Physiology of Osseointegration

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KEYWORDS

• Bone conduction implant • Conductive hearing loss • Single-sided deafness
• Osseointegration • Titanium • Osseoimmunology

KEY POINTS

- Bone conduction implant devices rely on osseointegration, which create a structural interface between titanium implant surface and bone of the underlying skull.
- Osseointegration incorporates processes in the initial tissue response to implantation: peri-implant osteogenesis and peri-implant bone remodeling, which ultimately lead to de-novo bone formation on the implant surface.
- Osseointegration is immune-mediated, driven by the complement system and macrophages and characterized by tissue reparative features.
- Implant design, composition, and surface topography modifications can enhance osseointegration.
- Other factors that affect osseointegration include patient local and systemic factors, surgical technique, adequate healing time, and loading characteristics.

INTRODUCTION

Bone conduction implant devices (BCIDs) are indicated in the auditory rehabilitation of patients with conductive or mixed hearing loss who are unable to wear traditional hearing aids or for patients with single-sided deafness. The first implantation of BCIDs was in 1977 by Anders Tjellstrom[1] and since then, there have been more than 200,000 recipients of BCIDs worldwide.

BCIDs rely on osseointegration with the skull, the process of creating a structural and functional interface between the surface of a load-bearing bioactive implant and living bone, without intervening soft tissue.[1,2] The aim is to achieve endosseous healing and to induce de-novo bone formation surrounding and directly onto the implant surface, which prevents any further relative movement between implant and

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bone under normal conditions of loading. Intimate bone apposition to the implant material generates improved stability, decreased risk of failure, and creates implant longevity. Ideally, vibrations generated by the device are transmitted efficiently to the bone without loss.

The term "osseointegration" was coined by Per-Ingvar Brånemark of Sweden, after he observed this process occurring with titanium implants in rabbit bones.[3] The implant titanium oxide layer became permanently incorporated within the bone, such that the 2 could not be separated without fracture. The concept of osseointegration today can be studied clinically, anatomically, histologically, and ultrastructurally.[4]

Most of our understanding about osseointegration in-vivo comes from experience with dental implants and limb prostheses but while these are often made of alloys, manufacturers of BCIDs have favored pure titanium compositions. Apart from high tensile strength, the titanium oxide layer provides corrosion resistance and has excellent biocompatibility, being nontoxic to macrophages and fibroblasts.[5] In addition, the oxide layer has the ability to repair itself by reoxidation when damaged. The surface characteristics of implants may also be altered to enhance osseointegration or shorten the time taken for bone fixation.

STAGES OF OSSEOINTEGRATION

The stages of osseointegration[4] are as follows:

- Initial tissue response to implantation
- Peri-implant osteogenesis
- Peri-implant bone remodeling

Initial Tissue Response to Implantation

The initial stage of osseointegration commences with drilling the implant socket within the bone followed by inserting the titanium implant into the bed. Immediately after surgical insertion, primary implant stability is from passive mechanical apposition and engagement between implant and bone. Cortical bone is preferable to cancellous bone for primary stability. Meticulous surgical technique is important, including the use of copious cooling irrigation solution and low speed drilling. Subjecting titanium implants to a temperature elevation of 47°C for 1 minute can cause bone necrosis.[6]

The trauma of implant placement and injury to the underlying bone generate an inflammatory response characterized by release of growth factors and cytokines that form an extracellular matrix and hematoma for bone repair.[2,7] Within the clot, platelets undergo a cascade of adhesion and aggregation and the resultant fibrin matrix serves as a scaffold for migration (osteoconduction), proliferation, and differentiation (osteoinduction) of leukocytes and mesenchymal cells from post-capillary venules to the peri-implant site.[4,8,9] This process occurs within 1 to 3 days after surgical implantation.

