnostic information: the loss coefficient and energy return profile. The Periometer is currently being used for research at the University of California, Irvine, California; the Newport Coast Oral-Facial Institute in Newport Beach, California; and the Veterans Administration Medical Center, San Diego, California.

Tissue engineering research for tooth replacement

The ultimate solution for dental tooth loss is the actual fabrication of complex tooth structures by some method of tissue engineering to produce a biologic tooth substitute. Globally, many research teams are working to understand odontogenesis. The three main areas of focus are the tissue cells to be generated, the extracellular matrix, and the scaffolding on which the tissues grow. Artificial scaffolds lack critical cell signaling capabilities and can interfere with new tissue growth. Natural biodegradable materials, such as collagen, alginate, and silk, can be used to create scaffolds that are compatible with the desired cell and tissue functions and are eventually biodegradable. Understanding the molecular mechanisms that control tooth development can help identify the developmental processes that control tooth shape, tooth number, and cuspal development.

Structurally correct teeth have been grown by several approaches, including building teeth from existing dental cells or growing them from progenitor tissues [60–63]. Remaining challenges include growing roots and identifying ideal raw materials for bioengineered human teeth. Progress has been achieved to the point that many researchers believe that test-tube teeth may become the first engineered organs.

Young and colleagues [60] dissociated porcine and rat tooth buds into single-cell suspensions and seeded them onto biodegradable polymer scaffolds [63]. As demonstrated in Fig. 8, rat hosts produced recognizable tooth structures that contained dentin, odontoblasts, a well-defined pulp chamber, putative Hertwig's root sheath epithelia, putative cementoblasts, and a morphologically correct enamel organ. This was the first successful generation of tooth crowns from dissociated tooth tissues that contained dentin and enamel and suggested the presence of epithelial and mesenchymal dental stem cells in porcine and rat tooth bud tissues.

Despite these remarkable achievements, the bioengineered teeth were still small and did not conform to the scaffolds. It should be noted that the scaffolds were implanted into the omentum as opposed to the mandible or maxilla. Inadequate mechanical stimulus could have been one of the factors that

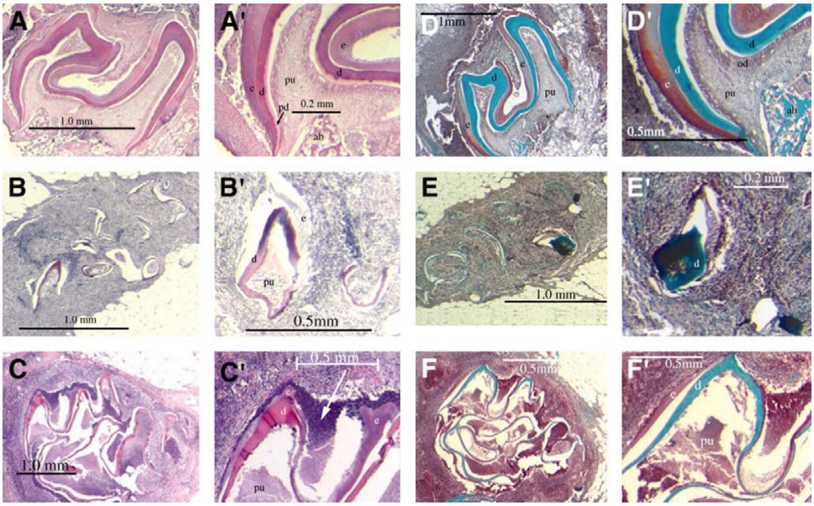

Fig. 8. Histologic analysis of scaffolds that contain rat tooth bud cells after 12 weeks of implantation in the omentum. Positive control intact tooth bud implants exhibited dentin, enamel, and pulp tissues (*A, A′*). Dental cell seeded in biodegradable polyglycolic acid (*B, B′*) and polylactic co-glycolic acid (*C, C′*) scaffold tooth tissues also generated dentin, enamel, and pulp tissues. Infiltrating lymphocytes were occasionally observed in dental implants (*C, C′*) (*arrow*). Goldner's stain of positive control intact tooth bud implants revealed blue-stained dentin, red-stained immature enamel, and gray-stained mature enamel (*D, D′*). Polyglycolic acid– and polylactic co-glycolic acid–bioengineered teeth exhibited blue-stained dentin, whereas polyglycolic acid generally produced mature, gray-stained enamel at 12 weeks, and polylactic co-glycolic acid generated red- and gray-stained mature enamel (*E, E′, F, F′*). d, dentin; e, enamel; em, enamel matrix; pe, pre-enamel; pu, pulp. (*From* Duailibi MT, Duailibi SE, Young CS, et al. Bioengineered teeth from cultured rat tooth bud cells. J Dent Res 2004;83(7):592; with permission.)

led to the observed deficiency in tooth formation. The authors cited the need to better understand cell–scaffold interactions and the underlying mechanisms that direct the growth of the tooth tissues [60,63]. As evidenced by the works reviewed in this article, dynamic loading plays an important role in these mechanisms. A greater understanding of the role that mechanical loading plays in governing tissue formation and remodeling must continue to be achieved if tissue engineering in general is to reach its full potential.

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