
Osseointegration of Plateau Root Form Implants: Unique Healing Pathway Leading to Haversian-Like Long-Term Morphology

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Paulo G. Coelho, Marcelo Suzuki, Charles Marin, Rodrigo Granato, Luis F. Gil, Nick Tovar, Ryo Jimbo, Rodrigo Neiva, and Estevam A. Bonfante

Abstract

Endosteal dental implants have been utilized as anchors for dental and orthopedic rehabilitations for decades with one of the highest treatment success rates in medicine. Such success is due to the phenomenon of osseointegration where after the implant surgical placement, bone healing results into an intimate contact between bone and implant surface. While osseointegration is an established phenomenon, the route which osseointegration occurs around endosteal implants is related to various implant design factors including surgical instrumentation and implant macro, micro, and nanometer scale geometry. In an implant system where void spaces (healing chambers) are present between the implant and bone

P.G. Coelho, DDS, MS, Ph.D. (✉)
Department of Periodontology and Implant Dentistry,
New York University, New York, NY, USA

Department of Engineering, New York University
Abu Dhabi, Abu Dhabi, UAE

Department of Biomaterials and Biomimetics,
New York University, New York, NY, USA
e-mail: pgcoelho@gmail.com

M. Suzuki
Department of Operative Dentistry and
Prosthodontics, Tufts University School of Dental
Medicine, Boston, MA, USA

C. Marin • R. Granato
Postgraduate Program in Dentistry, UNIGRANRIO
University, Duque de Caxias, RJ, Brasil

L.F. Gil
Department of Dentistry, Universidade Federal de
Santa Catarina, Florianópolis, SC, Brasil

N. Tovar
Department of Biomaterials and Biomimetics,
New York University, New York, NY, USA

R. Jimbo
Faculty of Odontology, Department of
Prosthodontics, Malmö University, Malmö, Sweden

R. Neiva
Department of Periodontology, University of Florida,
Gainesville, FL, USA

E.A. Bonfante
Department of Prosthodontics, University of Sao
Paulo – Bauru College of Dentistry, Bauru, SP, Brazil

immediately after placement, its inherent bone healing pathway results in unique opportunities to accelerate the osseointegration phenomenon at the short-term and its maintenance on the long-term through a haversian-like bone morphology and mechanical properties.

Keywords

Implants • Osseointegration • Bone healing • Tissue engineering • Bone regeneration • Plateau root form

7.1 Introduction

The phenomenon of bone presenting intimate contact to titanium implants was first reported in 1940 by Bothe et al. (1940) and later described in 1951 by Leventhal (1951). Decades later, it was characterized in more detail by a Swedish group (Branemark et al. 1969, 1977), whereas the term osseointegration was first coined only in 1981 (Albrektsson et al. 1981; Albrektsson and Johansson 2001). While its definition has constantly changed/evolved over the years, it is currently recognized as the intimate contact of material and bony tissue without the growth of fibrous tissue at the bone-implanted material interface (Dorland 2012). This phenomenon has for over five decades affected the well-being of millions of patients as the basis for dental and orthopedic rehabilitations that rely on the surgical placement of bioinert, biocompatible and osseoconductive implants followed by the adequate healing and remodeling of bone around the device (Eitner et al. 2012). During its discovery and characterization years, key factors for the successful establishment of osseointegration relied on both device (biocompatibility, osseoconductivity, sterility, and others) and patient related (local and systemic) characteristics (Albrektsson et al. 1981).

Currently, an online scientific literature search with the keyword osseointegration exceeds 10,000 references, and over 50 years the phenomenon has gone from discovery to medical device industry commodity. Such increase in fabrication scale has occurred due to the increasing world demand for cost-effective oral rehabilitation along with substantial evolution of manufacturing techniques.

However, while the number of devices fabricated worldwide per year is constantly increasing, this increase is rarely founded by robust research and development strategies that result in improvements for the population in need. In contrast, when trials are performed to validate new implant designs, a decreased probability of annual failures has been associated with industry-sponsored research compared to non-industry associated trials, which not only suggests that strong bias may exist in the literature, but most importantly that a potential detour in proper decision making may be present regarding tooth preservation and governmental health care policies (Popelut et al. 2010). Such scenario has eventually led to “commodity development” in the field of implant dentistry, in the sense that the market accepts hardware versions without serious validation specific to that version (Henry 1995).

When considering the number of dental implant systems commercially available, a plethora of implantable devices with different characteristics (geometry, surface treatment, surgical instrumentation) are available. Common to all these devices is that they ultimately rely on the same phenomenon to perform their rehabilitative role in bone (Esposito et al. 2014). However, while the same intimate interaction between bone and implant is responsible for the rehabilitation system biomechanics competence, how it is achieved on the short-term may substantially vary among different implant systems and ultimately results in variations in the long-term structure/property of bone surrounding the implanted devices (Coelho and Jimbo 2014a, b). This chapter initially discusses how short- and long-term osseointegration is affected by two key

parameters that consist the implant shape and its associated surgical instrumentation dimensions especially when screw root form and plateau root form implants are concerned. Then strategies to hasten the process of osseointegration such as implant surface treatments, tissue engineering approaches, and surgical instrumentation parameters are discussed.

7.2 Early Osseointegration Pathway: Interfacial Remodeling, Intramembranous-Like Healing (Healing Chambers), and Hybrid Healing

It is a general consensus that properly cleaned and sterilized biocompatible titanium-based alloys (primarily comprised by commercially pure Ti and Ti-6Al-4V) devices will be incorporated within the bone tissue after installation (Williams 1977). While osseointegration has gone from discovery to commodity, its establishment after implant placement has endemically been thought to occur through the same pathway for any given implant system by the dental profession despite previous publications describing otherwise (Berglundh et al. 2003; Leonard et al. 2009; Coelho et al. 2010a, b, c). The difference in how surgical hardware (implant and surgical instrumentation shape) affects initial bone healing has been recently published in more detail (Coelho et al. 2010c, 2011) and the two main early healing modes are summarized below.

