Safety of bone-anchored prostheses in lower extremity amputation

Robin Atallah

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COLOFON

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Safety of bone-anchored prostheses in lower extremity amputation

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Chapter 1

General Introduction

Introduction

The general purpose of this thesis is to improve the quality of care for individuals with a lower extremity amputation experiencing difficulties using a socket-suspended prosthesis (SSP). This is achieved by evaluating the surgical indications, safety, and influence of treatment adaptations in individuals treated with a bone-anchored prosthesis (BAP) using an osseointegration implant (OI).

1. Extremity amputation

Large differences in amputation incidence occur among different parts of the world, influenced by the occurrence of peripheral vascular disease, diabetes, and combat-related activities.[1] In the western world, the prevalence of limb loss or extremity amputation is relatively high and expected to increase over the coming years, as a result of the aging population and an increase in individuals with dysvascular conditions such as diabetes mellitus.[2,3] Ziegler et al.[3] estimated the prevalence of limb loss in the United States to be 1.6 million in 2005, and predicted it to more than double to 3.6 million by the year 2050. This expected increase in extremity amputation mainly has a dysvascular origin, and is driven by the increased prevalence of diabetes mellitus, resulting in a 12-fold increased risk of amputation compared to individuals without diabetes.[1-4]

A recent Dutch epidemiological study evaluating extremity amputations between 2012-2020 could not confirm this expectation, and reported a stable trend of lower extremity amputations over the years (Frolke et al. 2023, submission in progress). Although stable, this still amounted to a mean incidence of 12.7/100.000 major lower limb amputation (i.e. transfemoral, through-knee, transtibial) in the Netherlands per year. Even though the incidence of amputation due to traumatic injury is low, it accounts for a substantial prevalence, demonstrated in the United states in which trauma accounted for 16% of all amputations, but for 45% of the prevalence due to the fact that over 2/3 of trauma-related amputations occurred among individuals <45 years of age.[3] This results in major socioeconomical problems, as return-to-work rate post-amputation is only 66%, and a change of occupation is necessary in 33-88% of cases.[5]

For centuries individuals with an extremity amputation have been treated with socket-suspended prostheses.[6] Even with great advancements in prosthetic technology, such as high-tech micro-processed knee joints, energy storing feet and ankle designs, and mind-controlled prosthetics; the socket-residuum interface remains an important limiting factor in clinical success.[7,8] Despite innovations to socket materials, designs and liners, a large number of individuals experience socket-related problems.[8-14] Socket-related issues such as dermatologic or mechanical problems result in discomfort and eventually influence patient mobility.[8-14] Dermatologic problems such as pressure ulcers or infections occur

in 33%-63% of socket prosthesis users, and at least 54% complain about thermal-related discomfort. [10, 11, 13, 14] The high occurrence rate of skin problems is inherently linked to prosthesis intolerance. [9] Up to 78% of socket users experience mechanical problems such as inadequate socket fitting, also resulting in skin breakdown. [12] Furthermore, 44% of transfemoral socket prosthesis users experience discomfort during sitting, and mobility is highly affected compared to healthy age-matched controls. [15, 16] These problems lead to diminished prosthesis use and satisfaction, resulting in impairment of quality of life. [17-22] Rates of dissatisfaction vary between 33%-57%, and prosthesis use varies between 48-84% for individuals with extremity amputations. [19, 21-23]

2. Bone-anchored prostheses

2.1 The concept of osseointegration

A potential strategy of addressing the socket-related problems is by eliminating the socket-residuum interface, by directly connecting the artificial limb to the body. This is accomplished by the process of "osseointegration", defined as the direct structural and functional connection between living bone and the surface of a load-carrying implant. [24-28] It is an anchorage mechanism in which a nonbiological component is incorporated into living bone, which persists under normal loading conditions. [27] It was first discovered by accident by Swedish scientist Professor Per-Ingvar Brånemark in 1952, when an in vivo implanted and incorporated titanium chamber could not be removed from the adjacent bone of a rabbit once healed. [28] He observed that, following introduction of a titanium implant into bone, after a period of immobilization, cortical bone formation around the implant occurred without interposition of soft tissues at the bone-implant interface; even when pierced through the skin. [28] The research in rabbits and dogs with major mandibular and tibial bone defects resulted in the development of clinical reconstructive procedures for the treatment of the edentulous jaw. [24, 26, 28] As such, osseointegration has been in use in prosthetic teeth replacement since 1965 with 15-years survival rates of 80% and 90% in the maxilla and mandible, respectively. [24, 25] Bone-anchored hearing aids (BAHAs) following the same principles, have been in clinical use since 1977 with 5-year implant survival rates of 90-95%, followed by the use of auricular and maxillofacial prostheses. [28]

2.2 Developments in implant designs and treatment over time

- **Osseointegrated Prostheses for the Rehabilitation of Amputees (OPRA)**

Professor Brånemark extrapolated the acquired knowledge, developing an osseointegration implant (OI) for the treatment of individuals with an extremity amputation. Ultimately, his son (and orthopedic surgeon) Dr. Rickard Brånemark, continued the research and development taking the OI to an advanced level. The OI functioned as an anchorage mechanism for an artificial limb, similar to earlier applications of osseointegration, and was mainly used in individuals with a transfemoral amputation

(TFA).[27, 29, 30] This percutaneous OI, named the Osseointegrated Prostheses for the Rehabilitation of Amputees or "OPRA Implant system" (Integrum AB, Mölndal, Sweden) followed the same principles as in the edentulous jaw. It consisted of 3 components: 1) the fixture: a screw-type, threaded, cylinder-like, laser-etched intramedullary implant made of commercially pure titanium initially, which was later modified to a stronger titanium alloy (Ti6Al4 V), 2) the abutment: a polished percutaneous component mounted into the distal end of the fixture, to which a prosthetic limb is attached, 3) the abutment screw: connecting the abutment and fixture together (**Fig. 1**).[31]

The treatment consisted of two surgeries with an interval of 6 months. During the first surgery the titanium fixture was inserted in the residual bone by screwing it into the tapped medullary canal, after which the skin was closed and no weight bearing was allowed. This period of unloading allowed osseointegration (i.e. bone ingrowth) to occur, resulting in a firm fixation of the implant. During the second surgery, the abutment was inserted into the distal fixture end via an opening in the skin, called the stoma. As such, the second stage of treatment resulted in a BAP, connecting the external artificial limb directly to the skeleton.[29]

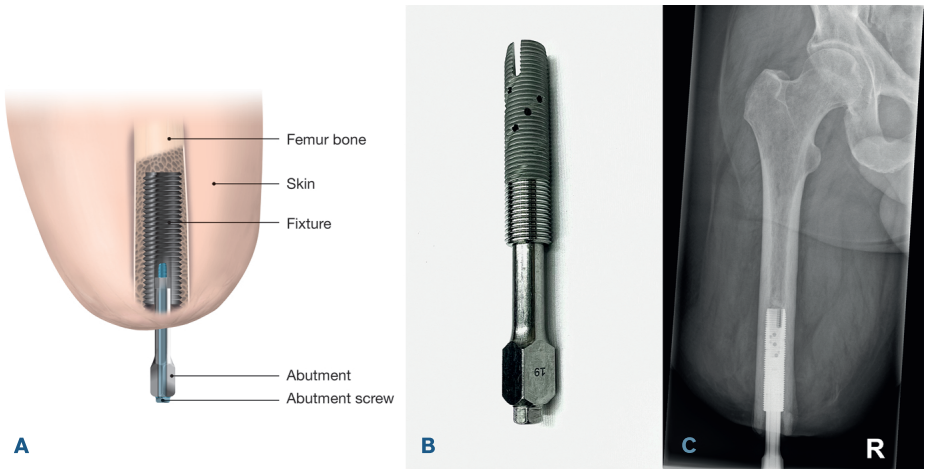

Figure 1. Osseointegrated Prostheses for the Rehabilitation of Amputees (OPRA) implant

A Schematic image of the modular implant with its components.
B Image of the fixture and abutment.
C Anteroposterior radiograph of OPRA implant in a femur.

The treatment was executed for the first time in 1990 and had no standardized rehabilitation protocol, similar to when the procedure was applied in the dental field. Patients encountered infectious problems more frequently as a result of high stresses and tractions at the skin opening, than compared to the oral and craniofacial situations with stable soft tissue interfaces.[32] These complications led to adaptations to surgical technique based on experience obtained from the BAHAs, aiming for a thin, hair-

free, immobile skin-implant interface. Furthermore, the surgical technique was also adapted in which the fixture was countersunk 20mm at implantation as a mitigatory measure against the occurrence of distal bone resorption.[31] In 1999, based on earlier experience, standardization took place of 1) implant system, 2) surgical technique, and 3) postoperative rehabilitation protocol; consisting of the gradual loading of the bone-implant interface over a period of 6 months. It was named the OPRA program or treatment protocol (Sahlgrenska University Hospital, Göteborg, Sweden).[32]

- Integral Leg Prosthesis (ILP)

Bone-anchored prosthesis treatment for individuals with an extremity amputation was first introduced in Germany in 1999 with the development of a press-fit cobalt-chrome-molybdenum (CoCrMo) OI, by Dr. H. Aschoff and Dr. H. Grundei (Lübeck, Germany).[33, 34] Cobalt-chrome-based alloys had been widely used in dental and orthopedic implants, because of their favorable mechanical properties.[35] The implant known initially as the Endo-Exo Femoral Prosthesis (EEFP, ESKA Orthopedic Handels, Lübeck, Germany), currently known as the Integral Leg Prosthesis (ILP, Orthodynamics GMbH, Lübeck, Germany), is made of a cast CoCrMo alloy and has a radius of 1800mm following the anatomical femoral antecurvation. It contains a 1.5mm thick tripod-like structure of trabecular metal (Spongiosa-Metal II, Orthopdynamics GMbH, Lübeck, Germany), aimed at enhancing the surface area for osseointegration; and is implanted in a two-stage surgery with an interval of 6 to 10 weeks.[30, 36] The OI results in a difference in anchorage of the artificial limb compared to a SSP, also restoring skeletal alignment (**Fig. 2**) The modular implant system consists of 1) the intramedullary CoCrMo alloy stem, 2) the Dual cone adapter (DCA) with a press-fit Morse taper, connecting the stem with the prosthetic limb via, 3) the adapter (**Fig. 3**). The implant design has been changed multiple times over the years, which will be further discussed in paragraph 2.3.1.

The main difference in surgical technique of the ILP compared with the OPRA is the fact that the ILP requires press-fit implantation, while the OPRA is screwed in a canal that has been tapped. As such, the ILP steps during the first surgery include: cortical reaming with curettes, broaches and a flexible drill, press-fit implantation of the endoprosthesis, and closure of the soft tissue envelope. The second stage surgery includes opening the skin at the level of the implant, removal of soft tissue between implant-skin, and insertion of the transcutaneous DCA.[37]

The main reasons for the difference in time interval between surgical stages when comparing the OPRA to the ILP system are suggested to be: 1) differences in osseointegration capacity due to differences in 1a) length of the implant (OPRA: 80mm versus (vs) ILP: 140-180mm), and 1b) coating/surface roughness (OPRA: laser-etched inducing nanoporous structure vs ILP: tripod-like 1.5mm thick macroporous structure); and 2) differences in fixation methods (OPRA: screw, ILP: press-fit).[31, 38] Differences in fixation methods (i.e. screw vs press-fit) likely result in differences in primary implant

stability, in which a threaded connection offers adequate initial mechanical stability in the longitudinal direction and relies on friction for rotational stability; while a press-fit interface solely relies on friction for the initial longitudinal and axial stability.[31]

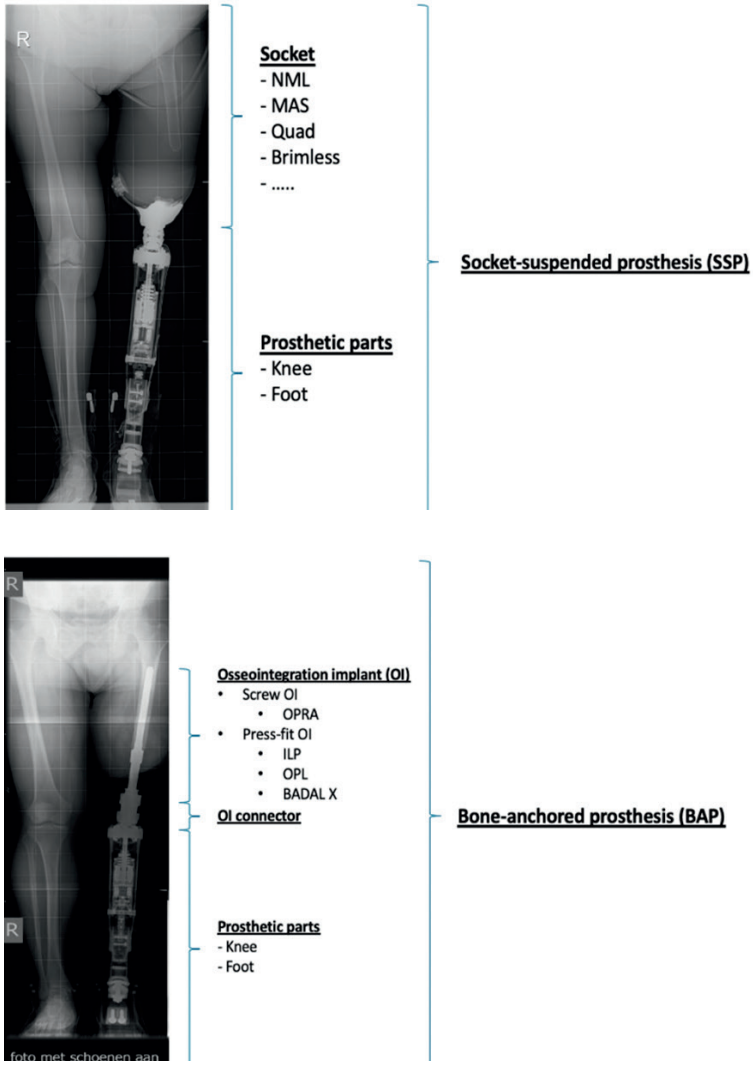

Figure 2. Components and skeletal alignment of a socket-suspended prosthesis versus bone-anchored prosthesis

OI: Osseointegration implant. OPRA: Osseointegrated Prostheses for the Rehabilitation of Amputees. ILP: Integral Leg Prosthesis. OPL: Osseointegrated Prosthetic Limb. BADAL X: Bone Anchoring Device for Artificial Limbs.

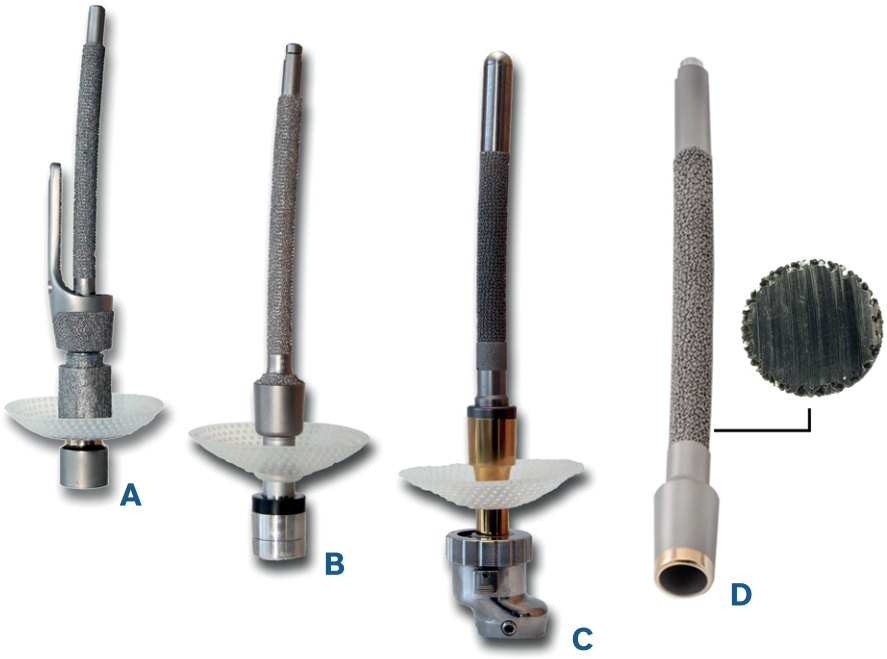

Figure 3. Integral Leg Prosthesis (ILP) design changes over time

A Initial ILP design. Rough surface on intramedullary stem with antecurvation radius and on transcutaneous portion with bone-stabilizing bracket
B Second design. Removal of the rough design of the transcutaneous portion.
C Third design. Removal of the bracket, revised connection to exoprosthesis with dual cone connection.
D Current design. Small changes to tripod structure and transcutaneous portion. Transverse view of trabecular metal surface.

- **Osseointegrated Prosthetic Limb (OPL)**

After some adaptations to the ILP design, introduction of the BAP took place in the Netherlands (Radboud University Medical Center, Nijmegen) in 2009, and in Australia (Norwest Private Hospital, Sydney) in 2010.[7, 39] The Australian group went on to design and use a press-fit forged titanium alloy (Ti6AL7Nb) implant called the Osseointegrated Prosthetic Limb (OPL, Permedica SPA, Merate, Italy) in 2013. The implant with a standard length of 160mm contains a radius of 2000mm following the femoral antecurvation. The proximal half of the implant is grit blasted and contains longitudinal flutes providing additional rotational stability; while the distal half is coated with plasma-sprayed titanium aimed at enhancing bone-to-implant contact and subsequent bony ingrowth; and the extramedullary head is fully coated with a highly polished titanium niobium oxynitride (TiNbON) (**Fig. 4**). The implant was also introduced in the Radboud University Medical Center in 2015 after multiple stem breakages had occurred of the ILP implant that was in use in the previous period.[38, 40, 41]

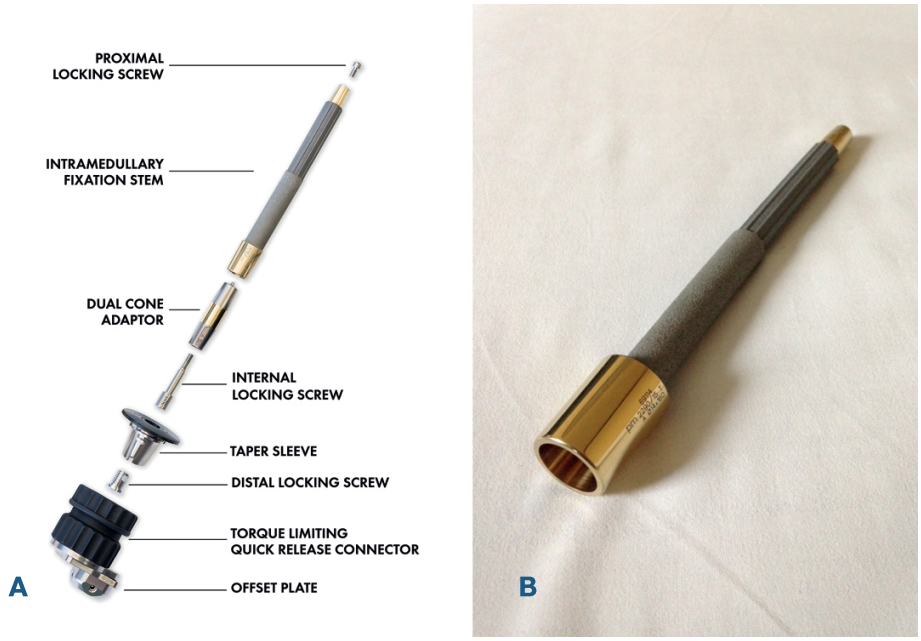

Figure 4. Osseointegrated Prosthetic Limb (OPL)

A Modular ILP system components.
B ILP implant with titanium plasma-sprayed coating of intramedullary portion. Distal extramedullary head polished and coated with titanium niobium oxinitride.

• Bone Anchoring Device for Artificial Limbs (BADAL X)

The Bone Anchoring Device for Artificial Limbs (BADAL X, OTN Implants, Arnhem, The Netherlands) was introduced in 2019. The BADAL X is a modular system, manufactured from a titanium alloy (Ti6Al7Nb) by forging. The BADAL X system contains 3 types of stems with different designs for the treatment of standard length TFA (Osseointegration femur implant curved: OFI-C), short TFA (Osseointegration femur implant gamma: OFI-Y), and transtibial amputation (TTA) (Osseointegration tibia implant: OTI) (described in detail in Chapter 3). The OFI-C was the only stem to have a rough titanium plasma spray (TPS) coating facilitating osseointegration initially, while the OFI-Y and OTI were 3D printed from titanium including a 3D lattice structure of 1mm (see chapter 3) (**Fig. 5**). This was modified, and at the time of writing all stems are forged with an average 0.35mm thick macroporous TPS surface structure. Just like the OPL, the proximal half of the OFI-C contains longitudinal flutes providing rotational stability, also containing a 2000mm radius. The OFI-C implant is CE-marked and thus complies with the requirements for use in the European Union. The OFI-Y and OTI implant are patient-specific implants fabricated based on pre-operative CT-scans. The proximal part of the OFI-Y stem contains a 125 degrees oblique hole through which a lag screw can be inserted, stabilizing the implant in the femoral neck and head. The OTI can be proximally stabilized with one or

two transverse screws and was designed with an anatomical droplet shape at the distal part, intended to match the anatomy and thus seal the intramedullary canal of the tibia.

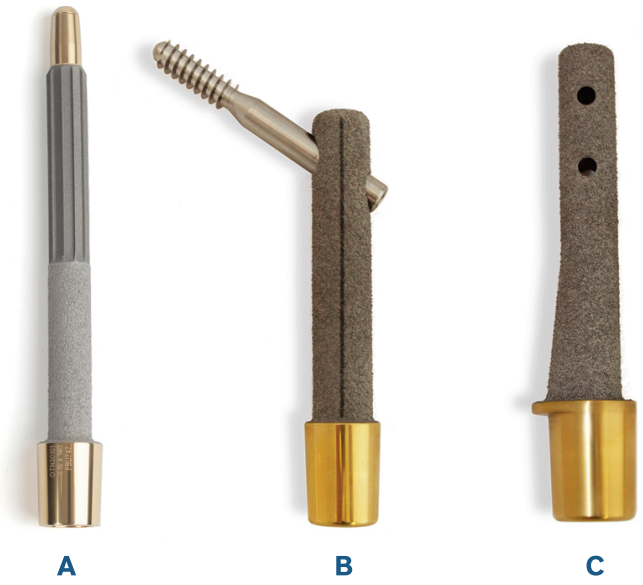

Figure 5. Bone Anchoring Device for Artificial Limbs (BADAL X)

A Osseointegration femur implant type curved (OFI-C).
B Osseointegration femur implant type gamma (OFI-Y) with lag screw option for fixation in femoral head.
C Osseointegration tibia implant (OTI) with two transverse screw options and distal anatomical droplet shape.

2.3 Indications for bone-anchored prostheses

Bone-anchored prostheses utilizing OIs have predominantly been used in individuals with a TFA. [37, 39, 42-44] Inclusion criteria for individuals with a lower extremity amputation have been analogous in the different centers worldwide, being mostly individuals with a TFA experiencing problems using a SSP due to socket-related problems. [29, 37, 39, 42] A common requirement has been to establish that these socket-related problems result in a decreased level of activity, participation and/or quality of life, while optimization of the socket, components, and/or rehabilitation do not result in a satisfactory solution of the encountered problems.

Contraindications have been defined as: severe diabetes mellitus, extended peripheral vascular disease, major skeletal deformities, an immature skeleton, bone disease of the affected limb (i.e. exposure to radiation, infection, etc), chemotherapy, unrealistic expectations of treatment, and acute psychiatric problems (inability to comply with the rehabilitation protocol). [29, 37, 39, 42] Due to initial concerns of ascending infection with subsequent implant loosening, it was hypothesized that comorbid peripheral vascular

disease would result in an increased risk of complications, therefore these individuals were excluded from treatment as well.[38, 42]

The treatment of individuals with a TTA with a BAP remains infrequent worldwide. This may be explained by the belief that individuals with a TFA experience more difficulties and dissatisfaction with their SSP when compared to individuals with a TTA.[45] Furthermore, in individuals with a TTA, implant fixation is required in the tibial metaphysis (short, drop-like canal shaped), while for individuals with a TFA it is achieved in the femoral diaphysis (long, circular canal shape).[46] These morphological differences result in increased concerns with regard to implant fixation for TTA and the frequent necessity for custom made implants, thus making using OIs more strenuous and/or troublesome.[47]

However, an indication for the use of BAPs in individuals with a TTA certainly exists. For instance, the prevalence of TTA is similar to that of TFA in the United States.[2, 3] Additionally, individuals with a TTA using a SSP experience dermatological issues frequently as well. Dudek et al.[10] even reported that a transtibial residual limb is 4 times more likely to develop a skin problem than a transfemoral residual limb. This finding is somewhat contrasted by Meulenbelt et al.[14] who reported an incidence of skin problems of up to 82%, equally distributed between individuals with a TFA and TTA. Furthermore, dissatisfaction rates with SSP of 33-57% showed no differences between individuals with a TFA and TTA.[19, 21] Therefore, as the prevalence of TTA is high, and socket-related problems and dissatisfaction with a SSP is frequent, exploring the potential advantages of BAPs in this patient population is justified.

2.4 Advantages of bone-anchored prostheses

Bone-anchored prostheses potentially offer multiple advantages in individuals with a lower extremity amputation, in addition to the elimination of the socket-residuum interface and its associated problems. These benefits in outcomes can be classified under functional outcomes, quality of life, and satisfaction level. Examples of potential benefits include an increased prosthesis comfort, a larger hip range of motion, and reduced oxygen consumption while ambulating; which ultimately results in an increased prosthesis use, walking ability, and overall quality of life.[29, 39, 48-50] Additionally, individuals using BAPs experience something termed “osseoperception”, defined as the ability to identify tactile thresholds transmitted through the prosthesis.[27] The measured perception of vibrations with an OI is comparable to that of the sound contralateral limb and enhances an individual’s awareness of the environment, aiding in ambulation.[27] However, it should be taken into account that these potential benefits on an individual level often are the results of a functional comparison between a suboptimal preoperative situation using a SSP yielding low baseline values to a favorable situation using a BAP afterwards.[51] Accordingly, adequate patient selection is of great importance, in the pursuit of improvements to functional outcomes with acceptable risks of treatment.

2.5 Safety of bone-anchored prostheses

Advantages of treatment are opposed by the potential occurrence of adverse events influencing overall treatment safety. Risk assessment using Failure Mode and Effect Analysis (FMEA) methodology was performed evaluating all potentially occurring procedure-related adverse events.[52, 53] A systematical analysis resulted in the following types of adverse events: 1) Infection (of soft tissues, bone, or implant), 2) Implant failure (aseptic loosening/failure of osseointegration, or mechanical failure of components), 3) Stoma-related problems (hypergranulation/keloid formation, or stoma redundant tissue), and 4) Periprosthetic fracture.

- **Concepts of the skin-implant-interface**

As with all orthopedic implants, implant infection is considered to be a serious adverse event, occurring in 1% to 2% of primary hip and knee arthroplasties, potentially associated with high morbidity and the need for complex interdisciplinary treatment strategies.[54, 55] Two main differences between endoprostheses and OIs in BAP-treatment result in the distinction between prosthetic joint infection's (PJI) and OI infections in BAP-treatment. With regard to OIs in BAP-treatment these are: 1) their percutaneous nature, breaching the protective soft tissue barrier, and 2) the lack of a synovial joint capsule and/or necessity for movable components.

Extensive research has been conducted into the skin-implant-interface of multiple percutaneous devices, and with regard to BAP-treatment using OIs these can be divided into two hypotheses:

1. **The deer antler model:** The skin-implant-interface aims to achieve an effective integration of the surrounding soft tissue onto the device, creating a strong seal.

As a theoretical concept, the deer antler model gives the impression of additional safety against ascending infection but gives rise to a problem called marsupialization. Marsupialization stands for epithelial downgrowth of cells along the surface of a percutaneous device ultimately resulting in a sinus tract.[56] Jeyapalina et al. investigated the possibility of a stable skin-implant interface, in two sheep studies with 9 and 24 months follow-up using distally porous-coated titanium implants, but failed to prevent marsupialization.[57, 58] Another animal study, using titanium implants with deep porosity, accomplished bony and fibrous connective tissue ingrowth in cats but failed in pigs, ultimately resulting in a stoma (see next paragraph).[59] It was hypothesized that the high mobility of skin and soft tissue in the pig thigh resulted in failure. Up to this date, no research group is believed to have achieved a stable skin-implant interface.[56] However, research in humans by the Swedish osseointegration groups was performed in which surgical technique adaptations were implemented, aiming for a thin, hair-follicular-free and immobile skin around the abutment.[32] It was discovered that direct healing of skin

to bone is crucial to reduce soft tissue problems. However, it remains unclear if this technique results in a long term stable skin-implant interface.

2. **The stable stoma model:** The skin-implant-interface should result in a permanent artificial opening, called a stoma, in which no integration takes place and space is left between the device and the surrounding soft tissue.

The stable stoma model follows a different philosophy, in which it is believed that a natural continuous drainage of fluids is necessary as a means to prevent local or ascending infection. It can also be hypothesized that this technique is a practical solution used in the absence of achieving a long term sealed stable skin-implant interface. Contrary to dental implants and BAHA, frequent movement and traction occurs at the level of the stoma in individuals with an extremity amputation treated with an OI.[32] Juhnke et al.[60] reported the initial attempts of the German team to achieve a soft tissue seal, by also coating the transcutaneous portion of the implants with a roughly textured surface; in the hope the skin would attach to the device. Eventually the philosophy was changed, leading to device modifications (reducing the diameter and length of the bridging connector, polishing a coating of the extramedullary portion of the implant with nonabrasive TiNbON), as well as surgery changes (stoma creation 3mm larger circumferentially than implant shaft) (see also chapter 2.5.1 Infection). These changes ensured that no integration of skin occurred to the implant, allowing for more gentle motion of soft tissues surrounding the implant, and the possibility of drainage of fluids outwards.

2.5.1 Infection

In the current clinical application of BAPs a stable stoma model is used. Up until the start of this PhD project in 2017, multiple studies were published presenting implant survival and complication data in the Swedish[43, 44, 61-64], German[33, 36, 37, 47, 60], Dutch[39, 42] and Australian[42, 65] groups. Some of these studies assessed the odds of infection, reporting rates varying from 0-77%, with explantation rates (i.e. the surgical removal of an implant) greatly differing as well, ranging from 0-66%.[33, 36, 37, 40, 42-44, 47, 60, 62-67]

As OIs breach the skin barrier, bacterial colonization of the stoma is inevitable and physiological. Beck et al.[68] reported that the microbial diversity of the stoma declines over time in months to reach a steady-state in which S. Aureus and Coagulase-negative staphylococci become dominant. But despite colonization with these potentially virulent bacteria, only few infections lead to disability or implant removal. Tillander et al.[63] cross sectionally surveyed 39 individuals with screw-type BAPs of the upper- and lower-extremity twice, and reported an 18% implant infection rate, but prosthetic use was not affected in 5/7 patients diagnosed with implant infection. Brånemark et al.[61] prospectively evaluated 51 individuals treated with screw-type femoral BAPs, and reported 14 cases of deep infection in 11/51 patients at a fixed 5-year follow-up, resulting in implant removal only once.

Therefore, although bacterial colonization is unavoidable it does not frequently result in implant failure, and even potentially plays a protective role as commensals against catastrophic infection.[68] Adequate osseointegration of the implant at the bone-implant-interface creates a tight seal, possibly preventing the ability of bacteria to ascend, nestle, and form a biofilm.[61, 63] This also explains why treatment initially involved surgery in 2 stages, in which the skin was closed after implant insertion at stage 1; allowing for bony in/ongrowth at the bone-implant-interface with a closed wound, in sterile conditions. This follows the concept defined in 1987 as "the race to the surface", in which the fate of a biomaterial after implantation is a competition between host tissue integration versus bacterial adhesion.[69]

Although infectious-related disability or implant removal is infrequent, multiple studies have reported high rates of stoma infections and/or stoma related problems. From the Swedish group (i.e. screw type), Tsikandylakis et al.[64] established superficial infections to be the most common adverse events occurring in 38% of patients at 5 years follow-up, while Branemark et al.[43] reported an incidence of 55% at 2 years follow-up, treated most frequently with oral antibiotics. Juhnke et al.[60] reported on the initial German cohort (i.e. press-fit) with variable follow-up times (ranging from approximately 1 month – 12 years) and found an incidence of soft tissue infection of almost 77%, most of which requiring surgical debridement. Al Muderis et al. from the Australian group (i.e. press-fit) reported an incidence of soft tissue infection ranging from 34-57%, in 2 studies with 12 and 34 months average follow-up, respectively, all of which treated with either oral or parenteral antibiotics.[40, 42]

After risk assessment of these frequently occurring modes of failure, multiple mitigatory measures were implemented aimed at reducing (soft tissue) infectious adverse events, as suggested in the FMEA model. As mentioned in paragraph 2.2.A, the Swedish group (screw-type, OPRA) adapted the surgical technique, using knowledge acquired from treatment with BAHAs, aiming for a thinner, immobile skin-implant-interface.[32] The German group implemented changes to implant design and surgical technique, as the implant initially contained a large diameter porous coated sleeve and an additional anterior flange at the transcutaneous part.[33, 36] The flange was supposed to provide additional load distribution and the porous coated sleeve aimed to provide a stable skin-implant attachment, but both proved to be prone to complications leading to chronic irritation of the soft tissues, subsequently resulting in stoma infections.[36] After removal of the flange, reduction of the outer diameter of the sleeve, and changes to the coating of the sleeve to a smoothly polished surface (TiNbON); a drastic reduction in soft tissue complications occurred.[37, 60] It was also discovered that the additional thinning of the subcutaneous fat surrounding the sleeve and decreasing the length resulted in less stoma complications.[60] Implementation of these design and surgical changes resulted in an absolute risk reduction of soft tissue complications of 42-55%, from the previously high incidence of surgical intervention secondary to infection of 77%.[60]

2.5.2 Implant failure

• **Failure of osseointegration/Aseptic implant loosening**

Following implantation of the OI, the cascade of wound healing, blood clot formation, bone forming cell invasion, and novel bone deposition takes place. Implant design, coating, and distance between implant and host bone influence the implant's primary or mechanical stability. The secondary or biological stability is dependent on novel bone formation, initially being woven bone, eventually remodeled to lamellar bone. [70] Reported rates of aseptic implant loosening in initial studies varied from 0-3% for press-fit femoral OIs, while high rates of loosening of up to 29% have been reported in very small cohorts of individuals treated with tibial OIs. [40, 42, 60, 65, 66] Excessive early implant motion or insufficient primary stability can inhibit osseointegration and lead to aseptic loosening or implant failure. [70] Therefore, Hagberg et al. [44], presenting data of a screw-type BAP-users, illustrated the learning curve; by emphasizing the importance of a well-defined rehabilitation protocol and controlled loading regime. They reported high rates of implant removal, often due to aseptic loosening, which decreased from 66% to 6.7-8.5% after implementation of a loading protocol. [44]

• **Mechanical failure of components**

Daily use of the modular BAP system may result in mechanical wear and fatigue leading to failure of components of the system. These can be subdivided by severity into breakage of 1) the intramedullary stem (OI), or 2) the extramedullary components (DCA or connector (figure 4). Breakage of the OI requires major surgical revision, while extramedullary components may often be replaced in an outpatient setting. Reported incidence rates of intramedullary stem breakage in press-fit femoral OIs range from 0-3% in the studies presenting short- to mid-term follow-up data , all of which requiring explantation of the implant. [40, 42, 60, 65, 66] Al Muderis et al. [42] reported an incidence of extramedullary device breakage of 29%, specified as breakages of the pin used as a safety weak point in the DCA. This stress fail mechanism is designed to protect the bone-stem interface from torque and rotational forces in case of falling or pathological loading of the BAP. [7] In the case of screw-type femoral OIs, Branemark et al. reported an incidence of 8% (4/48 patients, 9 events) of mechanical complications with the abutment and/or abutment screw at 2-years follow-up, which increased to 37.5% (15/40 patients, 43 events) at 5-years follow-up. [43, 61]

2.5.3 Stoma-related problems

The formation of a stoma can result in the occurrence of certain stoma-related adverse events. These can be subdivided in 1) hypergranulation or keloid formation or, 2) the occurrence of stoma redundant tissue. Hypergranulation or keloid formation is defined as an overgrowth of connective or scar tissue, and is only reported in two studies with a range in incidence of 3-20% in individuals treated with a press-fit femoral BAP. [42, 60]

The occurrence of stoma redundant tissue can lead to mechanical problems, as a result of friction and subsequent irritation of the soft tissues against the implant while walking. Its occurrence is seldomly reported, with incidence rates ranging from 3-16%,[42, 60, 65] although more studies have reported it to be a frequent reason for surgical intervention, such as stoma refashioning surgery.[40, 42, 60, 65, 66] As mentioned before, mitigatory measures such as adaptations to implant design and surgical technique may affect the occurrence of these stoma-related problems.[36, 60]

2.5.4 Periprosthetic fractures

The incidence of periprosthetic fractures has increased, with an increase in the number and implanted duration of orthopedic implants. Periprosthetic fractures around primary total hip arthroplasties (THA) have been reported in up to 10% of patients in the Australian annual joint registry.[71] Similar to periprosthetic fractures surrounding uncemented femoral stems in THA, these can also occur around an OI, and are most often the cause of a fall. Bone fractures have been reported in studies presenting data from femoral BAPs with rates ranging from 0-10%, all of which surgically treated in these studies.[40, 42, 47, 60, 65, 66]

The main difference, when comparing periprosthetic fractures around a THA and an OI, is the fact that the hip joint and trochanteric region is situated proximal to the OI. As hip fractures (i.e. femoral neck or intertrochanteric fractures) have very high rates of incidence (ranging from 346-920/100.000 age-standardized annual incidence rates in European women)[72], their future occurrence in individuals treated with a BAP is to be expected. These fractures, proximal to the OI, can be compared with Vancouver type C fractures in THA (fractures distal to the tip of the femoral stem), in which involvement or loss of fixation of the OI is likely absent.[73] Depending on how proximal the OI is situated, these hip fractures can often be treated with standard open reduction and internal fixation using conventional implants such as a dynamic hip screw or cannulated screws.[60, 65] It is also possible to treat certain non-displaced fractures conservatively, removing the artificial limb for a period of non-weight bearing.

3 Knowledge gaps

3.1 Overview of adverse events

The main focus of previous studies reporting on safety has been towards the occurrence of infectious adverse events. Due to the lack of a standardized definition or diagnostic tools for infection related to an OI, the incidence of infection remains unclear. Multiple investigators have used different criteria to evaluate the occurrence of infections based on different combinations of: 1. clinical symptoms, 2. laboratory findings (C-reactive protein, erythrocyte sedimentation rate), 3. tissue cultures (from skin-implant interface, intraoperatively obtained bone marrow aspirate, percutaneous bone biopsy), 4. radiographic signs (osteolysis with or without periprosthetic periosteal sclerosis).[42,

[62, 63] Diagnosing implant infections remains a difficult endeavor and standardizing the definition of infection is important, to create an adequate overview and uniform treatment algorithm, allowing for comparison of medical literature, such as is being attempted in prosthetic joint infections. [74]

Additionally, most studies focusing on safety have only reported a portion of potentially occurring adverse events, such as infection or reasons for implant removal. [44, 60] Studies should attempt to report all potentially occurring adverse events, to result in an improved understanding of their occurrence after BAP treatment. The ultimate goal of reporting all adverse events and of using the same criteria would be to enable comparison of outcomes from different treatment centers worldwide, and from different implant designs. [42, 44, 60] Such a comparison is necessary as worldwide BAP numbers are low and quality assurance using data pooling would likely result in earlier recognition of failure modes and implementation of improvements.

