Orthopaedic Osseointegration: State of the Art

Abstract

Osseointegration is a surgical approach that permitted the direct attachment of an external prosthesis to the skeleton in some select patients with amputation, who had failed to tolerate conventional sockets, thereby obviating related issues such as discomfort, skin breakdown, and poor fit. In this specific population, osseointegration offers the potential for enhanced biomechanical advantage and rehabilitative potential. Multiple percutaneous implant systems exist for clinical use internationally, each attempting to create a stable bone-implant interface while avoiding complications such as infection and loosening. Prospective clinical trials are now underway in the United States. This article will review the history and biology of osseointegration, indications and contraindications for use of currently available implant systems, and reported outcomes. Future directions of orthopaedic osseointegration technology, including electronic systems capable of biomimetic bidirectional volitional motor control of, and sensory/propruoceptive feedback from, external prosthetic devices, will also be discussed.

Amputation can occur secondary to multiple conditions, including trauma, malignancy, infection, and peripheral vascular disease. Positing a permanent change to a limb’s anatomy and function, amputation carries lifelong risk of physical and psychological impairments, as well as social, vocational, and recreational activity reintegration barriers. Although the leading cause of extremity amputation in the developed world is dysvascular disease, trauma and war-related injury are the principal etiologies in the developing world. In the United States, amputation has recently received increased attention because the US Military estimates that amputation represents up to 7.4% of major extremity injuries sustained during war, often affecting young, highly functioning individuals. Although modern artificial limbs have undergone substantial technological advancements, patients remain limited, often unable to return to their baseline level of activity. Conventional prostheses rely on attachment to a socket that fits over the residual limb with a compression- or suction-based fit and suspension. Use of a standard socket prosthesis is associated with a host of complications such as suboptimal fit, pain, and dermal issues, with an estimated 40% of patients suffering skin breakdown and 30% of patients experiencing pain in the residuum.

Osseointegration, first described by Per-Ingvar Brånemark in the early 1950s in a rabbit model and then in dental implants, is defined as the direct skeletal anchorage of a fixture by the formation of bony tissue around the device, without the

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growth of fibrous tissue at the bone-implant interface. Over the decades, multiple applications of osseointegrated titanium devices have evolved, including bone-anchored hearing aids, maxillofacial reconstructions, and orbital implants. In a patient with an amputation, a percutaneous osseointegrated device allows for a continuous structural connection to an external prosthesis, thus bypassing the issues associated with typical socketed design. In addition to eliminating socket-associated complications such as poor fit and skin difficulties, osseointegration carries many potential benefits for patients who tolerate their socket systems poorly, including reduced energy expenditure, improved range of motion, walking ability, and sitting comfort, as well as indirect sensory feedback through what has been termed osseoproprioception or osseoperception.

Osseointegration as a concept in advancing prosthetic limb design has been gaining traction with trials of several systems being conducted in the United States and worldwide. The article aims to provide clinicians with an overview of the current status of orthopaedic osseointegration.

Biology of Osseointegration

Successful osseointegration relies on the incorporation of a nonbiologic implant to the host bone to create a direct structural and functional connection between the musculoskeletal system and the implant, thus enabling physiologic load bearing. Similar to bone healing around other devices, osseointegration begins with activation of an osteogenic process with a tightly regulated cascade of intracellular and extracellular biologic events. Immediately following implant or fixture placement, the formation of a hematoma at the bone interface allows for clot formation at the surface of the implant. Within this clot, platelets undergo a number of changes to stimulate the production of a fibrin matrix that serves as a scaffold for osteoprogenitor cells to differentiate to osteogenic cells. The development of calcified matrix on the surface of the device gives rise to woven bone formation that subsequently transitions to lamellar bone. This peri-implant trabecular bone corresponds to early biologic fixation. The bone that is in direct contact with the implant responds to mechanical loading and undergoes morphologic remodeling and adaptation similar to the native host bone.

A variety of factors may promote or inhibit osseointegration. Implant design, including composition and surface treatments, quality of the host bone, device fit, and pharmacologic agents have all been implicated in the success and failure of osseointegration. In terms of design, the biocompatibility of the implant material is vital to successful osseointegration. Titanium has emerged as an ideal material for osseointegration because of its biocompatibility, its ability to resist corrosion, and its unique capacity for creation of a surface oxide layer, allowing for damage resistance.