7.2.1 Interfacial Remodeling Healing Pathway

This early healing scenario is typically observed for tight fit screw type implants (i.e. the majority of implant systems available in the market) as these are placed in the osteotomy in intimate contact between the implant and bone throughout the device's threaded bulk. Such intimate interplay between device and osteotomy dimensions renders the system initial or primary stability where

reduced biologic interplay yet exists (Leonard et al. 2009; Coelho et al. 2010c, 2011). This mechanical interlocking is variably influenced by the implant geometry and implant osteotomy site dimensions, and regulate the distribution of strain applied to the hard tissue in proximity with the implant. From a clinical standpoint an important misinterpretation occurs at this point, where some clinicians generically and equivocally assume that high insertion torque levels of any given implant design lead to proportionally high resistance to micromotion and therefore to improved osseointegration levels (Campos et al. 2014; Freitas et al. 2012). Whereas some clinicians may still quest for very high implant insertion torque, it must be acknowledged that, if the strain applied to bone in such scenario exceeds its given threshold, its stability would decrease over time due to microfractures and excessive strain that may result in pressure necrosis, since both phenomena result in bone remodeling (Campos et al. 2012; Galli et al. 2015; Jimbo et al. 2014; Coelho et al. 2013). After an interfacial cell-mediated bone resorption, subsequent bone apposition most often occurs from the pristine bone wall towards the implant surface. Such bone removal and subsequent apposition has been theoretically (Raghavendra et al. 2005) and experimentally (Gomes et al. 2013) demonstrated and is regarded as implant stability dip, where primary stability obtained through the mismatch between implant macrogeometry and surgical instrumentation dimensions is lost due to the cell-mediated interfacial remodeling to be regained through bone apposition (Coelho and Jimbo 2014a, b; Jimbo et al. 2007). This healing mode sequence concerns implant placement in sites that were surgically instrumented to dimensions that approximate the inner diameter of the implant threads (Bonfante et al. 2013) and its pathway is illustrated in detail in Fig. 7.1. In summary, a cell-mediated process whose extension is proportional to the amount of strain incurred to the bone surrounding the implant takes place prior to new bone formation. In general, such remodeling extends to several hundred micrometers away from the implant surface and this void space is filled by newly formed bone. At early

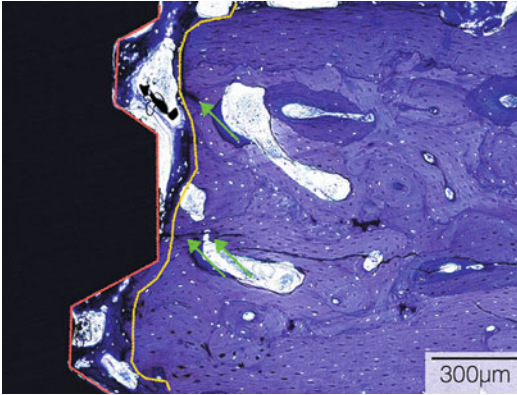


Fig. 7.1 Representative optical micrograph of a screw type implant placed in a rabbit tibia instrumented to the inner diameter of the implant thread. The *blue line* depicts the implant perimeter that was in direct contact with bone immediately after placement (the cortical plate fully occupied the region between the *blue* and *yellow lines*). The *yellow line* depicts the distance from the implant surface (*red line*) which cell mediated interfacial remodeling occurred due to osteocompression and/or bone cracking (*arrows*). The dark stained bone tissue between the *blue* and *yellow lines* is bone formed after a void space is created due to interfacial remodeling to eliminate tissue excessive strain. Toluidine Blue stain

time points, an almost continuous bone-implant interface renders the system implant primary stability. At this stage, microfractures depicting that the yield strength of bone has been exceeded due to high stress levels are visualized along with initial remodeling taking place between the implant threads due to pressure bone necrosis (Bashutski et al. 2009; Halldin et al. 2011; Verborgt et al. 2000; Chamay and Tschantz 1972). As time elapses *in vivo*, an extensive remodeling region is evident presenting void spaces partially filled by newly formed bone. Thus, the scenario that has been histologically observed in multiple instances confirms the theoretical and experimental basis for the initial stability rendered by mechanical interlocking between implant and bone that at some point in time after placement under stable conditions decrease due to extensive bone resorption (Fig. 7.1). Subsequently, the resorbed area will be filled by newly formed woven bone, which eventually reestablishes the contact to the

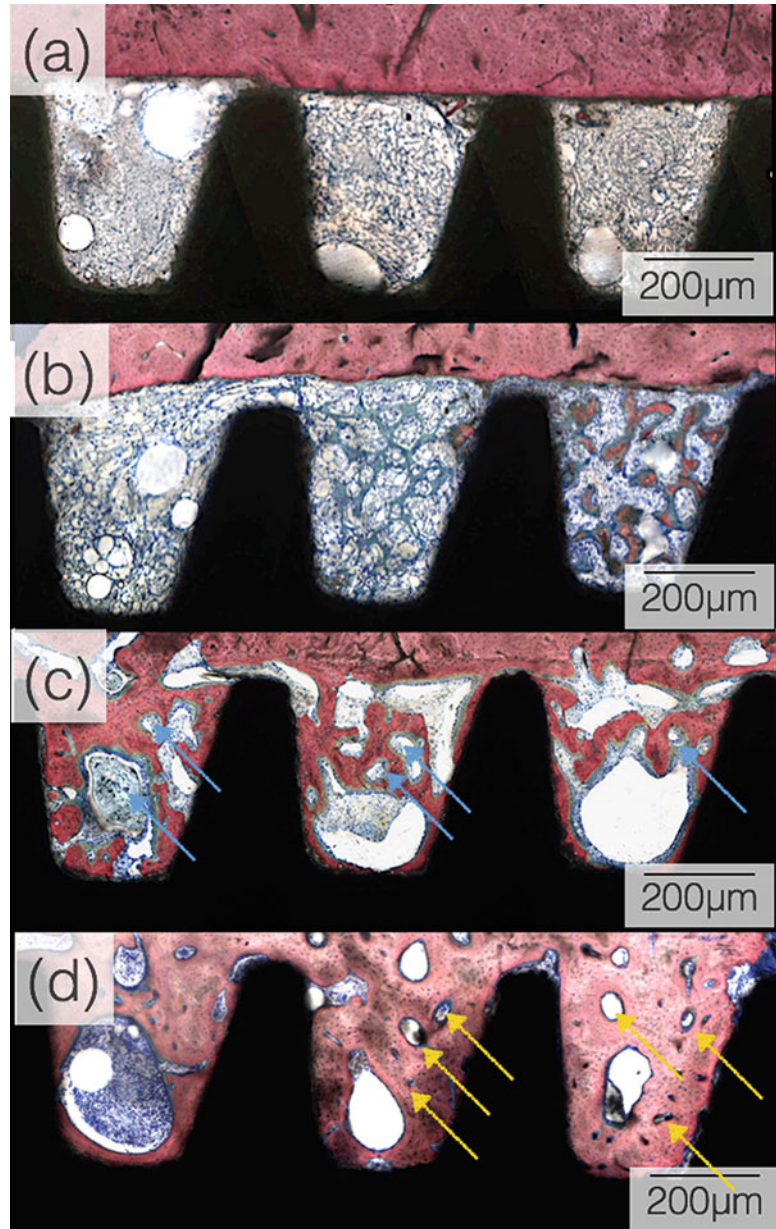
implant interface (secondary stability) (Berglundh et al. 2003; Leonard et al. 2009; Coelho et al. 2010c, 2011) (Fig. 7.1).