3.2 Non-conventional cohorts

As more data emerges of individuals with a standard TFA treated with a BAP, it is also necessary to assess the functionality and safety of treatment in the case of individuals with other types of amputations; such as a transtibial- or short transfemoral-amputation. [47] Individuals with a TTA experience the same socket-related problems, possibly more frequently than individuals with standard length TFA and may benefit from BAP treatment. [10, 75] Additionally, it is also necessary to evaluate the feasibility and safety of treatment in certain individuals with dysvascular amputations (which are currently typically excluded for BAP treatment), as these account for the largest number especially in the western-world. [2, 3]

3.3 Prospective standardized data collection

As for many emerging treatments, initial reports are often presented in a retrospective manner, with relatively short follow-up periods and without fixed follow-up moments. Research is needed to investigate long term effects and prospectively collected data and fixed follow-up moments would aid in facilitating comparison of outcomes.

3.4 Influence of treatment adaptations

Identification of failure modes or high rates of adverse events is often followed by implementation of an action plan aimed to reduce failure rates. [52, 53] Implementation of changes warrants the requirement of investigation assessing if the failure modes have been eliminated or reduced. In the case of an emerging treatment such as this, in which different implants, surgical techniques, and treatment protocols are used, it is important to report on the effect of implemented changes in a methodical fashion.

4 Aims and outline of this thesis

The general aim of this thesis is to improve overall quality of care of individuals with a lower extremity amputation treated with a bone-anchored prosthesis.

The following aims are addressed in this thesis:

1. To provide an overview of adverse events and related treatment options in individuals with extremity amputations treated with different types of bone-anchored implants. (Knowledge gap 1)
2. To evaluate feasibility, safety and effectiveness of bone-anchored prostheses in individuals with a transtibial, short femoral remnant and/or dyvascular amputation. (Knowledge gap 2)
3. To evaluate safety, and effectiveness of femoral bone-anchored prostheses at a mid-term follow-up. (Knowledge gap 3)
4. To investigate the impact of adaptations to surgical technique, implant design, and learning curve on the occurrence of frequently occurring soft tissue infections and stoma-related complications. (Knowledge gap 4)

5 Outline of thesis

In **chapter 2**, a systematic review of the literature is presented, aimed to provide an overview of bone-anchored prosthesis-related adverse events occurring in individuals with an upper or lower extremity amputation treated with a screw, press-fit, or other type of bone-anchored implant, as well as interventions related to these complications.

In **chapters 3 & 4** the safety and effectiveness of nonconventional bone-anchored prostheses at one year follow-up is described, comparing functional outcomes after treatment to pre-operative values using a socket-suspended prosthesis. **Chapter 3** illustrates treatment safety and effectiveness in individuals (n= 90) with a normal and short transfemoral amputation, and with a transtibial amputation; treated with 3 different types of press-fit titanium osseointegration implants. **Chapter 4** describes the first case series in individuals (n= 5) with dysvascular transtibial amputations.

In **chapter 5** the safety and effectiveness of bone-anchored prosthesis treatment in individuals (n= 39) with a transfemoral amputation with a 5-year follow-up is reported, focusing on adverse events, including infection, implant failure, and stoma-related problems.

In **chapter 6** the data is presented of individuals (n= 79) treated with a transfemoral osseointegration implant, reflecting on 10 years of clinical experience, in which major

changes to the implant and surgical technique were applied. The primary aim was to evaluate the impact of adaptations in treatment on soft tissue complications. The secondary aim was to investigate the rate of serious complications such as bone/implant infection, aseptic loosening, intramedullary stem breakage, and periprosthetic fracture.

Chapter 7 presents the general discussion and conclusion.

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Chapter 2

Complications of bone-anchored prostheses for individuals with an extremity amputation: A systematic review

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Abstract

Background

This study aimed to provide an overview of device-related complications occurring in individuals with an upper or lower extremity amputation treated with a screw, press-fit or other type of bone-anchored implant as well as interventions related to these complications.

Method

A systematic literature search was conducted in the MEDLINE, Cochrane, EMBASE, CINAHL and Web of Science databases. The included studies reported on device-related complications and interventions occurring in individuals with bone-anchored prostheses. The outcomes evaluated were death, infection, bone/device breakage, implant loosening, soft tissue complications, systemic events, antibiotic and surgical treatment. Subgroup analyses were performed for the following groups: a) implant type (screw, press-fit and other types of implants) and b) level of amputation (transfemoral, transtibial and upper extremity amputation).

Results

Of 309 studies, 12 cohort studies were eligible for inclusion, all of which had methodological shortcomings and 12 studies were excluded due to complete overlap of patient data. Implant infection were rare in certain transfemoral implants (screw: 2-11%, press-fit: 0-3%, Compress: 0%) but common in transtibial implants (29%). The same was observed for implant loosening, in transfemoral (screw: 6%, press-fit: 0-3%, Compress: 0%), transtibial implants (29%) as well as for upper extremity implants (13-23%). Intramedullary device breakage were rare in transfemoral implants (screw: 0%, press-fit: 1%, Compress: unknown) but frequent in individuals with transradial implants (27%) and absent in transtibial implants. Soft tissue infections and complications were common and underreported in most articles.

Conclusions

Major complications (e.g. implant infection, implant loosening and intramedullary device breakage) are rare in transfemoral bone-anchored prosthesis and seem to occur less frequently in individuals with press-fit implants. Minor complications, such as soft tissue infections and complications, are common but are substantially influenced by the learning curve, implant design and surgical technique. Data for patients treated with a transtibial, upper extremity or Compress implant are underreported, precluding definitive conclusions. There is a need for either an international database to report on or a standard core set of complications as well as the need to follow classification systems that result in unequivocal data.

Keywords: Amputees, osseointegration, adverse events, prosthesis failure.

Introduction

The prevalence of individuals with extremity amputation is high and is only expected to increase in the coming years.[1, 2] Large differences occur among different parts of the developed world depending largely on the prevalence of peripheral vascular disease, diabetes and combat-related activities.[3] Most lower limb amputations are due to vascular disease, with the incidence increasing annually, while upper limb amputation is most often the result of trauma.[1, 2]

For the past six centuries, the rehabilitation of individuals with an upper or lower extremity amputation has been achieved with socket-mounted prostheses.[4] Despite significant technological innovations to socket materials, liners and design,[5] individuals with an upper or lower extremity amputation still exhibit significant socket-residuum interface problems, such as skin irritation, pain and problems with prosthetic fixation.[6-10]

Approximately 56% of individuals with an upper and 80-95% with a lower extremity amputation use a prosthetic limb, with a rate of dissatisfaction with the prosthesis ranging from 18- 57%.[11-14] Skin problems are frequent in both upper and lower prosthetic limb users, ranging from 34-63% of all users [8, 15-21], and falling occurs in roughly half of individuals with a lower limb amputation due to poor proprioception and disbalance.[7, 22] Problems with prosthetic fixation and weight are more prevalent in individuals with upper extremity amputation.[10, 12] These socket-residuum interface problems lead to prosthesis intolerance and abandonment and have a severe impact on people's activity levels and quality of life.[6, 9, 16, 23-25]

The only way to eliminate the socket-residuum interface and prevent the occurrence of these problems is by directly attaching the prosthesis to the bone of the residual limb via the process of osseointegration, which is defined as the direct connection of a 'nonvital' component incorporated in living bone.[26] This technique, originating from the field of dentistry in 1965, has been well established for the treatment of the edentulous jaw for many years, demonstrating a 5 and 10-year survival of dental implants in mandibular bone of 98% and 95%, respectively.[27-29] Bone-anchored hearing aids have been developed using this technique and have been applied on a world–wide scale since 1977, with 5-year implant survival rates of 90-95%.[30] Since its first introduction in 1990 in individuals with amputation, bone-anchored prostheses offer multiple potential benefits for the treatment of selected individuals with amputations experiencing socket-related problems. These potential benefits include improved osseoperception, prosthesis wearing time, a larger hip range of motion, and reduced oxygen consumption while walking,[31-36] which are associated with an improved mobility level, walking ability and overall quality of life.[32, 34, 37, 38] Since 1990,[26] bone-anchored prostheses have been used predominantly in individuals with a non-vascular cause of amputation, but small series have already been published

showing the results of osseointegration treatment in individuals with stable vascular disease.[39, 40]

Several certified bone-anchored implants are currently available for humans: the Osseointegrated Prosthesis for the Rehabilitation of Amputees (OPRA),[32, 41-43] which is a screw implant made of titanium alloy. Also currently available are the Integral Leg Prosthesis (ILP, previously known as Endo-Exo Femur/Tibia Prosthesis; EEFP/EETP)[34, 44-50] and the Osseointegration Group of Australia-Osseointegration Prosthetic Limb (OGAP-OPL);[43], which are both press-fit implants, made of cobalt-chromium-molybdenum or titanium alloy respectively. Several newer systems are currently under development of which some have reached the stage of clinical experiments in humans.[51, 52] Initially, bone-anchored prostheses have been implanted in a two-stage procedure similar to their dental pre-ancestors, with an interval of six months and six to eight weeks for the screw and press-fit implants, respectively.[41, 43, 46] A protocol for single stage implantation of an osseointegrated prosthesis has recently been published, for which results regarding safety and efficacy remain to be evaluated.[53]

Over the last few years, multiple clinical studies have been performed to evaluate complications and the survival of bone-anchored prostheses for the treatment of individuals with upper and lower extremity amputation. At present, no systematic evaluation of complications after upper extremity amputation has been published. Reviews by van Eck et al.[54], Hebert et al.[55] and Al Muderis et al.[56] evaluated the complication rate in individuals restricted to lower extremity bone-anchored prosthesis. However, none of these reviews stratified the complication rate at the amputation level. Furthermore, van Eck et al. and Al Muderis et al. did not stratify for the type of bone-anchored prosthesis, resulting in limited clinical usability. The latter is important because the fixation principle of these implants are different because they are being developed for dentistry (screw) and orthopedic surgery (press-fit).[57, 58] Another limitation was that insight in the level of overlap in participants in the included studies was not [54, 56] or insufficiently provided [55] despite the often partial and occasionally even total overlap of the embedded cohort of participants.

Therefore, the two aims of this study were to provide (a) a stratified overview of device-related complications in individuals with a lower or upper extremity amputation treated with a screw, press-fit or other type of bone-anchored prostheses and (b) a stratified overview of the complication-related interventions that occur in these individuals treated with bone-anchored prosthetics.

Methods

Design

This systematic review of published, peer-reviewed articles with original data was conducted following the guidelines of the PRISMA statement.[59] The initial review protocol has been registered in the PROSPERO database.[60] The focus of the initial review protocol was screw or press-fit bone-anchored prostheses, nonetheless upon writing we decided to include other types of bone-anchored prostheses following the classification by Thesleff et al. [52]

Data collection

A comprehensive search was performed by the second author (RL) on 8 January 2018 in MEDLINE (accessed via PubMed), Cochrane Central Register of Controlled Trials, Embase (accessed via OvidSP), CINAHL, Web of Science and System for information on Grey Literature. Several combinations of terms and expressions were used, including both MeSH and free text terms. The final search string included (osseointegrat* OR osseo-integrat* OR bone-anchored prosthe*) AND (amput*). No date limits or geographical restrictions were used. Search strings for each database are provided in **S1 Appendix**.

Eligibility criteria

The eligibility of studies was independently assessed by RA and RL. We included articles of randomized controlled trials, controlled clinical trials and prospective and retrospective observational studies (including before-after, cohort and case–control studies). Articles were included if they reported device-related complications and/or complications related to interventions in people with an upper and/or lower extremity amputation treated with bone-anchored prostheses. We excluded studies that were not in the English, Dutch or German language. Furthermore, we excluded studies that presented completely duplicated data, studies that presented no original data (e.g., systematic reviews) and studies without having a full text. The individual studies embedded in systematic reviews were screened using the same eligibility criteria.

Study selection

Study selection was completed in two phases by two reviewers (RA, RL) independently. During the first phase, titles and abstracts of studies retrieved using the search strategy were screened to identify studies potentially meeting the inclusion criteria. The full text of these potentially eligible studies were retrieved and independently assessed for eligibility by both reviewers during the second phase. Additionally, a manual search of the reference list of the included articles was performed (**Fig. 1**). In case of disagreement in any screening stage, conflicts were resolved in a consensus meeting. Reasons for exclusion of the title and abstract of the reviewed articles are outlined in **S2 Appendix**. If articles presented a partial overlapping cohort of participants, the authors were contacted to provide source data aiming to include only unique cohorts of participants. If no response

was obtained after one reminder, we included all involved articles to avoid the loss of relevant data. If the cohorts of participants completely overlapped, the study with the largest cohort was included.

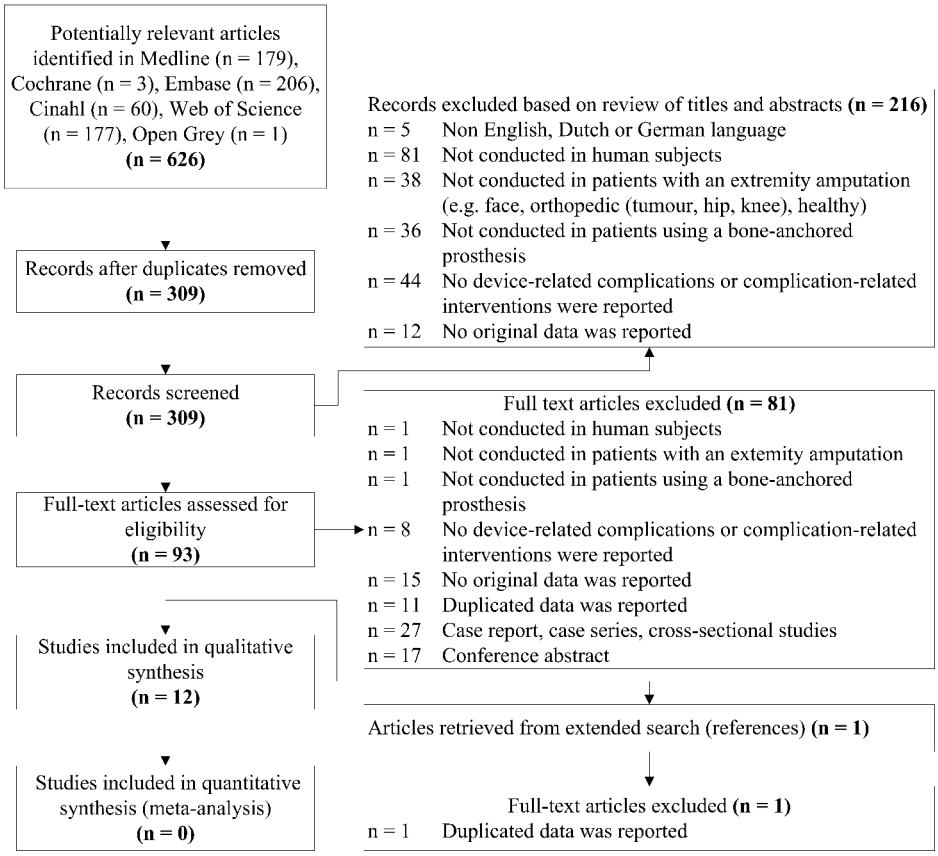

Figure 1. Flowchart for included studies

Data extraction and analysis

Data extraction was performed by two authors independently (RA and RL). Again, if any discrepancies occurred, a consensus was provided in discussion. Data were extracted using a standardized form and included authors, publication year, study location, follow-up period, study design, time interval of inclusion, participant demographics, type of intervention (single or two stage surgery), type of implant (screw, press-fit or other), device-related complications (death, infection, bone fracture, device breakage, implant loosening, stoma hypergranulation, stoma redundant tissue and systemic events) and complication-related interventions (antibiotic use and surgical treatment). If possible, the level of infection was categorized using a classification system for infection based on clinical and radiographic signs, which was published by Al Muderis et al. Table 1.[61] If

an article only described specific complications, all other complications were scored as "unknown". Complications were scored as a percentage of the total individuals in which they occurred. If enough unique homogeneous studies were included with overlapping follow-up time points, a meta-analysis was conducted to pool the incidence of device-related complications and complication-related interventions. Outcomes were analyzed separately for short-term (less or equal than one-year), mid-term (two to five year) and long-term (equal or more than five-year) follow-up. If the necessary data were available, subgroup analyses were performed for the following groups: a) implant type (screw, press-fit or other) and b) level of amputation (transfemoral, transtibial and upper extremity amputation).

Table 1. Classification of 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 • Parenteral Antibiotics • Surgical Intervention	1A 1B 1C
High-grade soft tissue infection	Pus collection, purulent discharge, raised level of C-reactive protein	• Oral Antibiotics • Parenteral Antibiotics • Surgical Intervention	2A 2B 2C
Bone infection	Radiographic evidence of osteitis (periosteal bone reaction), radiographic evidence of osteomyelitis (sequestrum and involucrum)	• Oral Antibiotics • Parenteral Antibiotics • Surgical Intervention	3A 3B 3C
Implant failure	Radiographic evidence of loosening	• Parenteral antibiotics, explantation	4

Methodological quality

The methodological quality of the included articles was independently assessed by two reviewers (RA and RL), after which disagreements were discussed in consensus meetings. In the case of persistent disagreement, a third reviewer was consulted to mediate (TH). The methodological quality (risk of bias) was scored using the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies.[62, 63] The EPHPP was chosen because we anticipated retrieving different types of non-randomized observational studies. The EPHPP Quality Assessment Tool assesses six aspects of methodology: (1) selection bias, (2) study design, (3) control of confounders, (4) blinding of participants and investigators, (5) data collection tool validity and reliability, and (6) proportion of withdrawals and drop-outs. Every study was assessed using the tool, and the studies were rated as "strong", "moderate" or "weak" with respect to the above-mentioned aspects using standard criteria. [62, 63] Combining the ratings of all six aspects of methodology resulted in an overall rating of quality (global rating), with studies classified as having "strong" methodology when no aspects were rated weak, "moderate" when only one aspect was rated weak and "weak" when multiple aspects of methodology were

rated weak.[62, 63] Inter-rater agreement on aspects of methodology was measured with a linear, weighted Cohen's κ coefficient.[64] Values were classified as follows: 0.41-0.60: fair agreement; 0.61-0.80: good agreement; 0.81-0.92: very good agreement; 0.93-1.00: excellent agreement.[65]

Results

Selected studies

We identified 309 unique articles in the search and 1 from screening references (**Fig. 1**). Twenty-four articles met our in-and exclusion criteria of which 12 articles were excluded because the cohorts of participants overlapped completely.[34, 38, 41, 42, 44-46, 48, 66-69] The 12 remaining eligible articles [43, 47, 49-51, 61, 70-75] described a total of 537 individuals with a lower and 67 individuals with an upper limb amputation. All individuals were treated with bone-anchored prostheses in eight different centers worldwide, but some articles presented partial overlapping cohorts of participants. The three articles of the Australian center had overlapping data in the period from 2011-2013 and 2013-2014,[43, 61, 70] the articles of the German center had an overlap in data in the period from 2003-2013,[47, 49, 50] the articles of the Swedish center regarding individuals with upper extremity amputation had an overlap in the period 1995-2010 [71, 75] and the article by Tillander et al. from 2010 had an unclear interval of inclusion.[74] A Gantt chart was made to provide a better overview of the amount of overlap in data between studies (**Fig. 2**). Due to Tillander et al. [73] reporting on all the individuals with transfemoral amputation which were also partly reported on by Li et al. [71] we only included the individuals with an upper extremity amputation from the article by Li et al.

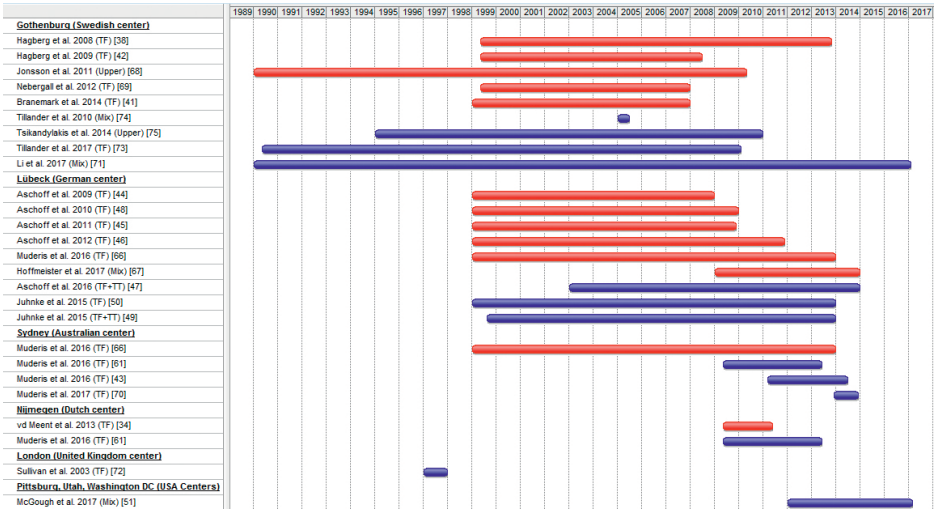

Figure 2. Gantt chart of overlapping data

Study characteristics

Table 2 provides the characteristics of the included articles. The 12 articles presented six retrospective cohort studies,[47, 49, 50, 70, 73, 75] three prospective cohort studies [43, 61, 74] and three cohort studies with an undefined design.[51, 71, 72] Three articles described two separate patient cohorts based on the amputation level or implant type.[47, 49, 50] We stratified our results by the number of cohorts described, resulting in a total of 15 cohorts. One of these cohorts was described by Tillander et al.[74], who used a combination of individuals with lower and upper extremity amputation and thus the outcome of this cohort will be mentioned separately to avoid clouding the overall results. The follow-up period of all cohorts ranged from 1 to 288 months no study was included with a fixed follow-up. The most common cause of amputation was trauma. One article presented cohort data from two centers in different countries.[61] Surgery was performed in eight centers in six countries: Australia [43, 61, 70], Germany [47, 49, 50], the Netherlands [61], Sweden [71, 73-75], the United Kingdom [72] and the USA [51]. The OPRA screw implant was used in Sweden and the United Kingdom, the ILP/OPL press-fit implant was used in Australia, Germany and the Netherlands and the Compress implant was used in the USA.

Of the 604 individuals in the 15 included cohorts, 206 were treated with a screw implant, 387 were treated with a press-fit implant and 11 were treated with the Compress implant. A total of 522 individuals were treated with a transfemoral amputation (screw: 139, press-fit: 373, Compress: 10), 15 with a transtibial amputation (screw: 1, press-fit 14) and 67 individuals with an upper extremity amputation (screw: 66, press-fit: 0, Compress: 1), of which 40 had a transhumeral amputation (screw: 39, Compress: 1), 14 a transradial amputation and 13 a thumb amputation.

The mean age at the time of implantation surgery was 45, 47 and 48 years in individuals treated with a screw, press-fit or Compress implant respectively. The mean time from primary amputation to implantation was 10.3 and 12.3 years for individuals treated with a screw and press-fit implant, respectively and was not described in the article regarding the Compress implant.

In each article if possible, loss to follow-up was determined by calculating the amount of individuals lost to follow-up that were not subdivided in any other category of complications.

Table 2. Study characteristics

Authors (years) Study location	Study design	Time interval inclusion of patients	Mean follow-up (months) ± SD (median) [range]	Participants (n), Implants Sex (M/F), Level of amputation	Cause of amputation (%)	Mean age (years) at surgery ±SD (median) [range]	Mean time (years) from primary amputation to surgery SD (median) [range]	Type of Intervention: type of implant / type of alloy / type of surgery(1-step, 2-step)
Al Muderis et al. Australia (2017) [70]	Retrospective cohort	December 2013 to November 2014	14 ± ? (?) [10-30]	N= 22 (22 implants), (16 M, 6 F) 22 uni-TF	Trauma (73), Tumour (18), Infection (9)	46 ± ? (?) [20-67]	? ± ? (?) [?]	Press-fit: OPL / (titanium / 1-step
Li et al. Sweden (2017) [71]	Cohort	TR: 1990 to 2017 Thumb: 1990 to 2014 TH: 1995 to 2010	TR ? ± ? (?) [?] Thumb ? ± ? (?) [?] TH ? ± ? (96) [24-228]	N= 42 (43 implants)*, (TR: 10 M, 1 F; TH: 10 M, 3 F; Thumb: ?) 10 uni TR, 1 bi-TR, 13 uni-thumb, 18 uni-TH	TR: ?, Thumb: Trauma (85), Tumour (15) TH: ?	? ± ? (?) [?]	? ± ? (?) [?]	Screw: OPRA / Titanium / 2-step
McGough et al. USA (2017) [51]	Cohort	2012 to 2017	? ± ? (?) [?]	N= 11 (11 implants), (10 M, 1 F) 10 uni-TF, 1 uni-TH	Trauma (55), Tumour (36), Infection (9)	47 ± ? (?) [26-68]	? ± ? (?) [?]	Compress / ?? / 1-step (n=6) and 2-step (n=5)
Tillander et al. Sweden (2017) [73]	Retrospective cohort	May 1990 to January 2010	95 ± ? (74) [18-235]	N= 96 (102 implants), (60 M, 36 F) 90 uni-TF, 6 bi-TF	Trauma (71), Tumour (20), Ischemia (5), Infection (5), Other (1)	43 ± ? (?) [19-65]	11.5 ± ? (?) [<1-44]	Screw: OPRA / Titanium / 2-step
Al Muderis et al. Australia, The Netherlands (2016) [61]	Prospective cohort	May 2009 to May 2013	? ± ? (34) [range 24-71]	N=86 (91 implants), (65 M, 21 F) 76 uni- TF, 5 bi-TF	Trauma (76), Tumour (13), Infection (9), Congenital (1), Other (1)	48 ± 14 (?) [25-81]	16 ± 14 (?) [?]	Press-fit: ILP/ Cobalt-chromium-molybdenum/2-step

Table 2. Study characteristics (continued)

Authors (years) Study location	Study design	Time interval inclusion of patients	Mean follow-up (months) ± SD (median) [range]	Participants (n), Implants Sex (M/F), Level of amputation	Cause of amputation (%)	Mean age (years) at surgery ±SD (median) [range]	Mean time (years) from primary amputation to surgery SD (median) [range]	Type of Intervention: type of implant / type of alloy / type of surgery(1-step, 2-step)
Al Muderis et al. Australia (2016) [43]	Prospective cohort	March 2011 to June 2014	22 ± ? (?) [range 1-?]	N=50 (50 implants), (34 M, 16 F) 50 uni-TF	Trauma (64), Tumour (16), Infection (10), Congenital (4), Blast injury (6)	48 ± ? (?) [24-73]	? ± ? (?) [2-65]	Press-fit: ILP (Cobalt-chromium-molybdenum)/OPL (titanium)/2-step
Aschoff et al. Germany (2016) [47]	Retrospective cohort	January 2003 to December 2014	? ± ? (?) [?]	N=86 (94 implants), (68 M, 18 F) 73 uni-TF, 6 bi-TF, 5 uni-TT, 2 bi-TT	Trauma (77), Tumour (8), Other (15)	[17-76]	? ± ? (?) [?]	Press-fit: EEFP + EETP = ILP=cobalt chrome molybdenum/2-step
Juhnke et al. Germany (cohort 1) (2015) [50]	Retrospective cohort	January 1999 to December 2008	74 ± 31 [6-144]	N=30 (31 implants), (25 M, 5 F) 29 uni-TF, 1 bi-TF	Trauma (77), Tumour (17), Infection (3), Other (3)	46 ± 13 [17-69]	11 ± ? (?) [?]	Press-fit: ILP design A and B/ Cobalt-chromium-molybdenum/2-step
Juhnke et al. Germany (cohort 2) (2015) [50]	Retrospective cohort	January 2009 to December 2013	32 ± 18 (?) [1-59]	N=39 (42 implants), (31 M, 8 F) 36 uni-TF, 3 bi-TF	Trauma (72), Tumour (5), Infection (5), Burn (3), Other (15)	45 ± 12 (?) [24-76]	11 ± ? (?) [?]	Press-fit: ILP design C/Cobalt-chromium-molybdenum/2-step
Juhnke et al. Germany (2015) [49]	Retrospective cohort study	August 1999 to December 2013	? ± ? (?) [?]	N=74 (80 implants), (59 M, 15 F) 63 uni-TF, 4 bi-TF, 5 uni-TT, 2 bi-TT	Trauma (76), Tumour (9), Other (15)	46 ± ? (?) [17-76]	11 ± ? (?) [?]	Press-fit: EEFP and EETP= ILP/?/2-step
Tsikandylakis et al. Sweden (2014) [75]	Retrospective cohort	1995 to 2010	? ± ? (96) [24-288]	N=18 (18 implants), (16 M, 2 F) 18 uni-TH	Trauma (89), Tumour (11)	42 ± ? (?) [19-69]	9 ± ? (?) [2-33]	Screw: OPRA/ Titanium/2-step

Table 2. Study characteristics (continued)

Authors (years) Study location	Study design	Time interval inclusion of patients	Mean follow-up (months) ± SD (median) [range]	Participants (n), Implants Sex (M/F), Level of amputation	Cause of amputation (%)	Mean age (years) at surgery ±SD (median) [range]	Mean time (years) from primary amputation to surgery SD (median) [range]	Type of Intervention: type of implant / type of alloy / type of surgery(1-step, 2-step)
Tillander et al. Sweden (2010) [74]	Prospective cohort	January 2005 to June 2005	36 ± ? (?) [?] / Time BAP to inclusion: 54 ± ? (?) [3 -132]	N=39 (45 implants), (21 M, 18 F) 31 uni-TF, 1 bi-TF, 2 uni-TR, 1 bi-TR, 3 uni-TH, 1 uni-TT	Trauma (?), Tumour (?)	49 ± ? (?) [28-74]	? ± ? (?) [?]	Screw: OPRA/ Titanium/2-step
Sullivan et al. United kingdom (2003) [72]	Cohort	1997	? ± ? (?) [?]	N=11 (11 implants), (? M, ? F) 11 TF	?	? ± ? (?) [?-?}	? ± ? (?) [?-?}	Screw: OPRA/ Titanium/2-step

SD= standard deviation, M= Male, F= Female, OPRA= Osseointegrated Prosthesis for the Rehabilitation of Amputees, OGAAP= The Osseointegration Group of Australia Accelerated Protocol, TF= Transfemoral, TT= Transtibial, TH= Transhumeral, TR= Transradial, Uni-= Unilateral, Bi-= Bilateral, ILP= Integral Leg Prosthesis, OPL: Osseointegration prosthetic limb (OGAP-OPL), EEFP= Endo-exo Femur Prosthesis, EETP= Endo-exo Tibia Prosthesis, BAP= Bone-anchored prosthesis, ?= Unknown/unclear

* With exclusion of individuals with TF amputation due to the overlap with Tillander et al.[73]

Methodological quality assessment

The inter-rater agreement of the assessment expressed as ƙ was 0.93±0.04, with 96% inter-rater agreement between the two reviewers on the ratings of the individual domains of methodological quality. The most common shortcomings of the studies were failure to blind assessors and participants, lack of adjustment for confounding variables and limited validity or reliability of the data collection methods. The few disagreements about domain errors were due to errors in comprehension or differences in interpretation of the methodological quality criteria. Disagreements were resolved in a consensus meeting. Scores for the six domains of methodological quality and the global EPHPP scores are presented in **table 3**.

Synthesis of results/meta-analysis

Because many cohorts partially overlapped, we could not conduct a meta-analysis. None of the contacted authors were able to provide source data. Due to the heterogeneity in follow-up time-points, we could not stratify the outcomes in short-, mid- and long-term outcomes. We stratified the outcomes of individual studies into two categories: a) implant type (screw, press-fit and other) and b) level of amputation (transfemoral, transtibial and upper extremity amputation).

Table 3. Methodological quality assessment ratings based on the Effective Public Health Practice Project tool for quantitative studies

Authors (year)	Selection bias	Study design	Confounders	Blinding	Data collection	Withdrawals and drop-outs	Global rating
Al Muderis et al. (2017)[70]	Moderate	Moderate	Weak	Weak	Weak	Strong	Weak
Li et al. (2017)[71]	Moderate	Moderate	Weak	Weak	Weak	Weak	Weak
McGough et al. (2017)[51]	Moderate	Moderate	Weak	Weak	Weak	Weak	Weak
Tillander et al. (2017)[73]	Moderate	Moderate	Weak	Weak	Weak	Strong	Weak
Al Muderis et al. (2016)[61]	Moderate	Moderate	Weak	Weak	Weak	Strong	Weak
Al Muderis et al. (2016)[43]	Moderate	Moderate	Weak	Weak	Weak	Strong	Weak
Aschoff et al. (2016)[47]	Moderate	Moderate	Weak	Weak	Weak	Weak	Weak
Juhnke et al. (2015)[50]	Moderate	Moderate	Weak	Weak	Weak	Weak	Weak
Juhnke et al. (2015[49])	Moderate	Moderate	Weak	Weak	Weak	Weak	Weak
Tsikandylakis et al. (2014)[75]	Moderate	Moderate	Weak	Weak	Weak	Weak	Weak
Tillander et al. (2010)[74]	Weak	Moderate	Weak	Weak	Weak	Strong	Weak
Sullivan et al. (2003)[72]	Moderate	Moderate	Weak	Weak	Weak	Weak	Weak

Results of individual studies

Table 4 presents the device-related complications, and **table 5** presents the complication-related interventions occurring in individuals with bone-anchored prostheses.

Table 4. Device-related complications

Authors (years)	Implant type/ Level of amputation	Loss to follow-up (%) (reason)	Un-eventful course (%)	Infection (%) (grade (% of patients))	Bone fracture (%)	Device breakage (intr., DCA/abut. (% of total))	Implant loosening (%)	Stoma hyper-granulation (%)	Stoma redundant tissue (%)	Other soft tissue complications (%)	Systemic events (MI/PE) (%)
Transfemoral											
Tillander et al (2017) [73]	Screw	2 (50 DU death, 50 ?)	?	? (grade 1-2: ?, grade 3: 13, grade 4: 11)	?	?	?	?	?	?	?
Sullivan et al. (2003) [72]	Screw	?	?	?	?	45 (abut.: 100)	?	?	?	?	?
Al Muderis et al. (2017) [70]	Press-fit	5 (DU death)	?	57 (grade 1: 48, grade 2: 10)	0	0	0	?	?	?	?
Al Muderis et al. (2016) [61]	Press-fit	?	36	34 (grade 1: 29, grade 2: 5)	3	31 (Intr.: 6 (2% of patients), DCA: 94 (29% of patients)	1	20	16	?	?
Al Muderis et al. (2016) [43]	Press-fit	6 (100 DU death)	32	42 (?)	8	2 (intr.: 100)	2	?	14	?	?
Aschoff et al. (2016) [47]	Press-fit	?	?	?	8	1 (Intr.: 100)	0	?	?	?	?
Juhnke et al. (cohort 1) (2015) [50]	Press-fit	?	20	77 (grade 1-2: ?, grade 3: ?, grade 4:3)	10	3 (?)	?	?	?	?	?
Juhnke et al. (cohort 2) (2015) [50]	Press-fit	?	87	0 (-)	5	0	3	3	3	3 (fistula)	?
Juhnke et al. (2015) [49]	Press-fit	?	?	? (grade 1-2: ?, grade 3: ?, grade 4: 3%)	10	?	?	?	?	?	?
McGough et al. (2017) [51]	Compress	?	73	0	18	?	0	?	9	?	?

Table 4. Device-related complications (continued)

Authors (years)	Implant type/ Level of amputation	Loss to follow-up (%) (reason)	Un-eventful course (%)	Infection (%) (grade (% of patients))	Bone fracture (%)	Device breakage (intr., DCA/abut. (% of total))	Implant loosening (%)	Stoma hyper-granulation (%)	Stoma redundant tissue (%)	Other soft tissue complications (%)	Systemic events (MI/PE) (%)
Transtibial											
Aschoff et al. (2016) [47]	Press-fit	?	?	?	?	?	29	?	?	?	?
Juhnke et al. (2015) [49]	Press-fit	?	?	? (grade 1-2: ?, grade 3: ?, grade 4: 29%)	?	?	?	?	?	?	?
Upper extremity											
Li et al. (2017) [71]	Screw (Mixed upper extremity)	TR: ? Thumb: ? TH: 11 (at 2 year FU)	TR: ? Thumb: 46 TH: ?	?	?	TR: 27 (Intr. 100) Thumb: ? TH: ?	TR: ? Thumb: 23 TH: 13	?	?	?	?
Tsikandylakis et al. (2014) [75]	Screw	0	?	44 (grade 1: 28, grade 3: 6, grade 4: 11)	0	?	?	44	?	?	?
Tillander et al. (2010) [74]	Screw (Mixed upper/lower extremity)	5 (100 unspecified NM)	?	Inclusion: 23 (grade 1-2:18, grade 3:5), FU: 49 (grade 1-2: 30, grade 3:11, grade 4: 8)	?	?	3 (100: TF)	?	?	?	?

Grading of infection= Grade 1: Superficial soft tissue, Grade 2: Deep soft tissue, Grade 3: Bone infection, Grade 4: Implant infection. DCA= Dual cone adaptor, Intr.= Intramedullary device, Abut.= Prosthetic abutment, MI= Myocardial infarction, PE= Pulmonary embolism, TF= Transfemoral, TT= Transtibial, TH= Transhumeral, DU= Device-unrelated, DR= Device-related, Loose.= Implant loosening, No-S2= Not yet after Surgery 2, NM= Non-medical, FU: follow-up

Table 5. Complication-related interventions

Authors (years)	Implant type/ Level of amputation	Oral antibiotics (%)	Parenteral antibiotics (%)	Surgical debridement (%) (% of total: infection, hypergranulation, stoma redundant tissue, other)	Explantation (%) (% of total: infection, loosening, bone/ implant fracture, other)	Successful re-implantation (% of explantation)	Fracture treatment (% of fractures) (conservative/ surgical)
Transfemoral							
Tillander et al. (2017) [73]	Screw	?	?	?	17 (63: inf., 38: ?)	6 (100% of infection explantations) *	?
Sullivan et al. (2003) [72]	Screw	?	?	?	18 (100: inf.)	?	?
Al Muderis et al. (2017) [70]	Press-fit	48 (all grade 1 cases)	10 (all grade 2 cases)	29 (100: redund.)	0	NA	NA
Al Muderis et al. (2016) [61]	Press-fit	27	1	22 (27: inf., 73: redund.)	3 (33: loose., 67: intr. device break.)	100	100: surgical
Al Muderis et al. (2016) [43]	Press-fit	26	10	20 (30:inf., 70: redund.)	4 (50: loose., 50: intr. device break.)	100	100: surgical
Aschoff et al. (2016) [47]	Press-fit	?	?	? (6 of total TF+TT (100: redund.))	6 (80: inf., 20: device break.)	Unknown (38% of total explantations TF+TT)	100: surgical
Juhnke et al. (cohort 1) (2015) [50]	Press-fit	?	?	77 (100:inf.)	13 (100: inf.)	50	100: surgical
Juhnke et al. (cohort 2) (2015) [50]	Press-fit	?	?	8 (33: hyperg., 33: redund., 33: ilizarov treatment)	3 (100: loose.)	100	100: surgical
Juhnke et al. (2015) [49]	Press-fit	?	?	?	6 (unknown)	50	100: surgical
McGough et al. (2017) [51]	Compress	?	?	9 (100: redund.)	9 (100: bone fract.)	100	50: surgical in combination with implant revision, 50: awaiting revision

Table 5. Complication-related interventions (continued)

Authors (years)	Implant type/ Level of amputation	Oral antibiotics (%)	Parenteral antibiotics (%)	Surgical debridement (%) (% of total: infection, hypergranulation, stoma redundant tissue, other)	Explantation (%) (% of total: infection, loosening, bone/ implant fracture, other)	Successful re-implantation (% of explantation)	Fracture treatment (% of fractures) (conservative/ surgical)
Transtibial							
Aschoff et al. (2016) [47]	Press-fit	?	?	? (6 of total TF+TT (100: redund.))	43 (33: inf., 67: loose.)	Unknown (38% of total explantations TF+TT)	?
Juhnke et al. (2015) [49]	Press-fit	?	?	?	57 (unknown)	25	?
Upper extremity							
Li et al. (2017) [71]	Screw (Mixed upper extremity)	?	?	?	TH: 19 (67: loose., 33: glenohumeral osteoarthritis) TR: ?, Thumb: ?	TH: 33	?
Tsikandylakis et al. (2014) [75]	Screw (TH)	22	?	11 (100: inf.)	17 (67: loose., 33: glenohumeral osteoarthritis)	33	?
Tillander et al. (2010) [74]	Screw (Mixed upper/lower extremity)	?	?	?	14 (60: Deep inf. (TF), 20: loose (TF), 20: Chronic skin inf. (unknown))	40	?

