

Osseointegration: a review of the fundamentals for assuring cementless skeletal fixation

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Abstract: Direct skeletal fixation, termed osseointegration, has expanded in the last century and includes use in total joint replacements, the edentulous mandible and maxilla, and percutaneous osseointegrated prosthetics. Although it is well known that titanium and bone have the ability to form a durable bone–implant interface, new applications have emerged in the field of orthopedics, which requires a more thorough assessment of the literature. This review aims to introduce the basic biological principles for attaining osseointegration and discusses the major factors for assuring successful cementless fixation.

Keywords: osseointegration, bone, skeletal attachment, total joint replacements, dental implants, percutaneous

Introduction to osseointegration

Surgical implantation of metals and ceramics has been used to restore function for individuals with diseased and compromised tissue for the past 200 years.¹ However, the success of direct skeletal attachment with metal substrates remained limited until Per-Ingvar Brånemark discovered the integration potential between titanium and bone.² Brånemark and his coworkers coined the term “osseointegration” (OI) to describe the ability of titanium to form a mechanical and functional interconnection with osseous tissue without the formation of interpositioned connective tissue.³ The definition of OI has continued to evolve over the years given the advancement in imaging and microscopic tools available for assessing the bone–implant interface (Table 1). Current descriptions of OI include the need of the periprosthetic bone to resist shear and tensile forces⁴ and to be within 50 µm distance from the implant surface to host bone to prevent fibrous tissue attachment.⁵

Since the initial scientific discovery by Brånemark and his colleagues, fixation of metallic and nonmetallic implants to bone has increased exponentially in the fields of dentistry and orthopedics. OI has been used as a means to fix dental implants, bone-anchored hearing aids, spinal fusion implants, and endo-exo prostheses. Clinical follow up of oral, craniofacial, and cementless total joint replacements (TJR) has reported long-term clinical success rates with high implant survivorship.^{6–17} The principle factors for achieving direct skeletal fixation have been reported to include: the implant surface properties; quality of the host bone; surgical site preparation; loading conditions; implant design; and preventing initial and chronic infections. These factors are reported within this review, with the goal of improving the current understanding of OI and spurring future innovation in this field.

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Table 1 Advantages and disadvantages of various testing modalities

Testing modality	Advantage	Disadvantage	References
Light microscopy	Inexpensive technique	Does not provide sufficient detail at the interfacial zone because the resolution capacity is only 0.1 mm	143
Microcomputed tomography (μ -CT)	Provides three-dimensional images of the bone–implant construct	Image artifacts occur due to the opaque nature of the titanium-based implant	144–148
Resonance frequency	A nondestructive technique shown to correlate with mechanical removal forces and bone ingrowth or ongrowth	Implant stability quotient values do not provide sufficient detail of host bone–implant integration	149–154
Backscatter electron imaging	High resolution	Expensive technique	155,156

Bone biology and osseointegration

The implant surface

Various metals, ceramics, and biostable polymers have been used to achieve OI. The major metal types have included: cobalt chromium,^{18–20} tantalum,²¹ stainless steel,^{19,20,22} zirconium,^{23,24} and commercial pure titanium and its alloys.^{19,20,22} However, titanium has been widely advocated as the most biocompatible material for promoting OI, due to its excellent mechanical properties,²⁵ resistance to corrosion,^{25,26} and its ability to develop an oxide layer on the surface (comprised of a dioxide chemical structure, TiO₂).^{27,28} Most interestingly, this oxide layer thickness has been noted to be dynamic, ranging between 1,000–2,000 Å at 7 years postoperative follow up – much higher than the initial measurement of 60–100 Å reported at the time of implantation.^{4,21} The ability for bone to both mechanically and chemically bind to the surface of titanium has been known to facilitate durable OI and long-term implant survivorship (Figure 1).