7.2.2 Intramembranous-Like Healing Pathway (Healing Chamber Osseointegration)

The second osseointegration pathway concerns the opposite scenario of the tight fit screw type implant, where void spaces between the implant bulk and the surgically instrumented drilled site walls are formed (plateau root form implants) (Berglundh et al. 2003). These void spaces left between bone and implant bulk, often referred to as healing chambers, will be filled with blood clot immediately after placement and will not contribute to primary stability. These however, have been regarded as a key contributor to secondary stability due to its rapid ossification and morphology presenting high degrees of cellular and vascular content (Huang et al. 2015).

Berglundh et al. (2003) discussed the early healing biology and kinetics (Fig. 7.2) of bone formation in healing chambers and the effect of healing chamber size and shape (know to have a significant effect on how fast bone fills these chambers) on bone formation has also been pre-clinically evaluated (Coelho et al. 2011; Marin et al. 2010). Such healing chambers, filled with the blood clot, will evolve towards osteogenic tissue that subsequently ossifies through an intramembranous-like pathway (Berglundh et al. 2003). The bone forming within the healing chamber presents high cellular and vascular content at early time points, noticed by the early replacement of woven bone by lamellar bone surrounding the perimeter of primary osteons. Noteworthy is that unlike the interfacial remodeling healing pathway, healing chamber configurations do not encompass the initial cleanup process due to microfractures and excessive osteocompression (Berglundh et al. 2003; Coelho et al. 2010b, c, 2011; Marin et al. 2010; Granato et al. 2009, 2011).

Fig. 7.2 Sequence of intramembranous-like healing osseointegration. **(a)** 1 week, **(b)** 3 weeks, **(c)** 6 weeks, and **(d)** 12 weeks in vivo in a beagle dog model. **(a)** The blood filling the space between pristine bone and device will develop towards a connective tissue network that provides a seamless pathway for cell migration within the space once filled by the blood clot. **(b)** Such healing configuration allows initial bone formation throughout the healing chamber from **(c)** all available surfaces (implant surface, instrumented bone surface) and within the chamber volume, presenting substantial deviation from the classic interfacial remodeling healing pathway observed in tight fit screw-type implant. The bone forming within the healing chamber presents high cellular and vascular content at **(a)** and **(b)** early time points, noticed by **(c)** and **(d)** the early replacement of woven bone by lamellar bone surrounding the perimeter of primary osteons (*arrows*). Stevenel's Blue Von Giesson's acid fuchsin stain



7.2.3 Current Trend: Hybrid Healing Pathway: Integrating Interfacial Remodeling and Intramembranous-Like Bone Healing Modes

Recent investigations have employed either experimental implant designs with an outer thread that provided stability while the inner

thread and osteotomy dimensions allowed healing chambers (Berglundh et al. 2003; Abrahamsson et al. 2004, 2009) or alterations in osteotomy dimensions in large thread pitch implant designs (Coelho et al. 2010c; Campos et al. 2012; Vandeweghe et al. 2013). The rationale for these alterations lie upon the fact that thread designing may allow for both high degrees of primary stability along with a surgical

instrumentation outer diameter that is closer to the outer diameter of the implant allowing healing chamber formation. Since healing chambers allow rapid intramembranous-like rapid woven bone formation (Witek et al. 2013; Bonfante et al. 2011), such rapid bone growth may compensate for the implant stability loss due to compression regions where implant threads contacts bone for primary stability (Coelho et al. 2013).

7.3 Long-Term Osseointegration: Healing Pathway Effect on Osseointegration, Bone Morphology, and Bone Mechanical Property Evolution

While studies concerning early osseointegration are more easily achieved in both preclinical and clinical scenarios, tracking devices in place over the years represent a significant logistic and economic challenge (Lemons 1988a, b, 2010; Lemons et al. 2010). While a plethora of preclinical studies have shed light onto both the early and long-term osseointegration (Coelho and Jimbo 2014a, b; Coelho et al. 2009a; Elias and Meirelles 2010), clarification of the actual temporal implant-bone interaction under functional loading is a remarkable challenge as discussed in important past consensus (NIH 2000). The main difficulty arises from ethical aspects of retrieving stable implants from patients. Furthermore, sample inhomogeneity due to differences in implant design (mainly macrogeometry), surface treatment and topography, time of functional loading, loading protocols, and clinical parameters during the time of placement makes it extremely difficult to draw conclusions (Lemons 1988b; Coelho et al. 2009a). Thus, in reality, most of the existing human retrieval studies are based on failed implants or on limited number of stable implants that were extracted for different reasons such as inadequate position within the arch (Iezzi et al. 2012, 2013a, b, c, 2014; Mangano et al. 2013; Degidi et al. 2009a, b, c; Shibli et al. 2007; Grassi et al. 2007), which eventually limit the amount of variables required to provide an informed design

rationale for device engineering and associated surgical and prosthetic guideline developments.

While limited in the number of reports and sample size, histologic human retrieval studies report that over the first year under functional loading, bone around implants undergoes remodeling and the initial woven bone in proximity of the implant surface is replaced by bone presenting higher degrees of organization in a lamellar configuration (Degidi et al. 2009a, b, c; Grassi et al. 2007). The same body of literature also supports that as time further elapses with implants in function, higher degrees of organization are achieved, which is reflected by multiple remodeling sites within the lamellar bone (Iezzi et al. 2012, 2013a, b, 2014).

The difficulty in obtaining human retrieved samples is such that studies comprising samples retrieved from the same implant system placed under the same surgical guidelines and latency period prior to prosthetic loading are limited in number (four only) (Baldassarri et al. 2012; Coelho et al. 2009b, 2010d; Gil 2015).