TF= Transfemoral, TT= Transtibial, TH= Transhumeral, Inf.= Infection, Redund.= Stoma rendundant tissue, Loose.: Implant loosening, Intr.= Intramedullary device, Fract.= Fracture, Break.: Breakage, Hypergr.= Hypergranulation tissue

* No data on successful reimplantation of individuals with explantation with unknown reason

Infection

The occurrence of infection was reported in 11 out of 15 cohorts (73%).[43, 49-51, 61, 70, 73-75] The infection rate ranged from 23-49% in individuals treated with screw implants compared with 0-77% in individuals treated with press-fit implant and 0% in individuals treated with the Compress implant. Soft tissue infections in the skin-penetrating area (Grade 1-2) occurred in 28% and 0-57% of individuals treated with screw and press-fit implants, respectively. Bone infection (Grade 3) occurred in 5-13% and 0% of individuals treated with screw and press-fit implants, respectively. Infections resulting in implant loosening (Grade 4) occurred in 8-11% and 3-29% of individuals treated with screw and press-fit implants, respectively.

Examination of infections rates in relation to amputation level revealed a rate of infection ranging from 0-77% in individuals with transfemoral amputation treated with press-fit implants and 44% in individuals with upper extremity amputation. The rate of infection in individuals with transfemoral amputation treated with screw implants or individuals with transtibial amputation was unkown. The rate of soft tissue infections (Grade 1-2) ranged from 0-57% in individuals with transfemoral amputation treated with press-fit implants and there was a rate of 28% in individuals with upper extremity amputation. There was no reported rate in individuals with transfemoral amputation treated with screw implants or individuals with transtibial amputation. Bone infection (Grade 3) occurred in 13% of individuals with transfemoral amputation treated with screw implants and 6% of individuals with upper extremity amputation. There was no reported rate in individuals with transfemoral amputation treated with press-fit implants or in individuals with transtibial amputation. Implant loosening due to infection (Grade 4) occurred in 0-11% of individuals with transfemoral amputation (screw-fit: 11%, press-fit: 0-3%), 29% of individuals with transtibial amputation and 11% of individuals with upper extremity amputation, all of which being individuals with transhumeral amputation.

The article by Juhnke et al.[50] was the only one reporting infection rates before and after adaptation of surgical technique and implant design and presented a decrease in infection rates from 77% to 0% in press-fit transfemoral implants. The article by Tillander et al.[74] was the only one to report the incidence of infection in individuals attending a scheduled or emergency visit who were surveyed at inclusion and three years later. The reported incidence of infection was 23 and 49% (among which 8% implant loosening) at inclusion and three years later, respectively, among a cohort of individuals with an upper- and lower-extremity amputation treated with screw implants.

Peri-prosthetic bone fracture

The incidence of peri-prosthetic bone fracture was described in nine of 15 cohorts (60%) with an incidence of 0% in individuals treated with a screw implant, 0-10% in individuals treated with a press-fit implant and 18% in individuals treated with the Compress implant.[43, 47, 49-51, 61, 70, 75] Three articles reported the cause of bone fracture which were

falls in all studies.[43, 51, 61] All reported peri-prosthetic bone fractures occurred in individuals with press-fit transfemoral bone-anchored implants. No fractures occurred in individuals with upper extremity bone-anchored implants and no data reported on the incidence of fractures in individuals with transfemoral amputation treated with screw implants or individuals with transtibial bone-anchored implants.

Device breakage

The incidence of device breakage were mentioned in eight of 15 cohorts (53%) and subdivided in fractures of the intramedullary implant, of the abutment (screw) and of the dual cone adaptor (press-fit).[43, 47, 50, 61, 70-72] Device breakage occurred in 27-45% and 0-31% of individuals treated with screw and press-fit implants, respectively. These device breakages were of the abutment and intramedullary part in screw implants (transfemoral: 100% abutment, transradial: 100% intramedullary component) and mostly breakages of the dual cone adapter in press-fit implants (up to 94%). Device fractures were not reported in the cohort treated with the Compress implant.[51]

No intramedullary device breakages were reported in individuals with transfemoral amputation treated with screw implants, while intramedullary device breakages occurred in, on average, 1% of individuals with transfemoral amputation treated with press-fit implants. No device breakages were reported in individuals with transtibial bone-anchored prostheses. There was an incidence of intramedullary device breakage of 27% in individuals with transradial screw implants. The article by Juhnke et al.[50] did not specify the part of the device in which a breakage occurred.

Implant loosening

The incidence of implant loosening of the bone-anchored implants was reported in nine of the 15 cohorts (60%).[43, 47, 50, 51, 61, 70, 71, 74] It ranged from 3-23% and 0-29% in individuals treated with screw and press-fit implants, respectively. No implant loosening occurred in individuals treated with the Compress implant.

The rate of implant loosening was not described in individuals with transfemoral amputation treated with screw implants and was 0-3% in those treated with press-fit implants. Implant loosening occurred in up to 29% of individuals with transtibial amputation treated with press-fit implants and in 13% and 23% of individuals with transhumeral and thumb amputation respectively, treated with screw implants. Implant loosening was not reported in individuals with transradial amputation. All implants (3%) that presented with loosening in the cohort reported by Tillander et al.[74] were transfemoral screw implants.

Soft tissue complications

Soft tissue complications were subdivided into stoma hypergranulation, stoma redundant tissue and other soft tissue complications. The incidence of stoma hypergranulation

and redundant tissue was reported in five of the 15 cohorts (33%) with other soft tissue complications also being reported in the cohort assessed by Juhnke et al. (Table 4).[43, 50, 51, 61, 75]

Stoma hypergranulation occurred in 44% and 3-20% of individuals treated with screw and press-fit implants, respectively, and was not reported in individuals treated with the Compress implant. Stoma redundant tissue was not reported in the cohorts of individuals treated with screw implants, but occurred in 3-16% and 9% of individuals treated with press-fit and the Compress implant respectively. All cases of stoma hypergranulation and stoma redundant tissue reported on in individuals treated with press-fit or Compress implants occurred in individuals with transfemoral amputation.

Soft tissue complications in individuals with upper extremity amputation were reported in one cohort, with a rate of stoma hypergranulation of 44% in individuals with transhumeral amputation treated with screw implants.[75] No soft tissue complications were reported in individuals with transtibial amputation.

Systemic events and death

No cohorts described systemic events such as pulmonary embolism and myocardial infarction and no device-related deaths have been reported.

Antibiotics treatment

In four of the 15 cohorts (27%), the use of antibiotics was reported: one in screw implants and three in press-fit implants.[43, 61, 70, 75] Oral antibiotics were used in 26-48% of individuals with transfemoral amputation treated with press-fit implants and in 22% of individuals with transhumeral amputation treated with screw implants. Parenteral antibiotics were used in 1-10% of individuals with transfemoral amputation treated with press-fit implants. No clear overview of the use of antibiotics for the treatment of infections was provided in the other cohorts.

Surgical debridement

The need for surgical debridement was subdivided according to the indication as follows: infection, hypergranulation, stoma redundant tissue or other and was reported in nine of the 15 cohorts (60%), seven of which were cohorts of individuals treated with press-fit implants.[43, 47, 50, 51, 61, 70, 75] The incidence of surgical revision was 11% and 9% in individuals treated with a screw and Compress implant respectively and ranged from 6-77% in individuals treated with press-fit implants. A revision rate of 77%, all due to infection, was reported in the first cohort described by Juhnke et al. [50] consisting of individuals with transfemoral amputation treated with first-generation press-fit implants. The revision rate was 8% in the second cohort after iteration of the surgical technique and implant design, none of which were due to infection. The main overall reasons for surgical revision in all cohorts were stoma redundant tissue and infection.

Explantation and re-implantation

The incidence of explantation was described in all cohorts and ranged from 14-19% in individuals treated with a screw implant,[71-75] from 0-57% in individuals treated with a press-fit implant [43, 47, 49, 50, 61, 70] and was 9% in individuals treated with the Compress implant.[51]

Assessment of the level of amputation revealed an explantation rate of 17-18%, 0-13% and 9% in individuals with transfemoral amputation treated with a screw, press-fit or Compress implant, respectively. Two reasons for the explantation of transfemoral implants were intramedullary device breakage, which only occurred in the press-fit implants; and bone fracture, which only occurred in the Compress implant. Implant loosening and infection were other reasons for explantation of transfemoral implants and occurred in both the screw and press-fit implants but not the Compress implant. The rate of explantation was much higher in individuals with transtibial amputation ranging from 42-57%, with Aschoff et al.[47] reporting high rates of implant loosening. All these individuals were treated with press-fit implants. The explantation rate was 17-19% in individuals with transhumeral amputation treated with screw implants. An explantation rate of 14% was reported in the cohort evaluated by Tillander et al.[74] comprising a combination of individuals, all of which being individuals with transfemoral amputation treated with screw implants.

The incidence of re-implantation was reported in 13 of the 15 cohorts (87%); it was performed successfully in 100% of individuals treated with the Compress implant and in 6-40% and 25-100% of the cohorts of individuals treated with screw and press-fit implants, respectively.[43, 47, 49-51, 61, 70, 71, 73-75] Only Tillander et al. [73] reported on re-implantation in individuals with transfemoral amputation treated with screw implants, being successful in 6% of individuals all of which explanted due to infection. They did not report on re-implantation rates for the individuals treated with explantation with other etiologies. Thus successful re-implantation rates were unclear in individuals with transfemoral amputation treated with a screw implants while being successful in 50-100% and 100% of individuals with transfemoral amputation treated with a press-fit and Compress implant respectively. Re-implantation was successful in 25% of individuals with transtibial amputation in the cohort described by Juhnke et al.,[49] while the exact rate of successful re-implantation was not clearly reported in the cohort reported by Aschoff et al.[47] Re-implantation was successful in 33% of individuals with transhumeral amputation, and Tillander et al. [74] reported a successful re-implantation rate of 40% in their cohort of individuals with an upper- and lower-extremity amputation treated with screw-fit implants.

Peri-prosthetic fracture treatment

The occurrence of peri-prosthetic fracture treatment was described in seven of the 15 cohorts (47%); of which six cohorts involving individuals with transfemoral amputations treated with press-fit implants and one involving individuals treated with the Compress implant.[43, 47, 49-51, 61] In these cohorts, all peri-prosthetic bone fractures were treated

surgically and treatment was combined with an implant revision in the cohort of individuals treated with the Compress implant.

Discussion

This is the first study to provide a complete and detailed overview of device-related complications in both individuals with lower and/or upper extremity amputation treated with screw, press-fit or other types of bone-anchored prostheses, while also providing an overview of complication-related interventions.

The occurrence of explantation of implants was the only outcome reported in all cohorts, followed by re-implantation (87%), infection (73%) and implant loosening (60%). For the purpose of comparison, complications rates reported by Branemark et al. [41], which was excluded due to complete overlap with Tillander et al. [73], that did not come to light in the other cohorts will be included in the discussion (Total infection 67% (grade 1-2: 58%, grade 3: 6%, grade 4: 2%), device fracture: 8% (all of which abutment), implant loosening: 6%, explantation 8%). a) Explantation rates seemed to vary greatly when comparing different implants (screw: 8-19%, press-fit: 0-57%, Compress: 9%), but due to the high explantation rates of transtibial implants (43-57%), all of which were press-fit, these rates provide a biased representation of the outcome. If only explantation rates of transfemoral implants are compared, press-fit implants seem to be less frequently explanted than screw-fit implants (0-13% vs 8-18%) with a similar rate of explantation of the Compress implant (9%), being the only implant that had to be explanted due to a bone fracture. Explantation rates in individuals with transhumeral amputation treated with screw implants ranged from 17-19%. The article by Jonsson et al.[68], which was excluded due to complete overlapping data with Li et al.[71], reported in more detail the explantation rates in individuals with transradial and thumb implants treated with screw implants, being 10% and 30% respectively. b) Re-implantation was typically more successful in individuals treated with a press-fit or Compress implant, especially in individuals with transfemoral amputation (Press-fit: 50-100%, Compress: 100%, screw: 6%); however these rates may also be biased, as only one Compress implant was re-implanted and it is also possible that re-implantation was attempted more often in certain subgroups. The article by Tillander et al.[73] reported on a successful re-implantation rate of 6% in individuals that had their implant explanted due to infection, only they did not report on re-implantation rates of the individuals that underwent explantation on other accounts. c) Total infection rates varied substantially between studies, with no infections occurring in the small cohort treated with the Compress implant and seemingly showing a favorable trend of implant infections (Grade 4) for the screw over the press-fit implant (screw: 2-11%, press-fit: 0-29%); although these numbers, again, are greatly affected by transtibial implants in which there is less expertise. When comparing implant infections between transfemoral screw and press-fit implants (screw: 2-11%, press-fit: 0-3%) there is a considerable difference, and when

looking at amputation level (transtibial (press-fit): 29%, upper extremity (screw): 11%) it is clear that there are high rates of implant infections in transtibial implants. d) Again, when examining implant loosening and comparing implants (screw: 3-23%, press-fit: 0-29%, Compress: 0%) a biased representation is created due to the high rate of complications in individuals with a transtibial and upper extremity amputation. When only comparing rates between individuals with a transfemoral amputation, the rates seem to be slightly lower in press-fit implants (screw: 6%, press-fit: 0-3%), with increasing rates in upper extremity screw implants (Thumb: 23%, transhumeral 13%) and very high rates of implant loosening in individuals with press-fit transtibial implants (29%).

Other noteworthy findings concern the incidence of device breakage and surgical revision; a) Device breakages occurred at rates of 0% in the small Compress implant cohort and 8-45% and 0-31% in individuals treated with screw and press fit implants respectively, but were mainly due to breakage of external replaceable parts of the prosthetic system, except for the individuals with transradial implants (27% fixture breakage). Breakage of the intramedullary device was rarely observed in individuals with transfemoral implants, with an incidence of 0% in screw transfemoral implants and 1% in press-fit transfemoral implants. b) The need for surgical revision varies greatly between all cohorts (8-77%), and has only been reported in 60% of cohorts. Infection and stoma redundant tissue appear to be the main reasons for surgical revision, and these rates could be considerably affected by iterations of the implant design and the surgical technique.[50] The treatment of infection with, for instance, antibiotics, and the occurrence of soft tissue complications were greatly under-reported by the included articles, even though multiple articles concluded that infection and soft tissue complications were the most commonly encountered problems in individuals treated with bone-anchored prosthetics.[47, 49, 50, 53]

To help interpret the complication rate of bone-anchored prostheses, a head-on comparison with the complication rates in primary total hip arthroplasty (THA), which is considered standard orthopedic care, with acceptable complication rates has been performed.[76] Gundtoft reported a cumulative 5-year incidence of prosthetic joint infections in 29.077 individuals treated with 32.896 primary THA's of 1%.[77] These deep infections or prosthetic joint infections are equivalent to the grade 4 infections mentioned above and, especially in the case of press-fit transfemoral bone-anchored implants, show potentially similar results (0-3%). The systematic reviews by van Eck et al. [54], Hebert et al. [55] and Al Muderis et al [56] had an overlapping research question with this review and briefly reported on the complications of bone-anchored prostheses. Of the 12 articles included in this systematic review, only two, [72, 74] six [43, 50, 61, 70, 72, 74] and two [72, 74] were included by van Eck et al., Hebert et al. and Al Muderis et al., respectively, to evaluate complication incidence. The cause of this difference is that we excluded articles with complete overlap and included participants with an upper extremity amputation. It was not possible to compare our result with the above- mentioned reviews because van Eck et al. did not stratify the extracted data, Hebert et al. only presented the data per included article but

failed to present overall complication ranges and Al Muderis et al. presented only non-detailed descriptive data.

Strengths and limitations

A number of factors may have led to distortion of the findings of this review. First, most articles only reported limited complications, with no article providing a complete review of all possibly occurring complications. Explantation was the only complication mentioned in all articles. Second, despite our efforts to prevent overlap, there most likely was partial overlap of patient data in some of the included studies, due to an overlap in the periods of inclusion of individuals (**Fig. 2**); which can lead to duplicate data and may affect outcomes. Third, in many of the included studies, it was unclear how the complications were reported [47, 49, 51, 71], and the study by Tsikandylakis et al. [75] was the only one that reported on the type of examiner that registered complications at follow-up. In most studies, it was unclear whether the complications were collected in specific databases, by investigating electronic patient files or by acquiring information from general practitioners or other hospitals. Fourth, a certain type of selection bias might have occurred, for instance, in the article by Tillander et al. [74], which included individuals attending the clinic for scheduled or emergency visits. Fifth, all included articles were cohort studies, prospective or even retrospective, also giving rise to questions regarding the methodological quality. Sixth, given the small number of individuals included in every study and the varying number of studies reporting certain outcomes, the overall complication rates could be greatly influenced by single outliers. Seventh, the learning curve for the treatment and adaptation of technique and design can also affect complication rates. The article by Juhnke et al. [50] reported a very high incidence of surgical re-intervention in its first cohort, which decreased substantially as a result of iterations of the device design and surgical technique. The article by Hagberg et al. [42], which was excluded due to complete overlap with Tillander et al. [73], also stated that most failures occurred in the early group of individuals that was not treated with a standardized rehabilitation protocol. Eighth, a number of factors may have led to the underestimation of certain complications. It can be suspected that minor complications are likely to be treated by the general practitioner, possibly resulting in an underestimation in the report. Another reason for the possible underestimation of complications is the presence of multiple studies that did not clearly report the occurrence of infections, with some only reporting major complications, such as high grade infections (Grade 3-4), that led to surgical interventions.[47, 49, 50] Complications are often patient-reported, which can also result in an underestimation. Some form of publication bias may have also led to an underestimation of overall complications found in this review, as it is possible that studies with negative outcomes might have not been published. Ninth, it is important to note that conclusions drawn should be interpreted as originating from included studies with a generally weak nature of quality. Assessing the methodological quality of articles reporting complications can lead to difficulties due to the lack of a gold standard classification system to establish complications after bone-anchored prostheses surgery or a consensus regarding specific data collection methods.

Other aspects ranked by critical appraisal tools, such as controlling for confounders and the level of blinding, can rarely be avoided because complication data are mostly collected during daily clinical care.

The first and most important strength of this review is that subgroup analyses were performed regarding the implant type and level of amputation, resulting in improved clinical utility. Thus, when more data are available in the future, it might be possible to supply targeted advice regarding the choice of implant type in terms of the level of amputation. We also clarified that, given the way data have been published to date, it is not possible to stratify complications as short- , mid- or long-term complications. More studies with fixed follow-up periods, such as the study by Branemark et al., [41] are necessary to clarify this point. Complications have been well-defined in most studies and regular follow-ups with substantial overlap between different articles, but these follow-ups were not used as specific time points for reporting complications in these publications. A second strong point is that we have given a clear insight in the great amount of patient data overlap through the Gantt chart depicted in **figure 2**. To correct for the effect of the overlapping cohorts and duplicate data, we aimed to perform an individual patient data (IPD) meta-analysis. Rather than extracting summary data from the study publications, we searched for the original research data directly from the researchers to exclude any duplicates. Performing this IPD meta-analysis was not possible because the approached researchers were not able to share their original data. A third strong point is the high level of agreement between the two reviewers about ratings of methodological quality.

Recommendation for future research

As mentioned above, there was no clear consensus in the studies included regarding which complications were reported. In future research, it would be beneficial if all studies would report the same complications in the same manner. A core set should be formulated to provide a representation of the most important complications that should be reported. The content of this core set could be as follows: infection, soft tissue complications, bone fracture, device breakages, implant loosening, explantation, surgical revision, antibiotic use, re-implantation, systemic events and death and uneventful course (**Table 4**).[43, 50, 61] Within this core set, it would also be beneficial to have strict follow-up times (for example 1, 2, 3, 5 and 10 years). When reporting certain complications, it would be beneficial to follow a certain classification system, such as, for example, the classification system for infection as proposed by Al Muderis et al. Table 1.[61] Furthermore, to interpret the current data in an improved fashion, an IPD meta-analyses is suggested for future research. To facilitate the process of data collection, it is advisable to construct a central database in which all data are stored that follows the core set of above-mentioned complications. We were not able to perform a meta-analysis due to the heterogeneity of the data in terms of outcomes and follow-up intervals. To facilitate a meta-analysis in the future we suggest the following fixed follow-up periods: one, two, five, 10- and 20-year post-operative follow-ups.

Conclusion

In conclusion, this systematic review revealed that in individuals treated with a transfemoral implant the incidence of major complications such as implant infection, implant loosening and explantation was lower in users of a press-fit implant compared to a screw implant. Individuals treated with a transtibial or upper extremity implant and compress implant were underreported, precluding definitive conclusions. The current data revealed that the complication rates encountered in these subgroups of individuals exceed what is deemed acceptable for regular orthopedic interventions. In general, minor complications are most common, such as complications or infections of the soft tissues, which may be greatly affected by the learning curve, implant design and surgical technique, and breakage of external replaceable parts of the implant.

To improve future treatment and research, it will be necessary to formulate a core set of complications that should be reported at fixed time points, as well as to follow a classification system that results in clear and unequivocal data and research. This review could also help professionals and patients in the choice of implant type with respect to the amputation level. However, it should be kept in mind that our conclusions are based on articles of low methodological quality.

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Supporting information

S1 Appendix: Search string for each database

MEDLINE (accessed via PubMed) => 179 hits:

(Amputation[MeSH] OR Amputees[MeSH] OR Amputation, Traumatic[MeSH] OR Amputation Stumps[MeSH] OR Amput*[Title/Abstract]) AND (osseointegration[MeSH Terms] OR osseointegrat*[Title/Abstract] OR osseo-integrat*[Title/Abstract] OR osseointegrat*[ot] OR bone-anchored prostheses[Title/Abstract] OR boneanchored prostheses[Title/Abstract])

Cochrane Central Register of Controlled Trials => 3 hits:

#1	MeSH descriptor: [Osseointegration] explode all trees
#2	osseointegrat*:ti,ab,kw (Word variations have been searched)
#3	"'osseo-integrated":ti,ab,kw (Word variations have been searched)
#4	"osseo-integrate":ti,ab,kw (Word variations have been searched)
#5	"osseo-integrat":ti,ab,kw (Word variations have been searched)
#6	"osseo-integration":ti,ab,kw (Word variations have been searched)
#7	"bone-anchored prostheses":ti,ab,kw (Word variations have been searched)
#8	"bone-anchored prosthesis":ti,ab,kw (Word variations have been searched)
#9	"bone-anchored prosthetics":ti,ab,kw (Word variations have been searched)
#10	MeSH descriptor: [Amputation] explode all trees
#11	MeSH descriptor: [Amputation Stumps] explode all trees
#12	MeSH descriptor: [Amputation, Traumatic] explode all trees
#13	ampu*:ti,ab,kw (Word variations have been searched)

S2 Appendix: PRISMA Checklist

Section and Topic	#	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6 + 7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7

Section and Topic	#	Checklist item	Location where item is reported
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10 + 11
Risk of bias within studies	19	Present data on risk of bias for each study and, if available, any outcome level assessment (see item 12).	14 + 15
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	16 - 25
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	16
Risk of bias across studies	22	Present results of any assessments of risk of bias across studies (see item 15).	14 + 15

Section and Topic	#	Checklist item	Location where item is reported
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see item 16]).	16
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	26 - 28
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	28 – 30
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	30 – 31
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	30

Fr*om:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Chapter 3

Safety, prosthesis wearing time and health-related quality of life of lower extremity bone-anchored prostheses using a press-fit titanium osseointegration implant: a prospective one-year follow-up cohort study

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Abstract

Background

We described safety and functional one-year follow-up outcomes of individuals with lower limb amputation treated with bone-anchored prostheses using titanium press-fit osseointegration implants.

Methods

All consecutive individuals treated between March 2015 and June 2018 with curved osseointegration femur implant (OFI-C) indicated for a long femoral remnant, gamma osseointegration femur implant (OFI-Y) indicated for a short femoral remnant, or osseointegration tibia implant (OTI) were eligible for this study. All adverse events were evaluated, infections were graded as follows: grade 1 and 2: low- and high-grade soft tissue infection, respectively, grade 3: deep bone infection, grade 4: septic implant failure. Functional outcome measures included prosthesis wearing time (PUS), health-related quality of life (GS), and the overall situation as an amputee (GS Q3); evaluated with the Questionnaire of persons with trans-femoral amputation (Q-TFA) before surgery and at one-year follow-up.

Results

Ninety of 91 individuals were included (mean age: 54±14 yrs, 26 females); treated with 53, 16 and 21 OFI-C, OFI-Y and OTI, respectively. Soft tissue infections (grade 1: 11 events, grade 2: 10 events) were treated successfully with antibiotics except in two (OFI-C and OFI-Y), who required additional surgery due to recurrent stoma irritation and peri-stoma abscess drainage. One individual with dysvascular amputation (OTI) developed septic implant loosening and occlusion of the femoral artery resulting in a transfemoral amputation. No aseptic loosening's occurred. One individual (OFI-Y) required stoma surgical refashioning due to soft tissue redundancy. At baseline mean ±SD and median (25^{th} to 75^{th} PCTL) Q-TFA PUS and GS were 52±39, 52(7-90) and 40±19, 42(25-50) and improved significantly to 88±18, 90 (90-100) and 71±15, 75 (67- 83) at one-year follow-up. The GS Q3 improved over time.

Conclusion

Titanium osseointegration implants can be safely used within a one-year follow-up period. The performance improved compared to the use of a socket-suspended prosthesis.

Keywords: Amputees; Osseointegration; Complications; Bone anchored prosthesis; Performance.

Introduction

Bone-anchored prostheses (BAP) using an osseointegration implant (OI) are a suitable alternative for individuals with amputations experiencing pain, pressure sores, and mobility restrictions related to the use of socket-suspended prostheses (SSP).[1]The advantage of an OI is that it provides a direct skeletal attachment for an artificial leg.[2] This results in a more physiological and stable prosthetic control, osseoperception, improved walking, and sitting conditions as well as eliminating the socket-residuum interface with all its associated problems.[3-6] Currently, there are two different OI systems commercially available.[7] The oldest, with the longest follow up evaluations, is the titanium screw fixation system developed by the Swedish Brånemark group and available as Osseointegrated Protheses for the Rehabilitation of Amputees Implant system (OPRA) manufactured by Integrum AB Sweden.[8] A second relatively more recent designed OI system is the press-fit fixation system developed and used by the German/Dutch/Australian osseointegration groups available as the Integral leg prosthesis (ILP)/Osseointegrated femur or tibia prosthesis (OFP-OTP)/Osseointegration prosthetic limb (OPL, type A-D) implant systems manufactured by Eska Orthopedics GmbH, Germany/OTN Implant BV, Netherlands/ Permedica SPA, Italy; respectively.[6, 9-12] All afore mentioned OI's are of a titanium alloy with exception of the ILP which is made of a chromium-cobalt-molybdenum alloy. The press-fit OI system is adopted from the uncemented total hip implants in which the stem has a rough macroporous surface to provide solid and fast osseointegration by means of bony ingrowth.[13] Therefore, the total treatment period for press-fit implants is currently less time-consuming than for screw type implants, meaning that the period until full weight bearing is much shorted when treated with a press-fit implant.[1, 6, 14] A recent systematic review of the safety of BAP showed a slightly better femoral OI survival for press-fit implants compared to screw implants.[15] Several studies have shown favourable performance data when comparing BAP to SSP leading to increased level of function, activity, and health-related quality of life.[1, 4-6, 16]

Previous risk-benefit studies of BAP using a press-fit OI have predominantly included selected individuals with transfemoral amputation treated with the curved press-fit osseointegration femur implant (OFI-C), both with a chromium-cobalt-molybdenum and a titanium alloy.[15] Currently almost half of the candidates referred to our center for OI treatment have either short femoral remnants or a transtibial amputation. For individuals with transfemoral amputation with short femoral remnants and individuals with transtibial amputation, a gamma press-fit osseointegration femur implant (OFI-Y) and press-fit osseointegration tibia implant (OTI) is used, respectively. Safety and performance data focusing on the OFI-Y and OTI are scarce. There are only a few case series with short follow up that report on safety and performance data of individuals with transtibial amputation.[5, 17-19] For further expansion of the application of BAP using OI in the broader population of individuals with a lower extremity amputation, insight in the risk/benefit

ratio of the OFI-Y and OTI is needed; especially when compared to the risk/benefit ratio of the more widely used OFI-C.

The aim of this one-year follow-up study was to present the adverse events, prosthesis wearing time and health-related quality of life of OI's made of a titanium alloy both in general and stratified by OI type (OFI-C, OFI-Y, and OTI).

Materials and methods

Study Design

This article presents one-year follow-up data of an on-going cohort study. The performance data was prospectively collected as part of a larger longitudinal study.[20] One year follow-up results of a subcohort were published earlier.[5] The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement was followed for the preparation of the manuscript to ensure methodological quality provided in **S1 Appendix**.[21] The study was conducted according to the principles of the Declaration of Helsinki (64th version, 19-10-2013). The protocol of this study (registration number 2014/196) was approved by the Ethics Committees of Radboudumc.

Participants

All consecutive individuals who received a titanium press-fit OFI-C (OFP and OPL type A), OFI-Y (OFP) or OTI (OTP) at the Radboud university medical center (Radboudumc), between March 2015 and June 2018, were eligible for this study. During this period a small subset of individuals were treated with other types of implants (ILP and OPL type B) but these were excluded because a) we implanted only small numbers or b) the implant was made of chromium-cobalt-molybdenum alloy. Individuals are eligible for an OI if the primary amputation is congenital or due to a trauma, tumor resection, dysvascular disease, infection, or other causes such as joint replacement infections. Additionally they have to meet the inclusion and exclusion criteria as presented in table 1, with the inclusion criteria being based on certain items of the Q-TFA.[6] Prior to the inclusion a written informed consent was obtained from all participants.

Patient selection

The patient selection was performed with a multidisciplinary team including an orthopedic (trauma) surgeon, rehabilitation physician, and a physical therapist. Prior to their visit, the candidates completed the Questionnaire for Persons with a Transfemoral Amputation (Q-TFA) and underwent plain X-ray radiologic examination of the femoral or tibial remnant and calibrated total view of both lower extremities. A computed tomography (CT) scan was performed in individuals with a tibial amputation or in individuals with short femoral remnants as further detailed below. General information was given in a group presentation and informed consent was obtained individually by the surgeon. Three months after the

general intake, mutual agreement with informed consent for the treatment was achieved based on in- and exclusion criteria, medical history, physical examination, and radiology results. Candidates who revealed unrealistic, expectations of their future functioning with a bone-anchored prosthesis, were referred to a clinical psychologist for discussion and adjustment of expectations. Candidates with a medical history of peripheral vascular disease as the cause of amputation were additionally screened by a vascular surgeon assessing the presence of femoral artery pulsations in the groin as well as skin perfusion oxygen pressure and evaluating duplex ultrasonography of the limb. A transcutaneous oxygen pressure less than 40 mmHg, measured at the tip of the stump, was used as an exclusion criterion for osseointegration surgery. Transcutaneous oxygen was measured with the Precise 8001 (MediCap Homecare GmbH, Germany).

Table 1: Inclusion and exclusion criteria

Inclusion criteria: OI implant is indicated when at least one item is answered yes.	Exclusion criteria
The prosthesis is used less than 50 hours per week due to socket-related problems	Severe diabetes (including a medical history of multi-organ failure)
The prosthesis restricts walking distance: less than 2 km (with or without walking aids)	Systemic/local infection
The prosthesis is considerably unreliably attached during daily activities	Age <18 (immature bone)
The prosthesis is considerably uncomfortable to sit down	Bone deformity, -dysplasia, -metabolic disorders
The prosthesis causes sores, chafing, or skin irritation	Radiotherapy on residual limb within 3 months before OI surgery
The prosthesis considerably causes troubles by heat/ sweating during hot weather	Chemotherapy within 3 months before OI surgery
The problems experienced with current prosthesis are considerable	Immunosuppressive drugs use

OI: Osseointegrated implant.

Surgery and implant details

Patients included for OI surgery were scheduled for standard two stage surgery with an interval of 6-8 weeks in between. In selected cases the surgery was performed as a single stage approach, most often necessary when there was insufficient skin to cover the tip of the intramedullary component of the OI. For patients who opted for an OFI the minimum length of the femoral remnant is 160mm or 40mm below the mid lesser trochanteric line in case of an OFI-C or OFI-Y, respectively (**Fig. 1, 2**). For an OTI the minimum length of the tibial remnant is 60mm below the tibial plateau (**Fig. 3**). There is also a maximum length of the femoral and tibial remnant for prosthetic parts to be able to fit properly to the dual cone adapter (DCA) using an OI connector (**Fig. 4**). Both the OFI-C and OFI-Y

contain a cylindrical distal portion of the intramedullary stem which can adequately seal off the intramedullary canal of the diaphyseal portion of the femur. The OTI differs from the OFI as its distal portion contains a drop-like shape to provide optimal sealing of the tibial intramedullary space (**Fig. 5**). The OI is a modular system comprising of an intramedullary stem, either with or without an additional lag/locking screw; and a DCA with an internal locking screw (**Fig. 6**). The OI is then connected to the prosthetic parts via an osseointegration implant connector (**Fig. 7**). Additional implant details can be found in **Table 2** and additional information regarding the pre-surgical planning, the surgical procedure, the components and the prosthetic alignment can be found in **S2 Appendix**.

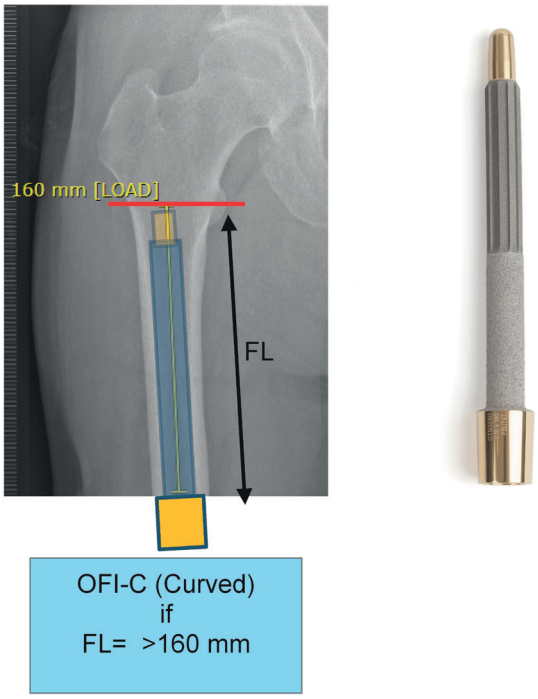

Figure 1. Preoperative planning and measurement of femoral remnant in OFI-C

OFI-C: Osseointegration Femur Implant curved type, FL: Femur length

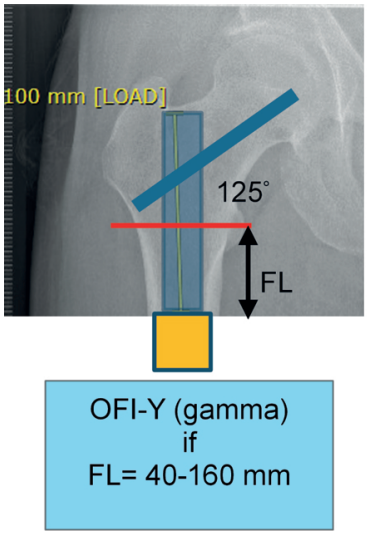

Figure 2. Preoperative planning and measurement of femoral remnant in OFI-Y

OFI-Y Osseointegration Femur Implant Gamma type, FL: Femur length

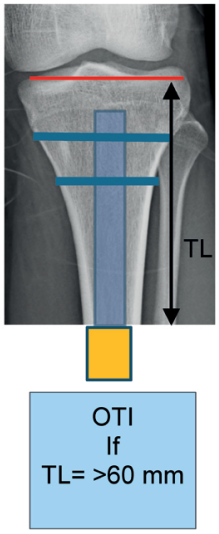

Figure 3. Preoperative planning of tibial remnant in OTI

OTI: Osseointegration Tibia implant, TL: Tibia length

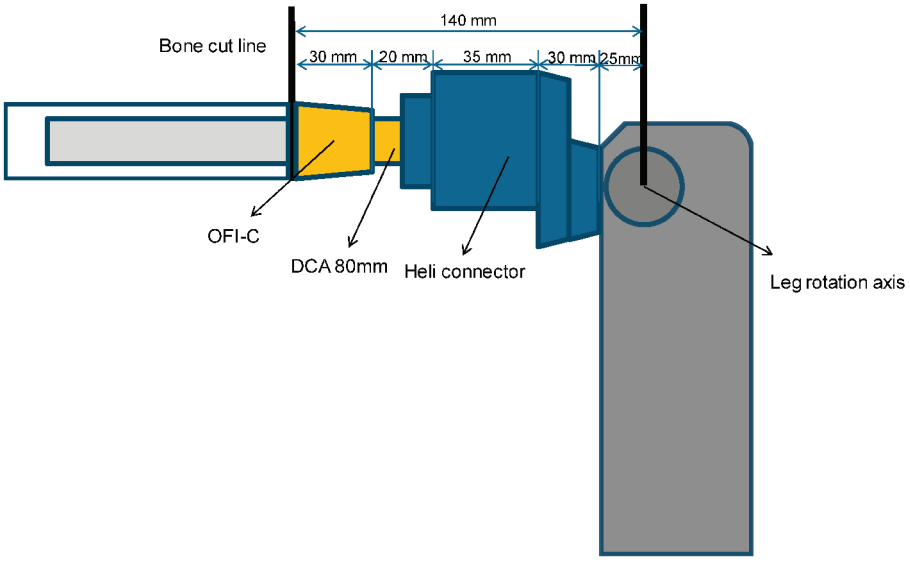

Figure 4. Schematic presentation of presurgical planning OFI-C

OFI-C: Osseointegration Femur Implant Curved type, DCA: Dual cone adapter, Heli connector produced by OTNInnovations

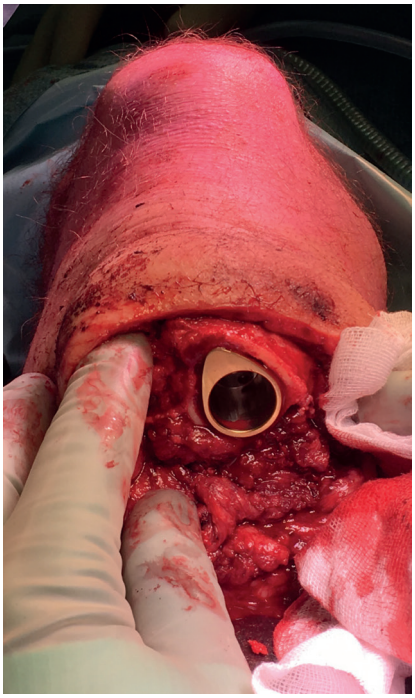

Figure 5. Seal of intramedullary canal by drop-like shaped implant

Figure 6. Dualcone adapter and internal locking screw

Figure 7. Osseointegration implant connector (A: OTN connector, B: OPL/Hermle connector)

Table 2: Implant details

	Length (mm)	Shape	Material	Surface	Rotational stability
OFI-C	140 or 160	Curved (radius 2000mm)	Titanium	Coating plasma sprayed titanium	Proximal longitudinal flutes stem
OFI-Y	80 to 140	Straight with 125° lag screw hole	Titanium	3D lattice structure 1mm	One lag screw hole
OTI	60 to 100	Straight with drop-like distal portion	Titanium	3D lattice structure 1mm	Two locking screw holes

OFI-C: Osseointegration Femur Implant curved type, OFI-Y: Osseointegration Femur Implant Gamma type, OTI: Osseointegration Tibia implant, mm: millimeters, 3D: 3 dimensional.

