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# Osseointegration for Amputees: Past, Present and Future: Basic Science, Innovations in Surgical Technique, Implant Design and Rehabilitation Strategies

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# OSSEOINTEGRATION FOR AMPUTEES: PAST, PRESENT AND FUTURE

## Basic Science, Innovations in Surgical Technique, Implant Design and Rehabilitation Strategies

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## ABSTRACT

Loss of a leg or arm is a tremendous disability. Immediate and obvious impairments are decreased mobility or diminished functional capacity. Not quite as obvious are the difficulties associated with activities of daily living, quality of life impairments, sometimes loss of independence or employment, and the mental health issues which often accompany limb loss. The interface between native tissue and the prosthetic limb presents the greatest challenge to amputee rehabilitation. Computer-controlled robotic limbs have been widely available since the 1990s. However, the weight of prosthetic limbs, coupled with the difficulty of where to locate the components, requires substantial loads to be transferred through the human-implant interface. This interface has always been a skin-squeezing mechanism which results in repetitive soft-tissue loading and trauma, in both compression and shear, which inevitably causes multiple problems (pain, skin breakdown and infection, hyperhidrosis, allergic reaction to the material) leading to periodic or prolonged prosthesis disuse. So unfortunately, despite all the effort and expense invested in the prosthetic limb itself, patients often were unable to benefit.

Percutaneous EndoProsthetic Osseointegration for Limbs (PEPOL) is a revolutionary technique that involves anchoring a metal implant directly to a patient's skeleton, then permanently passed through the patient's skin, and attached to a prosthetic limb. By doing this, the weight of the prosthesis is borne by the patient's skeleton and is directly powered by muscles, leading to a lighter and more native experience. The skin is no longer compressed and traumatised, eliminating the aforementioned issues. Since learning about this technology in the mid-2000s and performing my first independent procedure in 2009, I have investigated and pioneered the world's leading surgical techniques and rehabilitative methods for PEPOL. Treating nearly 1000 amputees via the Osseointegration Group of Australia and the MQ Health Limb Reconstruction Centre at Macquarie University has allowed research to be performed on this technology, documented, and discussed in the

Body of Work. Patients almost always improve their objective and assessed mobility performance (Overall 38.6% distance improvement on the 6MWT), they wear their prosthetic limb more (Overall 38.1% increase in the Q-TFA Prosthetic Use Score), and they are subjectively more satisfied with their condition as an amputee (Overall 41.1% increase in the Q-TFA Global Score) . While these benefits are consistent, my research has also identified the fortunately limited problems with infection and soft tissue management (29% of all patients required re-operations due to direct or indirect complications). PEPOL clearly provides excellent improvement for the vast majority of patients, and the continued investigation of this technology should lead to even greater improvements in progressing from what is already successful, make it more readily available, and ameliorate its existing challenges.

**ACKNOWLEDGMENTS**

Those who deserve the greatest recognition are the patients who were brave enough to consider surgery that, at the time, seemed adventurous and far outside the familiar path. They placed their livelihoods, their lives, and their futures in the care of myself and my clinical team. It has been through them that the Osseointegration Group of Australia and the MQ Health Limb Reconstruction Centre at Macquarie University has become not only a reality but truly the world leader in limb osseointegration.

I would like to thank Professor George Mendz and Dr Kevin Tetsworth under whose supervision I embarked on this Degree. Thank you for supporting me in this world of medical research. Your guidance and encouragement from the initial to the final level enabled me to develop the confidence to complete this thesis.

Only a step behind in recognition are all the people on my medical and surgical support team. Although I am the lead surgeon, full patient care neither begins nor ends with a surgery. From patient registration through preoperative evaluation through postoperative rehabilitation and long-term follow-up, the dozens of office staff, research assistants, practice managers, registrars and fellows, and consulting physicians and associate surgeons have helped immeasurably.

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### Introduction

Humans have innovated replacements for amputated body parts for centuries. The oldest currently known prosthesis is a great toe found on an Egyptian mummy in a Thebes-West necropolis, dated to 1550-700 BC (Figure 1)1. While this toe likely was of relatively low functional demand, Roman general Marcus Sergius led charges in multiple campaigns using an iron right hand and shield prosthesis during the Second Punic War (218-201 BC)2. Detailed prosthetic drawings by Ambroise Paré3 reveal that fundamental interface designs have not substantially changed since the 1500s: a replacement body part is attached to the remaining limb by compressing and adhering to the skin and being suspended from the soft tissues (Figure 2)4. Despite possibly romanticized notions of prosthesis performance in history, today's prosthesis users know many serious challenges significantly diminish their quality of life with traditional skin-suspended solutions. Challenges related to prosthetics can be briefly summarized to include the following: dermatologic problems causing intermittent prosthesis disuse in at least 15-41% of patients[5]; on average, nine prosthetist clinical service visits are needed annually[6]; a new socket is required at least every other year[7–9]; one in three patients may not regain employment[10]; and an estimated 25% of these patients struggle to walk 500 metres[11].

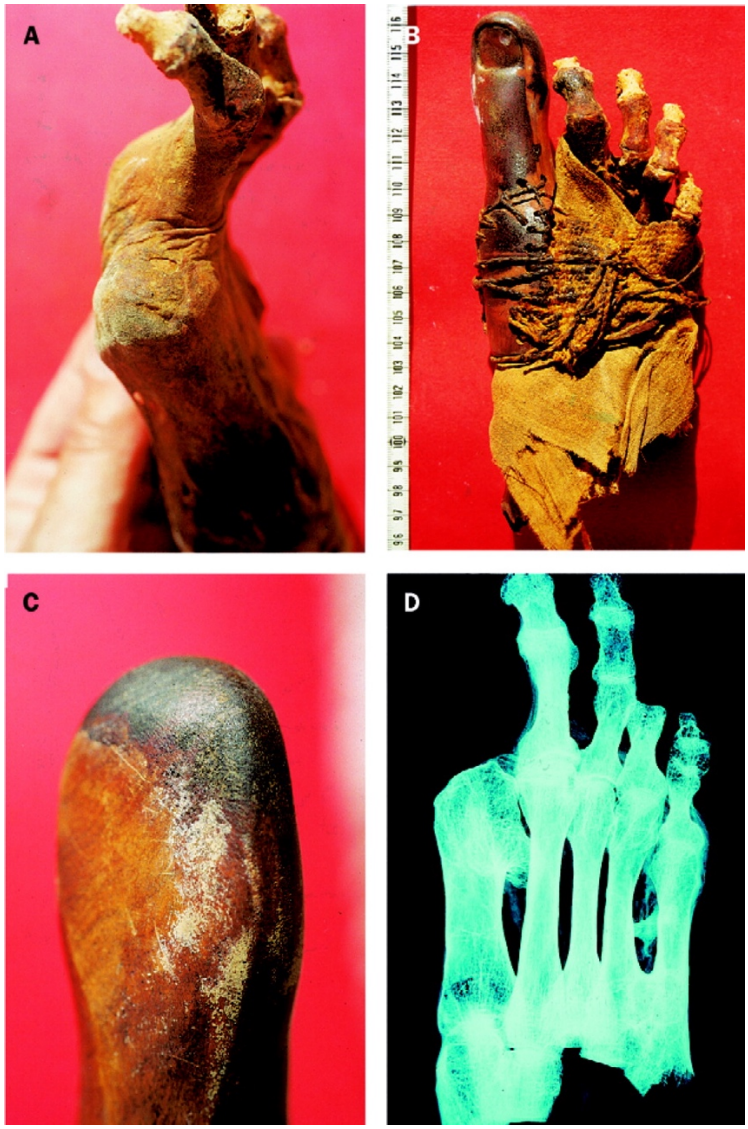


Figure 1. Oldest known prosthesis.
Right great toe found on mummy from Thebes-West. A) side view of the preserved foot shows the great toe was amputated while the patient was alive, as skin (now preserved) had healed over the amputation. B) A wooden prosthesis is strapped to the forefoot by a fabric lace. C) Plantar surface of prosthesis shows abrasion, indicating use while alive. D) Radiograph showing healing bone response of the first metatarsal indicating long term survival of the patient following amputation. Reproduced with permission from Nerlich AG, Zink A, Szeimies U, Hagedorn HG. Ancient Egyptian prosthesis of the big toe. The Lancet. 2000 Dec 23;356(9248):2176-9.

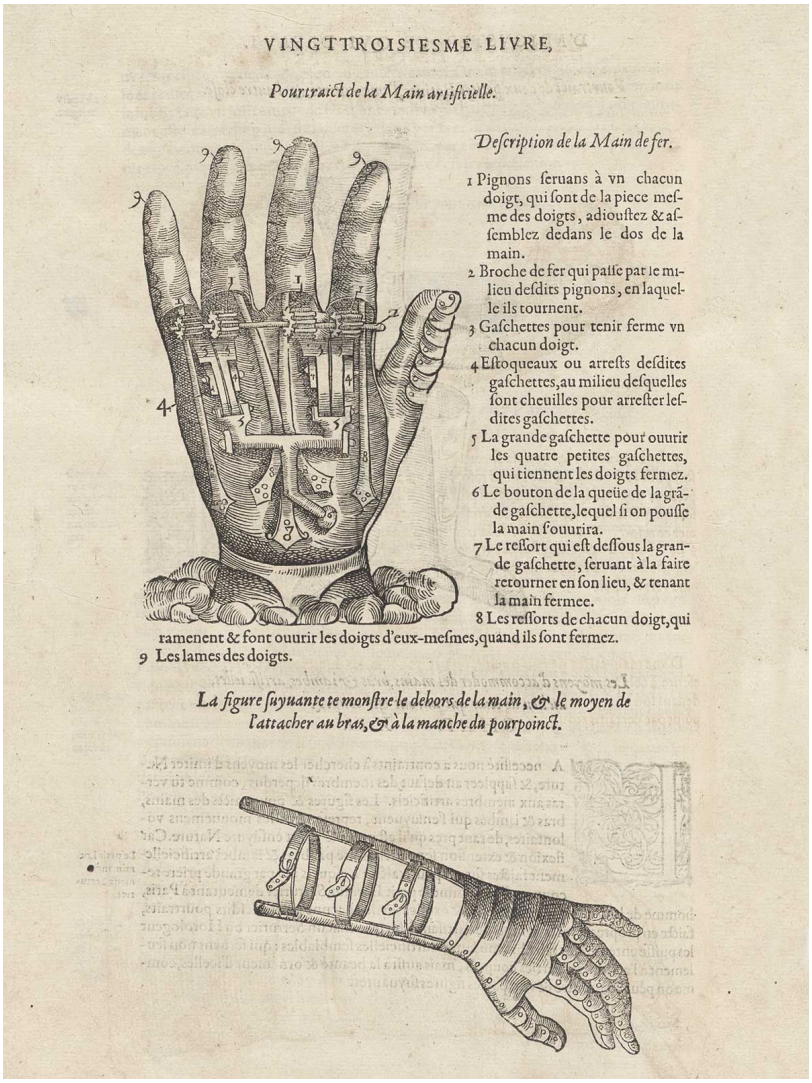


Figure 2. Two drawings from barber/surgeon Ambroise Paré.
The top drawing of the "iron hand" shows mechanisms to move the fingers. The bottom drawing shows buckle straps are used to suspend the hand by squeezing the residual forearm skin. Reproduced with permission courtesy of the National Library of Medicine. Paré, Ambroise. [Les Oeuvres]. page 916. A Paris: Chez Gabriel Buon, 1585. https://www.nlm.nih.gov/exhibition/historicalanatomies/Images/1200_pixels/ixcxvi.jpg accessed 7 Feb 2020.

In 1990, a critical technical achievement occurred. The first long-term durable bone-anchored prosthesis was successfully implanted into a femoral amputee. This proof-of-concept allowed fundamental changes in human-prosthesis interfacing to occur which led to a paradigm shift in rehabilitation care for amputees. First, having a bone-metal-prosthesis linkage permitted nearly lossless energy transfer from person to prosthesis. Second, the skin of a person's extremity was no longer subject to constant pathologic compression. These key principles facilitated prosthesis designs which routinely result in better quality of life for most amputees[12]. The following

sections present a concise history of PEPOL, how it is both similar to and different from its slightly older cousin dental osseointegration (DOI) and discuss the currently relevant PEPOL implants.

## History

The term “osseointegration” is defined as the phenomenon of bone growing directly onto and attaching to the surface of a material without an intermediate layer such as fibrous tissue. This process was formally recognized by Dr. Per-Ingvar Brånemark. As early as 1952[13], while performing studies investigating blood circulation, his team serendipitously discovered that titanium implants screwed into rabbit bone bonded tightly and without a fibrous tissue layer[14]. Titanium was a material of recent medical interest, with other researchers identifying there was no inflammatory response elicited from dog muscle just a few years earlier[15]. By 1965, following a series of experiments on dogs[13], Dr. Brånemark became the first to use titanium as a long term implant into human bone, specifically dental implants (Figure 3)[16,17], and by 1977 formally documented the term “osseointegration[18,19].” The impact of DOI is unquestionable: a PubMed search for “Brånemark” produces hundreds of articles describing dental implants and the Brånemark System is a registered commercial dental implant[20]. Per-Ingvar’s son, Rickard Brånemark, performed the first long-term successful PEPOL on 15 May 1990[21] for a 25-year-old woman who had lost both her legs 10 years prior due to a tram accident. The following year she had the other leg treated in the same manner (Figure 4). This progression of PEPOL from DOI was important, because even though DOI had been successful for almost thirty years, other surgeons had tried and failed with PEPOL.

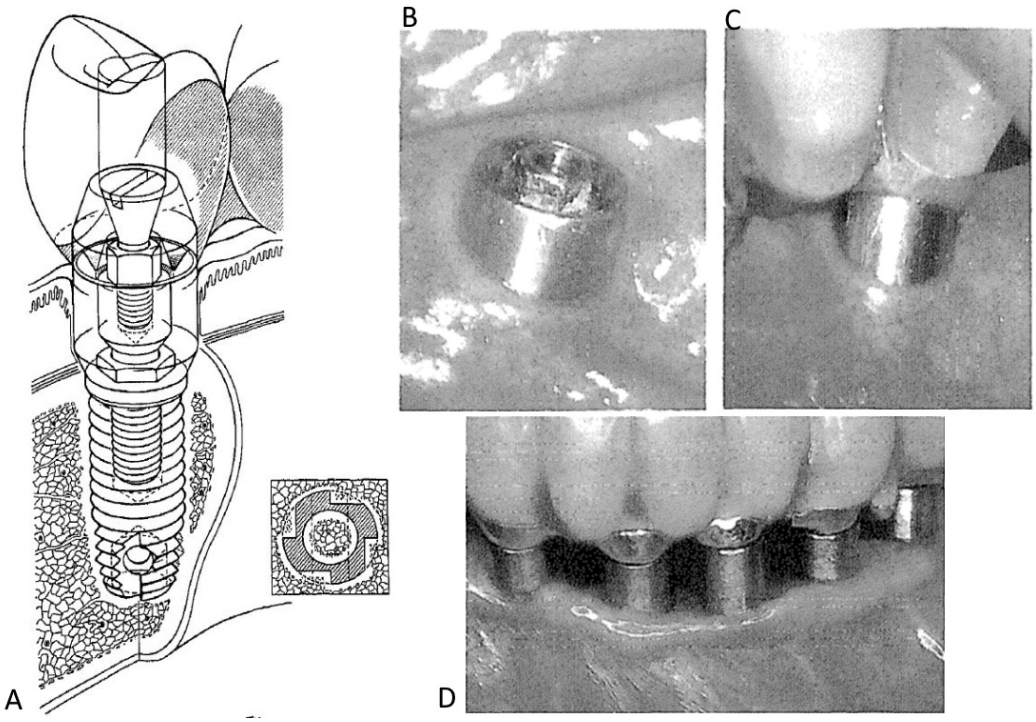


Figure 3. Brånemark style dental osseointegration.
A) Schematic showing titanium implant with a screw fixation design. There are three components of this style of implant: 1, titanium post that achieves osseointegration with the jaw; 2, abutment which screws into the post and remains smooth and motionless at the gingiva; and 3, the crown which is designed to match the patient's tooth. B) The design is modular with the post separate from the crown. C and D) Single and multiple crown prostheses attached to an osseointegrated post. Figures adapted with permission from Adell R, Lekholm U, Rockler BR, Brånemark PI. A 15-year study of osseointegrated implants in the treatment of the edentulous jaw. International journal of oral surgery. 1981 Jan 1;10(6):387-416.

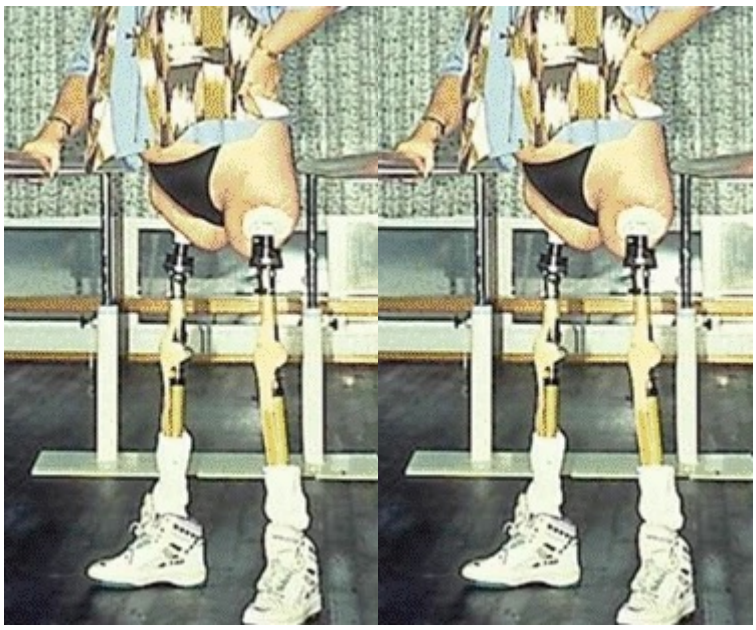

Figure 4. Photograph of the first patient with long term successful osseointegration.
Figure adapted with permission from Li Y, Brånemark R. Osseointegrated prostheses for rehabilitation following amputation. Der Unfallchirurg. 2017 Apr 1;120(4):285-92.

The first documented repetitively successful implementation of a transcutaneous orthopedic device may have been Joseph-François Malgaigne's double sided hook. Designed in 1840, the construct featured a double hook design at each end which penetrated the patient's skin and clamped the superior and inferior poles of the patella, providing compression forces to reduce a fracture (Figure 5). Soon after, he also innovated on an early type of external fixation device[22,23] though more recognizable external fixation instrumentation was described by Codivilla and Steinmann between 1903 and 1910[24–28]. One specific insight Malgaigne had was particularly ahead of his time: redness, necrosis, and other signs of inflammation did not occur so long as the hooks did not slip and skin motion was eliminated.

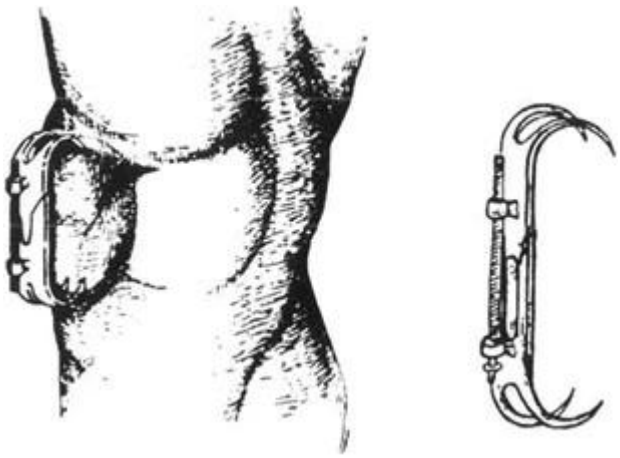

Figure 5. Double sided metal clamp designed by Joseph-François Malgaigne in 1840. This is the first documented repetitively successful transcutaneous orthopaedic device.

The history of early osseointegration can be pieced together thanks to Hulbert *et al*[29] and Murphy[30] in the 1970s, with recent developments being outlined by Webster *et al*[31]. The first documented skeletally linked transcutaneous prosthetic attempts were likely the pilot studies performed by Dr. Elliott Culter and Dr. James Blodgett as early as 1942 at Harvard University sponsored by the United States Office of Scientific Research and Development. Those surgeons tested stainless steel and Vitallium screws inserted into the intramedullary canal of 18 dogs (Figure 6). Vitallium retained stability better and the researchers determined that the implant must remain motionless relative to the bone to prevent loosening. Along with Dr. Tait

Chisholm, they also implanted a Vitallium screw-style anchored tooth in a dog[30,32]. By 1949, the United States Veterans Administration felt the surgical challenges for success in humans were too great and suspended further investigation.

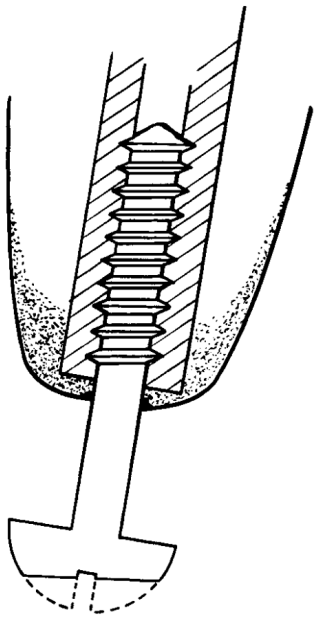

Figure 6 Schematic of osseointegration implant used experimentally in dogs.
This was by Dr. Elliott Culter and Dr. James Blodgett in the 1940s.
The retention is achieved by a screw design. The dotted lines identify the portion of the implant that had worn away with prolonged use. Reproduced with permission from Murphy EF. History and philosophy of attachment of prostheses to the musculo-skeletal system and of passage through the skin with inert materials. Journal of biomedical materials research. 1973 May;7(3):275-95.