Roughness, porosity, topography, and surface energy all contribute to the host response to a titanium implant placed in apposition with cortical and/or cancellous bone.^{29,30} While a complete review of each of these topics is not within the scope of this paper, some brief generalizations regarding the material surface are worth noting. It is well observed that the implant

surface morphology directly influences osteoblast and osteoclast attachment and metabolism.³¹ Skeletal fixation is most effective when using porous implants (50–400 μ m)³² with roughened surfaces, where ingrowth and interdigitation of the newly formed bone into the porous structure stabilizes the interface (Figure 2). As stated by Boyan et al, implant surfaces should have a 4–7 μ m layer of roughness to ensure proper osteoblast cuboid morphology,³³ an essential characteristic for assuring OI. Osteoblasts seated on roughened surfaces have demonstrated increased proliferation, and previous in vivo animal models have reported that the textured surfaces required higher removal torques compared with smooth controls.²⁹

The implant surface is a key factor in direct skeletal fixation, with implant survivorship dependent upon the specific device design and anatomical location for OI. Given the differences in mechanical loading conditions, vascular integrity, host bone quality (bone mineral density [BMD] and bone mineral content [BMC]), and bone type (cortical vs cancellous), surface properties may in future be tailor-made for each unique application (Figure 3). While in general, smooth implants do not have a microtexture conducive for osteoconduction, Balshe et al noted, when comparing 2,182 smooth-surface dental implants and 2,425 roughened implants postoperatively, that survival rates were 94.0% and

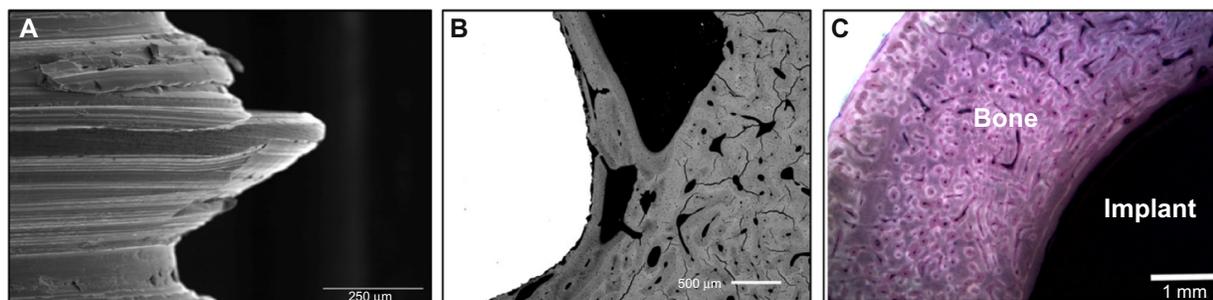


Figure 1 (A) Representative scanning electron microscope image demonstrating high resolution along the screw threads of an implant used for osseointegration. (B) BSE micrograph of bone–implant cross section, clearly depicting the bone on-growth (gray) onto the implant (white) within 50 μ m. (C) Bone–implant cross-section stained with Sanderson's Rapid BoneStain™ and counter stained with acid fuchsin, showing bone and implant interconnection.

Note: Sanderson's Rapid Bone Stain™ (Surgipath Medical Industries, Richmond, IL, USA).

Abbreviation: BSE, back-scattering electron.

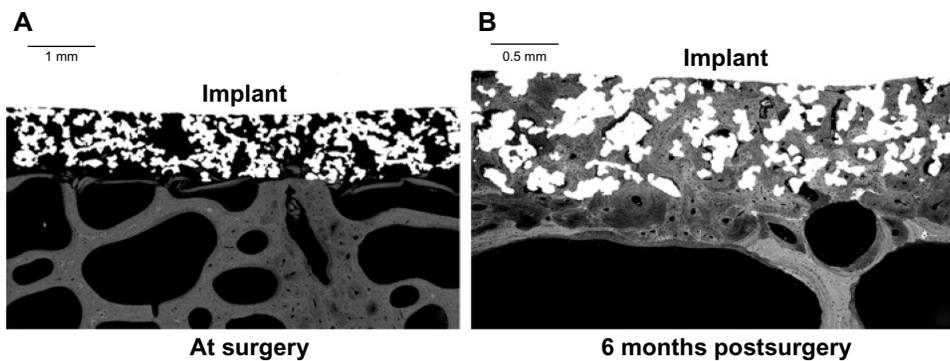


Figure 2 A representative set of BSE micrographs showing the ingrowth and interdigitation of new bone tissue into the porous, coated region at 6 months postsurgery (**B**) compared with time 0 (at surgery), when the implant was placed in close apposition with the host bone (**A**). The image shows porous coating (white), bone (gray), and marrow cellular components (black).

Abbreviation: BSE, back-scattering electron.

