Abstract

The limb amputation is one of the oldest surgical procedures performed and it still represents an event that drastically changes the life of an individual. Despite the technological progress, the difficulties related to the realization and daily use of the socket remain very common. Among the different technologies adopted in the prosthetic field, this project focused on the osseointegration technique. This technique consists in implanting a stem within the medullary canal of the amputated skeletal segment that extends outside the amputation stump with a prosthesis, later connected to the metal extension. The objective of this PhD project is to treat and to evaluate selected patients with osseointegrated prosthetic implants for the treatment of lower limb amputations.

Patients are recruited at the Rizzoli Orthopaedic Institute and at the Prosthesis - INAIL center of Vigorso (Budrio) during outpatient visits, while the surgical procedure is performed by the same expert surgeon in the II Orthopaedic and Traumatology Clinic of the Rizzoli Orthopaedic Institute. The project is still ongoing, to date three patients had completed both procedures, but due to various personal problems, just one of them is included in the analysis. This patient increased his percentage of prosthesis use and the level of mobility with an overall improvement of quality of live after the procedure.

The osseointegration technique represents a promising alternative method of treatment for amputees who are not satisfied with their socket prosthesis. In the coming years it will continue the collection of clinical, radiographic and kinematic data of subjects undergoing this procedure in order to perform a long-term monitoring of both clinical outcomes and quality of life.

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EVALUATION OF DEAMBULATION IN A PROTECTED ENVIRONMENT AND IN THE PUBLIC GREEN IN LIMB AMPUTATED SUBJECTS TREATED THROUGH A NEW OSTEOINTEGRATION METHOD

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Table of contents

Introduction

Limb amputation represents an event that drastically changes the life of an individual, limiting autonomy, quality of life and participation in daily life activities.
In developed countries the main cause of lower limb amputation is represented by vascular pathology. The prime reason for this is atherosclerosis, although up to a third of patients have concomitant diabetes. On the contrary, in developing countries, traumatic etiology linked to work accidents, road trauma and blast trauma in war scenarios is the most frequent cause [1, 2]. Another important cause, especially in young male subjects, is musculoskeletal tumors [3].
Although technological progress has allowed the realization of prostheses customized to individual needs, the difficulties related to the realization and daily use of the socket remain very common among patients with lower limb amputation and represent the main causes of dissatisfaction. In fact, pressure sores, skin abrasions from friction, excessive skin sweating, stump volume variations, lack of balance, and walking difficulties represent very frequent problems among amputee patients, who abandon the use of the socket, globally reducing their quality of life [4-10].
The osseointegration technique represents an alternative method of treatment for amputees with socket-related problems and low quality of life. This technique consists in implanting a stem within the medullary canal of the amputated skeletal segment that extends outside the amputation stump (Fig. 1 and Fig. 2). A prosthesis is later connected to the metal extension via a quick-connect system.

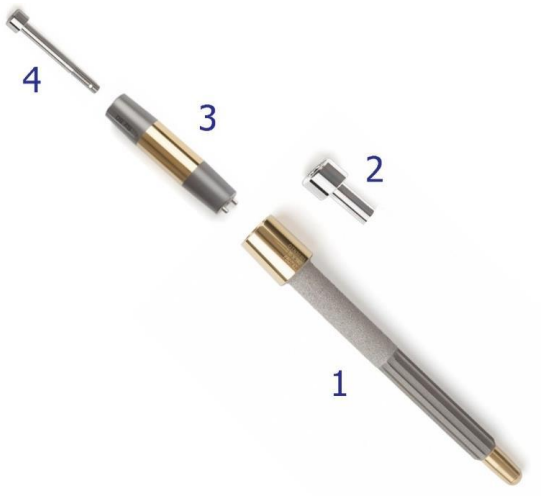

Figure 1 - The osseointegrated femoral prosthesis. From top to bottom: locking screw (4), double-cone transcutaneous adapter (3), press-fit femoral stem equipped with proximal screw (1). To the side: healing plug (2).

Figure 2 - Detail of the stem implanted inside the femoral medullary canal, connected to the adapter for attachment of the external prosthesis.

This technique was introduced in Sweden in the second half of the 90's by orthopedic surgeon Rickard Branemark. He based his work on the studies carried out by his father, a pioneer of dental implants, developing implants dedicated to major bone segments. These implants exploit the properties of the recipient's bone to grow within the micro-irregularities present on their external porous surface, a process that leads to osseointegration within the amputated bone [11].

The ability to attach the external prosthesis directly to the amputated skeletal segment has many advantages for the patient, including the elimination of the socket with all the associated skin problems, increased skeletal proprioception, and improved gait cycle efficiency, with increased walking speed and improved muscle control of the stump [5, 12-17].

However, osseointegration also has disadvantages that must be taken into account, such as possible infections of the skin stoma, which requires careful daily cleaning, and periprosthetic or implant fractures [18]. These disadvantages have generated much distrust in the scientific community in the use of osseointegration on a large scale, but with the right indications and following infection management protocols, this technique presents acceptable complication rates compared to the expected benefits.

Therefore, in recent years the interest in this technique has grown considerably, and more and more patients not satisfied with their socket are turning to our center asking to undergo this innovative surgical treatment, with the hope of regaining the autonomy lost after amputation.

Nowadays osseointegration surgery is performed in Sweden, Holland, Germany, Australia and North America.
Thanks to the Me.Ta.COs research project, the result of a collaboration between the IRCCS Istituto Ortopedico Rizzoli, the University of Bologna and the INAIL Prosthesis Center of Vigorso di Budrio, the osseointegration technique has been introduced in Italy. After the enrollment and the treatment of first three patients, the procedures have been started so that this surgical treatment, currently executable only abroad and within research projects, can be recognized by the Italian National Health System or at regional level as normal clinical practice, giving the opportunity to many patients to undergo the procedure for free.
The aim of this PhD thesis is to describe the experience gained with this treatment, which has led to the drafting of surgical, ostomy management and rehabilitation protocols. It will be also presented a case report with the functional results obtained by one of the patients who underwent surgery for osseointegrated prosthesis for transfemoral amputation at the II Orthopaedic and Traumatology Clinic of the Rizzoli Orthopaedic Institute.

The osseointegration technique applied to the prosthetic world

The concept of osseointegration was introduced at the end of the 50s by the Swedish researcher Per-Ingvar Brånemark, who defined it as "a direct, structural and functional connection between the bone tissue and the surface of an implant able to support the body weight". Subsequently, this definition has undergone changes, enriching its content: "[...] where there is no relative movement between the implant and the bone tissue with which it is in direct contact". It is a surgical technique that requires a suitable post-operative period, in order to allow the optimal growth of the bone around the implant, and it requires also an equally adequate load control in the first period of use, ensuring the primary stabilization of the implant. Bone remodeling, which occurs in the early stages of post-surgical rehabilitation, allows for secondary stabilization of the prosthesis and ensures optimal body weight loading [19]. Osseointegration represents a viable alternative for patients who are unable to walk with a normally fitted prosthesis, ensuring safety and functionality in use [5, 12].

Osseointegration history

The history of osseointegration began in the 1950s, when Swedish researcher Per-Ingvar Brånemark, during studies on microcirculation, discovered that titanium cells, which he had previously implanted in the tibia of some rabbits, were firmly integrated within the bone, without soft tissue reactions or rejection.

This unexpected discovery led Brånemark to consider exploiting titanium implants in the field of orthodontics and, specifically, in the intraosseous anchoring of dentures. His intuition turned out to be correct and, after experiments on animals, dental implants were applied for the first time on humans in 1965.

The application of the osseointegration technique in the treatment of subjects with major amputations began in the '90s, by the son of Per-Ingvar Brånemark, orthopedic surgeon Rickard Branemark, who later became Director of the Center for Orthopedic Osseointegration at Sahlgrenska University Hospital in Gothenburg, Sweden. He and his team of collaborators initiated a study of the biomechanical properties of osseointegrated implants first in rats, then in rabbits, dogs and finally in humans [20].

Thus, the first prosthesis for limb osseointegration (OPRA - Osseointegrated Prostheses for the Rehabilitation of Amputees) was born, consisting of a module implanted inside the intramedullary canal (femoral stem) and an external transcutaneous segment, fixed to the stem by a screw (Fig. 3).

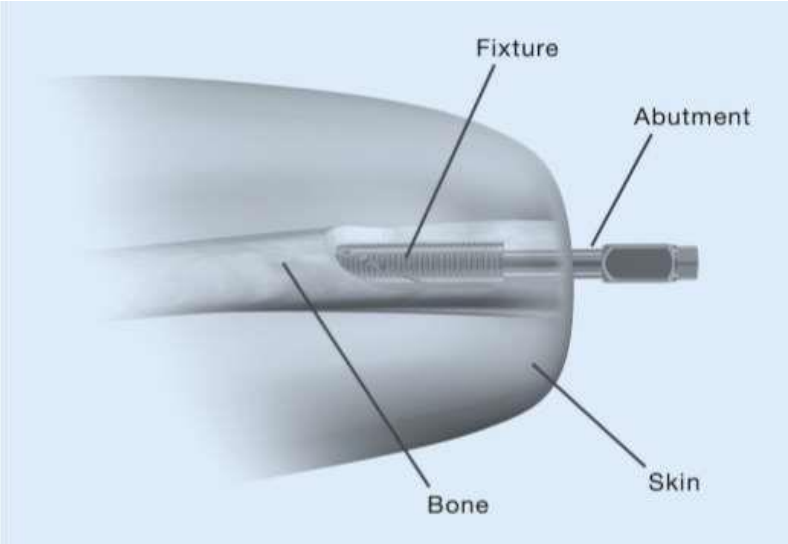

Figure 3 - Explanatory diagram of the first Swedish OPRA implant system. The three main components are the femoral stem (fixture), the external adapter (abutment) and the locking screw (abutment screw).

The first patient to undergo osseointegration surgery was a 25-year-old woman who had undergone bilateral transfemoral amputation following an accident. The first step of the treatment was held on May 15, 1990, and consisted in the implantation of the stem inside the femoral canal of the amputation stump; six months later, once the osseointegration was completed, the second surgical step was performed in which the ostomy was created and the transcutaneous connector was implanted. One year later, the same surgery was performed on the contralateral limb. After completing the rehabilitation course, the woman was able to walk again with crutches (Fig. 4).

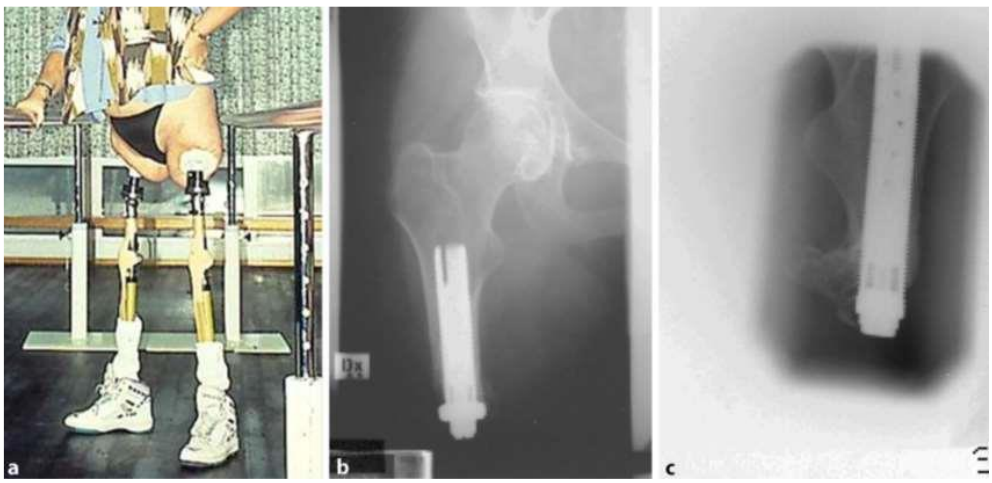

Figure 4 - Pictures of the first patient undergoing bilateral trans-femoral osseointegration surgery (a) and related radiographic images of the first prosthesis used (b and c). At the time, the implants used had a modular design, with a distal collar.

Evolution of implants and surgical technique during the 1990s

The rationale for the first osseointegrated limb prosthesis echoed the concepts of osseointegration of dental implants.
Unlike previous implants used at the oro-cranio-facial level, limb prostheses were found to be at risk of increased mechanical stress, both during movement and during any accidental falls. In addition, the action of the muscles throughout the normal daily activities made the skin around the implant constantly subject to stress in traction and rotation.
From the beginning, the problems related to the implant, in particular inflammations and infections of the ostomy, were evident. In addition to the main problems, which are still being studied today, the first implants were more prone to fatigue failure as a result of the loads they had to bear.
In the following years, in addition to the design of the implant, the surgical technique has been considerably improved concerning, for example, the management of the stump. An ad hoc technique was developed for the preparation of the skin flap that surrounded the site of the ostomy and it was decided to minimize the volume of the soft tissues in contact with the apex of the bone stump. In this way, a reduction in the infectious risks related to the implantation was achieved [20].
Along with the evolution of the surgical technique, guidelines for the rehabilitation of patients undergoing osseointegration were also drawn up.

Types of intramedullary implants in osseointegration prostheses

To date, there are two different designs of osseointegrated prostheses: screw type or press-fit.

Implant with screw fixation

Inspired by the design used for dental implants, the implant with screw fixation was developed in Sweden and used for the first time in 1990; since 1998 a standardized protocol for the surgical procedure and for the management of rehabilitation has been developed, which has allowed its diffusion in Europe and other continents.
It consists of an intramedullary titanium implant (called "fixture") 80 mm long, in the shape of a cannulated screw, which is inserted into the medullary cavity; 6 months after the first surgical treatment, time that is necessary for osseointegration to occur, this screw is connected to a titanium transcutaneous adapter (abutment) (Fig. 5) [11].

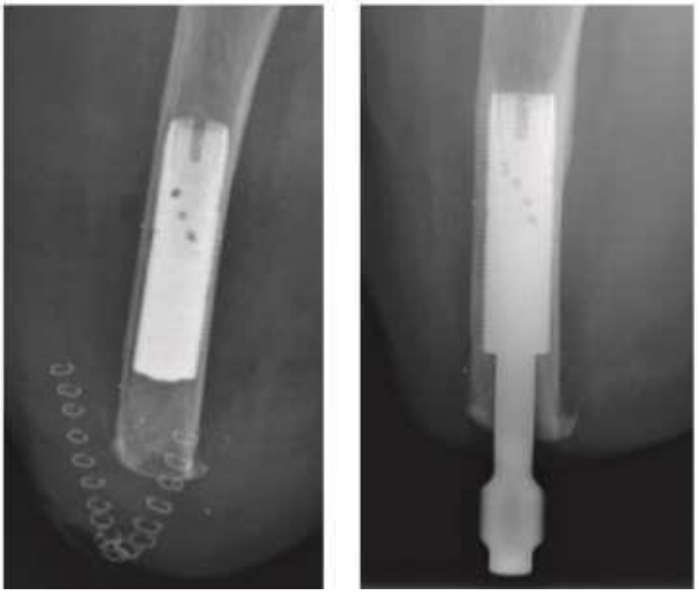

Figure 5 - Screw implant after the first (left) and after the second surgical step, with transcutaneous connector insertion (right).

After the second step, the patient begins the rehabilitation protocol, which involves gradual loading of body weight onto the prosthesis and lasts a total of six months. Gait training begins approximately 12 weeks after the second surgical step, but for an additional 3 months, walking with the support of two crutches is recommended [18].
It has been demonstrated that, with this implant, osseointegration occurs with an on-growth bone growth (i.e., on the external surface of the stem rather than within the macroporosity of the stem itself) rather than in-growth [21], and that the threaded design ensures an excellent primary stability, at the expense of a greater sacrifice of bone tissue and a non-physiological distribution of loads that leads to an accelerated bone resorption around the stem [22-24].
In fact, follow-up studies, performed by static radiostereometric analysis (RSA), have demonstrated the presence of areas of bone resorption in the distal part (with narrowing of the cortical) and in the intramedullary one (in the portion of the bone in contact with the prosthesis). Foci of *cancellization* (increase in the porosity of the cortical surrounding the fixture) were observed in the medial portion of the diaphysis, at the proximal end of the implant, mostly two years after surgery. However, no implant showed a progression of these phenomena at five years of follow-up [25].
However, these features prompted the development of alternative solutions that would facilitate osseointegration and spare the available bone tissue.

Implants with press-fit fixation

Implants with press-fit fixation consist of a stem (made of titanium or cobalt-chrome-molybdenum, depending on the type of implant), 140 to 180 mm long, with slight curvature and a macroporous surface [26]. This implant has been developed in Australia

and the Netherlands [18] and has reduced osseointegration time compared with the screw-type implant. In addition, the press-fit system facilitates in-growth bone growth.

Endo-Exo-Femurprosthesis/ILP (Integral Leg Prosthesis)

The first model to be produced was the Endo-Exo-Femurprosthesis/ILP (Integral Leg Prosthesis), which consists of a molybdenum-cobalt chromium alloy covered with a 1.5 mm thick macroporous metal surface that reduces the femoral stem diameter by 3 mm. The diameter of the pores covering the surface is around 300-1500 micrometers [21].
The design of this prosthesis, from the 1990s to the present, has evolved with the aim of improving its functionality and safety:

- ✓ Design A (Fig. 6a): consists of two main components, namely the intramedullary module and the transcutaneous connector, both made of a cobalt-chromium alloy. This implant has a third component, a flange with holes for the screws that externally covers the femur and acts as a support for the anchorage of the prosthesis to the bone, a device considered useful to prevent breakage due to implant fatigue. The surface of the stem is covered by a structure called "spongiosa-metal 2", designed to promote the adhesion of skin and bone, creating a physical barrier against infections from the external environment. However, this surface proved to be the cause of mechanical abrasion and irritation to the skin and soft tissues, responsible for phenomena of hypergranulation of soft tissues that required surgical debridement. These phenomena hindered the creation of a stable ostomy [27];
- ✓ Design B (Fig. 6b): the surface consisting of the "spongiosa-metal 2" was removed in the distal portion in order to avoid ostomy irritation. The fixation holder was shortened. The diameter of the connector has been reduced;

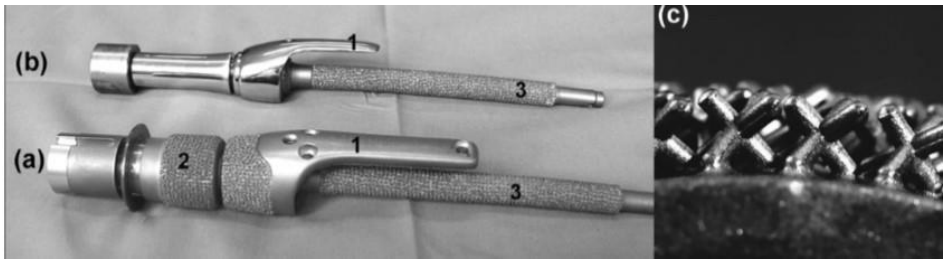

Figure 6 (a and b) - Design A (a) and design B (b) compared. 1= support for anchoring the prosthesis to the bone; 2= distal portion of the implant; 3= intramedullary stem. (c) detail of the "spongiosa-metal 2".