The first attempt to replace an amputated limb with a skeletally anchored prosthesis in a human appears to have been Dr. G. Dümmer in 1946[30]. He treated four transtibial amputees with a stainless steel intramedullary implant which featured a cross-screw for maintaining position (Figure 7). These implants were removed after an unspecified but apparently short period of time, possibly due to infection, and perhaps even before obvious signs of failure presented. During 1956-1969, with renewed interest from the United States Veterans Administration (VA), Dr. John Esslinger began a series of experiments with dogs and a monkey aimed at evaluating how to overcome two challenges: 1) a stable and healthy skin-implant interface, and 2) a reliable, stable integration of implant to skeleton. He experimented with stainless steel, titanium, Teflon, and rubber implants, preferring a two-stage technique. The first stage was to insert an implant and then close the

wound to allow the bone to integrate with the implant, followed by a second procedure to insert a transcutaneous connector to attach a prosthesis. He found that a Teflon intramedullary implant with a mushroom shaped cap over the distal bone end prevented bone overgrowth and seemed the most successful over several years. However, all options eventually failed and had to be removed. His report was more observational than mechanistically driven and did not feature histologic descriptions, tables of results, or any figures demonstrating these novel techniques[33].

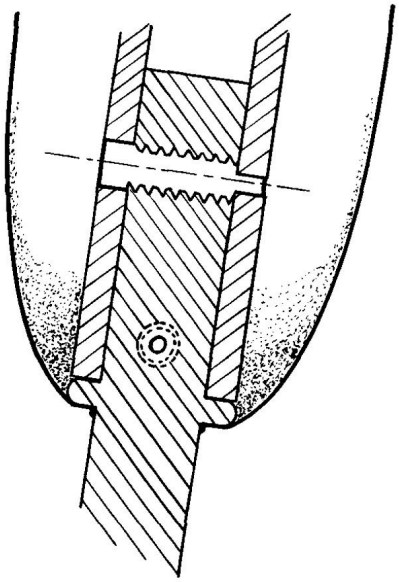

Figure 7 Schematic of first skeletally implanted transcutaneous prosthetic anchor documented to be used in a human, designed by Dr. G. Dümmer in 1946.
The retention mechanism was the two cross-pins through the bone and implant. Reproduced with permission from Murphy EF. History and philosophy of attachment of prostheses to the musculo-skeletal system and of passage through the skin with inert materials. Journal of biomedical materials research. 1973 May;7(3):275-95.

In 1967, Dr. Charles William Hall and his team, also working with the VA, described using stainless steel intramedullary implants in dogs and even connected the remnant muscles of the amputated limbs to articulating distal joints with artificial tendons (Figure 8)[34,35]. Feeling optimistic, in 1974 they wrote “a permanently attached artificial limb is an achievable dream within the foreseeable future. The problems remaining to be solved are the interfaces which need to be maintained between the prosthetic device and bone, and between the prosthesis and the skin

through which it protrudes[36]." In 1967 Dr. Vert Mooney, working at the rehabilitation center Rancho Los Amigos, tried using a porous ceramic in a patient's humerus which became loose and infected by around 8 months (Figure 9)[37]. One issue identified was the deeper the grooves of the implant, the longer the intraosseous vascular channels had to be to metabolically support the interdigitating bone. Recognizing the success of using polymethylmethacrylate (PMMA, bone cement) for total hip replacements[38], Dr. Mooney attempted cementing an implant into three patients. These uniformly also became loose and required removal within a year (Figure 10)[39]. Titanium was considered a good candidate because it formed a stable protective oxide, was reasonably closer modulus of elasticity to bone, had the mechanical working advantages of metal, and developed bonding to bone without inciting an inflammatory response either in bone or soft tissue[15,40]. Rapid and excellent integration was proven by inserting titanium blocks with sintered threads in rabbits and dogs: no foreign body reactions occurred, and maximum pull-out strength was achieved by 2 weeks[41].

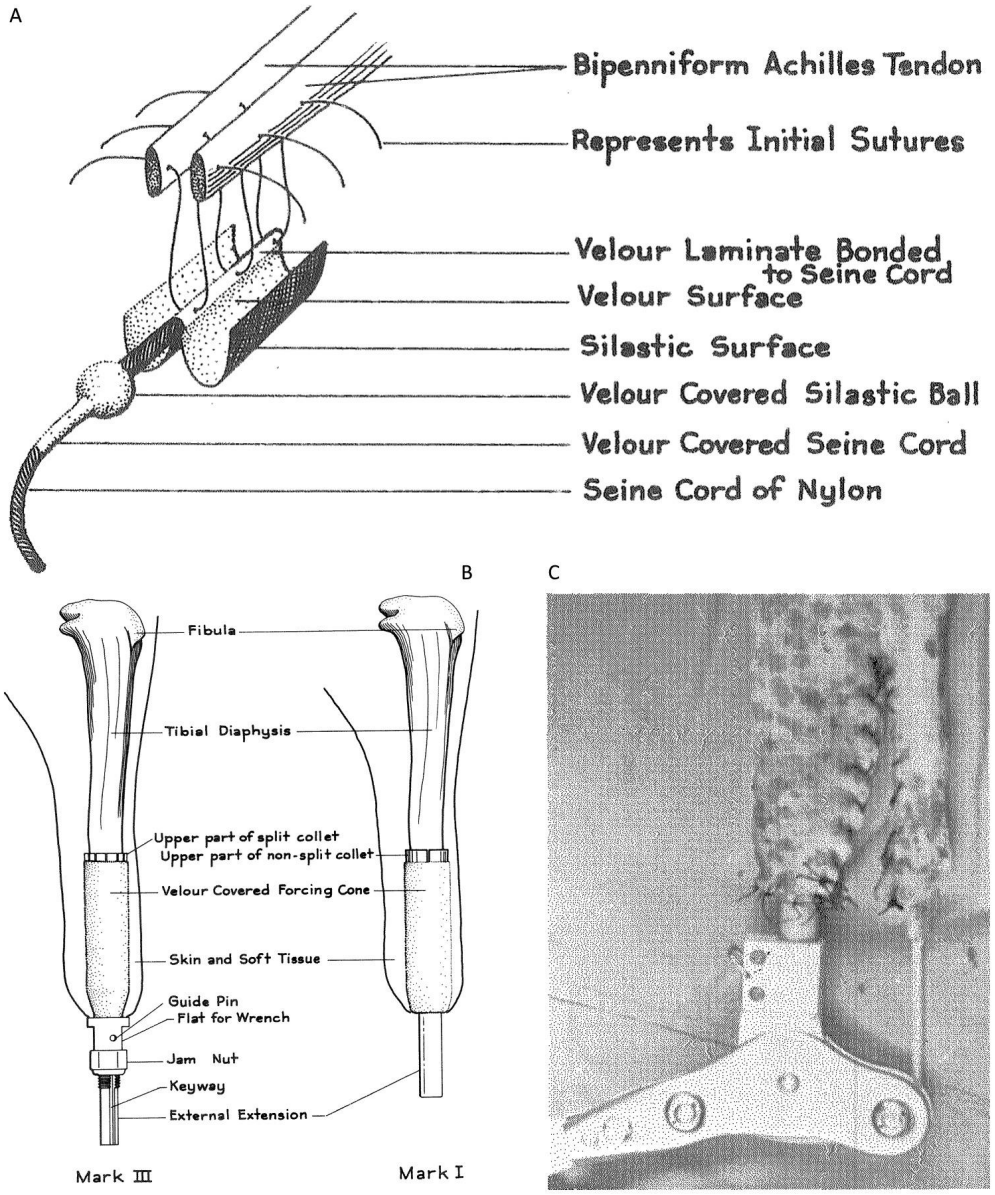


Figure 8. Osseointegration implant experimental devices used by Dr. Charles W. Hall in the 1960s. A) Some designs aimed to allow remnant muscle to power external prosthetic joints by sewing an artificial tendon to the muscle and passing it through the skin and attaching it in a way that mimicked native attachment locations. B) Schematic of early bone anchored prosthesis designs. The material was stainless-steel. A unique feature is the implant clamped onto the external surface of the bone rather than fitting into the intramedullary canal, as Dr. Hall's group believed the vascular supply would be better. Reproduced with permission from Hall CW, Cox PA, Mallow WA. Skeletal extension development: criteria for future designs. Bull Prosthet Res. 1976 Spring;(10-25):69-96.

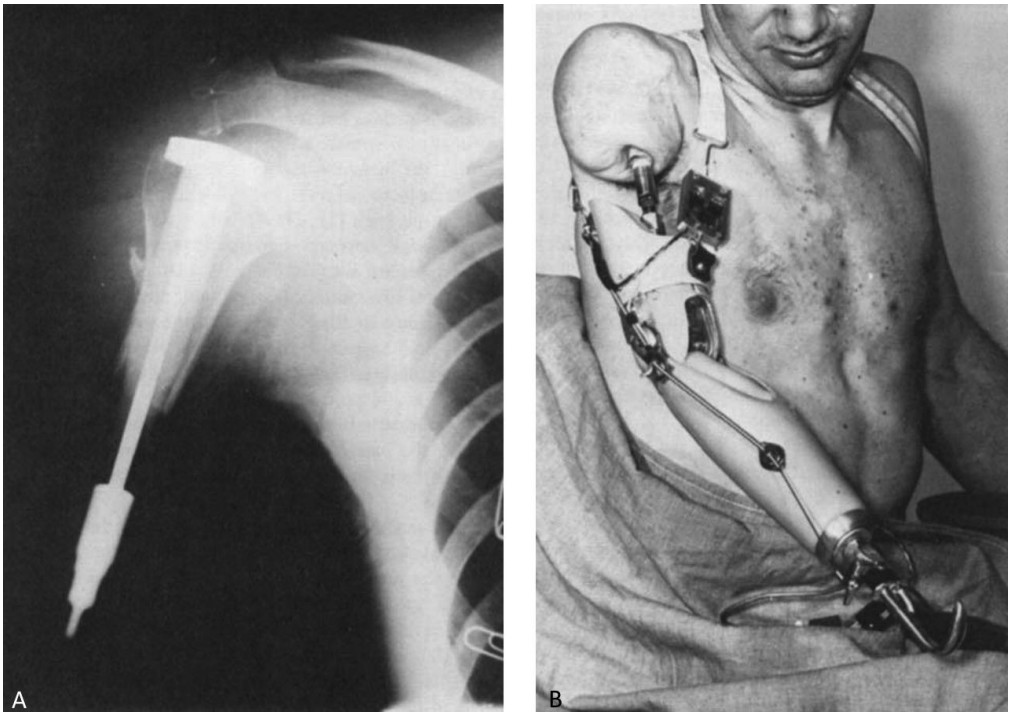


Figure 9. Cerosium implant used by Dr. Vert Mooney in 1967.
A) Radiograph and B) clinical photo of patient with a right humerus implant. Figures adapted with permission from Mooney V, Predecki PK, Renning J, Gray J. Skeletal extension of limb prosthetic attachments–Problems in tissue reaction. Journal of Biomedical Materials Research. 1971 Nov;5(6):143-59.

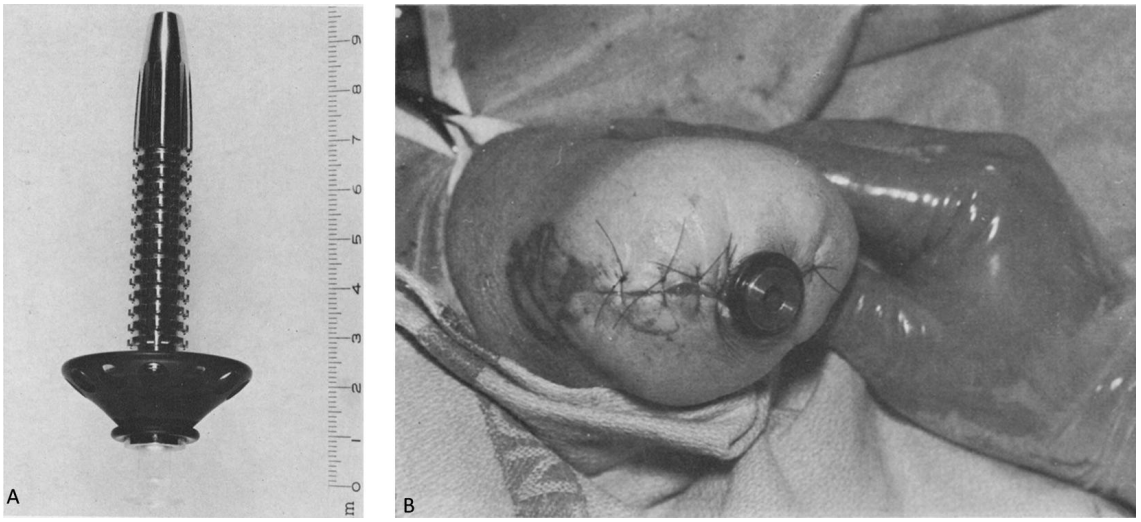


Figure 10. Early attempts of cementing a stainless-steel implant.
A) Stainless-steel implant B) cemented into trans-humeral amputees in the 1970s using a cement retention strategy. Adapted with permission from Mooney, V., Schwartz, S.A., Roth, A.M. et al. Ann Biomed Eng (1977) 5: 34.

Despite DOI being increasingly used with consistent success and the routine integration of bone into enclosed titanium implants, Dr. Hall lamented “years of experimental frustration have led investigators to accept the fact that penetration of

the skin at the end of the amputated stump will always fail because prevalent biaxial stresses tend to enlarge the exit site and tear the interfacial bond[42].” This was written in 1985, in what appears to be his final article and culmination of his two decades of work dedicated to this endeavour[43]. The final material they reported using was a titanium alloy (Ti6Al4Va). This is essentially the same as is used in current implants, and identical to the implant used by Dr. Richard Brånemark just five years later which resulted in more than twenty years of patient mobility. It appears that in their focus to establish a tight skin seal, Dr. Hall’s team as well as most others before them had experimented with various polymers and fabrics attempting to get the skin to stabilize around, grow into, or otherwise form an impermeable seal and completely prevent bacterial invasion. Based on contemporary experience, perhaps such a seal is not mandatory, or may even be a hindrance, to achieving excellent clinical results.

## Implants and Devices

There are three design paradigms for currently relevant osseointegration implants: a threaded screw, a spring-loaded platform inducing constant compression, and a press-fit intramedullary stem. We describe the key design and surgical features of each below and provide a summary in Table 1.

Table 1. Comparison of Osseointegration Implant Systems

| | OPRA | ILP | OPL | Compress |
|---|---|---|---|---|
| Material | Titanium | Cobalt chrome molybdenum | Titanium | Titanium |
| Retention | Threaded | Press fit | Press fit | Cross pin |
| Anatomic suitability | Long bones, digits | Long bones | Long bones, pelvis | Humerus, femur |
| | | | | |
| Bone-Implant Interface | Laser etch | Czech hedgehog 1.5 mm | Plasma spray up to 0.5 mm | Porous coat, axial compression |
| Skin-Implant Interface | Polished | Polished | Polished | Polished |
| | | | | |

| | | | | |
|---|---|---|---|---|
| Surgical Stages | 2 | 1 | 1 | 1 |
| Months from Implantation to Full Weight Bearing | 3-18 | 2-3 | 2-3 | unspecified |

OPRA = Osseointegrated Prostheses for the Rehabilitation of Amputees
ILP = Integral Leg Prosthesis
OPL = Osseointegrated Prosthetic Limb

*Threaded Screw Implant*

Dr. Rickard Brånemark has used this design (Figure 11) since operating on his first patient in 1990. It is based upon his father's DOI design and was under specific investigation since at least 1983[13]. The marketed name is the Osseointegrated Prostheses for the Rehabilitation of Amputees (OPRA) (Integrum AB, Mölndal, Sweden). In 2011 laser etching surface finishing was added to improve osseointegration[44]. Two surgical episodes are recommended. The first is to screw the implant into the amputated bone at least 20 mm deep to the distal end, which buffers against progressive bone resorption. Six or more months later the transcutaneous abutment is attached, muscle is sutured to periosteum, and skin to muscle to create a stable stoma[21]. A prosthetic limb is then attached to the abutment. The United States Food and Drug Administration (FDA) has approved OPRA for Humanitarian Device Exemption for transfemoral use, and trials are currently underway for transhumeral use[45].

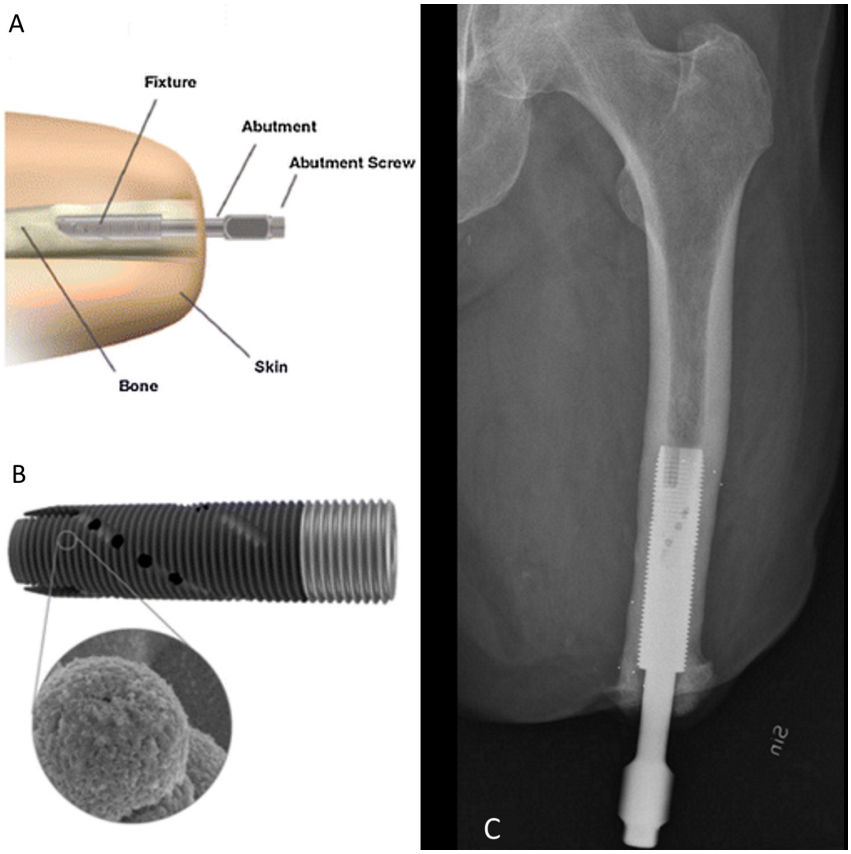


Figure 11. Osseointegrated Prostheses for the Rehabilitation of Amputees (OPRA).
A) Illustration depicting implant placed into the intramedullary canal, retained by a threaded screw design. B) Focused view of current style implant with scanning electron microscope zoomed window of the surface texture provided by laser etching. C) Radiograph of OPRA implanted in a femur.

*Spring Loaded Constant Compression Implant*

The Compress (Figure 12) (Zimmer Biomet, Warsaw, Indiana, USA) was developed during the 1990s[46] and it has been used surgically since 2000[47] as an arthroplasty megaprosthesis in situations such as bone tumor resection. It was later modified to accommodate a transcutaneous implant, with patient trials beginning in 2012[46]. The Compress is made of titanium, featuring a porous distal bone end platform. A thin intramedullary pin is coupled to this platform and anchored to proximal bone by smooth cross-pins. Turning a nut in the pin mechanism leads to progressive force applied to the bone by the platform via a Belleville disk washer spring mechanism. The theory is that an immediate and constant force applied to the bone end should promote bone integration, regardless of the patient's actual weight bearing[46,48]. A smooth transcutaneous adapter interfaces with the prosthetic limb.

The Compress is not commercially available; its FDA trial is currently in planning stages[45].

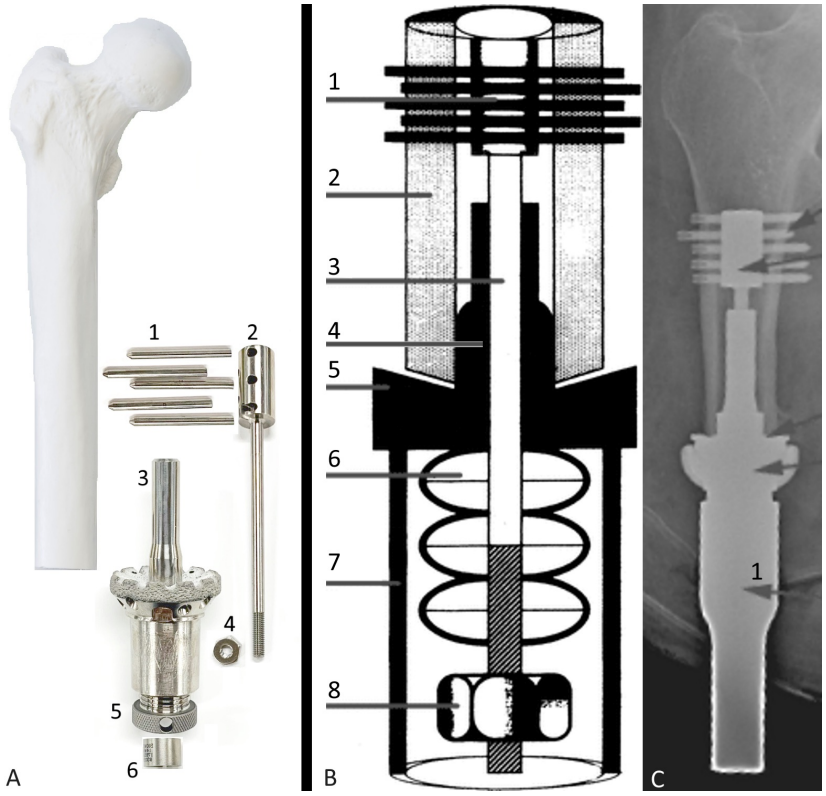


Figure 12. Compress.
The distinguishing feature of this device compared to the others is that the cross-pin design allows a screw and nut apparatus to transmit force from a Belleville spring-style washer system directly to the end of the residual bone, resulting in a compressive force, for which the product is named. The abutment is polished at the skin interface, and connection to a prosthetic limb is achieved with a customized attachment. Immediate implant retention is achieved via the unique spring and cross-pin mechanism. The main difference between the tumour endoprosthesis currently commercially available and the transcutaneous osseointegrated implant configuration under trial is the addition of a transcutaneous taper sleeve (intellectual property not available to be shown in photography). A) Exploded schematic of the device in approximate proximal-distal level as would be for a femoral amputee, once assembled. 1, transverse/retention pins. 2, anchor plug. 3, spindle with hydroxyapatite coating at bone interface. 4, Compress nut. 5, temporary compression cap before nut placement. 6, centering sleeve to position anchor plug in centre of intramedullary canal. B) Illustrated cross-section schematic of the device showing approximate in situ component positions. 1, transverse retention pins. 2, bone. 3, anchor plug. 4, centering sleeve. 5, spindle. 6, Belleville washers. 7, taper. 8, Compress nut. C) Radiograph of Compress in a femoral amputee. Arrow 1 identifies the transcutaneous taper sleeve. Frame A is provided for use by Zimmer Biomet. Frame B is adapted and published with permission from Springer Nature. International Orthopaedics. Compressive osseointegration promotes viable bone at the endoprosthetic interface: retrieval study of Compress® implants. Kramer MJ, Tanner BJ, Horvai AE, et al. 2007. Figure 5C is adapted and published with permission from Springer Nature. Der Unfallchirurg. The Compress® transcutaneous implant for rehabilitation following limb amputation. McGough RL, Goodman MA, Randall RL, et al. 2017.

