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Review Article

Periodontio-integrated implants: A revolutionary concept

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ABSTRACT

Though the fields of regenerative dentistry and tissue engineering have undergone significant advancements, yet its application to the field of implant-dentistry is lacking; in the sense that presently the implants are being placed with the aim of attaining osseointegration without giving consideration to the regeneration of periodontium around the implant. The following article reveals the clinical benefits of such periodontio-integrated implants and reviews the relevant scientific proofs. A comprehensive research to provide scientific evidence supporting the feasibility of periodontio-integrated implants was carried out using various online resources such as PubMed, Wiley-Blackwell, Elsevier etc., to retrieve studies published between 1980 and 2012 using the following key words: "implant," "tissue engineering," "periodontium," "osseo-integration," "osseoperception," "regeneration" (and their synonyms) and it was found that in the past three decades, several successful experiments have been conducted to devise "implant supported by the periodontium" that can maintain form, function and potential proprioceptive responses similar to a natural tooth. Based on these staunch evidences, the possibility of the future clinical use of such implant can be strongly stated which would revolutionize the implant dentistry and will be favored by the patients as well. However, further studies are required to validate the same.

Key Words: Implant, osseointegration, periodontium, tissue engineering

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INTRODUCTION

Since, the description of the process of osseointegration by Brånemark *et al.*, dental implants have become ideal replacements for missing teeth.[1] The term osseointegration was later defined by Albrektsson *et al.*[2] as the direct contact between living bone and implant at the light microscope level. This means that the implants are functionally ankylosed to the bone without periodontal ligament support. However, despite good success rates of osseointegrated oral implants, failures do occur, which can be attributed to the bone loss due to excessive occlusal load and/or infection.[3] Hence, the focus of implant dentistry has changed from merely obtaining osseointegration to the preservation and prevention of peri-implant hard and soft tissue loss.[4] Currently, lost teeth are being replaced by implants made of inert biomaterial, which are directly inserted into the alveolar bone to achieve osseointegration without considering the regeneration of periodontium. The field of oral and periodontal regenerative medicine has recently undergone significant advancements in restoring as close as possible the architecture and function of lost structures. However, to date, there has been a major "disconnection" between the principles of periodontal regeneration and oral implant osseointegration: the presence of a periodontal ligament to allow for a more dynamic role beyond the functionally ankylosed implant.[5] Therefore, an innovative approach is mandatory to create "periodontio-integrated implants" i.e., an implant suspended in the socket through periodontal ligament as opposed to functionally ankylosed osseointegrated

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implants. The authors of the present study believe that such advancement would revolutionize implant dentistry and would be significantly beneficial to patients.