Device finish also contributes to osseointegration. Roughened surfaces, which increase platelet and monocyte adhesion, favor osseointegration compared with smooth surfaces. Beyond design, early implant stability and fixation to the host bone are crucial for successful osseointegration. Excessive micro- and macro-motion at the bone-implant interface promotes the development of a fibrous membrane in lieu of the peri-implant bone, subsequently leading to aseptic loosening and eventual failure.

As percutaneous implant systems, these osseointegrated devices are subject to septic failure to a degree that might be an order of magnitude greater than that associated with conventional endoprostheses. For this reason, the interplay of relative immunosuppressed states (eg, diabetes and malignancy), iatrogenic immunosuppression (eg, chronic steroid use), and immunosenescence (eg, age-related waning of immune surveillance) with orthopaedic implants must be factored into decisions regarding patient selection and future research because these existing or potential accruing comorbidities may well foreseeably compromise the ultimate operational longevity of these transdermal procedures.

Indications and Contraindications

Patient selection is of utmost importance in osseointegration because the success of the procedure relies on a multitude of patient factors ranging from patient health status to compliance. Although inclusion criteria may vary between institutions and according to implant type, patients must have demonstrated complications with a conventional socket prosthesis; be skeletally mature, with adequate bone stock in the residual limb; be able to comply with the rehabilitation protocol; and be in good overall health. Contraindications to osseointegration largely revolve around circumstances that increase the risk for superficial and deep infection, or may otherwise inhibit bone ingrowth. Exclusion criteria include skeletal immaturity, active infection, peripheral arterial disease, diabetes mellitus, current chemotherapy or immunosuppressant drug use, active smoking status, osteoporosis, metabolic bone disease, or untreated skin disease of the residual limb.

Although all surgical programs generally adhere to the inclusion/exclusion criteria set forth above, the specific
indications and contraindications that any given center use is not always explicitly detailed in the literature. For instance, some surgeons may consider well-controlled type II diabetes to be a relative, rather than an absolute, contraindication to osseointegration. Furthermore, although guidance from the US FDA states that the “osseointegrated prosthesis for the rehabilitation of amputees (OPRA) device is indicated for patients who have transfemoral amputation due to trauma or cancer and who have rehabilitation problems with … a conventional socket prosthesis,” the system is also approved for use by patients who “cannot use … a conventional socket prosthesis.” Thus, although all of the percutaneous osseointegrated systems are primarily intended for use in patients with documented socket complications, even the FDA recognizes that patients expected to have socket complications can be considered as osseointegration candidates as part of an index procedure.

**Surgical Technique**

Although the surgical techniques for osseointegration in patients with amputation also vary according to the surgical center and implant system, there are similarities between approaches. Preoperative planning is imperative. The soft tissues of the residuum must be carefully considered in terms of integrity, quality, and morphology. The adequacy of bone stock must be confirmed with radiologic imaging. Plain radiographs can be used to judge bone length and quality; if necessary, bone density scans can assess the possibility and extent of osteoporosis. CT scans with reconstruction images can be used to determine endosteal diameter and cortical thickness.

Osseointegration surgery is often performed in a single stage, but it can be separated into two stages by a period ranging from 6 weeks to 6 months that allows for adequate skin and soft-tissue recovery as well as the development of solid osseointegration. Surgery begins with preparation of the medullary canal for implant or fixture insertion. The intramedullary component of the implant is placed into the distal aspect of the bone. Immediate stability of the fixture with respect to the endosteal surface (in the case of conventional osseointegration devices) or the distal osteotomy surface (in the case of compressive osseointegration) is needed to prevent micro-motion. During a single-stage approach, the skin interface is prepared because the device is brought through the skin and subsequently loaded according to a supervised rehabilitation schedule. For two-stage protocols, once soft tissues have healed after the initial surgery, socket use without end-bearing is sometimes allowed. The second surgery involves connection of the osseointegrated fixture to a percutaneous abutment, with careful management of the surrounding muscles, flaps, and skin-implant interface so as to create a stable soft-tissue construct that decreases the chance for infection. Graduated advancement of weight bearing with specialized external prostheses begins after wound healing.

**Current Implant Systems**

There are numerous osseointegrated implants under development for patients with amputation. The five most commonly available systems are the following: OPRA, the compress transcutaneous implant (CTI), the integral leg prosthesis (ILP), the osseointegrated prosthetic limb (OPL), and the percutaneous osseointegrated prosthesis (POP). Although all devices have the same purpose of achieving solid osseointegration and external prosthetic accommodation, design variability is considerable. Published outcomes are summarized in Table 1.