### *Press-Fit Intramedullary Stem*

Implants of this category are shaped like a rod, curved to match an average femur radius of curvature, with a wide distal platform against which the transected bone end will abut. Each design has various distinguishing features.

The oldest implant from this category (Figure 13) was designed by Dr. Hans Grundei, first used in 1999, and was named the Endo-Exo (ESKA Orthopaedic Handels GmbH). Unlike all other contemporary implants, the material is a cobalt chrome molybdenum alloy. Key design features are a stabilizing lateral bracket with a rough surface and a 1.5 mm deep Czech hedgehog surface (three dimensional "+" sign) into which bone grows. However, the lateral bracket seemed to interfere with proper placement and stoma healing issues were attributed to the rough implant surface at the skin interface. Thus, the bracket was removed in the first revision, and later the skin interface was polished. The current version of the implant is called the Integral Limb Prosthesis (ILP) (Orthodynamics GmbH, Lübeck, Germany). All versions connect to the prosthetic limb via a dual cone transcutaneous adapter. The ILP is used in Germany, the Netherlands, Iraq, and Australia, but does not have FDA approval[45,49].

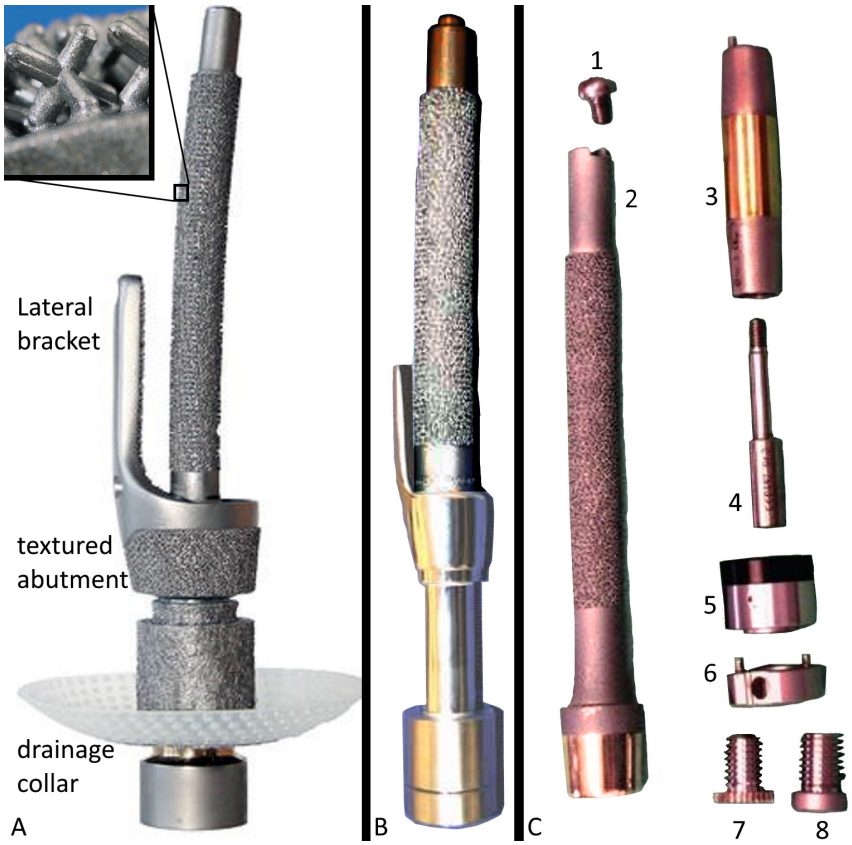

Figure 13. Press-Fit Intramedullary Stem Endo-Exo and ILP.
Endo-Exo (A and B) and Integral Limb Prosthesis (ILP) (C). All iterations of this implant are made of cobalt chrome molybdenum, with an intramedullary nail-type stem featuring onlaid 1.5 mm Czech hedgehogs (a three dimensional "+" sign, featured in Figure frame A) to promote bone ingrowth. All models achieve immediate implant retention via the press fit implantation, analogous to hip arthroplasty, and the external prosthetic limb is mounted via a multi-component dual cone and screw system. A) The original version of this device featured a distal collar which was porous coated to promote skin adhesion, and a lateral stabilizing bracket to fit over the external bone surface to enhance torsional stability. Early failures were attributed to this bracket and the rough collar, which prompted modifications. B) A revised version retained the bracket but polished the collar. C) The next version, renamed to ILP, removed the bracket and coated the collar with titanium niobium oxynitride ceramic to prevent skin adherence. Note that bone osseointegration is only designed to occur at the textured surface approximately 1.5 cm proximal to the abutment, not on the smooth surface between the abutment and the textured surface. 1, proximal cap screw. 2, ILP body with main portion textured, distal flare untextured, abutment highly polished with titanium niobium oxynitride ceramic surface. 3, dual cone abutment adapter. 4, safety screw. 5, taper sleeve. 6, distal bushing. 7, permanent locking propeller screw. 8, temporary cover screw. Frame A is adapted and reprinted by permission from Springer Nature. Sports Engineering. Direct skeletal attachment prosthesis for the amputee athlete: the unknown potential. Muderis MA, Aschoff HH, Bosley B, Raz Guy, Gerdesmeyer L, Burkett BJ. 2016. The zoom-in box of ILP texture is adapted and reprinted by permission from Springer Nature. Der Orthopäde. Juhnke DL, Aschoff HH. Endo-Exo-Prothesen nach Gliedmaßenamputation. Der Orthopäde . 2015. Frame B is adapted from the article Kennon RE. A Transcutaneous Intramedullary Attachment For AKA Prostheses. Reconstructive Review 3(1), licensed under Creative Commons BY 4.0. Frame C is adapted and reprinted by permission from Springer Nature. Operative Orthopädie und Traumatologie. Implantation der Endo-Exo-Femurprothese zur Verbesserung der Mobilität amputierter Patienten. Aschoff HH, Clausen A, Tsoumpris K, et al. 2011.

While training with the surgeon who designed the Endo-Exo, I proposed the use of a highly polished titanium niobium surface, which in fact did significantly improve stoma healing. After using the ILP in my own practice for several years, I designed the Osseointegrated Prosthetic Limb (OPL) (Permedica Manufacturing, Milan, Italy) in 2013 (Figure 14). Maintaining the press-fit stem concept, key modifications to the ILP were: 1) to use the more osteoconductive titanium Ti6Al4V, 2) create surface pores of 500 μm, 3) design a fluted proximal half to prevent rotation during insertion and early loading, 4) include a tapered proximal abutment which can mate with an arthroplasty implant, 5) texturing the surface with a coarse plasma spray of 500um on the distal half and 150 μm on the proximal half. This different texture design promotes preferential osseointegration distally, whereas the proximal part serves more to prevent stress shielding. The distal half of the implant is 1 mm wider than the proximal half, and the proximal half has 10 flutes each 1 mm tall to maintain initial rotational stability. While all these modifications are believed to be important, the decision to coat the distal portion of the stem, including the abutment surface, seems critical, as it prevents the issue of distal bone resorption seen in patients with ILPs (the most distal portion of the ILP stem is untextured). The OPL is

widely available around the world including Australia, the Americas, Europe, the United Kingdom, and the Middle East[45,49,50].

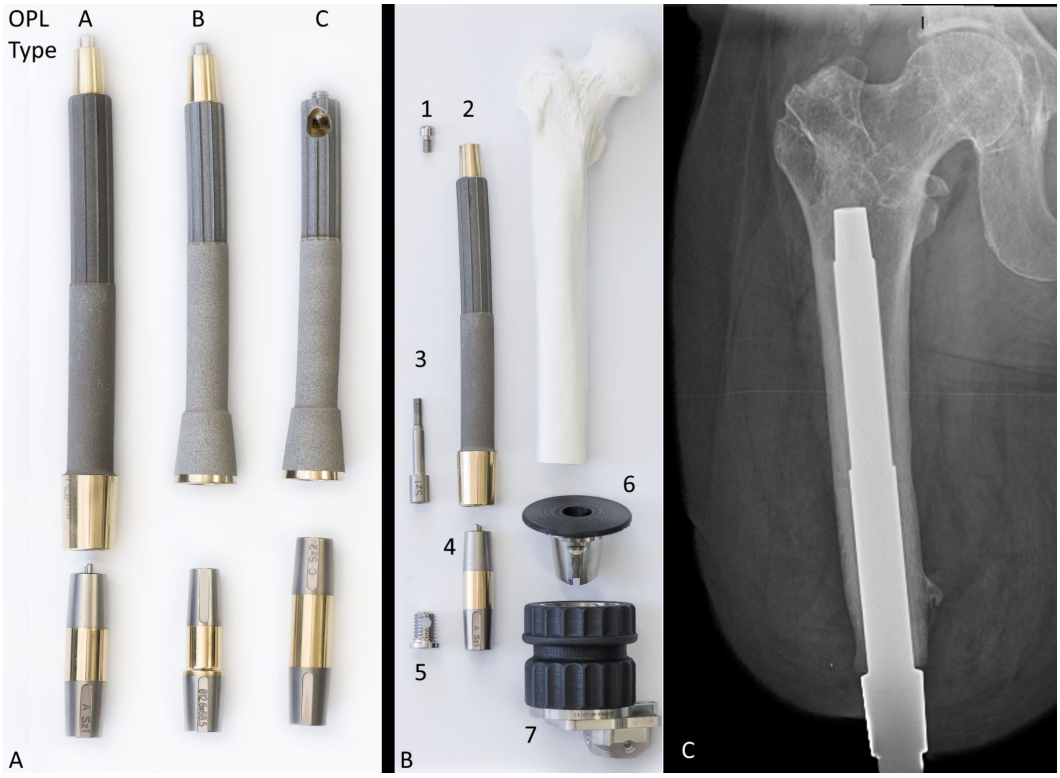


Figure 14. Press-Fit Intramedullary Stem Osseointegrated Prosthetic Limb (OPL).
Three models exist, labelled A, B, and C. The OPL is a forged titanium alloy stem-shaped implant whose surfaces have a plasma-sprayed coating, up to 0.5 mm thick, to promote bone ingrowth and rapid integration. The external portion of the collars are treated with titanium niobium oxynitride ceramic to promote smooth soft tissue gliding, limiting the probability of symptomatic soft-tissue adhesion and tethering. Proximal fluted fins provide initial rotational stability, akin to a Wagner-style hip arthroplasty stem. (Figure frame A) OPL types A, B, and C as labelled at top, with matching dual cone abutment adapters. Type A has a flat abutment with a relatively long smooth collar, and a proximal tail which is tapered to accept an extension nail or an arthroplasty attachment, when indicated. Type B has a conical abutment which embeds into the distal bone with a smaller smooth extra-osseous collar; these also possess the tapered tail adapter, identical to Type A. Type C features the same abutment and collar style as Type B but the body is shorter, and instead of a tapered tail adapter there is a 135 degree hole bored near the proximal tail to accept a femoral neck screw which can prophylactically be used to prevent neck of femur fractures. This type is most suitable for short femoral residua. All models use a similar dual cone connection mechanism to the external prosthetic limb. All models' dual cone adapter features titanium niobium oxynitride ceramic at the portion exposed to skin to prevent skin adhesion. (Figure frame B) Exploded view of a Type A implant in approximate proximal-distal level as would be for a femoral amputee, once assembled. 1, proximal cap screw. 2, OPL body. 3, safety screw. 4, dual cone abutment adapter. 5, permanent locking propeller screw. 6, proximal connector. 7, prosthetic connector. (Figure frame C) Radiograph of OPL Type A in femoral amputee.

Two other implants in this category include the Percutaneous Osseointegrated Prosthesis (POP) (DJO Global, Austin, Texas, USA) and the Intraosseous Transcutaneous Amputation Prosthesis (ITAP) (Stryker Orthopaedics,

Kalamazoo, Michigan, USA). Limited information is available regarding either. The POP features only a few cm of textured surface at the distal portion[51] and was first implanted in 2015[52], with only preliminary outcomes of 10 patients being reported[53]. POP is not approved for routine use anywhere though further investigation is being considered[45]. The ITAP featured hydroxyapatite coating to the intramedullary component as well as the transcutaneous portion. The hydroxyapatite lining did not provide adequate intramedullary retention and led to skin problems. The ITAP concluded its trial and will not be marketed[54].

*Theoretical and Practical Appraisal of Designs*

An ideal osseointegration implant should provide rapid full weight bearing, resist infection, be mechanically durable, be scalable to various size bones such as extremely short residual limbs or those with capacious canals, be technically familiar to a broad audience of surgeons, permit simple management of expected complications such as patient injury, accommodate adjacent joint arthroplasty, be reasonably removable in cases of implant failure or untreatable infection, accommodate future prosthetic and neural connective technology, and minimize manufacturing and utilization cost. The remainder of this section briefly reflects on the actual or theoretical issues relevant to the various implant designs. Because of the different maturity and eras of use among the implants, a valid comparison of outcomes is difficult to perform.

Although the OPRA was the first to demonstrate that osseointegration is a viable technique, several design features seem suboptimal. Paramount is the screw concept. Manual creation of a straight tunnel (for the screw track) in a non-straight tube (bone) can lead to an in-out-in trajectory, due to misjudging the curvature of the bone or inaccurate determination of diameter given the non-circular canal shape of some bones (these issues are identified in the OPRA technique guide[55]). Second, because the implant is screwed into position without a load applied until the second stage is completed, bone ingrowth may be delayed or reduced (Wolff's Law)[56]. For this reason, the designer recommends implants should be placed 20 mm deep.

Further, the screw design may lead to body weight force only being transferred through a limited number of threads, leading to potential implant twisting if a patient applies a strong rotational moment through the prosthesis. It is acknowledged that no documented event of this third concern has been identified. The OPRA is the only system which has documented use for small digital prostheses[57], non-limb prosthesis[58] and neural control adaptation (e-OPRA)[59].

The immediate and constant end compression provided by the Compress seems beneficial: it should prevent situations of distal stress shielding, minimize bone resorption and optimize bone density due to constant force application. However, placing the cross-pins in the proximal bone for eventual anchoring sometimes leads to pin misdirection or breakage, increasingly likely as soft tissue around the bone increases. Additionally, despite a centering guide, achieving the correct orientation remains difficult and can lead to improper loading at the distal bone. Fractures in the residual limb due to patient injury tend to result in the implant also being damaged and requiring revision and at least a small additional bone resection[46]. While this complication is likely infrequent, nonetheless it is inevitable in a certain percentage. This may lead to difficulty treating these patients if they are not near a surgeon with specific implant experience, or for patients whose bone is initially very short this may result in a uselessly short residual bone. Furthermore, the Compress is not suitable for bones with cortices less than 2.5 mm thickness. This likely excludes a large proportion of amputees due to cortical thinning resulting from disuse osteoporosis. The technical difficulty and limited indications make the scope of use of the Compress limited to younger, healthier bone in patients with relatively recent amputation and it has so far been used principally in oncology.

The press-fit intramedullary stem design, particularly the OPL, achieves many of the previously stated implant goals. Since it requires no centering or retention devices, the tools needed for implantation are a scalpel, an appropriately sized implant, flexible reamers, broaches, a mallet and suture. Similarly, although a customised removal set can speed extraction, it can be removed with simply an osteotomy of the surrounding cortical bone subsequently reduced, fixed and

retained. The monoblock construction is familiar to orthopedic surgeons and can be easily sterilized in any autoclave. Its texturing has proven to facilitate stable osseointegration within a few weeks; patients who sustain periprosthetic fractures have all been able to retain the implant, have routine fracture care with standard plates and screws and regain independent ambulation at or above their pre-implantation level[60]. The full body texturing has allowed the proximal portion to be cut short and successful osseointegration has been achieved to just the distal portion and abutment. The OPL is the only implant to have been used in patients with an associated total hip[61] or knee[62] replacement.

With the origins and foundation of PEPOL summarised, I will focus on how I became involved and eventually the preeminent surgeon, in osseointegration for amputees.

## MY BODY OF WORK: IMPROVING AMPUTEE LIFE VIA OSSEOINTEGRATION

Lower extremity amputation (LEA) is associated with substantial quality of life (QOL) reduction. Pain and ability to wear a prosthetic limb are factors directly associated with the amputee's extremity which predictably lower QOL[63]. Indirectly associated factors include employment, social support and depression[64]. While difficult to tabulate the worldwide LEA census, it has been estimated an amputation performed every thirty seconds worldwide due to diabetic complications alone[65], not accounting for other causes such as trauma. In 2008 the United States had approximately 1.6 million lower extremity amputees, a number predicted to double by 2050[66]. A 2014 Australian study estimated LEA incidence as 13% transtibial, 10% transfemoral and 75% transmetatarsal[67]. Most patients with lower extremity amputations above the ankle will seek a prosthesis to aid their mobility.

The typical rehabilitation solution for lower extremity amputees is skin-suspended socket (SSS) prosthesis, with design principles established at least as early as the 1500s3. Some examples of SSS include: a silicone liner with a distal pin which clips into the prosthetic leg, layered residual limb socks which suspend a rigid socket by friction, or a rigid socket that is suspended upon the residual limb the creation of a vacuum. Unfortunately, significant problems persist. One-third to three-quarters of patients develop skin-socket interface problems such as ulcers, dermatitis, or intolerable perspiration[68,69]. Mobility and fit is troublesome due to residuum size fluctuation[70] or the feeling of instability from altered proprioception[71,72]. Most patients require frequent socket refitting8. Transfemoral amputees often lack confidence navigating uneven surfaces: one-quarter report a poor or extremely poor lifestyle[73] and 2.2% sustain a residual limb fracture within five years[74].

With such substantial population and individual health burden, addressing patient-prosthesis interface problems would tremendously improve not only each individual amputee's health situation but accordingly also that of their family and friends. Furthermore, when more people are better able to participate in society, the

communities of these amputees likely can benefit as well. Percutaneous EndoProsthetic Osseointegration for Limbs (PEPOL) has proven a very effective way to address the patient-prosthesis interface. This Body of Work summary describes my academic journey and contributions to the field of PEPOL surgery which have led to me being the most experienced PEPOL surgeon in the world.

## PART 1 - My Clinical and Basic Science Contributions

One of my early publications in 2007[75] investigated the effect of pamidronate therapy on children, specifically the radiographic appearance and their subsequent growth. Bisphosphonates are a class of pharmaceuticals which impair osteoclast cell reproduction. By reducing osteoclast number, there is less bone resorption, and the relative predominance of osteoblasts results in a net increase of bone production and thus bone density. In 1968, etidronate became first bisphosphonate used for medical treatment, and in the 1980s it began to be used for medical treatment of postmenopausal osteoporosis[76]. In the late 1990s pamidronate given in cyclical doses was cautiously being considered for children with fragile bone conditions such as osteogenesis imperfecta[77]. An interesting observation was that when administered to skeletally immature patients in these cyclic doses, a radiographically dense line was observed which correlated with the timing of administration. Not only was this visually striking but it would allow skeletal growth to be measured in serial radiographs. This finding can be of significant benefit to measure the rate of growth in these individuals, particularly considering children receiving cyclical bisphosphonate usually suffer from growth disturbances.

It was during my orthopaedic training when I had the opportunity to investigate these phenomena. Evaluating the serial radiographs and clinical visits of 36 children with bone fragility, this project had two goals. First, to assess to what extent bisphosphonate therapy (specifically cyclical pamidronate) might negatively alter development of the immature skeleton. Secondly, to name this radiographic phenomenon. The answer to the first question was clearly that no adverse patient

growth velocity was identified. By clinical measurement as well as assessment with radiographs, computed tomography, and magnetic resonance imaging, no adverse bone effects were identified. We ended up coining the term “zebra stripes” to describe the parallel white-and-black layers seen on radiographs (Figure 15). Beyond the direct scientific knowledge, I learned about bone metabolism and how it can be safely and directly modulated with pharmaceuticals, and I learned the importance of naming. The term “zebra stripes” has the following benefits: it is short and simple; the evoked image is immediately intuitive upon seeing the radiograph; it is distinct from any other orthopaedic phrase; and it is a term that children and also their parents can hear and think about it in relation to themselves or their children, and not have a negative connotation. The term is now frequently used in routine discussion regarding cyclic pamidronate therapy for children and is widespread enough to be easily searchable on PubMed.