PERIODONTIO-INTEGRATED IMPLANTS VERSUS OSSEOINTEGRATED IMPLANTS

Localized bone loss around osseointegrated implants represent a clinical challenge.[6] Excessive stress that accumulate at the crestal region of the implants leads to bone loss at this region.[7] This concentration of stresses at the crestal region is mainly attributed to the lack of the periodontal ligament, which is essential for distributing the forces throughout the length of the root. Periodontal ligament additionally dissipates these forces through the compression and redistribution of its fluid elements, as well as through its fiber system and hence provides shock absorption and cushioning effect to the teeth in response to these forces.[8] Furthermore, the periodontal ligament has a sensitive proprioceptive mechanism and is therefore capable of detecting and responding to a wide range of forces applied to the teeth. When these forces are transmitted through the periodontal ligament, they result in the remodeling of the alveolar bone to allow tooth movements (as seen in orthodontics) or in the widening of the periodontal ligament space leading to an increase in tooth mobility in response to excessive forces (e.g., occlusal trauma).[9] The osseointegrated dental implants on the other hand, physiologically differ from natural teeth as they lack periodontal ligament support and hence when loaded mechanically, evoke a peculiar sensation, which has been termed as osseoperception. Hence the osseointegrated implants not only become a part of the body but also of the mind and this mental acceptance named as osseoperception[10] has been described as a kinesthetic oral perception, which is derived from temporomandibular joint, cutaneous, muscle, mucosal and periosteal mechanoreceptors that provides mechanosensory information on oral kinesthetic sensibility in relation to jaw function and contacts of artificial teeth, in the absence of a functional periodontal mechanoreceptive input.[11,12] Furthermore, the passive threshold level of implants determined by the application of an external stimulus has been found to be 50 times higher than that of natural teeth;[13] which means that patients with osseointegrated implants will subjectively feel tangible sensation only when a force greater than that required to evoke sensation in natural teeth is applied. Hence, one of the reasons for the diminished ability of dental implants to adapt to occlusal trauma can be attributed to this lack of periodontal proprioceptive mechanism, which results in microfractures of the crestal bone and ultimately leads to bone loss. Moreover, connecting teeth to osseointegrated implants presents a biomechanical challenge due to the differential support and mobility provided by the implant and the tooth and consequently have also shown a higher rate of failures and complications.[14] However, when tooth-implant supported restorations would be fabricated using support from periodontio-integrated implants higher success rates can be expected due to similar resilience of tissues supporting teeth and implants. Furthermore, considering the use of osseointegrated implants in growing patients and the influence of maxillary and mandibular skeletal and dental growth on the stability of these implants, it is recommended to wait for the completion of dental and skeletal growth[15] since, the osseointegrated implants behave as an ankylosed element and don't follow the growth and evolution of the jawbones and certainly not of the alveolar process and hence, may disturb a normal development of the jawbones, leading to unesthetic situations, especially in the anterior region (e.g., resulting in "relative" infraocclusion or labioversion).[16] Nonetheless, with the provision of peri-implant tissue remodeling offered by the periodontio-integrated implants it would not only be possible to successfully place implants in patients undergoing craniofacial/skeletal growth process, but also to move them orthodontically.[5] It has been seen that peri-implant infections progress faster than the infections around natural teeth. Lindhe *et al*.[17] demonstrated larger inflammatory cell infiltrate and destruction around implants, which extended more apically when compared with a corresponding lesion in the gingival tissue around natural teeth. In addition, the tissues around implants are more susceptible to plaque-associated infections that spread into the alveolar bone, primarily due to the lack of a periodontal ligament, making them more prone to bone loss. Periodontal ligament by virtue of its rich vascular supply is a reservoir of defense cells and undifferentiated mesenchymal cells; hence, the presence of the periodontal ligament around implants would not only provide better defensive capacity, but also enhance repair and regeneration of bone defects in their vicinity.[5]

TISSUE ENGINEERING: FOUNDATION OF PERIODONTIO-INTEGRATED IMPLANTS

Tissue engineering as defined by Langer and Vacanti[18] is an interdisciplinary field that applies the principles of engineering and life sciences for the development of biological substitutes that restore, maintain or improve tissue function.[18] The main requirements for producing an engineered tissue are: The appropriate levels and sequencing of regulatory signals, the presence and numbers of responsive progenitor cells, an appropriate extracellular matrix or carrier construct and an adequate blood supply.[19] The discovery of stem cells in periodontal tissue and the outstanding progress in biomaterial research has opened up many possibilities for periodontal regeneration. To achieve successful periodontal regeneration, it will be necessary to utilize and recruit progenitor cells that can differentiate into specialized cells with a regenerative capacity, followed by the proliferation of these cells and synthesis of the target specialized connective tissues.[20] Because periodontal ligament-derived cells have multipotential characteristics, these cells are harvested and utilized as sources for the regeneration of periodontal tissues containing bone, cementum and periodontal ligament.[21] Clearly, a tissue-engineering approach for periodontal regeneration will need to utilize the regenerative capacity of these cells residing within the periodontium and would involve the isolation of such cells and their subsequent proliferation within a three-dimensional framework. Recent advances in mesenchymal stem cell isolation, growth factor biology and biodegradable polymer constructs have set the stage for successful tissue engineering of many tissues, of which the periodontium is considered a prime candidate for such procedures.[20] Sonoyama *et al*.[22] demonstrated the possibility of constructing the entire root/periodontal complex by inserting a hydroxyapatite/tricalcium phosphate block coated with periodontal ligament-derived mesenchymal stromal cells into the tooth sockets of mini-pigs. Furthermore, to avoid repeated harvestings of therapeutic cells for each treatment, successful cryopreservation of the periodontal ligament derived mesenchymal stromal cells, was also demonstrated by Seo *et al*.[23] Another possible option for periodontal ligament regeneration is gene therapy that comprises the insertion of genes into an individual's cells in order to promote a specific biological effect and requires the use of vectors or direct delivery methods to transfect the target cells.[24]

The aim of this review article was to identify and analyze those studies that investigated the feasibility of the development of periodontium around an implant and it's functioning *in vivo*.