**Osseanchored Prostheses for the Rehabilitation of Amputees**

**Implant Design**

The OPRA system (Integrum AB) was first introduced in 1998 in Sweden with a femoral implant, followed by forearm and humeral devices in 2003. The OPRA componentry consists of a fixture, an externally threaded intramedullary implant that allows for osseointegration; an abutment, a percutaneous implant that is fitted into the distal aspect of the fixture and serves as an attachment for an external prosthesis; and an abutment screw that threads into the distal aspect of the abutment and functions to secure the abutment to the fixture (Figures 1 and 2). The implant is composed of commercially pure titanium. To promote osseointegration, the fixture has a surface treatment to create a nanoporous structure. The current OPRA protocol is a two-stage procedure, separated by as little as 3 months. During stage I, the implant is placed within the intramedullary canal. Local reamings or autologous bone graft from the iliac crest are used to augment the distal bone to provide a smooth surface. During stage II, a thin cutaneous flap is fashioned over the bone grafted portion of the bone, after which the transdermal abutment is attached to the underlying fixture.

**Outcomes**

In an initial prospective study of 18 patients undergoing transfemoral osseointegration, Hagberg et al found statistically notable improvements in patient-reported outcome studies, including a validated score specific to this population, the
Questionnaire for persons with a transfemoral amputation (Q-TFA)\(^{30}\) (Table 1). In 2009, Hagberg et al presented the results of 100 patients treated with a transfemoral OPRA implant from 1990 to 2008 with an average follow-up of 5 years (range, 0.25 to 15.5 years) following the second-stage surgery.\(^{23}\) Sixty-eight patients were continuing to use their original OPRA, with 11 patients having had the implant removed.\(^{23}\) Most failures occurred early in the lifetime of the implant and the authors attributed this outcome to lack of a standardized surgical and rehabilitative protocol at that time.

Brånemark et al have published 2- and 5-year minimum follow-ups of a prospective cohort of 51 patients with a transfemoral OPRA system.\(^{22,31}\) The cumulative survival of the OPRA implant remained 92%, but the revision-free survival rate was just 45%. Both superficial and deep infections were noted to be progressively increasing complications, affecting two-thirds and more than 20% of patients, respectively. Of equal concern, the most recent experience reports a mechanical failure rate affecting more than one-third of patients. Similar to the series published by Hagberg et al in 2008, there was notable improvement in

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<th>Table 1</th>
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<td>Agarwal (2018)(^{41})</td>
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ILP = integral leg prosthesis, NR = not reported, OPL = osseointegrated prosthetic limb, OPRA = osseoeanchored prosthesis for the rehabilitation of amputees, POP = percutaneous osseointegrated prosthesis, Q-TFA = Questionnaire for persons with a transfemoral amputation, TUG = timed up and go, 6MWT = six-minute walk test
patient-reported outcomes, as measured by the Short Form-36 and Q-TFA scores.

In a 2017 study, Tillander et al detailed the risk of osteomyelitis in 96 transfemoral patients who had undergone implantation of the OPRA device. At an average follow-up of 7.9 years (range, 1.5 to 19.6 years), 16 patients (16.7%) developed osteomyelitis, with 10 patients (10.4%) requiring removal of the implant for eradication of the infection. The median time from implantation to diagnosis of osteomyelitis was 2.6 years (range, 0.3 to 13.8 years), with Staphylococcus aureus as the leading cause.

Tsikandylakis et al published on the outcomes of 18 transhumeral amputees who underwent osseointegration with the OPRA device. At the 2- and 5-year follow-up (range, 2 to 19 years), implant survival rates were 83% and 80%, respectively. Two patients experienced septic loosening (11.1%) that required two-stage revision surgery, with one of these patients experiencing recurrent loosening that required explantation. No episodes of late loosening were observed. There was a total of 15 superficial infections (83.3%) that were managed conservatively. Eight patients experienced an incomplete fracture at the distal aspect of the residuum (44.4%); six of these were treated without intervention, one required modified physical therapy, and one required autologous bone transplantation.

**Current Status**
The transfemoral OPRA system has achieved approval by the FDA through a Humanitarian Device Exemption pathway. The FDA has allowed use of the transhumeral OPRA device as part of an Investigational Device Exemption (IDE) study. Institutional Review Board-approved clinical trials for both upper and lower extremity implants are underway at the Walter Reed National Military Medical Center and the University of California, San Francisco.