✓ Design C (Fig. 7): Introduced in 2009, it represents the final evolution of the ILP, and was used until 2013. The fixation support was eliminated and the connector was shortened. The surgical technique was also modified: shortening the connector allow the soft tissue layer at the apex of the stump to be contained. Both the connector and the distal portion of the stem were covered with a non-abrasive ceramic of titanium oxynitride and niobium ([Ti,Nb]ON). This coating prevents skin and soft tissue abrasion

and, combined with proper stump hygiene and improved surgical technique, limits bacterial biofilm formation. In addition, the corrosion-resistant coating allows for less release of metal ions into the peri-prosthetic soft tissue, preventing allergic or sensitization reactions [27].

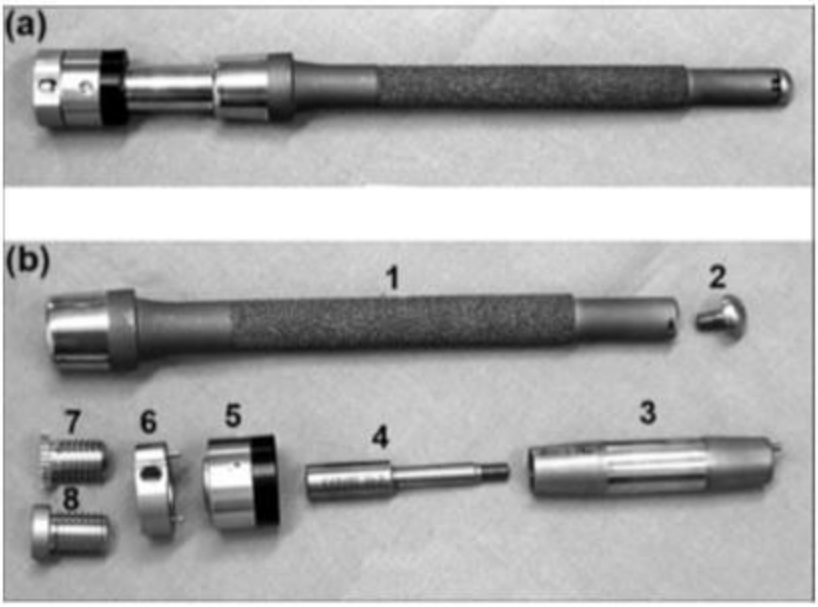

Figure 7 - Design C assembled (a) and disassembled (b). 1= femoral stem; 2= temporary cover screw; 3= dual-cone adapter; 4= security screw; 5= cover 6= rotating disc and temporary screw (to be used until final prosthesis is completed); 7= helix screw; 8= temporary screw.

This implant was considered as an effective and safe alternative for lower limb stump reconstruction. However, it was shown that the pore distribution in the macroporous coating surface promoted distal resorption of the bone stump, due to stress-shielding [21].
Another critical point of this implant is the stem length, which does not fit shorter stumps: the minimum femoral residual stump length should be about 12-15 cm.

OPL (Osseointegrated Prosthetic Limb)

After about 15 years of use, to overcome the numerous episodes of stem failure and distal bone resorption, the ILP implant has been progressively abandoned and replaced (since 2013) by the OPL (Osseointegrated Prosthetic Limb) implant, with the aim of improving outcomes in terms of bone integration [28]. The OPL implant is made in Italy (by Permedica S.p.a., Merate LC).
The proximal portion (80 mm long) of the intramedullary portion has a smooth surface, crossed longitudinally by several sharp tabs (protruding about 1 mm from the implant surface), created to ensure primary rotational stability. The distal portion (length: 80 mm), on the other hand, is wider at the apex, in order to support axial stability. The stem is manufactured from a rough titanium alloy, covered with a surface of plasma-sprayed hydroxyapatite: this solution facilitates the penetration and anchorage of the bone to the prosthetic implant. These features are designed to facilitate distal cortical thickening

and in-growth of bone. In addition, the titanium alloy possesses characteristics that more closely approximate the elastic modulus of the skeletal structure.
The double-cone adapter represents the portion that connects the intramedullary stem to the external prosthesis. It consists of a polished surface coated with titanium and niobium dioxide to minimize soft tissue adhesion. Its proximal part is equipped with a safety "pin", designed in such a way as to yield under excessive tension forces, safeguarding the bone from periprosthetic fractures and/or the implant from possible breakage.
The standard length of the implant is 160 mm (implant designed for transfemoral amputees). Two variants have been developed:

- ✓ OPL type A: the distal portion of the stem is extramedullary and made of polished niobium (Fig. 8a);
- ✓ OPL type B: the distal portion of the stem remains intramedullary. It is used in distal femur amputations (thus with a longer residual stump) (Fig. 8b).

In cases where the residual femur is shorter than 160 mm (or if the amputation is transtibial), a custom-made prosthesis is applied, stabilized by fixation screws to ensure adequate primary stability (Fig. 8c, d, e). This type of implant is covered with a 0.5 mm 3D macroporous net coating, which allows for rapid osseointegration.

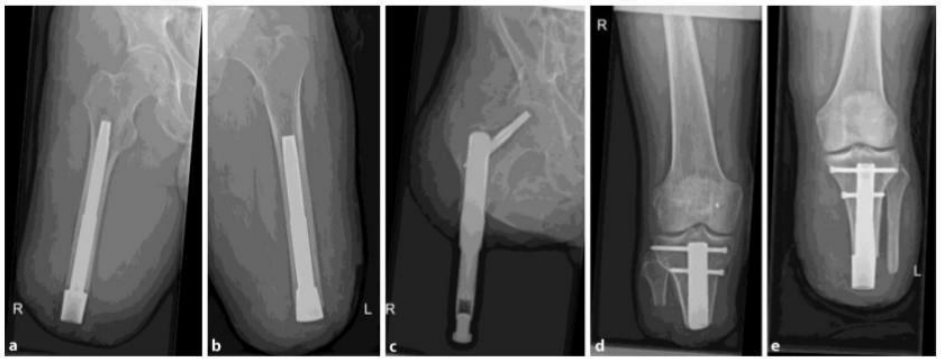

Figure 8 (a and b) - Example of OPL plant variants: OPL type A (a), OPL type B (b) and custom-made plant (c, d, e).

In contrast to the screw-type implant, the interval between the first and second surgical steps is reduced to 6-8 weeks (for both IPL and OPL). Full load on the operated limb is granted as early as 8-12 weeks after the second surgical step [5,27].
The OPL implant maximized the benefits of an osseointegrated implant, implementing the quality of life and motor functions of the amputee and minimizing undesirable effects. It uses innovative features in the surface design and geometry of the implant, which are essential to achieve satisfactory long-term results. The progressive strengthening of the bond between the prosthesis and the bone is guaranteed, preventing loosening of the implant [21].
The short-term infection risks (in terms of prevalence and severity) of OPL implantation are comparable to those reported in ILP, an implant with longer follow-up.

In any case, the lack of data with long-term follow-up for the OPL implant prevents it from being considered as the best choice for amputees.

Advantages and complications associated with osseointegration implantation

Advantages

The advantages of osseointegrated prostheses over traditional socketed prostheses consist of:

- ✓ Elimination of skin rubbing on the socket support points, which are responsible for the most common pain phenomena [14].
- ✓ Elimination of problems associated with difficulty in fitting the socket, providing a quick and comfortable method of attaching the prosthetic limb [12, 15];
- ✓ Management of body weight loading in a more physiological manner;
- ✓ Improved degree of proximal joint motion relative to the level of amputation [5, 20, 29-30];
- ✓ Restitution of direct sensory feedback through skeletal proprioception, making possible better patient control of the prosthesis [5, 17, 29];
- ✓ Improved gait quality and speed [5];
- ✓ Improvement in the subject's autonomy, time of use of the prosthesis, and walking distance [29-30];
- ✓ Ability to sit more comfortably, making it easier to use public and private transportation and attend crowded public places [29-30];
- ✓ Reduction of pain in the spine and contralateral limb, often present in patients using a socketed prosthesis [13];
- ✓ Improved quality of life and overall well-being, with increased patient self-esteem [29-30].

Complications

Several articles have been published in the literature reporting the risks and potential adverse effects associated with osseointegration surgery. These data have allowed the optimization of patient inclusion criteria and preventive measures to be taken according to the different risk categories [29].

The most common adverse effects are at related with the ostomy, i.e. the circular opening of the skin that allows the passage of the transcutaneous adapter, allowing the connection between the intramedullary implant and the external prosthesis. In particular, multiple cases of irritation (hypergranulations caused by rubbing of redundant soft tissues) and superficial infections have been reported (Fig. 9) [19, 31].

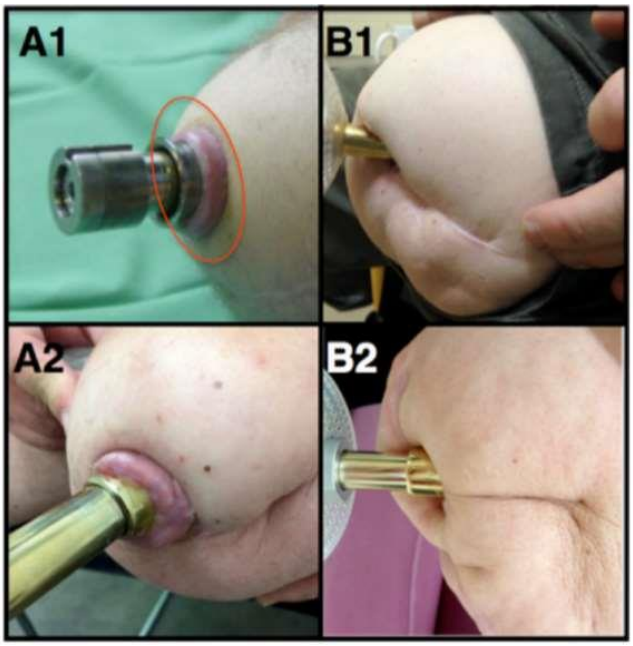

Figure 9 - Typical appearance of ostomies with hypergranulation (A1 and A2) and ostomies with soft tissue redundancy (B1 and B2).

Other adverse effects involve the osseointegrated implant and the amputated limb. The most serious complications reported were:

- ✓ Inadequate osseointegration of the intramedullary prosthetic implant, with necessary replacement of the femoral stem with one of larger diameter or, in severe cases, removal of the same;
- ✓ Fracture and replacement of the double cone adapter or clamping screw;
- ✓ Fractures of the proximal femur;
- ✓ Deep infections.

Deep infections represent the most important complication, involving long-term treatment with one or more antibiotics in combination; in some cases, surgical treatment is required, but rarely there is a need to remove the implant. Cases of implant failure due to infection have occurred in patients in whom an infection was known to exist prior to osseointegration surgery [19].

Rarely, in very active subjects, the transcutaneous adapter had to be temporarily removed because of problems generated by friction between the soft tissues of the ostomy and the implant.

Regarding mechanical complications, breakage or damage of implant components have occurred mainly as a result of overloads applied to the prosthesis, for example, following an accidental fall; usually, the presence of safety pins causes loosening of the transcutaneous adapter without causing bone fractures and safeguarding the osseointegrated stem [29].

A Body Mass Index (BMI) greater than 25 and muscular hypotrophy of the residual limb are among the primary underlying causes of soft tissue overgrowth around the ostomy. Proper management of soft tissue around the ostomy helps prevent these issues. In addition, implantation of a medullary stem that is too small in diameter relative to the

patient's BMI and activity level can lead to a delay in osseointegration, leaving part of the stem uncovered and leading to an increased risk of stem fracture [29].
The impact on patients' quality of life following complications was investigated by questionnaires. It was found that, in each case, these events were not a source of major problems [11].
The few cases of serious adverse events confirms that the risk-benefit ratio is in favor of the treatment [29].
It is possible, especially in the immediate postoperative period, that the patient cannot accept the appearance of the ostomy. In this case, a psychological support and the possibility to confront with other patients who have faced the same path is helpful.

Classification of infections

The causes, prevalence, and types of recurrent infections in the osseointegration technique have, in the past, already been extensively described in studies related to dental implants [29].
The titanium implant used for osseointegration seems to prevent more infections than other materials used in internal prostheses [32].
Infections are divided into four classes according to the level of severity and are classified according to clinical conditions and radiographic examinations; precise signs and symptoms correspond to each classes [29, 32] (Tab. 1) (Fig. 10):

- ✓ Low-grade infections (87% of total events): present with signs of inflammation, such as redness, swelling, warm, swollen skin, and stinging pain that increases with body weight load (1A-1B-1C);
- ✓ High grade infections: are characterized by the presence of purulent collections and/or secretions and elevated C-reactive protein values (2A-2B-2C);
- ✓ Bone infection: diagnosed by radiographic findings of osteitis or osteomyelitis (3A-3B-3C);
- ✓ Implant failure due to septicemia: detectable radiographically (4).

Table 1 - Classification of infections in transfemoral osseointegrated prostheses and their treatment.

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

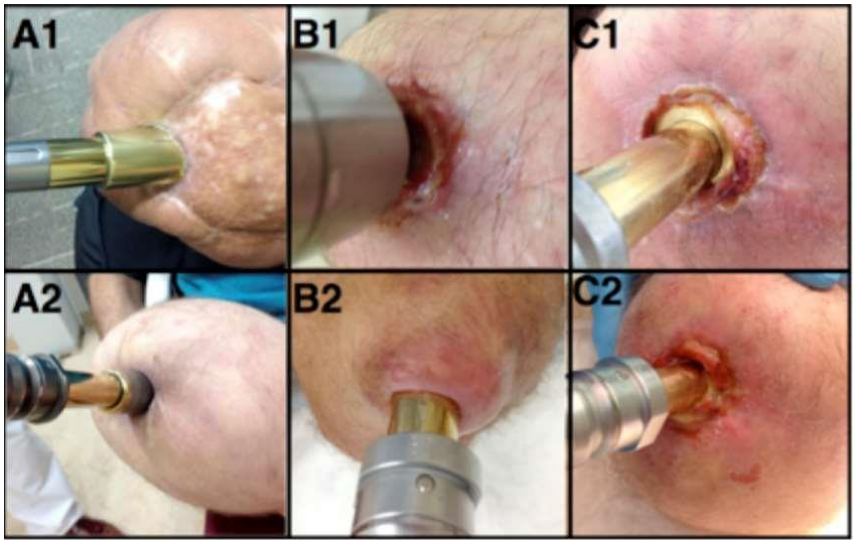

Figure 10 - Typical appearance of normal ostomies (A1 and A2), with grade 1 infection (B1 and B2) and with grade 2 infection (C1 and C2).

The first two levels of infection represent the complications that occur most often. Implant removal due to septic problems, on the other hand, is a rare event. Most infections cause only a temporary functional limitation in the patient.

Osteomyelitis is defined as an infection of the bone tissue around the implant and/or the spinal canal, supported by the finding of positive bone biopsies or bone marrow aspirates on tissue culture infection test; it can be classified as definite, probable, or possible [32]. The definition is based on the same diagnostic algorithms used for prosthetic joint infections. It is well established that spinal canal contamination can occur during double-cone adapter replacement as a result of pressure on the implant. The presentation of osteomyelitis may be acute, subacute, or chronic and may occur with or without fistulas.

Depending on the severity of the picture, different therapeutic solutions are indicated [29]:

a) Cycle of oral antibiotics (if they do not prove effective, proceed to point "b");
b) Parenteral course of antibiotics (if not effective, proceed to point "c");
c) Surgical cleaning;
d) Prosthesis removal, a treatment limited to cases of sepsis that do not benefit from a course of parenteral antibiotics.

The episode of infection should be identified as early as possible, differentiating it from other causes of pain (eg, muscle pain or phantom limb pain). Usually, pain at rest should be considered a sign of infection and therefore deserves further investigation.

It is recommended to perform a bacterial culture for each new diagnosis in order to set up treatment with the most sensitive antibiotic. Preparations are obtained from percutaneous biopsies or bone marrow aspirates [32-33], while cultures on peripheral blood are, usually, not considered. Staphylococcus Aureus infections appear to be more common than other coagulase-negative staphylococci and enterococci.

Clinical improvement does not always correspond to actual recovery from the infection. Infections are considered resolved if the patient has no symptoms for a period of 12 months after discontinuation of antibiotic therapy.
If the patient does not respond to antibiotic therapy, a deep infection should be suspected and further examinations, such as ultrasound (to detect purulent collections), CT, and other nuclear diagnostic examinations, should be performed with protocols similar to those used in arthroplasty infections [29].
Surgery consists of tissue debridement or prosthesis removal and is followed by intense antibiotic treatment. Prosthesis removal is only indicated if the patient does not respond to any conservative treatment, or if there are clear signs of implant loosening.
In addition, it would seem that smoking habits and female sex are correlated with a greater occurrence of severe infections, which is why it is useful to take these characteristics into account during the visit prior to surgery. Other factors to consider are Body Mass Index (BMI), diabetes, and patient age.
Regarding the pain, it has been found that phantom limb syndrome is the main reason for prosthesis nonuse. Often, the adoption of an osseointegrated prosthesis was not able to modify either phantom limb pain or low back pain reported by patients [30].
In addition, studies investigating the safety level of the osseointegrated prosthesis in competitive sports activities are still ongoing and remain discouraged at this time.

Candidate patient characteristics

Generally, patients who are candidates for trans-femoral osseointegration surgery are recovering from amputation as a result of trauma, tumor, infection, or congenital defect [29].
Patients who come to the physician's attention complain of socket-related skin problems and various complaints of the amputated limb [5, 29, 34].
It is necessary to identify which of these patients have problems that cannot be resolved with a classic socket and who may be good candidates for osseointegration surgery.
The patient is then evaluated by a multidisciplinary team consisting of orthopedists, physiatrists, orthopedic technicians, and psychologists. The evaluation consists of a clinical examination in which the shape and trophism of the stump, the presence of irregular scars, skin abrasions at the points of contact with the socket, the presence of neuropathic or phantom limb pain are evaluated. In addition, an interview is performed in which anamnestic data are collected, data related to the autonomy of the subject, the prosthetic model used and finally, an interview with a psychologist is performed to investigate the attitudes, and motivations of the subject.
In particular, with regard to the use of the prosthesis, the patient is submitted to a questionnaire for subjects with transfemoral amputation (Q-TFA), with which the use of the prosthesis is investigated in terms of quality and time of use, the degree of mobility allowed by the classic prosthesis with socket, the problems related to it and the general condition of the patient [5, 26, 31, 35]. If the subject is unable to wear the prosthesis for more than 50 hours per week and to travel more than 2 kilometers per day, he or she may be a good candidate for osseointegration surgery [5].