Peri-Implant Osteogenesis

During the first 7 days, angiogenesis takes place within the peri-implant gap,[10] and from day 1 to around 2 weeks, the mesenchymal cells differentiate into osteoblasts, which form a cell-rich, immature, woven bone through intramembranous ossification.[10] The mesenchymal cells produce a 0.5-mm thick afibrillar, noncollagenous extracellular matrix layer, rich in calcium, phosphorus, osteopontin, and bone sialoprotein,[11] on the implant surface. There is a separate 20 to 50 mm layer of osteoblast-like cells, calcified collagen fibrils, and early mineralization at the

implant-bone interface.[12] Woven bone continues to form over 2 weeks after implantation, with the implant surface acting as a biomimetic scaffold.[13]

Marrow tissue with its rich vasculature supports the mesenchymal cells and provides precursors of osteoclasts. Woven bone has low mechanical competence due to random orientation of collagen fibers but from about day 10, the rapidly formed trabecular bone with its bridgelike architecture provides early active biological fixation of the implant. This optimally occurs when the gap between implant and bone does not exceed 500 μm. The valley regions of threaded implants are believed to be associated with increased bone formation kinetics.

Peri-Implant Bone Remodeling

Osteoclasts drive the process of bone resorption and remodeling of the woven bone and replacement by lamellar bone with a higher degree of mineralization. Titanium induces the host to favor bony remodeling over resorption. The osteoclasts attach to the mineralized collagen matrix, forming a sealing zone, depositing bone directly onto the implant surface. Lamellar bone allows adaptation to a greater load, with bone fibers deposited in parallel formation and new osteons circling around the implant with their long axes perpendicular to the long axis of the implants. This provides active secondary fixation of the implant through biological bonding.[14] At 3 months postimplantation, a mixed texture of woven and lamellar bone can be found around titanium implants, whereas the late stage of osseointegration can take a year or longer to complete. During this time, on the implant side, oxidation of the titanium is observed.

In the area up to 1 mm of bone from the implant surface, there is a continual dynamic process of remodeling in response to stress and mechanical loading months to years following implantation. This is confirmed by the long-term presence of marrow spaces containing osteoclasts, osteoblasts, mesenchymal cells, and vascular tissue next to the implant surface.

The degree of stability achieved by osseointegration is more important than the actual degree of contact between the surfaces, measured by bone-implant contact (BIC) percentage. Failure of osteogenesis can occur due to[4] the following:

- Decreased number and/or activity of osteogenic cells
- Increased osteoclastic activity
- Imbalance between anabolic and catabolic factors on bone formation
- Micromotion of the implant or mechanical stress leading to osteolysis
- Impaired vascularization of peri-implant tissue

Excessive implant micromotion during healing results in tensile and shear motions, stimulating a fibrous membrane formation around the implant and causing displacement at the bone-implant interface. This can cause aseptic loosening, inhibition of osseointegration, and implant loss. In a canine study, 20 μm of oscillating displacement was compatible with stable bone ingrowth, whereas 40 and 150 μm of motion were not tolerated and led to exuberant bone formation in the bone-implant gap.[15]

OSTEOIMMUNOLOGY

Early research focused on the role of osteoblasts and osteoclasts in osseointegration. More recently, there is increasing evidence that osseointegration is in fact an immunologically driven process, relying on advantageous inflammatory pathways that promote de-novo bone formation as part of the host response to bioactive implants, and reducing the negative tissue responses that could lead to rejection.[16,17] Titanium

implants are classified as bioactive implants, which have the ability to drive inflammation and differ to chemically inert implants that merely elicit a short-lived foreign body response that results in fibrous encapsulation. Studies have shown that application of nonsteroidal antiinflammatory drugs in animal models, which inhibit prostaglandins such as PGE2, led to inhibition of angiogenesis and osseointegration.[18,19] The main driving force for osteoimmunology is the host innate immunity, particularly the complement cascade and macrophage activation.

Macrophages are the major effector cell in immune reactions to biomaterials, controlling inflammation, healing, and even long-term response to different stimuli. Monocytes and macrophages are abundant in bone marrow and periosteal and endosteal tissues, where they are known as OsteoMacs,[16,20] and they regulate tissue homeostasis and provide immune surveillance. OsteoMacs constitute approximately one-sixth of all cells residing in bone marrow. OsteoMacs release bioactive growth factors such as tumor necrosis factor α,[21] transforming growth factor β,[22] interleukins 6 and 1,[23,24] osteopontin,[25] 1,25-dihydroxy-vitamin D3,[26] and BMP-2,[27] which induce extracellular matrix deposition and facilitate neoosteogenesis. Macrophages can be classified into 2 specific cell types: classic M1 proinflammatory macrophages that facilitate osteoclastogenesis and M2 tissue reparative macrophages.[17,28] The M2 phenotype is thought to be dominant in osseointegration.