Rehabilitation and aftercare

Rehabilitation started one week after the second OI surgery, or 3 weeks after single stage OI surgery, with loading the full-length prosthesis based on pain (numeric grading score 0-10: aim score <5) building up to full bodyweight. [5, 22]The rehabilitation was given in group sessions twice per week with sessions of two hours each and a total duration of 4 weeks or 11 weeks for tibial and femoral BAP, respectively. Follow-up visits including radiologic examination and performance tests were scheduled prior to stage 1 surgery and one year after stage 2 surgery.

Adverse events

The adverse events during the first year after OI surgery were retrospectively extracted from the participants' medical files. All adverse events related to OI surgery were reported and were included in the database such as: infection, bone/implant breakage, implant aseptic loosening (radiographic evidence of loosening with the absence of infection), stoma redundant tissue (soft-tissue surplus around the transcutaneous connection), and death as well as the necessary treatment. Infections were graded using the classification described by Al Muderis et al., grade 1 (low-grade soft tissue infection), 2 (high-grade soft tissue infection), 3 (deep bone infection), 4 (septic implant failure); which can also be found in **S3 Appendix**.[9] Adverse events were graded severe (Grade 3 and 4 infection, implant breakage, aseptic loosening, bone fracture, death) or minor (Grade 1 and 2 infection, stoma redundant tissue).[5]

Performance measures

Prior to OI surgery, each participant underwent pre-operative evaluation using their SSP and the evaluation with BAP was performed twelve months after the second surgery. Prosthesis wearing time was scored using the Q-TFA prosthetic use score (range 0-100). Health-related quality of life was measured with the Q-TFA global score (range 0-100).[23] The global score is not applicable for patients who are non-prosthetic users.[16] Therefore the third question of the global score "How would you summarize your overall situation as an amputee?" with five response options (extremely poor, poor, average, good, extremely good) was specifically used, which is also applicable for non-prosthetic users. The Q-TFA questionnaires were sent electronically to the patients using a web-based database (Castor EDC, Amsterdam the Netherlands) prior to their visit and were either in Dutch or English.

Statistical analysis

All safety and performance data were stored and processed using a web-based database (Castor EDC, Amsterdam the Netherlands). Demographics and participant characteristics are presented descriptively. Categorical data was presented as exact numbers. Percentages were calculated for the various levels. For continuous data, means and standard deviations were calculated for normally distributed variables. For data not-normally distributed median, 25th and 75th percentile were used. Q-TFA PUS and GS were presented in means, standard deviations as well as median and 25th and 75th percentile. Changes between pre- and post OI surgery were analyzed using a complete case analysis for both the entire cohort and stratified by OI type (OFI-C, OFI-Y, and OTI). Normally distributed continuous outcomes were statistically analyzed with a paired student-t test (Q-TFA GS). Not-normally distributed continuous were analyzed using the Wilcoxon signed-rank test (Q-TFA PUS). To compare infection rates between the 3 subgroups of different sizes we calculated the infection/implant-year ratio as described by Tillander

et al.[24] A p-value of <0.01 was considered statistically significant. A p-value of <0.01 was used to reduce the risk of type I errors due to multiple testing. All analyses were performed using SPSS v23 (SPSS Inc., Chicago, Illinois, United States).

Results

Between March 2015 and June 2018, 90 consecutive individuals met the in- and exclusion criteria as indicated in **Table 1**. These included 66 transfemoral (3 bilateral), 20 transtibial (1 bilateral), 3 through-knee amputations, and 1 without an amputation but with a non-functional leg which was covered with split-skin grafts due to a trauma and therefore was not eligible for a SSP (94 OI's). One additional patient was implanted with a titanium OI (OTI) within the inclusion period but was excluded from the study because of severe diabetes. The overall and OI-specific patient baseline characteristics and amputation and surgical details are summarized in **Table 3**. The cohort of 90 individuals had an average age of 54 years (range 20-86) and included 26 females. The average age at primary amputation was 40 years and average age at OI implantation was 54 years. The cause of primary amputation was; trauma n=50, dysvascular n=12, infection n=12, tumor n=8, congenital n=3, other n=8. Of the 94 OI's the number of implanted OFI-C, OFI-Y, and OTI was 55, 17, and 22 respectively. The median applied OFI-C diameter was 16mm and all OFI-C had a length of 160mm. The median applied OFI-Y diameter was 21mm with a median length of 140mm and the median OTI diameter was 21.5mm with a median length of 90mm.

Two patients were lost to follow-up (OTI and OFI-C), who did not attend the outpatient clinic at 1 year follow-up due to reasons unrelated to the BAP (**Fig. 8**).

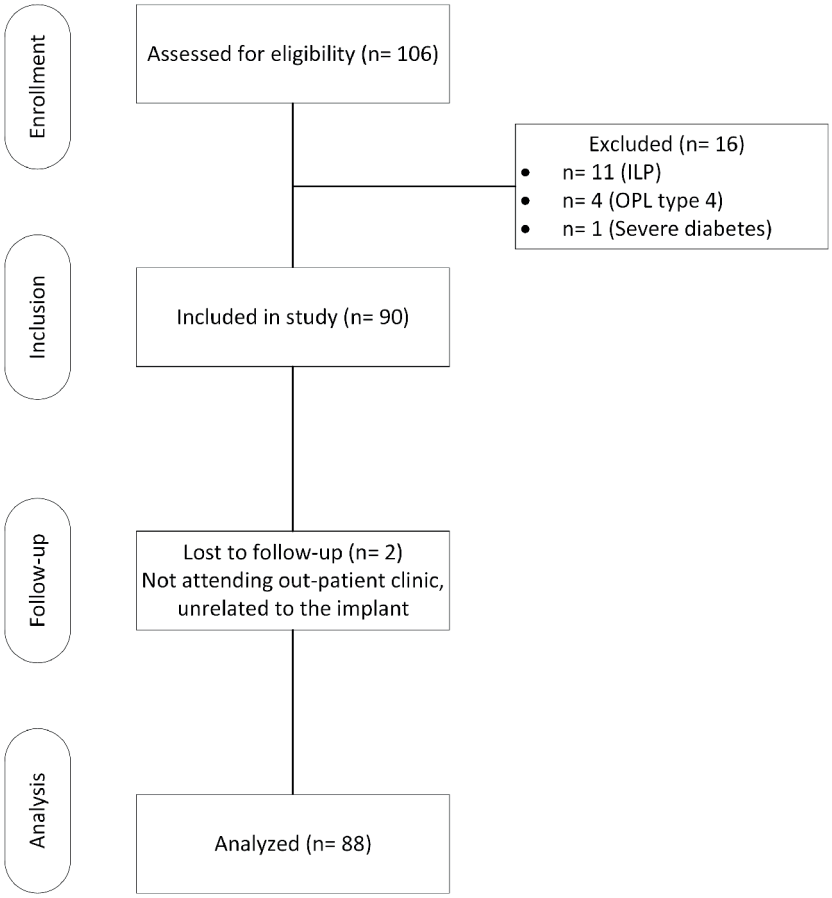

Figure 8. Participant flow diagram

ILP: Integral leg prosthesis, OPL type B: Osseointegration prosthetic limb type B

Table 3: Patient demographics

	Total (N=90)	OFI-C (N=53)	OFI-Y (N=16)	OTI (N=21)
Patient demographics				
Sex*				
Male	64 (71%)	36 (68%)	13 (81%)	15 (71%)
Female	26 (29%)	17 (32%)	3 (19%)	6 (29%)
Age (y)				
At amputation†	40 ± 18	44 ± 19	31 ± 17	37 ± 16
At implantation†	54 ± 14	57 ± 14	50 ± 15	48 ± 13
Interval between amputation and implantation (y)‧	8 [4 to 8]	6 [4 to 17]	17 [8 to 28]	6 [3 to 13]
Country of origin				
Netherlands	82 (91%)	48 (91%)	14 (88%)	20 (95%)
United Kingdom	3 (3%)	2 (4%)	0 (0%)	1 (5%)
United states of America	1 (1%)	0 (0%)	1 (6%)	0 (0%)
Norway	1 (1%)	1 (2%)	0 (0%)	0 (0%)
Italy	1 (1%)	0 (0%)	1 (6%)	0 (0%)
Aruba	1 (1%)	1 (2%)	0 (0%)	0 (0%)
Serbia	1 (1%)	1 (2%)	0 (0%)	0 (0%)
Baseline amputation characteristics				
Level* (per limb: N=93^)				
TFA	69 (74%)	52 (95%)	17 (100%)	NA
TTA	21 (23%)	NA	NA	21 (100%)
TK	3 (3%)	3 (6%)	NA	NA
Side* (N=89^)				
Left	42 (47%)	22 (42%)	7 (44%)	13 (65%)
Right	43 (48%)	29 (55%)	8 (50%)	6 (30%)
Bilateral	4 (4%)	2 (4%)	1 (6%)	1 (5%)
Cause (per limb: N=93^)				
Trauma	50 (54%)	25 (46%)	11 (65%)	14 (67%)
Dysvascular	12 (13%)	9 (16%)	0 (0%)	3 (14%)
Infection	12 (13%)	9 (16%)	1 (6%)	2 (10%)
Tumor	8 (9%)	5 (9%)	3 (18%)	0 (0%)
Congenital	3 (3%)	1 (2%)	2 (12%)	0 (0%)
Other	8 (9%)	6 (11%)	0 (0%)	2 (10%)

Table 3: Patient demographics (continued)

	Total (N=90)	OFI-C (N=53)	OFI-Y (N=16)	OTI (N=21)
Surgical details (per implant: N=94)				
Single stage*	17 (18%)	6 (11%)	4 (24%)	7 (32%)
Two stage*	76 (81%)	49 (89%)	13 (77%)	14 (64%)
Primary amputation + Implantation OI in one stage*	1 (1%)	0 (0%)	0 (0%)	1 (5%)
Implant characteristics (per implant: N=94)				
Width (cm)·	NA	16 [15 to 17]	21 [18 to 23]	21.5 [19 to 23]
Length (cm)·	NA	160 [160]	140 [95 to 163]	90 [79 to 106]

* The values are given as the number of patients/implants with the percentage in parentheses.
† The values are given as the mean and standard deviation.
· The values are given as the median and 25th and 75th percentile.
^One individual/limb less at baseline due to not having underwent amputation yet. Y: years, NA: Not applicable, N: Participants, TFA: Transfemoral amputation, TTA: Transtibial amputation, TK: Through knee amputation, Cm: centimeters. OFI-C: Osseointegration femur implant curved type, OFI-Y: Osseointegration femur implant gamma type, OTI: Osseointegration tibia implant

Severe adverse events

In 88 individuals (92 OI's), one individual with an OTI (1%) developed a grade 4 septic implant loosening resulting in subsequent transfemoral amputation. The primary cause of amputation was chronic arterial occlusive disease and at inclusion patient had palpable femoral pulsations. One month after OI surgery he developed a complete femoral artery occlusion. No grade 3 or aseptic implant loosening occurred during the follow-up time period. No intramedullary stem breakage occurred. Four breakages of the transcutaneous component (DCA) of the BAP occurred; three individuals (two with OFI-Y and one with OTI) had a breakage of the distal taper and one individual with OFI-C had broken weakpoints of the DCA. All broken DCAs were successfully replaced in an outpatient clinic setting. Two individuals experienced bone fractures, one hip neck fracture after a fall (OFI-C) which was treated successfully with dynamic hip screw osteosynthesis and one lumbar vertebra fracture after a fall (OFI-C) which was treated non-operatively with a brace. The adverse events are summarized in **table 4**.

Minor adverse events

Eleven of the 88 individuals (13%) developed a grade 1 soft tissue infection and 10 individuals (11%) developed grade 2 soft tissue infection. All grade 1 and 2 soft tissue infections were pin-track infections and occurred in the first months after OI surgery. All grade 1 infections were successfully treated with oral antibiotics (grade 1A). Grade 2 infections were treated successfully with oral antibiotics in 8 cases (grade 2A), while two individuals required additional soft tissue surgery (grade 2C), due to either recurrent irritation and infection or a peri-stoma abscess (OFI-C n=1, OFI-Y n=1). Antibiotics used were floxacillin, amoxicillin/clavulanic acid or ciprofloxacin. Five individuals

that underwent two stage OI surgery experienced wound infections after stage 1 and therefore, step two of the surgery was performed earlier (OFI-C n=2, OFI-Y n=2, OTI n=1); on average 2.5 weeks after stage 1. In one individual step two was performed earlier due to pain, operative swabs taken did not show any growth of bacteria. The number of individuals with soft tissue infections related to OFI-C, OFI-Y, and OTI were: 8, 5, and 8, respectively. No individuals experienced multiple events of infections of the same grade. Correcting for the differences in numbers per group by using the infection/implant-year ratio this amounts to a ratio of 8/54 (infections per implant with 1 year follow-up: 14.8%), 5/17 (29.4%) and 9/21 (42.9%) for the OFI-C, OFI-Y, and OTI, respectively. One individual, treated with an OFI-Y, required soft tissue surgery due to redundancy of soft tissue. Other reported adverse events included; pulmonary embolism after stage 1 OFI-C implantation successfully treated with anticoagulants (n=1), transient knee pain after OTI (n=1), transient groin pain after OFI-C (n=1), and distal femoral heterotopic bone formation (OFI-C) in one patient that used Aclasta intravenously for the treatment of glucocorticoid-induced osteoporosis. One patient (OFI-C) developed transient nausea, hypertension, and pain at 5 months after OI surgery but these complaints disappeared suddenly and inexplicable with few minor adaptations of the prosthetic alignment.

Table 4: Adverse events

Adverse events	Total cohort (n=88)%	OFI-C (n=52)%	OFI-Y (n=16)%	OTI (n=20)%
Infection				
Grade 1	11 (13%)	4 (8%)	3 (19%)	4 (20%)
Grade 2	10 (11%)	4 (8%)	2 (13%)	4 (20%)
Grade 3	-	-	-	-
Grade 4	1 (1%)	-	-	1 (5%)
Bone breakage	2 (2%)	2 (4%)	-	-
Implant breakage				
Intramedullary stem	-	-	-	-
DCA	4 (5%)	1 (2%)	2 (13%)	1 (5%)
Aseptic loosening	-	-	-	-
Stoma redundant tissue	1 (1%)	-	1 (6%)	-
Death	-	-	-	-

N: participants, OFI-C: Osseointegration femur implant curved type, OFI-Y: Osseointegration femur implant gamma type, OTI: Osseointegration tibia implant, DCA: Dual cone adapter. - = 0 (0%)

Performance

Sixteen of the 90 individuals (18%) were non-prosthetic users at baseline (OFI-C: 8/53 (16%), OFI-Y: 8/16 (50%), OTI: 0/21 (0%)). At follow-up, 87 individuals were ambulators using their BAP; including all individuals that were non-prosthetic users at baseline, while there was missing data for 3 individuals (loss to follow-up n=2 and septic implant loosening n=1).

One individual underwent amputation and implantation in a single setting and thus had missing Q-TFA data at baseline. The performance data for the entire cohort and stratified by implant are summarized in **table 5 and 6**. Both the PUS and the GS increased significantly at follow-up for the entire cohort and when stratifying per OI type. An improvement in the overall situation as an amputee is seen when comparing baseline to one year follow-up since the percentage of participants who scored "good" or "very good" increased over time both for the entire cohort and when stratifying per OI type (**Table 6**).

Table 5: Performance outcomes (Q-TFA Prosthetic use score and Global score)

	Baseline (T0)		1 year FU (T1)		Difference (T1 - T0) Mean ± SD	p-value·
	Mean ± SD	Median (25th to 75th PCTL)	Mean ± SD	Median (25th to 75th PCTL)		
Q-TFA PUS						
Total cohort (n=87)*	52 ± 39	52 [7 to 90]	88 ± 18	90 [90 to 100]	NA	<0.01·
OFI-C (n=52)*	59 ± 37	71 [25 to 90]	86 ± 19	90 [76 to 100]	NA	<0.01·
OFI-Y (n=16)*	31 ± 41	5 [0 to 69]	93 ± 12	100 [90 to 100]	NA	<0.01·
OTI (n=19)*	50 ± 39	52 [10 to 90]	87 ± 21	100 [90 to 100]	NA	<0.01·
Q-TFA GS						
Total cohort (n=70)*	40 ± 19	42 [25 to 50]	71 ± 15	75 [67 to 83]	32 ± 22	<0.01^
OFI-C (n=44)*	42 ± 19	42 [25 to 50]	67 ± 16	75 [58 to 75]	25 ± 19	<0.01^
OFI-Y (n=8)*	31 ± 18	42 [12 to 42]	79 ± 10	75 [75 to 83]	48 ± 17	<0.01^
OTI (n=18)*	38 ± 21	33 [23 to 54]	79 ± 11	79 [75 to 83]	41 ± 24	<0.01^

* Number of individuals included in the analysis,
· Calculated using the Wilcoxon signed-rank test,
^ Calculated using the paired student-t-test, Q-TFA: Questionnaire for persons with a Transfemoral amputation, PUS: prosthetic use score, GS: Global score, OFI-C: Osseointegration femur implant curved type, OFI-Y: Osseointegration femur implant gamma type, OTI: Osseointegration tibia implant, PCTL: percentile, N: Participants, FU: Follow-up, NA: not applicable.

Table 6: Overall situation as an amputee (Q-TFA Global score question 3)

Overall situation (Q-TFA GS Q3)	Total cohort (n=87/90)*		OFI-C (n=52/53)*		OFI-Y (n=16/16)*		OTI (n=19/21)*	
	Baseline	1 year FU	Baseline	1 year FU	Baseline	1 year FU	Baseline	1 year FU
Extremely poor	3 (3%)	1 (1%)	1 (2%)	1 (2%)	1 (6%)	0 (0%)	1 (5%)	0 (0%)
Poor	25 (29%)	0 (0%)	16 (31%)	0 (0%)	2 (13%)	0 (0%)	7 (37%)	0 (0%)
Average	32 (37%)	17 (20%)	18 (35%)	14 (27%)	7 (44%)	1 (6%)	7 (37%)	2 (11%)
Good	20 (23%)	55 (63%)	13 (25%)	29 (56%)	4 (25%)	11 (69%)	3 (16%)	15 (79%)
Extremely good	7 (8%)	14 (16%)	4 (8%)	8 (15%)	2 (13%)	4 (25%)	1 (5%)	2 (11%)

Q-TFA GS Q3: Questionnaire for persons with a Transfemoral amputation global score question 3. N: participants, FU: follow-up, OFI-C: Osseointegration femur implant curved type, OFI-Y: Osseointegration femur implant gamma type, OTI: Osseointegration tibia implant, * Number of individuals included without missing data out of total.

Discussion

Taking the short follow-up into account our results indicate that OI surgery is a safe treatment option for individuals with a lower extremity amputation, regardless the level of amputation, who experience complaints with SSP. The most prevalent adverse events are transient soft tissue adverse events that are fairly easy to handle with either more intensive stoma care and/or antibiotics.

The benefits, with regard to prosthesis wearing time and quality of life, greatly outweigh the drawbacks they encounter. Individuals with an OFI-Y showed the largest improvement in the PUS at follow-up probably because 50% of individuals with OFI-Y were non-prosthetic users at baseline. This result clearly identifies a specific group with high level transfemoral amputation that benefits greatly from BAP.

We assumed that the incidence of aseptic loosening would possibly be higher in individuals treated with an OFI-Y or OTI due to differences in fixation, in which the OFI-Y/OTI fixate in meta- and epiphyseal bone while the OFI-C has a diaphyseal fixation. The OFI-Y and OTI are also much shorter which would result in a smaller surface area for osseointegration. To compensate for the smaller osseointegration area the OFI-Y and OTI were designed with a 3D lattice structure, which creates a 3.7 times larger surface area when compared to an implant without a 3D lattice structure. In this study no aseptic implant loosening occurred which might indicate that OI's with short implant lengths provided with the correct mesh surfaces and additional locking screws may lead to adequate integration in short femoral or tibial remnants. This finding creates favorable perspectives for individuals with short residual limbs as this group often experiences the most problems with socket-suspended prostheses, when looking at our own clinical experience.

Differences in shape and volume of the stump might have influenced soft tissue adverse events in this study. In our experience individuals treated with an OFI-Y most often have excess soft tissue and therefore might need soft tissue refashioning more often. In our experience individuals with a transtibial amputation often have limited excess of and therefore need single stage surgery more often. Single stage surgery was performed for OTI, OFI-Y and OFI-C in 32%, 24%, and 11%, respectively. Individuals with OTI experienced the most infectious soft tissue adverse events, which may be related to less adequate tissue blood perfusion at the relatively distally located stoma areas.

Individuals treated with an OFI-C experienced the least amount of infectious soft tissue adverse events, compared to OFI-Y and OTI, while individuals treated with a tibial OI encounter the most problems as is seen by comparing the infection/implant-year ratio. In our entire cohort we report an incidence of grade 1, 2, 3 and 4 of 13%, 11%, 0% and 1%, respectively. This differs when compared to infection rates in individuals treated with an OPL previously presented by Al Muderis et al. with an incidence of grade 1, 2, 3 and 4 infection being 45%, 9%, 0% and 0%, respectively .[10] This contrast might be explained by differences in in- and exclusion criteria as we report on a case-mix of individuals with a transfemoral and transtibial amputation and also included individuals with a dysvascular cause of amputation. Inter-rater variability with the use of a non-validated grading system might also influence the differences in outcome between studies. To this date, adverse events occurring in individuals treated with an OTI are typically under-reported as was stated in a review by Atallah et al. [15]. Serious adverse events that were reported were aseptic loosening: 29%, grade 4 implant infection: 29% and explantation: 43%.These disappointing results are in strong contrast with the results of tibial OI presented in this study in which one individual with dysvascular amputation developed grade 4 implant infection (5% of OTI). Better patient selection, improved surgical technique, implant design and better understanding of daily loading profile might play a key role in reducing adverse events associated with OTI treatment.[25]

Although the number of infectious soft tissue events in the group treated with a tibial OI was higher compared to the group treated with a femoral OI, this did not affect the quality of life and prosthetic use scores in the tibial OI group. We assume that the temporary and mild aspect of the infectious soft tissue events ultimately have no effect on the quality of life and prosthetic use scores. Although one individual developed septic implant loosening, we suspect that this is related to comorbidity and aetiology of amputation. The fact that no other septic loosening occurred and that other infectious soft tissue events did not lead to implant loosening within the first year after OI surgery is a promising result and long-term follow-up studies are required to evaluate implant survival in the longer term.

There are limitations associated with this study. First, the short follow-up period of one year precludes us from definitive conclusions with regard to implant survival on a long

term. Second, adverse events were collected retrospectively based on patient reports, and no general practitioners were contacted; which may lead to an underestimation of the total number of adverse events. Third, the infectious complications were graded using an earlier developed system by Al Muderis et al. (S3 Appendix), which is not validated and thus may lead to inter-rater variability. Fourth, a subset of individuals was treated with single stage surgery while the rest was treated with two-stage surgery. This may have led to misinterpretation of the results, while there is still a lack of knowledge with regards to the safety of single stage surgery, especially in individuals with a transtibial amputation.[26] Fifth, there is little insight in confounders such as loading during daily living or alignment of components used, possibly associated with certain adverse events; such as the four DCA breakages that occurred.[25] Earlier research in individuals treated with screw-type implants revealed potential limitations of load monitoring, differences in loading compliance, and benefits of using certain instruments to monitor static load bearing.[27-29]

Future research should be performed to gain more insight in the effects of load bearing, during the rehabilitation time and in daily living with regard to adverse events such as component breakages and the effects of modifications of soft tissue surgical technique of the stoma with regard to soft tissue adverse events.

Conclusion

This study shows that press-fit OI's can be safely used in individuals with different levels of amputations, leading to an improvement in performance and acceptable complication rates at 1-year follow-up. These results may contribute to inform individuals with a lower extremity amputation and medical professionals of the risks and benefits of OI treatment so they can make an educated choice. Additional research with longer follow up period is required and currently on-going.

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Supporting information

S1 Appendix: STROBE Checklist

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9

STROBE Statement—checklist of items that should be included in reports of observational studies (continued)

	Item No.	Recommendation	Page No.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	4-20
Study size	10	Explain how the study size was arrived at	4-5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	9-10
		(*c*) Explain how missing data were addressed	9-10
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	9-10
		(*e*) Describe any sensitivity analyses	NA
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10-11
		(b) Give reasons for non-participation at each stage	10-11
		(c) Consider use of a flow diagram	11
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-13
		(b) Indicate number of participants with missing data for each variable of interest	10-13
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	13-17
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	

STROBE Statement—checklist of items that should be included in reports of observational studies (continued)

	Item No.	Recommendation	Page No.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13-17
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13-17
Key results	18	Summarise key results with reference to study objectives	17-19
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19-20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

S2 Appendix: Clinical pathway

Pre-surgical planning

CT scans and antero-posterior (AP) X-rays with calibration ball/ruler were used for pre-surgical planning and to define the right size of the intramedullary component of the osseointegration implant (OI). For an OFI-C the minimum length of the femoral remnant has to be 160mm, for an OFI-Y 40mm, from the mid lesser trochanteric line caudally. (**Fig. 1, 2**). For an OTI the minimal length of the tibial remnant has to be 60mm below the tibial plateau (**Fig. 3**)

For individuals with a longer femoral remnant, a calibrated AP full leg length conventional radiograph was used to calculate the desired femur length and optional shortening to equalize with the contralateral knee axis. For generally available prosthetic knee joints, the distance between the tip of the femur and the contra-lateral knee joint space should be at least 140mm (**Fig. 4).** For individuals with a longer tibial remnant the distance between the tip of the tibia and the tibial plafond should be at least 170mm to fit generally available prosthetic feet. The size of the DCA was estimated based on the thickness of the subcutaneous fat layer with the aim for at least 20mm of titanium niobium nitride (TiNbN) coating of the DCA to penetrate through the skin (**Fig. 4**).

Surgical procedure

OI surgery was performed under general or spinal anaesthesia including prophylactic intravenous antibiotics cephazolin (2g) at induction of anaesthesia. The patient was placed in supine position on a radiolucent operation table. Draping and prepping was performed in a fashion similar to that used for standard total hip or knee replacement. During the first surgery the medullary canal preparation involved reaming in a stepwise fashion with radiographic guidance to obtain cortical press-fit contact with the intramedullary component of the OFI or OTI. For OFI-C, diaphyseal reaming started with flexible reamers and was followed by OFI-C-specific curved reamers with a 2000mm radius with 1mm increments depending on the bone quality. For OFI-Y and OTI the medullary diaphyseal canal preparation was achieved with rigid drills with either 1mm increments or not using power tools. Soft tissue surplus at the level of the distal stump was resected when indicated and the wound subsequently closed. Myodesis was performed only in OFI-C cases with burr holes at the distal end of the femoral remnant. During the second stage surgery a transcutaneous connection to the intramedullary component was created with a coring device ('stoma') and the DCA of the OFI/OTI was mounted to the intramedullary component.

Osseointegration Femur Implant: Curved type (OFI-C)

The OFI-C is a slightly curved (radius 2000mm) intramedullary component used for femoral remnants with a length of at least 160 mm measured starting from the mid-lesser trochanter line (**Fig. 1**). The non-tapered stem of the OFI-C is curved to match the

anatomical antecurvation of the femur diaphysis. The OFI-C is manufactured by CNC milling from titanium (ISO 5832-11 Ti6Al7Nb). The extramedullary distal head is mirror polished and TiNbN coated creating a smooth surface allowing free movement of soft tissue at the stoma. The distal 70mm of the intramedullary stem is coated with plasma sprayed titanium (TPS) which promotes early osseointegration. The proximal part of the OFI-C stem is grit blasted also allowing osseointegration and has a portion with 10 flutes in longitudinal direction providing initial rotational stability which was adopted from the Wagner-shape femoral hip stems.[1] The OFI-C is available in two types depending on the length and diameter: the OFI-C OPL are manufactured by Permedica SPA (Merate, Italy) with a length of 160mm and diameters of 14 to 22mm with 1mm increments while the OFI-C OFP has a length of 140mm and diameter of 15 to 22mm with 1mm increments being manufactured by OTN Implants BV (Arnhem, the Netherlands). The OPL and OFP are identical regarding material, design, coating and surgical technique but the OFP is 20mm shorter than the OPL thus providing a larger application area because of the possible use in individuals with shorter femoral remnants.

Osseointegration Femur Implant: Gamma type (OFI-Y)

The OFI-Y is a straight intramedullary component indicated to be used in individuals with short femoral remnants, being less than 160mm from the mid-minor trochanteric line to the tip of the femur **(Fig. 2)**. The OFI-Y is manufactured by direct metal laser sintering (DMLS) three-dimensional (3D) printing technology from titanium powder (ISO 5832-11 Ti6Al7Nb). The OFI-Y stem has a 1mm thick 3D lattice structure allowing for early bony ingrowth, while the extramedullary distal head is mirror polished and TiNbN coated. The proximal part of the stem has an 125 degrees oblique 10.5mm diameter hole (caput-collum-diaphyseal angle) which can be used to add a 10.45mm titanium cannulated lag screw through the implant into the femoral head. This lag screw fixation can be used as an option to provide maximal primary stability and may prevent stress fractures of the femoral neck in the long term. The length of the OFI-Y stem varies from 80 to 140mm with 10mm increments and the diameter varies from 16 to 23mm with 1mm increments. The OFI-Y used in this study is the OFP manufactured by OTN Implants BV (Arnhem, the Netherlands).

Osseointegration Tibia Implant (OTI)

The OTI is a straight intramedullary component for the tibial remnant (**Fig. 3**). The OTI is manufactured by direct metal laser sintering 3D printing technology from titanium powder (ISO 5832-11 Ti6Al7Nb). The OTI stem has a 1mm thick 3D lattice structure allowing for early osseointegration similar to the OFI-Y. The distal head is mirror polished and TiNbN coated. The proximal part of the stem has two 5.0mm diameter holes which can be used to insert 5.0mm transverse locking screws. The OTI stem fans out in a drop like shape distally to provide an adequate sealing of the intramedullary space of the tibia (**Fig. 5**). The drop-like shape portion of the OTI stem is grit blasted to allow osseointegration. The length of the OTI stem varies from 60 to 100mm with 10mm increments and the

diameter from 17 to 30mm with 1mm increments. The OTI used in this study is the OTP manufactured by OTN Implants BV (Arnhem, the Netherlands).

Dual cone adapter and locking screw (DCA)

The DCA is a cylindrical transcutaneous component that is attached to the 16/18 taper of the intramedullary component of the OI with a M6 locking screw (**Fig. 6**). The DCA has two 16/18mm morse tapers. The proximal taper connection with the intramedullary component is provided with two weakpoints which are indicators for a proper connection. The weakpoints will break when the taper connection unexpectedly becomes loose during daily activities or as a result of high rotational impact forces as part of a safety mechanism protecting the bone and intramedullary implant. The distal taper of the DCA has a M14 thread which can accommodate a M14 abutment screw. The DCA and locking screw are manufactured by CNC milling and are made from titanium (ISO 5832-11 Ti6Al7Nb). The cylindrical part of the DCA is mirror polished and TiNbN coated. The DCA is available in 5 sizes, varying in length from 70 to 110mm with 10mm increments; and with a diameter of 18mm. The DCA and locking screws are manufactured by Permedica (Merate, Italy) and OTN Implants BV (Arnhem, the Netherlands).

Osseointegration implant connector

The osseointegration connector is a quick release-attach system for connecting the prosthetic parts to the DCA. It comprises a male and female part. The male part of the connector is attached to the distal DCA taper with a M14 abutment screw. The female part of the connector contains a clamp mechanism for quick attach and release fixation to the connector male part. The OI connector is provided with different and adjustable off-set sizes. The artificial limb is attached to the OI connector with a universal pyramid adapter. OI connectors used in this study are manufactured by OTN BV (Wychen, the Netherlands) and Hermle GmbH (Gosheim, Germany) (**Fig. 7**).

Prosthetic components and alignment

All individuals started their rehabilitation with the same prosthetic components as prior to the OI surgery, there were no specific component requirements for inclusion. The socket was removed and replaced by an OI connector. Prosthetic components used at baseline and at one-year follow-up can be found in **Table 1**. Based on our clinical experience we optimized the alignment using the LASAR Posture system (Otto BocK GmbH, Germany). The alignment in frontal plane was adjusted to provide a narrow base of support with the aim to decrease the patients' effort to position the center of gravity above the center of pressure during single leg stance without an ipsilateral bending of the trunk. In transfemoral BAP, ideally a valgus angle was applied in the pyramid adapter of the OI connector to position the femoral remnant in adduction so that the abductor muscles are able to work more physiologically. In case of the presence of an abduction contracture we adjusted the alignment step-by step from a varus alignment to a valgus alignment. Depending on the degree of hip flexion contracture, an offset of 0 to 60mm in

the sagittal plane was applied below the OI connector. Depending on the decrease in hip flexion contracture in the first year after OI surgery, the offset was gradually reduced. For transtibial BAP, the foot was positioned more medially or lateral using a sliding adapter based on clinical signs of excessive valgus or varus stress in the knee. In the sagittal plane an off-set of 0-20mm was usually applied in individuals with an OTI to facilitate a yielding in the early stance phase.

Table 1: Prosthetic component data

	Baseline		One-year follow-up	
	Prosthetic knees (MPK vs non-MPK)*	Prosthetic feet (ESAR vs non-ESAR)*	Prosthetic knees (MPK vs non-MPK)*	Prosthetic feet (ESAR vs non-ESAR*
OFI-C (n=53)	28 MPK , 18 non-MPK	40 ESAR, 6 non-ESAR	35 MPK, 18 non-MPK	48 ESAR, 5 non-ESAR
OFI-Y (n=16)	6 MPK, 2 non-MPK	7 ESAR, 1 non-ESAR	9 MPK, 7 non-MPK	15 ESAR, 1 non-ESAR
OTI (n=21)	NA	19 ESAR	NA	17 ESAR, 2 non-ESAR

MPK: Microprocessor knee, ESAR: Energy storing and return, OFI-C: Osseointegration Femur Implant curved type, OFI-Y Osseointegration Femur Implant Gamma type, OTI: Osseointegration Tibia implant. N: total number of individuals in cohort subgroup, * Number of individuals using a prosthesis at certain time point.

References

1. Wagner SL Revision®Hip. http://wwwzimmernl/medical-professionals/products/hip/wagner-sl-revision-hiphtml.

S3 Appendix: Classification of infection

Table 1. Classification of 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 • Parenteral Antibiotics • Surgical Intervention	1 1A 1B 1C
High-grade soft tissue infection	Pus collection, purulent discharge, raised level of C-reactive protein	• Oral Antibiotics • Parenteral Antibiotics • Surgical Intervention	2 2A 2B 2C
Bone infection	Radiographic evidence of osteitis (periosteal bone reaction), radiographic evidence of osteomyelitis (sequestrum and involucrum)	• Oral Antibiotics • Parenteral Antibiotics • Surgical Intervention	3 3A 3B 3C
Implant failure	Radiographic evidence of loosening	• Parenteral antibiotics, explantation	4

Chapter 4

Osseointegrated transtibial implants in patients with peripheral vascular disease: A multicenter case series of five patients with one-year follow-up

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Abstract

Background

Osseointegration is an alternative treatment for amputees who are unable to wear or have difficulty wearing a socket prosthesis. Although the majority of limb amputations are due to vascular disease, such amputations have been perceived as a contraindication to osseointegration surgery. We report the outcomes of osseointegrated reconstruction in a series of 5 patients with limb amputation due to peripheral vascular disease.

Methods

Five patients with transtibial amputation and a history of peripheral vascular disease who received an osseointegration implant from 2014 to 2015 were followed for 12 months. Clinical and functional outcomes were assessed, including pain, the amount of time for which the patient wore the prosthesis, mobility, walking ability, and quality of life. Adverse events, including infection, fracture, implant failure, revision surgery, additional amputation, and death, were monitored and recorded.

Results

Five transtibial amputees (56 to 84 years of age) followed for 1 year after osseointegration surgery were included in this case series. The mobility of all patients was improved at the time of follow-up. Three patients were wheelchair-bound prior to the surgery but all 5 were able to walk and perform daily activities at the time of follow-up. Four of the 5 patients were pain-free at 12 months postoperatively, and all 5 were using the osseointegrated prosthesis. Two patients had a single episode of superficial soft-tissue infection.

Conclusions

An osseointegrated implant may be considered a feasible alternative to the conventional socket prosthesis for patients with peripheral vascular disease.

Level of Evidence

Therapeutic Level IV. See Instructions for Authors for a complete description of levels of evidence.

Introduction

Socket-mounted prostheses have traditionally been used by lower-limb amputees for the last 6 centuries[1]. Nevertheless, many amputees continue to manifest socket-interface problems that substantially reduce their quality of life and ability to walk.[2-4] Up to one-third of patients experience dermatologic problems, including discomfort, sweating, heat, chafing due to friction, and skin ulceration.[5,6] Mechanical problems resulting in poor socket fitting can also lead to decreased proprioception, pain, and pistoning, which make it difficult for patients to walk confidently for any distance on smooth or uneven surfaces.[2,3,7] Over the last 2 decades, osseointegration has emerged as a new technology and has revolutionized the rehabilitation of amputees by completely eliminating socket-interface problems.[8,9]

Osseointegration involves direct insertion of a metal implant into the residual bone and percutaneous attachment of this implant to a prosthetic limb through a small skin opening.[9] This technology has been used successfully in dentistry since 1965, and long-term studies have shown implant survival rates of 90% at 15 years in mandibular bone.[10,11] To date, osseointegration has been used predominantly for the treatment of transfemoral amputees with socket-related problems and is associated with multiple beneficial effects.[12] Demonstrated advantages include improvements in prosthetic use, hip range of motion, mobility level, walking ability, and quality of life as well as reduction of the energetic cost of walking.[4,13-15] At our centers, tibial osseointegrated reconstruction has been attempted in >60 cases. Nevertheless, detailed results have yet to be published on this subject.

Several studies have investigated the safety of transfemoral osseointegrated implants. Recently, a large safety study of 91 cases of transfemoral amputation (86 patients) followed by osseointegration surgery showed a 34% prevalence of soft-tissue infections and no deep infection or implant loosening after a median of 34 months of follow-up.[16] Another study, of 512 cases of transfemoral amputation (48 patients) followed by osseointegration surgery, showed a cumulative implant survival rate of 92% after 2 years of follow-up.[13] A study of 18 transhumeral amputees showed 2 and 5-year implant survival rates of 83% and 80%, respectively.[17] Severe infections leading to implant loosening were rare in these studies, and the most common adverse events were soft-tissue infections and skin irritation at the skin penetration site.[13,16-19]

To date, amputation due to vascular disease has been an exclusion criterion for osseointegration.[4,13,16] Most vascular diseases, such as peripheral vascular disease, are slowly progressive circulation disorders in which the narrowing and blockage of blood vessels lead to severe pain, infected gangrene, and often amputation as the final outcome. Circulatory dysfunction is the leading cause of lower-limb amputation in developed countries.[20-23] Studies investigating the health-related quality of life of patients with

peripheral vascular disease have shown that suicidal ideation and depressive symptoms are frequent and quality of life is primarily determined by mobility impairment.[24,25] The 1-year mortality rate of these patients reaches 48% following amputation and is usually due to stroke or myocardial infarction.[26-28] The restoration of function and improvement of mobility may therefore have a substantial protective role in such patients, and contribute to the reduction of the risk factors associated with vascular disease.[26]

The purpose of this paper is to examine the feasibility of osseointegrated reconstruction in patients with limb amputation due to peripheral vascular disease.

Materials and methods

Study design

This study is a case series with 12-month follow-up from 2 centers. Clinical outcomes, functional outcomes, and adverse events were monitored and evaluated.

Participants

Although peripheral vascular disease has been considered an exclusion criterion for osseointegrated reconstruction, 5 patients with such disease underwent the procedure between September 2014 and August 2015 in Sydney, Australia, and Nijmegen, the Netherlands. Because of a failure to control their underlying conditions, osseointegration surgery was offered to these patients in an attempt to salvage the knee joint and/or to improve their chances of maintaining a high mobility level. Specific inclusion criteria included an age over 18 years, unilateral transtibial amputation, and a history of peripheral vascular disease. Exclusion criteria included smoking, psychological instability, limb exposure to radiation, ongoing chemotherapy, and an inability to comply with the rehabilitation and follow-up program. This study was approved by the human research ethics committee and all participants provided informed consent (Sydney: 014153S, and Nijmegen: 2014/196).