Regarding quality of life, the subject is asked whether:

- ✓ Perceives the prosthesis as unreliable, so he feels unsafe while wearing it;
- ✓ Experiences discomfort in sitting while wearing the prosthesis;
- ✓ Complains of skin irritation, chafing, or ulcers related to wearing the prosthesis;
- ✓ Frequently experiences problems with sweating or heat sensation from the stump;
- ✓ Considers these problems, related to socket prosthesis use, to have a significant impact on quality of life.

If the subject answers yes to at least four of the previous seven questions, the osseointegration procedure could bring real benefit to the patient [5].

Exclusion criteria

It is important to ascertain the quality of the socketed prosthesis and the patient's reasons for undergoing the procedure. The orthopedic surgeon (or physiatrist) examines the prosthesis worn by the patient. In the event that the subject's performance is limited due to manufacturing and alignment errors of the external prosthesis, or any error that makes the prosthesis inadequate, it is advisable to first seek a solution other than osseointegration surgery [5].

In addition, in the newly amputee patient, it is advisable to first complete the rehabilitation course involving the use of the classic socketed prosthesis [26].

The absolute exclusion criteria for a standard trans-femoral osseointegrated prosthesis are as follows [5, 19, 21, 29, 31]:

- ✓ Residual amputated limb with a length (measured from the small trochanter to the apex of the stump) less than 15 cm;
- ✓ Uncontrolled diabetes;
- ✓ Cause of amputation related to vascular disease, a possibility that precludes surgery because of increased risk of infection;
- ✓ Radiation treatments on the amputated limb;
- ✓ Ongoing chemotherapy treatments;
- ✓ Positive history of cognitive or psychiatric problems;
- ✓ Poor compliance in following the rehabilitation protocol and follow up program;
- ✓ Inability of the individual to abstain from cigarette smoking or drug use;
- ✓ Current pregnancy;
- ✓ Age <18 years or >70 years;
- ✓ Bone maturity not yet reached (developing subject);
- ✓ Skin disease affecting the amputated limb;
- ✓ Ongoing treatment with corticosteroids or other medications that may compromise successful surgery or post-operative care;
- ✓ Immunosuppression.

In addition to these criteria, there are others that do not necessarily preclude surgery but that should be deeply considered:

- ✓ Doubts by the patient about undergoing surgery;
- ✓ Phantom limb pain, for which osseointegration surgery would not lead to resolution;
- ✓ Body Mass Index (BMI) >25 kg/m2.

Tests used in patient study

The tests generally used for the evaluation of subjects with trans-femoral amputation, allow to compare the results related to the quality of life and the performance achieved by the patients, before and after the prosthetic treatment. The same tests are used in the remote study of subjects with osseointegrated prostheses.
In the latter case, each test is administered pre- and post-operatively, during the follow-up visits. It is also investigated the possible occurrence of adverse effects related to the implant.
Follow-up visits are scheduled at 3, 6, 12 and 24 months after the second surgical stage [19]; studies performed in Europe up to 8 years of follow-up are also available.
During the visits, the same examinations are always repeated, in order to be able to evaluate the progress of the individual patient and record the results over time.

Quality of life questionnaires

Most of the results in this area are obtained through self-completed questionnaires. There are several questionnaires that can be used for this purpose, but the two most commonly used (because they are considered valid and reliable) are the Q-TFA and the SF-36.

Questionnaire for Transfemoral Amputation

The Questionnaire for Transfemoral Amputation, or Q-TFA [19, 30, 34], was designed in Sweden in order to investigate the quality of life of patients with an above-knee amputation. Currently, it is available in Swedish and English. Since it was initially conceived only for those using a socketed prosthesis, Brånemark himself included two questions specifically concerning osseointegration [19].
This questionnaire is structured in four sections, each of which has a score that can be expressed as a percentage:

- ✓ Patient's overall health status (0 to 100);
- ✓ Prosthesis use (from 0 to 100, where 0 means that the prosthesis is never used, while 100 means that it is used every day, for more than 15 hours per day), measured in hours per week;
- ✓ Level of mobility achieved by the patient with the prosthesis (0 to 100);
- ✓ Problems related to the prosthesis (in this case the score ranges from 100 to 0).

The two questions included specifically for osseointegrated patients relate to:

- ✓ To the impact on quality of life related to skin problems arising in the area of the ostomy;
- ✓ The fear felt by the patient regarding the possibility of incurring complications related to the surgery.

Summarizing, this test allows to analyze not only the quality of life, but also the level of use and satisfaction of the patient regarding the prosthesis provided. Moreover, it allows to have an idea of the degree of movement of the person; being a self-completed test, of course, it does not allow to collect data through repeatable measurements, but it allows to understand the level of autonomy perceived, in first person, by the subject.

Furthermore, in subjects who are candidates for the treatment, the results help to identify who is suitable, or not, for such treatment [26].

Short Form Health Survey

The SF-36 health questionnaire [19, 30, 34, 36] is a generic test that investigates the subject's perceived level of physical and mental health. It consists of:

- ✓ SF-6D (health status from 1, full health, to 10, death);
- ✓ PF (physical functioning);
- ✓ PSC (physical component score).

It too provides a score from 0 to 100 for each of the 8 subcategories, directly proportional to the level of quality of life reported. In addition, this test also allows to investigate the level of pain felt by the patient.

It is designed so that it can be applied to the general population and is not specific to amputee patients.

Euro quality of life - 5 Dimension (EQ-5D-5L)

This questionnaire measures the perceived quality of life in 5 domains that are assigned a score ranging from 1 (best possible result) to 5 (worst possible result): mobility, self-care, daily activities, pain/concern and anxiety/depression. These are then joined by a domain related to general health ranging from 0 (worst possible health) to 100 (best possible health). It is shorter and more general than the SF-36 and, for that reason, is easier to use [37].

Functional level test

Most studies assess walking ability using one or two of the following tests. The most commonly used are the Walk Test and the Timed Up and Go test.

6 minutes' walk test

The 6-Minutes' Walk Test (6MWT) [30, 36, 38] assesses the distance (expressed in meters) that the subject is able to walk in six minutes. It is not a specific test for orthopedic patients, but it allows an effective study of the functional status and autonomy of the patient. The execution is very simple: before starting the test, the patient's anamnesis is collected (age, sex, BMI, concomitant pathologies) and the vital parameters are measured. The subject is asked to walk at the maximum speed possible for him for six minutes on an unobstructed walking surface, along a straight path. The subject may stop whenever deemed necessary. At the end of the test, the distance covered is recorded in meters, the vital parameters are measured again and the subjective perception of breathlessness (dyspnea), and the subjective perception of fatigue are recorded, using the Borg scale. In addition, the number of stops lasting >5 sec are recorded.

Timed Up and Go (TUG)

Again, this is not an exclusive test for orthopedic patients. The TUG [30, 36] is a simplified version that is faster to perform than the 6MWT. It is measured in seconds. Patients are

asked to stand up from a chair, walk a distance of 3 meters, turn around, repeat the reverse path back to the chair, and sit down again. In amputee patients, this test allows assessment of mobility while walking and balance while changing direction and sitting/standing up from the chair.

Amputee Mobility Predictor

The Amputee Mobility Predictor (AMP) [36, 39] is a quick and easy to perform test that allows the study, from a functional point of view, of the mobility status of a patient with a lower limb amputee (not only transfemoral). It is usually performed together with the 6MWT. The patient is asked to perform a series of tasks, obviously taking care to perform them safely; depending on the result, a score is assigned:

- ✓ 0 if the patient is unable to perform the task;
- ✓ 1 if the task was performed uncertainly or needed assistance;
- ✓ 2 if the task was performed entirely and independently.

May be performed with (AMPPRO) and without (AMPnoPRO) the use of a prosthesis. The total score ranges from zero to 42 points in the case of the AMPPRO and from zero to 38 points in the AMPnoPRO; if the patient uses a support to perform the tasks, the maximum scores in the two categories increase to 47 and 43, respectively.

In addition, depending on the score made, it allows the patient to be categorized into one of the K- levels.

K-levels

The Medicare functional classification level, or K classification level [30, 31, 34], is so called due to the fact that the 5 classification stages are all indicated by the letter "K", followed by a number from 0 to 4. It includes the patient in a certain category based on certain characteristics: level of function, level of activity, general condition, muscular status, and visual ability, walking speed, stump status (whether it is sore or not), and mental condition.

Oxygen consumption (PWS)

Oxygen consumption is recorded (in mL/minute) while walking on a treadmill, at the subject's preferred speed [5].

Test results

Several articles have analyzed the levels of performance and satisfaction achieved by osseointegrated patients during follow-ups [19, 21, 30].

In a study published by Brånemark in 2018, results were analyzed regarding the Q-TFA and SF-36 tests among 51 patients with transfemoral amputation, 2 and 5 years after surgery. Of the 51 patients, 45 reached the 2-year follow-up; three patients were excluded from the study due to causes unrelated to the osseointegration surgery, and three others underwent prosthesis removal. There were 40 patients at five years follow-up. Regarding the 5-year implant survival rate, it's reported a result of 92%; during the same time period, 45% of the patients did not need any implant revision (Fig. 11). The reasons that led to the need for revision of the prosthesis can be linked to mechanical

complications (breakage of parts of the implant) and the onset of deep infections. With regard to the first aspect, this type of complication has been shown to be related to a particularly intense use of the prosthesis by very physically active subjects.

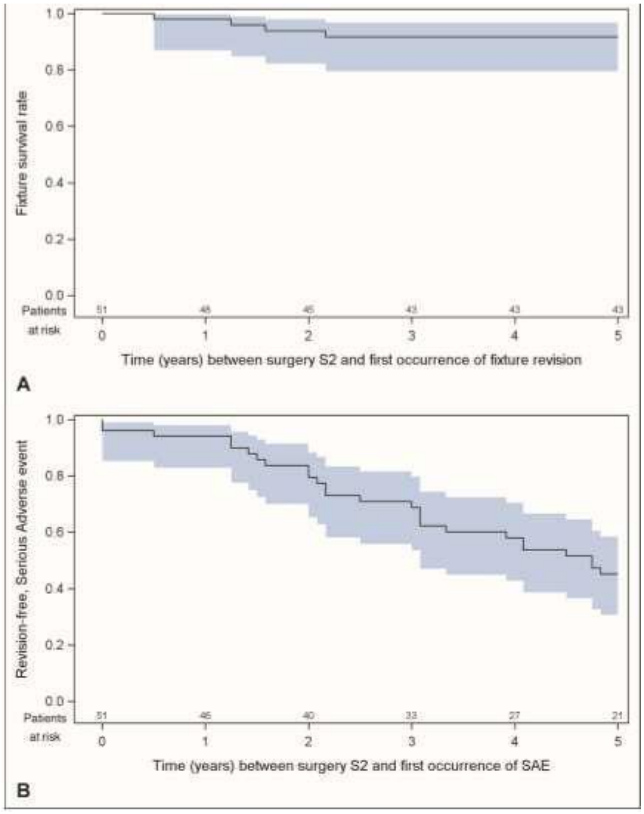

Figure 11 - Kaplan-Meier diagram showing the intramedullary implant survival curve over time (A) and the implant survival rate without revision (B). SAE= serious adverse event.

With regard to the Q-TFA and SF-36 questionnaires, a comparison between the preoperative results and the 5-year follow-up showed a statistically significant improvement ($p<0.0001$) in all aspects investigated by the Q-TFA questionnaire; with regard, instead, to the SF-36 questionnaire, the significant results involved physical performance (PF), physical well-being (RP) and the overall score with respect to physical health (PCS) (Fig. 12). Regarding prosthesis use, before surgery only 29 of 42 patients (69%) were able to use the prosthesis an average of 13 hours per day, whereas five years later 28 of 40 patients were able to walk (70%). There were no major differences between the data provided in the two-year follow-up versus the five-year follow-up.

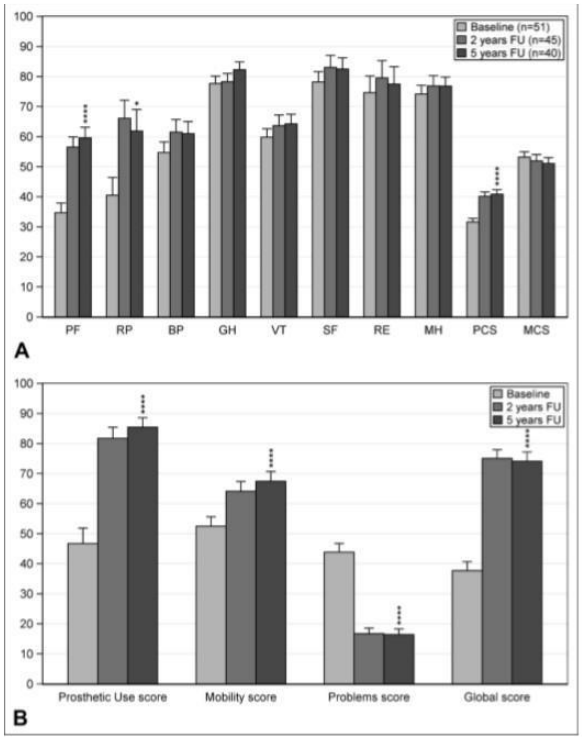

Figure 12 - A) Graphic showing the results of the SF-36 questionnaire pre-surgery and at 2 and 5 years. PF= physical functioning, RP= role physical, BP= bodily pain, GH= general health, VT= vitality, SF= social function, RE= role emotional, MH= mental health, PCS= physical component score, MCS= mental component score; - B) Graphic showing the results of the Q-TFA questionnaire in the pre-surgery and after 2 and 5 years. Scores are divided into subclasses. From left: level of prosthesis use, level of mobility, level of difficulties encountered, and overall score.

In an article published by Al Muderis in 2017 [21], a retrospective study was carried out on 22 patients with transfemoral amputation who underwent osseointegration surgery between 2013 and 2014, recording the test results in the immediate postoperative period and at 14 months distance. The Q-TFA and SF-36 questionnaires were used regarding the quality of life survey and the 6MWT and the TUG with regard to functional abilities. Only patients who were able to use the prosthesis preoperatively as well were considered (Fig. 13).

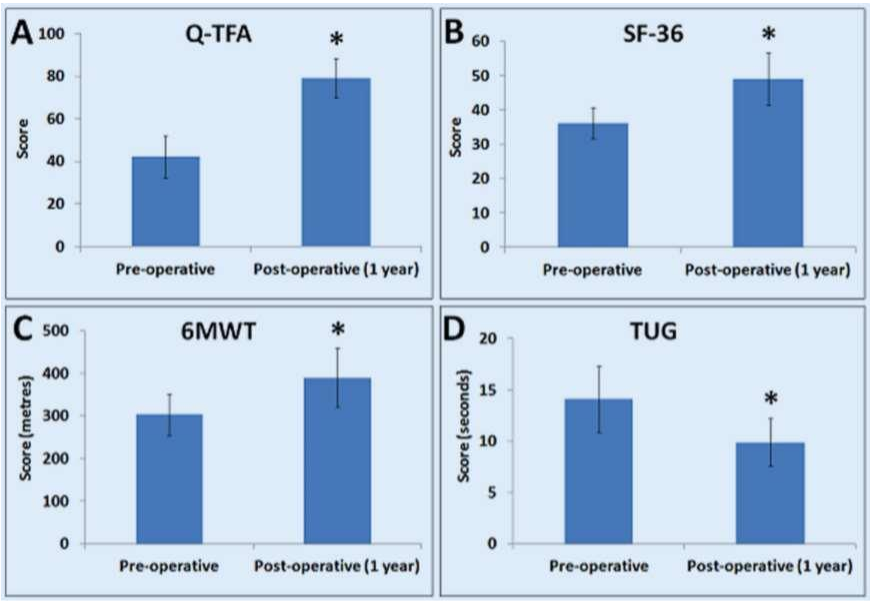

Figure 13 - Graphics showing the results of questionnaires and tests administered at preoperative and one-year follow-up.

The patients included were between 20 and 67 years of age. At one year postoperatively, they were all able to walk using the prosthesis, including the 10 participants who used only a wheelchair preoperatively. Compared to the results collected before surgery, all parameters assessed in the questionnaires and tests were found to be improved overall. For the 6MWT, there was a 128% improvement and a 30% reduction in TUG time. In addition, the results reported in the studies concerning OPL plants were overlapping with previous studies using an ILP plant.

In an article published in 2016, the Dutch team of Van de Meent [34] performed a meta-analysis of the results taking into account the previously described tests and questionnaires (Q- TFA, SF-36, 6MWT and TUG), as well as the Physiological Cost Index, a test able to analyze the energy expenditure consumed during walking. The study laments the low quality of the analyses performed in the various items, secondary mainly to the use of different tests, the severely limited number of participants, and the lack of data on follow-ups performed at a distance greater than five years.

In 2018, a team of researchers from the University of Bristol (UK) [30] analyzed 177 potential articles and pooled the results of 22 selected studies. Due to the variety of measures and tests reported, it was not possible to perform a meta-analysis, but only a synthesis of the various results. With regard to the ability developed in walking, the most frequently used tests were the 6MWT and the TUG, and all articles reported significant improvement in this area between pre- and post-surgery. Analyzing the use of the prosthesis along with the use of the Q-TFA questionnaire, it emerged, also in this case, an increase between 68 and 100% in subjects analyzed at 1-6 years of distance. With regard to the level of motility achieved, many studies have considered other tests in addition to the Q-TFA questionnaire, such as AMPPRO and K-level, for example; all tests have reported satisfactory results. The quality of life reported by the patients was better

than that offered by a socket prosthesis and the patients were overall very satisfied with the outcome of the surgery.
In conclusion, there are a number of limitations present in such studies, including the small number of participants and the lack of long-term follow-up. The first of these two problems is partially remedied by performing studies comparison. The studies report an overall increase in prosthesis use from before to after surgery. In all articles, a significant increase in the patient's autonomy in ambulation was emphasized.