Knockout models have demonstrated that removal of OsteoMacs from in vitro cultures leads to a 23-fold decrease in osteogenic differentiation and mineralization.[20] In areas of bone modeling, OsteoMacs have been observed to encapsulate functionally mature osteoblasts and provide signals that dictate osteoblastic function. In knockout mice models, depletion of OsteoMacs can cause loss of endosteal osteoblasts, reduction of trophic cytokines at the endosteum, and a complete loss of bone modeling.[29]

Osteoclasts and osteoblasts maintain a steady state of bone formation and resorption. Bone remodeling provides the mechanism for adaptation to mechanical stress, repair of microdamage, and replacement of primary bone during osseointegration of implants. Macrophage precursors differentiate into osteoclasts under the influence of cytokines CSF1 and RANKL,[30,31] and their attachment and activation are mediated by integrins, particularly vitronectin receptor $\alpha V\beta 3$.[32] Attachment of $\alpha V\beta 3$ induces signaling mechanisms that control cytoskeletal reorganization.

Following implantation of biomaterial where the foreign particle is too large for macrophage phagocytosis, several macrophages under the influence of many different cytokines, including interleukin 4 and 13, fuse together to form multinucleated giant cells.[33] Research suggests giant cells around bony implants contribute more to tissue integration and wound healing than biomaterial rejection.[20,28,34] They can be identified at the surface of osseointegrated implants after many years, and it is postulated that chronic immune-mediated inflammation is present for the lifetime of the implant in the bone.

Implant failure due to bone loss is thought to be due to excessive bone resorption by osteoclasts. Furthermore, studies have shown that hydrophilic and anionic substrate surfaces cause less macrophage adherence, increased apoptosis, and decreased giant cell formation.

IMPLANT SURFACE CHARACTERISTICS

The literature reports that modification of the implant surface to increase roughness has a significant effect on favoring osseointegration.[35,36] Rough surfaces allow platelet and monocyte adhesion, enhancement of osteoblast attachment and

subsequent proliferation and differentiation, and increase in surface area of implant in contact with the host bone. In addition, macrophage cell proliferation and adhesion, release of proinflammatory markers, and TGF-β and BMP-2 gene expression[37] are increased in implants with greater surface roughness. Lastly, surface roughness promotes M2 macrophage phenotype[38] and accelerates differentiation of macrophages into osteoclasts.[39]

Surface topography can be modified on multiple levels from macroscopic design or shape of implant, to introduction of microscopic, submicron, or nano-textures superimposed on one another. Surface roughness can be increased by machining, plasma spray coating (spraying titanium dissolved in heat onto the implant surface), grit blasting (spraying particles with ceramic or silica), acid etching (applying hydrofluoric, sulfuric, or nitric acid), sandblasting and acid etching, anodizing (applying voltage to breakdown the titanium oxide layer), or biomimetic coating.[40]

These modifications can create nanostructures of varying shapes on biomaterial surfaces, including porous, tubular, or pitlike shapes. The ideal dimension, aspect ratio, or distribution of nanostructures on implant surfaces to provide optimal functionality remains under intense research. Matching the implant surface characteristics to the hierarchical architecture of actual bone seems to provide ideal bioactive potential.[41]

Wennerberg and Albrektsson propose the following categories for surface roughness based on the surface area (Sa) value[41]:

- Smooth surfaces: Sa value less than 0.5 μm
- Minimally rough surfaces: Sa value 0.5 to less than 1.0 μm, include the Brånemark turned fixture
- Moderately rough surfaces: Sa value 1 to less than 2.0 μm, include the Astra Tech TiOblast and Osseospeed implants
- Rough surfaces: Sa value greater than or equal to 2 μm, include implant surfaces treated with plasma spray