94.5%, respectively.³⁴ However, Balshe et al reported that the implant length and anatomic location were significant predictors for smooth implant failure³⁴ and that surface properties may be overridden when implants were placed at a sufficient depth within the osseous tissue. Pak et al³⁵ supported the potential for smooth implant attachment and noted, in their histomorphometric studies of dental implants with three separate surface treatments (commercially pure titanium, tricalcium phosphate, and anodic corrosion), that there were no differences in bone–implant contact or localized bone volume density at 3 and 6 weeks, respectively, thereby signifying the importance of proper implant “fit and fill.”

Quality of the host bone

Biological fixation between a titanium implant and host bone depends upon the quality and architecture of the supporting bone used in the OI procedure.³⁶ The human skeleton is com-

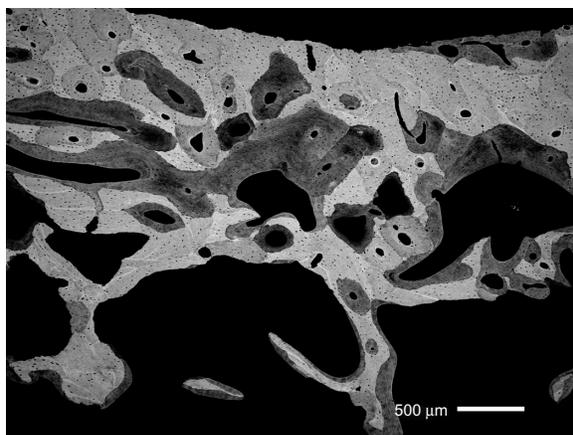


Figure 3 BSE micrograph demonstrating the wide range in bone mineralization levels during remodeling.

Abbreviation: BSE, back-scattering electron.

posed of approximately 80% cortical bone and 20% cancellous bone; however, the ratio between these bone types varies greatly between anatomical locations. For instance, the cortical to cancellous bone ratio of the vertebra is 25:75, compared with 50:50 in the femoral head and 95:5 in the radial diaphysis.³⁷ Given that cortical bone is typically less metabolically active than trabecular bone,³⁷ the placement of an orthopedic implant is critical for long-term success. Also, bone formation at the periprosthetic interface has shown to be a slow but a dynamic and tightly coupled process³⁸ coordinated between cells,³⁹ hormones,⁴⁰ and enzymes.³⁸ Modeling and remodeling of bone tissue around an OI implant results from complex chemical interactions and mechanical stimuli.

It has been largely accepted that bone adapts to mechanical loads in accordance with Wolff’s law.⁴¹ The functional adaptation of bone, most studied in the proximal femur, demonstrates the unique ability of bone to alter its trabecular orientation as a result of loading conditions.⁴² Bone biologist, Harold Frost also described the transformation of bone as a strain-driven event.⁴³ Frost hypothesized that a “minimal effective strain” was required to maintain bone architecture⁴³ and that physiologic bone strains rarely exceeded 3% in vivo.⁴⁴ In the absence of the minimum effective strain, bone volume will be reduced (as was the case with early astronauts who went into space). Moreover, loss of crestal bone may also result from highly localized stresses that induce microfractures. Thus, in order to maintain a healthy host bone volume and to preserve bone tissue, dental and orthopedic implants should permit adequate mechanical stimulation to the surrounding skeletal tissue.

A complete review of bone biology and the mechanical effects on bone formation has been reported in the literature previously.^{45,46} However, it should be noted that both BMC and BMD significantly impact the durability of OI by altering cell proliferation and protein synthesis.⁴⁷ Minor increases in

bone mineralization exponentially increase the modulus of elasticity of bone^{48,49} and subsequently, the durability of the bone–implant construct. However, there is a known inverse relationship between bone stiffness and fracture toughness, so minor decreases in BMC may allow the host bone to absorb higher energy prior to deformation.⁴⁹ This balance in BMC may affect the longevity of OI implant survivorship, as highly mineralized bones may fracture due to their inability to absorb the kinetic energy⁴⁹ – which may occur from an abrupt fall, to a patient with an OI implant.