Evaluation of implant migration using Roentgen Stereophotogrammetric Analysis (RSA)

The Roentgen Stereophotogrammetric Analysis (RSA) is a technique that allows determining the precise position in space of two distinct objects, in order to recreate an image with two-dimensionality [40]. In the last decade it has become a tool of considerable help in the study of the evaluation of micromovements of two contiguous objects and is considered a tool capable of predicting implant mobilization [41].
RSA is based on a radiographic examination: it employs two radiogenic sources (called "fires"), from which two beams of rays are emitted simultaneously, both affecting the same target, the object of study; in this way, two x-rays of the same object are obtained, but from two distinct angles (Fig. 14): in this way, using two distinct projections of the same area of interest, it is possible to reconstruct the three-dimensional position of the objects circumscribed in that area. To allow an accurate calculation of the three-dimensional coordinate system, a uniplanar or biplanar calibration cage (cage) is used in RSA, depending on the type of examinations [25, 40]. Modern calibration cages are made of carbon fibers.

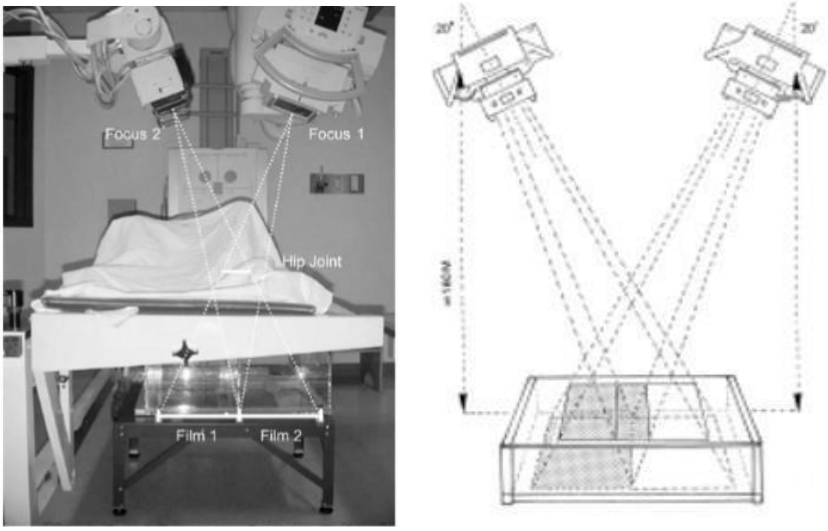

Figure 14 - Left, historical image showing the acquisition of the two x-rays for static radiostereometric analysis. The body segment to be evaluated is positioned in the center of the direction of the two focuses (focus 1 and focus 2). Below the couch, the uniplanar calibration cage and the two plates (film 1 and film 2) are visible. On the right, the schematic drawing

represents the same situation: the two focuses are placed at a height of about 160 cm from the cage and are both tilted 20° from the vertical.

RSA is based on Euler's concept of rigid bodies: in simple geometry, a rigid body is defined as a system of mass points in which the distance between all pairs of points remains constant throughout the movement. This means that by taking any three points, which are not aligned with each other, it is possible to trace the position of the entire body in space. Since the distance between these points remains constant, at least 6 parameters are needed to describe the exact position of a rigid body in space, the so-called 6 degrees of freedom. RSA studies the motion of a rigid body (such as, for example, the stem of a hip prosthesis) by taking a second object (e.g., the proximal femur bone) as a reference, using a coordinate system [40].
In order to apply this principle within the human body, each segment to be investigated is marked by at least three tantalum spheres, applied directly to the bone structure (and also to the prosthesis, if it represents the object of study). Tantalum is an easily identifiable element in radiographs, thanks to its high atomic number; moreover, it is a biocompatible and corrosion-resistant material. The most commonly used diameter is 0.8-1mm. [40]
Tantalum beads are inserted using a steel cannula (Fig. 15) or a special device. The exact position within the bone can be verified by fluoroscopy, but this is rarely necessary [40].

Figure 15 - Tool used to insert tantalum beads into place.

Although theoretically only 3 misaligned markers are needed for each segment of interest, usually 5 to 9 tantalum spheres per area are inserted to compensate for any markers lost or not visible on radiographs. The markers should be randomly distributed over the anatomic segment to be studied, with a different proximal-distal distance, so as to facilitate their identification. To increase accuracy, the tantalum beads should be inserted in such a way as to create large rigid bodies. If the configuration of the markers were erroneously approximate to a straight line, the "condition number" (a measure expressing the inverse of accuracy) would increase and the accuracy of the technique would be compromised. It is also important that the markers do not move within the

bone: the amount of marker movement is calculated using computer algorithms and is represented by a number known as the "mean error" (EM), applicable to rigid bodies. Cases with an average error greater than 250 μm are generally excluded from studies [42].
The motion between the two structures is calculated by placing each object in a coordinate system [40]. The motion analysis is performed using dedicated software that can locate the spheres and landmarks and derive the three-dimensional position of the markers, objects of interest, and any displacements. Usually UmRSA software (RSA Biomedical Innovations AB, Umeå, Sweden) is used, as indicated by the guidelines [42].
Of course, as with any technique, the study using RSA also has its own limitations, including: mobilization from the original site of the tantalum spheres (e.g., as a result of bone resorption) [42], early subject exit from follow-up courses, and failure of data analysis using the software [25]. In addition, the exact number of markers to be implanted represents a critical issue that often arises during the course of various studies, because not always all tantalum spheres are easily detectable on radiographs [42].

Accuracy of RSA technique

RSA achieves better accuracy than conventional radiography [40]. The 99% confidence interval with respect to the measurements obtained is estimated to be around 0.22 mm for translation (cranio-caudally) and 0.47°, 0.96°, and 0.26° for rotations along the transverse (x), longitudinal (y), and sagittal (z) axes, respectively.
For this reason, it finds numerous applications in studies related to the fixation of prosthetic components after hip and knee arthroplasty, allowing the evaluation of micromotions between the endoprosthesis and the bone at a distance of time, with an accuracy on the order of 50 μm [25,40,41]. At accordance with the data obtained, RSA is also able to provide the risk of implant loosening [42, 43].

RSA technique applied to osseointegration prostheses

The RSA technique has also been applied in the field of osseointegration prostheses. In 2012 Brånemark studied the levels of fixation and long-term stability of OPRA implants using this technique: this study analyzed the microdisplacements of the prosthesis at six months and at 1, 2, 5, 7 and 10 years after surgery.
Prior to the first surgical phase, the prosthetic stem was marked with 6 tantalum spheres, while 6 to 8 markers were placed at the level of the femoral cortical, around the implant.
A uniplanar calibration cage was used during radiographic image acquisition to serve as a reference and allow various comparisons between each measurements. The patient was positioned so that the femur was centered within the reference points placed on the cage itself; specifically, the subject was oriented so that the femur (and, therefore, the implant) was parallel to the y-axis. After performing two radiographic frames perpendicular to each other, the 3D coordinates of the tantalum beads were determined. The position of the femur relative to the implant was defined by at least 3 beads in each region.

The resulting images were scanned and analyzed using dedicated software (Fig. 16) with double measurement to confirm sample accuracy.

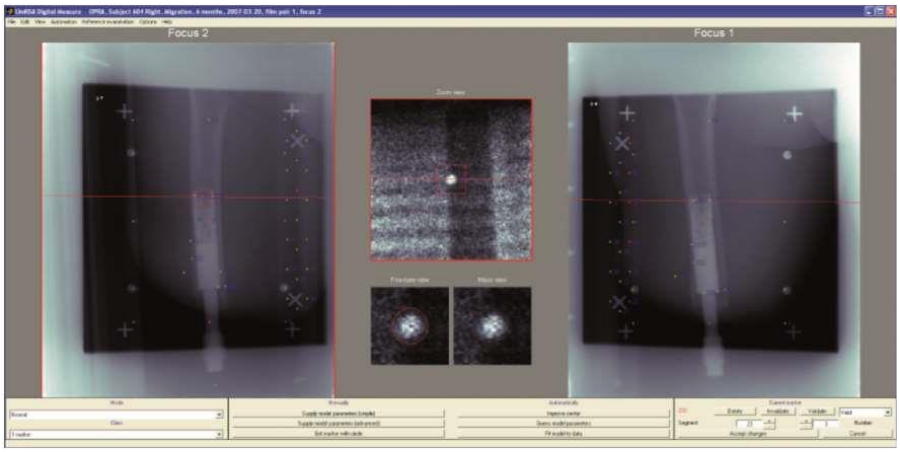

Figure 16 - Images analyzed using the dedicated software for RSA. Note the tantalum beads marked in green and red in the cage, in the implant, and in femoral bone. A tantalum bead from the osseointegrated prosthesis is shown in detail in the central box.

The data obtained from the images acquired 6 months after the second surgical phase were compared with those related to the migration of the intramedullary stem relative to the femur in subsequent follow-ups, keeping monitored any possible rotation or migration of the prosthesis over time.

The mean error limit (ME) in the study reviewed was set at 0.25. Translations (migrations) were measured starting from the gravitational center of the markers inserted in the device. The movements of the implant along the cranio-caudal direction were defined as negative movements (-), while movements in the opposite direction were indicated as positive movements (+); rotations are understood as both forward tilt (+) and backward tilt (-), as internal rotation (+) and external rotation (-), and as varus tilt (+) and valgus tilt (-). These movements correspond to rotations along the transverse (x), longitudinal (y), and sagittal (z) planes (Fig. 17).

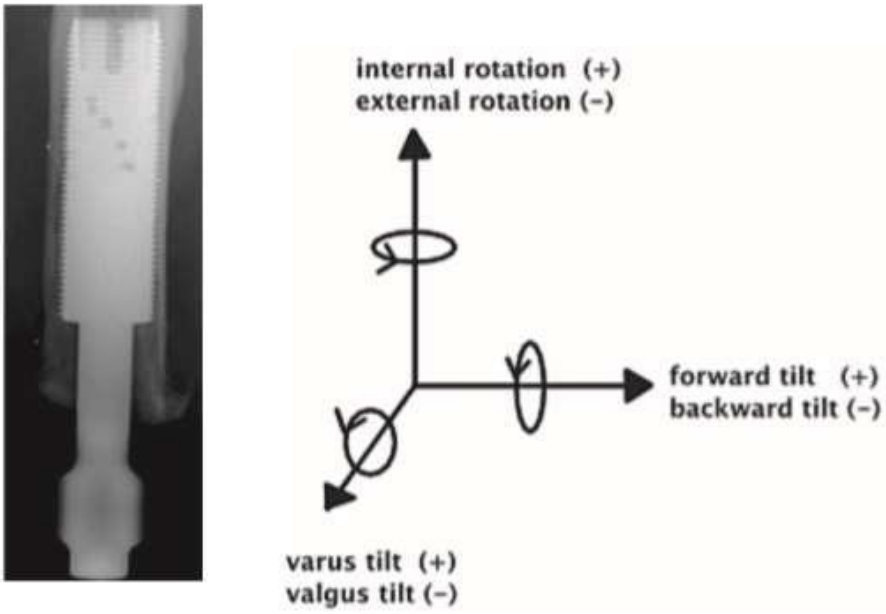

Figure 17 - Rotation axes of the implant.

In conclusion, no relevant migrations emerged in the OPRA osseointegration implant during the various follow-ups, both in the cranio-caudal direction and with regard to rotations along the three planes. It is important to consider that measurements along the longitudinal axis have, for geometrical reasons, a lower resolution than the transverse and sagittal planes, which is why certain data could be biased. Furthermore, the presence of rotational movements in the first six months after implantation in no way precludes satisfactory bone remodeling and proper implant stability in the long term.

Italian protocols on transfemoral osseointegration and case reports

The technique of osseointegration applied to prosthetic limbs is currently practiced by several orthopedic centers both in Europe and in the rest of the world.
Thanks to the Me.Ta.COs research project, the result of a collaboration between the Istituto Ortopedico Rizzoli, the University of Bologna and the INAIL Prosthesis Center of Vigorso di Budrio, this technique has recently been imported in Italy. Following the experience gained in the management of the first patients, the Italian protocols regarding the surgical procedure, the rehabilitation pathway and the treatment of the ostomy were drawn up.
A total of 3 patients have been operated, but only one patient is currently available for follow-up.
The case report is then presented, with data on the functional and kinematic results of the last patient who underwent osseointegrated prosthesis surgery for trans-femoral amputation. The surgery was performed by the orthopaedic team led by Prof. Zaffagnini, director of the Orthopaedic and Traumatology Clinic II at the Rizzoli Orthopaedic Institute in Bologna. The implantation of the external prosthesis and the rehabilitation of the patient were followed by orthopaedic technicians, physiatrists and physiotherapists of the INAIL Prosthesis Center of Vigorso di Budrio.

Osseointegration surgical procedure

This project focuses on patients with a transfemoral amputation treatable with a standard osseointegrated implant, applied to femurs with residual length greater than 140 mm, calculated from the small trochanter to the distal apex of the bone stump.
A press-fit type implant, marketed by OTN Implants (BV, Arnhem, The Netherlands), was chosen to replace the previous OPL implant from the Italian company Permedica.

Implant Description
The femoral prosthesis for transfemoral osseointegration includes the following components (Fig. 18):
1) Press-fit type femoral stem (diameters available from 15 to 22 mm; length 140 mm);
2) Healing plug;
3) Transcutaneous dual-cone adapter (available lengths from 70 mm to 110 mm);
4) Locking screw

Figure 18 - OTN transfemoral osseointegration implant. From top to bottom: locking screw (4), double-cone transcutaneous adapter (3), femoral press-fit stem (1). To the side: healing plug (2).

Preoperative planning

The objectives of the preoperative planning are: the choice of the most appropriate femoral stem diameter, the level of regularization of the distal femoral stump and the choice of the length of the transcutaneous double cone adapter that allows to equalize the joint line level of the prosthetic knee with the contralateral knee. In any case, it is advisable to keep all sizes of the femoral stem in the operating room, in case the planned diameter does not guarantee optimal primary stability of the press-fit device.

Planning is performed on orthostatic panoramic radiographs of the lower limbs, with external prosthesis on, plus lateral projection of the amputation stump. Although not essential, a CT scan of the stump is recommended for selection of the correct diameter of the intramedullary implant (Fig. 19).

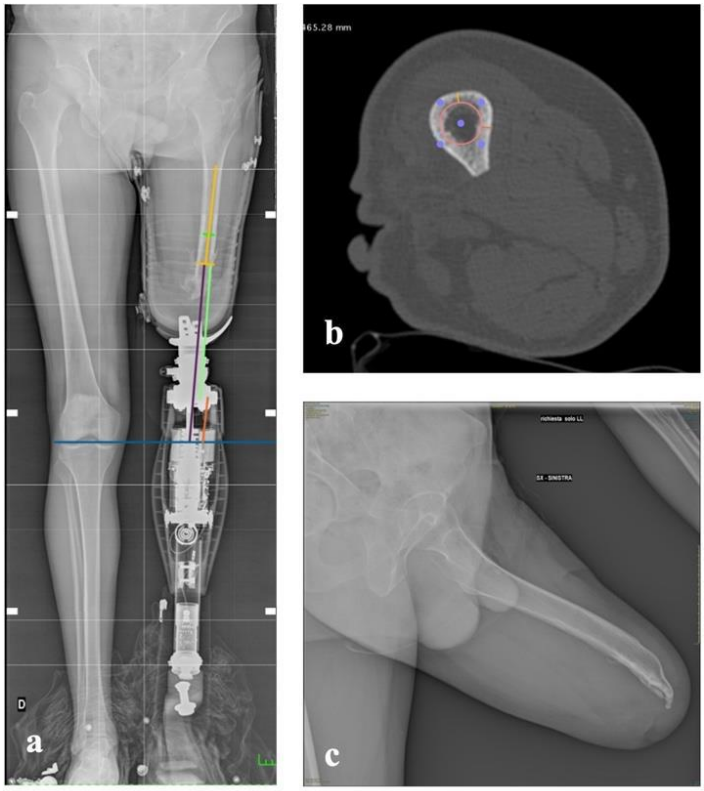

Figure 19 - a) Panoramic radiograph in orthostatism with prosthesis worn for preoperative planning; b) CT axial section for the choice of the diameter of the intramedullary implant; c) Lateral projection of the stump with evidence of irregularities in its distal portion.

Regularization of the distal femur is necessary in two cases:

- ✓ In cases where the distal bone profile is irregular (a frequent condition, given by the formation of bone callus following amputation) and/or in certain cases of long bone stump (distal third). In the first case, it is necessary to regularize only the apex of the stump, preserving as much bone tissue as possible;
- ✓ If the distance between the distal apex of the bone stump and the articular line of the contralateral knee is not sufficient to accommodate the external prosthetic components between the stump and the articular center of the knee, i.e.: the external portion of the double cone adapter, the Heli connector and the proximal part of the prosthetic knee.

  According to the instructions for use for the prosthetic implant used in this project (OTN Implants BV, Arnhem, Netherlands), the femur should be adjusted to provide a distance of 140 to 180 mm from the distal end of the bone stump to the articular rim of the contralateral knee. Based on this distance, the appropriate length of the double-cone adapter is selected. In addition, the thickness of the subcutaneous fat tissue must be taken into account when selecting the double-cone adapter in order to ensure enough space for the Heli connector to attach without decubitus skin damage. A distance of at least 5 cm between the ostomy and the distal portion of the double cone adapter is required to avoid abrasion or decubitus of the external prosthesis connector with the skin of the stump.

  Available lengths of the double-cone adapter are 70, 80, 90, 100, and 110 mm.

  The distal ends of the Double Cone Adapter fit at:

- ✓ Level of the distal end of the stem to a depth of approximately 25 mm;
- ✓ Level with the proximal portion of the Heli connector, to a depth of about 35 mm.

The Heli connector is available in only one length (75 mm).

In addition, depending on the prosthetic knee that the patient is wearing, the size of the proximal portion (i.e. the portion above the joint center) may vary. Therefore, it is essential to know the model, size, and function of the patient's prosthetic knee with the assistance of an experienced Orthopaedic Technician.

Indications for custom implants

In cases of a short stump, with a residual femur length of less than 140 mm from the distal end of the bone stump to the small trochanter, a custom prosthesis, consisting of a shorter femoral stem and a cephalic screw, should be used. The use of a standard femoral stem (140 mm) in short stumps could involve the limitation of osteosynthesis in case of possible femoral neck fractures and the impossibility to perform a hip arthroplasty in case of ipsilateral coxarthrosis.

Surgical technique

The prosthesis for transfemoral osseointegration involves two distinct surgical times, commonly called "steps", about 60 days apart: this interval allows the complete healing of surgical scars and soft tissues and the initial osseointegration of the femoral stem of press-fit type and it is fundamental in order to start the rehabilitation process in a safe way.

It is advisable to avoid prolonging the interval between the two surgical times more than necessary, because the fibrotic tissue that interposes between the apex of the stump and the skin could make it difficult to identify the point of repere to create the ostomy.