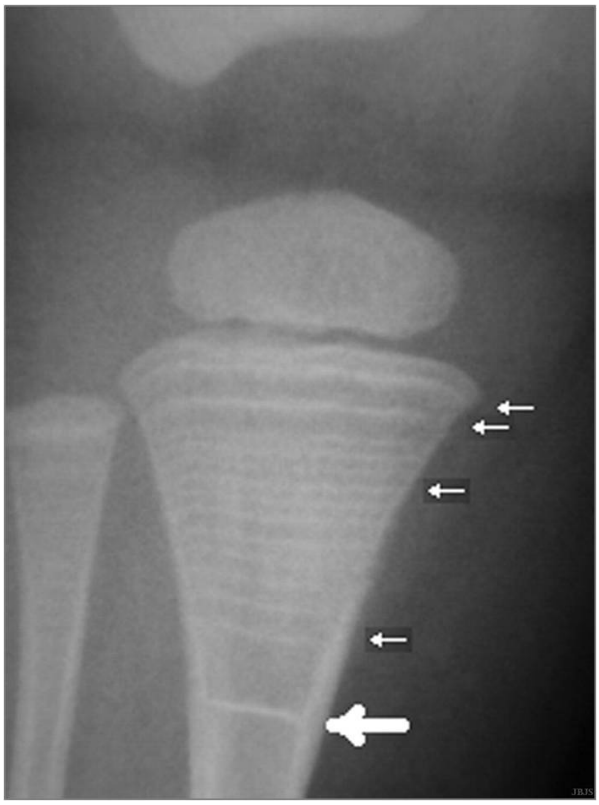

Figure 15. Zebra Lines.
Radiograph of the proximal parts of the tibia and fibula, showing multiple zebra lines (small arrows) and a Harris growth arrest line (large arrow). Reproduced with permission from Al Muderis, M. MD1; Azzopardi, T. FRCS(Ed)1; Cundy, P. FRACS1 Zebra Lines of Pamidronate Therapy in Children, The Journal of Bone & Joint Surgery: July 2007 - Volume 89 - Issue 7 - p 1511-1516 doi: 10.2106/JBJS.F.00726.

Several years later, while in fellowship in Germany, I had another opportunity to learn about bone metabolism and its manipulation. Total hip arthroplasty (THA), recently celebrated as the "operation of the 20th century,"[78], only became predictably successful in the 1950s and 1960s following the innovations of Sir John Charnley[79]. One of Charnley's critical innovations was to link the prosthetic femoral head and stem to the native femur using polymethylmethacrylate ("bone cement"). Bone cement acts as a grout-type interface agent which provides implant retention by penetrating the cancellous bone. As bone cement is metabolically inert, there is no progressive biologic interaction between itself and the bone, and in fact a fibrous layer tends to form between them over time[80]. This does not promote bone health and can ultimately lead to implant loosening.

A cementless implant is the main alternative to a cemented implant. The first cementless THA implants were used in the 1950s, but routinely successful use was not achieved until the 1980s[81]. Those cementless implants relied on a phenomenon called osseointegration. Osseointegration is defined as the intimate ongrowth/ingrowth of bone (osteoblasts) onto a foreign material with no intermediary layer. The phenomenon was observed by researchers as early as 1940[82,83], but Per-Ingvar Brånemark was the first to appreciate and consider its use for surgical applications[14], and eventually coined the term in 1977. It was observed to occur best for implants made of titanium.

Considering that the long-term success with cementless THA was only achieved starting in the 1980s, 20-year outcomes were only able to be evaluated in the 2000s. Curious to better understand the longevity of osseointegrated implants, I helped investigate patients who received Spongiosa-I fully coated cancellous metal surface THAs[84]. At a follow-up time of 242-275 months, the implant survival was quite excellent in this cohort of patients. The probability of survival of both components at twenty years, with revision for any reason as the end point, was 97%. The probability of survival of the acetabular component was 98%, and the probability of survival of the femoral component alone was 86%. Particularly interesting was that

the probability of component survival was significantly increased among older patients (70 years or older at surgical date), which was further explored in a related follow-up article [85]. This meant that “old bone” was not intrinsically compromised bone, but in fact metabolically suitable for cementless osseointegrated THA. I did not know it at the time, but this recognition influenced many of my later decisions regarding patient selection for PEPOL surgery. I participated in the publication of a similar article on another cohort of patients in Germany showing equivalent results[86].

I began my orthopaedic surgery practice in 2009 after completing fellowships in Germany in arthroplasty and adult limb reconstruction, which included exposure to PEPOL. I recognised the potential significance of this revolutionary rehabilitation surgery so I knew I had to include it in my own practice, for Australia’s amputees. As with any surgery, understanding complications and how they happen, so as to work to minimise their frequency and severity, is critical to the safety of PEPOL, I partnered with a group in the Netherlands to prospectively evaluate 86 patients (91 cases) over a four year period[87]. All patients were followed for the customary minimum two years (24-71 months), and all adverse events were documented. At this early stage in my career, 31 patients had an uneventful course. Twenty-nine experienced soft tissue infection. Twenty-six others experienced problems such as soft tissue redundancy or stoma hypergranulation requiring intervention. This paper identified a number of interesting outcomes with several clinically important conclusions. First, it confirmed that press-fit PEPOL using spongy metal surface cobalt-chrome implants coated with titanium, were successful at achieving strong osseointegration. This is very similar in principle to the cementless osseointegration article I had previously written. Next, none of the patients experienced a catastrophic adverse event such as death, systemic illness or disability, or proximal level amputation. Another important lesson was the difficulty of managing the soft tissue. Skin tends to become loose when its native attachments to underlying fascia and muscles are disrupted, and also when muscle atrophy occurs following extended periods of reduced activity as is often the case for amputees. Further, amputee skin has been compressed and stretched non-physiologically for years when they use a socket prosthesis. Clearly, soft tissue management had to be an essential consideration in future PEPOL surgery. A final major impact of this paper was the

establishment of a grading system for infection as related to osseointegration (Table 2). I introduced this grading system, which remains the most widely used system to grade osseointegration infection[87]. The system differentiates first to what extent the infection invades the body (skin-only, soft tissue deep to skin, bone infection, or peri-implant infection). It additionally identifies how much intervention was required to manage the infection (oral antibiotics, intravenous antibiotics, surgical intervention, or implant removal). This provided a language for future surgeons to use when considering and presenting their infection cases.

Table 2. Classification of Osseointegration Infection

| Level of Severity | Symptoms and Signs | Treatment | Grade |
|---|---|---|---|
| Low-grade soft-tissue infection | Cellulitis with signs of inflammation (redness, swelling, warmth, stinging pain, pain that increases on loading, tense) | Oral antibiotics<br>Parenteral antibiotics<br>Surgical intervention | 1a<br>1b<br>1c |
| High-grade soft-tissue infection | Pus collection, purulent discharge, raised level of C-reactive protein | Oral antibiotics<br>Parenteral antibiotics<br>Surgical intervention | 2a<br>2b<br>2c |
| Bone infection | Radiographic evidence of osteitis (periosteal bone reaction), radiographic evidence of osteomyelitis (sequestrum and involucrum) | Oral antibiotics<br>Parenteral antibiotics<br>Surgical intervention | 3a<br>3b<br>3c |
| Implant failure | Radiographic evidence of loosening | Parenteral antibiotics, explantation | 4 |

At this point, having some early experience with osseointegration patients, I wanted to confirm whether the improved patient activity would produce objective improvements in their bone health, measured by cortical bone thickness and density. Amputee bone is not loaded evenly when they are reasonably mobile, so they tend to become osteopenic or osteoporotic[88]. Wolff's Law suggests that should these patients become more active after PEPOL, they would walk more and the load from walking would be transferred directly through their residual bone and proximally

through their entire skeleton. I began two studies which took several years to complete, as patients had to be enrolled and then have adequate time to ambulate and load their bone following surgery. Evaluating 28 patients for periprosthetic bone remodeling at about 3 years after PEPOL[89], we found that the bone immediately surrounding the prosthesis actually decreases in density but increases cortical thickness. In a related study of 48 PEPOL patients[90], the ipsilateral femoral neck bone density increased at 1-3 years following osseointegration, much more so for patients who had a stem-only style implant rather than a stem with a fitted femoral neck screw. These papers utilised the term “reverse Gruen zone” introduced in one of our prior radiographic evaluation papers[91], which visually identifies regions surrounding the PEPOL, a term modified from the original term “Gruen zones” used for THA[92]. It seems clear that Wolff’s law of bone remodeling occurring in response to loading remains true for these patients, and thus excessive fixation appears to induce undesirable stress shielding (the reduction of bone density due to load transfer of a non-skeletal load bearing implant)[93]. To further explore the unexpected thick-not-dense bone appearance identified in the former paper, we have been working with an advanced radiographic modeling team, from Cambridge University in the United Kingdom, who can determine cortical bone density and thickness immediately next to metal implants using specialised artifact reduction software. It is anticipated that not only will data from these studies help us understand the post-operative bone remodeling, but perhaps also help us better plan preoperative surgical care and optimisation for amputees.

With many of the most pressing aspects of PEPOL being established in these papers, and with my insights from performing an increasing number of surgeries on amputees, I became motivated to expand PEPOL to a wider population. A previous PEPOL surgeon had recommended only the absolute narrowest criteria of amputees should be considered for PEPOL: very healthy and relatively young patients[94]. That would include the civilian population who have amputations secondary to traumatic injuries and potentially also military veterans. Indeed, we specifically invested in a military cohort and identified most do quite well, as they were healthy and active immediately before having a traumatic injury[95]. Another project I led revealed young healthy athletes were also particularly enthusiastic about the benefits

osseointegration provided to their sporting endeavors[96]. But when considering all amputees as a whole, this limitation excludes the majority of potential patients. Based on the aforementioned research, my clinical and research teams and I felt it was safe and purposeful to carefully expand our indications. The following series of case reports and case series helped prove that in fact, when appropriately performed, press-fit PEPOL is safe and beneficial for more patients than were traditionally considered.

The first tradition that we felt could be safely improved was that of two surgical stages. Prior surgeons advocated for, and only performed, two-stage surgeries for PEPOL[94,97]. The reason for this was to give the bone-anchored portion of the implant enough time to establish strong osseointegration so that when it was loaded, there would not be an early catastrophic failure due to bone-implant loosening. Indeed, a two-stage protocol is what I employed when first starting[98]. All 50 patients were followed for at least one year and all achieved ambulation on their osseointegrated prosthesis[98]. The patient-reported outcomes and objective mobility tests improved significantly for the cohort[98]. However, based on this experience and that of the cementless total hip articles described above, along with the basic science provided by other researchers in the 1970s[41], the established science and clinical experience suggested that light loading and tension should present no risk of loosening immediately after surgery, and by 7-10 days the maximum pull-out strength is likely achieved. We therefore developed a protocol for a single-stage surgical treatment plan[99], and nearly all subsequent patients have been cared for with a single surgical event. We have not noted issues with increased pain, implant retention, infection, or other problems.

Many amputees also experience degenerative joint disease, leading to arthritic pain. These patients may seek PEPOL for its mobility and QOL benefits, but also have hip or knee arthritis which also significantly reduces their mobility and QOL. Traditionally, these patients would have to choose one or the other: PEPOL or THA/TKA. Considering that I am a high-volume hip and knee replacement surgeon, as well as a PEPOL specialist, I felt it would be safe to provide both a joint

replacement and PEPOL for appropriate patients. In 2015 we published our case series of four amputees who had a TKA in combination with tibial osseointegration (Figure 16)[62]. As the PEPOL was linked directly to the TKA, two surgical episodes were necessary, despite our preference for a single stage surgery. In the first episode, a relatively typical TKA surgery was performed. Notably, the tibial component was designed to be osseointegrated into the bone rather than relying on cement retention, as is most common for TKAs. The reason for this is that the subsequent PEPOL was linked directly to this tibial component; if cement retention were to be used it would be more likely to eventually become loose with multidirectional forces acting upon the implant-cement-bone interfaces. Whereas with an osseointegrated retention, the biologically active bone would continue to remodel and hold fixation in response to the various stresses. Therefore, at 4-6 weeks following the first surgery, the second surgery to connect the PEPOL to the tibial component was performed. In this series, one patient experienced a superficial infection that did not require further surgery, and all four patients improved their self-reported subjective satisfaction and objective mobility as measured by the Six Minute Walk Test. Similarly, three transfemoral amputees had an osseointegrated THA performed, also with 5-8 weeks separating the two stages[61]. The thought process for this was identical to that of the TKA. Just as in the TKA, one patient experienced superficial infection which did not require further surgery. All patients improved on their self-reported QOL surveys and also their objective mobility tests.

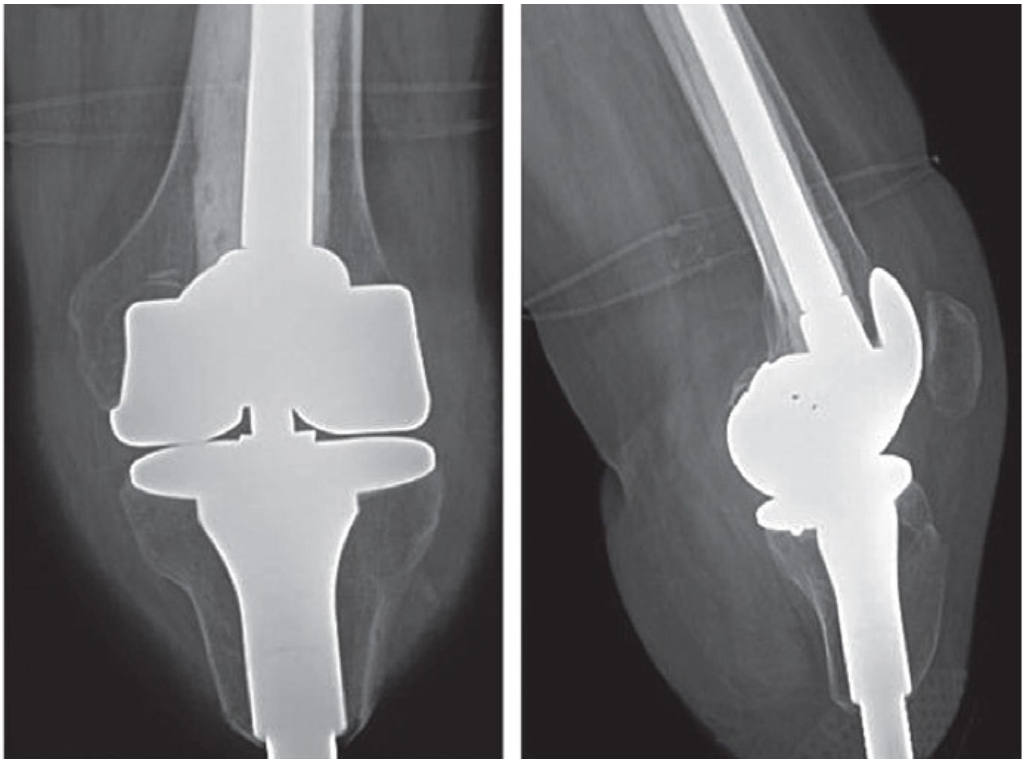

Figure 16. AP and lateral radiographs of a patient who has a total knee arthroplasty connected to a tibial osseointegration prosthesis.
Reproduced with no permission necessary from Khemka A, Frossard L, Lord SJ, Bosley B, Al Muderis M. Osseointegrated total knee replacement connected to a lower limb prosthesis: 4 cases. Acta orthopaedica. 2015 Nov 2;86(6):740-4.

Patients with potentially compromised bone geometry or quality was another potential contraindication. Standard PEPOL implants are 16 cm long, and while it was known that less than full implant contact could result in a successful outcome, some patients had as little as 3 cm of residual femur remaining. This was considered an extremely high risk for failure to osseointegrate. Not only would an unsuccessful osseointegration be harmful and costly to the patient which would require additional surgery, but they may not have enough bone remaining to reattempt osseointegration. The solution I innovated was to use an intramedullary lengthening nail to make the bone longer before attempting osseointegration (Figure 17). Complicating matters even more was the fact that the shortest lengthening nail was 13 cm, and as aforementioned, many of the patients had residual femurs lengths that were substantially less. So, we had to also innovate new ways to link the lengthening nail to such a short bone. I came up with two strategies: linking the bone to the nail using a cable technique, and eventually the preferred option was to link them using a

locking plate which was bent to fit during surgery[100]. Even though some patients required adjuvant surgery to provide bone graft, all eventually received their PEPOL, and we are in the process of analyzing their outcomes for upcoming submission as well.

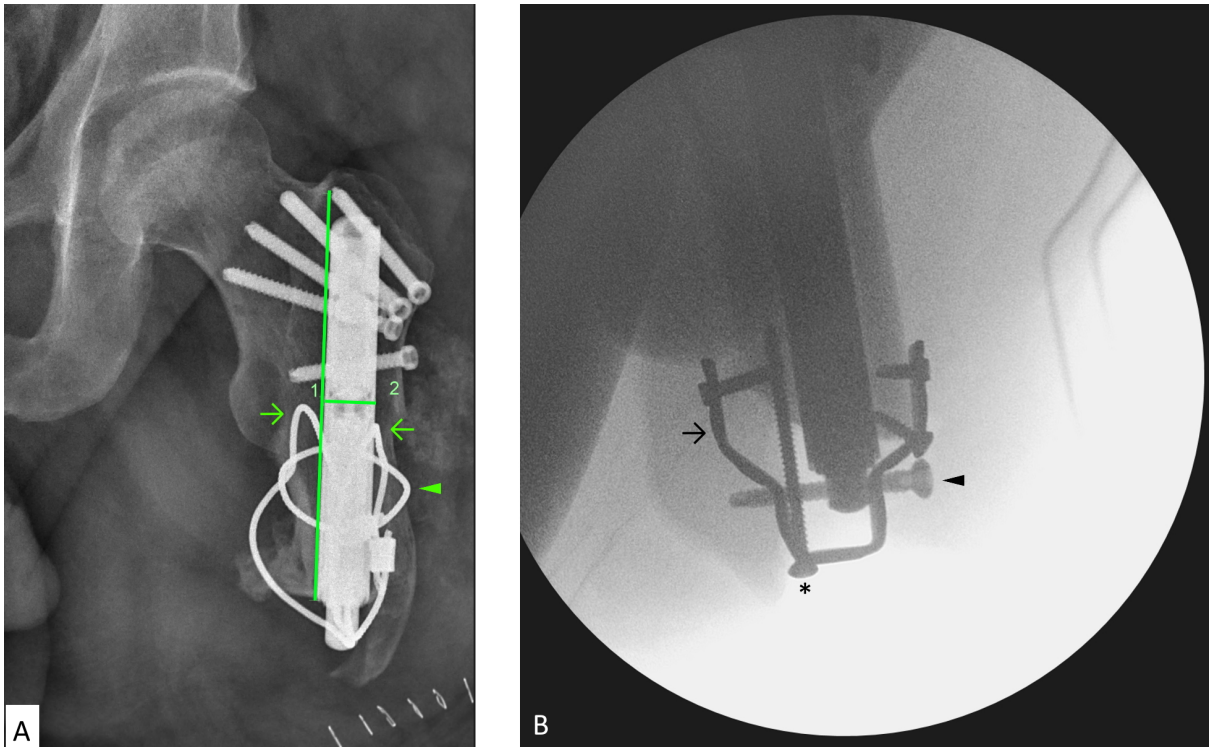


Figure 17. Femoral Lengthening Technique.
(A) Triple cable lasso technique. The nail extended beyond the femur, so the following technique was used to link the nail to the distal femur segment. Two holes were drilled in the distal segment, each passing transcortically through both the lateral and medial cortices. One cable was passed through each pair of drill holes, then through the distal limb lengthening nail (LLN) hole (indicated by arrows). Both cables were gently tightened and routinely secured. Because bone amputated years before can be osteopenic, these cables can cut through after initiating distraction. Thus, a circumferential cable (indicated by arrowhead) secured the 2 longitudinal cables to the distal segment, capturing them transversely around the strongest portion of the remaining bone, the cortex. (B) Contoured locking plate technique. A one third tubular locking plate (indicated by arrow) was contoured around the distal femur which allowed one screw (indicated by arrowhead) to capture the distal limb lengthening nail (LLN) hole. One long intracortical screw (indicated by asterisk) and 3 additional unicortical screws linked the nail to the distal bone segment.

Perhaps the most important category of amputees to remove from contraindication are those whose amputations were from diabetic or vascular etiologies; many patients have both comorbidities. In the United States of America, more than half of lower extremity amputations are performed due to complications resulting from diabetic and/or vascular pathology[101] and the rate of amputations for

diabetic patients is 10 times that of non-diabetic patients[102]. From 2013 to 2016, eight patients whose amputation was due to diabetic complications were treated with PEPOL[103]. As diabetes mellitus carries an increased risk of infection for many orthopaedic surgeries, particularly when the glucose levels are uncontrolled[104], we ensured they all had improved their diabetic control since the amputation and had maintained long term stable glucose and A1c levels. Through one year of follow-up, all patients had improved objective mobility performance; specifically, five patients were confined to a wheelchair before PEPOL but were independently ambulatory afterward. Two patients required surgical debridement for soft tissue infection, but all retained their implant. A longer-term follow-up study of 56 patients is currently in preparation for publication, and early analysis suggests similarly favorable outcomes. Immediately following the recruitment of patients with diabetes, we treated five patients with amputation due to complications of peripheral vascular disease[105]. Three patients were wheelchair-bound before PEPOL, whereas one year later all five patients were independently ambulatory. Two patients had one episode of superficial soft tissue infection. Encouraged by this cohort's successful outcomes, we recruited more patients who were followed longer. This article was recently accepted and is currently in press[106]. Following six patients for 3-6 years after PEPOL, all patients improved the objective mobility performance, wore their prosthetic legs at least 12 hours daily, and remained independently mobile. Three patients required soft tissue debridement. One patient developed a myocardial infarction and died. These studies into the biological feasibility and safety of PEPOL for patients whose amputations were due to diabetes and/or vascular disease -- the two most common causes for amputation worldwide -- are truly critical. They prove that a tremendous proportion of amputees may be able to be treated with PEPOL, something that was previously considered unreasonable.