In the case of OI within long bones, cortical bone porosity ranges between 5%–10% in skeletally mature individuals, while the porosity of cancellous bone varies between 50%–95%.³⁹ The increased pore space of cancellous bone results in an approximate three- to eightfold reduced bone density compared with cortical bone⁴⁴ and explains the 30-fold reduction in strength and stiffness between the two bone types.⁴⁴ Aside from the biomechanical advantage of cortical bone, Charnley also noted that cancellous bone does not have a periosteum along the surface of the trabeculae,⁵⁰ thus contributing to one of the known metabolic differences between cortical and cancellous bone remodeling.^{5,51,52} Moreover, cancellous bone heals in an appositional manner, with very little callus formation (<1%), which significantly differs from the healing patterns/cascades of fractured cortical bone; this would affect bone remodeling if accidental trauma occurred to the site where an osseointegrated implant was placed.

Surgical site preparation/implant stability

While proper instrumentation and operative techniques help to minimize disturbance to the localized vascular network during OI procedures, uncontrolled thermal or mechanical factors (reaming, rasping, or drilling) used to ensure proper implant “fit and fill” or fixation may damage the host bone’s ability to remodel.^{53,54} Insertion of an orthopedic implant into the host bone results in a localized region of necrotic tissue.⁵⁵ While it has been generally agreed upon that this amount of necrotic bone should be reduced during the initial implantation, Albrektsson et al have speculated that a minor region of dead bone may act as an early implant stabilizer during the preliminary phase of bone remodeling²¹ and may even be beneficial for anchoring osseointegrated implants in situ. In order to prevent premature implant failure, primary implant stability must occur immediately⁵⁶ to eliminate micromotion at the bone–implant site⁵⁷ and to also prevent fibrous tissue formation.⁵⁸ Gaps in excess of 50–150 μm between the implant surface texture and host bone may lead to fibrous tissue without skeletal attachment.^{5,59,60}

To improve the likelihood for dental implant survivorship, novel techniques have been developed that use computed tomography scans from the patient’s mouth, and computer-aided design.⁶¹ Advanced implant planning in a virtual environment may improve the accuracy of dental implant fabrication and provide patient-specific replicas for surgery. In fact, a study performed by Valente et al, using computer-aided oral surgery in a series of 25 patients resulted in a 96% implant survivorship, with mean deviations being less than 2 mm in any direction⁶² – thereby demonstrating the usefulness of this technique for positioning and for selecting an appropriate implant size.

Trauma to the host bone tissue during surgery may also accelerate local bone turnover.^{63–65} This has been termed the “regional acceleratory phenomenon” (RAP), which was first defined by Frost, using noxious stimuli, and then by Bloebaum et al.^{64,66,67} The RAP may occur for two reasons: the first being that placement of an intramedullary OI implant alters the dynamic strains to the host bone tissue. Depending on the “fit and fill,” the implant may result in high concentrations of localized stress or “stress shielding,”^{66,68,69} second, the surgical procedure itself disrupts the blood supply to the endosteal wall (which results in a local tissue response to reestablish bone vascularity) – thus causing an increase in cortical bone porosity.^{70,71} This increased vascular network is optimal for bone remodeling but will impact overall strength. Knowledge of the RAP is vital for the success of OI implants. In dentistry, increasing the severity of the RAP has been reported to accelerate the rate of orthodontic tooth movement.⁷²

Loading conditions

One challenge with cementless fixation has been preventing micromotion during the early phases of healing and allowing the bone to form a strong skeletal interlock;^{21,73} if this is not achieved, a fibrous tissue interface (Figure 4) may form and prevent OI.^{74–77} As noted above, limiting the initial forces on an OI implant has been based on the principle that stress must be exerted gradually to promote firm skeletal attachment since under- or overloading may compromise the integrity of the host bone. To prevent mechanical loosening at the bone–implant construct, OI procedures for dental applications initially have required periods of restricted load-bearing, to avert overloading.^{78–87} However, the dental and TJR literature now indicates that immediate implant loading may not compromise the integrity of the bone–implant interface or prevent OI if micromotion is controlled with properly designed implants.^{73,80–82,86–90} However, key design elements must be