7.3.1 Long-Term Morphology of Implants That Undergo Interfacial Remodeling

Screw root form implants are typically placed in drilled sites that are narrower than the implant diameter (Coelho and Jimbo 2014a, b). According to preclinical studies, this mechanical interlocking due to differences in screw root form implant and drilled site diameter results in a substantial bone volume under compression immediately after placement that is subsequently remodeled prior to further bone apposition (Berglundh et al. 2007; Davies 2003). Following osseointegration of a screw root form implant, it is a general consensus that further bone remodeling occurs under functional loading resulting in higher degrees of bone organization (Coelho and Jimbo 2014a, b). Remodeling seems to be more evident at the coronal aspect of implants, where most of the occlusal forces are concentrated. Morphologically, however, bone surrounding these implants has been often described as compact mature lamellar bone with

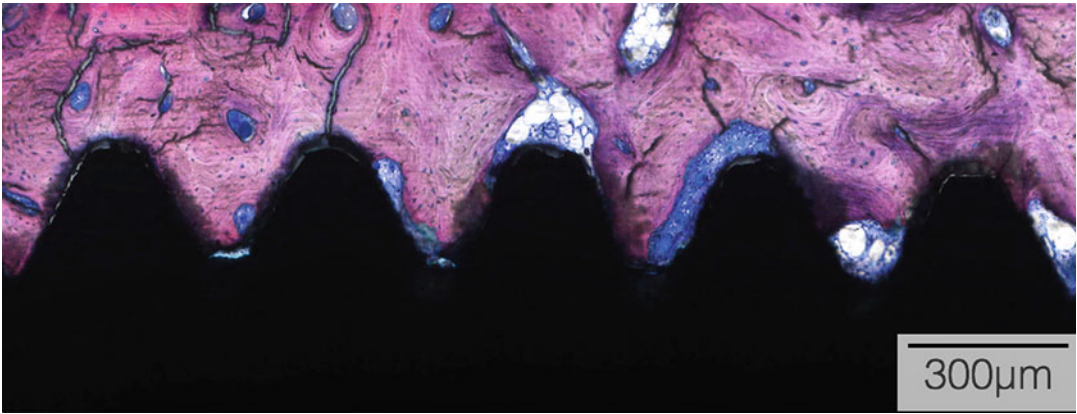


Fig. 7.3 A human retrieved sample showing direct agreement with other reports for screw type implants placed in undersized drilled sites. The bone surrounding these

implants present a compact mature lamellar bone with few and small marrow spaces. Stevenel's Blue Von Giesson's acid fuchsin stain

few and small marrow spaces (Iezzi et al. 2012, 2013b, 2014; Mangano et al. 2013) (Fig. 7.3). To date, no study regarding screw root form implant has presented sufficiently large sample size to determine the time course alteration of osseointegration or to make a clear assessment of bone mechanical property evolution as a function of implantation time.

7.3.2 Long-Term Morphology, Bone Mechanical Property, and Temporal Osseointegration of Implants That Undergo Intramembranous-Like Healing

Four sizable implant retrieval studies are currently available, concerning plateau root form implants (Baldassarri et al. 2012; Coelho et al. 2009b, 2010d; Gil 2015). The first two studies reported the basic morphologic and morphometric evaluation of textured titanium surface and hydroxyapatite coated plateau root form implants as a function of implantation time (Coelho et al. 2009b, 2010d). While these studies provided valuable data regarding the unique bone morphology presenting cortical-like characteristics irrespective of implant and patient-dependent characteristics, the sample size was not sufficient for an appropriate assessment of osseointegration

measurable parameters as a function of functional loading time. The results of these two studies showed that regardless of functional loading time and any other implant/clinical parameter, similar bone morphologic scenarios were observed between specimens. Intimate contact between bone and implant surface was observed at all regions of the implant perimeter. Varying degrees of bone filling were observed between plateaus for all samples. No signs of epithelial migration or connective tissue was observed. In general, bone morphology around implants that were loaded up to 1 year presented a mixture of woven and lamellar bone embedding primary osteons as presented in Fig. 7.4a. For all other implants, which were retrieved after approximately one and half years of implant placement, a remarkably similar structure was observed as presented in Fig. 7.4b, c. All optical micrographs showed that the predominant bone morphology observed between plateaus presented a lamellar configuration in varied directions depicting multiple remodeling cycles in a cortical-like fashion throughout the implant life under loading.

The third study considered various implant surfaces for 30 implants that were under functional loading for as long as over 20 years (Baldassarri et al. 2012). While the sample size was also not sufficiently powerful to determine

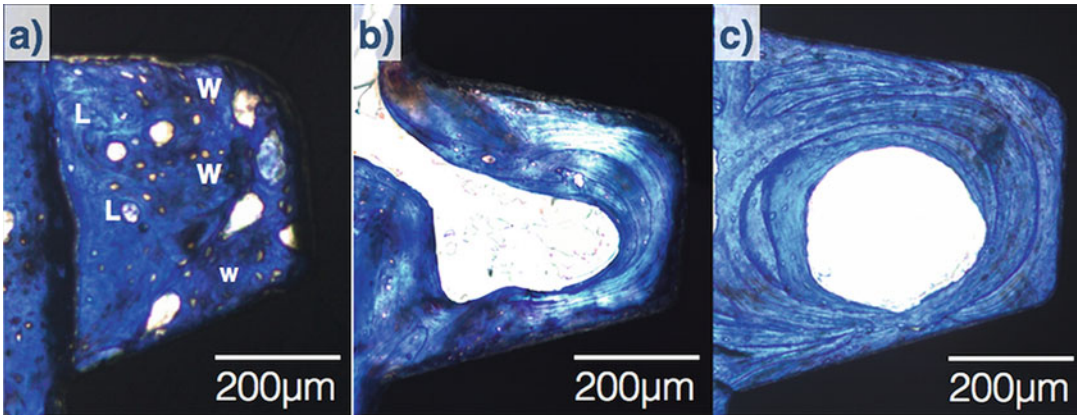


Fig. 7.4 Optical micrographs representative of (a) implants that were loaded up to 1 year in vivo demonstrated a mixed bone morphology with regions of woven (w) and lamellar bone. Implants that remained loaded for

longer periods of time such as in (b) 8 years and (c) 17 years primarily presented a cortical-like lamellar structure. Toluidine Blue stain

the status of osseointegration over time, nanoindentation measurements of bone around implants was able to depict that bone mechanical properties (hardness and elastic modulus) did increase over time, strongly suggesting that osseointegration is a dynamic phenomena and that bone is always adapting to functional loading over time to increase the overall system biomechanics. In summary, this mechanical study determined that cortical-like bone properties are achieved and maintained after 5 years of implantation time irrespective of patient-specific and implant design variables (Fig. 7.5).