Another frontier my team and I pioneered was the simultaneous amputation and osseointegration of patients with an intact but functionless or QOL-impairing limb. A common example of such a patient is one with chronic pain. While there may be multiple reasons for chronic pain, we focused on one specific cause: complex regional pain syndrome (CRPS). CRPS is characterised by, among other things, the inability to alleviate the pain due to the inability to specifically identify the cause of

the pain. CRPS is a diagnosis of exclusion, so they are unable to be treated for identifiable pain-causing pathology such as vascular insufficiency, infection, arthritis, or other discernible discrete pathology. There is controversy surrounding amputating an extremity for anything other than life-threatening concerns. However, if a limb is so painful as to confine patients to wheelchairs, prevent them from seeking work, and requiring narcotic and other addictive medications in an attempt to alleviate the pain, the limb would almost certainly be considered more of a pathologic situation than a benign, let alone functional, appendage. Prior surgeons have reported that amputating proximal to the level of symptoms reliably alleviates CRPS pain[107]. The trouble is that wearing a socket prosthesis is very tiring for adults and often is not actually achievable, leading to many patients now having substantially reduced pain, but effectively non-ambulatory[108]. Furthermore, there is always the fear of developing CRPS in the residuum due to problems with the skin-socket interface. I was presented with three patients who had unrelenting CRPS of the lower leg, who had unresolvable pain despite years of physical and pharmacological therapy. They were unable to ambulate, had dropped out of school or lost work due to their pain, and were on narcotics and other addictive medications. Following transfemoral amputation and PEPOL, all patients were again able to achieve independent ambulation, regained employment, or returned to school, and have been able to walk stairs and uneven surfaces without issue. One patient pursued additional nerve surgery without consultation and experienced additional pain and is undergoing corrective nerve surgery to address that pain[109]. Publishing this series was very important not only because it identified that patients with this specific diagnosis can do well after PEPOL, but more because no other publications report performing simultaneous amputation with osseointegration as single stage surgery for this devastating condition.

One case report on PEPOL for femoral deficiency[110] inspired providing PEPOL to a patient with a hip disarticulation. A soldier who had sustained an explosive rocket injury to his leg had been managed with a hip disarticulation in order to save his life. However, that left him confined to wheelchair mobility as he was unable to fit a socket prosthesis without severe pain. Never before had PEPOL been performed for a non-tubular bone (radius/ulna, humerus, tibia, femur). Planning this

surgery required many geometric considerations that were far beyond what is typical. Whereas extremities have substantial motion and are already positioned in a way that people can rest and sit, a device anchored to the pelvis cannot move. The positioning must be in a way so as to not only allow ambulation but perhaps more importantly, that permits the patient to sit and lie down to sleep. An additional step into the unknown with this surgery was whether the pelvis would be sturdy enough to support a patient's weight in the geometry that was introduced. Whereas tubular bones are designed for axial loading, the pelvis does not normally support weight the same way. As such, we relied on tangential instead of circumferential cortical bone contact. Fortunately, through careful planning and technical execution, the patient achieved independent ambulation and has resumed work as a livestock farmer, can carry two-handed objects, and can even ascend and descend a flight of stairs without using a railing[111].

An additional very large group of amputees that has been nearly neglected by the entirety of PEPOL surgeons is transtibial amputees. Only six publications report on 27 total transtibial osseointegration (TTOI) surgeries, each documenting under ten cases (Figure 18)[62,105,112–115]. I commenced transtibial PEPOL in 2014. Knowing this was a future groundbreaking area of research, we formally planned a study of these patients[116]. We have submitted a study of 91 patients with 102 transtibial PEPOL procedures, which represents almost four times the existing number of patients reported by all other researchers. We hope this report will be accepted later this calendar year.

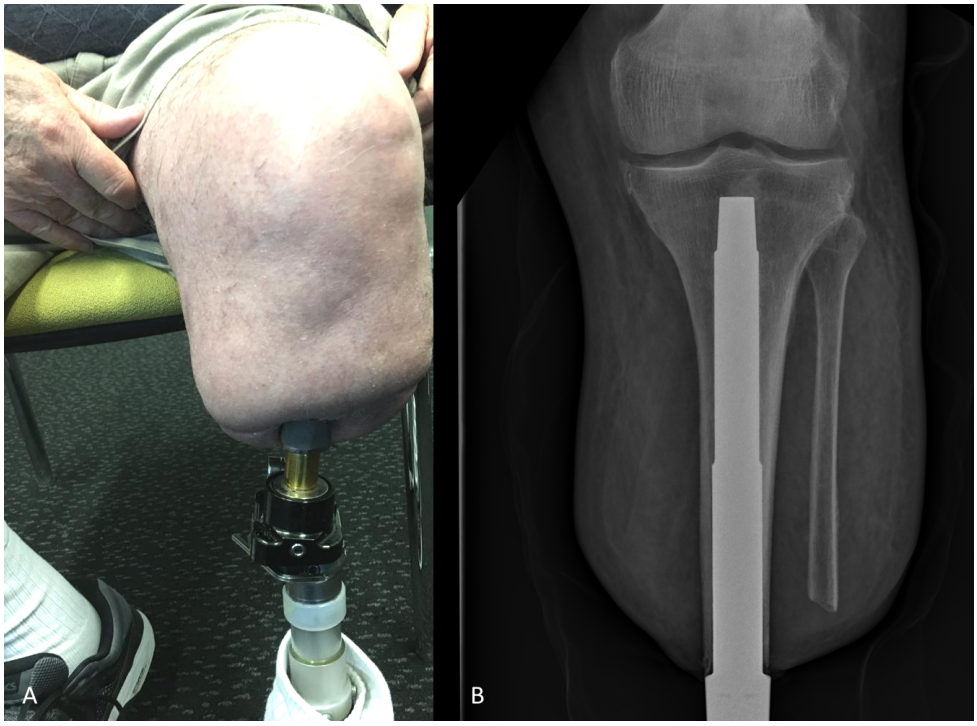

Figure 18. (A) Clinical photograph and (B) radiograph of patient with a transtibial osseointegration.

Two papers investigated the management of two less common complications, but which had never received focus before. First, that of implant-patient size mismatch. As PEPOL remains uncommon worldwide, some surgeons are attempting to perform the procedure but may not have adequate implant sizes available. A surgeon who may be treating only one patient with PEPOL may try to minimise costs by custom-producing only a few implants of varying size, according to the preoperative templating performed based on patient imaging. In one case, this led to the largest available implant still being too small for the patient's true intramedullary diameter[50]. That surgeon decided to cement the implant in place to provide a safe chance for the patient to have PEPOL-like mobility. Although the first few months this patient reported a good experience, within a year the implant loosened and had to be removed. That patient went on to have true PEPOL surgery after successful revision and is now ambulatory.

The other paper that focused on management of complications looked at periprosthetic fractures[60]. Along with infection concerns, this is the other most frequently mentioned concern among surgeons considering PEPOL. Indeed,

periprosthetic fracture and its management is a major area of concern for total joint replacement[117]. Considering that PEPOL patients have an acute change in their limb attachment (due to the PEPOL now being the prosthesis attachment point) they could be at increased risk of falls. Or alternatively, if their bone is so osteopenic as to be unable to bear their weight it might fracture with very low forces. Fortunately, our study revealed fractures occurred in only 6% of all patients who had PEPOL, and only in transfemoral patients. All patients could have standard treatment that is available at almost any hospital that provides orthopedic fracture care (Figure 19). All the patients who experienced a fracture regained independent mobility. Those were all important insights from that paper that no other researcher had previously identified. Additionally, we learned that nearly all fractures occur within 1 year of attaining a new prosthetic leg, whether it be the first year after surgery or several years following surgery. In our opinion, it was the change of balance and proprioception that was the risk factor. This is a very important point that had not been previously identified and that made a substantial impact in the way prosthetists and physiotherapists counsel patients.

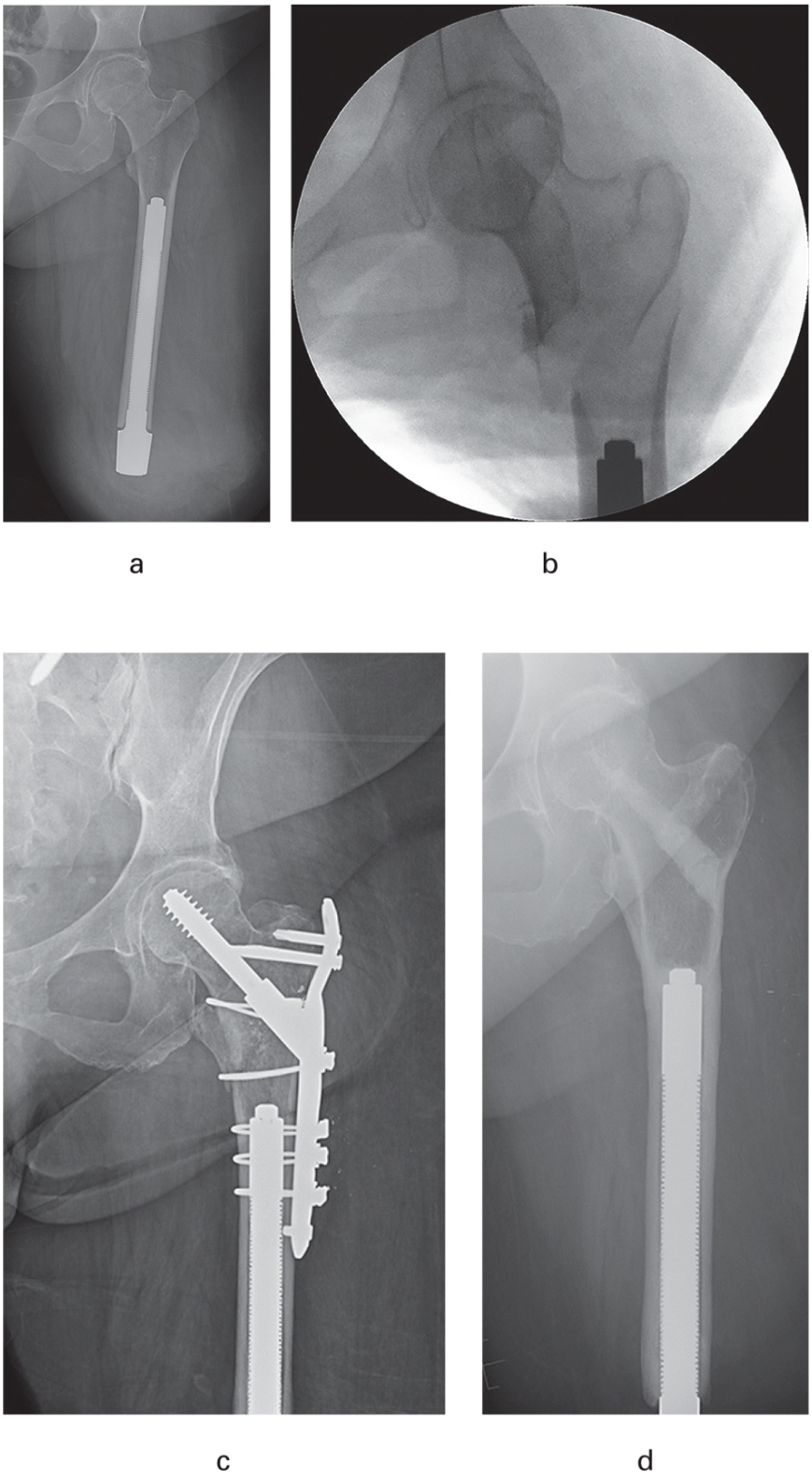


Figure 19. Periprosthetic fracture fixation.
Anteroposterior radiographs (A, C, and D) and image intensification (B) of a 64-year-old woman who had a left transfemoral amputation for chronic infection after total knee arthroplasty. (A) immediate post osseointegration appearance (15 years and two months after amputation). (B) she sustained an intertrochanteric fracture eight months later. (C) she was treated with a hybrid dynamic hip screw with features of a reconstruction plate. (D) there was persistent discomfort, and the hardware was removed one year later. She has not needed further care in the subsequent six years.

As our PEPOL volume became increasingly busy and diverse, it became clear that we needed to ensure we were providing the very best care for our patients. This is only discernible by first understanding what the other standards are. One way of evaluating standards is to systematically review the published outcomes of other surgeons, so we performed this review[118]. As very few surgeons perform this surgery, and because amputee characteristics are so diverse, nearly all published studies lack the rigor to provide confidence in the parameters they investigate. Nonetheless, the areas of interest provide excellent insight into what matters, at least to some patients and researchers. Tactile sensation is important to amputees, as it helps them better interpret and successfully negotiate the ground they walk on; only two published studies obliquely investigated this topic, and we are therefore planning research into this area ourselves. The biomechanics and gait parameters of amputees is extremely complex; there are intimations of better gait with PEPOL vs a socket prosthesis, and this is very expensive to appropriately investigate as it requires a gait lab. PEPOL of course carries an initial expense as it is an additional procedure (whether or not it is performed simultaneously to amputation or later). However, whether the long-term costs are justified is important. Two studies have tried to investigate this but are of insufficient quality to understand whether the better QOL and mobility can be quantified also with respect to economic cost. Patient-reported outcomes are important in all areas of medicine, and unfortunately for amputees there is only one survey instrument[119] and it is not designed for patients with PEPOL. Patient mobility and energy consumption are the most studied aspects of PEPOL, and these are generally clear: following PEPOL, patients are equal, or superior compared to how they were with a SSS prosthesis.

As a world leader for PEPOL surgery, I was requested to write a review of osseointegration, summarising the currently available implants and techniques, as well as providing thoughts about where the field may go in the near future[120]. This review covered the two then-available press fit stem-type implants (Osseointegrated Prosthetic Limb and Integrated Limb Prosthesis) as well as two tried but failed stem-type implants (Intraosseous Transcutaneous Amputation Prosthesis and Percutaneous Osseointegrated Prosthesis), the oldest design screw-type (Osseointegrated Prostheses for the Rehabilitation of Amputees), and a currently

investigated active compression type (Compress). The review also details the morphology, surface design, material properties, and surgical principles of each implant.

These peer-reviewed articles demonstrate the most important developmental milestones in my philosophical and academic progression from a young orthopaedic surgeon to one who is recognised as the world leader in osseointegration. In the coming sections I will describe techniques that I have not yet submitted for publication, and design innovations which currently remain proprietary.

**PART 2 - My Innovative Surgical Techniques for Osseointegration**

Prior to my involvement with PEPOL, there were a few other groups performing PEPOL with different surgical techniques. One of which was the ITAP System from the UK at Stanmore, which has been under a complete veil of secrecy and has not progressed to commercialisation to this date of writing[54]. The Swedish system, led by Dr Rickard Brånemark utilising the OPRA screw fixation device mandates a two-stage surgical technique, minimum six months apart, followed by an extensive 18-month period of rehabilitation[21]. Alternatively, the German system, led by Dr Horst Aschoff utilising the ESKA Endo-Exo Press Fit system also adopted a two-stage surgical technique with six-eight weeks in between stages and patient-led post-operative rehabilitation[45,49]. When I started performing PEPOL I preferred to use a press-fit implant, so I started using the German ESKA system with two-stage surgery. However, from the early days I felt the necessity for establishing a robust rehabilitation protocol that is tailored for different categories of patients. A protocol that was safe and allowed patients with variable degrees of osteoporosis to progress through a gradual program of incremental loading, earlier mobility, and return back to independence.

In 2010 I started performing PEPOL as two stage surgery for above knee amputees. In the first stage I would make an elliptical incision, usually horizontal at

the distal end of the stump, resect the skin and subcutaneous tissue down to the muscular layer, and then depending on the integrity of the prior muscle myodesis or myoplasty I would make a horizontal incision in the muscle layer down to the bursa covering the distal end of the bone. Next, I would excise the bursa and resect the distal most 2.5cm of the skeletal residuum in order to get to healthier cortical bone. I would then identify the sciatic nerve, resect the neuroma and ligate the distal end using 1-0 Vicryl, and then embed the nerve into the surrounding soft tissue. The bone canal would then be sequentially broached using Endo-Exo curved broaches. The Endo-Exo broaches are cylindrical rasps with multiple sharp triangular teeth of 1.0mm in height, randomly oriented on the broach surface to enable scraping of the intramedullary surface of the bone. Broaching the canal is performed sequentially by hammering the broach handle in and out using a mallet until facing significant resistance and the broach becomes rotationally stable inside the canal. The final stage of bony preparation involves a face reamer to flatten the distal end of the bone. Bone that is harvested during this process is then cleaned from any fat and blood clots, and dried using a sponge. The bone graft is coated over the Endo-Exo implant which is then press-fit and impacted into the femoral canal using a mallet. The final implant position is confirmed with an image intensifier.

The soft tissue is then addressed by removing the redundant overhanging muscles, then suturing the deep muscle layer into the periosteum at the base of the implant collar. The more superficial muscle layers are myodesed around the implant collar in a purse string suture fashion. This technique allows the muscles to control the residuum. The subcutaneous fat is thinned without compromising the blood circulation to the overlying skin, the excess skin is removed, and the wound is closed over the implant using skin staples. An occlusive dressing is then applied, and the stump is bandaged using a crepe bandage.

Patients undergo postoperative rehabilitation including range of motion exercises and strengthening, stretching to prevent the development of flexion contractures, and lymphatic drainage. The wound is maintained clean, alternate

staples are removed at two-weeks post-surgery, and the remainder at the three-week post-operative mark.

The second stage surgery takes place six weeks after. With the help of an image intensifier, the centre of the distal end of the implant is located using a guidewire; a coring device is then inserted over the guidewire, coring the skin over the implant in a rotational manner. A measuring device is then inserted into the tapered end of the implant to decide the size of the dual cone by measuring the distance from the implant to the surface of the skin. The dual cone is then attached to the implant and secured by the internal screw, along with the taper sleeve, the bushing, and the distal locking screw.

After the second stage the patients would stay in the hospital for the acute postoperative period, and after a few days they get transferred to a rehabilitation hospital. The dressing is usually a dry sterile gauze dressing, webril cotton and crepe bandage around the distal end of the stoma. It is very common that there will be a significant amount of serous fluid discharge in the early days, some of which has been accumulated between the two surgical stages. This discharge settles gradually over time and the patient usually is fitted with a loading device to allow them to load on a bathroom scale gradually, depending on their protocol, for a period of two to six weeks. These patients will then be fitted with their temporary trial prosthesis to learn how to mobilise with two crutches in parallel bars. The trial prosthesis period lasts until the patient is comfortable walking with crutches, and then the patient is transferred to their permanent prosthesis. The progression in rehabilitation protocol is later discussed in Part Four.

It was after I had operated on my sixth patient, I noticed the development of an infected haematoma in between stage one and stage two. This developed two weeks after the first stage. It was at this point the patient returned to theatre and after the wound was debrided and washed, I noticed that the implant had been solidly fixed inside the femur, so the decision was then made intraoperatively to proceed to the second stage rather than waiting another 4-6weeks. Fortunately, this patient did

extremely well, and this bolstered our confidence in a more accelerated rehabilitation protocol. It was after this incident occurred on a few occasions when I began to question not only the necessity of two stage surgery but also the safety. Another downside of two-stage surgery I found was the significant amount of soft tissue redundancy that was required to close the skin around the 3cm collar of the German ILP implant. Based on these two factors, in 2014 I made the decision to perform single stage surgery.

The move towards single stage surgery resulted in a dramatic shift in our soft tissue management. I began more aggressive soft tissue excision, resulting in minimal distance between the bone and the skin, which solved the issue of soft tissue redundancy. This also resulted in less movement around the soft tissue implant interface, reducing the potential for inflammation and infection and the need to use a longer dual cone due to the once overhanging tissue. This transition to single stage surgery raised the necessity to develop a new implant design that would provide immediate postoperative stability rotationally and axially, allowing the patient to begin early loading rehabilitation. In the next section I will describe in detail how we developed the OPL implant and how that encouraged me to be more confident when performing single stage surgery.

With single stage surgery, the patient undergoes anaesthetics and is positioned supine on the orthopaedic table. I perform a larger elliptical or fish-mouth incision into the distal end of the stump. Depending on the size of the tissue redundancy, I remove skin and subcutaneous tissue fat down to the muscle layer. I make a horizontal incision in the muscle layer down to the bursa of the bone. The bursa is excised completely along with the distal end of the bone, to a healthy margin where there is good cortical bone. The distal end of the bone is physically and radiologically inspected. Using an oscillating saw, I remove any excess bony exostoses, shorten excess bone length, remove severely osteoporotic bone and reshape the distal end perpendicular to the longitudinal canal allowing maximum bony contact with the shoulder of the implant collar (Figure 20).