It is also opportune to instruct the patient on the execution of stretching and muscular strengthening exercises to be carried out at home, independently, in the weeks preceding the operation. This allows to maintain an adequately toned stump, facilitating the functional recovery in the post-operative period.

Step 1 (S1)

Osseointegration surgery is performed under general or spinal anesthesia, with intravenous antibiotic prophylaxis at induction (Cefazolin 2 g or Clindamycin 600 mg). The patient is placed supine on the operating table. The sterile field is set up.

Below, the steps of the surgical procedure are listed:

1) Incision of the skin and fascia and exposure of the distal portion of the femur (Fig. 20);
2) Removal of scar tissue, isolation of the sciatic nerve, removal of any neuroma, and regularization of the nerve (Fig. 21);
3) Regularization of the distal femur with an oscillating saw as determined in the preoperative planning and removal of redundant skin and soft tissue (Fig. 22);

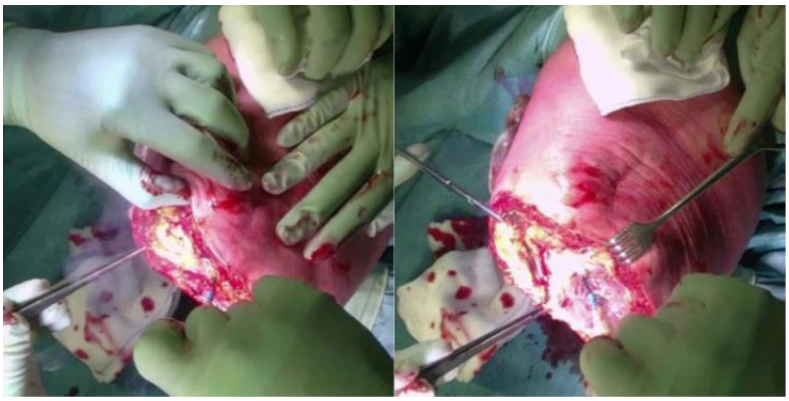

Figure 20 - Skin and soft tissue incision.

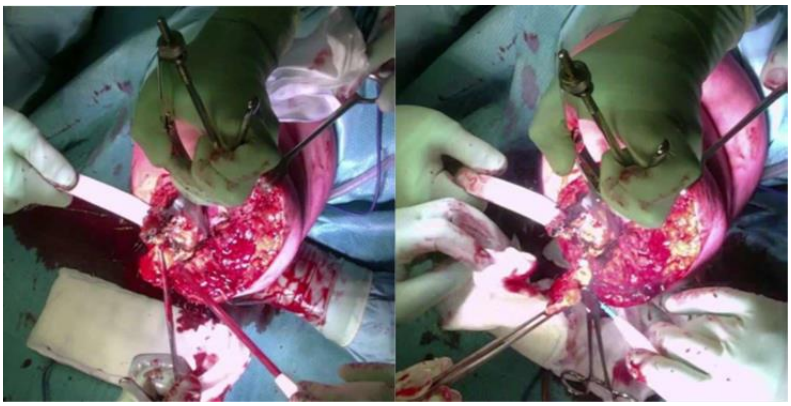

Figure 21 - Identification and regularization of the sciatic nerve.

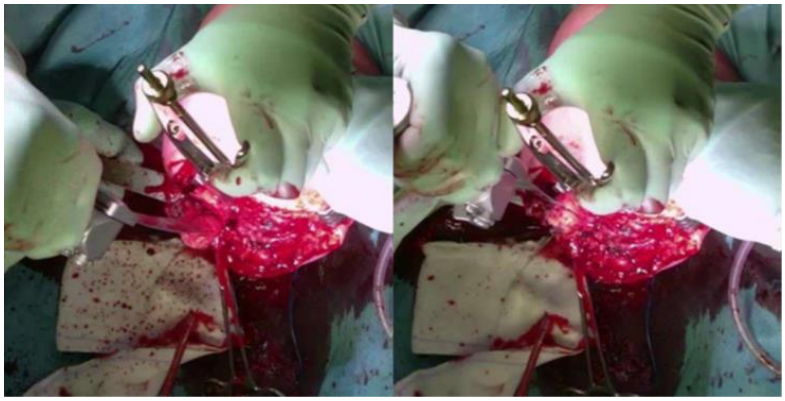

Figure 22 - Bone stump adjustment.

4) Insertion of ball-tipped guiding wire into the femoral diaphysis. Reaming of the medullary canal with standard flexible non-cutting reamers under ampliscopic control. The bone marrow tissue obtained by reaming is preserved. It will be applied later as a bone graft. The last diameter of the flexible reamer should be 1 mm smaller than the planned femoral stem diameter (Fig. 23);
5) Rasping of the intramedullary canal with appropriate curved rasps. Use the lateral projections of the ampliscope to check the positioning of the rasp with respect to the

ante-curvature of the femur. Rasp until the planned diameter of the femoral stem is reached (Fig. 24);

6) Adjustment of the distal femur with a cup burr to create a distal plane of the femur exactly perpendicular to its longitudinal axis. The size of the cup burr is chosen according to the created femoral intramedullary diameter;
7) Marking the final rotation of the curved rasp on the distal femur using the appropriate aiming device;
   Note 1: The position of the curved rasp must correspond exactly to that of the femoral stem being implanted;
8) Drill four 1.25-mm holes with Kirschner wire and pass transosseous sutures with 2 gauge resorbable wire (Fig. 25)

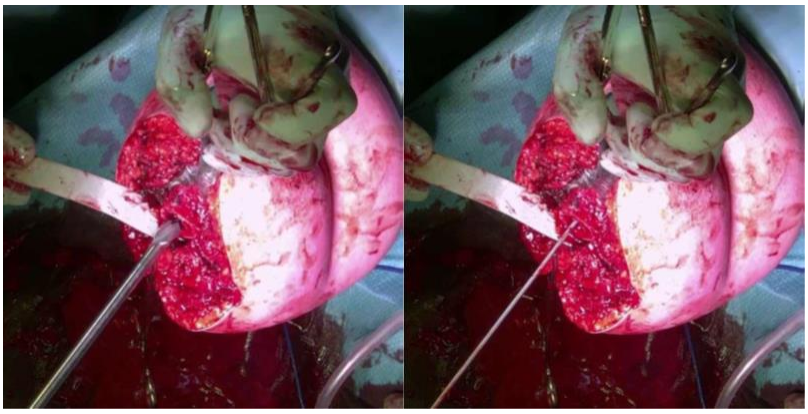

Figure 23 - Channel reaming on guide wire.

Figure 24 - Working the intramedullary canal with rasps of increasing size.

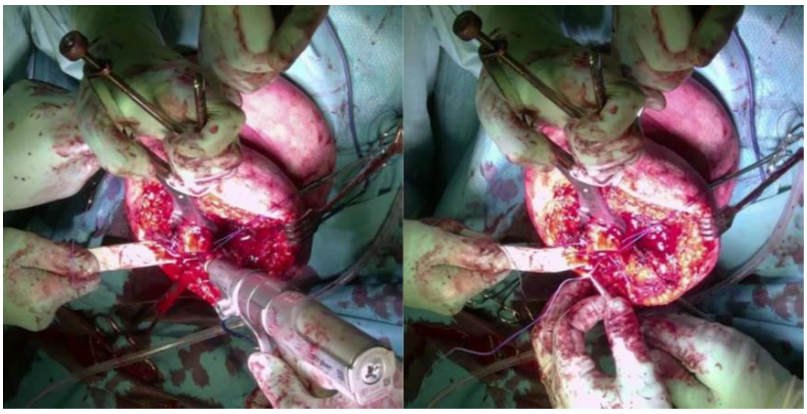

Figure 25 - Transosseous sutures for distal myodesis.

9) Tightening of the screw on the proximal morse taper of the femoral stem with the appropriate 4.0 mm hex screwdriver;
10) Implantation of the femoral stem using the appropriate instrumentation, making sure to maintain proper rotation (Fig. 26); Application of the bone marrow tissue obtained from reaming the canal as a bone graft around the distal contact zone between the stem and the femoral cortical bone;
    Note 2: The diameter of the selected femoral stem must match the last diameter of the curved rasp used in order to achieve optimal fixation of the press-fit implant; undersizing may lead to failed integration and oversizing may lead to intraoperative fracture of the distal femur.
    Note 3: If there is difficulty in positioning the press-fit implant (e.g., in case of excessively rigid cortical bone), the tapered installer may be used to facilitate stem advancement.
    Note 4: Avoid unnecessary contact with the final femoral stem, including contact with the operator's gloves, which must be replaced prior to implantation.
11) Placement of the healing plug within the distal cone of the femoral stem (Fig. 27);
12) Abundant washing with saline;
13) Execution of the distal myodesis by suturing the muscle groups to the bone using the previously applied transosseous sutures (Fig. 27);
14) Identification of the site where the ostomy will be performed and removal of excess subcutaneous tissue (Fig. 28);

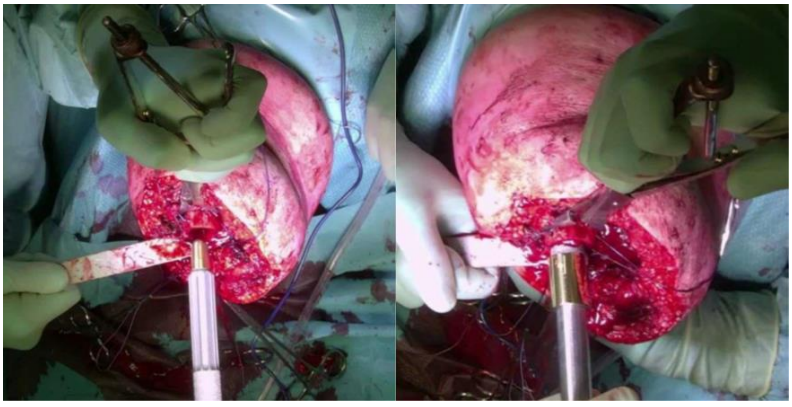

Figure 26 - Femoral stem implantation with press-fit technique.

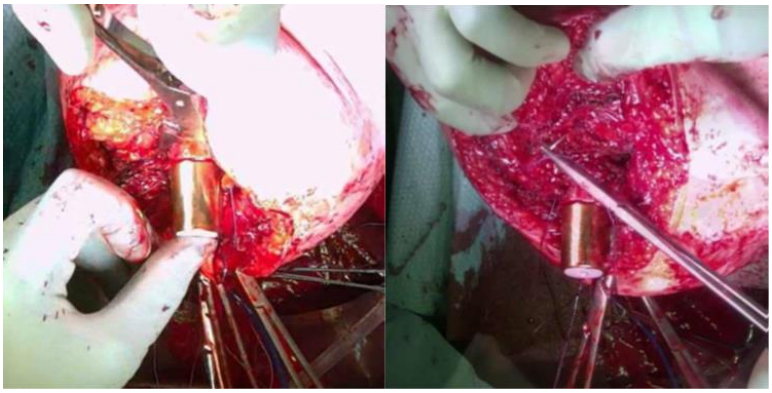

Figure 27 - Healing plug placement (left). Distal myodesis (right): the muscles are reinserted on the distal portion of the bone stump, around the stem.

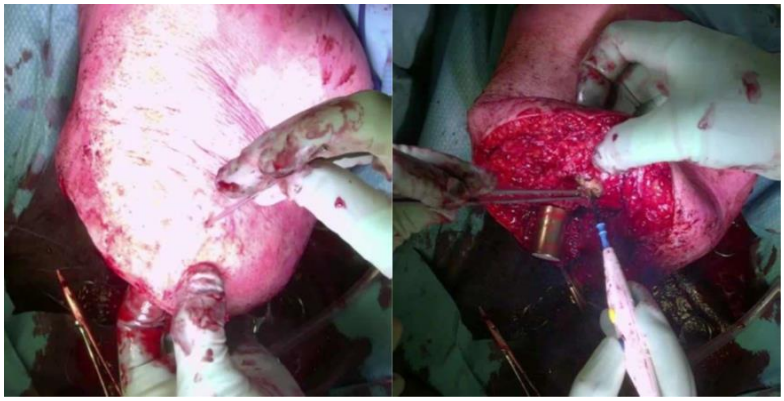

Figure 28 - Identification of ostomy site and removal of excess subcutaneous tissue.

15) Insertion of a perinervous catheter for postoperative local anesthesia at the level of the sciatic nerve (Fig. 29);
16) Flat wound suturing according to the surgeon's standard technique (Fig. 30);

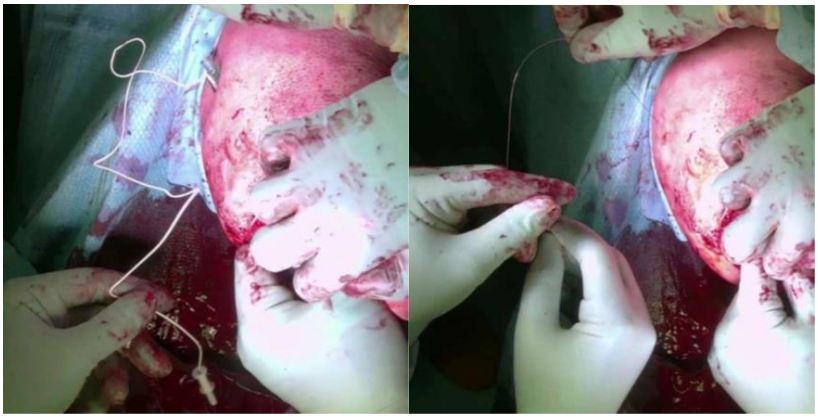

Figure 29 - Sciatic perinervous catheter insertion for postoperative pain control.

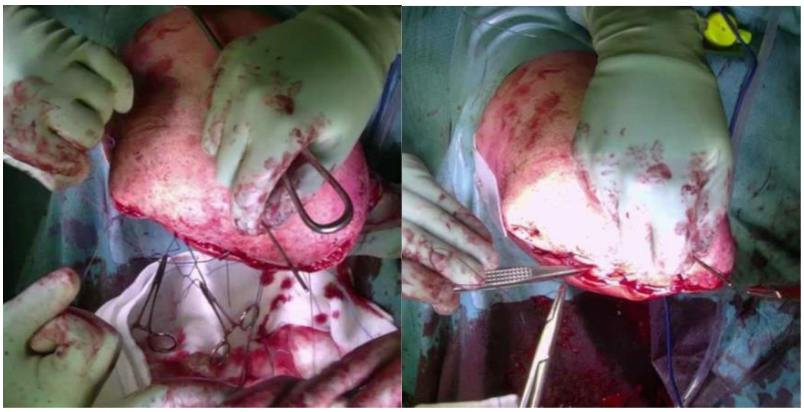

Figure 30 - Plane suture.

17) Application of a compressive bandage dressing on the stump (Fig. 31);
18) Final radiographic check (Fig. 31).

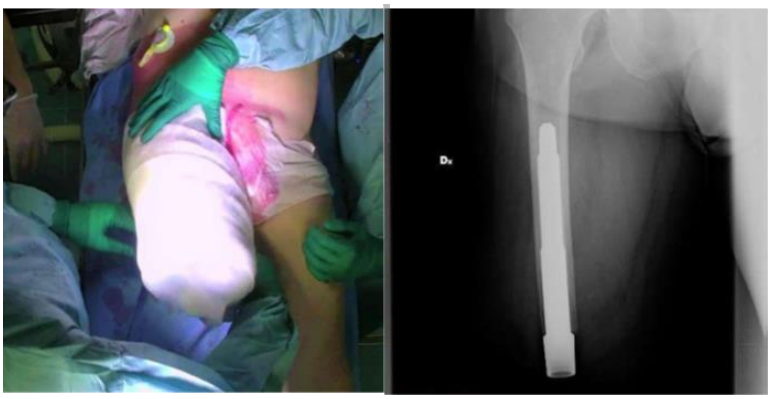

Figure 31 - Compression bandage (left) and postoperative radiographic control (right).

Step 2 (S2)

The surgical steps of the second step are listed below:

1) Localization of the center of the healing plug by palpation and percutaneous placement of a Kirschner (K) wire within the plug itself (Fig. 32);

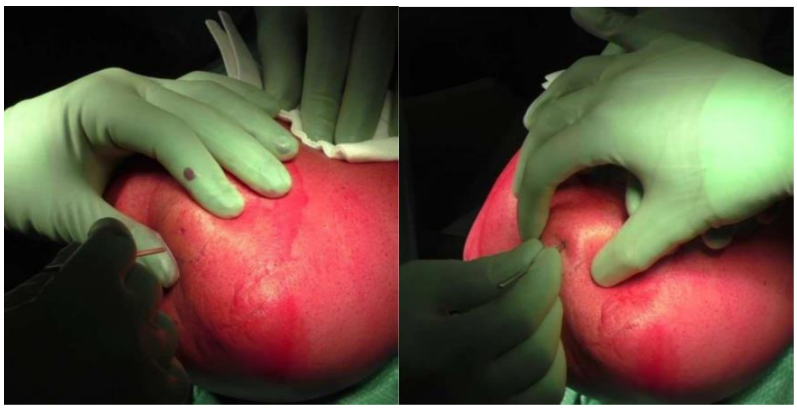

Figure 32 - Healing plug localization placement of a Kirschner wire.

2) Realization of the ostomy by incising the skin using the appropriate Corer, under the guidance of the Kirschner wire (Fig. 33);

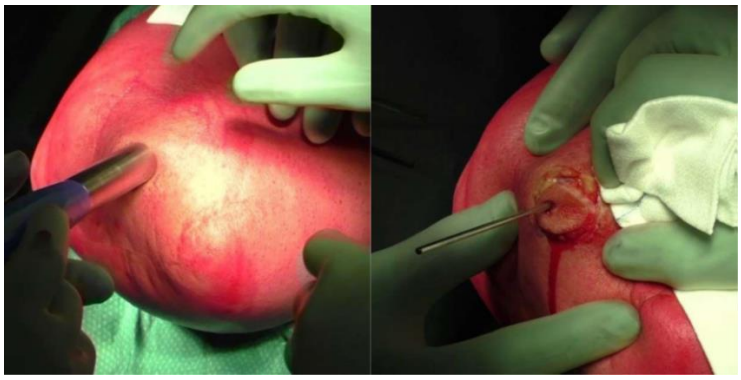

Figure 33 - Creation of the ostomy using a Corer.