These three studies, each presenting between 24 and 30 implants, resulted in limited power when one attempts to correlate the effect of clinical and dental implant design variables in osseointegration and bone measurable parameters (Baldassarri et al. 2012; Coelho et al. 2009b, 2010d). Among these three studies, only one has presented sufficient statistical power to determine the positive effect of time under functional loading on bone mechanical property evolution (Baldassarri et al. 2012). Thus, while insightful, these studies lack appropriate sample size for appropriate statistical inferences regarding the effect of patient-dependent and implant parameter variables on osseointegration. The most valuable feature of all these studies is that the surgical and prosthetic protocols were comparable and thus one study may be directly compared to the

other and over time the samples can be collapsed for more statistically comprehensive analyses.

Thus, the fourth and most comprehensive study retrieved over a period of approximately 15 years, 210 human samples that were under functional loading from 0.3 to 24 years due to retreatment reasons (Gil 2015). All implants were retrieved for prosthetic reasons (primary treatment planning alteration due to tooth loss that required different treatment modalities; no clinically failing implants were considered). A retrospective patient chart review revealed that all retrieved implants were restored with a single crown and subjected to functional loading approximately 6 months after surgical placement. Data regarding implant design parameters such as surface, length, and diameter and patient related characteristics as jaw placement (maxilla vs. mandible), region (anterior vs. posterior), and functional loading time were collected. The final analysis considered 93 implants—72 hydroxyapatite (HA, Integra-CP, Bicon LLC, MA), 8 titanium plasma sprayed (TPS, Bicon LLC) and 13 uncoated (Integra-Ti, Bicon LLC). On average, these implants were retrieved after about 6 years (SD=5.2); 21.5% were retrieved within a year, and the longest retrieval interval was almost 18 years. Analysis of variance (ANOVA) was used to evaluate relationships between outcome measures of bone-to-implant contact (BIC), bone area fraction occupancy (BAFO), and ranked

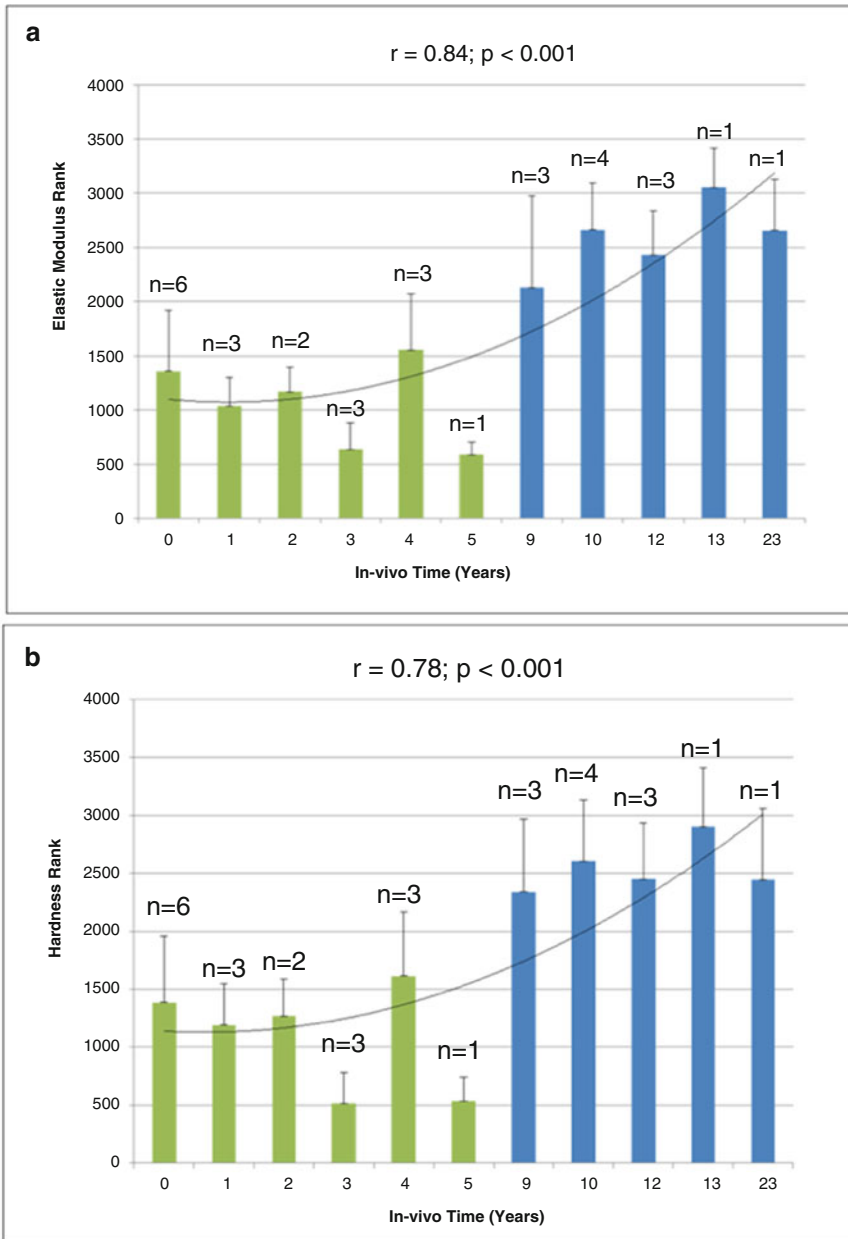


Fig. 7.5 (a) Elastic Modulus (GPa) vs. implantation time and (b) hardness (GPa) vs. implantation time. Each bar shows mean and standard deviation for specimens with

similar time in function. Note the significant increase in bone mechanical property around the implants after 5 years of implantation time

functional loading time and independent variables of surface material, implant diameter, implant length, arch, and anterior/posterior location. Patient age and gender were excluded from the analysis as these presented non-significant influence in any dependent variable. Linear regression analyses (IBM, Armonk, USA) were

used to evaluate the relationship between time of functional loading, BIC, and BAFO.