MATERIALS AND METHODS

To provide the scientific evidence supporting the feasibility of periodontio-integrated implants, a literature search was conducted using various online resources such as Medline through PubMed, Wiley-Blackwell, Elsevier, Google scholar etc., to retrieve studies published between 1980 and 2012 using the following key words are: "implant," "tissue engineering," "periodontium," "osseointegration," "osseo-perception," "regeneration" (and their synonyms). A total of 608 articles were found, out of which only 17 were considered appropriate to be included in this review. The results from the studies that were reviewed are summarized in Table 1[25-41] as well as discussed below.

Evidence based periodontio-integrated implant dentistry

Extensive research and several experiments have been carried out to develop periodontal ligament around an implant, i.e., for the creation of a bio-root, which would provide ideal conditions for the implant-supported treatments in future.[42] Nyman *et al*.[43] suggested that the cells of the periodontal ligament possess the ability to reestablish connective tissue attachment. Nunez *et al*.[44] have further validated the regenerative potential of periodontal ligament-derived cells in a proof of principle study. Several *in vivo* experiments have demonstrated the formation of cementum-like tissue with an intervening periodontal ligament, when the dental implants were placed in proximity to tooth roots.[25,28,31,36] The mechanism of this phenomenon appeared to be due to the migration of cementoblast and periodontal ligament fibroblast precursor cells towards dental implants due to contact or proximity of the tooth-related cell populations to those implants.[5] Although partial regeneration of the periodontium consisting of cementum, periodontal ligament and alveolar bone, was possible, application of such methods in patients seemed impossible due to technical and physical factors.[42] Yet, the potential for the clinical implementation of

Table 1: Studies demonstrating the feasibility of formation of periodontium around dental implants

Author and year	Aim	Material and method	Animal/ human study	Results	Conclusion
Buser *et al*. (1990A)[25]	To determine if cementum formation with inserting collagen fibers can be accomplished on dental implants	Titanium implants placed in the mandible of monkeys, in areas having retained apical root portions and later examined histologically	Animal study	Implant surface with inserting collagen fibers was achieved around implants placed in close relationship to retained roots	Dental implants with a true PDL can be accomplished
Buser *et al*. (1990b)[26]	To examine wound healing events around titanium implants in the presence of retained root tips whose periodontium could serve as a source for cells playing the role in healing	Hollow cylinder TPS surface implants placed in the mandible of monkeys in areas having retained apical root portions examined histologically after a healing period of 12 months	Animal study	Regions where implants were close to retained roots, a PDL with collagen fibers oriented perpendicular to the implant surface, inserting into the cementum on the implant surface as well as to the opposing bone was seen	It may be possible to achieve an anchorage of certain dental implants with a periodontium
Caiazza *et al*. (1991)[27]	To evaluate experimental PDL for dental implants	Device made of titanium, poly (methylmethacrylate) coated with dacron tissue implanted in mandibular bone of rabbits for 3 months	Animal study	Dacron filamentous tissue became incorporated in the bone at 3 month post-implantation	Dacron coating provides a reliable mechanical anchorage to the implant and a barrier against epithelial proliferation and microbial contamination
Warrer *et al*. (1993)[28]	To determine if a PDL can form around the self-tapping, screw type titanium dental implants	Implants inserted in contact with the PDL of root tips retained in the mandibular jaws of 7 monkeys. Ground sections produced for histological analysis 3 months after implant placement	Animal study	Neo-cementum deposited on the implant surface in the contact area between the implant and the retained roots, whereas osseo-integration was found on the remaining part of the implant surface placed without contact to the retained root tips	PDL can form on self-tapping, screw type titanium dental implants in areas where a void is present between the surrounding bone and the implant at the time of insertion
Takata *et al*. (1994)[29]	To determine whether connective tissue attachment can occur on implant materials by repopulating PDL-derived cells	Bioglass, hydroxyapatite, titanium alloy and partially stabilized zirconium implanted into root cavities of cat canines where PDL-derived cells could populate the surface of the materials	Animal study	New connective tissue attachment occurred on bioactive materials such as bioglass and hydroxyapatite, while little or no cementum deposition was seen on bioinert materials such as titanium alloy and partially stabilized zirconium	PDL-derived cells can form new connective tissue attachments on implant materials. Yet, it is influenced by the bioactivity of the materials
Piattelli *et al*. (1994)[30]	To evaluate the potential of the different cells of the forming tooth bud to induce the formation of dental hard tissues and PDL around titanium implants	Four implants placed in a pig's mandible near the tooth buds. A wide artificial bone defect created around one of the implants; all implants covered with Gore-Tex membranes. After 3 months, samples histologically analyzed	Animal study	All implants were covered by a mineralized tissue with a histologic appearance similar to cementum and separated from the bone by a periodontal-like space filled by collagen fibers	Tooth bud cells can induce formation of dental hard tissues and PDL around titanium implants
Urabe *et al*. (2000)[31]	To assess whether or not the nature of the material affects the migration, proliferation, and differentiation of the progenitor cells for periodontium formation	The material-specific morphogenetic potential of periodontium-derived cells for inducing cell migration from the functioning periodontium onto bioactive (HA) and bioinert (TA) material was histologically evaluated	Animal study	Histologically, total periodontium including calcified cementum-like tissue only formed on HA and not on TA. Morphometrically, the length of fibrous connective tissue formed on HA was the same as on TA	The bioactivity of the material does not affect the migration of periodontium-derived cells but strongly influences cell differentiation
Choi (2000)[32]	To investigate whether a new PDL attachment can form on titanium implants	PDL cells obtained from the teeth of 3 dogs cultured and attached to the surface of titanium implants. The implants placed in the mandibles of the dogs and examined histologically after 3 months	Animal study	On some implant surfaces, a layer of cementum-like tissue with inserting collagen fibers had been achieved	Cultured PDL cells can form tissue resembling a true PDL around implants