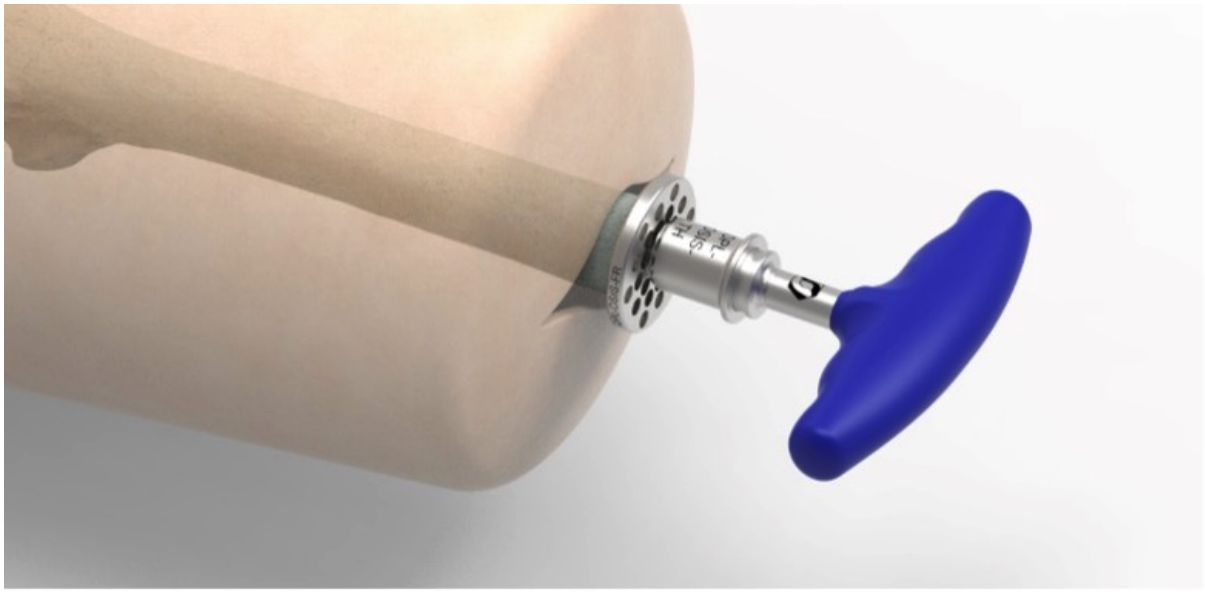

Figure 20. Face Reamer.
After a new amputation level of the bony residuum is established, the distal end is reshaped with a special reamer to achieve a perfectly flat surface perpendicular to the longitudinal canal for maximum bony contact with the implant.

The intramedullary canal is then prepared by sequential reaming using flexible reamers, similar to what is used with the Endo-Exo implant, harvesting the bone that is necessary for future bone grafting (Figure 21). Broaching then takes place using the designated OPL broaches (Figure 22). These broaches are the same shape as the implant. They have sharp cutting fins in the proximal 80 mm of the broach, and they have cylindrical impaction grasps in the distal 80 mm to impact the bone in that area. Sequential broaching is performed until the broach faces resistance to further impaction with a mallet and provides rotational stability. With this new implant design, we engineered a face reamer which is drilled to shape the distal end of the femur to match the shoulder of the implant collar. The bone that is harvested is then reimplanted, once clean, into the bone and impacted using an undersized broach. The definitive implant is press-fit into the bone under the guidance of an image intensifier. The soft tissue is addressed and the nerves are identified, including the sciatic (with its two branches) and the saphenous nerves. Targeted muscle reinnervation is then performed by implanting the common peroneal, tibial, and saphenous nerves into motor branches supplying the biceps femoris, one of the pes, such as semitendinosus, and adductor longus muscles (Figure 23).

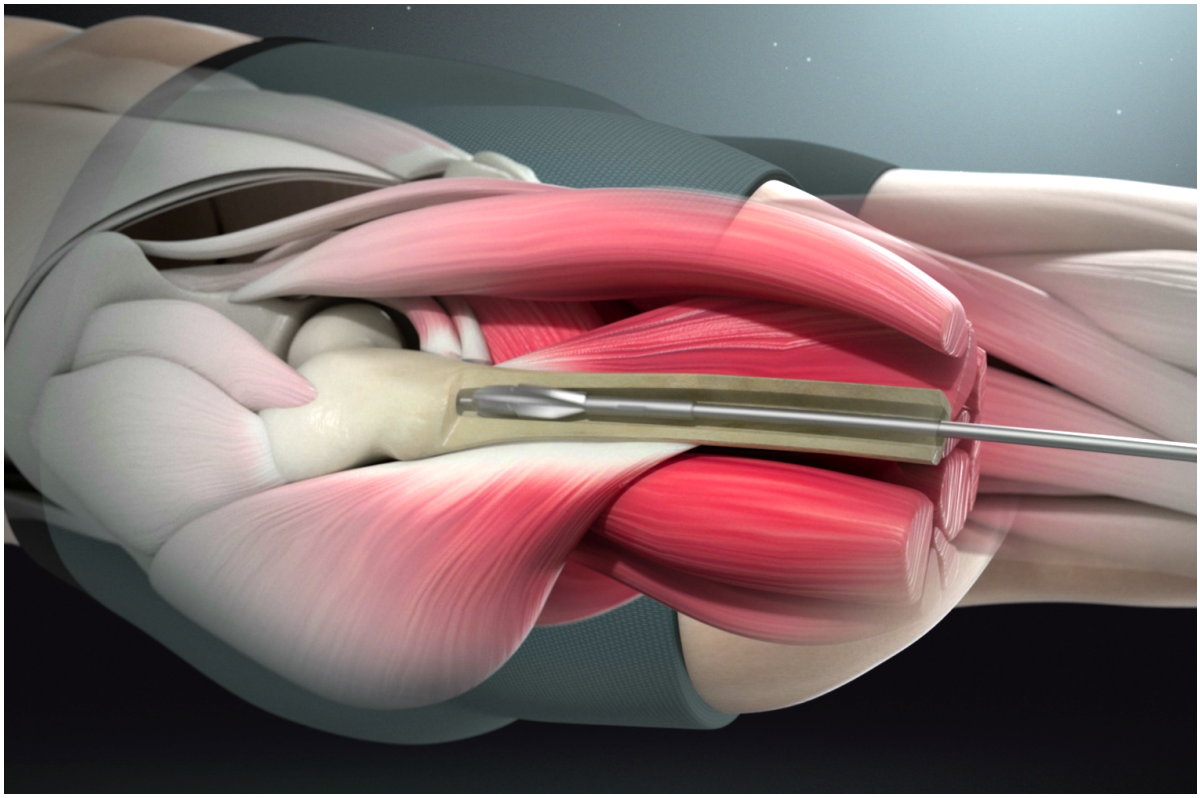

Figure 21. Preparing the intramedullary canal with Flexible Reamers.
Sequential reaming is performed with a flexible reamer until cortical bone is reached. Bone grafts are collected at this phase and reinserted along with the final implant.


Figure 22. Broaching
Sequential broaching of the canal with designated OPL broaches prepares the canal into a suitable shape for receiving the implant. The broaching activities also provide the surgeon direct indication of the fixation level to help determine the ideal implant size (diameter).

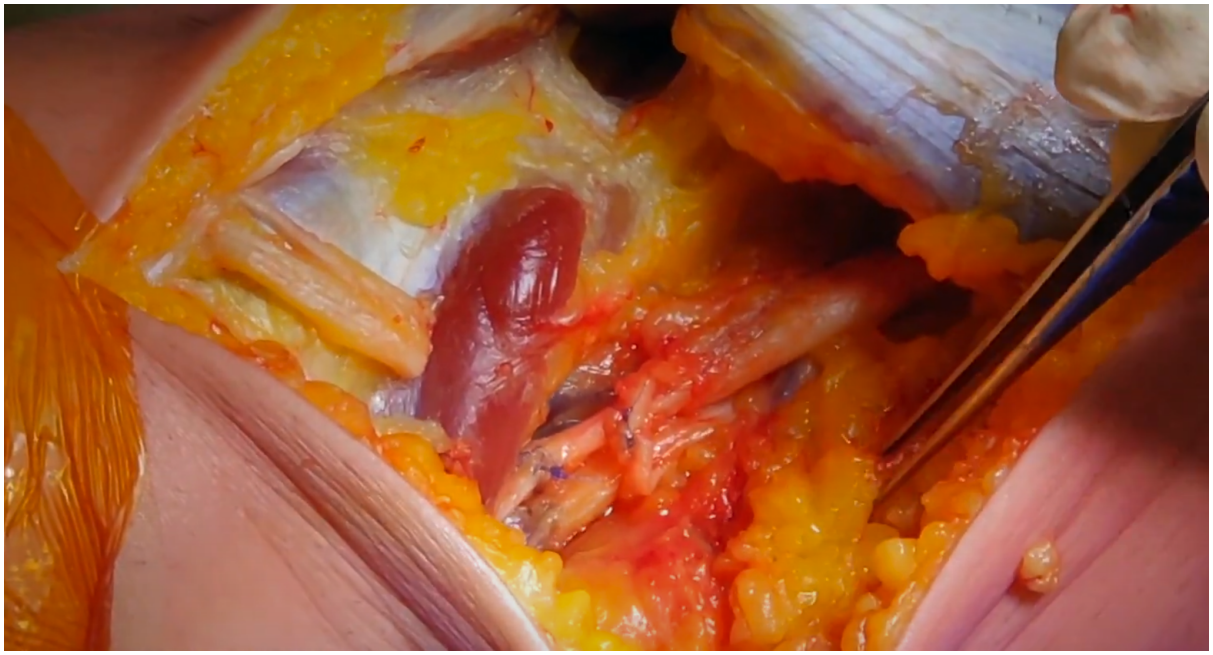

Figure 23. Targeted muscle reinnervation.
This is often performed along with the primary surgery by implanting the common peroneal and tibial into motor branches supplying the biceps femoris, one of the pes such as semitendinosus muscles.

The next step is to address the muscle groups. The deepest layers of muscles are sutured into the periosteum. I always leave the periosteum longer than the bone in order to allow later suturing with the muscles. I suture the deep layer to the bone from all angles around the collar of the implant, and then the fascia of the more superficial muscle layers are sutured around the collar of the implant on both sides, at 3 o'clock and 9 o'clock. I re-anchor the flexors to the extensors utilising their fascia and around the collar of the bone to provide a proper myodesis around the distal end of the implant. The subcutaneous tissue fat is then thinned, without compromising the circulation to the overlying skin. The subcutaneous tissue is closed from both sides of the wound in a firm fashion to prevent any redundancy, by excising the redundant tissue. Depending on the shape of the distal end of the residuum, there are two methods of closing the skin. One is by forming a skin flap over the implant collar and closing the wound completely, then coring the skin using a special device over the tip of the implant. This allows the implant collar to protrude through, away from the wound. If there is insufficient skin to form a flap, then the skin is closed around the base of the collar allowing the implant to protrude through the wound.

To this date there is no consensus as to which is the better approach. I trialed both techniques, and there is no significant difference in the results. Although making a separate core hole in the skin as a skin flap would provide a more cosmetic healing wound, it increases the risk of development of skin necrosis of the area on the edge of the flap, so there are pros and cons with both approaches. Regardless of the approach, the principle of firm closure to minimise soft tissue movement is essential. The skin is sutured using absorbable sutures and no drain is left in situ. The dual cone is then attached to the implant with the internal screw, along with the taper sleeve, the bushing, and the distal locking screw. These patients commence rehabilitation straight away from day one after the surgery and the same dressing is used as if it were the second stage procedure with dry gauze, webril cotton and crepe bandage.

Once I reached the stage of perfecting the surgical technique of transfemoral PEPOL, I decided to embark on helping a more challenging group of patients, the transtibial cohort of amputees, as this represents a larger cohort. The majority of the published literature targeted transfemoral amputees when it came to PEPOL surgery. Very few attempts had been made to perform transtibial PEPOL by the OPRA and the German teams. Both groups came to the same conclusion and abandoned doing the surgery on below knee amputees due to high complication rates. Considering that below knee amputees share the same challenges that above knee amputees face with SSS prosthesis, I felt it was only fair to further explore performing PEPOL in this cohort.

I began performing transtibial osseointegration in 2014. As expected, the journey was not as smooth as with transfemoral amputees and this was due to a number of reasons. Apart from the lack of data to build our techniques and protocols on, there were challenges with different anatomy considering the cross section of the tibia is triangular in shape, while proximally at the metaphysis it widens and becomes cancellous. These anatomical features mandated a change in design of the implant to provide initial stability and later osseointegration. The skin and subcutaneous tissue below the knee is closely adherent to the bone anteriorly and medially while there is significant bulk of soft tissue (both muscle and subcutaneous fat) in the calf. This anatomical change in soft tissue bulk necessitated a shift in surgical management

when compared to my approach with transfemoral amputees, especially given the presence of the fibula. Furthermore, it has been established that vascularity to the lower limb decreases distally which results in problems with healing and an increased chance of surgical failure.

With the aim to maximise osseointegration, I needed to make the implant wider with a rougher surface to match the cancellous bone of the proximal tibia. This was achieved by utilising 3D printing. To supplement the initial rotational stability, I added multiple cross screw fixation through the implant into the tibia (Figure 24).

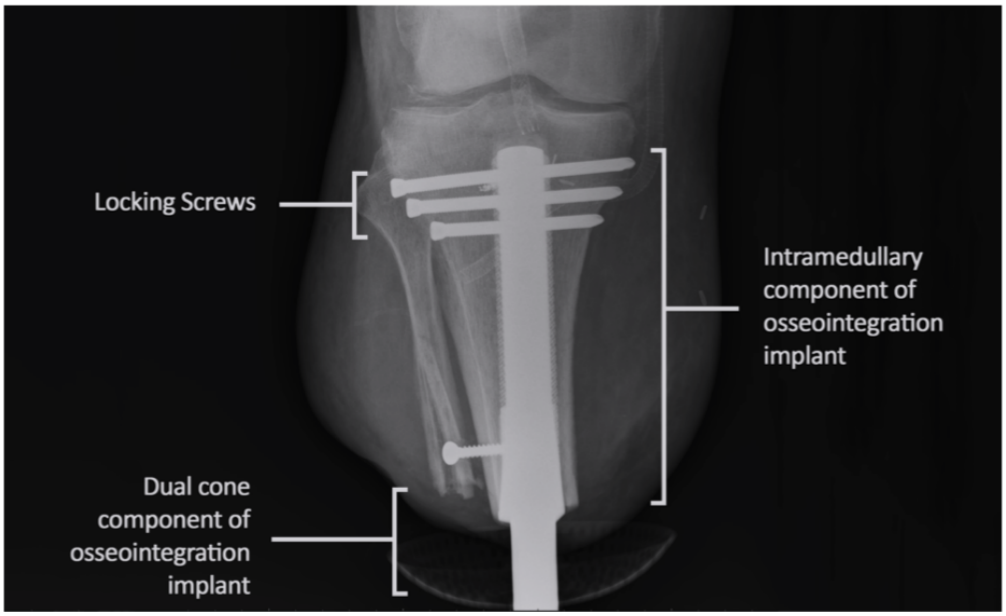


Figure 24. Radiograph of a transtibial implant showing the rough surface structure of the implant and three proximal cross fixation screws.

The surgery is performed by making a horizontal incision over the distal end of the tibia. Care must be taken to preserve the periosteum, as the tibia anteriorly and medially lies just under the skin. The only separating tissue between the skin and the bone is a thin bursa, while posteriorly in the calf there is an abundance of muscle tissue. This soft tissue arrangement makes wound closure around the implant more challenging. I learnt to make a larger posterior flap in order to provide sufficient coverage for later closure.

The bone is then identified and the centre of the canal is located radiologically with the help of an image intensifier. The aim is to position the implant centrally in the tibia on AP and lateral views, considering that due to the pyramidal shape of the proximal tibia, it is possible to malposition the implant in varus or valgus position. Care must be taken during the reaming and broaching steps to ensure accurate positioning of the instruments by using frequent x-rays. Furthermore, there is a significant discrepancy in the cortical thickness of the proximal tibia, as the bone is very thick anteriorly relative to posteriorly and laterally. This makes reaming and broaching more challenging as the bone can be excessively thinned posterolaterally whilst remaining thick anteriorly. Often rasping the anterior cortex is required to balance the cortical thickness. Once the intramedullary canal is prepared, the implant is press-fit in a similar fashion to transfemoral PEPOL surgery. Although I initially incorporated cross screw fixation, I later abandoned this concept as though it added initial stability, I found it was a contributing factor to failure of the osseointegration and subsequent loosening. The bulk of the calf muscle is removed, and the distal end of the fibula is resected 5cm to ensure it is shorter than the residual tibia, facilitating proper wound closure. Targeted muscle reinnervation is performed locally at the stump by re-anastomosing the nerves to motor branches of local muscles. The tibial nerve is re-anastomosed to the soleus muscle, the superficial peroneal to peroneus longus, the deep peroneal nerve to peroneus brevis, and the saphenous nerve to the medial gastrocnemius or tibialis anterior muscles. On occasions the sural nerve is re-anastomosed to the lateral gastrocnemius nerve motor branch. The muscles are re-attached posteriorly and laterally around the tibia by suturing them to the periosteum. In a similar manner to a transfemoral procedure, the wound is then closed using a posterior flap over the distal end of the implant. The remaining steps are similar to that of a transfemoral PEPOL surgery.

## PART 3 - My Osseointegration Implant Design Innovations

### The Endo-Exo Implant and Subsequent Design Improvements

Due to my clinical experience with patients presenting with complex limb deformity and amputation, I have been actively researching PEPOL as an effective treatment option for my patients. I was immediately intrigued by the life-changing nature that this technology may be able to bring to amputees, especially those who are unable to tolerate a traditional SSS. Shortly after I started my practice in Sydney Australia in 2009, I began researching relevant options available in the Australian market, which opened my journey towards a specialty in this field. While the concept of PEPOL has been explored by various research teams for quite some time, there were only two implant designs that reached commercial viability in the market by 2009. These were the OPRA implant originating from Sweden, based on the dental implant concept, as well as the more radical, orthopaedic open mesh surface structure design developed by Dr. Ing. Hans Grundei in Germany. Each of the implant designs carry a number of pros and cons, which through my clinical experiences enabled me to come up with several design changes to perfect and revolutionise this treatment technology.

The German implant, now more commonly known as the ILP-System, was initially registered and manufactured by the German company ESKA Implants as “Integrales Prothesen System, Endo-Exo Prothese” (translated: Integral Prosthesis System, Endo-Exo Prosthesis). As part of a commercial asset deal, the UK based Summit Medical Group acquired the assets of ESKA Implants in April 2010 and renamed the company Orthodynamics. As a result of that, the Endo-Exo Prosthesis was renamed to Integral Leg Prosthesis, also known and described as ILP, without making any design changes. The majority of the ILP components were manufactured out of cast cobalt alloy (CoCrMo) in accordance with ISO 5832-4, and considers the natural bow and antecurvation of the femur (r=1,700). In order to ensure a reliable osseointegration in the femur, the femoral stem has a Spongiosa Metal® surface

structure, which was also used in various other orthopaedic implants on the market. Bony integration of the femoral stem is promoted by means of this three dimensional, macroporous grid structure. The surface features a three-dimensional interconnected grid micro-architecture which is adapted to the human cancellous bone structure (Figure 25). This Spongiosa Metal® surface structure is not a coating, but rather part of the casting process of the implant which makes it unique in nature. This feature provides the macroscopic potential of not just bony ongrowth but bony ingrowth and penetration, which lead to complete osseointegration between the implant and the bone (Figure 26).

Figure 25 Spongiosa Metal®
This was developed to mimic the structure of cancellous bone and is clinically shown to achieve good levels of bone integration over time [113].

Figure 26. Figure 26. Magnified image of the Spongiosa Metal® surface showing that this structure is part of the implant core rather than being a coating. Osseointegration showing the bony penetration.

In the early days, a major obstacle for the success of transcutaneous implants was considered to be the implant–skin interface due to common complications at this site including infection, marsupialisation (epithelial down growth and pocket formation), and permigration (the gradual extrusion of a percutaneous implant secondary to inappropriate epithelial growth) all of which can ultimately lead to implant failure. Several attempts have been made by different groups such as the original ESKA team, the ITAP team in the UK, as well as Dr. Ronald Hugate in the US, to create a region of soft-tissue ingrowth into the implant in order to form a concealed implant-skin interface. Materials such as a plasma spray porous skirt section (Figure 27) or porous tantalum and HA coated flanges (Figure 28) have been explored in various publications and animal studies. However, clinical evidence supporting this design has so far been absent. In fact, based on our experience, the highly porous yet rigid nature of these implant-skin interfaces often resulted in more irritation to the soft tissue region during ambulation, and made any treatment strategies for managing infections much more difficult.

Figure 27. An older design of the Endo-Exo Implant
Featuring a rough and porous soft-tissue interface (Lunow et al. 2010). *An implant designed and patented in the US also employing a similar approach with a coarse Porous Material Skirt made of porous Tantulum*[122].

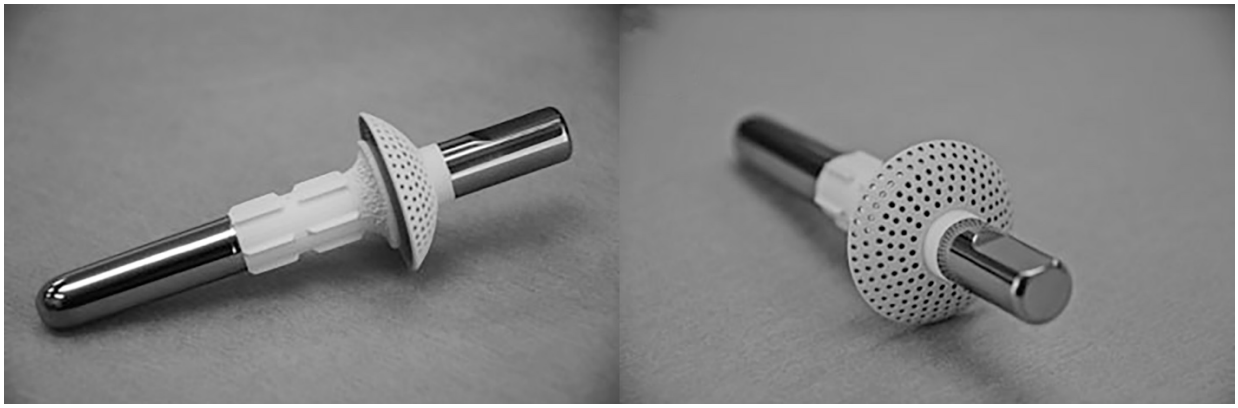

Figure 28. HA coated implant surface (ITAP).