The results of this study (Gil 2015) is presented in Table 7.1 that shows mean levels of BIC, BAFO, and functional loading time as a function of implant characteristics and clinical independent variables. Mean functional loading

Table 7.1 Mean (SD) BIC, BAFO, and time in vivo (ranked) as a function of surface material, implant diameter, implant length, region and arch Different superscript letters indicate statistically homogeneous groups

Measure	N	BIC %	BAFO %	Loading time (ranked)
Surface				
HA	72	65.4 (13.6)	63.2 (17.2)	40.5 (25.5) ^a
TPS	08	72.0 (11.0)	56.3 (14.1)	70.5 (9.1) ^b
Uncoated	13	72.6 (9.3)	71.0 (11.5)	68.3 (24.3) ^b
Diameter (mm)				
4.0	38	69.6 (12.2)	67.4 (15.9)	60.3 (26.9) ^a
4.5	21	61.4 (14.4)	60.3 (18.6)	28.7 (19.4) ^b
5.0	34	67.5 (13.0)	61.6 (15.8)	42.7 (24.3) ^c
Length (mm)				
6.0	24	64.2(13.0)	62.1 (15.6)	26.8 (15.7) ^a
8.0	39	65.1 (13.8)	62.9 (18.7)	38.3 (24.3) ^b
11.0	30	71.6 (11.9)	65.9 (14.7)	72.8 (15.4) ^c
Region				
Anterior	28	63.8 (12.5)	63.2 (16.3)	40.3 (23.5)
Posterior	65	68.4 (13.2)	63.9 (16.7)	49.9 (28.0)
Arch				
Maxilla	40	68.5 (12.7)	65.8 (15.9)	53.0 (28.6)
Mandible	53	65.9 (13.4)	62.1 (16.9)	42.5 (25.0)

time was significantly lower in HA than other implants; significantly increased with implant length; was highest in 4 mm diameter implants, lowest in 4.5 mm implants and intermediate in 5 mm implants (significantly different between 3 diameters); and did not vary with either anterior/posterior region or arch. No implant and patient related characteristics were statistically related to either BIC or BAFO. Figure 7.6 shows that both BIC ($R=0.38$, $p<0.001$) and BAFO ($R=0.25$, $p<0.02$) increased as a function of (ranked) functional loading time.

The overall BIC and BAFO results presented by the 93 implants evaluated in the described study (Gil 2015) were in direct agreement with previous studies concerning plateau root form implants that were under functional loading from 0.3 to over 20 years (Baldassarri et al. 2012; Coelho et al. 2009b, 2010d). The substantially larger sample size evaluated also allowed a more powerful analysis regarding how BIC and BAFO were possibly affected by different implants design and patient-related clinical parameters.

While preclinical studies concerning the effect of plateau root form implant surface on early

osseointegration have shown that calcium-phosphate coated implants presented higher degrees of osseointegration over time (Coelho et al. 2010b; Granato et al. 2009, 2011; Suzuki et al. 2009, 2010), no difference in BIC and BAFO were detected between the three different surfaces evaluated in the described human retrieval study involving the same implant design (Gil 2015). In addition, concerning specific implant design parameters evaluated, no individual or combination of parameters (implant diameter, length, and surface) resulted in higher BIC or BAFO, suggesting that after osseointegration is successfully achieved, implant diameter, length, and surface have minimum to no effect on its temporal fate. Specific to implant diameter and length, despite being design features that are well known to affect the overall bone-implant environment biomechanics, the results obtained in that human retrieval study (Gil 2015) suggest that the bone configuration and mechanical properties were sufficient to maintain clinically sufficient levels of osseointegration. Of special interest were the clinical independent variables evaluated: maxilla or mandible, and whether the

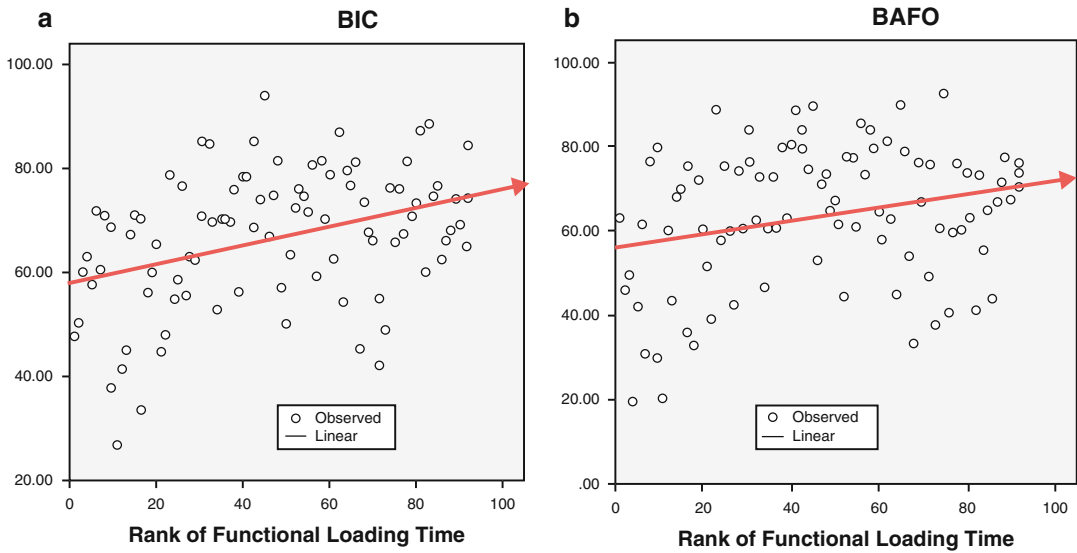


Fig. 7.6 Human retrieved implants (a) BIC and (b) BAFO as a function of rank of functional loading time

implants were placed in the anterior or posterior regions of the arch. Surprisingly, statistical analyses showed that none of these parameters affected either BIC or BAFO. While it is known that denser bone is usually available in the mandible relative to the maxilla, and anteriorly relative to posterior, the long-term bone-implant interfacial interactions are not affected by the bone quality in this specific implant geometry (plateau root form implants) (Gil 2015).

Finally, when BIC and BAFO were collapsed over all implant design and clinical independent variables, both BIC and BAFO regression models showed an increase as a function of (ranked) functional loading time (Gil 2015). These data suggest that, over time and functional loading, osseointegration is a cumulative process in plateau root form implants (Fig. 7.6). Statistical analysis also showed that increased integration as a function of functional loading time is not specifically related to any implant design parameter and clinical variables such as arch location and anterior/posterior position. Thus, the longer a plateau root form implant stays under functional loading, osseointegration is expected to increase (Fig. 7.6).