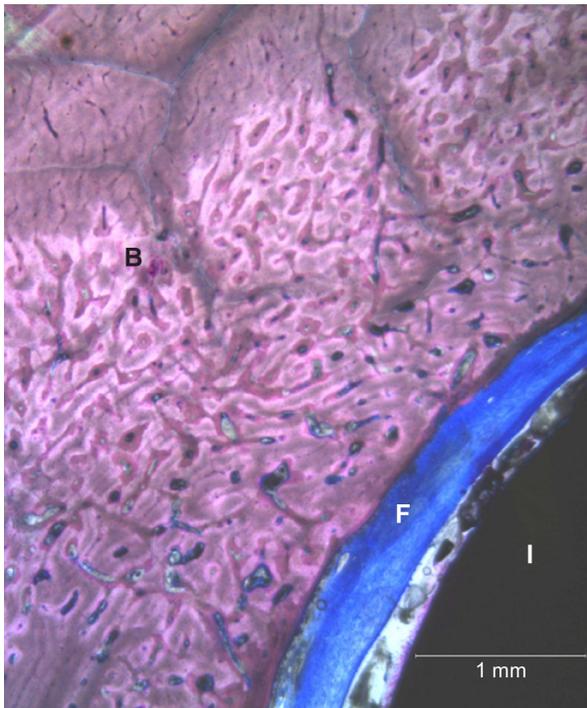


Figure 4 A representative bone-implant cross section that was stained with Sanderson's Rapid BoneStain™ showing the interpositioned fibrous capsule (F) between the implant (I) and the host bone tissue (B).

Note: Sanderson's Rapid Bone Stain™ (Surgipath Medical Industries, Richmond, IL, USA).

considered and include the implant neck design, screw shape, abutment design, etc during the oral implant design.

Most importantly, a delayed weight-bearing protocol deviates from the TJR paradigm, in which patients with total knee arthroplasty (TKA) or total hip arthroplasty (THA)

bear loads within hours of the procedure. Literature further indicates that immediate load-bearing may occur without compromising skeletal attachment.^{91,92} Implant-retrieval studies have further demonstrated that early load-bearing may be permitted if careful operative protocols and implant designs with optimal porous coatings are used.^{52,76,77}

Since the time when delayed loading for dental and orthopedic implants was first introduced, several authors have evaluated immediate loading and found high success rates that are comparable with or better than short-term protocols that require a “nondisturbed healing period.”^{93–97} Degidi and Piattelli studied the clinical prognosis of 646 immediately loaded dental implants placed in 152 patients and found only six failure cases within the first 6-month period.⁹⁸ Additionally, recent studies by Jeyapalina et al confirmed that when an immediate-loading protocol was used with percutaneous OI implants placed within the intramedullary canal, there were no signs of implant loosening postoperatively for up to 1 year.^{63,99–101} The appositional bone index, calculated at predetermined time points, demonstrated progressive bone interconnection and further validated the importance of “fit and fill” (Figure 5). These findings provide further evidence for an immediate implant loading once primary implant stability has been achieved.

Implant design

Novel designs for orthopedic implants have recently been developed using finite element analysis as a prerequisite. Hansson^{102,103} used computational modeling and finite element analysis of the femoral neck to reduce the peak

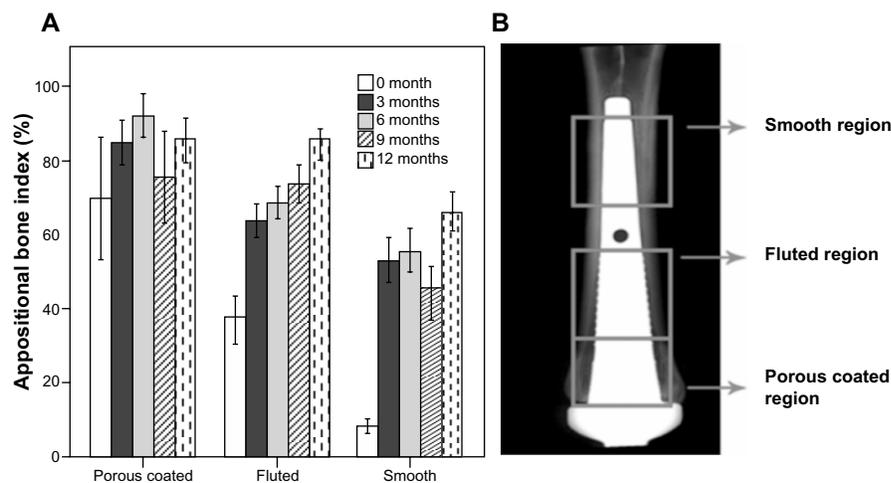


Figure 5 (A) ABI values at the time of the surgery (time 0) and at 3, 6, 9, and 12 months postsurgery. Data was obtained from a translational animal model, where sheep were implanted with a percutaneous OI implant in their fused right metacarpal III, IV bone. Statistically significant differences were found, between time 0 and all other time points, of fluted and smooth regions. **(B)** A radiographic image of the intramedullary implant, schematically showing the regions used for the ABI measurements.