In contrast with a rough, porous surface structure, I observed that dental implants, as well as the PEPOL device designed by the Swedish team, made very little interventions in the stoma region and kept the transcutaneous portion a natural cylindrical structure. This led to my hypothesis that a simplified stoma management approach would be more appropriate in this application and was later clinically demonstrated to be correct. These ideas translated towards the initial

conceptualisation of a smooth transcutaneous region on the ILP system, which was the complete opposite to what had been attempted previously. Instead of a rough region to encourage soft tissue attachment, I adopted a highly polished surface to decrease soft tissue attachment. A further coating was introduced based on Titanium Niobium (TiNb or TiNb(ON)) for even lower friction, improved biocompatibility, as well as  antimicrobial properties (Figure 29). The low friction of this cylindrical transcutaneous region was later shown to offer much better clinical outcomes due to the following advantages:

- Low friction enables the soft tissue to move up and down naturally during ambulation, resulting in less irritation, inflammation and infections.
- The inner soft-tissue skin-bone interface naturally reduces and attaches to the distal portion of the bony periosteum.
- Any potential inflammation or infections can simply be drained through the interface and easily flushed in a clinical setting whenever required.

Along with improved surgical techniques, particularly in soft-tissue management as well as adopting a single-staged approach, a complete redesign of the ILP implant was introduced through the implementation of these concepts, which resulted in a greatly improved overall success rate of PEPOL at the time.

Figure 29. Newly designed ILP implant.
Reintroduced based on my design inputs featuring a completely smooth distal transcutaneous region that is highly polished and coated with a TiNbN ceramic layer to achieve minimal friction to the skin.

## Development of the OPL implant

While the improved version of the ILP implant resulted in a much better clinical outcome, after regular clinical use in my own practice, I further identified several issues that we were able to improve. First were the underlying material properties of the cast cobalt alloy (CoCrMo) used in the construct of the ILP design. This material, while biologically inert, is inherently stiff, often leading to issues such as stress-shielding and subsequent bone resorption at the distal end of the implant (Figure 30). The inherent inert nature of CoCrMo also greatly limits the structural integrity due to the necessity of a non-structural spongiosa region, resulting in a very narrow core and compromised structural strength (Figure 31). The cylindrical shape of the implant translates to limited rotational stability of the implant, resulting in several clinical cases where the implant inadvertently rotated early post-operatively.

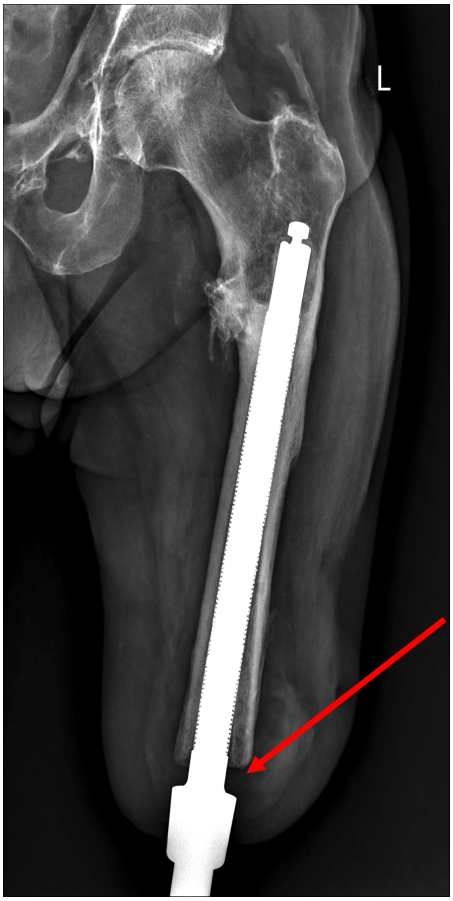


Figure 30. Stress shielding at the distal portion of the implant.
While the ILP integrates well with the femoral canal over time through the spongiosa surface, the distal portion of the implant lacks the coating and as such, results in the reabsorption of the distal femur end.

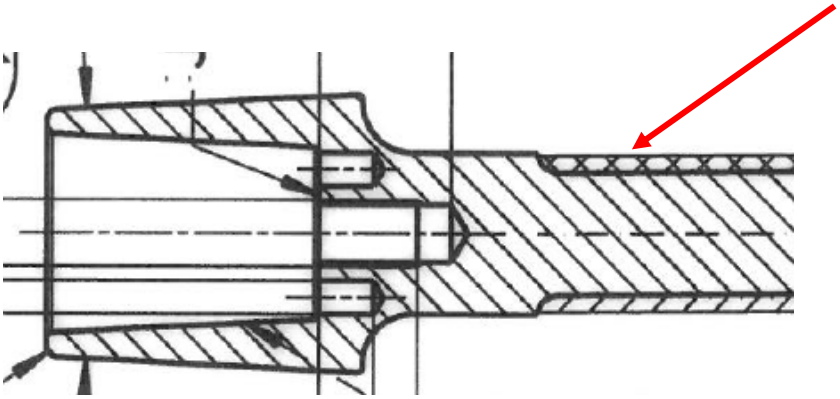

Figure 31. ILP implant cross section.
A mechanical drawing of the cross-section of the ILP implant showing the spongiosa coating region for bony integration. This spongiosa region provides limited structural support to the overall implant strength and the load is taken up through the narrow implant core.

In my opinion, the biggest design flaw of the ILP implant was the distal portion. (Figure 32). The segment distal to the Spongiosa Metal® is smooth and represents a 15mm area that is 1mm wider in diameter. If this wider diameter is not accommodated for by the surgeon during bone canal preparation, a fracture can result during stem insertion. Simply, the original design of the Endo-Exo rasps did not accommodate for this wider section. Even with successful implantation without fracture, this section was often the area where stress shielding occurred due to its smooth surface which did not allow osseointegration. Furthermore, the point of transition from the Spongiosa Metal® portion of the implant to the smoother wider area created a stress raiser on the implant. This was due to the fact that the Spongiosa Metal® portion often is well osseointegrated, while the adjacent smooth area is not. There have been several cases of implant fracture at the transition point[60].

Figure 32. The ILP implant has a 1mm wider smooth surface segment of 15mm in length.

In order to overcome these limitations, I began conceptualising the next generation implant that utilises more modern materials and manufacturing methods. Based on my experience with many orthopedic devices, titanium alloy became the obvious choice due to its superior osteoconductivity, lower elastic modulus, and lighter weight. Taking the successful design characteristics of the ILP implant and coupling it with a modernized titanium-based manufacturing technology, I was able to develop a new implant design called the Osseointegration Prosthetic Limb (OPL) (Figure 33), which has now become the most widely used PEPOL implant in the world [121].

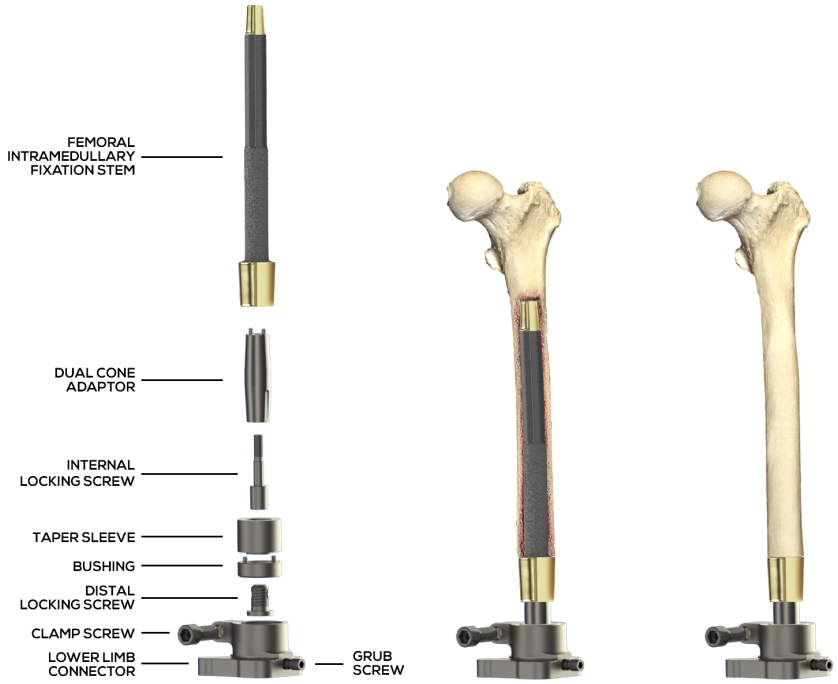


Figure 33. An overview of the Osseointegration Prosthetic Limb (OPL) implant.
Designed in Australia and manufactured by both Osseointegration International Pty Ltd in Australia and Permedica S.p.a in Italy.

During the development of the OPL implant, the introduction of the titanium alloy enabled me to change the implant design from the spongy surface structure of a cylindrical implant to a plasma sprayed pure titanium coating, identical to many modern arthroplasty implants. The distal half of the implant is coated with porous Ti plasma spray that is designed to facilitate rapid osseointegration. In order to provide immediate rotational stability, the proximal half of the implant was made with ten sharp

longitudinal fins, 1mm in height, creating grooves inside the inner cortex during implantation (Figure 34).

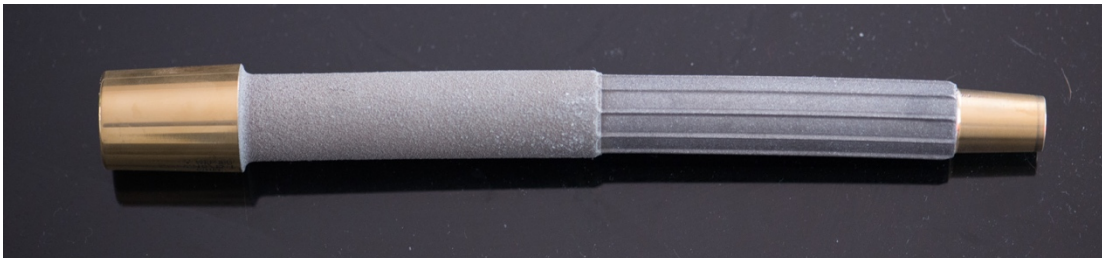

Figure 34. A view of the OPL implant showing the distal half with coarse porous coating and a narrow proximal half with longitudinal sharp fins.

To address the distal bone resorption, I made the distal half of the implant 1mm wider with a much coarser porous coating. This would allow the osseointegration and the bone loading to be concentrated distally. The collared part of the implant at the distal end was also coated with Ti plasma spray coating all along the shoulder region to provide immediate axial stability (Figure 35). All these features add immediate stability to the implant design and encourages early osseointegration which facilitated the transition to single stage surgery.

Figure 35. A view of the OPL implant showing the distal portion with the plasma spray coating along the shoulders of the collar.

In addition to the original ILP design, in order to allow the implant to be suitable for use with a wider range of patient anatomy, I further introduced variants (Type B/C) to the OPL range incorporating a distal flared portion to reduce implant subsidence as well as a proximal lag screw option for patients with a short bony residuum (Figure 36). Although the majority of patients are suitable to be fitted with a Type A OPL implant, the characteristics of Type B & Type C implants were necessary to provide better coverage of challenging anatomy presentations, especially when working with traumatic and congenital amputees.

Figure 36. Type A, B C variants of the OPL system.
Designed to enable the system to cater towards patients presented with a standard (Type A), long (Type B) and short (Type C) bony residuum. The Type B and C implants featured a flared collar distal end and allowed the implant to recess into the femoral canal. The Type C also features a lag screw hole to enable additional fixation through the femoral neck when required.

Considering that a significant portion of amputees are elderly and would eventually develop arthritic changes in the hip joint, I added a proximal taper that can attach to a modular hip arthroplasty stem (Figure 37).

Figure 37. The proximal taper of the OPL implant allowing for attachment of a hip arthroplasty stem.

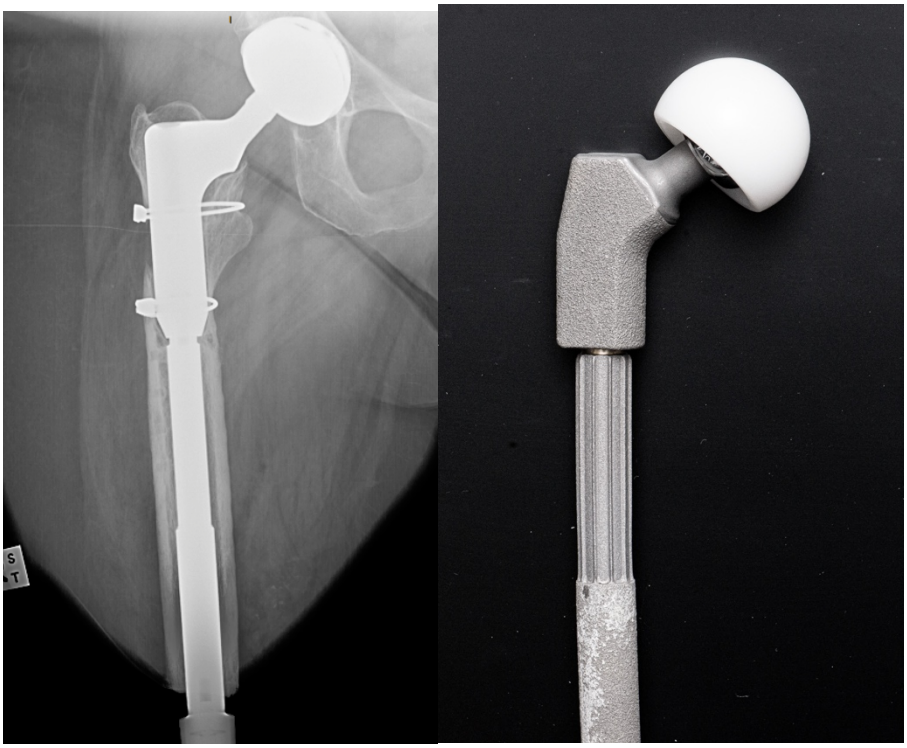

Figure 38. The proximal attachment of a modular hip arthroplasty stem to an OPL implant.

These designs ultimately led to the regulatory approval and commercialisation of the OPL device in both Europe and Australia, and was recently granted a worldwide patent [123] application. These new implant characteristics offered by the

OPL combined with a completely revamped surgical technique and rehabilitation protocol, which I will discuss in subsequent sections below, enabled the successful transition to single-staged PEPOL. Compared to the original established precedent of 8-12 months of rehabilitation, my team and I were able to shorten the entire reconstruction period to 4-6 weeks, greatly improving the feasibility of this technology and enabling more amputee patients to be able to benefit from it.

## PART 4 - My Innovations in Rehabilitation Strategies for Osseointegration Patients

In most areas of orthopaedic surgery, the rehabilitation strategies receive far less attention. Surgeons tend to get more involved with overseeing aspects such as indications, patient selection, implants, surgical technique, imaging characteristics, and complication rates. Even for extremely common surgeries such as rotator cuff repairs, which have long-term engaged therapy after surgery, comparisons of rehabilitation techniques are almost entirely consensus-based rather than evidence-based[124]. For PEPOL, only one other author has published a postoperative rehabilitation strategy, and that remains as a preference without evaluation or comparison[94]. I am currently preparing our transfemoral postoperative rehabilitation protocol for peer review, which is summarised in the table below. Since nearly every patient is treated with a single-stage PEPOL, I no longer maintain a typical protocol for patients in between the first and second stage; those who have a two-stage surgery simply work on their range of motion in their ipsilateral limb before having the second stage. The Swedish team have their own rehabilitation protocol that is essentially dependent on slow but gradual loading of the implant, followed by training while wearing a prosthesis over a lengthy period that may extend to 18 months[19]. The Germans did not follow a structured rehabilitation protocol and have not published anything regarding rehabilitation to date. Considering that I used a very similar press-fit implant technology to that of the German system, I could not use the Swedish protocol which was based on a screw-fixation device. I therefore established an OGAP-OPL rehabilitation protocol in 2010 that would be more

suitable for press-fit implants. This protocol has been updated over time to accommodate implant design improvements in accordance with our learning curve and patient feedback. The rehabilitation process starts the day following surgery and is divided into six phases (Table 3).

Table 3. Phases of Rehabilitation

| Phase | Prosthetist | PT Goals and Frequency | Hands-On Treatment | Exercises | Self-Care |
|---|---|---|---|---|---|
| 1: Exposure<br><br>Fit patients with strong bone can be Fast (0-2 weeks)<br><br>Others Slow (0-6 weeks) | 1. Choose prosthetic option<br>2. Measure and template a training leg | 1. Load 50% BW, good alignment, minimal pain<br>2. Control swelling<br>3. Intact leg SL balance<br>4. Full ROM exercises<br>5. Fitting with training leg | 1. Gentle residual limb massage and lymphatic drainage<br>2. Desensitising therapy<br>3. Muscle release of gluteals, rectus femoris, adductors as required | 1. Static axial loading 5kg, 20 min twice daily.<br>2. Increase 5 kg/day until 50 kg or 50% BW | 1. Prone lying<br>2. Showering<br>3. Incision remains uncovered<br>4. Moderate sun exposure can promote dryness and bacterial control<br>5. Start salt baths week 2 |
| 2: Dependence<br><br>Patients introduced to skills but require high supervision | 1. Fitting and adaptor education<br>2. Adjustment for alignment | 1. No unsupervised walking or prosthesis wear for 2 weeks (prevent falls)<br>2. Supervised 2 x FC walking<br>3. Balancing with training leg<br>4. Independent don/doff<br>5. Independence with HEP with prosthetic leg | 1. 2 x FC for 6 weeks after prosthesis fit<br>2. Flat indoor walking<br>3. No turns/pivots<br>4. 5-10 minute sessions x3 with rest<br>5. Stairs: step-to GAS/SAG<br>6. Video and Mirror feedback | 1.PT 5-6 days weekly, 2-3x sessions daily for gait training | 1. Daily HEP: strength and stretching<br>2. Ice and compression pre/post PT<br>3. Daily salt baths<br>4. Weekend rest<br>5. Wear prosthetic limb for rehab walking and exercise only |
| 3: Transition<br><br>Patients begin early independence | 1. Alignment review<br>2. Weekly increases in prosthetic height<br>3. Consider increasing knee resistance | 1. Independent 2 x FC walking<br>2. Improve balance and strength<br>3. Ramp training | 1. Mostly learning to “ride the knee”<br>2. Ramp training | 1. Taper gait training PT to 3-4/week | 1. Wear prosthesis at meals, rehab walking, and exercise only<br>2. Daily strength and stretching |
| 4: Development<br><br>Patients develop their routines and preferences guided by clinicians | 1. Fortnightly increase knee resistance<br>2. Achieve even leg length<br>3- Optional: introduce microproces | 1. Start alternate crutch gait<br>2. Increase prosthesis wear to near full-day<br>3. Begin uneven ground and outdoor walking | 1. Alternate crutch training<br>2. Ramp training<br>3. Hard ground outdoor walking<br>4. Controlled simulated uneven ground walking<br>5. Weaving and tight space walking | 1. Taper gait training PT to 2-3/week | 1. Improve independence |

| | | | | | |
|---|---|---|---|---|---|
| | sor knee | | | | |
| 5: Maturation<br><br>Patients begin to determine and assess goals | 1. Permanent full weight prosthesis | 1. Single FC without gait pattern regression<br>2. Improve distance endurance<br>3. Progress uneven ground stability with single FC<br>4. Begin stair mode practice (microprocessor knee) | 1. Obstacle and decision challenges<br>2. Grass and uneven outdoor mobility<br>3. Fall training | 1. Taper gait training PT to 1-2/week | 1. Wear leg entire day |
| 6: Maintenance<br><br>Nearly all patients achieve independence by 3-6 months | As required only | 1. Taper to cane/unaided per patient skills/goals<br>2. Independence with up-stairs mode (Microprocessor controlled knees) | 1. Progress obstacle, decision, surface challenges | 1. Taper gait training to as needed only | 1. Patient becomes self-directed "expert" in prosthesis use |

BW= body weight. PT=physiotherapy. SL=single leg. FC=forearm crutches. HEP=home exercise program. GAS/SAG=order of gait when training stairs: good-affected-stick (up) then stick-affected-good (down).

**Phase one, Exposure.** The goal of this phase is to expose patients to each of the categories of rehabilitation: physiotherapy, prosthetics, hands-on treatment, exercises, and self-care. Some patients have never had physiotherapy, and those who have, may have not had it for an extended period or may have been exposed to varying levels or have different expectations. It is important for the patient and therapist to become familiar with one another, to build trust and understand the patient's abilities and limitations. This is similar to the patient's relationship with their prosthetist. The physiotherapist must expose the patient to skills and techniques such as axial loading, joint-mobilising exercises, and self-care strategies. Many patients have developed joint contractures, and these must be reduced as much as possible; for example, hip flexion contracture is the most common, and lying prone is a simple and effective strategy for patients to reduce that contracture gradually. One critical decision that must be made by the surgeon is whether a patient is to be on the Fast or Slow progression protocol. This is based on the overall health and fitness of the patient, and involves assessment of the patient's muscular strength, physical stamina to participate in physiotherapy, and, perhaps most importantly, the bone

quality at the time of surgery. Avoiding significant setbacks such as periprosthetic fracture or implant pull-out is absolutely critical to the ultimate success or failure of the surgical procedure.

**Phase 2, Dependence.** When the patient has acclimated to the goals of the Exposure phase, they are ready to do early activities, but remain dependent on the prosthetist and physiotherapist. Early fitting or sizing for a lightweight temporary prosthesis can occur. The patient can walk, but only under the highly attentive supervision of the physiotherapist, as their equilibrium is usually poor and they do not have adequate balance skills and fall mechanisms learnt and able to be executed. It is critical for every patient to continue with bilateral forearm crutches for at least six weeks while their body relearns their balance, their confidence in their gait improves, and they come to internalise this new limb. Healthy people do not learn to ice skate in a week, and neither can people learn to walk with a new leg immediately. It is also critical to avoid significant torsional force. While the implant is strongly held to the bone within the first few weeks, the bone itself remains osteopenic until it has had adequate time to remodel in response to loading. While this exact number is not known, it almost certainly takes at least six weeks as that is the time for early osteoclastic resorption and osteoblastic deposition for fractures. Tubular bone is by nature most susceptible to fracture by torsion[125], so two forearm crutches or parallel bars must be used at all times. During this phase patients should begin to develop habits of a home exercise program (HEP) which they will maintain in a focused manner during the 3-6 months following PEPOL and then continue to adhere to for the rest of their active lives.