**Compress Transcutaneous Implant**

**Implant Design**
The CTI system (Zimmer Biomet), is a modification of the Compress endoprosthetic device originally designed for limb salvage procedures. Compress technology was first used clinically in 1993, and the first transcutaneous osseointegration procedure was performed in 2012. The device is composed of an intramedullary anchor plug fixed with transverse pins that is joined to a preloaded compression device at the distal aspect of the residual limb to promote osseointegration through the use of high compressive loads. The modular transdermal Compress device can be implanted in a single- or two-stage procedure.

**Outcomes**
A single 2017 report detailed 11 (10 transfemoral, 1 transhumeral) patients having undergone osseointegration surgery with a CTI from 2012 to 2017. Five patients underwent a two-stage procedure, 12 to 18 weeks apart. The remaining six patients were treated with a single-stage surgery. Although no follow-up time frame was indicated, there have been no reported infections in this cohort. One subject required a soft-tissue revision due to local irritation from excessive soft tissue along the transcutaneous post. Two patients experienced periprosthetic fractures after falls. Both required revision. There have been no reported episodes of loosening or mechanical complications. No patient-reported outcomes have been published.

**Current Status**
The CTI system is not yet available, although a multi-center FDA IDE trial is being planned. Devices for

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**Figure 1**
AP femoral radiograph demonstrating percutaneous placement of the OPRA implant.

**Figure 2**
Clinical photograph showing the OPRA percutaneous abutment to which the external prosthesis attaches.
the femur and humerus are being used under compassionate use (custom device) designations (Figures 3 and 4).

**Integral Leg Prosthesis**

**Implant Design**

The ILP (OrthoDynamics GmbH) was introduced in 1999 in Germany (earlier designs being termed the Endo-Exo prosthesis), with programs starting in the Netherlands and Australia in 2009 and 2010, respectively. The ILP was initially designed for transfemoral amputees; however, tibial and humeral applications have been described. The ILP is composed of two major components; an intramedullary endomodule and a transcutaneous bridging connector that are mated with a dual cone adaptor and a screw. The endomodule contains a macroporous surface coating to facilitate osseointegration and relies on a press fit into the residual bone. The endomodule contains a slight bow to provide rotational stability. The implant is composed of cobalt-chrome-molybdenum. More recent designs have replaced the roughened porous surface at the stomal interface with a smooth one in an attempt to address the high rates of soft-tissue irritation. The distal aspect of the bridging connector attaches to the artificial limb.

**Outcomes**

Four publications of three iterations of the ILP report on as many as 86 patients, with less than 3-year average follow-up (Table 1). The combined aseptic and septic failure rate was on the order of 10% or less. Similar to other implant systems, superficial infections were found to be very common, affecting up to three-fourths of patients.

**Current Status**

The ILP has not been approved by the FDA for implantation in the United States. The device is being used in Germany and the Netherlands.

**Osseointegrated Prosthetic Limb**

**Implant Design**

The OPL (OrthoDynamics) was first introduced in Australia in 2013, followed by the Netherlands in 2015. The system is used for persons with transfemoral, transtibial, and transhumeral amputations. It is composed of an intramedullary device that is secured to a dual-cone transcutaneous implant with a locking screw. The OPL is composed of Ti6A14V with a plasma-sprayed surface coating on the intramedullary implant to promote osseointegration. The OPL exists in two forms for distal femoral applications, type A and type B. The type A OPL has an extramedullary implant distally, whereas the type B OPL has an intramedullary implant distally.

**Outcomes**

In the most recently reported OPL experience, Al Muderis et al describe a prospective cohort of 22 transfemoral single-stage procedure patients who received an OPL osseointegrated prosthesis (Table 1). At 1-year average follow-up, the implant failure rate was acceptably low, but more than half of patients experienced a superficial infection. Favorable outcomes were noted using both patient-reported and functional (walking speed and timed up and go [TUG] tests) metrics.

The OPL is also being used in transtibial amputees. Robin et al reported on the prospective outcomes at 12 months of five patients with dysvascularity who underwent transtibial osseointegration with the OPL system. All patients in this study were able to ambulate unassisted. There was a notable improvement in functional outcomes from baseline to one year, including improvement in the TUG and the
six-minute walk test. In addition, there was a notable improvement in outcomes as measured by the Q-TFA. No episodes of loosening were reported. Two patients sustained superficial infection that resolved with conservative management.