Notes: ABI values are expressed as %. The error bars indicate 95% CI ($P < 0.05$).

Abbreviations: ABI, average appositional bone index; CI, confidence interval; OI, osseointegration.

interfacial shear forces and promote axial load transfer over a greater area of peri-implant bone interfaces. Furthermore, tapered implants using this design approach and microtextured surface features, such as a porous coating, may provide more effective force dissipation over a greater bone volume – thus improving the likelihood of successful OI.¹² For instance, follow up studies of the Zweymüller® hip implant system (Zimmer Holdings, Inc., Warsaw, IN, USA) have demonstrated no stem revisions and exceptionally high implant survivorship using a tapered design.^{104,105}

Preventing and treating initial and delayed infections

Although most of the OI procedures performed in controlled sterile clinical settings are successful, implant failures have been reported and may require revision surgery. The three primary reasons for OI implant revisions are due to 1) osteolysis and related aseptic implant loosening; 2) mechanical failures due to lack of OI; and/or 3) infection.^{106,107} A discussion of infection is as follows.

Total joint replacement

Implant-related infection is one of the challenging obstacles to THA and TKA. It has been reported that 0.8%–1.9% of TKAs and 0.3%–1.7% of primary THAs fail due to infection, aseptic loosening, dislocation, or fracture.¹⁰⁸ In the case of infection, the most common conventional therapy is antibiotics. However, if antibiotic therapies are unsuccessful, then the implant is often removed and reimplanted in a revision surgery. However during the revision surgery, the risk of infection is increased and has been reported to be as high as 10%¹⁰⁹ (this is because the dermal barrier is broken once more, allowing bacteria to reach the surgical site). In some instances the pathogen may include methicillin-resistant *Staphylococcus aureus*, which has high patient morbidity and mortality. One study by Mortazavi et al noted that 57% of the staphylococcal organisms cultured following deep infections after revision TKA were methicillin-resistant.¹¹⁰ Further compounding this problem, these bacteria may establish biofilms (sessile communities), which are difficult to eradicate with conventional antibiotic therapy.^{111,112} Since most chronic infections are attributed to biofilms, reoccurring deep tissue infection that cannot be managed by antibiotic therapy may require removal of all infected, devitalized, and foreign materials including the arthroplasty components. Often, the biofilm-forming bacteria may readhere to the implant if they are still present within the surrounding tissue. Therefore, in order for OI between the implant and host tissue to be successful, the revised implant must be placed in a sterile environment. To ensure sterility of the site, a two-stage

reconstruction surgery is often considered, with local and systemic antibiotic treatments used in between the surgeries for cementless fixation.^{113–115}

Dental OI implants

Bacterial colonization on dental implants may not lead to ultimate implant failure; however, prolonged exposures may generate host tissue inflammatory reactions, which slow OI progression. There are two major types of dental implant infection: peri-implant mucositis and peri-implantitis.¹¹⁶ While peri-implant mucositis is defined as a reversible inflammatory reaction in soft tissues surrounding an OI dental implant, peri-implantitis is considered to be an inflammatory reaction with the loss of supporting bone surrounding an implant.^{116,117} Pontoriero et al studied the clinical and microbiological response to the development of experimental gingivitis and experimental peri-implant mucositis and concluded that there were no significant differences found between them.¹¹⁸ The treatment option for peri-implant mucositis largely is based upon the management of plaque control, where surface debridement constitutes the basic element for treatment.

Peri-implantitis has an overall incidence rate of 12%–43%.¹¹⁹ If the early stages of peri-implantitis persist, implant–bone integration may be compromised, and subsequently, the implant will be lost. Presently, no single pathogen has been closely associated with infection of any implant system;¹²⁰ however, the microbial floras of failing implants have been associated with the pathogens of periodontitis.¹²⁰ Several reports cited that these implants were colonized with putative periodontal pathogens, including *Peptostreptococcus micros*, *Fusobacterium* spp., enteric gram-negative rods, and yeast.^{120–123} Moreover, the frequency of peri-implantitis in patients with a history of periodontitis has been reported to be four- to fivefold higher than that of individuals with no histology of periodontitis,¹²⁴ thereby indicating a closer tie between both types of infections. A review of the treatment used for peri-implantitis has revealed that surgical removal of the lesion followed by cleaning of the affected implant with hydrogen peroxide, chlorhexidine, citric acid, tetracycline, lasers, etc, and a systemic antibiotic therapy are effective methods.^{120,122,125–128}