(*Continued*)

Table 1: Studies demonstrating the feasibility of formation of periodontium around dental implants (Continued)

Author and year	Aim	Material and Method	Animal/ human study	Results	Conclusion
Guarnieri *et al*. (2000)[33]	To evaluate histologically the characteristics of the tissue present between a titanium implant and a retained root	Implant positioned in contact with root residue of a mandibular right canine, lost because of trauma in a 40-year-old man. The implant as well as retained root fragment extracted after 1 year as a result of peri-implantitis examined under the microscope	Human study* (case-report)	A continuous layer of cementum adhering to the implant and innumerable cementocytes, with a clear demarcation between dentin and cementum apposition on the implant surface was seen	Further studies are required to establish whether the neoformation of cementum and collagen fibers on an implant in the presence of root residues occurs in humans
Akira *et al*. (2005)[34]	To observe the effect of remaining PDL on the healing of the implant placement	Titanium implants placed into the tooth socket of Wistar rats with adhering PDL after extraction. At 7, 14, 21 and 28 days after implantation rats perfused with 4% paraformaldehyde solution	Animal study	Mechanical strength of the peri-implant ligament increased markedly from 14 to 28 days. Cementum-like hard tissues formed on the surface of the titanium implants along with many collagen fiber bundles between the cementum-like tissues and alveolar bone at 21 and 28 days	Placement of an implant into a socket with PDL leads to the formation of new cementum with functionally oriented collagen bundles and development of adequate mechanical strength
Parlar *et al*. (2005)[35]	To explore the formation of periodontal tissues around titanium implants	Custom-made, titanium implant with TPS and SLA surfaces placed in 9 mongrel dogs. Each implant submerged into the center of a dentin chamber prepared by hollowing roots and then slitting the cavity wall to create passages from the chamber to the PDL area. Histological sections analyzed after 4 months	Animal study	Newly formed PDL, alveolar bone, and root cementum filled the space between the implant and the wall of the chamber. Cellular cementum was deposited on one TPS and one SLA implant and on the dentinal walls of the chamber	Maintenance of original periodontal tissue domains prevevnt osseo-integration of the implants and show remarkable capacity for new periodontal tissue formation at a site where no such tissues ever existed
Jahangiri *et al*. (2005)[36]	To investigate the feasibility of PDL generation on an implant surface	Orthodontic tooth movement initiated for 4-6 weeks to tip the first premolar roots into contact with HA coated titanium implant placed in the extraction sites of 6 beagle dogs. Tooth-to-implant contact maintained for further 6 weeks and then separated for 2 weeks. Histological samples prepared and subjected to polarized light microscopy	Animal study	Formation of PDL-like structure with the formation of cellular cementum on the implant surfaces, in 4 out of 6 animals	Tooth-to-implant contact leads to partial generation of PDL on a bioactive implant surface
Marei *et al*. (2009)[37]	To achieve experimental formation of periodontal structure around titanium implants utilizing bone marrow mesenchymal stem cells	After canine teeth extraction, immediate implant placed in 5 goats. Control site: Implant with poly DL-Lactide-co-Glycolide scaffold around the titanium fixture. Test site: Implant with same scaffold but seeded with autogenous bone marrow-derived mesenchymal stem cells. One animal killed 10 days post-operatively and the others killed after 1 month	Animal study	Control site: Early signs of connective tissue regeneration around the implant at 10 days, but not shown in the 1 month specimens. Test site: Periodontal-like tissue with newly formed bone demonstrated both at 10 days and after 1 month	Undifferentiated mesenchymal stem cells are capable of differentiating to form cementum, bone and PDL