7.4 Hastening the Osseointegration Process

While promising developments have been made over the last five decades regarding implant hardware designing and how it dictates early bone healing and long-term bone morphology around implants, it is widely recognized that other design features do in fact hasten bone healing around implants and can further increase the performance of implant hardware (Coelho and Jimbo 2014a, b; Coelho et al. 2009a; Palmquist et al. 2010). For instance, lower length scale design parameters have been designed in an attempt to change the degree of intimacy between host biofluids and implant surface while also changing cell phenotype to hasten biological response (Hamilton and Brunette 2007; Leclercq et al. 2013; Yang et al. 2013; Zambuzzi et al. 2011). However, their early effects are directly related to their strategic hierarchical placement as a function of implant hardware design since, as previously presented, healing mode and kinetics drastically shift as a function of the macrometer

scale variables. It is thus intuitive that implant hardware should be strategically designed to maximize interaction between the host biofluids and the implant surface.

For instance, the reduced length scale design features intended to improve the establishment and maintenance of continuous pathway for bone forming cell migration towards the implant surface will not be as effective in hastening bone healing in regions where cell-mediated interfacial remodeling initially occurs after placement due to initial hardware design interaction with bone (Gomes et al. 2013; Bonfante et al. 2013). Thus, implant hardware designs that allow healing chamber formation are more suited to deliver adequate conditions for improved micrometer and the nanometer length scale design features performance in hastening early osseointegration (Coelho and Jimbo 2014a, b).

A plethora of preclinical studies concerning surface modifications and tissue engineering strategies concerning plateau root form implants have been conducted to date (Leonard et al. 2009; Coelho et al. 2010b, c, 2011; Marin et al. 2010; Granato et al. 2009, 2011; Suzuki et al. 2009, 2010). Common to all these studies is the fact that modifications of implant design at the micrometer and nanometer scale with or without biomolecular tagging have been performed in an attempt to improve the early bone response to plateau root form implants.

The initial studies comprised direct biomechanical and histometric comparison between an alumina-blasted/acid-etched surface (IntegraTi™) that has been available for the Bicon implant system for several decades (used as control), and a variety of candidate surfaces that primarily comprised thin coatings of calcium-phosphate based bioactive ceramics (Suzuki et al. 2009, 2010). For this series of studies, a cylindrical prototype implant macrogeometry was utilized and promising results were histometrically detected for the bioactive ceramic thin-coated implants relative to the uncoated IntegraTi™. The significantly higher osseoactivity around thin-coated implants was approximately 35 % higher than controls. When the plasma-sprayed calcium-phosphate coating (PSCaP, IntegraCP™) was compared to

IntegraTi™ and thin bioactive ceramic coated implant groups, a significant increase in biomechanical fixation and bone mineral apposition rate was detected for the PSCaP coated implants, indicating that relatively thicker coating hastened bone healing to a higher degree compared to the other surfaces, warranting investigations utilizing plateau root form implant prototypes. Then, a second series of studies also compared the IntegraTi™ and thin bioactive ceramic coatings on plateau root form implant prototypes (Granato et al. 2009, 2011). As expected, due to the favorable environment provided by the surface treated healing chambers, measurable osseointegration indicators depicted a more sizable effect in both biomechanical and histometric parameters for the thin-coated implant relative to IntegraTi™ when differences were compared to the previous studies considering cylindrical implant prototypes that mostly healed through the interfacial remodeling pathway (Coelho and Lemons 2009; Coelho et al. 2009c, d).

A third series of studies comparing IntegraTi™, thin-coated bioactive ceramics, and IntegraCP™ was conducted on plateau root form implant prototypes. This series of preclinical studies in different animal species unequivocally demonstrated the superiority of the IntegraCP™ surface treatment when improvements in early bone healing around plateau root form is concerned (Coelho et al. 2010b; Bonfante et al. 2012; Quaranta et al. 2010).

Subsequently, attempts to hasten early bone healing around plateau root form implants comprised strategies to improve the early interaction between the blood clot and implant surface in an attempt to provide a seamless pathway for osteogenic cells to migrate through the osteogenic connective tissue present in the healing chambers towards the implant surface. Such approach utilized an argon-based atmospheric pressure plasma (APP) source applied to the implant immediately prior to implantation (Giro et al. 2013; Coelho et al. 2012). When such strategy was applied in a beagle dog model, osseointegration levels increase over 300 % for the APP-treated IntegraTi™ surface relative to the untreated IntegraTi™ surface (Coelho et al.