Current Status
The OPL has not been approved by the FDA for use in the United States. It is being used in Australia and the Netherlands.

Percutaneous Osseointegrated Prosthesis

Implant Design
The (POP) system (DJO Global) was designed for transfemoral applications at the University of Utah and is currently being evaluated as part of an FDA Early Feasibility Study that began in 2016. The prosthesis is composed of an intramedullary bone implant region mated to a subcutaneous collar to which the percutaneous post attaches. The intramedullary portion of the prosthesis contains a ribbed region proximally and a porous coated region distally to aid in osseointegration. The subcutaneous collar uses a porous coating as well. The external prosthesis attaches to the percutaneous post using a titanium adapter.

Outcomes
The 1-year average follow-up of 10 transfemoral POP patients has been reported in abstract form only (Table 1). Two patients required device removal (20%); one for early loosening at 5 weeks and one for a periprosthetic fracture due to trauma at 7 months. Compared with reports of other osseointegrated implant systems, these early aseptic failure and fracture rates, at 10% each, are of concern.

Current Status
Accrual for the POP Early Feasibility Study is currently closed. An IDE trial is being considered.

Future Directions
On the technical side of existing osseointegration systems, optimization of implant properties down to the nano level (eg, metallurgic composition, surface texturing) will remain an important focus of research efforts to enhance bone ingrowth and minimize aseptic loosening. From a macro mechanical point of view, all implant systems would benefit from the development of a truly fail-safe decoupling mechanism to obviate periprosthetic spiral fracture risk.

Although not the exclusive focus of this article, increasing attention will be devoted to neuromuscular integration that enables volitional motor control of, and proprioceptive and sensory feedback from, the artificial limb, especially in the upper extremity. The enhanced OPRA (e-OPRA) system allows for bidirectional communication between implanted neuromuscular electrodes and the external prosthesis through a system known as the e-OPRA implant is the subject of an FDA IDE study at the Brigham and Women’s Hospital and the Massachusetts Institute of Technology.

Other biologic control strategies that hold promise are the regenerative peripheral nerve interface and the dermal sensory interface in which a divided peripheral nerve reinnervates a free muscle or skin graft, respectively. Such constructs allow electrodes to transmit functionally selective, high amplitude motor control signals from the brain, and sensory signals to the central nervous system. A transhumeral e-OPRA FDA IDE study using regenerative peripheral nerve interfaces is planned at the University of California, San Francisco, and the University of Michigan.

Although still in its early stages of development, neuromuscular integration coupled with osseointegration will allow more natural prosthetic function and improved outcomes.
A Word of Caution

When compared with other durable orthopaedic implant systems such as arthroplasty implants, transfemoral implants are in their infancy. Few besides the OPRA implant system have a proven track record beyond 10 years. Because of this, it is critical that each system be evaluated rigorously, within the context of observational clinical trials. Doing so requires participation from a variety of specialists including orthopaedic surgeons, reconstructive surgeons, rehabilitation physicians, mental health practitioners, infectious disease specialists, prosthetists, therapists, and research support staff. Because of the infrastructure needed, clinical trials involving osseointegration implants are offered in relatively few centers across the United States, although custom devices involving unique designs have been used elsewhere under compassionate use protocols.

The number of unique implant designs coupled with a paucity of long-term outcomes, necessitates the creation of an osseointegration quality registry. Doing so will track implant-related complications such as aseptic and septic loosening, stress shielding, and revision procedures. Outcomes, especially early failures, can be identified by comparing implant systems similar to what is currently done with existing population-based arthroplasty registries. Patient-reported outcomes and functional status, which help justify the risks of transdermal implantation, must also be collected.

Summary

Osseointegration is an appropriate surgical alternative for a select group of amputees who are unable to tolerate a conventional socket prosthesis. It represents a promising treatment option for carefully selected patients, which may become the standard of care in the relatively near future. The benefits of osseointegration from improved functional outcomes, quality of life, and increased prosthesis utilization have been outlined by a number of studies. However, a number of unique designs are being used, and the technique of transdermal implantation remains in its early stages, warranting postmarketing surveillance within a centralized registry. Superficial infection remains the most common complication across all prosthesis types; nonetheless, most instances can be successfully managed with conservative treatment. The future of osseointegration is encouraging because modern technology will allow for seamless neuromuscular integration for a more natural functioning prosthesis, in hopes of allowing patients with amputation to achieve a higher level of function.

References

References printed in bold type are those published within the past 5 years.