3) Removal of the healing plug and thorough washing of the wound and the inside of the morse cone, to remove any scar tissue present inside (Fig. 34);

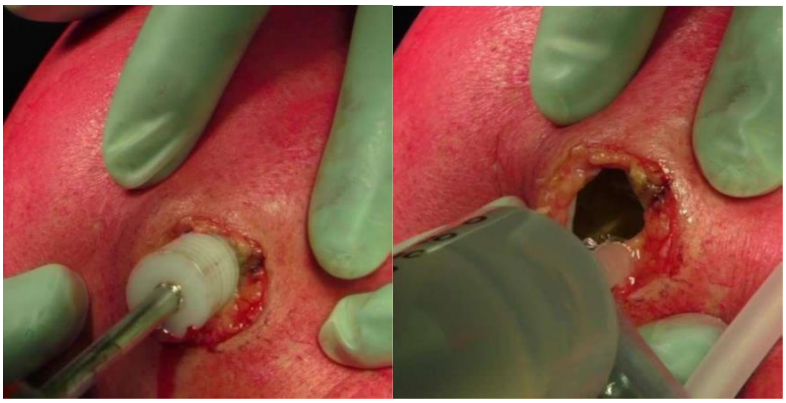

Figure 34 - Removal of the healing plug and thorough washing of the wound.

4) Selection of the correct adapter length based on soft tissue thickness.
Note 5: It is necessary that the double cone adapter protrudes at least 50 mm outside the skin ostomy;
5) Insert the correct adapter and tighten the locking screw using the counter torque wrench and screwdriver (Fig. 35);
Note 6: The counter torque wrench is a tool that prevents rotational forces on the stem when tightening the locking screw;

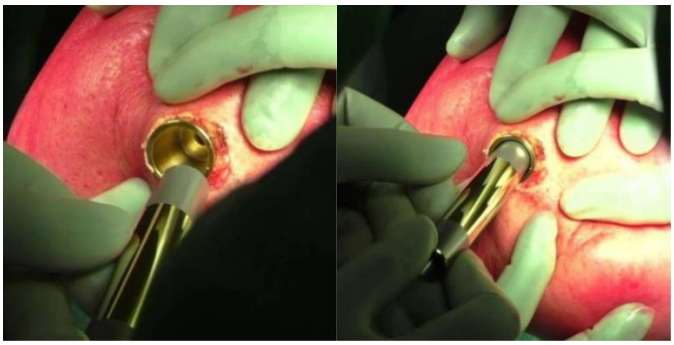

Figure 35 - Implantation of the dual-cone adapter (making sure it protrudes 50 mm outward).

6) In order to create a stable morse cone connection between the femoral stem and the adapter, the latter is fixed inside the morse cone of the femoral stem using the beater and the hammer (Fig. 36); then, the locking screw is tightened again to 19 Nm with the hexagonal head dynanometric screwdriver, always using the counter torque wrench.
At the end of the procedure, the double cone adapter must protrude from the skin for at least 5 cm and the ostomy must be well adherent to the implant but still free to move in order not to create pain in movement (Fig. 37).

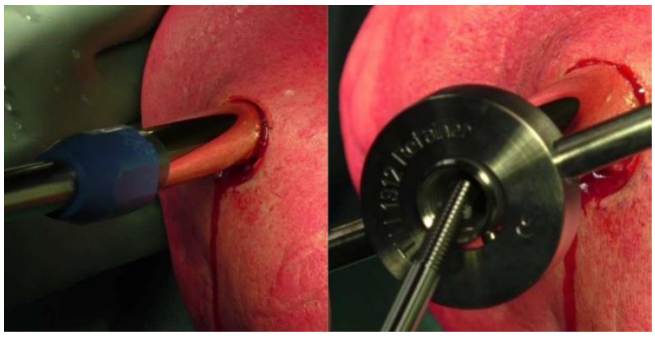

Figure 36 - Attaching the adapter with beater and screwdriver using the counter torque wrench.

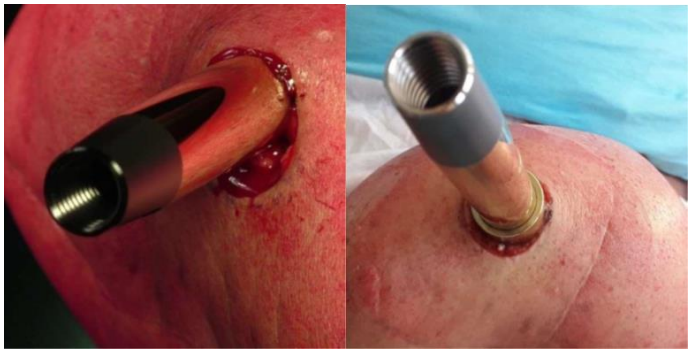

Figure 37 - Postoperative final result.

Possible replacement of the double-cone adapter
If the adapter needs to be replaced, it can be removed from the morse taper with the remover and 10 mm cylinders. At this point, the new adapter is inserted by repeating steps 5 and 6 described in the second surgical step.

Surgical instruments used in Step 1

General instrumentation

- ✓ Basic surgical instruments for orthopedic surgery (forceps, scissors, scalpels, monopolar and bipolar scalpels etc.);
- ✓ Oscillating saw;
- ✓ Power drill;
- ✓ Set of flexible reamers with ball bearing guide wire;
- ✓ 1Kg hammer.

Recommended tools (Fig. 38)

- ✓ Size 15-22 curved rasp (in 1 mm increments);
- ✓ Hole cutter size 13-21 (in 2 mm increments);
- ✓ Installer;
- ✓ Tapered installer;
- ✓ Hexa 4 screwdriver;
- ✓ Adjusting device.

Surgical instruments used in Step 2

General instrumentation

- ✓ K. 2 mm wires;
- ✓ 1 kg hammer.

Recommended Instrumentation (Fig. 38)

- ✓ Corer diameter 20 mm;
- ✓ Hexa 4 screwdriver (= 4.0 mm hex screwdriver);
- ✓ Punch;
- ✓ Retainer;
- ✓ Removal device;
- ✓ Cylinder;
- ✓ Torque wrench.

Figure 38 - Surgical instrumentation used in the two surgeries: rasps of increasing size (right) and dedicated instrumentation used in both Step 1 and Step 2 (left).

Standards of care and hygiene of ostomy and stump in osseointegrated prosthesis

The need to dedicate a protocol to the care of the ostomy arises from the fact that the amputated limb with an osseointegrated implant presents different characteristics with respect to those of a normal stump. Therefore, it needs a particular treatment, necessary to prevent episodes of irritation or infection. Moreover, it turns out to be a useful tool for the medical staff in the assistance of the amputee, helping to discriminate the different causes of pain affecting the newly operated limb and to set the correct therapy.
The protocol of care and hygiene of the ostomy has been thought to be used not only by doctors and nurses, but also by the family doctor and by the patient himself, in order to maintain the correct hygiene in the stump and to promptly recognize the onset of possible adverse effects.

Characteristics of the osseointegrated amputated limb

The ostomy is the opening in the skin through which the distal portion of the prosthetic implant (adapter) protrudes outward. In the post-operative period (Fig. 39), the ostomy should be treated as a surgical wound; in the course of the weeks, the internal wall is

covered by a tissue similar to the epithelium of a mucosa. Despite that, in the first weeks, the ostomy represents a particularly vulnerable and sensitive site: therefore, it is possible that it may bleed or be subject to infection. Once the epithelium has formed, the risk of bleeding, irritation and soft tissue infections decreases.
It is necessary to educate the patient on the correct management of the ostomy and on the early recognition of changes in the ostomy that need to be managed by medical/nursing personnel.

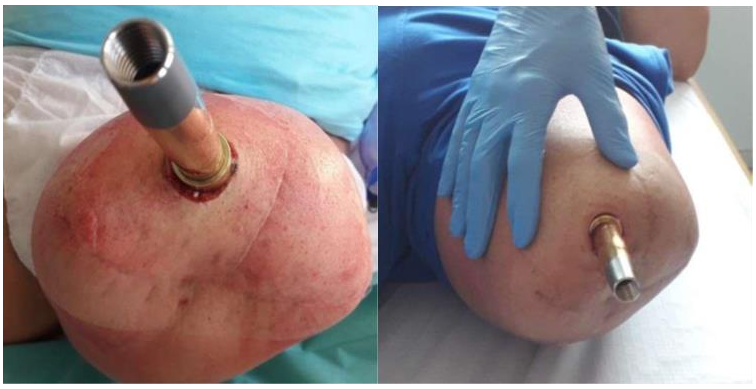

Figure 39 - Ostomy presentation on the first postoperative day (left) and on the third postoperative day (right).

The ostomy must be sanitized twice a day to prevent any irritation or infection of the skin and soft tissues. The care starts from the day after surgery; in the first weeks the ostomy must be carefully irrigated with the simple jet of water of the hand shower. The use of neutral soaps is allowed, however, an abundant washing with water is more than sufficient.
If the ostomy continues to bleed, it is advisable to rinse with cold water and apply a series of gauze, applying compression. In case of recurrent bleeding, reduce activities and keep the stump in drainage.
Caution: gauze pads are not to be considered sterile.

Ostomy management

Instructions for proper ostomy cleaning

1) Remove the gauze pad;
2) Irrigate the ostomy with the hand shower (Fig. 40) or with a water pump (we recommend the Braun Oral B - Oxyjet water pump or the Panasonic Dentacare EW1211 water pump). For your convenience, we recommend that you purchase a cleaner with adjustable water jet levels and an integrated water tank;
3) Remove any deposits (scale) from the system with a gauze pad, soap and water (Fig. 40);

Figure 40 - Cleaning the ostomy with the hand shower (left) and cleaning the adapter with gauze (right).

4) Ensure that the prosthetic implant is perfectly clean and free of debris;
5) Massage the skin and muscles during rinsing and ensure that no adhesions occur between the inner lining of the ostomy and the implant;
6) After rinsing, proceed by removing residual water with a towel. If necessary, cover the ostomy with a 10x10 cm gauze, properly folded on the long side and tied around the implant.
   Attention: cover the ostomy with a gauze only when there is an important secretion. The purpose of using a gauze is simply to prevent stains from forming on the clothes: the ostomy cover is not meant to keep the area sterile. The ostomy must be carefully cleaned even after all those activities that expose it to a greater risk of contamination (sweating, contact with sea or swimming pool water, etc.).
   One of the first signs of irritation of the ostomy is redness, which can be accompanied by swelling of the soft tissues, heat and pain.
   It must be remembered that the presence of repeated irritations or infections in the same subject can be traced back to a poor or insufficient hygiene of the stump, to an overabundant subcutaneous fat layer around the area of the ostomy and/or to the smoking habits of the subject.

Inflammation or infection of the ostomy

Infection presents itself as pain around and inside the ostomy, accompanied by yellow-green purulent discharge, redness, swelling, skin warm to the touch and C-reactive protein elevation.
In case of inflammation or infection (Fig. 41) proceed as follows:

- ✓ Clean the ostomy frequently with mild soap and water;
- ✓ Disinfect with chlorhexidine gluconate 0.5% + ethanol 70% (SANITAS) twice a day, after cleaning the ostomy with water; alternatively, irrigate the ostomy with 4mL of hydrogen peroxide (hydrogen peroxide) for 5 minutes before rinsing with water, repeating the operation twice a day for two weeks. A syringe can be used to aid in the procedure;
- ✓ Patients suffering from repeated infections at the level of the ostomy sometimes benefit from a long-term treatment with a hydrophilic ointment based on fusidic acid (Fucidin 20 mg/g ointment) to be applied around and inside the ostomy twice a day.

Alternatively, a dermatological ointment based on hydrocortisone/oxitetracycline hydrochloride/polymyxin B can be applied, but in Italy it is marketed for auricular or ocular application (Terra-Cortril, Pfizer);

- ✓ If, despite everything, the infection continues beyond the month of treatment (with pain, redness and formation of purulent secretion) ask the family doctor to prescribe an antibiotic for at least 10 days. More than 90% of ostomy infections are caused by Staphylococcus Aureus, therefore targeted antibiotics are recommended.

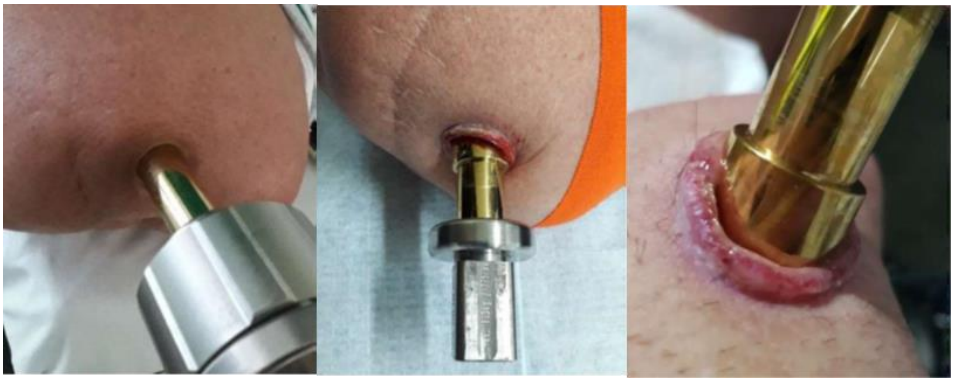

Figure 41 - Comparison between healthy ostomy (left) and inflamed ostomy (center) and with superficial infection (right).

If the subject present a redundancy of adipose tissue in the subcutaneous layer around the ostomy, a surgical solution should be considered. By removing as much adipose tissue as possible, the thickness of the ostomy channel is reduced, creating the so-called "short" or "dry stoma", which has the advantage of being easier to keep clean; moreover, it often represents the solution to the excessive rubbing of the soft tissues around the prosthetic implant, reducing the episodes of irritation and inflammation of the ostomy.

Irritation and/or dryness of the ostomy

Irritation (Fig. 42) presents as pain or a burning sensation around and within the ostomy, potentially accompanied by a change in the quality of secretions. No redness, swelling, warmth to touch, or C-reactive protein elevation should be present.

Often the irritation is caused by continuous rubbing between the soft tissue around the ostomy and the part of the prosthetic implant that passes through it. In cases of "dry stoma", the inner wall of the ostomy may be more sensitive.

It is possible to use Instillagel Almed, a sterile lubricating gel based on hydroxyethylcellulose and lidocaine and chlorhexidine that acts as a lubricant, local anesthetic and antibacterial. It is available in 11 mL syringes by prescription only. It should be applied 1 to 2 mL every hour of the day, reaching deep inside the ostomy. Since it has a poor cutaneous absorption, it is possible to use the gel continuously in case of dry ostomy and adherent to the prosthetic component. Alternatively, in less severe cases, it is possible to apply vaseline on the ostomy and on the implant.

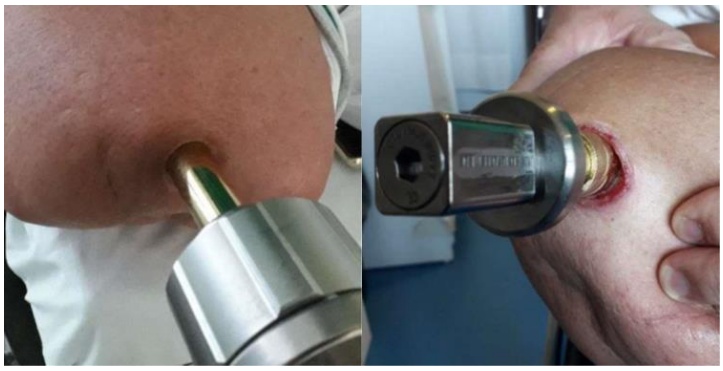

Figure 42 - Comparison of healthy ostomy (left) and irritated ostomy (right).

Presence of scar tissue and/or hypergranulation at the margins of the ostomy
Apply Terra-Cortril twice a day after cleaning the ostomy. Discontinue use once the situation has resolved. Use for more than four consecutive weeks is highly discouraged.

Pain management of the osseointegrated limb
It is common to experience pain in an osseointegrated limb. The causes can be different: the most common occur during the rehabilitation phase of the newly integrated subject and are, for the most part, treatable.
It is important, for a correct management, to identify the origin and treat it in a specific way. A large part of the pain comes from the ostomy and the healing bone tissue, as well as from the soft tissues present in the amputated limb (tendons, muscles, joints). Most of the soft tissues are affected by prolonged disuse following amputation and/or the use of a socketed prosthesis; with the adoption of an osseointegrated prosthesis there is a reactivation of muscle groups and this, at first, can be a cause of pain.
It is necessary to explain this possibility to the subject and reassure him/her. Normally, by adopting an active lifestyle, controlling body weight and avoiding smoking, the subject can experience a benefit both at the level of the amputated limb and overall.
In some cases, however, it is necessary to integrate other medical treatments.

Muscle pain (myalgia) at the level of the amputated limb
This is the most common type of pain encountered during the post-surgical rehabilitation period. Prolonged inactivity of muscle groups is caused by both the use of the wheelchair and the classic socket prosthesis. As a result, the subject often presents with loss of muscle tone and strength at the level of the amputated limb.
After stump plastic surgery and implantation of an osseointegrated prosthesis, the soft tissues and joints are brought to regain the motor patterns of a non-amputee, which is why the stump quickly experiences fatigue and functional impotence. Once the tone and trophy of the limb are recovered, pain and muscle fatigue diminish; the speed with which this occurs depends on the rhythms and activities undertaken during the subject's rehabilitation, as well as the duration of the period of inactivity following the amputation before undergoing osseointegration surgery.
It is useful to follow some precautions:

- ✓ Train daily and consistently, without excess, especially in the beginning;

- ✓ Continue rehabilitation and lighten the workload. If necessary, prolong the use of crutches. Suspension of exercises is not a solution, as it would only slow down the formation of the tendon structure;
- ✓ If the pain in the limb becomes unbearable, the use of a painkiller is possible, after medical evaluation.

Pain at the apex of the ostomy

This is a pain that arises mainly in transfemoral amputation and involves the soft tissues of the distal apex of the ostomy, especially in the anterior part. It is caused by the overloading of the muscles sutured to the cortical of the femoral bone during the first surgical step (myodesis); this anchorage, at the beginning, is weak and only physical exercise and walking allow the formation of a solid tendon junction between the cortical surface of the bone and the distal portion of the stump muscles.

The subject usually complains of a sensation of heat and burning at the apex of the ostomy, with an onset related to the activities performed during the rehabilitation session and sometimes accompanied by bleeding.

The pain could worsen at the moment in which the total load on the implant is granted, that is, after the abandonment of the aids (canes or crutches).

Coxofemoral joint pain

Hip pain or coxalgia is the consequence of overloading the coxo-femoral joint. When wearing a transfemoral prosthesis with socket, the joint is deprived of the physiological load, since it is discharged directly on the pelvis; this leads to a thinning of the articular cartilage, due to disuse. In the case of an osseointegrated prosthesis, the weight is redistributed along the physiological axis and the hip may become painful.