In 2012, Cochlear introduced the Baha DermaLock (BA400) abutment on its percutaneous Baha Connect implants into clinical practice (Cochlear BAS, Mölnlycke, Sweden). This technology applies a hydroxyapatite coating on the concave-designed abutment surface, providing greater bioactivity and larger surface area than conventional titanium. The ceramic surface is purported to create better dermal adherence to the implant, thereby preventing downgrowth and migration of the overlying epidermis and allowing soft tissue preservation surgery.[42] This has been part of an evolution in surgical strategy world-wide in which there is less subdermal tissue reduction, and more preservation of full thickness tissues, which seem to decrease postoperative soft-tissue complications, decreased pain, less paraesthesia, shorter operative times, and better cosmesis.[43–45] Other possible advantages of hydroxyapatite coatings are faster osteoblast differentiation, enhanced biomechanics resulting in higher carrying loads, and increased bone penetration.

In a clinical review of 30 consecutive patients undergoing implant surgery using the Cochlear DermaLock (BA400) abutment, 86.7% of patients had no soft-tissue reactions, and mean time from implantation to processor loading was 4.5 weeks.[46]

The use of DermaLock is in addition to Cochlear's use of TiOblast titanium, with increased roughness at the actual bone interface. The TiOblast surface is manufactured with a physical subtractive procedure, by sandblasting the surface with spherical particles of titanium dioxide, and gives an Sa value of 1.1 μm.[47] In vivo tests demonstrate that the titanium dioxide particles, which carry negative charge, facilitate the deposition of calcium ions onto the implant, and stimulate the activity of osteoprogenitor cells to create more dense bony trabeculae (**Fig. 1**).

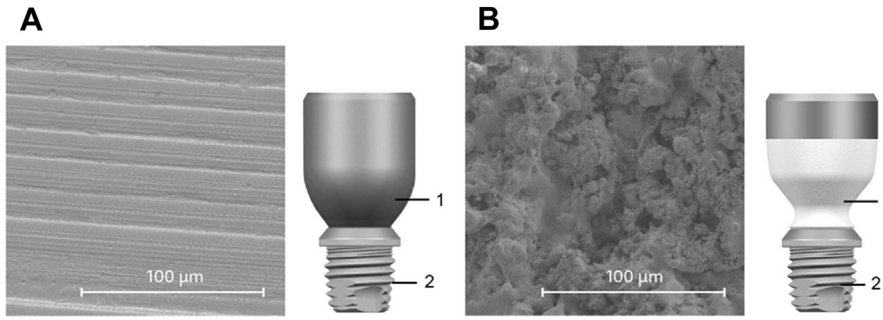

Fig. 1. Comparison between the Cochlear BA300 and Cochlear DermaLock BA400 abutments. The scanning electron microscopy images of their respective surfaces compare the surface topography of (*A*) a machined surface finish (BA300) and (*B*) a sandblasted finish with hydroxyapatite coating (BA400). (With permission from Oticon Medical, © 2017.)

In 2015, Oticon Medical released their Ponto BHX implant, which combines OptiGrip geometry and the Brånemark Biohelix surface modification (Oticon Medical AB, Askim, Sweden). The OptiGrip geometry refers to the gradual relieving behind the cutting edge of the implant, which means less tissue pressure and friction at time of implantation.[48] There is still a high bone-implant contact surface afforded by an increase in the threaded area along the length of the implant, which allows a smaller drill diameter at surgery while maintaining higher primary stability of the implant shortly following surgery.

The Biohelix surface is created by a micromachining process, where an oscillating laser beam is used to heat and ablate the titanium at the root or inner part of the thread of the abutment. This induces a nanoporous structure and roughness to the implant surface in a process that does not require addition of any chemicals.

In an animal model, laser-modified titanium screws had significantly higher biomechanical anchorage, as determined by removal torque measurements, compared with machined titanium screws.[49] The laser-modified screws had higher microroughness and increased surface titanium dioxide layer thickness. Histologic and electron microscopy analysis of the bone and extracellular matrix composition involved in the osseointegration process was similar between the 2 types of implants (**Fig. 2**).