(*Continued*)

Table 1: Studies demonstrating the feasibility of formation of periodontium around dental implants (Continued)

Author and year	Aim	Material and Method	Animal/ human study	Results	Conclusion
Gault *et al.* (2010)[38]	To describe the technical development and the clinical application of so-called "ligaplants", the combination of PDL cells with implant biomaterial	Cells isolated from PDL and cultured in a bioreactor on titanium pins and then implanted in enlarged dental alveolae in dogs for 55-73 days as well as in humans	Animal and Human study*	Dog model: Histological examination revealed cells arranged in a typical ligament-like fashion. Human patients: Product safety was ascertained for 6-60 months. Probing and motility of the implants were well integrated with mechanical properties similar to those of teeth. Radiographs demonstrated the regeneration of deficient alveolar bone, the development of a lamina dura adjacent to a mineral-devoid space around the implant and implant migration in an intact bone structure	Ligament-anchored implants, have potential advantages over osseo-integrated oral implants
Rinaldi and Arana-Chavez (2010)[39]	To describe the ultrastructure of the interface between periodontal tissues and titanium mini-implants	Titanium mini-implant placed between the buccal roots of the mandibular first molar of 24 adult rats. Ultrastructural analysis done after 21, 30, 45, 60, 90, and 120 days of implantation	Animal study	Thin cementum-like layer formed at longer times after implantation at the areas in which the PDL was in contact with the implant	Titanium surface through its well-known biocompatibility exerts an effect on the periodontal ligament to lay down a cementum-like layer on the implant surface
Lin *et al.* (2011)[40]	To validate the possibility of formation of bioengineered periodontal tissue on titanium dental implants	Test site: PDL derived autologous DPCs seeded implants placed in the molar region of the rat model. Control site: Non-cell-seeded implants placed in the molar region of the rat model	Animal study	Test site: PDL-like structures containing condensed collagen fibers were apparent in 8-12, and 18-week specimens, although bioengineered cementum-like tissue was observed in only 10% specimen. Control site: After 8, 12, and 18 weeks, well-vascularized granulation tissue formed at new bone-implant interface	Suggested the potential to replace missing teeth in humans with dental implants augmented with autologous cell-derived bioengineered periodontal tissues
Kano *et al.* (2012)[41]	To evaluate the effects of HA coating and occlusion on the regeneration of PDL around tooth-shaped titanium implants	HA−/OCL−, HA+/OCL−, and HA+/OCL+ immediately implanted into extracted tooth sockets with remaining PDL of rat molar model and the regeneration of PDL examined histomorphometrically and histologically	Animal study	HA−/OCL− implant interface: Mobility M0-M2, peri-implant radiolucency, bony attachment and/or soft tissue running parallel to implant surface. HA+/OCL− Implant interface: Direct bony attachments found. HA+/OCL+ implant surface: Soft peri-implant tissue seen between the implant and surrounding alveolar bones which exhibited alkaline phosphatase with a distribution and activity similar to those of the PDL. Collagen fiber bundles were found functionally oriented in some regions of the peri-implant tissue	The remaining PDL tissue around extracted sockets has the ability to regenerate bone and PDL-like tissues on HA-coated tooth-shaped implants. Occlusal loads to the HA-coated implants may induce regeneration of PDL-like tissue in the peri-implant tissue