**Phase 3, Transition.** This phase is characterised by patients transitioning to understanding themselves in the context of their new extremity. They can begin to explore early intimations of independence, such as identifying what fits their gait while developing greater confidence and gaining comfort with their prosthesis fitting. They can begin to walk with reduced supervision, still using two forearm crutches. They can begin ramp training and start to involve the knee joint within their normal gait cycle, something that is notoriously difficult to acquire considering they have

often ambulated with a grossly distorted gait for many years previously. They can start to taper their gait training if the physiotherapist feels they are able to self-coach and guide their own development. They are still limited to wearing the prosthesis at exercise and meals (to train sitting and standing from a chair) to prevent excessive muscle fatigue, so they are not truly independent for an entire day at a time yet.

**Phase 4, Development.** As the patient develops their preferences and routines as an osseointegrated amputee, they continue their transition from the prior phase towards independence and decision making. Fewer prosthetist visits are necessary as the patients become more stable in their gait and acquire functional muscle balance. For patients that choose to use a microprocessor-controlled knee joint, this is usually the best time to introduce it. At the prosthetist and physiotherapist's guidance, the patient can begin to wear the prosthesis all day long, as they have learned how to avoid torsional forces. As variable contoured ground is introduced, patients can rapidly progress their independence. However, bilateral forearm crutch use still remains critical, as patients are only beginning to be introduced to these different surfaces.

**Phase 5, Maturation.** At this phase the patient begins to determine and assess their goals. They may still need additional prosthetic visits for minor adjustments. They can begin to truly develop muscular stamina, as they have been wearing the prosthesis nearly or indeed all day long. Now permitted to use just one forearm crutch, they can work on balancing with a light load such as a grocery bag in their other hand. They should be able to carefully navigate varying surfaces with minimal supervision. Increasingly complex challenges and decision making, such as what route to take through simulated obstacles that may exist in city walking or country roads, are introduced commensurate with their level of skill. Safe falling training is critical to mitigate the risk of injuries or periprosthetic fractures. They can gradually taper their gait training sessions to one per week or fortnightly.

**Phase 6, Maintenance.** The patient is now using their permanent full weight prosthesis and wearing it nearly all day, has learned to fall safely, knows how to navigate most surfaces and stairs, and is tapering to one cane or no assistive device. They should now be considered capable of full ownership of their mobility and prosthesis requirements. Just like maintaining general health, exercise and practise are critical to maintaining the learned skills, and patients should repeat self-training sessions regularly, and continue to safely challenge themselves to become intimately familiar with their osseointegrated limb and how they use it in their own daily life.

## FUTURE GOALS AND POSSIBILITIES FOR OSSEOINTEGRATION

The field of osseointegration has existed for almost 30 years and now appears to be on the verge of greater acceptance and widespread implementation. Beyond providing an excellent mobility solution for an expanding spectrum of long bone amputees, some patients with a hip disarticulation, hemipelvectomy, or flail arm due to brachial plexus avulsion have already had their mobility or quality of life improved by relatively simple technical improvisations to the established fundamentals of osseointegration. Amputation and osseointegration may even prove to be a favourable alternative when compared with limb-salvage megaprosthesis for patients with appendicular skeletal tumors or those who have debilitating chronic pain in an extremity such as persistent complex regional pain syndrome [120]. In this section I will review the current challenges and future prospects of osseointegration limb reconstruction for amputees.

### A- Advances in Infection Prevention and Control

One of the biggest challenges to overcome before osseointegration surgery will be considered acceptable in the wider medical community is the risk of infection, due to the inherent nature of the surgery with an exposed implant. Almost all orthopaedic surgeons would regard exposed metal as the *sine qua non* of an implant infection, yet this is an integral part of the PEPOL strategy. Over the past two decades there have been many advances in infection prevention and eradication from arthroplasty implants, and similar principles can be also applied to PEPOL surgery. The following discussion provides some of the approaches currently being investigated for future applications in orthopaedic implants, and these provide a potential template for the development of the next generation of osseointegration implants.

#### 1- Smart Implant Coating:

New approaches to improve bone-implant integration should resolve the fundamental dilemma of uncontrolled inflammation by precisely switching on/off peri-implant inflammation. Inflammation characteristic of normal wound healing is required at early stages but should be suppressed later for better healing and osseointegration. A bioresponsive, endogenously triggered, smart coating material has been developed to sequentially harness and then subsequently abolish the power of inflammation to improve osseointegration, which represents a new strategy for designing immunomodulatory biomaterials for tissue regeneration. “Bridge-burning” coating material that comprises a macrophage-activating glycan covalently crosslinked by a macrophage-eliminating bisphosphonate to titanium implant surface has been designed. Upon implantation, the glycan instructs host macrophages to release pro-osteogenic cytokines (“switch-on”), promoting bone cell differentiation. Later, increasingly mature bone cells secrete alkaline phosphatase to cleave the glycan-bisphosphonate complexes from the implant, which in turn selectively kill the proinflammatory macrophages (“switch-off”) that have completed their contribution; hence, in the manner of “burning bridges”, and to promote healing and optimise PEPOL [126]. Another smart biodegradable implant coating with poly (ethylene glycol)-poly (propylene sulfide) polymer provides a controlled, "smart" local delivery of antibiotics, that combines passive elution of antibiotic with an active-release mechanism that "targets" bacteria and helps in decreasing the bacterial burden. This strategy could be used to prevent postoperative implant-related infections [127].

**2- Mechanical inactivation of Staphylococcus aureus and Pseudomonas aeruginosa:**

Titanium is the material of choice for the manufacture of orthopaedic and dental implants because of its excellent corrosion resistance and proven biocompatibility. The incidence of premature implant failure due to implant-associated infections, however, remains a major concern for clinicians. Titanium substrata possessing micron-scale surface architectures have been fabricated using a process of mask-less plasma etching of bulk titanium for periods of 5, 10, 20, 30 and 40 minutes. The resultant

surfaces were characterised using two-dimensional Fast-Fourier Transforms (2D-FFT), scanning electron microscopy (SEM), and atomic force microscopy (AFM), highlighting the formation of a two-tier pillared surface topology at the maximum etch period. Each of the substrata were assessed for antibacterial efficiency against two common human pathogens, Pseudomonas aeruginosa and Staphylococcus aureus bacteria, achieving maximum antibacterial efficiencies of 87.2 ± 2% and 72.5 ± 13%, respectively. Significantly, the formation of these three-dimensional (3D) hierarchical features has been found to minimise the extent of attachment of Staph aureus cells, directionally trapping the cells inside the micron size pillars with the second tier of pillars acting to kill the cells. The results of this work shed new light on the development of smart mechano-bactericidal surfaces based on tuning their micron-scale surface topology, and suggest that such complex hierarchical surfaces can be particularly effective towards inactivation of cocci bacteria, including Staph aureus [128].

### 3- Biofilm eradication:

Biofilm formation is currently the single greatest challenge in the treatment of bone-implant-associated infections, resulting in tolerance to both the immune system and most antibiotics. A synergistic photothermal/photodynamic therapy (PTT/PDT) strategy aiming for biofilm eradication on titanium (Ti) implants, integrated with MPDA loading with photosensitizer Indocyanine Green (ICG) by π-π stacking, has been developed. A therapeutic system consisting of mesoporous polydopamine nanoparticles (MPDA) to combat biofilm has been studied. MPDA has been functionalized with RGD peptide to endow the modified Ti sample (Ti-M/I/RGD) with enhanced cytocompatibility. More importantly, the Ti-M/I/RGD implant remarkably kills Staph aureus biofilms with an efficiency of 95.4% in vivo upon near infrared (NIR). After biofilm eradication, these implants still display excellent osteogenesis and osseointegration performance. Overall, this study provides a viable PTT/PDT strategy for the development of antibacterial Ti implants for potential orthopaedic applications [129].

4- **Simultaneous Monitoring of Loosening and Temperature in Orthopaedic Implants:**

Implant failure can have devastating consequences on patient outcomes following joint replacement, and the same holds true for PEPOL. Time to diagnosis affects subsequent treatment success, but current diagnostics do not provide adequate early warning and lack diagnostic sensitivity and specificity. An embedded ultrasound system to monitor implant fixation and temperature as potential indicators of infection has been studied. Requiring only two implanted components, a piezoelectric transducer and a coil, pulse-echo responses are elicited via a three-coil inductive link. This passive system avoids the need for batteries, energy harvesters, and microprocessors, resulting in minimal changes to existing implant architecture. This simple smart implant approach minimises the need to modify well-established implant designs and could therefore enable mass-market adoption [130].

**5- Realtime information on implant infection:**

Millions of orthopaedic implant procedures are performed annually. Nonetheless, 15% of these implants fail, mainly due to poor osseointegration and/or bacterial infection. Real-time monitoring of the physiological parameters at the tissue-implant interface can reveal important information about the onset and severity of infection, allowing for more timely intervention. Iridium oxide sensors are the most suitable of the putative devices due to their low drift, high sensitivity, and high durability. This information can also be transferred indirectly to an external device, such as a smartphone or tablet, providing the potential for real-time monitoring of the local conditions [131].

**6- Adjuvant therapeutic agents - Delivery Options:**

Adjuvant therapeutic agents such as recombinant growth factors, lipid mediators, antibiotics, antiphlogistics, and proangiogenics, as well as other promising anti-resorptive and anabolic molecules may be able to contribute to improved bone healing and osseointegration, especially when they are released in a targeted and controlled manner during crucial bone healing phases. The development of smart biocompatible and biostable polymers such as implant coatings, scaffolds, or particle-based materials for drug release will be a crucial component. Innovative chemical, physical, and biochemical approaches for controlled tailor-made degradation or the stimulus-responsive release of substances from these materials, and more, could all prove to be advantageous [132].

**7- Nanotechnology and Nanomaterials:**

Nanotechnology has the potential to provide a plethora of novel tools for applications in translational orthopaedic research and may eventually revolutionize the biomedical fields. The demerits of the clinically available orthopaedic implants include poor osseointegration at the tissue-implant interface, which subsequently results in loosening due to low inadequate mechanical fixation, immunological rejection, production of wear debris, and implant-related infections. Nanomaterials are promising for orthopaedic applications because of their excellent tribological properties, wear and tear resistance, sustained drug delivery, osseointegration, and tissue regeneration capabilities [133].

**8- Nanobiotechnology - Prevention and Treatment of Orthopaedic Implant Associated Infection:**

Nanobiotechnology has shown remarkable progress in recent years, particularly in biomaterials, diagnostics, and drug delivery systems. Many of these advanced strategies hold genuine promise for the prevention of orthopaedic implant related

bacterial infection: novel "smart" drug delivery systems that release antibiotics locally in response to stimuli such as pH, temperature, enzymes or antigens; implant surface modifications on the nanoscale that inhibit bacterial adhesion and propagation at the surgical site; biological approaches such as gene therapy to neutralize bacterial virulence, and biomolecules to inhibit the quorum sensing adhesion of bacteria, with disruption of biofilms [134].

## B- Advances in Production and Biomaterials:

Currently, one of the major hurdles in advancing PEPOL technology for amputee rehabilitation is the cost involved, primarily due to the less frequent use of this technology. With the economy of scale this cost is expected to naturally reduce over time, as the technique is more widely used. In addition, advances in 3D technology and the development of new biomaterials can help to further offset future expenses if implants can be printed locally at a lower unit cost. The challenge remains how to best regulate the use of this technology in certain health care models where there is less accountability. The following discussion elaborates on reported advances in implant production and the future direction of biomaterials development.

### 1- Three-dimensional (3D) Printing:

Three-dimensional (3D) printing has transformed the way we can treat various medical pathologies. A form of additive manufacturing, 3D printing fuses materials together in a layer-by-layer fashion to construct a final 3D product. This technology allows greater flexibility in the design process and enables efficient production of both off-the-shelf and personalized medical products that accommodate patient needs better than traditional manufacturing processes. In the field of orthopaedic surgery, 3D printed implants and instrumentation can be used to address a variety of pathologies that would otherwise be challenging to manage with products made from traditional subtractive manufacturing [135,136]. There are numerous applications that add value to

the personalised treatment of patients: advanced preoperative planning, surgeries with specific tools for each patient, customised orthotic treatments, personalised implants or prostheses and innovative developments in the field of bone and cartilage tissue engineering [137]. 3D printing technology has revolutionized and gradually transformed manufacturing across a broad spectrum of industries, including healthcare [138].

### 2- Customised Implants:

3D printing technology provides an excellent capability to manufacture customised implants for patients. Computed tomography (CT) and magnetic resonance imaging (MRI) help to provide images of the unique anatomy and pathology of an individual patient, and these images are then used to generate patient-specific implants, guides, and jigs [139].

### 3- Natural Medicinal Compounds in Bone Tissue Engineering:

Natural medicinal compounds (NMCs) with osteogenic potential can be incorporated into 3D-printed parts to improve bone formation and therefore enhance implant performance [140].

### 4- Cost Effectiveness of 3D Printing implants:

Application of three-dimensional (3D) printing facilities in orthopaedic surgery is gaining popularity even in resource constrained countries. It is cost- and resource-efficient and assists in preoperative planning and increases the efficiency of orthopaedic procedures. Furthermore, it improves educational training and provides

cheaper prostheses and allows for the creation of customised implants for complex and unusual cases [141]. In the last few years, 3D printable biomaterials have been tremendously advantageous in the fabrication of orthopaedic implants because of its light weight, minimum material wastage, porous structure for tissue ingrowth, as well as providing ease in making patient-specific and complex topology implants. The sustainability of the 3D printing technique, along with using sustainable biomaterials, can make the development of implants simultaneously more accurate and more biocompatible [142].

## 5- Meta-biomaterials:

Meta-biomaterials are designer biomaterials with unusual and even unprecedented properties that primarily originate from their geometrical designs at different (usually smaller) length scales. This concept has been primarily used in the context of orthopaedic biomaterials with the ultimate aim of improving the bone tissue regeneration performance of implants while decreasing the risk of implant-associated infections. At the macroscale, studies have discussed the concepts of patient-specific implants, deployable meta-implants, and shape-morphing implants. At the microscale, studies have discussed the concept of multi-physics meta-biomaterials while also covering the applications of auxetic meta-biomaterials for improving the longevity of orthopaedic implants. At the nanoscale, the different aspects of the geometrical design of surface nanopatterns that simultaneously stimulate the osteogenic differentiation of stem cells and are bactericidal have been developed (refs). The concept of origami-based meta-biomaterials and the applications of self-folding mechanisms in the fabrication of meta-biomaterials have been addressed along with the evidence regarding the superior performance of meta-biomaterials [143].

## 6- Functionalization of 3D-printed titanium alloy orthopedic implants:

Titanium alloy orthopaedic implants produced by 3D printing have been widely used in the field of orthopaedics in recent years. They combine the dual advantages of having a complex structure that cannot be manufactured by traditional techniques and the excellent physical and chemical properties of titanium and its alloys. The ability to design porous 3D-printed implants and the original modification processes for titanium alloys provide conditions for the functionalisation of implants which can then result in long-term stability with anti-infection or anti-tumor properties [144].

### C- Advances in Designs and feedback of Prosthetics:

Traditional orthopaedic devices do not communicate with physicians or patients post-operatively. After implantation, follow-up of traditional orthopaedic devices is generally limited to episodic monitoring. Real-time health monitoring systems are emerging in diverse medical fields, tracking biological and physiological signals for direct feedback to the user.

#### 1- SMART (sensing, measuring, and advanced reporting technology) Implants:

SMART orthopaedic implants incorporate technology that enables automated sensing, measuring, processing, and reporting of patient or device parameters at or near the implant [145] [146]. Sensors for next-generation smart implants will be small, simple, robust, and inexpensive, and will necessitate little to no modification to existing implant designs. With rapidly advancing technology, the widespread implementation of smart implants is imminent. New sensor technology that minimises modifications to existing implants is the key to seamlessly incorporating smart implants into daily clinical practice [147].

## 2- Technological Advances in Prosthesis Design and Rehabilitation:

Prosthetists have struggled to recreate the intuitive motor control, light touch sensation, and proprioception of the innate limb in a manner that reflects the complexity of its native form and function. Surgical advances such as targeted muscle reinnervation, regenerative peripheral nerve interfaces, agonist-antagonist myoneural interfaces, and targeted sensory reinnervation; development of technology designed to restore sensation, such as implanted sensors and haptic devices; and evolution of osseointegrated (bone-anchored) prostheses show great promise. Augmented and virtual reality platforms have the potential to enhance prosthesis design, pre-prosthetic training and incorporation to achieve the goal of multi-functional, self-identifiable, durable, and intuitive prostheses [148].

## 3-Biofeedback to Improve the Performance of Myoelectric Pattern Recognition:

Next generation prosthetics will rely extensively on myoelectric 'Pattern Recognition' (PR) based control approaches, to improve their users' dexterity. One major identified factor for the successful introduction of these approaches lies in the training of amputees and in their understanding of how these prosthetics work. An intuitive pattern similarity biofeedback mechanism can be easily used to train amputees and allow them to optimise their muscular contractions to improve their control performance [149].

### 4- Neurophysiological Evaluation of Haptic Feedback for Myoelectric Prostheses:

Evaluation of haptic feedback in myoelectric prostheses has been generally limited to task performance outcomes, which, while necessary, fail to adequately capture the extent of the mental effort of the user operating the prosthesis. Cognitive load is usually investigated with reaction time metrics and secondary task accuracy which are indirect and may not capture the time-varying nature of mental effort. Proposed wearable, wireless, functional near infrared spectroscopy (fNIRS) neuroimaging has provided a continuous direct assessment of operator mental effort during use of a prosthesis. Haptic feedback can further improve task performance and lower the cognitive load for prosthesis use and has demonstrated the potential for fNIRS to provide a robust measure of cognitive effort for other human-in-the-loop systems [150].

## D - Conclusions:

Osseointegration for the reconstruction of the amputated limb appears to now be poised to follow a trajectory similar to that demonstrated by total joint arthroplasty. After overcoming initial technical issues, arthroplasty benefitted from rapid and simultaneous advances in material science and surgical techniques. This allowed arthroplasty devices to gain universal acceptance and subsequently widespread adoption globally over the past 50 years[120].

I believe that the future of amputee rehabilitation is bright with the advances in implant manufacturing, biofeedback and infection prevention. Over the past ten years, I have contributed to many aspects relating to various breakthroughs in this technology. First of which was the maturation of implant design. My design iterations facilitated immediate rotational and axial stability, enabling patients to have shorter rehabilitation time and also making the procedure feasible as a single-stage surgery. By learning from the cementless arthroplasty experience, I managed to confidently

decide what would be the best material for surface coating (plasma spray) and the ideal porosity and thickness to achieve maximum osseointegration between the implant and the bone. This helped me achieve maximum stability and optimise the seal between the implant and bone. Both these features led to the reduction of bacterial invasion of the implant-bone interface, which in turn reduced the chance of bone infection. Improved understanding of how soft tissue interacts with the implant when open to the outside environment led to the development of making the transcutaneous surface of the implant highly polished with nanoparticle coating, to minimise the potential friction between the soft tissue and the implant. This was a progression from the original theory of trying to make the soft tissue heal directly to the implant, which often led to inflammation and a potential increase in the occurrence of soft tissue infection. The improved understanding of soft tissue repair around the implant provided tight closure that no longer compromised the blood supply of the muscular layers around the distal end of the implant, adding another barrier to bacterial invasion and the bone implant interface. This technique further lowered the chance of infection. Furthermore, the meticulous resection of subcutaneous fat without devascularising the overlying skin during wound closure made the skin heal more tightly onto the fascia covering the muscle layer. This led to reduced movement and friction that also previously contributed to inflammation and infection.

Having optimised the implant design and surgical technique for transfemoral amputees, with lower infections rate when compared to previously published data, this led me to embark on testing this technology on trans-tibial amputees. Osseointegration was trialed before in this cohort, but often failed. I progressed to more challenging and uncharted territories, such as treating diabetic and dysvascular amputees, and even expanded to other parts of the body, including trans-pelvic amputation. I went on to further improve the implant design and modified our rehabilitation protocol in order to tailor it for the anatomy, biology as well as physiology of this new group of amputees.

The next level to address was the “elephant in the room”, this being phantom limb pain. I started paying more attention to the nervous tissue of the residuum and began

performing regular targeted muscle reinnervation for two benefits. The first being for the treatment of phantom limb pain and sensation, and secondly to provide a potential source for signal transmission for the attachment of a myoelectrical prosthesis. In addition, I performed cases where I connected agonist- antagonist muscles to provide mind-controlled motorised prosthetic activation.

With the success of Percutaneous EndoProsthetic Osseointegration for Limbs (PEPOL), new challenges have arisen. Patients have become more active and therefore more demanding in terms of what the existing prosthetic limbs are capable of delivering. Every prosthetic limb has a life expectancy. They are generally designed for the activity levels of those with a skin-suspended socket (SSS) prosthesis, which are proven to be on average much less active than PEPOL patients. This has precipitated the need to consider developing a more robust prosthetic limb that can endure the higher level of activity expected of the PEPOL population.

Furthermore, PEPOL amputees are often embarking on tasks that are deemed very difficult, if not impossible, for those with a SSS prosthesis. Following PEPOL, the positive effects of osseoperception has meant that they can more readily overcome workplace obstacles such as ladders, scaffolding, and the like. These are obstacles that the vast majority of SSS patients are typically unable to safely negotiate.

All these technological advances have been conducted in parallel with the regulatory documentation I successfully obtained to use this technology in Europe and Australia. I continue to seek regulatory approval to allow this technology to be used in other parts of the world, including the United States of America, where I am in the process of establishing an IDE with the FDA to allow this technology to be available to the amputee population in the USA. Similar regulatory processes are being conducted in other parts of the world, such as Japan, South Korea, and South America. Ultimately, my goal is to make this technology available to the world-wide community

of amputees, and to eventually become widely accepted as the standard of care for all amputees.

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