Another BCID that relies on osseointegration is the BCI developed from collaboration between Chalmers University of Technology and Sahlgrenska University Hospital in Sweden. The device uses transcutaneous electromagnetic transduction of sound but the implanted component consists of a flat surface in contact with bone, rather than a screw-design implant. Despite the flat surface, preclinical and animal studies on sheep have demonstrated successful osseointegration of the implant, allowing comparable sound transmission to that achieved in percutaneous implants.[50] Further experimental implants have been described that may also exhibit osseointegration.

Currently studies are underway to evaluate the effects of many bioactive surface modifications, such as the addition of growth factors (bone morphogenetic proteins, osteogenic protein-1, insulinlike growth factor, transforming growth factor β, and fibroblast growth factor) and extracellular matrix components (collagen, chondroitin sulfate, fibronectin, and hyaluronic acid). The hypothesis is that these biocoatings may accelerate or enhance the quality of osseointegration, but so far early animal studies for dental implants with biological coatings have not shown any benefit.[51]

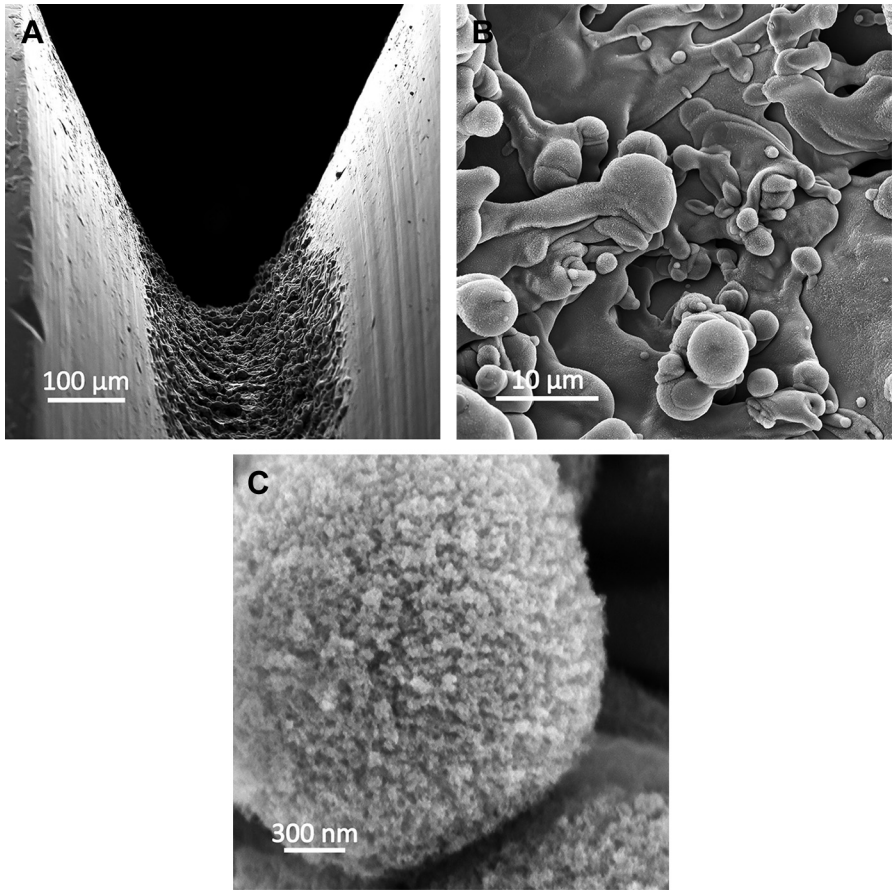

Fig. 2. The surface modifications on the Oticon Biohelix abutment surface at a (*A*) macroscopic, (*B*) microscopic, and (*C*) nanoscopic level. (Image courtesy of Cochlear Bone Anchored Solutions AB, © 2018.)

LOADING AND CLINICAL ASSESSMENTS FOR OSSEOINTEGRATION

Conventional or delayed functional loading after implantation is designed to allow the titanium implant to complete healing and establish secondary stability in order to avoid micromotion of the implant. As outlined previously, early integration occurs within a few weeks after implantation, but the full process of osseointegration can take months. Early in the development of BCIDs, loading of an implant would only occur after at least 3 months of undisturbed healing time. However, much shorter delays in loading are now implemented in most centers, on the order of 2 to 4 weeks, without significant impact on implant failure rate.