*Human study. TPS: Titanium plasma sprayed, SLA: Sand blasted with large grit and acid attacked, HA: Hydroxyapatite, TA: Titanium alloy, DPCs: Dental progenitor cells, HA−/OCL−: Non-HA-coated without occlusion, HA+/OCL−: HA-coated without occlusion, HA+/OCL+: HA-coated with occlusion, PDL: Periodontal ligament customized periodontal biomimetic hybrid scaffolds for engineering human tooth-ligament interfaces has been demonstrated by Park *et al*.[45] There is indeed a growing body of evidence validating the significant potential of the *in vivo* formation of ligamentous attachments to the biomaterials. Takata *et al*.,[29] in an animal study examined whether connective tissue attachment could occur on implant materials by repopulating periodontal ligament derived cells and found that while new connective tissue attachment occurred on bioactive materials such as bioglass and hydroxyapatite, little or no cementum deposition was seen on bioinert materials such as titanium alloy and partially stabilized zirconium, i.e., the formation of new connective tissue attachment was influenced by bioactivity of the materials. Choi,[32] placed implants with the cultured autologous periodontal ligament cells in the mandibles of the dogs and histologically revealed that after 3 months of healing, a layer of cementum-like tissue with inserting collagen fibers had been achieved on some implant surfaces, demonstrating that cultured periodontal ligament cells can form tissue resembling a true periodontal ligament around implants. In 2005, researchers also explored the formation of periodontal tissues around titanium implants using a novel dentin chamber model, which demonstrated newly formed periodontal ligament, alveolar bone and root cementum, filling the space between the implant and the wall of the chamber. This study displayed a remarkable capacity for new periodontal tissue formation at a site where no such tissues ever existed.[35] In a yet another study, implantation of titanium fixture with porous hollow root-form poly (DL-Lactide-co-Glycolide) scaffold seeded with autogenous bone marrow-derived mesenchymal stem cells in goats exhibited periodontium-like tissue with newly formed bone both at 10 days and after 1 month, substantiating that undifferentiated mesenchymal stem cells were capable of differentiating to provide the three critical tissues required for periodontal tissue regeneration: Cementum, bone and periodontal ligament around the titanium implants.[37] The cellular seeding methodology utilizing bioreactors to culture and maintain the ‘‘stemness’’ of these cells during the *in vitro* culture period before transplantation has allowed for a spatial distribution of cells over the surfaces of the prototype implant devices to eventually form the ligamentous constructs.[5] However, it was a scientific breakthrough when Gault *et al*.[38] demonstrated for the first time the tissue engineering of the periodontal ligament and cementum-like structures on oral implants in humans, to promote the formation of implant-ligament biological interfaces or ligaplants capable of true, functional loading. One of the interesting facts in the Gault research-work was that periodontal ligament fibroblasts could be harvested from hopeless teeth of mature individuals and cultured in bioreactors to preserve their state of differentiation. Out of the eight implants inserted, one implant was still in place and functioning even after 5 years and even exhibited substantial bone regeneration in the adjacent bone defect 2 years after implantation. This implies that future clinical use of ligaplants might also be able to avoid bone grafting, its expense, inconvenience and discomfort to the patient.[38] Lately, Kano *et al*.[41] have suggested that implants surrounded by periodontal ligament-like tissue could be developed, when immediately after the extraction, tooth-shaped hydroxyl-apatite coated titanium implants were placed into the tooth socket where some periodontal ligament still remained; maintenance of original periodontal tissue domains most likely being the cause of prevention of osseointegration of the implants.[41]

CONCLUSION

Although it has been revealed that generating a periodontal-like tissue around implants is possible, still a predictable and feasible method for producing dental implants with periodontal-like ligament has not been innovated. A major concern being the rational application of stem cell based tissue-engineering technology in clinical practice. Besides, the costs and time required from a practical standpoint for such tissue engineering applications is significant. Yet, this revolutionary approach to develop periodontio-integrated implants; however, opens up exciting possibilities for both periodontologists and oral implantologists and offers many interesting possibilities of utilizing ready-made, off-the-shelf biological tooth replacements that could be delivered to serve as hybrid-material-living oral implants.[5]

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