Coxalgia is an indication to limit the level of load or activity, taking care to always use a walking aid. If the condition worsens, it would be appropriate to investigate the state of joint degeneration by radiography. In the case of severe osteoarthritis resistant to conservative treatment, the need for hip replacement should be evaluated.

Neuroma and phantom limb pain

Neurologic-type pain in the amputated limb is often caused by the formation of a neuroma at the level of the amputated nerve. Hypersensitivity of the stump skin may be a manifestation of this.

Pain can be controlled by drugs that inhibit nerve signal transmission (e.g. gabapentin, pregabalin or amitriptyline); however, since they cause drowsiness, it is advisable to limit their use to the evening, in order to ensure proper rest of the subject and avoid drowsiness and fatigue during the day. If the patient needs a higher dosage, it is advisable to administer low dosages during daytime hours. Distractions such as sports, work, or socializing activities can be an effective tool to combat this type of pain, which is greatly affected by the subject's emotional state.

The use of Tecar therapy or a simple local massage can provide relief to the patient.

Caution: the use of a perinervous catheter connected to an external infusor represents a solution applicable only in the immediate postoperative period, but finds difficulty in

use during rehabilitation sessions, as it can be mobilized after careless movements or tractions on the catheter.

Rehabilitation of the patient with osseointegrated transfemoral prosthesis

The rehabilitation path is structured in order to allow a gradual load on the osseointegrated limb. Although recovery times may vary depending on the characteristics of the subject, it is appropriate to provide clear and precise indications on the type of exercises allowed depending on the phase of the rehabilitation process. These indications are designed to allow any specialized physiotherapy center to have the necessary tools to allow a proper rehabilitation of the osseointegrated patient.

General indications

Rehabilitation treatment begins in the preoperative period, when the patient's general condition, the status of the stump and the contralateral limb in terms of muscle strength and range of motion (ROM) are evaluated. If limitations or deficits are present, a personalized rehabilitation project is elaborated, which may include muscle strengthening and stretching exercises to be performed by the patient independently, both before surgery and during the pause between the two surgical steps.

The rehabilitation is preceded by the assembly phase of the external prosthesis by an Orthopedic Technician, who is responsible for the assembly of the Heli connector and the alignment of the prosthesis.

It is advisable that the physiotherapist and the orthopedic technician collaborate on the alignment of the prosthetic components during the duration of the rehabilitation phase, so that any necessary modifications can be made in a timely manner, optimizing the rehabilitation time.

The rehabilitation process begins with the patient being taken care of by the physiatrist who defines the objectives to be achieved with the personalized rehabilitation project, sharing them with the person concerned. The physiatrist, moreover, intervenes every time the subject complains of pain in the operated limb, in order to establish if it is possible to continue with the session or if, otherwise, the patient needs a day of rest. In this regard it is useful to use the NRS (Numerical Rate Scale) considering a pain intensity of intensity equal to or greater than 5 out of 10 deserving to be investigated before starting the execution of any exercise.

The rehabilitation pathway is divided into training sessions according to the functional/motor objectives established.

In the original Dutch version, the rehabilitation path of the transfemoral osseointegrated patient provides two hours of training twice a week, for a total of 22 sessions distributed in 11 weeks. A pause is foreseen after the tenth session, in order to allow the patient to familiarize with the correct use of walking aids, maintaining a correct gait pattern and at the same time strengthening the muscles, while waiting for the completion of the final rehabilitation phase; during this last phase, the reduction or, if possible, the abandonment of the aids during walking is foreseen.

The period of suspension from training can last 4 weeks, or extend up to 12 weeks, if the level of pain or limited muscle strength does not allow the continuation of rehabilitation. In the version adapted by the staff of the INAIL Rehabilitation Center, there are 44 sessions divided into two phases: the first concludes at the twentieth session and the second begins again at the twenty-first and ends at the forty-fourth, which corresponds to the end of the rehabilitation path. Also in this case, between the two phases, a period of suspension is included.
The sessions are carried out every morning, with a total duration of about three hours, from Monday to Friday. They can also be repeated in reduced sessions in the afternoon, provided that the patient does not experience pain or excessive fatigue.
The patient recovers ambulation by progressively reducing the need for support during walking.
The physiotherapist constantly follows the patient during the execution of each exercise, paying particular attention to the correct execution of the tasks suggested and the posture assumed by the subject.

Case report

In this section we present the case of a 44 years old patient, who had undergone a left transfemoral amputation following a motorcycle accident in 2003. In that occasion, the patient had also suffered an amputation of the fifth finger of the left hand at the proximal interphalangeal level, a lacerated wound at the level of the volar region of the left hand and a traumatic lesion of the extensor muscles of the left hand. The patient came to our observation because, despite the realization of several prostheses at the INAIL Center of Vigorso, he was not fully satisfied with his socket, which caused decubitus at the ischial and gluteal level, pain at the level of the scar, excessive sweating and easy fatigability during walking, with important limitation in the continuous and satisfactory use of the external prosthesis. He reported occasional numbness in the distal portion of the stump, in the absence of strength deficit. The shape of the stump was tapered distally, whereas the length of the stump was sufficient to accommodate a standard implant (Fig. 43). Ipsilateral hip movements were complete and pain free. No other major comorbidities were present. The external prosthesis provided to the patient was the Genium X3 (Ottobock, Italy).
After a preliminary evaluation by a multidisciplinary team composed of orthopedist, physiatrist, prosthetic technician and psychologist, the patient was indicated for revision surgery of the left transfemoral stump and implantation of an osseointegrated prosthesis, with the aim of allowing the patient to use the external prosthesis without socket with probable resolution of skin problems, better muscle control of the stump and an overall improvement in quality of life.

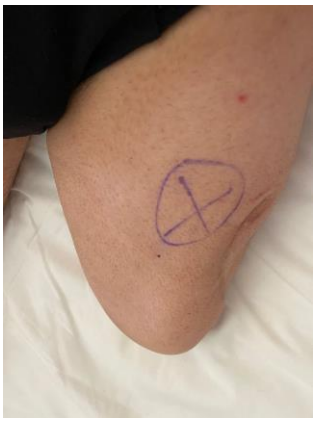

Figure 43 - Preoperative image of the amputation stump. Note the irregular shape that prevented optimal congruence with the socket.

Description of clinical trend

The patient was admitted to the II Orthopedic and Trauma Clinic of the Rizzoli Orthopedic Institute. Preoperatively, routine examinations and panoramic radiographs were performed in orthostatism with external prosthesis worn and calibrated, plus a lateral projection of the amputation stump. A preoperative gait analysis was also performed.

On March 3, 2021, the patient underwent the first surgical step of stump revision and implantation of the osseointegrated intramedullary stem (Fig. 44). During this procedure, 5 tantalum markers were also implanted to perform postoperative static RSA, with the purpose of monitoring possible implant migration.

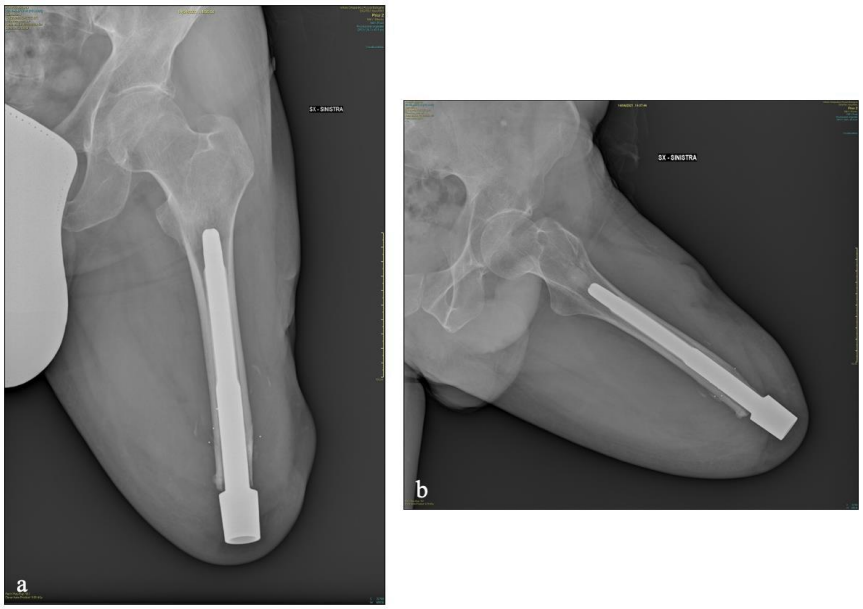

Figure 44 - Anteroposterior (a) and lateral (b) radiographic projection of the postoperative control after the second surgical step. The transcutaneous double-cone adapter can be noted.

In the postoperative period, a compressive bandage was packed to control the postoperative swelling of the stump. The patient had a smooth course and was

discharged on the third postoperative day in good general condition and with the surgical wound in order. The patient was not allowed to wear the socket in his possession so as not to interfere with the healing processes of the surgical wound and the osseointegration of the implant. In addition, the socket would not have adhered perfectly because the shape of the had been changed after bone regularization and muscle plasticity.
On 15/04/2021 the second surgical step of creation of the skin ostomy and implantation of the transcutaneous double-cone adapter was performed (Fig. 45).

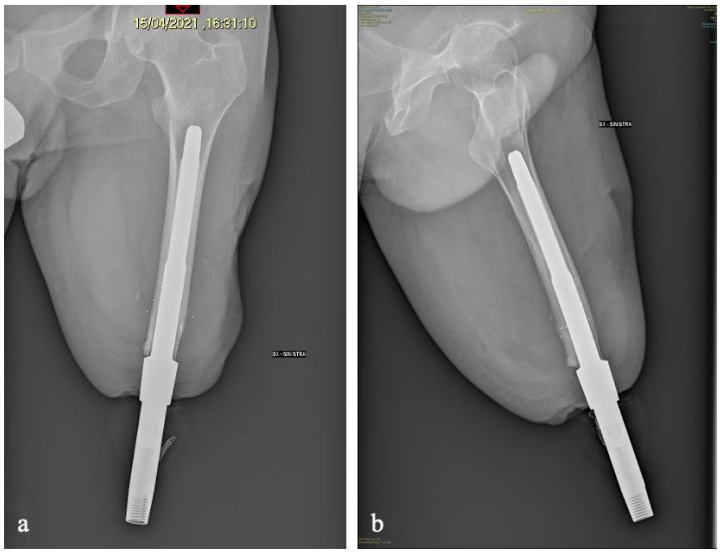

Figure 45 - Anteroposterior (a) and lateral (b) radiographic projection of the postoperative control after the second surgical step. The transcutaneous double-cone adapter can be seen.

The course was smooth and the patient was discharged on the second postoperative day.
After a convalescence period of 15 days, the patient started the rehabilitation path, lasting 17 days at the INAIL Prosthesis Center of Vigorso di Budrio. The osseointegration procedure had very positive results on the quality of life of the patient, who returned after a short time to wear the external prosthesis with ease and to use it for many hours a day. As shown by the results of the subdomains of the Q-TFA questionnaire, the percentage of prosthesis use increased from 51% to 90% at 3-month follow-up, the level of mobility improved from 79% to 95%, and problems decreased from 47% to 13%, with an overall improvement from 33% to 91%. Preoperative values were below average in all subdomains, whereas postoperative values were above average [44]. Regarding the EQ-5D-5L questionnaire, improvement was observed in all domains, particularly the one inherent to pain/annoyance, which went from 4 to 2. On the other hand, with regard to the stability of the implant by static RSA, the results are not yet analyzable, as they are awaiting subsequent follow-ups.

Kinematic gait analysis

Preoperatively, a functional gait analysis of the transfemoral amputee patient was performed using 15 wearable inertial sensors (XSens, Awinda). The sensors were placed in different body segments (head, forearm, arm, shoulder, trunk, pelvis, thigh, leg, and foot) (Fig. 46). The system provides real-time kinematics of the whole body in the three anatomical planes.

Figure 46 - Sensor placement for analysis.

The tests performed involved walking along a corridor for 10 meters and the Timed up and go (TUG).
The walking was performed in two modes:

- ✓ 2 times at the normal speed usually held by the subject;
- ✓ 2 times at the maximum possible speed.

The spatio-temporal parameters of the gait such as step length, in particular of the swing and stance phase, symmetry between the limbs, speed of execution of the movement, step cadence and joint kinematics were evaluated. This information was compared between healthy and amputee limbs and between walking performed at normal and maximal speed.
Preoperative kinematic analysis showed (Tab. 2) that the swing phase was longer for the amputee limb, a finding in line with the literature [45, 46]. In addition, greater limb differences emerged in midstance and no difference between fast and normal gait.

Table 2 - Preoperative spatiotemporal gait parameters.

Gait cycle (%)	Normal	Fast	Difference
Stance			
Amputee limb	51.94 ± 1.09	51.00 ± 0.98	0.94 ± 0.11
Sound limb	57.80 ± 0.70	58.15 ± 0.81	-0.35 ± -0.11
Difference	-5.87	-7.15	1.28
Symmetry [a]	1.12	1.13	
Swing			
Amputee limb	48.06 ± 1.09	49.00 ± 0.98	-0.94 ± 0.11
Sound limb	42.10 ± 1.21	41.71 ± 1.14	0.39 ± 0.07
Difference	5.97	7.30	-1.33

Furthermore, when analyzing individual body districts, the following kinematic differences were revealed (Fig. 47-48).
Regarding the ankle, no peak plantar flexion, eversion, and internal rotation were found in the swing.
Regarding the knee, no peak of flexion in stance, no peak of abduction and external rotation in the swing were found.
Clearly, it should be considered that the kinematics of knee and ankle is closely linked, for the amputated limb, to the prosthetic model used by the subject, i.e. the Genium X3. The ankle lacks the propulsive phase, as the prosthesis is passive.
As far as the hip joint is concerned, during the swing phase, no abduction has emerged, while a greater internal rotation has been found.
Analyzing the kinematics of the pelvis, a greater anteroversion was found, with greater tilt towards the amputated limb.
The trunk showed a persistent flexion and tilt on the amputated side, at the moment of the impact of the foot on the ground. This phenomenon, called limping, or lameness, emerged more markedly in fast gait (Fig. 49).

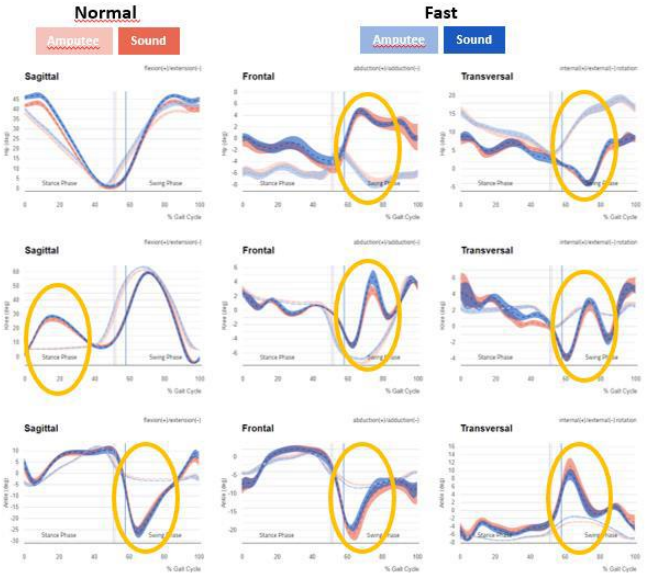

Figure 47 - Preoperative kinematic data of hip, knee, ankle

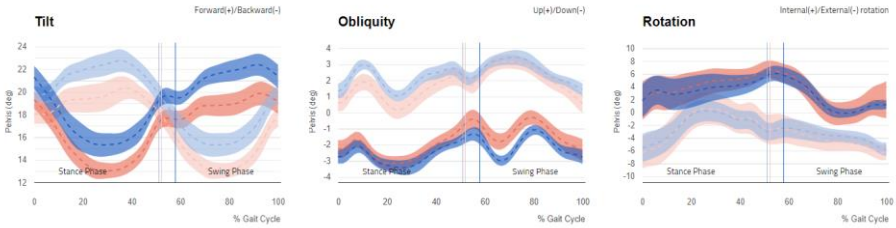

Figure 48 - Preoperative kinematic data of the pelvis.

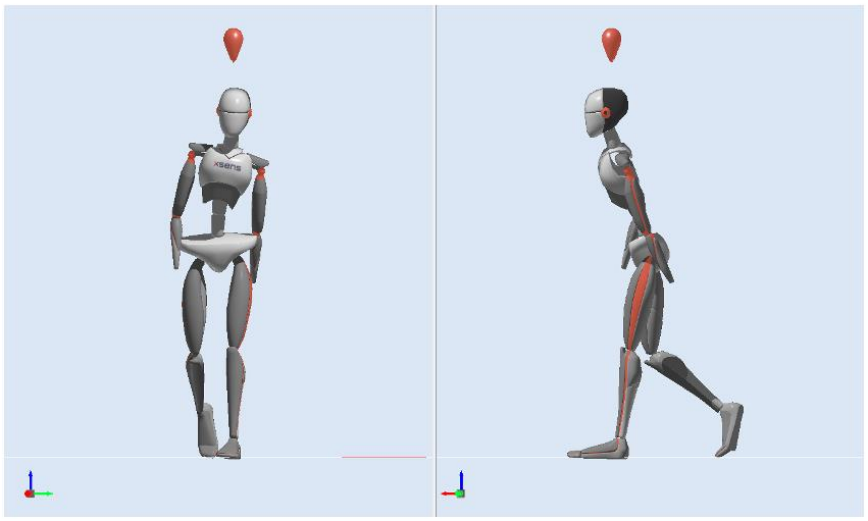

Figure 49 - Focus on altered trunk motion of subject in preoperative fast walk through Avatar in the inertial sensor software.

Regarding joint dynamics, sensors placed on the thigh and leg detected greater acceleration peaks in the healthy limb at heel strike, first motor impulse, and terminal swing. The acceleration peaks were of greater intensity during walking with a fast gait.

Below, the execution times related to the phases of the preoperative TUG test are listed:

- ✓ Lifting: 1.2 sec;
- ✓ Forward walk: 2.2 sec;
- ✓ 180° Flip: 2.0 sec;
- ✓ Walk backward: 2.8 sec;
- ✓ Sitting: 1.4 sec;
- ✓ Total: 9.6 sec.

In conclusion, in the preoperative, no problems emerged in fast walking and daily movements (as also reported by the patient), the altered spatio-temporal and kinematic parameters were in line with the literature.