Implant stability is an indirect indication of osseointegration and can be clinically assessed by various methods:

- Clinical mobility test
- Radiological imaging
- Resonance frequency analysis (RFA)

Radiological imaging is aimed at demonstrating direct contact between bone and implant, whereas radiolucency may indicate the presence of fibrous tissue at the bone-implant interface. Imaging resolution and lack of standardized radiographic reporting are limiting factors to its use.

An RFA device contains a piezoelectric element that induces oscillations and attaches to the implant and a probe that reads its corresponding resonance frequency. This frequency is translated into an implant stability quotient (ISQ), which ranges from 1 to 100, with 100 being the highest stability state. Exposed implant length, healing time, stiffness of the surrounding bone, implant geometry, and location of implant can affect the ISQ value. In addition, there are no established diagnostic threshold criteria available to guide clinical use.

FACTORS THAT AFFECT OSSEOINTEGRATION

Failure of osseointegration remains one of the main complications of BCIDs, in addition to skin problems such as overgrowth, infections, and allergy. Implant loss was recorded in 8.3% of patients in a study of more than 1000 percutaneous BCIDs,[52] with a meta-analysis reporting variable rates from 2% to 17%.[53] Higher rates are seen in the pediatric population and patients aged older than 60 years, thought to be due to less bone stock, reduced bone vascularity, and higher possibility of postoperative trauma to the abutment. Factors that may affect osseointegration both positively and negatively include the following:

- Implant factors: design, shape, length, diameter, composition and its biocompatability, surface macroscopic and microscopic topography and treatment, osteogenic biological coatings, surface energy and wettability, and implant micromotion;
- Host factors: implant bed site, bone cellularity and density (osteoporosis), intrinsic osteogenic potential, systemic illness (rheumatoid arthritis, smoking status, renal insufficiency, nutritional deficiency), medications (bisphosphonates, statins, immunosuppressants and steroids, cisplatinum, warfarin, heparins, nonsteroidal antiinflammatory drugs), and previous local radiotherapy;
- Surgical technique: minimal tissue injury, adequate clearance of soft tissue, continuous cooling, and low speed drilling may all enhance osseointegration;
- Undisturbed healing time and 2-stage surgical procedure (implant loading delayed until after submerged healing period) may be indicated in patients prone to poor osseointegration;
- Loading conditions: overloading may interfere with osseointegration.

From in vitro and animal studies, osteoporosis is associated with slower osseointegration and higher rate of implant failures.[54,55] Osteoporosis affects proliferation of mesenchymal cells, protein synthesis, and cell reactivity to local factors. Osteoblast numbers and activity are decreased, vascularity is impaired, and osteoclast numbers and activity are increased. Bisphosphonates that inhibit osteoclast-mediated bone resorption seem to enhance implant stability in patients with low bone density or metabolic bone diseases.[56,57]

The lipid-lowering statins are also believed to have an osteoanabolic effect. Histomorphometric studies have shown increased bone ingrowth, interface strength, implant stability, and osseous adaptation[58] in patients on these medications.

The effect of external beam radiation therapy on osseointegration remains unknown. Evidence suggests that it leads to delay in bone remodeling.[59] A study examined oral Brånemark implants retrieved from pre- or post-operatively irradiated sites[60]

and reported that implants with shorter duration in situ had sparse osseointegration but implants with longer time in situ had high BIC up to 70%. It is thought that osseointegration can still be successful in areas receiving full doses of irradiation but there are overall higher rates of implant failure.

SUMMARY

BCIDs rely on osseointegration and immune-driven process that creates a structural interface between titanium implant surface and bone of the underlying skull. This phenomenon is characterized by de-novo peri-implant osteogenesis and bone remodeling and when complete, prevents further movement of the implant in relation to the underlying bone. Implant design and modification, host systemic and local factors, surgical technique, and loading conditions contribute to the success or failure of osseointegration.

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