Surgery and rehabilitation

The osseointegration implant was press-fit into the residual bone during single-stage surgery in Sydney and 2-stage surgery in Nijmegen. Prior to surgery, a computed tomography (CT) scan and standard radiographs were used to accurately measure the dimensions of the residual bone. The measurements were used to aid in the design of a customized 3-dimensional-printed titanium implant (AQ Implants). An elliptical horizontal incision was made at the distal end of the stump, after which the soft tissues were reduced to a minimum. All vessels and nerves were ligated, and a flap of skin and subcutaneous tissue was created over the distal end of the stump. An exploration for neuromas was done, and a neurectomy was performed as necessary. The subcutaneous tissue at the tip

of the tibia was removed, and the dermis was sutured circumferentially to the periosteum, after which the wound was closed.

The stoma was created at the level of the tibia using a circular cutting device. The medullary canal was reamed, and the intramedullary component of the osseointegration device was press-fit into the canal under image-intensifier guidance. Multiple locking screws were used to stabilize the proximal part of the implant to the bone (**Fig. 1**). The dual cone component of the osseointegration device was then inserted into the intramedullary component and secured with an internal locking screw. In the Netherlands, the surgery was performed in 2 stages, with the first stage involving the reduction and reconstruction of soft tissues and implantation of the intramedullary component. The second stage was performed 6 to 8 weeks later and involved the creation of the stoma and subsequent insertion of the dual cone component.

The postoperative care and rehabilitation guidelines described in published protocols were followed.[29,30] Postoperative rehabilitation occurred in 3 stages: (1) application of static axial load (20 kg increased by 5 kg per day until either 50 kg or 50% of body weight was achieved); (2) fitting with a light rehabilitation prosthesis, accompanied by mobilizing exercises; and (3) fitting with the definitive prosthesis, typically at 4 to 6 weeks after surgery.

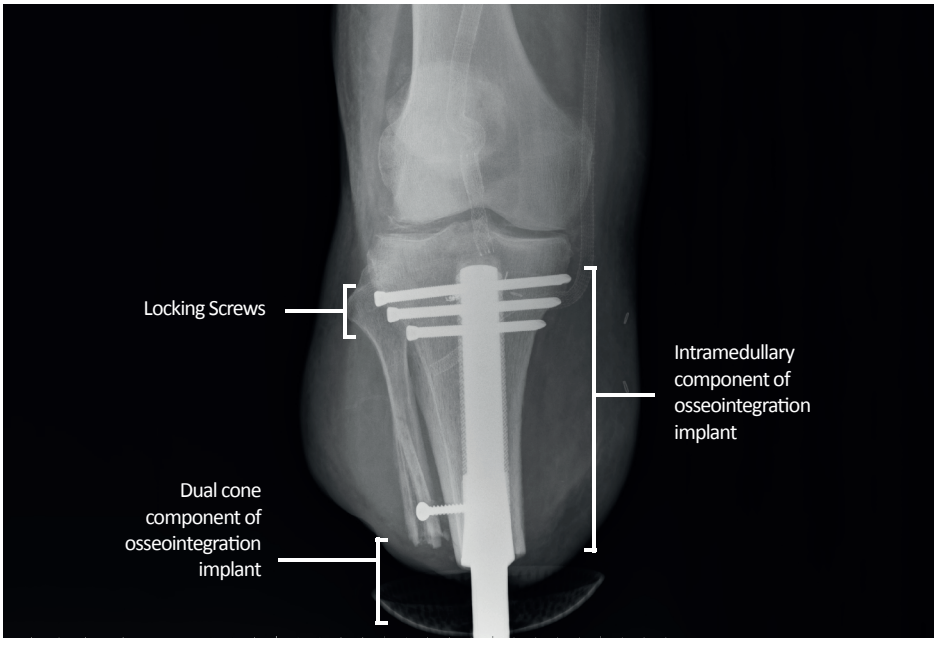

Figure 1. Representative radiograph of the osseointegration implant press-fit into the residual tibia of a patient with transtibial amputation and a history of vascular disease

Study outcomes

• Pain outcomes

Pain levels were assessed individually at baseline and at the 12-month postoperative follow-up visit by a pain specialist using a numerical rating scale.

• Functional outcomes

Functional outcomes were assessed at baseline and at the 12-month postoperative follow-up visit. The amount of time that the patient wore the prosthesis was assessed using the Questionnaire for persons with a Transfemoral Amputation (Q-TFA) and reported as the Prosthetic Use Score (PUS, 0 to 100 points).[31] Mobility was determined by the principal surgeon according to K-levels (K0 through K4, with K0 representing no ability or potential for ambulation and K4 representing the ability or potential for ambulation that exceeds basic ambulation skills).[32] Walking ability was evaluated using the 6-minute walk test (6MWT) and the timed "up and go" (TUG) test. [33, 34] Quality-of-life assessments were conducted using the Short Form-36 Health Survey (SF-36) (0 to 100 points) and the Q-TFA global score (0 to 100 points). The SF-36 assesses physical and mental aspects of quality of life.[35] The Q-TFA was originally developed and validated to study transfemoral amputees using a socket prosthesis and has been used as a standard outcome measure for patients converting from a socket to an osseointegrated prosthesis.[4,14,15] It also assesses aspects relevant to transtibial amputees and allows comparison with the more common transfemoral osseointegration procedure.[31]

• Adverse events

Radiographs were obtained at baseline and at 12 months after surgery. Adverse events related to the osseointegrated implant, including infection, fracture, implant failure, need for revision surgery, additional vascular procedures, additional amputation, and death, were monitored. Cases of infection were graded on the basis of clinical findings as 1 (low-grade soft-tissue infection), 2 (high-grade soft-tissue infection), 3 (deep bone infection), or 4 (septic implant failure).[16]

Data analysis

Differences between baseline and follow-up functional outcome measures were calculated in measurement units. Detailed statistical analysis was not performed because of the small patient cohort and limited collection of preoperative data.

Results

• Patient characteristics

Five patients (2 men and 3 women ranging in age from 56 to 84 years) were included in the study (**Table 1)**. A summary of the medical history and outcomes of each patient

is presented in **Table 2**. All patients had peripheral vascular disease and underwent transtibial amputation.

Table 1. Patient Demographic Information and Reasons for Osseointegration Surgery

Case	Center	Sex	Age (yr)	Time from Amputation to Osseointegration Surgery (yr)	Tibial Length Preop. (cm)	Reason for Osseointegration Surgery
1	Sydney	M	76	0	14.85	Osseointegration performed to salvage knee joint as alternative to above-the-knee amputation. Socket fitting on tibia difficult due to soft-tissue conditions
2	Sydney	F	66	13	14.22	Excessive phantom limb pain and socket-interface problems. Surgical removal of neuroma and bone spur failed to resolve problem
3	Sydney	M	84	0	15.85	Osseointegration performed to salvage knee joint as an alternative to above-the-knee amputation. Socket fitting on tibia difficult due to soft-tissue conditions
4	Sydney	F	56	4	9.47	Excessive phantom limb pain and socket-interface problems. Multiple stump revisions were attempted without positive results
5	Nijmegen	F	57	25	12.10	Patient underwent stump correction and used socket prosthesis for long time. Patient received Botox (botulinum) treatment for neuroma but pain returned, resulting in osseointegration surgery

Two patients (Cases 1 and 3) had had femoral-popliteal bypass surgery that failed, leading to compartment syndrome with necrosis in 1 (Case 1) and thrombosis of the bypass in the other (Case 3). Both patients were elderly (76 and 84 years) and presented with fragile skin conditions and minimal soft tissue, making below-the-knee socket fitting extremely difficult. It was decided to perform a below-the-knee amputation and subsequent osseointegrated reconstruction in an attempt to salvage the knee joint, thereby bypassing the soft-tissue limitations and allowing the patients to maintain high mobility

levels postoperatively. This was considered the best choice for these 2 patients as the alternative would have been an above-the-knee amputation and a socket prosthesis.

The remaining 3 patients (Cases 2, 4, and 5) underwent amputation several years prior to the osseointegration surgery. All had attempted to use a socket prosthesis but were unable to do so because of excessive phantom limb pain and socket-interface problems.

Table 2. Medical History and 12-Month Postoperative Clinical Outcomes for Each Case

Case	Preoperative Medical History	Outcome at 12 Months
1	Popliteal artery thrombosis treated with femoral-popliteal bypass. Bypass failed, leading to compartment syndrome with necrosis. Multiple vascular ops. afterward	Able to walk unaided with osseointegrated prosthesis, no pain, no infection events to date
2	Amputation originally caused by motor-vehicle accident, after which patient used socket. Patient later diagnosed with Wegener vasculitis; controlled with prednisone	Able to walk unaided with osseointegrated prosthesis, no pain, minor infection treated with oral antibiotics
3	Femoral-popliteal bypass that failed due to thrombosis, leading to transtibial amputation	Able to walk unaided with osseointegrated prosthesis, no pain, no infection events to date
4	Femoral-popliteal bypass that failed due to thrombosis, leading to multiple salvage operations and finally transtibial amputation	Able to walk unaided with osseointegrated prosthesis, no pain, minor infection treated with oral antibiotics
5	Peripheral vascular disease resulting in osteomyelitis of tibia with sequential amputation	Able to walk unaided with osseointegrated prosthesis, 1 episode of ischemic pain successfully treated with balloon dilatation with stenting, no infections or complications due to osseointegration surgery

- Clinical outcomes

All patients commenced static weight-bearing on day 3 after the surgery, beginning at 5 kg and increasing 5 kg per day until reaching 50 kg or half their body weight at around day 15. The patients were then fitted with a light prosthesis and continued rehabilitation using parallel bars. All 5 patients began full weight-bearing using the osseointegrated implant fitted with their definitive prosthesis 4 to 6 weeks after surgery and continued to mobilize until and beyond 12 months after the surgery. At the 12-month postoperative follow-up visit, all patients but 1 (Case 5) were pain-free and none reported phantom limb sensations.

Table 3. Outcome Measures for Each Patient*

Case	Prosthetic Use		Walking Ability			Quality of Life		
	Using Prosthesis	Q-TFA PUS	Mobility (K-level)	6MWT (m)	TUG (s)	SF-36 PCS	SF-36 MCS	Q-TFA GS
Baseline								
1	No	WB	0	WB	WB	22.2	32.8	WB
2	Yes	90	1	175	16.47	20.1	60.7	41.7
3	No	WB	0	WB	WB	16.6	68.3	WB
4	No	WB	0	WB	WB	32.6	51.1	WB
5	Yes	100	3	380	7.61	11.6	59.3	25
12-mo postop.								
1	Yes	32	2	300	9.61	40.1	41.2	58.3
2	Yes	90	3	406	8.59	38.9	62.2	58.3
3	Yes	100	2	144	26.08	38.9	70.3	83.3
4	Yes	90	2	275	12.69	44.4	53.3	58.3
5	Yes	100	4	433	6.28	41.9	60.2	58
Difference between baseline and follow-up								
1		—	2	—	—	17.9	8.4	—
2		0	2	231	–7.88	18.8	1.5	16.6
3		—	2	—	—	22.3	2.0	—
4		—	2	—	—	11.8	2.2	—
5		0	1	53	–1.33	30.3	0.9	33

*WB = wheelchair-bound at the time of examination so the test could not be performed; Q-TFA = Questionnaire for persons with a Transfemoral Amputation; PUS = Prosthetic Use Score (defined as the amount of normal prosthetic wear per week, with a score of 100 indicating that the prosthesis was worn every day for >15.5 hours a day); GS = global score (defining the overall amputation situation, including function and problems, with a score of 100 indicating the best possible overall situation); 6MWT = 6-minute walk test (distance in meters that an individual was able to walk in 6 minutes); TUG = timed "up and go" (time in seconds that an individual required to rise from a chair, walk 3 m, return, and sit down); SF-36 = Short Form-36 Health Survey; PCS = physical component summary score; and MCS = mental component summary score.

- Functional outcomes

Three patients were wheelchair-bound at baseline. At the 12-month postoperative follow-up evaluation, all 5 patients were able to walk unaided using the osseointegrated prosthesis. The results of functional outcome measures for each patient are presented in **Table 3**. The mobility level (K-level[32]) of all patients increased by 1 or 2 levels from baseline to the time of follow-up. The 2 patients who were ambulatory at baseline showed improvements in TUG results of 7.88 and 1.33 seconds and in 6MWT results of 231 and 53 m. The 3 previously nonambulatory patients were able to perform walking tests after surgery, achieving TUG results of 9.61 to 26.08 seconds and 6MWT results of 144 to 300 m. The SF-36 physical component summary score improved (by 11.8 to 30.3 points) between

baseline and the time of follow-up for all patients, while the SF-36 mental component summary score remained stable over time. The Q-TFA global score was assessed at baseline for the 2 patients who were ambulatory at that time, and it was increased by 16.6 and 33 points at the time of follow-up.[13] The Q-TFA global score ranged from 58.3 to 83.3 points at the time of follow-up of the 3 patients who had been nonambulatory at baseline.

Adverse events

Radiographs showed stable and well-aligned implants in all patients. Comparison between images obtained immediately postoperatively (**Fig. 2**) and those made at 12 months postoperatively (**Fig. 3**) showed evidence of osseointegration between the bone and implant, as indicated by no signs of bone resorption, osteitis, or loosening. All patients had complete healing of the stoma and minimal discharge at the time of follow-up. None presented with stoma irritation or excessive granulation. Cases 2 and 4 had 1 episode of superficial soft-tissue infection, which was successfully treated with a single course of oral antibiotics. Case 5 developed pain at the stoma site during walking, and removal of the transfixing cerclage wire had no effect. Physicians diagnosed ischemic pain, which was treated with balloon dilatation with stenting in the femoral artery, with good results. There were no reports of deep infection, implant loosening, revision surgery, additional amputation, or death.

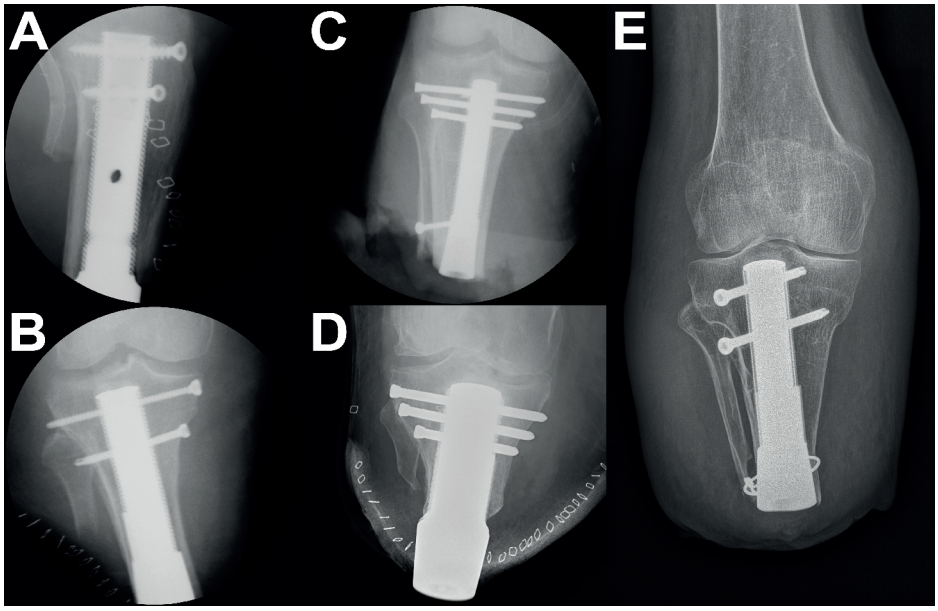

Figure 2. Representative radiographs of the limb containing the osseointegration implant, made immediately postoperatively, in Cases 1 (Fig. 2-A), 2 (Fig. 2-B), 3 (Fig. 2-C), 4 (Fig. 2-D), and 5 (Fig. 2-E).

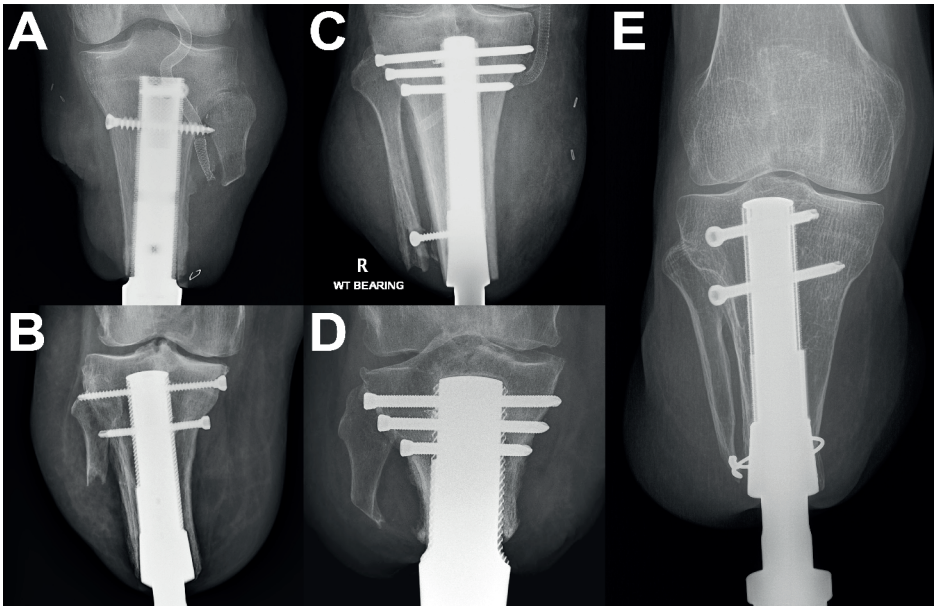

Figure 3. Representative radiographs of the limb containing the osseointegration implant, made at 12 months postoperatively, in Cases 1 (Fig. 3-A), 2 (Fig. 3-B), 3 (Fig. 3-C), 4 (Fig. 3-D), and 5 (Fig. 3-E).

Discussion

We believe that we are reporting the first case series of transtibial amputees with peripheral vascular disease who underwent osseointegration surgery. This special group of patients would not normally be considered candidates for osseointegration surgery, but the treatment resulted in a low prevalence of pain at the time of follow-up and improvements in the time for which the prosthesis was worn, mobility level, walking ability, and quality of life. No abnormalities were found on radiographs at the time of follow-up, and cases of superficial soft-tissue infection were treated successfully with oral antibiotics. Overall, osseointegration resulted in multiple benefits as well as acceptable outcomes in terms of the severity and rate of adverse events in this group of patients. Given the high mortality rates 1 year after amputation in patients with vascular disease, 12-month survival is considered an important outcome in this specific cohort.[26-28]

Patients with vascular disease often experience impaired wound recovery following surgery and are at substantial risk of developing infections. These patients have high mortality rates following major lower-extremity amputation: 14% at 30 days, 48% at 1 year, and 71% at 3 years.[26-28] Since the cause of death is usually myocardial infarction or stroke, increasing mobilization of these patients through osseointegrated reconstruction can play an important protective role.[36-39] Studies have shown that physical activity reduces

vascular risk factors, depending on the metabolic equivalent task (MET).[37] Even moderate physical activity (low MET) such as walking or leisure-time physical efforts are associated with a decreased occurrence of ischemic stroke and coronary events.[36-39] Therefore, the osseointegrated implant may bring benefits beyond the functional and quality-of-life improvements in patients with peripheral vascular disease, although we did not address that issue in this study.

Vascular disease associated with diabetes is the leading cause of lower-extremity amputations in developed countries and accounts for two-thirds of vascular-disease-related amputations in the United States.[23] Considering the positive results in this small cohort study and the reported advantages of osseointegrated reconstruction, we believe that it could be worthwhile to attempt osseointegration in similar but larger patient cohorts.[4,14,15]

In this case series, 2 of the 5 patients underwent osseointegration surgery within a week after transtibial amputation, despite one of the standard indications for osseointegration surgery being the inability to use a socket prosthesis. Below-the-knee amputation with a skin flap was not considered possible for those patients, who were not thought to have adequate soft tissue for wearing socket prostheses. Osseointegration was therefore offered as a solution to conserve the knee joint while enabling quick mobilization and early return to daily activities, which could have had a protective role in terms of patient survival.

Osseointegration surgery has predominantly been performed in transfemoral amputees with a nonvascular cause of amputation, and there have been multiple studies comparing the outcomes of socket and osseointegrated prostheses in such patients.[4,12-15,18] However, there have few been studies of osseointegration surgery in transtibial amputees.[40] All 5 patients in this case series had a transtibial amputation and showed substantial improvements in all outcome measures following osseointegration surgery. Nevertheless, independent studies examining different subgroups of transtibial amputees are necessary to confirm the effectiveness of osseointegration surgery for this indication.

In this case series, the improvements from baseline to 1 year postoperatively in the K-level (average, 2 levels) and the SF-36 physical component score (range, 11.8 to 30.3 points) were comparable with the outcomes in another case series, of 4 patients with transtibial amputation who underwent osseointegration surgery and were followed for 2 years.[18] K-levels are assigned by physicians—i.e., they are not a measured metric—and the physicians in this study were not blinded. Still, although this is a subjective outcome, it showed improvement in the ambulatory ability of these patients. The average improvement in the SF-36 physical component score at 1 year in our study (20.2 points) was also higher than that seen in a case series of 50 patients with transfemoral amputation

who were followed for the same amount of time after osseointegrated reconstruction (10.2 points).[29]

One limitation of this case series is the use of the Q-TFA for assessing health-related quality of life. The Q-TFA has been validated for use for non-elderly transfemoral amputees but not for transtibial amputees.[31] This outcome measure was chosen as it covered most aspects of health-related quality of life that were also relevant for transtibial amputees. Unfortunately, no tools specifically designed for use for transtibial amputees are currently available. To enable accurate assessment of outcomes, alternative validated assessments such as the Patient-Reported Outcomes Measurement Information System (PROMIS), Short Musculoskeletal Function Assessment Questionnaire (SMFA), or Prosthetic Limb Users Survey of Mobility (PLUS-M) should be considered.[41-43]

Other substantial limitations of this study are the short follow-up period and small number of subjects. Although we considered 1 year to be adequate for reviewing the outcomes of patients with peripheral vascular disease because of their high initial mortality rate, it does preclude the examination of long-term outcomes. Nevertheless, 1-year mortality is considered a major outcome measure for vascular surgery, and the first year after surgery is of the greatest relevance for patients with vascular disease as the majority of morbidity and mortality occur within that time.[26-28] No serious adverse events occurred during the 12-month postoperative follow-up period in this study, and superficial infections were successfully treated with oral antibiotics. Larger prospective case-control studies with longer follow-up are necessary to accurately examine the effects of osseointegration surgery in this patient cohort.

In conclusion, this study showed that osseointegrated implants can be an effective treatment for transtibial amputees with peripheral vascular disease and can result in benefits, including improved function, mobility, and SF-36 scores at 1 year. Additional evidence is required to confirm the feasibility of implementing osseointegration surgery as standard care for amputees with peripheral vascular disease.

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Chapter 5

Safety and performance of bone-anchored prostheses in persons with a transfemoral amputation: A 5-year follow-up study

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Abstract

Background

For almost 30 years, bone-anchored prostheses have offered an alternative solution to prosthetic sockets by attaching the artificial limb directly to the femoral residuum by means of an osseointegration implant. Osseointegration implant surgery was introduced in our center in 2009. The aim of the present study is to report on safety, prosthesis-wearing time, and health-related quality-of-life (HRQoL) for patients with femoral bone-anchored prostheses during a 5-year follow-up period.

Methods

All patients who underwent implantation of a press-fit osseointegration implant between May 2009 and November 2013 were eligible for the present study. Implantation was performed in 2 stages. Adverse events included infectious complications (grade 1 to 4), aseptic loosening, breakage, stoma-redundant tissue, and stoma hypergranulation. Prosthesis-wearing time and HRQoL were measured with the Questionnaire for Persons with a Transfemoral Amputation (Q-TFA) prosthetic use score and global score, respectively.

Results

Thirty-nine of 42 eligible patients were included. Thirty patients (77%) presented with some kind of infection (156 events in total), with 148 (95%) events being classified as grade I or II and 8 events (5%) being classified as grade III; the latter 8 events occurred in 4 patients. There were no instances of septic loosening. The intramedullary stem of the osseointegration implant broke in 2 patients. In total, soft-tissue refashioning had to be done 30 times in 14 patients. The Q-TFA median prosthetic use and global scores improved significantly from 71 to 100 and from 33 to 75, respectively ($p < 0.001$).

Conclusions

Despite the adverse events, patient prosthetic use and HRQoL improved significantly. Grade-I and II infections were frequent but could mostly be treated with nonoperative measures. Most infections seemed to occur in the first 2 years and did not lead to deep infections. Two broken intramedullary stems were revised successfully. Current developments focus on reduction of infectious complications and prevention of osseointegration implant breakage.

Level of Evidence

Therapeutic Level IV. See instructions for Authors for a complete description of levels of evidence.

Introduction

Performance of the prosthetic socket is often reported as unsatisfactory in patients with a lower-extremity amputation despite various developments in prosthetic socket technology.[1] Common socket-related problems include pain, blisters, skin infections, eczema, unpleasant smell, instability, back problems, pain in the sacroiliac joint, loss of the prosthesis, and time-consuming donning and doffing of the prosthesis.[2-4]

Since 1990, an alternative solution has been available, offering direct attachment of the prosthetic parts to the femur (bone-anchored prosthesis) and connection to an osseointegration implant.[5] The advantage of an osseointegration implant is that it provides a direct skeletal attachment for the artificial leg.[5] This solution results in more physiological and stable prosthetic control, osseoperception, improved walking and sitting conditions, and elimination of the socket-stump interface with all of its related problems.[6-9] Four CE (Conformitè Europëenne)-certified osseointegration implants are commercially available: the Osseointegrated Prostheses for the Rehabilitation of Amputees (OPRA; Integrum), the Integral Leg Prosthesis (ILP; Orthodynamics), the Osseointegrated Prosthetic Limb (OPL; Permedica), and the Osseointegrated Femur Prosthesis (OFP; OTN Implant BV). All of these osseointegration implants are press-fit implants, except for the OPRA, which is a screw-type implant.

Multiple studies investigating safety and quality of life (QoL) in individuals with transfemoral amputation have indicated a low frequency of osteitis (inflammation of bone) and/or septic loosening.[7-21] Soft-tissue infections have been seen frequently, although with significant increases in QoL and functional outcomes. Those studies presented either a short follow-up period of ≤2 years,[8,9,11] had no fixed follow-up period,[12,13,18,20] and/or involved the use of a screw osseointegration implant.[17,19,21] We believe that we are the first to report on the safety, prosthesis-wearing time, and health-related QoL (HRQoL) of a cohort of patients who were followed for 5 years after implantation of a press-fit osseointegration implant.

Materials and Methods

The STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines for observational cohort studies were used for the present study.

Study Design

The present study was a single-center retrospective cohort study with 5-year follow-up. One-year and minimum 2-year follow-up results for this sub-cohort were published earlier.[9,12]

Participants

All individuals who underwent osseointegration implant surgery at the Radboud University Medical Center between May 2009 and November 2013 were included, and informed consent was obtained. All individuals were registered in a web-based database (Castor EDC). The present study was approved by the institutional Ethics Committee (2017-3769). Patients were eligible for a bone-anchored prosthesis if they were experiencing irreversible socket-related problems and/or had difficulties using their socket-suspended prosthesis according to the patient-reported Questionnaire for Persons with a Transfemoral Amputation (Q-TFA)[22] and as assessed by our multidisciplinary outpatient team consisting of a surgeon, rehabilitation physician, physiotherapist, and prosthetist. The exclusion criteria for the use of a bone-anchored prosthesis were diabetes, peripheral vascular disease, exposure of the amputated limb to radiation, ongoing chemotherapy, an immature skeleton, mental illness, and the inability to comply with the rehabilitation protocol.[12]

Surgical Technique

A press-fit cobalt-chromium-molybdenum osseointegration implant (ILP; Orthodynamics) with an approximately 1.5-mm microporous tripod coating was used, with a 2-stage surgical approach (**Figure 1**). Stage 1 included any shortening of the femoral residuum at the calculated level, if applicable, combined with soft-tissue preparation; identification of the sciatic nerve stump and excision of neuroma, if applicable; release of any tethering tissue; reaming of the medullary canal; press-fit implantation of the intramedullary stem; and mounting of a temporary cannulated endcap with final closure of the stump.

Stage 2 was performed about 6 to 8 weeks later. A guidewire was used to localize the center of the cannulated endcap. A coring device was then passed over the guidewire, perforating the skin and subcutaneous tissue to create the so-called stoma. After removal of the endcap, a dual-cone adaptor of appropriate length was inserted into the intramedullary stem and was secured with an internal locking screw. This dual-cone adapter has a weak point, which acts as a safety system (**Fig. 1**). Specifically, the weak point breaks when high rotational forces are at work so that these forces will not be transmitted into the osseointegration implant.

Figure 1 Illustration of the osseointegration implant, including the intramedullary stem (1), the dual-cone adaptor (3), and the weak point as indicated by the arrow (2).

Rehabilitation Protocol

Rehabilitation started 2 weeks after the stage-2 procedure with loading on a short prosthesis.[23] After 2 weeks, loading was continued with a full-length prosthesis. Weight-bearing was gradually increased, depending on pain. The use of walking aids was phased out on the basis of gait analysis for the evaluation of gait asymmetry. If gait asymmetry permanently increased after the use of walking aids had been phased out, we advised the patients to continue the use of walking aids. Furthermore, walking with different speeds, on uneven surfaces, and on slopes was practiced. Patients attended group rehabilitation sessions twice a week; each session was 2 hours. In total, the duration of the predefined rehabilitation program was 13 weeks.

Study Procedure

All radiographs that were made during follow-up and all clinical data were retrospectively retrieved by 3 researchers (D.R., R.A., J.M.) from the patient records at our center and were registered in a certified cloud-based Electronic Data Capture platform (Castor EDC). In addition, the patients' general practitioners were approached to review the medical records for bone-anchored prosthesis-related problems in order to gain as full insight as possible into all adverse events within the 5-year follow-up. The descriptive notes of the patients' general practitioners were used to rank the adverse events.

Patients filled in the Q-TFA preoperatively and postoperatively. As mailing of postoperative questionnaires was not automated at the beginning of the study period, some postoperative Q-TFA scores were not obtained at exactly 5 years postoperatively. All available preoperative Q-TFAs and all postoperative Q-TFAs completed 4 to 7 years after the procedure were eligible for inclusion.

Study Outcomes

We focused on safety-related outcomes, including infections, aseptic loosening, osseointegration implant breakage, and stoma-redundant tissue (soft-tissue surplus around transcutaneous connection). Additionally, stoma hypergranulation (hypergranulation tissue at the transcutaneous opening) was registered (**Fig. 2**). Infections were classified with use of the system of Al Muderis et al. (**Table 1**) and were graded on the basis of clinical findings, conventional radiographic findings (on radiographs made during follow-up or as indicated), and treatments given as described in the electronic patient

records.[12] If an infectious event was not treated with antibiotics or surgery (e.g., syringing the stoma), it was classified as grade 1 to 3 without subdivision. Every new contact with a new kind of adverse event was counted as a new event. Prosthesis-wearing time was determined with use of the Q-TFA prosthetic use score (0 to 100 points; calculated as the product of hours per day and days worn divided by a given factor) and HRQoL was determined with use of the Q-TFA global score (0 to 100 points; calculated as the sum of scores divided by given factor).[22] Higher Q-TFA prosthetic use and global scores represent a longer prosthesis-wearing time and a higher HRQoL, respectively.

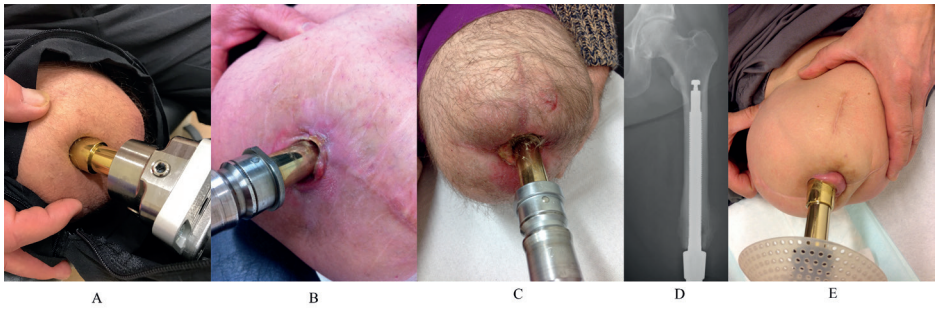

Figure 2. 2-A Normal Stoma. 2-B Grade-1 infection. 2-C Grade-2 infection with some purulent discharge. 2-D Radiograph showing a grade-3 infection, with distal osteitis. 2-E Stoma hypergranulation.

Table 1. Classification of infections*

Level of Severity	Symptoms and Signs, Treatment
Low-grade soft-tissue infection	Cellulitis with signs of inflammation (redness, swelling, warmth, stinging pain, pain that increases on loading, tense)
Grade 1	No antibiotic or surgical treatment
Grade 1A	Oral antibiotics
Grade 1B	Parenteral antibiotics
Grade 1C	Surgical intervention
High-grade soft-tissue infection	Pus collection, purulent discharge, raised level of C-reactive protein
Grade 2	No antibiotic or surgical treatment
Grade 2A	Oral antibiotics
Grade 2B	Parenteral antibiotics
Grade 2C	Surgical intervention
Bone infection	Radiographic evidence of osteitis (periosteal bone reaction), radiographic evidence of osteomyelitis (sequestrum and involucrum)
Grade 3	No antibiotic or surgical treatment

Table 1. Classification of infections* (continued)

Level of Severity	Symptoms and Signs, Treatment
Grade 3A	Oral antibiotics
Grade 3B	Parenteral antibiotics
Grade 3C	Surgical intervention
Implant failure	Radiographic evidence of loosening
Grade 4	Parenteral antibiotics, explantation

*Patients showing signs of grade 1 to 3 infections without antibiotic or surgical treatment (thus, other treatment such as better stoma hygiene) were classified as grade 1 to 3 without subdivision A to C. (Reproduced, with modification, from: Al Muderis M, Khemka A. Lord SJ, Van de Meent H, Frölke JP. Safety of osseointegrated implants for transfemoral amputees: a two-center prospective cohort study. J Bone Joint Surg Am. 2016 Jun 1;98[11]:900-9.)

Data Analysis

Descriptive statistics were used for participant demographic characteristics and safety-related outcomes. Changes over time in terms of prosthesis-wearing time and HRQoL were analyzed in a complete-case analysis with the Wilcoxon signed-rank test. The level of significance was set at $p < 0.05$. Categorical data were presented as exact numbers, and percentages were calculated for the various levels within a categorical variable. For continuous data, normally distributed data were presented as means and standard deviations and non-normally distributed data were presented as medians with 25th and 75th percentiles.

Results

Participant Characteristics

Thirty-nine of 42 eligible patients were included (**Table 2**). Three patients were lost to follow-up; 2 patients did not provide written informed consent, and 1 patient died (**Fig. 3**).

Two of the 39 patients requested removal of the osseointegration implant because of persistent pain. The outer part of the intramedullary stem was removed and the stoma was closed, 24 and 26 months after the initial osseointegration implant surgery, in order to allow for the use of a socket prosthesis again. All safety outcomes for these 2 patients were included in the analysis. During the 5-year follow-up, no infectious events occurred after closure of the stump, despite the fact that the proximal part of the osseointegration implant was still in situ. At the 5-year follow-up, 1 of these patients was wheelchair-bound and the other was mobile with a socket prosthesis again. For both patients, this level of functioning conformed to that prior to the osseointegration implant surgery.

Table 2. Participants characteristics

Participants characteristics	
No. of participants	39
Male sex (no. of patients)	30 (77%)
Age at inclusion* (yr)	48.7 ± 13.9 (22-80)
Age at primary amputation† (yr)	26 (21, 41) (13-69)
Time between primary amputation and inclusion† (yr)	12 (5, 33) (1-52)
Smoking (no. of patients)	
Yes	6 (15%)
No	32 (82%)
Missing	1 (3%)
BMI* (kg/m^2)	26.2 ± 4.0 (19.4-40.2)
Amputation side (no. of patients)	
Unilateral	38 (97%)
Bilateral	1 (3%)
Cause of primary amputation (no of patients)	
Trauma	29 (74%)
Tumor	6 (15%)
Infection	3 (8%)
Other (compartment syndrome)	1 (3%)

*The values are given as the mean and the standard deviation, with the range in parentheses. BMI: body mass index.
†The values are given as the median and the 25th to 75th percentiles, with the range in parentheses.

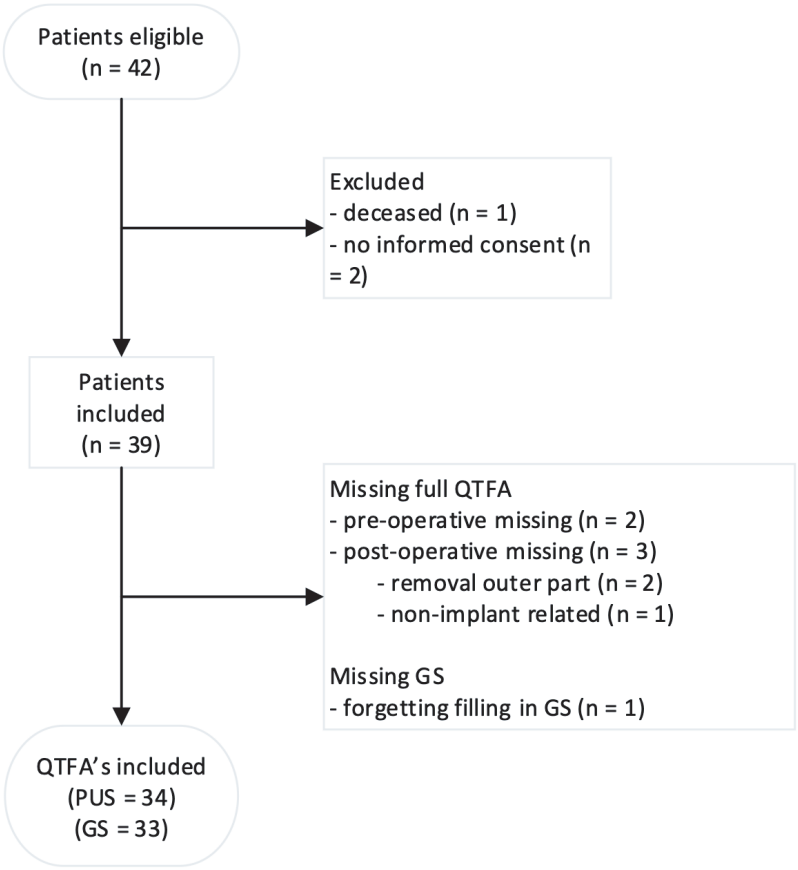

Figure 3. STROBE diagram showing the numbers of patients who were included and the number of Q-TFA scores that were used for the analysis. PUS = prosthetic use score, and GS = global score.

Safety-Related Outcomes

Nine (23%) of the 39 patients had an uneventful follow-up period, resulting in a complication rate of 77%. All safety-related outcomes are summarized in **Table 3**.

- Infection

During the follow-up period, 30 patients (77%) presented with a total of 156 infection-related events. Of these, 148 events (95%) were classified as grade I or II and 8 events (5%) were classified as grade III; the latter 8 events occurred in in 4 patients. No grade-IV infections occurred during the follow-up period. If an infectious complication had to be treated surgically, infected tissue was removed and possible abscesses were drained.

Seventy-nine (53%) of the 148 grade-I and II infections occurred in the first 2 years of follow-up, and 33 (22%) occurred in the first year of follow-up. Six (75%) of the 8 grade-III events occurred in the first 2 years, and 2 (25%) occurred in the first year of follow-up.

Zero to 1 infectious event occurred in 13 individuals, 2 to 3 events occurred in 10 individuals, and >3 events (range, 4 to 20 events) occurred in 16 individuals. Fifty-seven infectious complications occurred in 4 individuals (representing 37% of all infectious events and 10% of all individuals).