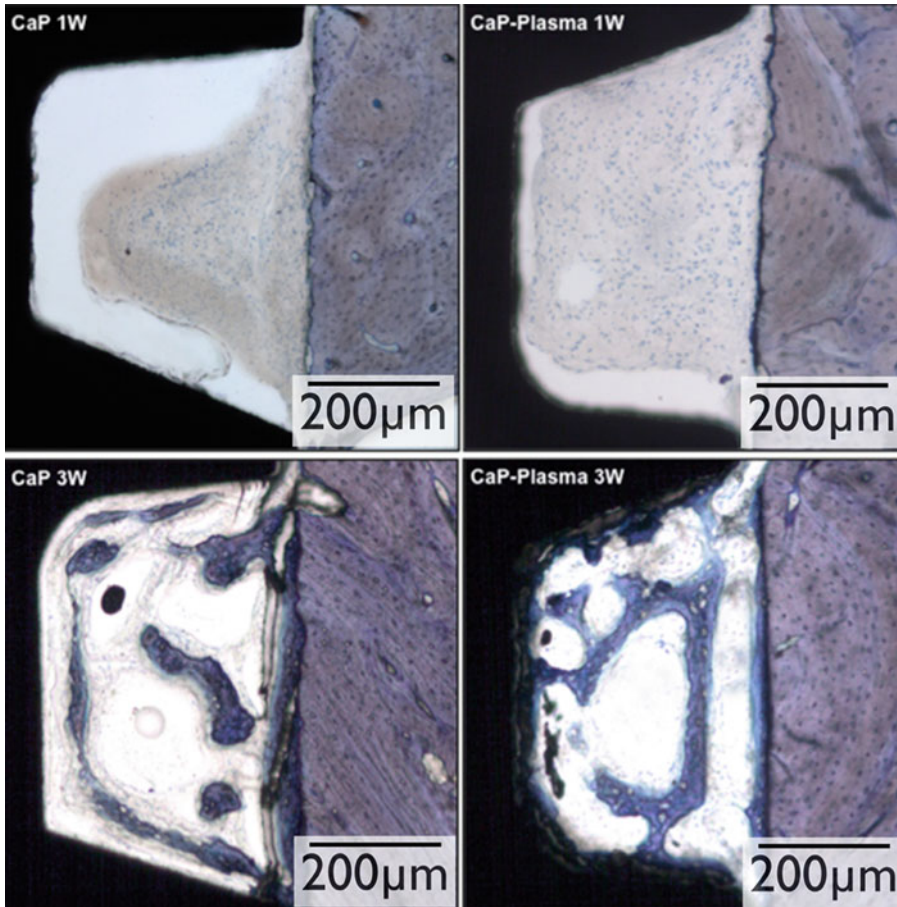


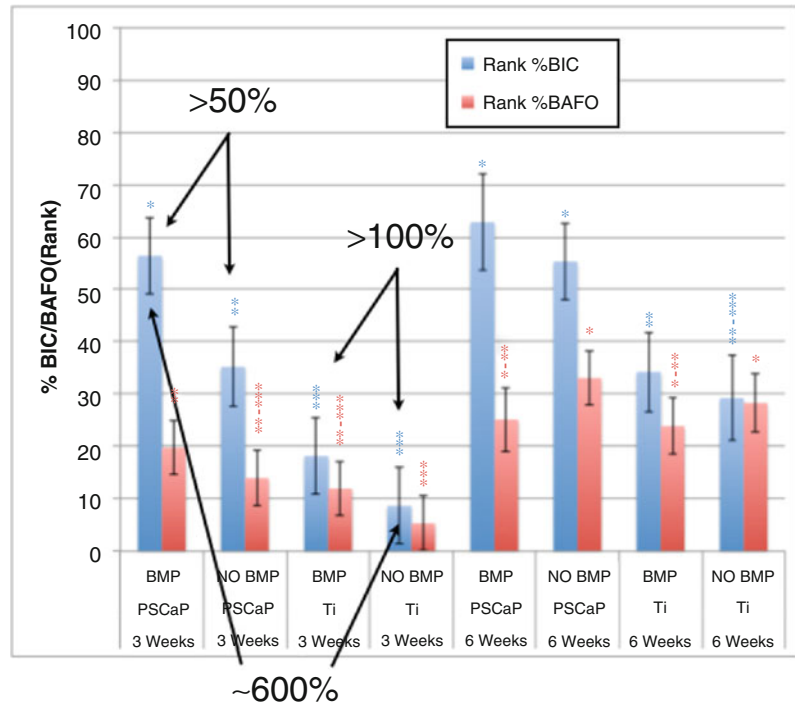
Fig. 7.7 Representative overview of the histological micrographs of PSCaP coated plateau root form implant groups at 1 and 3 weeks in vivo. At 1 week, the histologic sections of the CaP-plasma group showed initial signs of bone formation adjacent to the implant surface and the presence of layers of early connective tissue (stroma) in

intimate contact with the implant surface. In contrast, the CaP group presented the stroma collapsed to the center of the plateau. At 3 weeks, bone formation was observed throughout the healing chambers of both groups. Note the gap between tissue and implant surface was pronounced for the 1 week samples. Toluidine Blue stain

2012). When the approach was applied to IntegraCP™ surfaces, an increase in 80 % osseointegration was obtained for the APP-treated IntegraCP™ compared to untreated IntegraCP™ surface (Giro et al. 2013). The story telling histologic sections presented in Fig. 7.7 showed that the APP treatment of both IntegraTi™ and IntegraCP™ surfaces resulted in a more intimate interaction between the osteogenic tissue derived from the blood clot relative to untreated surfaces. Such panorama resulted in a seamless pathway for osteogenic cells to reach the implant surface compared to untreated surfaces.

To date, a tissue engineering approach has also been utilized to accelerate early bone healing around plateau root form implants. This strategy involved dip coating both IntegraTi™ and IntegraCP™ implants in rhBMP-2 prior to implantation in the hip of sheep (a bone that presents very low density) (Yoo et al. 2014). The results (Fig. 7.8) demonstrated that increases over 100 % and 50 % osseointegration was observed for the rhBMP-2 IntegraTi™ and IntegraCP™ groups, respectively, relative to their controls. Worth noting is that a difference of approximately 600 % was observed between the

Fig. 7.8 Statistical results summary (mean \pm 95 % CI) concerning ranked %BIC and %BAFO considering presence of rhBMP-2 (BMP), implant surface type, and time *in vivo*. Note that the number of asterisks depicts statistically homogeneous groups



rhBMP-2 IntegraCP™ group and regular IntegraTi™ were compared, demonstrating the efficacy of the combination of a PSCaP coating loaded with rhBMP-2 in increasing osseointegration levels of plateau root form implants (Yoo et al. 2014).

7.5 Final Remarks

Over the last 50 years, the phenomenon of osseointegration has not only revolutionized but also led to significant developments in dentistry and orthopedics, resulting in life-changing clinical outcomes that have not only provided or improved esthetics and function, but also promoted quality of life to millions of individuals worldwide. Research has attempted to maximize, accelerate, and perfect the physiologic events associated with the process of osseointegration. Significant improvements in short- and long-term osseointegration have been achieved over the years, with the most substantial, consistent, and reproducible

results being associated with more careful and gentle instrumentation protocols, enhanced implant surface treatments, and variations in implant macrodesign. While properly cleaned and sterilized biocompatible titanium-based alloys are capable of achieving osseointegration, implant surface treatments and coating methods such as alumina-blasted/acid-etched surface, plasma-prayed calcium-phosphate, argon-based atmospheric pressure plasma, and rhBMP-2 dipping have shown to substantially accelerate and enhance osseointegration, allowing for faster patient rehabilitation. While interfacial remodeling healing pathway still is accepted by many as the process likely to result in superior clinical outcomes, intramembranous-like healing or hybrid pathways are likely to change this misconception since such implant macrodesigns leading to the latter pathways have been shown to facilitate the enhancement of micrometer/nanometer and tissue engineering to hasten early bone healing around implants while permitting continuous osseointegration increase over time. Considering

that long-term stability of osseointegration currently is one of the major concerns in implant dentistry, this field of research is likely to gain even more attention in the future.

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