Craniofacial OI implants

Given the reduced number of craniofacial implants performed annually, less data is available for scrutinizing bacterial colonization on these implants. However, clinical studies on the skin penetrating abutments in the temporal region show that infections are rare. As reported by Albrektsson et al, 96% of the cases of craniofacial implant had minimal

to no skin irritation.¹²⁹ When infections have occurred, they have often been mitigated by proper implant site hygiene. Topical applications of antibiotics have been used to control superficial infection, if present.

Percutaneous OI implants

Although over 200 percutaneous OI prostheses have been fit to European patients with limb loss,^{130–132} there have been limited published reports on infection outcomes.^{130,133–136} When an infection signal is present, these have been frequently treated with topical/systemic antibiotic treatment and cleaning of the device abutment. However, with deep infections, device removal becomes almost necessary. The clinical resolution of deep infections for these OI prosthetic systems resembles that of the two-stage treatment protocol used in TJR surgeries, where, the first-stage is the removal of the infected endoprosthetic components and insertion of temporary spacer with antibiotic treatment, followed by a second-stage operation to insert a new implant system.¹³⁰

Although Gunterberg et al reported 75% superficial and 37.5% deep infections in his earlier patient population of 16 individuals,¹³⁴ their infection rate decreased to 37% and 18%, respectively over a 3-year study period after a standardized treatment protocol was introduced in 1999.¹³³ The suspected pathogens in these cases were reported to be *S. aureus*, coagulase-negative *Staphylococcus* spp., *Enterococcus faecalis*, and *Escherichia coli*.¹³³ The reported rate was also in agreement with the UK experience of the Brånemark OI system, which had deep infection rate of approximately 18% and in some cases, required implant removal.¹³⁷ In spite of the significant improvements – such as surgical techniques, implant design, material selection, and implant exit site hygiene – infection still remains a concern with this implant system. Bragdon et al reported approximately one infection per 2 patient-years with the OPRA (Osseointegrated Prostheses for the Rehabilitation of Amputees) implant system (Integrum AB, Mölndal, Sweden).¹³⁸

A publication by Juhnke et al from Lübeck, Germany appears promising.¹³⁶ After initially having a high frequency of stomal-associated infections and revision surgery (70%), this team reduced infections to 0% in their final design iteration.¹³⁶ The researchers reported that the best infection prevention strategy is daily cleansing of the skin/implant stoma with water and a mild soap and gentle debridement of the detritus and biofilm from the interface using a shaving brush. Finally, the data from an ongoing UK clinical trial led by Dr. Blunn indicated a successful skin-to-implant integration when HA coating is used.¹³¹ A recent personal communication with this group revealed a great clinical success of this implant type in 15 transfemoral amputees. One of these

amputees has already climbed mount Kilimanjaro with his percutaneous OI device.

Conclusion

Titanium and its alloys have been used in orthopedic and dental applications for the past 200 years and have significantly improved functionality for patients. While novel surface treatments continue to be developed, the basic bone healing principles still remain pertinent for OI and skeletal attachment. The initial attachment at the bone–implant construct is a vital prerequisite for successful OI. Durable biological fixation relies heavily on implant design and sizing in order to limit micromotion. The long-term implant survivorship varies based on the anatomical location and mechanical loading conditions.

In order to achieve durable implant–bone contact, adequate implant surface characteristics (roughness, porosity, depth of pores, etc)³² must be carefully designed to achieve skeletal fixation. Excessive micromotion between the implant and host bone will not have the structural integrity needed to withstand the dynamic shear/tensile/compressive forces occurring with load-bearing during ambulation.¹³⁹ While initial implant fixation is required to prevent micromotion and fibrous encapsulation,^{5,29,59,74,79,82,140–142} the long-term success of OI implants requires firm skeletal attachment, which may take up to 3 to 9 months postoperatively in human cancellous bone.⁷⁹ Immediate full load-bearing in the postoperative period has several benefits, including a shorter hospital stay, lower hospitalization cost, and an earlier return to daily living.

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Disclosure

The authors report no conflicts of interest in this work.

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