Table 3. Complications

Type of complication	No. of Patients (N=39)	No. of Events
Infection*		
Low-grade soft-tissue infection		
Grade 1	9 (23%)	9
Grade 1A	21(54%)	37
Grade 1B	2 (5%)	2
Grade 1C	2 (5%)	2
High-grade soft-tissue infection		
Grade 2	25 (64%)	37
Grade 2A	29 (74%)	48
Grade 2B	4 (10%)	5
Grade 2C	6 (15%)	8
Bone infection		
Grade 3	1 (3%)	1
Grade 3A	4 (10%)	5
Grade 3B	0	0
Grade 3C	2 (5%)	2
Implant failure		
Grade 4	0	0
Aseptic loosening	1	1
Intramedullary stem breakage	2	2
Dual-cone adaptor breakage		
Weak point	8	10
Distal taper	2	2
Stoma-redundant tissue	14	30
Stoma hypergranulation	8	13

*In all, a total of 30 patients had a total of 156 infections.

- Aseptic Loosening

One patient had radiographic evidence of aseptic loosening of the osseointegration implant (i.e., a radiolucent line) at the 1-year follow-up. The patient was asymptomatic and therefore was managed with observation. No signs of septic loosening or progression were seen on later follow-up.

- Osseointegration Implant Breakage

The intramedullary stem broke in 2 patients 57 and 48 months after implantation. In both cases, breakage occurred at the level of the junction between the end of the tripod coating and the head of the stem. Both patients underwent successful implant revision with a larger-diameter titanium implant (OPL; Permedica). Twenty-one dual-cone adaptors broke in 19 patients; 18 breakages occurred at the weak point, and 3 breakages occurred at the distal part of the taper. One dual-cone adaptor with distal taper breakage was replaced during a 1-day admission, and the rest of the dual-cone adaptor revisions were done in an outpatient clinic.

- Stoma-Redundant Tissue

Soft-tissue refashioning had to be done 30 times in 14 patients because of soft-tissue irritation. One patient underwent 9 of the 30 refashioning procedures.

- Stoma Hypergranulation

Eight patients showed hypergranulation tissue at the level of the stoma, with 13 events requiring local excision or treatment with silver nitrate.

Prosthesis-Wearing Time and HRQoL

The prosthesis-wearing time (Q-TFA prosthetic use score) and HRQoL (Q-TFA global score) were analyzed for 34 and 33 patients, respectively. The remaining patients had incomplete data because the patient had forgotten to fill in the preoperative global score (1 patient), the full preoperative Q-TFA score was missing (2 patients), or the full postoperative Q-TFA score was missing (3 patients, including the 2 previously mentioned patients who had had implant removal because of persistent pain) (**Fig. 3**). Follow-up data were derived at a median of 62 months (25th percentile, 58 months; 75th percentile, 64 months) (range, 52 to 77 months) postoperatively.

The median prosthetic use score increased significantly from 71 (25th percentile, 20; 75th percentile, 90) at baseline to 100 (25th percentile, 90; 75th percentile, 100) at the time of follow-up ($p < 0.001$).

The median global score improved significantly from 33 (25th percentile, 21; 75th percentile, 50) to 75 (25th percentile, 58; 75th percentile, 83) ($p < 0.001$). Changes over time are shown in **Fig. 4**.

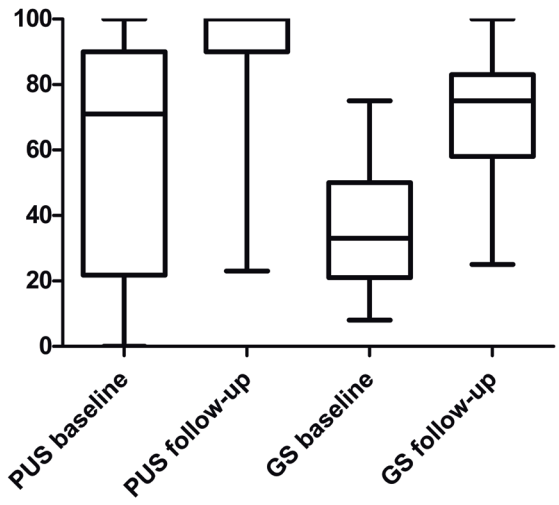

Figure 4. Box plots showing the Q-TFA prosthetic use score (PUS) and global score (GS) at baseline and follow-up. The top and bottom of each box represents the 25th and 75th percentile, and the line within the box represents the median.

Discussion

The present study demonstrated that prosthesis-wearing time and HRQoL improved significantly in association with the use of a bone-anchored prosthesis. Soft-tissue infections were common complications in this cohort of patients. Most infections could be treated with nonoperative measures. Deep infections did not occur during the 5 years of follow-up, although 2 implants were removed because of pain without signs of infection during the follow-up period. Two patients with osseointegration implant breakage were revised successfully.

During the 5-year follow-up, low-grade and high-grade soft-tissue infections were the most common adverse events in individuals with a transfemoral osseointegration implant; this finding is consistent with those in the short-term follow-up studies of this cohort.[9,12] It seems that there was no progression from grade-I/II to grade-III/IV infections, which is promising for the long-term use of bone-anchored prostheses.

Since introduction of osseointegration implant surgery, the technique of creating the so-called stoma (transcutaneous connection) was further developed.[18,24] Initially, the muscular fasciae were closed to cover the osseointegration implant during stage 1 in order to create a barrier between the outer surface and the osseointegration implant. However, this practice led to mechanical friction at the site of the dual-cone adaptor with

subsequent discharge ("wet stoma"), necessitating revision procedures for the treatment of stoma-redundant tissue. Therefore, the surgical technique was adapted, in 2012, by attaching the muscular fasciae to the distal part of the femur, close to the cutting edge, with removal of almost all of the subcutaneous tissue ("dry stoma").[24] In the first 27 patients in the present cohort, the initial technique was used at time of the primary procedure. Future studies, in a larger cohort, are in progress to compare the impact of both surgical techniques.

A learning curve also might have an influence on outcomes (e.g., infections, stoma-redundant tissue), as has been described in other studies on the implementation of new surgical techniques.[25,26]

Brånemark et al., in a recent 5-year follow-up study of 51 patients (55 implants), showed similar results in terms of soft-tissue infections in association with the use of a screw osseointegration implant (OPRA); in that study, 34 patients (67%) had a total of 70 such events.[17] However, they reported a higher percentage of deep infections, with 11 patients (22%) having a total of 14 such events. Matthews et al., in a study of 18 patients who were managed with a custom-made screw osseointegration implant between 1997 and 2008, reported a higher rate of deep infections (5 patients [28%]) but a comparable rate of soft-tissue infections (11 patients [61%]) over a follow-up period up to 19 years (range, 2-19 years).[21] Aschoff and Juhnke, in a study of 86 patients (94 implants) who were managed with a press-fit osseointegration implant (ILP) between 2003 and 2014, explanted 3 intramedullary components (3%) because of deep infection.[27] The limitation of that study was that the duration of follow-up was unclear for the included individuals.

No septic loosening occurred in our cohort within 5 years of follow-up, resulting in a prevalence of 0%; this rate is lower than the widely accepted rates of periprosthetic joint infection following total hip arthroplasty.[28,29]

Similar to the findings in studies with a follow-up period of up to 2 years,[7-9,11,19,20,30] HRQoL and prosthetic use increased significantly. Most studies have represented Q-TFA scores as means.[7,19,20,30] In those studies, the mean prosthetic use score increased significantly by 32 points (baseline scores ranged from 47 to 52 points; follow-up scores ranged from 79 to 84 points)[7,19] and the mean global score increased significantly by 26 to 39 points (baseline scores ranged from 38 to 48 points; follow-up scores ranged from 71 to 84 points).[7,19,20,30] The results for our earlier sub-cohort even showed these significant improvements 1 year after osseointegration implant surgery; the prosthetic use score improved from 56 hours per week at baseline to 101 hours per week at follow-up and the global score improved from 39 points at baseline to 63 points at follow-up.[9] As we used medians, it is difficult to compare our results with those of previous studies in a mathematical manner. On the basis of the results of the previously mentioned studies with follow-up periods of 1 to 2 years, it seems that the improvements in functional outcomes are maintained over 5 years.

The most important limitation of the present study was its retrospective design. The grading system for infections was implemented later in the treatment process. Thus, infections could not be graded in a prospective manner and had to be reproduced on the basis of data in the patient record. However, we believe that this factor might only have led to an overestimation of the frequency of infections. Second, because of the undefined follow-up moments, some of the Q-TFAs were missing and some Q-TFAs were not completed at the exactly 5 years postoperatively. However, we assume that there is no substantial difference between the Q-TFA scores that were collected at exactly 5 years and the Q-TFA scores that were derived after a median of 62 months as these scores were comparable with those in a previous 5-year follow-up study.[17]

The present study also had strengths. First, to our knowledge, ours is the first study of patients managed with a transfemoral bone-anchored prosthesis using a press-fit osseointegration implant with a fixed 5-year follow-up. Second, we included the data of the general practitioners in our analysis to present a complete overview of all adverse events.

For future studies, structural use of the infection classification system and prospective registration are mandatory to avoid misinterpretation.

In conclusion, this 5-year follow-up study on patients who were managed with an osseointegration implant after transfemoral amputation showed that prosthesis-wearing time and HRQoL improved significantly in spite of adverse events. Grade-I and II infections were frequent, without a trend of increasing severity over time. The majority of the adverse events were treated with simple measures.

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Chapter 6

Have surgery and implant modifications been associated with reduction in soft-tissue complications in transfemoral bone-anchored prostheses?

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Abstract

Background

The most frequently occurring adverse events in individuals with a transfemoral amputation treated with a bone-anchored prosthesis are soft tissue infections and stoma-related complications. These soft tissue complications are believed to be influenced by surgical technique and implant design, but little is known about the effect of changes to treatment on these events.

Questions/purposes

(1) What is the result of surgical technique and implant modifications on the incidence of soft tissue infections and stoma-related complications in transfemoral bone-anchored prosthesis users, depending on whether they had a conventional stoma and a cobalt-chrome-molybdenum (CoCrMo) osseointegration implant (treatment period 2009 to 2013), or a shallower stoma and titanium osseointegration implant (2015 to 2018)?

(2) What is the incidence of serious complications, such as bone or implant infection, aseptic loosening, intramedullary stem breakage, and periprosthetic fracture?

Methods

Between 2009 and 2013 we treated 42 individuals who had a lower extremity amputation experiencing socket-related problems resulting in limited prosthesis use with osseointegration implant surgery using a conventional surgical technique and a CoCrMo implant. We considered all individuals treated with two-stage surgery with a standard press-fit transfemoral osseointegration implant as potentially eligible for inclusion. Based on this, 100% (42) were eligible, and 5% (two patients of 42) were excluded because they did not provide informed consent, leaving 95% (40 of 42) for analysis. Between 2015 and 2018, we treated 79 individuals with similar indications with osseointegration implant surgery, now also treating individuals with dysvascular amputations. We used an adapted surgical technique resulting in a shallower stoma, combined with a titanium implant. Using the same eligibility criteria as for the first group, 51% (40 of 79) were eligible; 49% (39 of 79) were excluded because they were treated with transtibial amputation, patient-specific implant, or single-stage surgery; and 1% (one patient of 79) were lost before the 2 year follow-up interval, leaving 49% (39 of 79) for analysis. The period of 2013 to 2015 was a transitional period and was excluded in this study to keep groups reasonably comparable and to compare a historical approach with the present approach. Hence, we presented a comparative study of two study groups (defined by surgical technique and implant design) with standardized 2-year follow-up. The risk factors for adverse events were similar between groups, although individuals treated with the shallow stoma surgical technique and titanium implant potentially possessed an increased risk because of the inclusion of individuals with dysvascular amputation and the discontinuation of prolonged postoperative antibiotic prophylaxis. Outcomes studied were soft tissue

infections and stoma-related complications (hypergranulation or keloid formation, as well as stoma redundant tissue) and bone or implant infection, aseptic loosening, implant stem breakage, periprosthetic fracture, and death.

Results

Patients treated with the shallow stoma surgical technique and titanium implant experienced fewer soft tissue infections (13 versus 76 events, absolute risk 0.17 [95% CI 0.09 to 0.30] versus 0.93 [95% CI 0.60 to 1.45]; $p < 0.01$), which were treated with less invasive measures, and fewer stoma redundant tissue events (0 versus five events, absolute risk 0 versus 0.06 [95% CI 0.03 to 0.14]) than patients treated with the conventional stoma surgical technique and CoCrMo implant. This was contrasted by an increased incidence of surgical site infections occurring between surgical stages 1 and 2, when no stoma is yet created, after implementation of treatment changes (conventional surgery and CoCrMo implant versus shallow stoma surgery and titanium implant: one versus 11 events: absolute risk 0.01 [95% CI 0.00 to 0.08] versus 0.14 [95% CI 0.08 to 0.25]; $p = 0.02$). Patients treated with the shallow stoma surgical technique and titanium implant did not experience serious complications, although bone infections occurred (six events, 8% [three of 40] of patients), in the conventional surgery and CoCrMo implant group, all of which were successfully treated with implant retention.

Conclusion

Adaptations to surgical technique and newer implant designs, as well as learning curve and experience, have resulted in a reduced incidence and severity of soft tissue infections and stoma redundant tissue, contrasted by an increase in surgical site infections before stoma creation. Serious complications such as deep implant infection were infrequent in this 2-year follow-up period. We believe the benefits of these treatment modifications outweigh the disadvantages, and currently advise surgeons to create a shallower stoma with a stable soft tissue envelope, combined with a titanium implant.

Level of Evidence

Level III, therapeutic study.

Introduction

The prevalence of extremity amputation is high. An estimated 1.6 million individuals lived with limb loss in the United States in 2005; this is expected to more than double by 2050.[29] This poses a major social problem because individuals who undergo lower extremity amputation have a lower quality of life than people in the general population and a higher incidence of unemployment.[10, 11, 14, 26] For centuries, socket-suspended prostheses have been used, but despite technologic advances in designs and materials, individuals still experience socket-related problems such as skin irritation, prosthetic fixation issues, and pain.[12, 14, 22] As an alternative, directly fixing the prosthesis to the residual bone via an osseointegration implant results in a modular bone-anchored prosthesis, eliminating the socket-stump interface and its associated problems.[8] Additional suggested treatment advantages are improved function, activity, and quality of life, but serious complications may occur, potentially resulting in pain, loss of mobility, or revision surgery.[3, 4, 7, 17, 20] Prior studies have shown that soft tissue infections and stoma-related complications occur frequently, while serious complications such as deep implant infection are less common.[5, 9, 25] Soft tissue complications may be related to the surgeon's experience, implant design, and surgical technique. [2, 4, 5, 17]

The press-fit implant system for individuals with transfemoral amputation was introduced in 1999 and has evolved substantially since then.[15, 17] Evolutions have included changes to the implant's alloy that seek to reduce stem fractures, different coatings of the extramedullary portion of the implant, and improvement in surgical techniques creating the stoma, aiming to reduce soft tissue irritation and subsequent soft tissue related complications.[1, 16, 17] Juhnke et al. reported on 69 individuals divided into two groups who were treated with the initial three versions of a press-fit osseointegration implant, with variable follow-up times.[17] An absolute risk reduction of infection of 42% to 55% was reported after major device (bracket removal, bridging connector shortening, and coating of the extramedullary part) and surgical adaptations (additional subcutaneous tissue thinning and creation of a stoma with depth < 2 cm). However, determining the influence of treatment changes on complication rates in this study remains difficult because major implant modifications occurred between and within groups, changes to surgical procedures occurred, and the earlier groups had more time to accrue complications. Additionally, the definition or diagnosis of infections was unclear, and it appears only infectious complications resulting in surgical interventions were reported.

The aim of this study was to evaluate the influence of treatment modifications on complication rates, focusing on frequently occurring soft tissue infections and soft tissue complications; we compared groups with identical 2-year follow-up periods. The secondary aim was to report on overall treatment safety by reporting on serious complications.

Specifically, we asked: (1) What is the result of surgical technique and implant modifications on the incidence of soft tissue infections and stoma-related complications in transfemoral bone-anchored prosthesis users, depending on whether they had a conventional stoma and a cobalt-chrome-molybdenum (CoCrMo) osseointegration implant (treatment period 2009 to 2013), or a shallower stoma and titanium osseointegration implant (2015 to 2018)? (2) What is the incidence of serious complications, such as bone or implant infection, aseptic loosening, intramedullary stem breakage, and periprosthetic fracture?

Patients and Methods

Study Design and Setting

This was a single-institution, retrospective, comparative study of two groups (defined by surgical technique and implant design) with standardized 2-year follow-up periods. A fixed 2-year follow-up period was used to allow for comparability between groups, avoiding the bias of allowing an earlier group more time to accrue complications. Safety and functional outcome data of a portion of the groups were published earlier.[6, 19, 25, 27] We followed the STROBE guideline for observational studies.[28]

Participants

Individuals with an extremity amputation experiencing difficulties with their socket prosthesis were referred to our center by either orthopaedic technicians, rehabilitation physician, or their general practitioner.[13] Eligibility for press-fit osseointegration implantation was assessed by a multidisciplinary team including a surgeon, rehabilitation physician, physiotherapist, and orthopaedic technician based on medical history, physical examination, completed questionnaires, and radiographs. Inclusion criteria were adults with an extremity amputation experiencing socket-related problems resulting in limited prosthesis use, while the exclusion criterion was the presence of severe cognitive or psychiatric disorders.[18] Amputation for peripheral vascular disease or diabetes was initially an exclusion criterion in 2009, but after an assessment of the first study confirmed that osteitis or septic implant loosening was uncommon, the indications were broadened in 2014.[13]

Between 2009 and 2013, 42 individuals with a lower extremity amputation were treated with osseointegration implant surgery using a conventional surgical technique and CoCrMo implant. We considered all individuals treated with two-stage surgery with a Conformité Européenne-marked transfemoral osseointegration implant as potentially eligible. Based on this, 100% (42) were eligible; 5% (two of 42) were excluded because they did not provide informed consent, leaving 95% (40 of 42) for analysis. Between 2015 and 2018, 79 individuals with a lower extremity amputation were treated with osseointegration surgery using a modified surgical technique and a titanium implant. Using the same eligibility criteria as for the first group, 51% (40 of 79) were eligible, a

further 49% (39 of 79) were excluded because they were treated for transtibial amputation, with a patient-specific implant, or single-stage surgery; and 1% (one patient of 79) were lost before the 2-year follow-up interval, leaving 49% (39 of 79) for analysis. The period of 2013 to 2015 was a transitional period during which individuals were treated with the modified surgical technique and a CoCrMo implant. Baseline characteristics are presented for this group (Supplemental Table 1), but this group was excluded from further analysis to achieve a truer comparison of a historical approach with the present approach, because only a small number of individuals were treated during this period. A study flow diagram is presented for this study (**Fig. 1**).

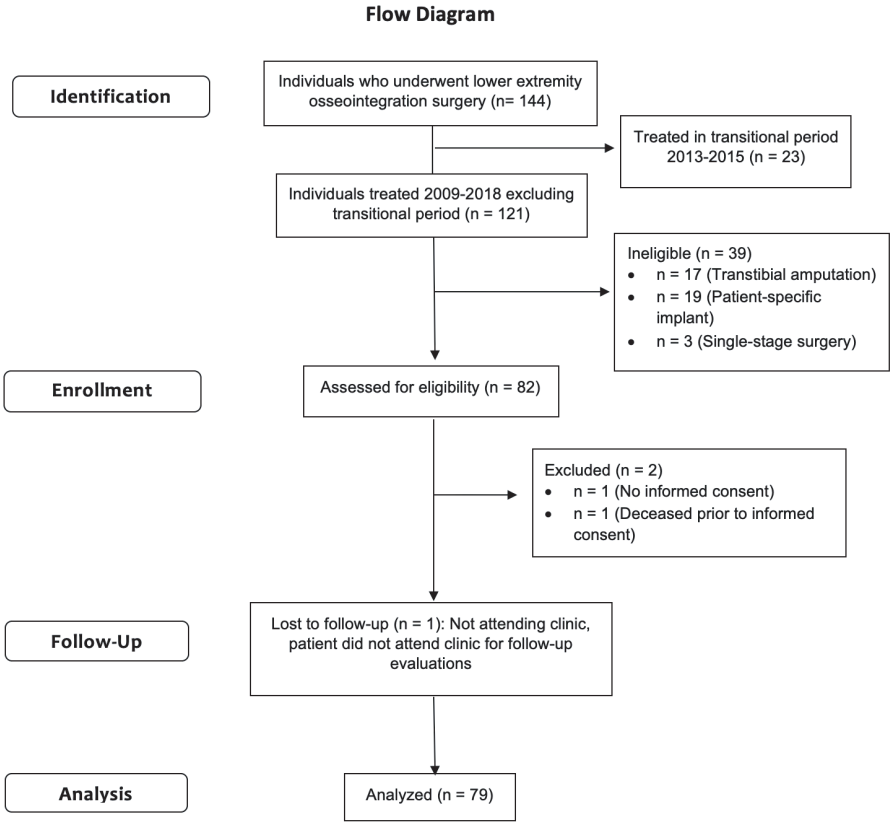

Figure 1. This flow diagram shows the participants who were included in the study.

Descriptive Data

Patient, surgery, and implant data of both groups are presented (**Table 1**). Treatment-related differences between groups were the interval between surgical steps 1 and 2, postoperative antibiotic prophylaxis use, implant length, and dualcone adapter size.

Shortly after the transition of implant used in 2015, prolonged postoperative antibiotic prophylaxis use was discontinued, following the manufacturer's instructions for use. Additionally, differences in implant length and dualcone adapter size were also considered to be treatment related. For the CoCrMo implant, different lengths could be used (160 mm to 180 mm), compared with only one size for titanium implants (160 mm). Differences in dualcone adaptor size are because of the modified surgical technique, because the dualcone size correlates with the depth of the stoma. Patient-related differences between groups were age at amputation and implantation and amputation etiology as treatment indications broadened with time, and older individuals and individuals with dysvascular amputations were deemed eligible for surgery. Group differences in antibiotic prophylaxis use and amputation etiology (such as an increase in dysvascular amputations) theoretically result in an increased risk of soft tissue complications for individuals treated with the adapted surgical technique and titanium implant, and are expected to negatively influence potential benefits encountered after treatment adaptations.

Table 1. Patient demographics, baseline amputation characteristics, surgical details, and implant characteristics

Parameter	Conventional surgery and Co-Cr-Mo implant (n = 40)	Modified surgery and titanium implant (n = 39)	p value
Women, % (n) (n)	25 (10)	36 (14)	0.29[a]
Age in years, median (IQR)			
Age at amputation	26 (21)	50 (38)	<0.01[c]
Age at implantation	48 (19)	60 (17)	<0.01[c]
Interval between amputation and implantation in years, median (IQR)	12 (26)	8 (11)	0.14[c]
Nonsmokers, % (n)	85 (34)	97 (38)	0.11[b]
Diabetes mellitus, % (n)			0.09[b]
No	98 (39)	85 (33)	
Noninsulin-dependent	3 (1)	10 (4)	
Insulin-dependent	0 (0)	5 (2)	
BMI in kg/m2, mean ± SD	26 ± 4	26 ± 5	0.96[d]
Baseline amputation characteristics			
Level (per limb: n = 80), % (n)	N= 41	N= 39	0.71[b]
TF	88 (36)	92 (36)	
TK	12 (5)	8 (3)	
Side (n=80) % (n)			0.04[b]
Left	63 (25)	41 (16)	
Right	35 (14)	59 (23)	
Bilateral	3 (1)	0 (0)	

Table 1. Patient demographics, baseline amputation characteristics, surgical details, and implant characteristics (continued)

Parameter	Conventional surgery and Co-Cr-Mo implant (n = 40)	Modified surgery and titanium implant (n = 39)	p value
Cause (per limb: n = 80), % (n)			
Trauma	76 (31)	41 (16)	
Dysvascular	0 (0)	21 (8)	
Infection	7 (3)	15 (6)	
Tumor	15 (6)	15 (6)	
Congenital	0 (0)	3 (1)	
Other	2 (1)	5 (2)	
Surgical details (per implant: n= 80)			
Interval in days between surgical step 1 and 2, median (IQR)	49 (14)	56 (18)	0.02[c]
Postoperative antibiotic prophylaxis % (n)	100 (41)	8 (3)	<0.01[a]
Implant characteristics (n = 80)			
Diameter in mm, median (IQR)	16 (3)	16 (2)	0.33[c]
Length in mm, median (IQR)	180 (20)	160 (0)	< 0.01[c]
Dual cone size, median (IQR)	5 (2)	3 (2)	< 0.01[c]

[a]p value was calculated using a chi-squared test. [b]p value was calculated using Fisher's exact test. [c]p value was calculated using the Mann-Whitney test. [d]p value was calculated using the independent samples t-test. N= number of participants, IQR = Interquartile range, TF = transfemoral; TK = through-knee amputation.

Surgical Technique

Standard two-stage osseointegration implant surgery was performed with a 6-week to 8-week interval between procedures for both groups, and cephazolin was administered intravenously at induction. Two surgical techniques were used, here termed "conventional" and "modified."

In the conventional surgical technique, used up to September 2013, the first stage of the procedure consisted of shortening the femur to an adequate length, removing neuromas and bone spurs, stepwise retrograde intramedullary reaming under radiographic guidance, and press-fit implantation of the intramedullary component. The muscle's orientation was corrected, followed by a myoplasty, including suturing of the ventral and dorsal muscle fascia over the implant and skin closure (**Fig. 2 A and B**).[3] In the second stage of the procedure, the surgeon created a stoma by using a coring device to create a circular skin defect at the level of the distal osseointegration implant, and then a dualcone adapter was mounted onto the osseointegration implant.

After September 2013, a modified surgical technique was used, with the following alterations to the first stage: further reduction of soft tissue surplus, removal of redundant

subcutaneous fat, and formation of a myodesis by drilling burr holes in the distal femoral end, through which sutures were passed and attached to the muscle fasciae. The aim was to create a shallow stoma canal less than 2 cm thick from the tip of the bone to the skin (**Fig. 2 C and D**).[13]

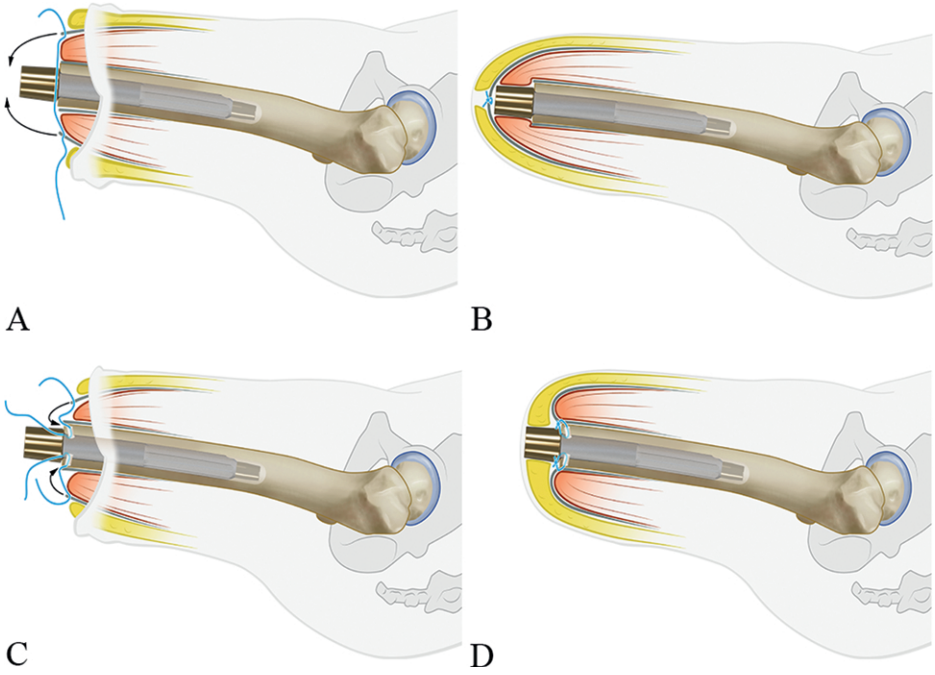

Figure 2. Schematic representation of surgical techniques.

A The conventional surgical technique: Formation of a myoplasty, by suturing the fascia over the implant.
B The conventional surgical technique: fascia sutured over the implant.
C The adapted surgical technique: Removal of soft tissue surplus and formation of a myodesis, fascia sutures passing through distal femur.
D The adapted surgical technique: fascia sutured onto the distal femur.

Implant Design

The implant used up to 2015 was made of a cast CoCrMo alloy (Endo-exo/Integral Leg Prosthesis, Orthodynamics) covered with a 1.5-mm-thick layer of trabecular metal to accommodate osseointegration. The distal extramedullary part was partially coated with smooth titanium niobium oxynitride (TiNbN) (**Fig. 3A**). According to the manufacturer's instructions, the implant was placed without tension on the overlying skin, with a 5-cm minimum distance between the distal osseointegration implant and the skin; this was considered the conventional surgical technique.

Because multiple breakages of the CoCrMo implant stem occurred by 3 years of follow-up, a new CE-marked implant was used from 2015 onwards.[23, 25] This implant was forged

from a titanium alloy (Ti6AL7Nb) in which the proximal half was grit-blasted. It contained longitudinal flutes providing rotational stability (Osseointegration Prosthetic Limb, Permedica SPA). The distal half was coated with plasma-sprayed titanium to enhance bone-to-implant contact, and the extramedullary part was fully coated with TiNbN (**Fig. 3B**).

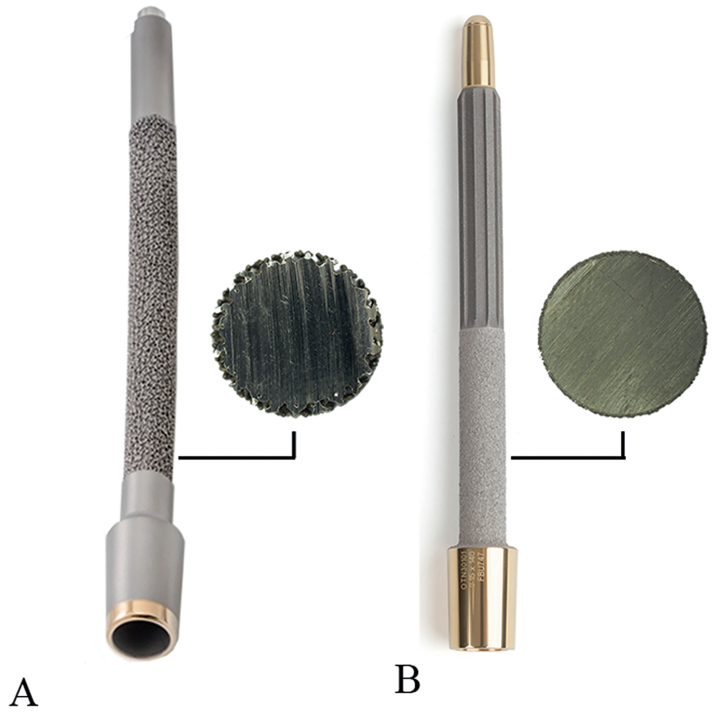

Figure 3. Implants

A Anterior and transverse view of the cobalt-chrome-molybdenum implant.
B Anterior and transverse view of the titanium alloy implant.

Aftercare, Rehabilitation, and Follow-up

Initially, patients received intravenous cephazolin for 5 days after the first procedure, based on the manufacturer's instructions for use. From July 2015 onwards, a change in practice occurred, and only single-dose preoperative antibiotics were administered, as suggested by the manufacturer of the newly used titanium implant. These instruction were followed because early serious infection rates remained low. Rehabilitation started 1 week after Stage 2, and a predefined rehabilitation program consisted of 11 weeks of outpatient physical therapy sessions, twice per week, that aimed to improve ambulation.[19] During rehabilitation, the prosthesis was gradually loaded to full bodyweight and the

use of walking aids was reduced based on the patient's pain level.[21] Follow-up visits were scheduled at 6 months, 12 months, and 24 months postoperatively and included a radiologic examination, performance tests such as the timed-up-and-go test, and an assessment of complications.

Primary and Secondary Outcomes

Baseline amputation characteristics, surgical details, implant characteristics, and complications were retrospectively extracted from our institutional registry and from medical records. Because general practitioners have a prominent role and are the gatekeepers in the Dutch healthcare system, they were also contacted by telephone to ascertain whether any complications occurred that had been treated outside the hospital. Because no classification system encompasses all treatment-related complications, we classified complications based on an adaptation of the classification system by Al Muderis et al.[3] (**Supplemental Table** 2) Complications were subdivided into serious or minor complications (**Table 2**). Complications were soft tissue infections, stoma-related complications (hypergranulation or keloid formation, as well as stoma redundant tissue), bone or implant infection, aseptic loosening, implant stem breakage, periprosthetic fracture, and death. Mechanical complications of the extramedullary components of the bone-anchored prosthesis (such as dualcone adapter body or weakpoint breakage) were outside the scope of this study because dualcone breakage was not believed to influence or be influenced by soft tissue infections or complications or the treatment changes implemented in this study, and because such breakage was not considered a serious complication, because these parts can usually be replaced in an outpatient setting.

Our primary study goal was to assess the influence of surgery and implant modifications on the incidence of soft tissue infections and stoma-related complications. To achieve this, we compared incidences of soft tissue infections and stoma-related complications in individuals treated with either a conventional surgical technique and a CoCrMo implant or a modified surgical technique and titanium implant. Complications occurring between surgical stages, when the stoma is not yet formed, were evaluated separately.

Our secondary goal was to report on the incidence of serious complications such as bone or implant infection, aseptic loosening, intramedullary stem breakage, and periprosthetic fracture.

Table 2. Simplified version of classification of soft tissue complications

Type of adverse event	Subtype	Symptoms and signs	Treatment	Grade	Severity
Infection[a]	1. Low-grade soft-tissue infection	Cellulitis with signs of inflammation (redness, swelling, warmth, pain)	Local measures	1A	Minor
			Oral antibiotics	1B	Minor
			Parenteral antibiotics	1C	Minor
			Soft tissue surgery	1D	Moderate
	2. High-grade soft-tissue infection	Abscess formation, purulent discharge, and/or raised level of C-reactive protein	Local measures	2A	Minor
			Oral antibiotics	2B	Minor
			Parenteral antibiotics	2C	Minor
			Soft tissue surgery	2D	Moderate
Stoma problems	Hypegranulation or keloid formation	Overgrowth of connective tissue at the stoma with absence of infection	Local measures[a]	A	Minor
			Sleeve[b]	B	Moderate
			Soft tissue surgery[c]	C	Moderate
	Redundant tissue	Presence of symptomatic redundant soft tissue with absence of infection	Local measures[d]	A	Minor
			Sleeve[b]	B	Moderate
			Soft tissue surgery[e]	C	Moderate
			Removal of extramedullary part of osseointegration implant	D	Moderate

[a]Use of instillagel, terracotrill ointment, and/or AgNO3. [b]Placement of a (protective) sleeve. [c]Scar tissue removal by conical excision. [d]Use of a stump dressing or shrinker. [e]Stump refashioning

Ethical Approval

Regional ethical review board approval was obtained for this study (number 2017-3767).

Statistical Analysis

Outcomes for both groups are presented using descriptive statistics, exact numbers with percentages, means with standard deviations, and median with interquartile range, according to data type and distribution. Differences in patient, surgery, and implant data in each group were statistically analyzed using a chi-squared or Fisher exact test for categorical data. For normally and non-normally distributed continuous data, an unpaired t-test or Mann-Whitney U test was used, respectively. Complications were evaluated at the patient and event level. Group comparisons were made regarding the number of soft tissue complications (such as soft tissue infections, hypergranulation or keloid formation, soft tissue redundant tissue, and surgical site infections between surgical stages 1 and 2) per implant, leaving grading and treatment out of the equation, and were analyzed with generalized estimating equations using a negative binomial model.

Absolute risks (AR) and risk ratios (RR) are presented. Based on clinical knowledge and considering variables with patient-related differences in distribution between treatment groups (**Table 1**), the following covariates were evaluated for model inclusion to adjust analyses: age at amputation, age at implantation, smoking status, sex, and presence of diabetes. However, all had p values > 0.2, and a model without covariates was fitted. The model was adjusted for the follow-up period of 2 years and for participants who underwent bilateral procedures. A two-sided p value of < 0.05 was considered statistically significant. Analyses were performed using SPSS version 23 (IBM Corp).

Results

Soft Tissue Infections and Stoma-related Complications

Soft tissue infections occurred less frequently and could be managed with less invasive measures in the group treated with the modified surgery and titanium implant than in the group treated with the conventional surgery and CoCrMo implant (13 events; AR 0.17 [95% CI 0.09 to 0.30] versus 76 events, AR 0.93 [95% CI 0.60-1.45]) (Table 3, full overview Supplemental Table 3). This resulted in a risk ratio for soft tissue infections of 5.61 (95% CI 2.71 to 11.57; p < 0.01) for the conventional surgery and CoCrMo implant group compared with the other group (Table 4).

There were no differences in the occurrence of hypergranulation or keloid formation between the conventional surgery with CoCrMo implant and the modified surgery with titanium implant groups (four events; AR 0.05 [95% CI 0.02-0.12] versus six events; AR 0.08 [95% CI 0.03 to 0.21]; p = 0.51). Soft tissue surgery was necessary in two individuals in the group treated with the conventional surgery and CoCrMo implant, and all events in the other group could be treated nonsurgically.

Stoma redundant tissue occurred less frequently in the group treated with the adapted surgery and titanium implant than in the group treated with the conventional surgery and CoCrMo implant (0 events; AR 0, versus five events; AR 0.06 [95% CI 0.03 to 0.14]). Soft tissue surgery and temporary removal of the extramedullary component of the implant was necessary two and three times, respectively.

All complications occurring between surgical stages, when no stoma had been created, were surgical site infections (**Table 3**). Surgical site infections occurred more often in the group treated with the modified surgical technique and titanium implant than in the group treated with the conventional surgical technique and CoCrMo implant (11 events; AR 0.14 [95% CI 0.08 to 0.25] versus one event; AR 0.01 [95% CI 0.00 to 0.08]). This resulted in a risk ratio for surgical site infections of 11.55 (95% CI 1.54 to 86.75; p = 0.02) for the modified surgical technique and titanium implant group compared with the other group. Surgical site infections required us to move the date of Stage 2 forward three times (three

of 11 events), allowing for debridement and abscess drainage, all in the adapted surgery and titanium implant group.

Telephone consultations with general practitioners revealed that 2% (two of 89 events) and 20% (two of 10 events) of soft tissue infections and hypergranulation or keloid formation were treated outside the hospital, respectively. No other complications were treated outside the hospital.

Table 3. Outcomes of soft tissue complications, and complications between surgical stages; as well as treatment (simplified).

Type of adverse event	Treatment	Grade	Conventional surgery & CoCrMo implant (n = 40)		Adapted surgery & Titanium implant (n = 39)	
			Patients % (n)	Events	Patients % (n)	Events
Soft tissue complications						
Low-grade soft tissue infection	Total		38 (15)	27	21 (8)	9
	Local measures	1A	15 (6)	6	5 (2)	2
	Oral antibiotics	1B	33 (13)	19	15 (6)	7
	Parenteral antibiotics	1C	3 (1)	1	-	-
	Surgical treatment	1D	3 (1)	1	-	-
High-grade soft tissue infection	Total		50 (20)	49	10 (4)	4
	Local measures	2A	35 (14)	19	-	-
	Oral antibiotics	2B	30 (12)	23	10 (4)	4
	Parenteral antibiotics	2C	5 (2)	2	-	-
	Surgical treatment	2D	10 (4)	5	-	-
Hypergranulation or keloid	Total		10 (4)	4	10 (4)	6
	Local measures	A	5 (2)	2	10 (4)	6
	Sleeve placement	B	-	-	-	-
	Soft tissue surgery	C	5 (2)	2	-	-
Stoma redundant tissue	Total		13 (5)	5	-	-
	Local measures	A	-	-	-	-
	Sleeve	B	-	-	-	-
	Soft tissue surgery	C	5 (2)	2	-	-
	Extramedullary implant removal	D	8 (3)	3	-	-
Complications between surgical stages (no stoma)						
Surgical site infection	Total		3 (1)	1	26 (10)	11
	Local measures		-	-	-	-
	Antibiotics		-	-	15 (6)	7
	Surgical treatment		3 (1)	1	10 (4)	4

CoCrMo: Cobalt-Chrome-Molybdenum. N: Participants.

Table 4. Total complications compared between groups at 2-year follow-up

Complication	Conventional surgery & CoCrMo implant (n=40; 41 implants)	Adapted surgery & Titanium implant (n=39; 39 implants)	p value
1. Total soft tissue infections	76	13	
Absolute risk (95% CI)	0.93 (0.60-1.45)	0.17 (0.09-0.30)	<0.01
Risk ratio group 1 vs 2 | group 2 vs 1 (95% CI)	5.61 (2.71-11.57)	0.18 (0.09-0.37)	
2. Total hypergranulation/ keloid formation events	4	6	
Absolute risk (95% CI)	0.05 (0.02-0.12)	0.08 (0.03-0.21)	0.51
Risk ratio group 1 vs 2 | group 2 vs 1 (95% CI)	0.64 (0.16-2.47)	1.57 (0.41-6.10)	
3. Total stoma redundant tissue events	5	0	
Absolute risk (95% CI)	0.06 (0.03-0.14)	0	-
Risk ratio group 1 vs 2 | group 2 vs 1 (95% CI)	-	-	
4. Total complications between surgical stages	1	11	
Absolute risk (95% CI)	0.01 (0.00-0.08)	0.14 (0.08-0.25)	0.02
Risk ratio group 1 vs 2 | group 2 vs 1 (95% CI)	0.09 (0.01-0.65)	11.55 (1.54-86.75)	

CoCrMo: Cobalt-Chrome-Molybdenum. N: Participants. CI: Confidence interval.

Serious Complications

Bone infection occurred in six events in 8% (three of 40) of patients of the conventional surgery and CoCrMo implant group, and was treated surgically with retention of the implant in one event. No bone infection occurred in the modified surgery and titanium implant group. No septic implant loosening, aseptic loosening with an unstable implant, intramedullary stem breakage, or periprosthetic fracture occurred in either group during the follow-up period of 2 years.

Discussion

Although studies reporting on complications in transfemoral bone-anchored prosthesis users have stated that soft tissue infections and stoma-related complications are the most frequently occurring,[5, 9, 25] no prior study reported on these soft tissue complications in a detailed manner. We presented the data of transfemoral bone-anchored prosthesis users, reflecting on 10 years of clinical experience in which major changes to the implant and surgical technique were applied. We aimed to evaluate the impact of alterations in treatment, focusing on frequently occurring soft tissue complications, and to describe osseointegration implant treatment in our clinical practice. Our findings suggest that modification of the surgical technique and implant design result in decreased soft tissue infections and stoma redundant tissue, confirming the direction many osseointegration surgeons are going with relation to more stable soft tissue envelopes.

Limitations

The retrospective study design with regard to the collection of data on complications may have led to an underestimation of the number of events. However, this might have been partially addressed by contacting general practitioners, because they play a prominent role in the Dutch healthcare system and are the first point of contact when patients experience problems. Furthermore, assessment bias may have occurred because we used a self-developed system that does not grade complications based on their importance to the patient. However, in the absence of a validated all-encompassing classification system, a similar grading system has been used in multiple other studies.[3, 25] Additionally, we focused on soft tissue complications, and no patient-reported outcome measures were collected; thus, we were not able to give insight into patient satisfaction in relation to the occurrence of complications. Nevertheless, earlier research demonstrates that most bone-anchored prosthesis users are satisfied compared with previous socket-prosthesis use, even with the occurrence of adverse events.[19, 24] Furthermore, a decrease in the incidence and severity of complications might increase patient satisfaction. Assessment bias, as well as the potential underestimation of complications, resulted in the tendency to overestimate the benefit related to treatment modifications,

Additionally, selection bias occurred because the individuals eligible for treatment were highly selected, and as such, these findings might not apply to the typical amputation practice, or for individuals treated with other types of osseointegration implants. However, because most individuals undergoing osseointegration implantation are treated with standard transfemoral implants, we believe reporting these results is relevant. Selection bias also occurred because we excluded individuals treated in the transitional period between 2013 and 2015. We believe this is justified, because inclusion of the limited number of participants (n= 13), with addition of a third combination of treatment strategies, overcomplicates any potential analysis. Furthermore, the presence of multiple confounders made it impossible for us to investigate the exact influence of a single procedural change on complications rates. For example, treatment-related group differences such as discontinuing prolonged postoperative antibiotic prophylaxis use may have influenced infectious outcomes. Cessation of prolonged antibiotic use may have downplayed the decrease in soft-tissue infections observed, while also influencing the increase of surgical site infections between surgical stages occurring after treatment changes. The change in implants also complicated our effort to evaluate the effect of changes to surgical technique, because changes to the coating of the extramedullary portion of the implant might also affect soft tissue complications. Obviously, for research purposes, it would be more favorable to evaluate treatment adaptations separately. However, in practice, when an implant is believed to be less safe because of the potential risk of breakage, its substitution is well-founded. Another confounder is the learning curve of the surgeon because an improvement in surgical technique is expected over time, potentially making the outcomes of the latter group seem superior. This effect will most likely have been relatively small, because changes implemented to surgical technique

combined with relatively small groups might have resulted in two learning curves. Lastly, the 2-year follow-up period precludes an assessment of long-term complications such as late reoperation. However, this study focused on soft tissue infections and complications, all of which predominantly occurred in the early- to mid-term after treatment, as opposed to certain complications with a more long-term nature such as aseptic implant loosening or periprosthetic fractures.[25]

Soft Tissue Infections and Stoma-related Complications

Patients treated with the modified surgical technique and titanium implant experienced fewer soft tissue infections (which were treated with less invasive measures) and fewer events of stoma redundant tissue. However, surgical site infections between surgical stages occurred more often in this group than in patients treated with the conventional surgical technique and CoCrMo implant. It seems that treatment adaptations to surgical technique and implant design play a beneficial role in reducing the incidence and severity of these frequently occurring soft tissue complications after the second stage of the procedure. This finding is contrasted by the increase in surgical site infections and the occasional necessity to expedite the second stage of surgery. We hypothesize this is caused by increased soft-tissue tension over the underlying implant after surgical stage 1 because of the additional reduction of soft tissues in the modified surgical technique, leading to tissue damage or necrosis. However, the possible effect of cessation of prolonged antibiotic prophylaxis use in the modified surgical technique group cannot be ruled out. Al Muderis et al. reported on transfemoral bone-anchored prosthesis users and found similar results with regard to the occurrence of soft tissue infections and stoma-related complications.[3] It remains clear that soft tissue complications are the most frequently occurring, while most soft tissue infections can be successfully treated with oral antibiotics (94% in the study by Al Muderis et al. versus 88% to 100% in the current study).[3] Juhnke et al. demonstrated an absolute risk reduction ([AR group 1 – AR group 2] x 100) of infection of 42% to 55% after surgical and device adaptations in individuals treated with a press-fit transfemoral osseointegration implant, comparable to our findings of 68% absolute risk reduction ([0.84-0.16] x 100).[17] Furthermore, surgical intervention for soft tissue infections were not necessary in their intervention group, similar to this study. Our study thus confirmed the findings of Juhnke et al., in which we attempted a more methodical and systematic analysis with a fixed follow-up period and present data regarding nonsurgical treatment.[17] Additional research is necessary to investigate the influence of solitary treatment adaptations on complications and to investigate late complications such as infection, periprosthetic fracture, and implant breakage or loosening.[23, 25] Lastly, with the increase of surgical site infections occurring between surgical stages, the potential benefit of performing single-stage surgery, thus eliminating soft tissue tension over the implant, should be investigated.

Serious Complications

Patients treated with the modified surgical technique and titanium implant did not experience serious complications, as found in this study. Bone infections occurred in the conventional surgery and CoCrMo implant group, and were successfully treated with implant retention. Because bone infection can occur as a consequence of ascending infection, treatment modifications resulting in a decrease in soft tissue infections might play a protective role. Larger studies are necessary to investigate this assumption. It remains clear, however, that the incidence of serious complications in transfemoral bone-anchored prosthesis users is low, as suggested by earlier studies focusing on treatment safety.[3, 5]

Conclusion

Ongoing treatment modifications to surgical technique and implant design, as well as learning curve and experience, have resulted in a decrease in the incidence and severity of soft tissue infections and stoma redundant tissue in this procedure, contrasted by an increase in surgical site infections before stoma creation. Serious complications did not occur in the group treated with the adapted surgical technique and titanium implant. Multiple bone infections occurred in the group treated with the conventional procedure and CoCrMo implant and all were successfully treated with implant retention. Therefore, because we believe the benefits of these treatment modifications outweigh the disadvantages, we advise surgeons to create a shallower stoma with a stable soft tissue envelope, combined with a titanium implant. Additional research is necessary to investigate additional ways to mitigate the occurrence and impact of frequently occurring soft tissue complications.

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Supplementary Table 1. Patient demographics, baseline amputation characteristics, surgical details, and implant characteristics of the excluded transition group from 2013 to 2015

Parameter	Transition group (n= 13)a
Women, % (n)	**23 (3)**
Age in years, median (IQR)	
Age at amputation	48 (19)
Age at implantation	57 (17)
Interval in years between amputation and implantation in years, median (IQR)	5 (22)
% Nonsmoker (n)	85 (11)
Diabetes mellitus, % (n)	
No	92 (12)
Noninsulin-dependent	0 (0)
Insulin-dependent	8 (1)
BMI in kg/m^2, mean ± SD	**27 ± 3**
Baseline amputation characteristics	
Level (per limb), n	
TF	13 of 13
TK	0 of 13
Side, n	
Left	6 of 13
Right	7 of 13
Bilateral	0 of 13
Cause (per limb), n	
Trauma	4 of 13
Dysvascular	2 of 13
Infection	4 of 13
Tumor	2) of 13
Congenital	0 of 13
Other	1 of 13
Surgical details (per implant)	
Interval in days between surgical step 1 and 2, median (IQR)	56 (25)
Postoperative antibiotic prophylaxis, n	13 of 13
Implant characteristics (n = 80)	
Diameter in mm, median (IQR)	17 (2)
Length in mm, median (IQR)	160 (0)
Dual cone size, median (IQR)	4 (2)

[a]n= 23 treated from 2013 to 2015: four patient-specific implants, three transtibial amputations, and three had no informed consent, resulting in 13 patients for analysis. TF = transfemoral; TK = through-knee amputation.

Supplementary table 2. Classification of complications

Type of adverse event	Subtype	Symptoms and signs	Treatment	Grade	Severity
Serious complications					
Infection[a]	3. Bone infection	Radiographic evidence of osteomyelitis[b] with other signs of infection[c] with a stable implant	Local measures	3A	Severe
			Oral antibiotics	3B	
			Parenteral antibiotics	3C	
			Surgical treatment	3D	
	4. Septic implant loosening	Radiographic evidence of osteomyelitis[b] with other signs of infection[c] with an unstable implant	Explantation	4	Severe
Implant failure	Aseptic loosening or failure of osseointegration	Radiographic evidence of loosening with unstable implant without infection	Revision		Severe
	Intramedullary stem breakage	Radiographic and/or clinical evidence of stem breakage	Revision		Severe
Periprosthetic fracture	Unstable fracture	Radiographic evidence of displaced fracture of the residual limb bone	Surgical treatment		Severe
Minor complications					
Infection[a]	1. Low-grade soft-tissue infection	Cellulitis with signs of inflammation (redness, swelling, warmth, pain)	Local measures	1A	Minor
			Oral antibiotics	1B	Minor
			Parenteral antibiotics	1C	Minor
			Soft tissue surgery	1D	Moderate
	2. High-grade soft-tissue infection	Abscess formation, purulent discharge, and/or raised level of C-reactive protein	Local measures	2A	Minor
			Oral antibiotics	2B	Minor
			Parenteral antibiotics	2C	Minor
			Soft tissue surgery	2D	Moderate

Supplementary table 2. Classification of complications (continued)

Type of adverse event	Subtype	Symptoms and signs	Treatment	Grade	Severity
Stoma problems	Hypergranulation or keloid formation	Overgrowth of connective tissue at the stoma with absence of infection	Local measures[d]	A	Minor
			Sleeve[e]	B	Moderate
			Soft tissue surgery[f]	C	Moderate
	Redundant tissue	Presence of symptomatic redundant soft tissue with absence of infection	Local measures[g]	A	Minor
			Sleeve[e]	B	Moderate
			Soft tissue surgery[h]	C	Moderate
			Removal of extramedullary part of osseointegration implant	D	Moderate
Implant failure	Aseptic loosening or failure of osseointegration	Radiographic evidence of loosening with stable implant without infection	Conservative treatment		Minor
	Dual-cone adapter body breakage	Clinical signs of breakage (such as instability)	Dual-cone exchange or adapted male part		Moderate
	Dual-cone adapter weakpoint breakage	Clinical signs of breakage (such as excess of rotation freedom dual-cone adapter)	Dual-cone exchange		Minor
Periprosthetic fracture	Stable fracture	Radiographic evidence of non-displaced fracture of the residual limb bone	Conservative treatment		Moderate

[a]Modification of the classification system by Al Muderis et al.[3] [b]Circular osteolysis of ≥ 2 mm around the implant. [c]Fever, pain, elevated C-reactive protein level, and/or purulent discharge. [d]Use of instillagel, terracotrill ointment, and/or AgNO3. [e]Placement of a (protective) sleeve. [f]Scar tissue removal by conical excision. [g]Use of a stump dressing or shrinker. [h]Stump refashioning.

Supplementary table 3. Serious and minor complications, and complications between surgical stages; as well as treatment

Type of adverse event	Treatment	Grade	Conventional surgery & CoCrMo implant (n = 40)		Adapted surgery & Titanium implant (n = 39)	
			Patients % (n)	Events	Patients % (n)	Events
Serious complications						
Bone infection	Total		8 (3)	6	-	-
	Local measures	3A	3 (1)	1	-	-
	Oral antibiotics	3B	8 (3)	4	-	-
	Parenteral antibiotics	3C	-	-	-	-
	Surgical treatment	3D	3 (1)	1	-	-
Septic implant loosening	Explantation	4	-	-	-	-
Aseptic implant loosening with unstable implant	Revision		-	-	-	-
Intramedullary stem breakage	Revision		-	-	-	-
Periprosthetic fracture with unstable fracture	Surgical treatment		-	-	-	-
Minor complications						
Low-grade soft tissue infection	Total		38 (15)	27	21 (8)	9
	Local measures	1A	15 (6)	6	5 (2)	2
	Oral antibiotics	1B	33 (13)	19	15 (6)	7
	Parenteral antibiotics	1C	3 (1)	1	-	-
	Surgical treatment	1D	3 (1)	1	-	-

Supplementary table 3. Serious and minor complications, and complications between surgical stages; as well as treatment (continued)

Type of adverse event	Treatment	Grade	Conventional surgery & CoCrMo implant (n = 40)		Adapted surgery & Titanium implant (n = 39)	
			Patients % (n)	Events	Patients % (n)	Events
High-grade soft tissue infection	Total		50 (20)	49	10 (4)	4
	Local measures	2A	35 (14)	19	-	-
	Oral antibiotics	2B	30 (12)	23	10 (4)	4
	Parenteral antibiotics	2C	5 (2)	2	-	-
	Surgical treatment	2D	10 (4)	5	-	-
Hypergranulation or keloid	Total		10 (4)	4	10 (4)	6
	Local measures	A	5 (2)	2	10 (4)	6
	Sleeve placement	B	-	-	-	-
	Soft tissue surgery	C	5 (2)	2	-	-
Stoma redundant tissue	Total		13 (5)	5	-	-
	Local measures	A	-	-	-	-
	Sleeve	B	-	-	-	-
	Soft tissue surgery	C	5 (2)	2	-	-
	Extramedullary implant removal	D	8 (3)	3	-	-
Aseptic implant loosening with stable implant	Conservative		3 (1)	1	-	-
Periprosthetic fracture with stable fracture	Conservative		-	-	-	-

Supplementary table 3. Serious and minor complications, and complications between surgical stages; as well as treatment (continued)

Type of adverse event	Treatment	Grade	Conventional surgery & CoCrMo implant (n = 40)		Adapted surgery & Titanium implant (n = 39)	
			Patients % (n)	Events	Patients % (n)	Events
Complications between surgical stages (no stoma)						
Surgical site infection	Total		3 (1)	1	26 (10)	11
	Local measures		-	-	-	-
	Antibiotics		-	-	15 (6)	7
	Surgical treatment		3 (1)	1	10 (4)	4

CoCrMo: Cobalt-Chrome-Molybdenum. N: Participants.

Chapter 7

Summary, Discussion and Conclusion

Introduction

The purpose of this thesis was to improve the quality of care for individuals with a lower extremity amputation experiencing difficulties using a conventional socket-suspended prosthesis (SSP). This was achieved by evaluating bone-anchored prosthesis (BAP) surgical indications, safety, and influence of treatment adaptations.

1. Summary of main Results

1.1 Adverse event data and data reporting

In **Chapter 2** an overview is provided of adverse events and related treatment options in individuals with extremity amputations treated with different types of osseointegration implants (press-fit, screw-type, compress). The overview was obtained by performing a systematic review of the literature, including 12 studies with 15 cohorts with a total of 604 patients (screw-type: 206, press-fit: 387, compress: 11; transfemoral: 522, transtibial: 15, upper extremity: 67).[1] The systematic review demonstrated a great diversity in presented adverse events and subsequent treatment, with the occurrence of explantation (i.e. implant removal) being the only outcome reported in all cohorts. Reviewing the literature revealed that infection, implant failure (aseptic loosening or mechanical failure of components), stoma-related problems (hypergranulation/keloid formation, stoma redundant tissue), and periprosthetic fractures were the adverse events possibly occurring after treatment with a BAP. The review also revealed major methodological shortcomings to the published literature such as the lack of use of fixed follow-up moments and large amounts of overlapping data, which will be further addressed in section 2 of this chapter "Methodological considerations". We concluded that, in individuals treated with standard femoral implants, the incidence of major complications such as implant infection, implant loosening, and explantation was lower in users of a press-fit implant compared to a screw type implant. Higher rates of major complications were reported in studies from the Swedish and German treatment groups, describing the initial results in the early phases of treatment (Swedish group 1990-1999, German group 1999-2008) after which changes were implemented (see general introduction: Swedish group: 1999 implementation of standard rehabilitation protocol OPRA, German group: 2009 changes to surgical technique and implant design).[2-7] Furthermore, the systematic review demonstrated that minor adverse events, such as soft tissue infections, stoma-related problems, and breakage of external parts of the prosthetic system were most common. Even though certain studies reported that these minor adverse events occurred most frequently, they were greatly underreported in the literature.[4, 5, 8, 9] No definitive conclusions could be drawn related to individuals treated with tibial, upper-extremity, or compress implants due to the small number of patients treated. Despite the relatively small sized studies, it was clear that the adverse event rates for these subcohorts exceeded what is deemed

acceptable for standard orthopedic interventions such as a total hip or knee arthroplasty. [10, 11]

1.2 Adverse events

Adverse events occurring after BAP-treatment can be subdivided in 1) major/serious or 2) minor complications, based on the impact to the patient and subsequent required treatment. Bone or implant infection, implant stem breakage, and aseptic implant loosening or periprosthetic fracture with subsequent implant loosening are considered major adverse events. Soft tissue infection, stoma-related problems (hypergranulation/ keloid formation, stoma redundant tissue) and breakage of the external prosthetic components are considered minor adverse events. We performed a thorough re-assessment of adverse events rates after BAP-treatment, as early studies from the Swedish and German treatment groups reported higher rates of major complications, and a tendency towards a decrease in incidence was observed in more recent literature. [2-7, 9, 12, 13]

The occurrence of major adverse events was assessed in **Chapters 3 – 6**. Safety outcomes were evaluated by stratifying the cohorts based on amputation level, implant type, and/ or etiology of amputation.

Data from individuals with a transfemoral amputation (TFA) treated with standard femoral osseointegration implants are presented in **Chapter 3 cohort 1** (n=53, 1 year follow-up), **Chapter 5** (n=39, 5 years follow-up), and **Chapter 6 cohorts 1 and 2** (cohort 1 overlaps completely with Chapter 5, cohort 2: n= 39, 2 years follow-up). [14, 15] Major adverse events were uncommon in these cohorts. Bone infection and intramedullary stem breakage only occurred in the cohort of 39 individuals presented in **Chapter 5** in 10% (4/39) and 5% (2/39), respectively. Periprosthetic fracture occurred in one out of 53 individuals in the cohort from **Chapter 3**, being a femoral neck fracture, treated surgically with a dynamic hip screw. No septic or aseptic implant loosening occurred in either cohort.

Data from individuals with a short transfemoral, transtibial, or dysvascular amputation treated with a BAP are presented in **Chapter** 3 (short TFA: 16, transtibial amputation (TTA): 21) and **Chapter 4** (dysvascular TTA: 5). [14, 16] Major adverse events were also uncommon in these studies reporting on the one year follow-up of these cohorts. Septic implant loosening occurred once in an individual with a dysvascular TTA, possibly related to vascular status, as femoral artery occlusion occurred postoperatively. A subsequent TFA was required, in which an osseointegration implant (OI) was simultaneously implanted on the patient's request, showing an uneventful course up until recent two years follow-up. No other major adverse events occurred in these cohorts.

Occurrence of minor adverse events was also assessed in **Chapters 3 – 6**. [14-16] Soft tissue infections were the most frequently occurring adverse events in all cohorts, unrelated

to amputation level or etiology, or implant type. Absolute risk, or implant infections per implant year ratios was quantified according to the definition suggested by Tillander et al.[7] Absolute risk rates ranged from 0.15-0.17 in individuals treated with standard femoral OIs, and from 0.29-0.43 in the small cohorts with short transfemoral, transtibial, and/or dysvascular amputations. The initial cohort of individuals with a normal length TFA treated prior to implementations of changes to surgical technique and implant design experienced soft tissue infection absolute risk rates of 0.76-0.93, compared to rates of 0.15-0.17 presented here (see also end of this paragraph). However, although frequent in occurrence, the studies in this thesis illustrated that >85-90% of these soft tissue infections could be successfully treated with oral antibiotics only, thus resulting in a limited negative impact for the patient.

The proof-of-concept studies presented in **Chapters 3 and 4,** demonstrated acceptable adverse events results in individuals treated with a nonconventional BAP (short femoral amputation, transtibial amputation, dysvascular amputation). Major adverse event rates were comparable to those observed in individuals with a TFA treated with standard femoral OIs. Furthermore, although experiencing higher soft tissue infection rates than the current rates in individuals treated with standard transfemoral OIs (short TFA, TTA, dysvascular amputation: 0.29-0.43 vs standard TFA: 0.15-0.17), the incidence was lower than in the initially treated cohort with standard transfemoral OIs (0.76-0.93). It should be noted that these proof-of-concept studies contained relatively small numbers of patients with a limited follow-up period of 1 year.

As a consequence of multiple short-term follow-up studies reporting high incidences of soft tissue infections, concerns arose with regard to the possibility of infectious disease progression to bone or implant infections.[2, 4, 5, 9, 17-19] These concerns were contradicted by the results presented in **Chapters 5 and 6**, reporting on outcomes at 5- and 2- years follow-up, respectively. The reported data indicated that the majority of soft tissue and bone infections occur within the first 2 years post-surgery, as a decrease in incidence of both soft tissue and bone infections was observed in time.[15] Beck et al. suggested that the stoma reaches a steady-state of microbial diversity resulting in a host-microbiota homeostatic relationship, potentially explaining this phenomenon.[20] These findings are also supported by the 10 years follow-up data reported by Hagberg et al.[21]

Chapter 6, a comparative cohort study with 2 groups, illustrated that the incidence and severity of frequently occurring soft tissue infections and of stoma redundant tissue could be greatly mitigated by adaptations to surgical technique and implant design, as well as by learning curve and experience of the surgeon. We studied the impact of surgical technique adaptations (i.e. additional reduction of soft tissue surplus, resulting in a more shallow stoma canal) and the change of OI used. The initial cobalt-chrome-molybdenum (CoCrMo) stem with a trabecular metal surface was replaced by a titanium alloy implant with a plasma-sprayed titanium coating of the stem and full TiNbN polished coating of

the extramedullary head. Implementation of treatment changes resulting in a 5-6 fold decreased risk of soft tissue infection. However, these improvements were contrasted by an increase in incidence of surgical site infections occurring between surgical stages 1 and 2, when no stoma is yet created. It was concluded that the benefits of treatment adaptations outweigh the disadvantages, leading to the advice to aim for a more shallow stoma with a stable soft tissue envelop combined with a titanium implant.

1.3 Functional outcomes

Functional outcomes were assessed in **Chapters 3 – 5,** comparing outcomes pre-operatively at baseline using a SSP with the follow-up using a BAP. Patient reported outcome measures (PROMs) were used to assess prosthesis wearing time and health-related quality of life (HRQOL), and performance tests were used to assess walking ability. [22] A significant improvement of the prosthesis wearing and HRQOL was reported, both at 1 and 5 year follow-up, in **Chapters 3 & 5**, respectively. [14, 15] This confirms the prolongation of improvements published in earlier short-term follow-up studies. [2, 13, 23-25] Additionally, prosthesis wearing time and HRQOL significantly improved both for the entire cohort as stratified by implant type (standard femoral implant, short femoral implant, tibial implant) (**Chapter 3)**. [14] Improvements in prosthesis wearing time, HRQOL, and walking ability were also observed in the 5 individuals with a dysvascular TTA after treatment with a BAP in **Chapter 4**. [16] No statistical analysis was performed in this study due to the small patient cohort. Additionally, **Chapters 3 & 4** demonstrated the possibility for substantial functional gain after BAP-treatment, illustrated by the fact that large portions of the cohorts were non-prosthetic users/wheelchair bound prior to surgery, while everyone was walking using their BAP at follow-up. This improvement was largest in the subgroup with a short TFA, often experiencing considerable difficulties with socket-suspension, with 50% being non-prosthetic users at baseline.

Based on the studies in this thesis we can conclude that lower-extremity BAP-treatment is feasible and major adverse events are uncommon in current practice, particularly when using press-fit titanium femoral implants. Minor soft tissue adverse events occur frequently. However, their incidence and severity can be substantially mitigated by surgical technique, implant design, and learning curve. Furthermore, BAP-treatment results in a significant functional gain regarding prosthesis use, HRQOL, and ability for ambulation compared to pre-operative SSP use. This improvement is observed both when using standard femoral implants as well as in nonconventional cohorts with a lower-extremity amputation.

2. Methodological considerations

2.1 Systematic review

The systematic review (**Chapter 2**) included an elaborate search and analysis while investigating: 1) device-related adverse events rates in individuals with an upper- or lower-extremity amputation treated with different types of BAPs, and 2) adverse events related interventions.[1] A strength was the data extraction and methodological quality assessment performed by two independent raters, resulting in an inter-rater agreement Cohen's K coefficient of 0.93 with 96% agreement. The guidelines of the PRISMA statement were followed and the initial review protocol was registered in the PROSPERO database.[26, 27] The Effective Public Health Practice Project (EPHPP) quality assessment tool for quantitative studies was used for methodological quality assessment of individual studies, and was chosen as we anticipated retrieving multiple types of non-randomized observational studies.[28, 29] All included studies had methodological shortcomings inherent to the nonrandomized observational design, such as: failure to blind assessors and participants, lack of adjustment for confounding variables, and limited validity or reliability of data collection methods; resulting in an overall weak global rating. Six of the 12 studies were retrospective cohort studies, 3 were prospective, and 3 were cohort studies with undefined design. There were no studies using fixed follow-up moments making stratification based on short- (up to 1 year), mid- (2 to 5 years), or long-term (5 years or more) outcomes impossible. Twenty-four articles met the in- and exclusion criteria, of which 12 articles were excluded reporting on cohorts of participants which overlapped completely.[2, 3, 17, 25, 30-37] To correct for the partially overlapping data in the included studies, as well as the heterogeneity of the data in terms of outcomes and follow-up intervals, we aimed to perform an individual patient data meta-analysis. This was ultimately impossible as approached researchers were not willing to share the original data for unknown reasons. Furthermore, due to the small numbers of individuals included in certain studies, overall complication rates could be greatly affected by single outliers, which probably also explains the rather high rates of major adverse events reported in the individuals treated with tibial implants (n= 9).[4, 8]

2.2 Retrospective cohort studies

The main methodological shortcomings with regard to the studies performed in **Chapters 3 – 6** are related to the study design and the associated limitations. All mentioned chapters present retrospective cohort studies, mostly with short follow-up, and often with small sample sizes. Functional outcomes were prospectively collected.

Chapters 3 and 4 present outcomes with a one year follow-up. This is short but not uncommon in the context of proof-of-concept studies for the initial evaluation of safety and effectiveness of emerging treatments. The reported functional improvements are influenced by selection bias, as high percentages of pre-operative non-prosthetic users were included, ensuing considerable functional improvements when comparing baseline

to post-intervention outcomes. As such, results are not representative for the normal amputation population. The inclusion of wheelchair bound individuals, having "less to lose", can be considered a logical step when attempting a novel treatment with potentially higher risks. PROMs used included the Questionnaire for Persons with a Transfemoral Amputation (Q-TFA), which was only validated for the use in individuals with a TFA but was also used in cohorts with a TTA.[22] The Q-TFA questions, however, are not specifically designed for individuals with a TFA and cover most aspects of HRQOL also relevant for individuals with a TTA. Additionally, certain Q-TFA outcome scores such as the global score provide statistical limitations when individuals are not using a prosthesis. The small cohort sizes also limit the possibility to draw definitive conclusions.

In **chapters 5 and 6** two longer follow-up studies are presented with a fixed 5- and 2-year follow-up, respectively. The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines were adhered to in both studies ensuing optimal reporting, and the fixed follow-up design facilitates comparison of outcomes with other studies.[38] The retrospective collection of adverse events outcomes is susceptible to underestimation of events. To compensate for this, all general practitioners (GPs) were contacted to assess if adverse events had occurred outside the hospital environment in both **chapters 5 & 6**. General practitioners play a predominant role in the Dutch healthcare system as gatekeepers prior to referral to the hospital. This additional assessment revealed that only 2% of soft tissue infections occurred outside the scope of the hospital environment, while all major adverse events resulted in a visit to our clinic and were not missed in the reporting.

Chapter 6 is the only chapter presenting a comparative cohort study, aiming to explore the influence of treatment adaptations on adverse events rates. The main limiting factor is the lack of correction for confounders, due to a lack of randomization and the retrospective design, while there was a high risk of bias due to the multiple changes that occurred over the course of 10 years of treatment. Changes included those to: 1) patient selection (eventually including dysvascular amputations and older individuals), 2) treatment protocols (discontinuation of postoperative antibiotic prophylaxis use), and 3) implementation of multiple major treatment changes in time (surgical technique and implant changes). Consequently, multiple factors may have attributed to improved outcomes making it impossible to evaluate a cause-and-effect relationship for one single factor.

As such, generalized conclusions emerging from **Chapters 3 – 6** need to be considered in the context of their methodological shortcomings.

2.3 Pioneering research

Assessment of causality or correlation of BAP-treatment on adverse events remains difficult due to the fact that this treatment is partly still in its pioneering/development phase

(**Chapter 6**). Early treatment outcomes resulted in relatively high rates of adverse events (Swedish group 1990-1999, German group 1999-2008), as demonstrated by Juhnke et al., reporting on 77% infection rates requiring surgical intervention.[5] To mitigate such rates, adaptations to treatment strategies were implemented, often prior to the systematical analysis and reporting of such outcomes. These treatment changes can result in a notion of prompt improvement of outcomes, and reduce the tendency to perform structural analyses of different treatment types in a field which is rapidly evolving. However, performing methodologically sound systematical analyses is the only way to adequately assess the influence certain treatment strategies changes have had. A pioneering phase is also inherently linked to cohorts with small patient numbers, associated with limitations regarding the interpretation of data. Nevertheless, and particular in this pioneering phase, reporting of results albeit small patient numbers, is important to allow for the further evolution of the treatment. The gradual understanding of important mechanisms resulting from fundamental and clinical research and its application to treatment protocols is extremely important. This enhanced understanding is subject to learning curves, peer consultation, cooperation amongst treatment centers, and the continued publication and discussion of clinical outcomes. Optimal application to individual patients, however, remains challenging. Ideally, outcome (functional and adverse events) of a potential improvement of the treatment would be evaluated using a randomized controlled trial design, as the gold standard for increasing the level of research evidence. However, this is unlikely to be an ethical approach, as in this pioneering phase, the outcome improves rapidly and obvious improvements of treatment make earlier practice obsolete.[4, 5, 13, 25, 32, 34] Thus, the methodological quality of our data remains governed by clinical observations and experience, in which potential treatment improvements tend to not be introduced in a scientifically controlled, stepwise fashion.

3. Future perspectives

3.1 Improving safety

3.1.1 Long-term safety

Previous studies reporting on safety have reported mostly on short-term outcomes, focusing on early major/serious adverse events potentially leading to treatment failure.[2, 7-9, 12, 17, 19, 31, 32, 39] The initial fear of early treatment failure as a result of implant infection has been disproven and thus, the focus should be transferred to longer term follow-up. These studies could include: aseptic loosening, implant breakage, and periprosthetic fracture. Aseptic loosening is the most common reason for late revision in joint arthroplasty, although often resulting from wear of movable prosthetic components with subsequent particle disease.[40] In BAP-treatment using OIs, a different pathogenesis of aseptic loosening may play a role, such as periprosthetic bone remodeling or stress shielding.[41, 42] Assessment of the long-term behavior of periprosthetic bone is important, and factors

related to stress shielding should be investigated, focusing on implant design (screw-type vs press-fit), materials (Cobalt-chrome-molybdenum vs Titanium alloys or other), and surface coating (distally coated and integrated vs completely coated an integrated over the full implant length) and coating type (trabecular metal, plasma sprayed, etched etc). [42-46]

Assessment of mechanical failures of the transfemoral press-fit CoCrMo implant revealed a 10% rate of intramedullary stem breakage failure (6/58), at a minimum of 5 years follow-up. [47] This incidence is higher than the 5% (2/39) reported in this thesis (**Chapter 5)**, possibly attributed to differences in follow-up period between studies. The stems were removed using custom-made hollow reamers and all implants were successfully revised within 12 months after failure. Stem failure was associated with smaller stem diameters and higher numbers of infectious events. The same study reported a 22% incidence (13/58) of minor mechanical complications of the external components (i.e. dual-cone adapter failure).

Hagberg et al. reported on the long-term follow-up (up to 15 years) of 111 individuals treated with the screw-type OPRA system focusing on implant failures.[48] A 4.5% rate of stem breakage was reported (5/111), all of which however occurring at the level of a tantalum bead used for pre-marking in a subset of the cohort included in a radiological study (n= 51, 55 implants, rate of breakage 5/55= 9%). Fifty-five percent of individuals experienced at least one mechanical complications, mostly problems with the percutaneous abutment or abutment screw. A positive correlation was found between the number of mechanical complications and the patients activity level resulting in the implementation of restrictions in use.

With a longer prosthesis indwelling time the risk of periprosthetic fracture increases. Hoellwarth et al. reported on 22 periprosthetic fractures (Femoral neck: 2, intertrochanteric: 14, subtrochanteric: 6) in 458 individuals with a femoral BAP with variations in follow-up time (range 1-10 years).[49] Most were sustained after ground-levels falls resulting in fractures proximal to the OI. An association was found with increased patient weight and female sex. Management involved conventional techniques /implants for lower-limb trauma care. No implant revision methods were presented, as all fractures occurred proximal to the implant without concomitant implant loosening.

Thus, with an increasing survival of bone-anchored prostheses, novel potential failure modes arise such as aseptic loosening, implant failure, and periprosthetic fracture, which require investigation.

3.1.2 Improving quality of evidence

The systematic review in this thesis (**Chapter 2**) illustrated the large amount of overlapping data in published articles using a Gantt chart. [1] Consequently, this data duplication

makes an adequate assessment of safety and effectiveness outcomes of BAP-treatment increasingly difficult. Additionally, cohorts are relatively small, particularly in upper extremity or transtibial amputation. Both of these problems warrant a solution, such as setting up a global registry, removing duplicate data and pooling numbers.[50] Such a registry has become a powerful tool in the field of orthopedics after being established in 1970, offering multiple benefits such as identification of best clinical practices, improvement of outcomes, informing about financial aspects, and identification of failing technologies.[51] Arthroplasty registries are of a national nature, but due to the fact that BAP-treatment is applied in relatively small numbers in few centers worldwide, this would require setting up a global registry.

Unrelated to the potential initiation of a global registry, a need exists for consensus regarding the definition, diagnosing, and treatment of adverse events occurring, especially infection. In the case of periprosthetic joint infection (PJI), Parvizi et al. stated "the availability of a standardized definition will allow for meaningful comparison of medical literature reporting on related issues".[52] The diagnosis of infections related to BAP-treatment should be based on a combination of clinical findings, laboratory results, microbiological cultures, histopathological evaluation, and/or intraoperative findings, as is the case in PJI.[52-54] An algorithm should be formulated combining these variables, with a distinct difference to those defined for PJI, as the physiological percutaneous nature of implants decreases the predictive value of positive cultures. Furthermore, the absence of a joint capsule and synovial fluid renders it more difficult to acquire and interpret periprosthetic cultures.[7, 20, 55, 56] Management of infections related to BAPs should be performed with an interdisciplinary approach of various specialists such as infectious disease physicians, microbiologists, and orthopedic surgeons, as is the case in PJI management.

When consensus is acquired in defining and diagnosing infections and other adverse events, a core set should be formulated of relevant adverse events to assess after surgery/treatment. Proposed domains of the core set would be as follows: infection, stoma-related problems, implant failure, periprosthetic fracture, and death. Consensus should also be obtained for a core set related to functional outcomes, such as PROMs and mobility tests, and with regard to standardized follow-up moments.[24] We suggest the use of fixed follow-up periods at 6 months and one, two, five, 10, 15, and 20 years post-surgery.

Standardizing the definition, diagnosis, and treatment of adverse events, combined with agreements on core sets for adverse events, functional outcomes, and follow-up moments, would allow for consistency in treatment and research, enhancing the potential for discussions and collaboration, ultimately resulting in improved patient care. Agreements regarding these matters would facilitate setting up a global registry, also making it possible to compare surgical techniques, implant types, and rehabilitation programs used. Ultimately, this would aid professionals in predicting outcomes

and informing patients about differences in surgical technique, implant design, and rehabilitation programs in relation to patient-specific factors.

3.1.3 Expanding treatment indications

When acceptable adverse event rates are achieved in the ideal patient cohort (in this case non-vascular transfemoral amputees) the potential for expanding treatment indications can be investigated. Half of the referred candidates for BAP-treatment present with either a short transfemoral or a transtibial amputation, and the majority of lower extremity amputations in the western world are of a dysvascular nature, with an expected increase due to the rising prevalence of diabetes mellitus. [57-59]

Chapters 3 and 4 concluded that, taking the small sample size and 1 year follow-up into account, BAP-treatment appears feasible, safe, and resulting in functional improvements in individuals with amputations previously excluded from treatment (i.e. short femoral, transtibial, and dysvascular amputation). [60] These proof-of-concept studies function as stepping stones to broaden treatment indications, and should be followed by studies with longer follow-up and larger cohorts. Akhtar et al. reported on the 3-5 year follow-up 6 individuals with a dysvascular TTA (part of the cohort from **Chapter 4)**.[61] One individual required TFA due to recurrent infection 3 years after initial surgery, ultimately resulting in death due to myocardial infarction shortly after the intervention. No implant loosening occurred within the follow-up period.

Microvascular pathologies such as diabetes mellitus are still often considered contraindications for BAP-treatment. Diabetes results in hyperglycemia with associated inflammation and vascular damage, resulting in impaired wound healing, giving rise to concerns for infection in a situation with a persistent wound (i.e. stoma). [62] Hyperglycemia also leads to increased bone resorption, potentially negatively impacting osseointegration. [63] However, Aghaloo et al. reported that adequate osseointegration could be achieved with dental implants with no observed differences between diabetics and non-diabetics at 3 months follow-up.[63] Additional research is necessary to investigate the feasibility and safety of BAPs in diabetics.

Apart from the consideration to expand the treatment to diabetic patients, another area where treatment expansion is considered is in patients with a TTA. For these patients challenges are to design implants that fit the endo-cortical cavity and to provide a secure long-term fixation. These challenges are related to the morphology of the tibia, in which fixation must be achieved in the funnel-shaped metaphysis and thin proximal cortex. [64] Difficulties occur related to primary implant stability, and diminished bone-implant contact area, also demanding non-cylindrical implant designs. These issues were tackled, as described in **Chapter 3**, by using drop-like shaped implants following the contour of the tibial medullar canal, with a 3D lattice structure coating increasing the surface area,

and by adding proximal locking screws.[14] What the ideal implant design will be aiming for long-term stable fixation, remains yet to be proven.

As exciting as it may be to expand surgical indications, application treatment to other patient groups should be done with great care. This can be highly challenging as demonstrated in the case of the Australian group who published two separate studies in which an OI was connected to either a total knee or hip replacement in the case of very short residual bones (TTA<4cm, TFA<10cm) or concomitant knee osteoarthritis.[65, 66] Improvements of functions were reported, and only 1 case of superficial soft tissue infection occurred in both cohorts (n=7), concluding this treatment to be feasible. Following up on the cohort treated with an OI connected to a total knee replacement, data from 9 individuals with a mean 41 months follow-up was gathered by myself during my research fellowship in Australia in 2018. This data revealed that 4 individuals required subsequent reamputation above the knee due to implant infection, and 1 individual underwent surgical interventions showing signs of implant loosening (Unpublished data, Atallah et al. 2018). The same treatment group recently published a case report of another potentially high risk treatment, reporting on an individual with right unilateral hip disarticulation treated with pelvic osseointegration with a follow-up of 2 years, in which no complications occurred.[67] It must be taken into account that these studies were published prior to the publication of the first multicenter study assessing safety in a cohort of individuals with a non-dysvascular TFA (i.e. the ideal patient).[9] Up to that date, there were only very limited reports of BAP-treatment in individuals with non-dysvascular TTA (n=8), with unacceptable rates of explantation (43-57%), implant infection (29%), and loosening (29%).[4, 8] This illustrates the occurrence of publication bias and a rapidly changing and developing field, validating the necessity for a global registry and international cooperation furthermore.

In conclusion, preliminary evidence of small cohorts with short term follow-up suggest BAP-treatment is safe and effective in carefully selected individuals with a short transfemoral, transtibial, and dysvascular amputation. A very careful stepwise consideration must be made, however, to assess if the clinical benefits outweigh the potential harms of these types of higher risk treatments.

3.1.4 Improving current treatment

Making an analogy to the development of the total hip arthroplasty, regarded by some as the 'operation of the century', the evolution of a treatment by learning from past experiences and mistakes is essential.[11, 68] Observing and reporting failure mechanisms of previous techniques, Charnley contributed substantially in 1961 by introducing the use of acrylic cement for component fixation, polyethylene as a bearing, and the concept of low-frictional torque.[11, 68-70] Over the years major advances in outcome were achieved by improvements to bearing surface, cementing techniques, and the evolution of different surgical approaches.[11, 71, 72]

Similarly, multiple aspects of BAP-treatment have been adjusted over time, such as rehabilitation protocols, implant design and materials, and surgical technique.[3, 5, 15, 47] Research has illustrated minor soft tissue adverse events to be most frequently occurring and greatly influenced by treatment adaptations (**Chapter 6**). Although not life-threatening, one can hypothesize that these adverse events have a substantial impact on patient satisfaction, due to their frequency of occurrence. Our lack of understanding of the delicate implant-soft tissue interface warrants more research to be performed. The focus should lie on gaining insight into the molecular, microbiological, and clinical properties, both in representative animal as well as human studies, in an attempt to decrease adverse event rates.[56] A positive shift in focus is already observed in recently published literature, addressing the growing role of the plastic surgeon and techniques for soft tissue contouring (i.e. formation of a snug muscular scarf seal at the bone-implant interface, medial thighplasty for soft tissue redundancy).[73, 74] Comparative studies within and between centers using either press-fit or screw-type implants will also improve the understanding of the implant-soft tissue interface, as differences in soft tissue handling are reported (See general introduction). Additionally, comparative studies are necessary to investigate the influence of single versus two stage surgery protocols on (soft tissue) adverse events (**Chapter 6**: occurrence of surgical site infections). At the introduction of BAPs, the initial hypothesis was that the period of bony ingrowth following implantation requires a sterile environment. As such, a noninferiority of the single stage procedure should be investigated, possibly resulting in patients not having to undergo multiple surgeries, also reducing treatment costs.[75] A protocol was published by the Australian group, having performed single stage surgery since April 2014, focusing mainly on an accelerated rehabilitation period.[39] Results, however, are still lacking. Prior to speeding up the program, the safety of such a procedure should be evaluated, as well as its potential for mitigating the increase in surgical site infections occurring between surgical stages as discussed in **Chapter 6**.

Research is also necessary investigating implant materials and design. Titanium is believed to have enhanced biocompatibility and antibacterial properties compared to cobalt-chrome alloys.[44] Intramedullary stem breakages have been reported in CoCrMo implants occurring 3 or more years post-implantation, but studies with longer follow-up are lacking investigating long term mechanical survival of titanium implants.[47] Implant material and design also influences periprosthetic bone behavior. Thompson et al. reported an increase in periprosthetic cortical thickness and implant bone coverage (i.e. less distal bone resorption) when comparing titanium to CoCrMo implants.[42] These findings are also supported by unpublished data from our own center. Distal stress shielding is also related to the level and length of implant fixation. In total hip arthroplasty, proximal stress shielding was initially observed in uncemented stems fixating with diaphyseal fixation. Design changes to stem shape and coating were implemented, in which the proximal portion was porously coated, enhancing metaphyseal loading and preserving bone stock.[11] Jeyapalina et al. reported on distal bone conservation/hypertrophy in a sheep study

using an OI with a porous coated distal region and end-loading collar.[43] Lastly, knowledge should be obtained regarding optimal implant coating, assessing the required coating structure, thickness, and length allowing for sufficient osseointegration. A thinner coating layer results in the use of a larger core diameter stem, decreasing the probability of stem breakage. [47] Coating/polishing of percutaneous components is suggested to influence soft tissue adverse event rates, and requires investigation. [5] In vitro studies have already been performed aiming to design surface coatings combining antimicrobial effects with good biocompatibility and fibroblast adhesion. [76]

In conclusion, treatment evolution and improvement require learning from past experiences and mistakes. As major adverse events are uncommon, while adverse events of the soft tissue occur most frequently in current practice, a paradigm shift is required regarding the focus of future adverse events research, focusing on the implant-soft tissue interface. Large gaps of knowledge still exist regarding optimal implant materials, designs, fixation types, and coating structures which require investigation.

3.2 Functional outcomes

Functional outcome assessment has been the primary goal of many studies, secondary to safety assessment. [3, 21, 23, 24, 34, 48, 77-81] Hagberg et al. recently reported significantly improved prosthesis use, function, and HRQOL at long term follow-up, with maintenance of the functional gain after 10 years.[48] It must be taken into account that studies focusing on functional outcomes have often compared baseline problematic SSP- with BAP-use, as experiencing socket-related problems remains the primary indication for treatment. [48] A recent study investigating functional outcomes of high-functioning SSP- vs BAP-users showed no differences in prosthetic use or mobility, although BAP-users experienced less problems and higher satisfaction. [82] More research is necessary to investigate eligibility of high-functioning SSP-users for BAP-treatment.

Nevertheless, the immense functional potential that a BAP-treatment offers is obvious, possibly even surpassing the treatment effect of primary total hip or knee arthroplasty. Treated individuals interviewed in a qualitative study reported BAP-treatment to be a revolutionary change in their life. [83] Besides the cosmetic and functional features experienced, the potential for a profound existential impact on life was described, with influences on body image, and the feeling of being like a normal person or the person they were before the amputation. [83]

Furthermore, recent research regarding Targeted Muscle Reinnervation (TMR) or the agonist-antagonist myoneural interface (AMI) has illustrated that we are barely grasping the functional possibilities of prosthetic limb use. [84-88] Besides possibly resulting in decreased phantom and residual limb pain, TMR gives the possibility to interact with the patient's nervous system. As such, combining TMR with BAPs results in intuitive control of neuromusculoskeletal prostheses, with improved mechanical and electrical interfaces.

[84-87, 89] Although mainly applied in upper extremity amputation, TMR's capabilities in lower extremity amputation can have a considerable impact as well. Furthermore, the surgical construct of the AMI seems to augment volitional motor control of adapted prostheses, maintain proprioception, and enables phantom limb sensation, potentially improving socket-related amputation care, but also gives rise to possibilities for interaction with BAP-treatment. [88]

3.3 Financial aspects

Bone-anchored prosthesis treatment has been performed in certain centers for a few decades and has proven to result in considerable functional improvements with acceptable adverse events rates in selected patient groups. [5, 26, 48] Despite these facts, and efforts made by treatment centers, provision of treatment is still not covered by healthcare insurance in most countries worldwide. Exemption procedures for the temporary remuneration of care exist in certain countries (Germany, Canada). In most of the rest of the world, treatment is performed in the context of research, funded by academic grants, workers compensation, personal injury cases, fundraising, or out-of-pocket expenses. A number of studies have assessed cost-benefit of BAP-treatment or compared prosthetic and service costs between BAP- and SSP-treatment, potentially aiding policy decision makers in their recommendation. [75, 90-92]

Bone-anchored prosthesis treatment results in fewer visits to prosthetic workshops and decreased costs related to stump or prosthetic component revisions, when compared to conventional socket care. [91, 92] However in BAP-treatment, high fixed treatment costs related to surgery, materials, and components, and costs of adverse events treatment compensate for the decrease in annual costs in SSP use. [75, 92] Cost-effectiveness of treatment is determined by assessing costs per additional quality adjusted life year (QALY) gained, with a threshold often set at $50.000/QALY. [93] Large differences in cost per QALY gained for BAP- vs SSP-treatment have been reported. [75, 90, 92] Studies comparing costs to effectiveness of single or two stage press-fit implant treatment reported a cost per QALY gained ranging from $13.740 to $44.660, [75, 90] while the study investigating two stage screw-type implant treatment described a cost/QALY of €83.374. [92] Inpatient stay, length of surgery, high cost of patient-specific implants, and relatively high complications rates were suggested as factors influencing costs. [75] These variables can probably be mitigated, decreasing costs and improving cost-effectiveness, with increased treatment numbers, experience and improvement of care. [85] Not taken into account in these studies is the possibility of a decrease in societal costs, as BAP-treatment improves the ability to work. [92] In comparison, an average cost of $18.300 per QALY gained is reported for a well-established treatment such as total knee arthroplasty, with a mean societal cost saving of $18.930. [94]

In conclusion, the functional possibilities BAP-treatment offers are extensive, comprising functional aspects such as prosthesis use and mobility, but also potentially influencing

existential aspects related to self-image. Novel research demonstrates the possibility for interaction with the nervous system offering the potential for intuitive control of neuromusculoskeletal prostheses.

Furthermore, BAP-treatment results in a decrease in annual prosthetic service costs but is associated with high fixed treatment costs due to high costs for surgery, implants/components, and treatment of adverse events. More experience and treatment numbers will most likely result in a decrease of surgery and implant costs, as well a decrease in adverse events rates and associated costs, thus improving treatment cost-effectiveness.

Conclusion

Bone-anchored prosthesis treatment for individuals with a lower extremity amputation offers substantial benefits related to function and prosthesis use. Treatment challenges are related to safety, but quantification of adverse events has demonstrated acceptable rates of major adverse events, while minor soft tissue adverse events occur most frequently. Soft tissue adverse events incidence and severity can be substantially decreased by adaptations to surgical technique, implant design, and learning curve. As such, we advise to aim for a shallow stoma with stable soft tissue envelop combined with a titanium implant. With adequate patient selection a favorable ratio between health gain and risk of adverse events can be obtained. Preliminary evidence of small cohorts with short follow-up suggests the feasibility and effectiveness of treatment for individuals with a short transfemoral, transtibial, and dysvascular amputation. A careful stepwise consideration is advised to assess if clinical benefits outweigh potential challenges of expansion of treatment indication. As we move from the pioneering phase towards standard care, there is an increasing demand for predictable outcomes both for function and adverse event risk. This demands for global cooperation as treatment numbers remain relatively small. Upcoming research on safety outcomes should shift from the assessment of short-term treatment failure towards 1) reducing rates of minor adverse events, 2) investigating long-term safety and potential novel failure modes, 3) assessing the potential for expansion of treatment indications. A novel treatment like this, with immense potential for improving quality of life for a select group of individuals, and only a fraction of acquired knowledge and experience, is the ideal field to conduct research and improve outcomes substantially in the nearby future. As such, this is the next goal we are committed to achieving.

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Addendum

Nederlandstalige samenvatting

Data management and medical research ethics

PHD portfolio

List of publications

Acknowledgment

About the author

Nederlandstalige samenvatting

Personen met amputaties van de extremiteiten worden al eeuwenlang behandeld met conventionele kokerprothesen om de mobiliteit en functie te herstellen. Ondanks grote vooruitgang ten aanzien van prothese technologie, innovaties rondom koker materialen, designs en liners, ervaren veel personen koker-gerelateerde problemen. Veelvoorkomende problemen zijn huidklachten van de stomp, klachten tijdens het zitten en mechanische problemen ten aanzien van de kokerfitting. Deze problematiek leidt tot verminderd gebruik van de kokerprothese, ontevredenheid en lagere kwaliteit van leven. Zodoende is vaak de interactie tussen de stomp en koker de limiterende factor voor het klinische succes van de prothese behandeling bij mensen met een beenamputatie.

Een strategie om de koker-gerelateerde problemen aan te pakken bestaat uit de eliminatie van de koker; door de prothese direct aan het lichaam te verbinden. Dit wordt gedaan door gebruik te maken van het fysiologische proces genaamd “osseointegratie”, waarbij er een structurele en functionele verbinding ontstaat tussen levend bot en een metalen implantaat. Dit type verankeringsmechanisme werd voor het eerst geïntroduceerd in de tandheelkunde in 1952, voor de behandeling middels beengeleidingshoortoestellen in 1977, en wordt sinds 1990 gebruikt bij de behandeling van personen met amputaties. Bij personen met een amputatie wordt tijdens een operatie een metalen implantaat in het bot gefixeerd middels een schroef of press-fit verbinding, dat via een huidopening, ook wel “het stoma” genoemd, door de huid steekt en waaraan de externe prothese onderdelen gefixeerd kunnen worden. Zo ontstaat uiteindelijk een botverankerde prothese. Naast het elimineren van de koker en koker-gerelateerde problemen gaat de behandeling met een botverankerde prothese potentieel gepaard met andere voordelen, zoals een toename van prothese gebruik, loopvermogen en kwaliteit van leven. Sinds de introductie van de techniek zijn er meerdere osseointegratie implantaten en diverse chirurgische technieken ontwikkeld door verschillende centra wereldwijd, die allemaal individuele klinische resultaten rapporteren. Wetenschappelijk onderzoek heeft zich met name gericht op veiligheidsaspecten van de behandeling, voornamelijk op het risico van infectie, gezien het feit dat het metalen implantaat de beschermende huid barrière doorkruist. De twee eerdere Nederlandse proefschriften over dit onderwerp gingen over implantaat ontwerpen en over functionele resultaten. Het huidige proefschrift heeft zich gericht op de chirurgische behandeling, met als overkoepelende doel om de kwaliteit van de botverankerde prothese behandeling te verbeteren door de huidige chirurgische praktijk te evalueren.

In **hoofdstuk 2** wordt een systematische review gepresenteerd waarin een overzicht wordt gegeven van de huidige kennis over complicaties en complicatie-gerelateerde behandelopties na een botverankerde prothese behandeling bij het gebruik van verschillende osseointegratie implantaten op verschillende amputatie niveaus. Uit deze review bleek dat complicaties zoals infectie, implantaat falen, stoma-gerelateerde

problemen en periprothetische fracturen kunnen ontstaan. Ook werd duidelijk dat de gepubliceerde literatuur duidelijke methodologische tekortkomingen vertoonde, zoals het ontbreken van vaste follow-up momenten en de grote hoeveelheid dubbele data in de diverse artikelen. Verdere tekortkomingen waren inherent aan het niet-gerandomiseerde observationele ontwerp van alle studies. Er werd aan de hand van de huidige literatuur geconcludeerd dat de incidentie van ernstige complicaties zoals implantaat infectie of loslating, en de noodzaak het implantaat te verwijderen lager was bij personen met een transfemorale amputatie behandeld met een zogenaamd press-fit implantaat ten opzichte van een schroef implantaat. Het onderzoek toonde verder aan dat minder ernstige complicaties zoals infecties van de weke delen, stoma-gerelateerde problemen en breuken van de externe componenten van het implantaten systeem het meest voorkwamen, ondanks dat deze zeer beperkt werden gerapporteerd in de literatuur. Er konden geen conclusies getrokken worden over personen behandeld met botverankerde prothesen voor de bovenste extremiteit, transtibiaal, of behandeld met het Compress implantaat systeem, door de beperkt aanwezige aantallen patiënten in de studies. Door het gebrek aan uniformiteit in de wijze en hoeveelheid van gepresenteerde data, en in de definities en diagnostiek van complicaties, werd voorgesteld om in de toekomst een standaard set van uitkomstmaten te gebruiken. Een internationale overeenstemming over welke complicaties te presenteren en de wijze van presentatie zullen samenwerking en het vergelijken van uitkomstmaten vergemakkelijken, met als doel te komen tot een verbetering van de behandeling. Er werd een voorstel gedaan voor een dergelijke standaard set in **hoofdstuk 2**.

In **hoofdstukken 3 en 4** worden proof-of-concept studies gepresenteerd waarin specifieke cohorten patiënten worden beschreven die voorheen niet in aanmerking kwamen voor een botverankerde prothese behandeling of waar nog weinig klinische ervaring van bekend was. Het gaat hier om personen met een zeer korte transfemorale amputatie, een transtibiale amputatie of een amputatie ten gevolge van vaatlijden. In **hoofdstuk 3** worden veiligheids- en functionele uitkomsten beschreven bij personen met een reguliere (n= 53) of zeer korte (n= 16) transfemorale amputatie of een transtibiale amputatie (n= 21) behandeld met titanium osseointegratie implantaten met 1 jaar follow-up. Eén persoon met een transtibiale amputatie ontwikkelde een septische loslating van het implantaat, waarvoor een transfemorale amputatie werd verricht, mogelijk gerelateerd aan diens vaatlijden. Eén persoon met een transfemorale amputatie liep een heup fractuur op proximaal van het osseointegratie implantaat waarvoor succesvolle operatieve fixatie plaats vond. Er ontstonden geen andere ernstige complicaties zoals bot-infectie, aseptische loslating of breuk van de intramedullaire steel van het implantaat. Infecties van de weke delen vonden het meest frequent plaats, met een absolute risico (AR) van respectievelijk 0.15, 0.29, en 0.43, voor personen met een standaard transfemorale, een zeer korte transfemorale, of transtibiale amputatie. In 91% van de gevallen volstond een behandeling met alleen orale antibiotica. Chirurgische revisie van de stomp was noodzakelijk bij één persoon met een zeer korte transfemorale amputatie, passend bij de

klinische ervaring dat personen in dit sub-cohort zich vaker presenteren met overtollige weke delen. In **hoofdstuk 4** worden veiligheids- en functionele uitkomsten beschreven bij een vijftal personen met een transtibiale amputatie op basis van vaatlijden, behandeld met titanium osseointegratie implantaten met 1 jaar follow-up. Er ontstonden 2 infecties van de weke delen, beiden succesvol behandeld met orale antibiotica. Andere complicaties vonden niet plaats. In **hoofdstukken 3 en 4** worden ook functionele uitkomsten vergeleken tussen het gebruik van een kokerprothese en een botverankerde prothese, vóór en na botverankerde prothese behandeling. In de studie van **hoofdstuk 3** werd een significante verbetering waargenomen van het prothese gebruik (vragenlijst voor personen met een transfemorale amputatie (Q-TFA) prothese gebruik score (PUS)) en kwaliteit van level (Q-TFA globale score (GS)) voor zowel het gehele cohort, als gestratificeerd per implantaat type/amputatie niveau. In **hoofdstuk 4** werd er een verbetering gezien bij alle vijf patiënten, alhoewel niet statistisch significant waarschijnlijk als gevolg van het kleine aantal patiënten, in het prothese gebruik (Q-TFA PUS), de kwaliteit van level (Q-TFA GS, korte formulier-36 gezondheidsvragenlijst (SF-36)), en de loopvaardigheid (6-minuten wandeltest (6-MWT), timed up and go (TUG)). Verder bleken alle personen hun botverankerde prothese te gebruiken bij follow-up, terwijl respectievelijk 16/90 (18%) en 3/5 (60%) personen in de studies in **hoofdstuk 3 en 4** geen prothese gebruikte vóór de behandeling en dus afhankelijk waren van loophulpmiddelen en/of een rolstoel. Beide studies toonden een acceptabel risico op complicaties in cohorten welke voorheen niet in aanmerking kwamen voor botverankerde prothese behandeling of waar nog weinig klinische ervaring van bekend was. Verder toonden de studies een evidente verbetering in de functionele uitkomsten en kwaliteit van leven na botverankerde prothese behandeling. In de toekomst dienden er studies met grotere cohorten plaats te vinden met een langere follow-up, om de veiligheid en effectiviteit van behandeling in deze sub-cohorten verder te bestuderen.

In **hoofdstuk 5** wordt een retrospectieve 5-jaars follow-up studie beschreven van de eerste groep patiënten behandeld in het Radboudumc waarbij veiligheids- en functionele uitkomsten worden gerapporteerd. Hierin werden 39 personen met een standaard niet-vasculaire transfemorale amputatie behandeld met een cobalt-chroom-molybdenum (CoCrMo) osseointegratie implantaat. Gedurende de follow-up periode ontwikkelden 4 personen 8 botinfecties (4/39= 10%), welke allemaal konden worden behandeld met behoud van het implantaat. Eén persoon ontwikkelde een asymptomatische distale aseptische loslating van het implantaat, wat vervolgd kon worden in de tijd zonder verdere aanpassingen. Intramedullaire steel breuk ontstond 2 keer (2/39= 5%), waarvoor beide implantaten werden gereviseerd naar titanium implantaten met een grotere diameter. Septische implantaat infectie kwam niet voor. Naast de twee revisies voor steel breuk werden er twee implantaten verwijderd op verzoek van patiënten op basis van hardnekkige therapieresistente pijn, zonder aanwijzingen voor infecties, waarvan er een werd herplaatst 7 jaar na het verwijderen op verzoek van patiënt. De meerderheid van de complicaties die voortkwamen waren minder ernstige complicaties van de weke delen. In

totaal ontstonden er 148 laag- en hooggradige infecties van de weke delen in 30 personen (30/39= 77%), waarbij 93% (138/148) conservatief behandeld kon worden. Stomp en stoma revisies waren 30 keer noodzakelijk bij 14 personen (36%) door recidiverende weke delen irritaties met infecties als gevolg. Verder ontstonden er 12 breuken van de externe component van het implantaten systeem (dubbelconus adapter), waarvan 10 beschouwd werden gevolg van een breuk van het veiligheidssysteem van de dubbel conus adapter. De meerderheid van de infecties in bot en weke delen vond plaats in de eerste 2 jaar na behandeling, waarna een afname in incidentie ontstond, hetgeen zorgen rondom infectie progressie van weke delen naar bot of implantaat wegneemt. Een significante verbetering van de Q-TFA PUS en GS werd vastgesteld na de behandeling met een botverankerde prothese na 5 jaar follow-up, wat het langere termijn behoud van de functionele winst aantoont ten opzichte van eerdere korte termijn follow-up studies. Deze studie bevestigt verder dat minder ernstige complicaties van de weke delen het vaakst voorkomen, terwijl ernstige complicaties minder frequent ontstaan.

In **hoofdstuk 6** wordt een vergelijkende studie gepresenteerd waarin een overzicht wordt gegeven van de veiligheidsuitkomsten van patiënten behandeld met een standaard transfemoraal press-fit osseointegratie implantaat. Het primaire doel van de studie was om te onderzoeken wat de invloed was van aanpassingen aan de chirurgische techniek en het implantaat ontwerp op de incidentie van frequent voorkomende complicaties van de weke delen, zoals infecties van de weke delen en stoma-gerelateerde problemen. Het secundaire doel was de rapportage van ernstige complicaties. Zodoende werden er 2 cohorten, met beide een 2 jaar follow-up, vergeleken op de verkregen behandeling: 1) originele chirurgische techniek en CoCrMo implantaat (n= 40), of 2) aangepaste chirurgische techniek (korter stoma kanaal, additionele weke delen resectie) en titanium legering implantaat (n= 39). Patiënten in groep 2 ontwikkelden minder infecties van de weke delen (13 vs 76 incidenten, AR 0.16 (95% betrouwbaarheidsinterval (BI) 0.09-0.31), vs 0.84 (95% BI 0.56-1.25, p<0.01), die behandeld konden worden met minder invasieve maatregelen en ontwikkelden minder vaak overtollig stoma weefsel (0 vs 5 incidenten, AR 0 vs 0.06 (95% CI 0.03-0.14), dan personen in groep 1. Deze uitkomsten stonden in contrast met de geobjectiveerde toename van wondinfecties, die ontstonden tussen operatie stap 1 en 2, na de implementatie van de behandel wijzigingen (groep 1 vs 2: 1 vs 11 wondinfecties, AR 0.01 (95% BI 0.00-0.08) vs 0.14 (95% BI 0.08-0.25), p= 0.02). Ernstige complicaties ontstonden niet in groep 2, terwijl 3 personen (3/40= 8%) 6 botinfecties ontwikkelden in groep 1, die allemaal behandeld konden worden met behoud van het implantaat. Deze studie toont aan dat de incidentie en ernst van frequent voorkomende weke delen complicaties aanzienlijk verminderd kunnen worden door aanpassingen van chirurgische techniek en implantaat ontwerp, alsook de leer-curve en ervaring van behandelaren. Deze aanpassingen gaan echter gepaard met een toename in incidentie van postoperatieve wondinfecties, mogelijk als gevolg van een toegenomen weke delen spanning over het implantaat in de aangepaste chirurgie techniek, hetgeen verder onderzocht moet worden. Aangezien wij de voordelen van behandel aanpassingen vinden

opwegen tegen de nadelen, wordt er in het kader van het verminderen van weke delen complicaties geadviseerd om een korter stoma met een stabiel weke delen manchet, in combinatie met een titanium implantaat na te streven.

In **hoofdstuk 7** werd een overzicht gegeven van de belangrijkste bevindingen en methodologische tekortkomingen van de studies en het onderzoeksgebied. Er worden verder aanbevelingen gedaan voor de toekomst van het wetenschappelijk onderzoek gericht op: 1) de noodzaak nieuwe vormen van falen te onderzoeken welke potentieel op de lange termijn voorkomen zoals aseptische loslating, periprothetische fracturen, of breuken van het implantaat systeem, 2) het verbeteren van de kwaliteit van data door het bundelen van data middels registers en door overeenstemmingen te creëren over de definitie, diagnose, en behandeling van complicaties middels een standaard uitkomst set, 3) het belang van een stapsgewijze zorgvuldige aanpak voor het uitbreiden van behandel indicaties en 4) de noodzaak om te reflecteren op eerdere ervaringen en fouten om de huidige behandeling te optimaliseren.

De inhoud van dit proefschrift toont dat de behandeling met een botverankerde prothese bij mensen met een beenamputatie die problemen ervaren met hun kokerprothese evidente voordelen oplevert in het kader van functie en prothese gebruik ten opzichte van eerder kokerprothese gebruik. Behandeluitdagingen zijn gerelateerd aan veiligheid, met een acceptabel risico op ernstige complicaties. De veelvoorkomende minder ernstige weke delen complicaties kunnen aanzienlijk worden verbeterd door aanpassingen aan de chirurgische behandeling en het implantaat en door toenemende ervaring van behandelaars. Een nieuwe behandeling zoals deze, met extreem veel potentie voor het verbeteren van de kwaliteit van leven voor een selecte groep personen en nog maar een fractie aan vergaarde kennis en ervaring, is het ideale onderzoeksveld om grote stappen te maken in de nabije toekomst. Dit is dan ook het volgende doel waar wij ons op zullen richten.

Data management and medical research ethics

Data management

The data gathered during this PhD project follow the Findable, Accessible, Interoperable, and Reusable (FAIR) guidelines. Data from all chapters was stored on the local servers of the Radboud university medical center and in a certified cloud-based Electronic Data Capture platform (Castor EDC). The study mentioned in **Chapter 4** was a multicenter study with a collaboration between the Radboud university medical center and the Australian osseointegration treatment group from the University of Notre Dame and Macquarie University in Sydney, Australia. For this study, data from Dutch patients was stored as mentioned above, while data from Australian patients was stored on local servers at the respective universities.

Published data generated or analyzed in this thesis are part of published articles, and the additional files are available from the associated corresponding authors on request. Data were anonymized and personal data were removed from the files once data was stored in Castor EDC, in order to protect the privacy of patients. All filenames, primary and secondary data and scripts used to provide the published results are documented along with the data, to ensure interpretability.

Datasets used and analyzed during these studies are available from the corresponding authors on request. Future research is only possible with health care purposes after approval.

Medical research ethics

All studies described in this thesis were conducted in accordance with the principles of the Declaration of Helsinki. The goal of all studies performed was to improve patient treatment and clinical care. The study described in **Chapter 2** was a literature review performed in the Radboud university medical center in which Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were applied for its report. The initial review protocol was registered in the International prospective register of systematic reviews (PROSPERO) database. The study in **Chapter 3** was a retrospective study with prospective functional data and was approved by the Radboud university medical center ethics committee (2014/196). The study in **Chapter 4** was a multicenter retrospective study which was approved by both human research ethics committees (Sydney: 014153S, Nijmegen: 2014/196). The studies presented in **Chapter 5 and 6** were retrospective cohort studies in which all patients gave their written informed consent, also agreeing to researchers contacting their general practitioner by telephone to gather additional adverse events data. The Radboud university medical center medical ethical review committee gave the approval to conduct both studies (**Chapter 5**: 2017-3769, **Chapter 6**: 2017-3767).

PhD portfolio of Robin Atallah

Department	**Orthopaedics**
PhD period	**01-08-2017 - 01-08-2023**
PhD Supervisor(s)	**Prof. M. de Kleuver, Prof. N. Verdonschot**
PhD Co-supervisor(s)	**Dr J.P.Frölke, Dr. R. Leijendekkers**

Training activities	Hours
Courses	
RIHS - Introduction course for PhD candidates (2018)	15.00
RU - Statistiek voor promovendi met SPSS (2018)	60.00
Radboudumc - eBROK course (for Radboudumc researchers working with human subjects) (2019)	26.00
Radboudumc - Scientific integrity (2020)	20.00
Courses Orthopaedic resident training (2016 - 2022) ATLS, ATLS refresher, AO basic principles of fracture management, AO Advanced, CASH-1, PACONU, Stralingshygiëne voor medisch specialisten, CCOC 1-2-3, Knieprothesiologie cursus, NVA arthroscopie cursus knie, NVA arthroscopie cursus schouder.	400.00
Additional courses Orthopaedic resident training (2019 - 2022) 8th Resident days on trauma Johnson & Johnson, Anterieure heup benadering cursus Johnson & Johnson, Schouderfracturen cursus "East Side" Radboudumc.	30.00
Conferences	
Poster presentations	
The use of osseointegrated titanium implants to treat transtibial amputees. ISPO 16th World Congress. Cape Town, South Africa 2017.	5.00
Osseointegrated transtibial implants in patients with vascular disease or diabetes. ISPO 16th World Congress. Cape Town, South Africa 2017.	5.00
Oral presentations	
Osseointegration for transtibial amputees (Osseointegration Symposium) OT World Congress. Leipzig, Germany 2018.	10.00
Reducing soft tissue complications of bone-anchored prostheses in individuals with a transfemoral amputation: a comparative consecutive cohort study. ISPO 17th World congress. Kobe, Japan 2019.	10.00
Reducing soft tissue complications of bone-anchored prostheses in individuals with a transfemoral amputation: a comparative consecutive cohort study. ISPO 18th World congress, Online edition 2021.	10.00
Safety and performance of osseointegrated bone-anchored prostheses in transfemoral amputees: a 5 year follow-up study. OT World congress. Leipzig, Germany 2022.	10.00
Have surgery and implant modifications been associated with a reduction of soft-tissue complications in transfemoral bone-anchored prostheses ISPO 19th World congress, Guadalajara, Mexico 2023	10.00
Safety and effectiveness of the bone-anchoring device for artificial limbs in individuals with transtibial amputation: A two-year follow-up study ISPO 19th World congress, Guadalajara, Mexico 2023	5.00
Radiological signs of osteoarthritis of hip and knee in lower limb amputees that apply for bone anchored prostheses ISPO 19th World congress, Guadalajara, Mexico 2023	5.00

Teaching activities	
Lecturing	
Hoorcollege/Werkgroep Complicaties in de fractuurgenezing/Osteoporose. Bachelor geneeskunde Radboudumc (2020)	5.00
Hecht en snijtechnieken onderwijs. Bachelor geneeskunde Radboudumc (2022)	5.00
Total	**631.00**

List of publications

International scientific publications

R. Atallah, D. Reetz, N. Verdonschot, M. de Kleuver, J.P. M. Frölke, R.A. Leijendekkers. Have surgery and implant modifications been associated with a reduction of soft-tissue complications in transfemoral bone-anchored prostheses? *Clinical Orthopaedics and Related Research*

D. Reetz, **R. Atallah**, J. Mohamed, H. van de Meent, J.P.M. Frölke, R.A. Leijendekkers. Safety and performance of bone-anchored prostheses in persons with a transfemoral amputation: A 5-year follow-up study. *Journal of Bone and Joint Surgery. American volume. 2020 Aug 5;102(15):1329-1335*

R. Atallah, H. van de Meent, L. Verhamme, J.P.M. Frölke, R.A. Leijendekkers. Safety, prosthesis wearing time and health-related quality of life of lower extremity bone-anchored prostheses using a press-fit titanium osseointegration implant: A prospective one-year follow-up cohort study. *PLoS One. 2020 Mar 9;15(3):e0230027*

R. Atallah, R.A. Leijendekkers, T.J. Hoogeboom, J.P.M. Frölke. Complications of bone-anchored prostheses for individuals with an extremity amputation: A systematic review. *PLoS One. 2018; 13(8):e0201821*

R. Atallah, J.J. Li, W. Lu, R.A. Leijendekkers, J.P.M. Frölke, M. Al. Muderis. Osseointegrated transtibial implants in patients with peripheral vascular disease: A multicenter case series of 5 patients with 1-year follow-up. *Journal of Bone and Joint Surgery. American volume. 2017 Sep 20;99(18):1516-1523.*

Other publications

R. Atallah, R.A. Leijendekkers, L. Verhamme, H. van de Meent, J.P.M. Frölke. Bone-anchored osseointegrated implants for transtibial amputees: Surgical aspects and implant design. *Orthopädie Technik 17/19.*

Conference proceedings

S. Rosenblatt, **R. Atallah**, W. Lu, J.J. Li, M. Al. Muderis. The use of osseointegrated titanium implants to treat trans-tibial amputees. Poster presentation at International Society for Prosthetics and Orthotics Conference: ISPO World congress. May 2017, Cape Town, South Africa.

R. Atallah, W. Lu. J.J. Li, R. Leijendekkers, J.P.M. Frölke, M. Al. Muderis. Osseointegrated implants in patients with peripheral vascular disease: A case series of 4 patients. Poster presentation at International Society for Prosthetics and Orthotics Conference: ISPO

World congress. May 2017, Cape town, South Africa. Conference Publication: paper number 249, page 104, May 2017.

R. Atallah. Osseointegration for transtibial amputees. Oral presentation at osseointegration symposium at Orthopädie Technic Conference: OT World Congress. May 2018, Leipzig, Germany.

R. Atallah. Osseointegration for transtibial amputees: Safety and clinical results of 2 different cohorts. Oral presentation at International Society for Prosthetics and Orthotics Conference: ISPO World Congress. October 2019, Kobe, Japan.

R. Atallah, D. Reetz, N. Verdonschot, M. de Kleuver, J.P.M. Frölke, R. A. Leijendekkers. Reducing soft tissue complications of bone-anchored prostheses in individuals with a transfemoral amputation: a comparative cohort study. Oral presentation at International Society for Prosthetics and Orthotics Conference: ISPO World Congress. November 2021, virtual edition.

D. Reetz, **R. Atallah**, J. Mohamed, H. van de Meent, J.P.M. Frölke, R.A. Leijendekkers. Safety and performance of bone-anchored prostheses in persons with a transfemoral amputation: A 5-year follow-up study. Oral presentation at Orthopädie Technic Conference: OT World Congress. May 2022, Leipzig, Germany.

R. Atallah, D. Reetz, N. Verdonschot, M. de Kleuver, J.P.M. Frölke, R. A. Leijendekkers. Have surgery and implant modifications been associated with a reduction of soft-tissue complications in transfemoral bone-anchored prostheses. Oral presentation at International Society for Prosthetics and Orthotics Conference: ISPO World Congress. April 2023, Guadalajara, Mexico.

J. Mohamed, **R. Atallah**, C. van Vliet-Bockting, J.P.M. Frölke, R. A. Leijendekkers. Safety and effectiveness of the bone anchoring device for artificial limbs in individuals with transtibial amputation: A two-year follow-up study. Oral presentation at International Society for Prosthetics and Orthotics Conference: ISPO World Congress. April 2023, Guadalajara, Mexico.

J. Mohamed, A. Wong, D Reetz, **R. Atallah**, H. van de Meent, J.P.M. Frölke, R. A. Leijendekkers. Radiological signs of osteoarthritis of hip and knee in lower limb amputees that apply for bone anchored prostheses. Oral presentation at International Society for Prosthetics and Orthotics Conference: ISPO World Congress. April 2023, Guadalajara, Mexico.

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About the author

Robin Atallah was born on the 8th of October 1993 in Saint-Mandé, France. At 1 years old he moved to Lebanon with his family where he grew up and finished his primary education. He moved to Hilvarenbeek, The Netherlands, with his mother and brother at the age of 10, where he started his secondary education at the Odulphus lyceum in Tilburg. After graduating in 2010, he went on to study medicine at the Radboud University in Nijmegen, acquiring his medical degree in 2016.

His interest in medical research was ignited during his master thesis, resulting in a research trip to Sydney, Australia, and amounting to a first publication, under supervision of his mentor dr. J.P.M. Frölke. This PhD trajectory was initiated in 2017, during the start of his clinical career as a medical doctor not-in-residency (ANIOS) at the department of orthopaedic surgery of the Radboud university medical hospital. He began the orthopaedic surgery residency program in 2018, following in his father's footsteps. He completed his clinical training in general surgery in the Canisius Wilhelmina Ziekenhuis (CWZ, Nijmegen) and continued his orthopaedics training at the Radboud university medical center (Nijmegen), the Sint Maartenskliniek (Nijmegen), and the Rijnstate hospital (Arnhem).

The work conducted during this thesis led to international collaborations and agreements, resulting in the introduction of a global "Special Interest Group for Bone-Anchored Limbs" (SIGBAL), by a primary initiation team, which he was a part of. Furthermore, he started a part-time fellowship in amputation care and osseointegration surgery at the AOFE clinics in 2022, next to his orthopedic surgery residency. He is currently working at the Sint Maartenskliniek and is in the final year of his residency program. Plans for the future include a residency rotation in the United States of America, the continuation of clinical care as well as research in the field of amputation and osseointegration, and applying for an arthroplasty fellowship.