There were signs of limited gluteal and trunk stability, probably caused by muscular hypotonia and poor socket ergonomics.
The kinematic gait analysis was repeated with the same functional tests at a follow-up of 3 months from the second surgical step, after the finish of the rehabilitation course.
The spatiotemporal results that emerged from this analysis were:

- ✓ An increased walking speed with a lower cadence, ie, a longer stride walk (Tab. 3);
- ✓ A reduced swing phase in the amputee limb after rehabilitation (Tab. 4).

Therefore, a greater safety in the support of the limb on the ground emerged, probably due to the more physiological distribution of the load through the prosthesis directly connected to the subject's skeleton. Moreover, the better muscular control of the stump allowed to optimize the gait cycle, which was faster and more physiological.
From what emerges in the literature, these spatiotemporal parameters correspond to a better quality of gait [45, 47-48].

Table 3 - Pre- and postoperative gait velocity data.

	Follow-up	Pre-op	Difference
Speed (m/s)	1.66	1.63	0.03
Cadence (steps/min)	127.67	131.67	-4.00

Table 4 - Spatiotemporal parameters of pre- and postoperative gait.

Gait cycle (%)	Follow-up	Pre-op	Difference
Stance			
Amputee limb	54.82 ± 1.30	51.00 ± 0.98	3.82 ± 0.32
Sound limb	59.62 ± 0.97	58.15 ± 0.81	1.47 ± 0.16
Difference	-4.80	-7.15	2.35
Swing			
Amputee limb	45.18 ± 1.30	49.00 ± 0.98	-3.82 ± 0.32
Sound limb	40.27 ± 1.35	41.71 ± 1.14	-1.44 ± 0.21
Difference	4.91	7.30	-2.39

Analyzing the individual body districts, at follow-up, the following kinematic differences were highlighted. In the amputated limb, there was a reduced abduction and internal rotation of the hip compared with preoperatively (Fig. 50), a reduced tilt and rotation of the pelvis toward the amputated limb (Fig. 51), and, as for the trunk, a partial resolution of flexion and tilt toward the amputated side at the moment of foot impact on the ground (Fig. 52).

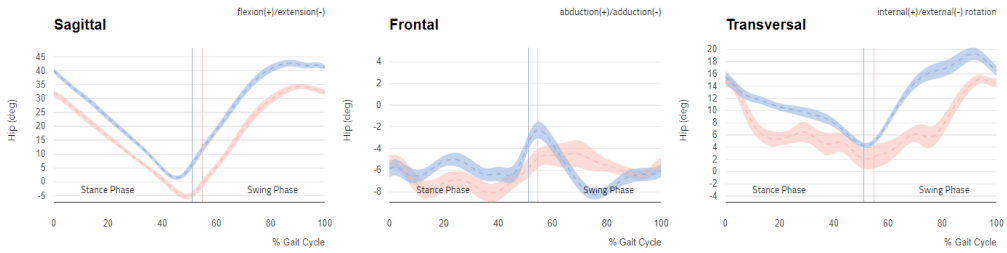

Figure 50 - Preoperative (blue line) and follow-up (red line) hip kinematic data compared.

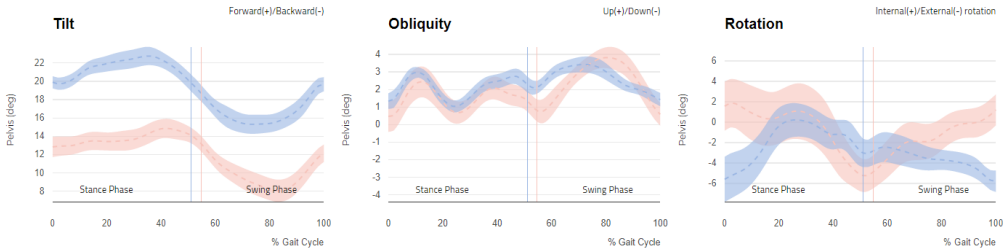

Figure 51 - Preoperative (blue line) and postoperative (red line) pelvis kinematic data compared.

These improvements in gait quality are indicators of improved muscular stability, particularly at the trunk and gluteal levels, which allowed for better motor coordination by reducing asymmetry between limbs.

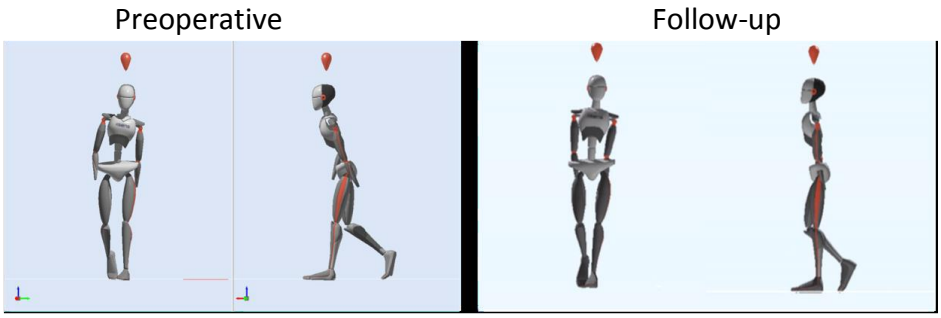

Figure 52 - Comparison of pre- and post-surgery osseointegration motion with particular focus on trunk mobility through Avatar in the inertial sensor software.

Below, the execution times related to the phases of the TUG test performed at 3-month follow-up are listed:

- ✓ Standing up: 1.0 sec;
- ✓ Forward walk: 2.3 sec;
- ✓ Flip 180°: 2.2 sec;
- ✓ Backward walk: 3.1 sec;
- ✓ Session: 1.5 sec;
- ✓ Total: 10.1 sec.

No substantial differences emerged with respect to the data acquired preoperatively. However, it must be emphasized that these results do not reflect the final results that will be evaluated at one year of follow-up.

Conclusions

Osseointegrated prosthesis surgery for transfemoral amputation represents a promising solution for the treatment of amputees who are not satisfied due to problems caused by the socket and have a poor quality of life. The experience matured thanks to the Me.Ta.COs project has allowed to introduce in Italy this treatment and to draw up protocols regarding the surgical technique, the adjustment of the prosthesis, the rehabilitation path and the management of the ostomy. The selection of the patient, that must be done by a multidisciplinary team considering not only the clinical aspects but also the psychological ones, and the follow up time, are fundamental to optimize the clinical results and to diagnose eventual complications at an early stage.

However, the research is going on, currently focusing on the development of customized implants for osseointegration, to be used in cases of short or irregular stump, in which some technical improvements developed during the course of this project will be implemented.

In the coming years it will continue the collection of clinical, radiographic and kinematic data of subjects undergoing this procedure in order to perform a long-term monitoring of both clinical outcomes and quality of life.

Procedures have also been initiated to obtain a reimbursement for health care costs, which will allow all subjects with transfemoral amputation, not satisfied by the use of the socket, to improve their quality of life through osseointegration.

References

[1] Ebskov LB, Schroeder TV, Holstein PE. Epidemiology of leg amputation: the influence of vascular surgery. Br J Surg. 1994 Nov;81(11):1600-3. doi: 10.1002/bjs.1800811111. PMID: 7827881.

[2] Marks LJ, Michael JW. Science, medicine, and the future: Artificial limbs. BMJ 2001;323:732–5. https://doi.org/10.1136/bmj.323.7315.732

[3] Kalbaugh CA, Strassle PD, Paul NJ, McGinigle KL, Kibbe MR, Marston WA. Trends in Surgical Indications for Major Lower Limb Amputation in the USA from 2000 to 2016. Eur J Vasc Endovasc Surg Off J Eur Soc Vasc Surg 2020;60:88–96. https://doi.org/10.1016/j.ejvs.2020.03.018.

[4] WORLD HEALTH ORGANIZATION, et al. United States Department of Defense, MossRehab Amputee Rehabilitation Program, MossRehab Hospital, USA. The Rehabilitation of People with Amputations. General: WHO/RHB/Distr, 2004.

[5] Van de Meent H, Hopman MT, Frölke JP. Walking ability and quality of life in subjects with transfemoral amputation: a comparison of osseointegration with socket prostheses. Arch Phys Med Rehabil 2013;94:2174–8. https://doi.org/10.1016/j.apmr.2013.05.020.

[6] Hagberg K, Brånemark R. Consequences of non-vascular trans-femoral amputation: a survey of quality of life, prosthetic use and problems. Prosthet Orthot Int 2001;25:186–94. https://doi.org/10.1080/03093640108726601.

[7] Buikema KES, Meyerle JH. Amputation stump: Privileged harbor for infections, tumors, and immune disorders. Clin Dermatol 2014;32:670–7. https://doi.org/10.1016/j.clindermatol.2014.04.015.

[8] Dudek NL, Marks MB, Marshall SC, Chardon JP. Dermatologic conditions associated with use of a lower-extremity prosthesis. Arch Phys Med Rehabil 2005;86:659–63. https://doi.org/10.1016/j.apmr.2004.09.003.

[9] Meulenbelt HEJ, Geertzen JHB, Jonkman MF, Dijkstra PU. Skin problems of the stump in lower-limb amputees: 2. Influence on functioning in daily life. Acta Derm Venereol 2011;91:178–82. https://doi.org/10.2340/00015555-1023.

[10] BOWERS, R. US Military Builds on Rich History of Amputee Care. Military in-Step, 2008.

[11] Brånemark R, Berlin O, Hagberg K, Bergh P, Gunterberg B, Rydevik B. A novel osseointegrated percutaneous prosthetic system for the treatment of patients with transfemoral amputation: A prospective study of 51 patients. Bone Jt J 2014;96-B:106–13. https://doi.org/10.1302/0301-620X.96B1.31905.

[12] Hagberg K, Häggström E, Uden M, Brånemark R. Socket versus bone-anchored trans-femoral prostheses: hip range of motion and sitting comfort. Prosthet Orthot Int 2005;29:153–63. https://doi.org/10.1080/03093640500238014.

[13] Tranberg R, Zügner R, Kärrholm J. Improvements in hip- and pelvic motion for patients with osseointegrated trans-femoral prostheses. Gait Posture 2011;33:165–8. https://doi.org/10.1016/j.gaitpost.2010.11.004.

[14] Hagberg K, Hansson E, Brånemark R. Outcome of percutaneous osseointegrated prostheses for patients with unilateral transfemoral amputation at two-year follow-up. Arch Phys Med Rehabil 2014;95:2120–7. https://doi.org/10.1016/j.apmr.2014.07.009.
[15] Hagberg K, Brånemark R, Gunterberg B, Rydevik B. Osseointegrated trans-femoral amputation prostheses: prospective results of general and condition-specific quality of life in 18 patients at 2-year follow-up. Prosthet Orthot Int 2008;32:29–41. https://doi.org/10.1080/03093640701553922.
[16] Schalk SAF, Jonkergouw N, van der Meer F, Swaan WM, Aschoff H-H, van der Wurff P. The Evaluation of Daily Life Activities after Application of an Osseointegrated Prosthesis Fixation in a Bilateral Transfemoral Amputee: A Case Study. Medicine (Baltimore) 2015;94:e1416. https://doi.org/10.1097/MD.0000000000001416.
[17] Lundberg M, Hagberg K, Bullington J. My prosthesis as a part of me: a qualitative analysis of living with an osseointegrated prosthetic limb. Prosthet Orthot Int 2011;35:207–14. https://doi.org/10.1177/0309364611409795.
[18] Hebert JS, Rehani M, Stiegelmar R. Osseointegration for Lower-Limb Amputation: A Systematic Review of Clinical Outcomes. JBJS Rev 2017;5:e10. https://doi.org/10.2106/JBJS.RVW.17.00037.
[19] Brånemark RP, Hagberg K, Kulbacka-Ortiz K, Berlin Ö, Rydevik B. Osseointegrated Percutaneous Prosthetic System for the Treatment of Patients With Transfemoral Amputation: A Prospective Five-year Follow-up of Patient-reported Outcomes and Complications. J Am Acad Orthop Surg 2019;27:e743–51. https://doi.org/10.5435/JAAOS-D-17-00621.
[20] Li Y, Brånemark R. Osseointegrated prostheses for rehabilitation following amputation : The pioneering Swedish model. Unfallchirurg 2017;120:285–92. https://doi.org/10.1007/s00113-017-0331-4.
[21] Al Muderis M, Lu W, Li JJ. Osseointegrated Prosthetic Limb for the treatment of lower limb amputations : Experience and outcomes. Unfallchirurg 2017;120:306–11. https://doi.org/10.1007/s00113-016-0296-8.
[22] Tomaszewski PK, Verdonschot N, Bulstra SK, Rietman JS, Verkerke GJ. Simulated bone remodeling around two types of osseointegrated implants for direct fixation of upper-leg prostheses. J Mech Behav Biomed Mater 2012;15:167–75. https://doi.org/10.1016/j.jmbbm.2012.06.015.
[23] Tomaszewski PK, van Diest M, Bulstra SK, Verdonschot N, Verkerke GJ. Numerical analysis of an osseointegrated prosthesis fixation with reduced bone failure risk and periprosthetic bone loss. J Biomech 2012;45:1875–80. https://doi.org/10.1016/j.jbiomech.2012.05.032.
[24] Frossard LA, Tranberg R, Haggstrom E, et al. Load on osseointegrated fixation of a transfemoral amputee during a fall: loading, descent, impact and recovery analysis. Prosthet Orthot Int 2010; 34:85–97
[25] Nebergall A, Bragdon C, Antonellis A, Kärrholm J, Brånemark R, Malchau H. Stable fixation of an osseointegated implant system for above-the-knee amputees: titel RSA and radiographic evaluation of migration and bone remodeling in 55 cases. Acta Orthop 2012;83:121–8. https://doi.org/10.3109/17453674.2012.678799.

[26] Frölke JPM, Leijendekkers RA, van de Meent H. Osseointegrated prosthesis for patients with an amputation : Multidisciplinary team approach in the Netherlands. Unfallchirurg 2017;120:293–9. https://doi.org/10.1007/s00113-016-0302-1.
[27] Juhnke D-L, Beck JP, Jeyapalina S, Aschoff HH. Fifteen years of experience with Integral-Leg-Prosthesis: Cohort study of artificial limb attachment system. J Rehabil Res Dev 2015;52:407–20. https://doi.org/10.1682/JRRD.2014.11.0280.
[28] Stenlund P, Trobos M, Lausmaa J, Brånemark R, Thomsen P, Palmquist A. Effect of load on the bone around bone-anchored amputation prostheses. J Orthop Res Off Publ Orthop Res Soc 2017;35:1113–22. https://doi.org/10.1002/jor.23352.
[29] Al Muderis M, Khemka A, Lord SJ, Van de Meent H, Frölke JPM. Safety of Osseointegrated Implants for Transfemoral Amputees: A Two-Center Prospective Cohort Study. J Bone Joint Surg Am 2016;98:900–9. https://doi.org/10.2106/JBJS.15.00808.
[30] Kunutsor SK, Gillatt D, Blom AW. Systematic review of the safety and efficacy of osseointegration prosthesis after limb amputation. Br J Surg 2018;105:1731–41. https://doi.org/10.1002/bjs.11005.
[31] Muderis MA, Tetsworth K, Khemka A, Wilmot S, Bosley B, Lord SJ, et al. The Osseointegration Group of Australia Accelerated Protocol (OGAAP-1) for two-stage osseointegrated reconstruction of amputated limbs. Bone Jt J 2016;98-B:952–60. https://doi.org/10.1302/0301-620X.98B7.37547.
[32] Tillander J, Hagberg K, Berlin Ö, Hagberg L, Brånemark R. Osteomyelitis Risk in Patients With Transfemoral Amputations Treated With Osseointegration Prostheses. Clin Orthop 2017;475:3100–8. https://doi.org/10.1007/s11999-017-5507-2.
[33] Widmer A. New developments in diagnosis and treatment of infection in orthopedic implants. Clin Infect Dis 2001; 33(Suppl 2): S94–S 106.
[34] Leijendekkers RA, van Hinte G, Frölke JP, van de Meent H, Nijhuis-van der Sanden MWG, Staal JB. Comparison of bone-anchored prostheses and socket prostheses for patients with a lower extremity amputation: a systematic review. Disabil Rehabil 2017;39:1045–58. https://doi.org/10.1080/09638288.2016.1186752.
[35] Hagberg K, Rickard B, Hägg O. Questionnaire for persons with a transfemoral amputation (Q-TFA): initial validity and reliability of a new outcome measure. J Rehabil Res Dev 2004;41:695–706. 10.1682/JRRD.2003.11.0167
[36] Resnik L, Borgia M. Reliability of outcome measures for people with lower-limb amputations: distinguishing true change from statistical error. Phys Ther 2011;91:555–65. https://doi.org/10.2522/ptj.20100287.
[37] Comparison of EuroQol-5D-3L and Short Form-6D Utility Scores in Family Caregivers of Colorectal Cancer Patients: A Cross-Sectional Survey in China Cheng-Yao Sun 1, Yang Liu 2, Liang-Ru Zhou 1, Ming-Si Wang 1, Xian-Ming Zhao 3, Wei-Dong Huang 1, Guo-Xiang Liu 1, Xin Zhang 1 Affiliations expand PMID: 34660519 PMCID: PMC8511410 DOI: 10.3389/fpubh.2021.742332
[38] Matos Casano HA, Anjum F. Six Minute Walk Test. 2021 Dec 8. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 35015445.
[39] Content comparison of four commonly used amputee mobility assessment scales in the literature by linking to the International Classification of Functioning, Disability, and

Health. Ekinci Y, Yaşaroğlu ÖF, Düger T.Prosthet Orthot Int. 2021 Dec 1;45(6):544-552. doi: 10.1097/PXR.0000000000000052.PMID: 34693937
[40] Bottner F, Su E, Nestor B, Azzis B, Sculco TP, Bostrom M. Radiostereometric Analysis: The Hip. HSS J 2005;1:94–9. https://doi.org/10.1007/s11420-005-0114-2.
[41] Ryd L, Yuan X, Löfgren H. Methods for determining the accuracy of radiostereometric analysis (RSA). Acta Orthop Scand 2000;71:403–8. https://doi.org/10.1080/000164700317393420.
[42] Aro E, Alm JJ, Moritz N, Mattila K, Aro HT. Good stability of a cementless, anatomically designed femoral stem in aging women: a 9-year RSA study of 32 patients. Acta Orthop 2018;89:490–5. https://doi.org/10.1080/17453674.2018.1490985.
[43] Zinno R, Di Paolo S, Ambrosino G, Alesi D, Zaffagnini S, Barone G, Bragonzoni L. Migration of the femoral component and clinical outcomes after total knee replacement: a narrative review. Musculoskelet Surg. 2021 Dec;105(3):235-246. doi: 10.1007/s12306-020-00690-8. Epub 2020 Dec 14. PMID: 33315156; PMCID: PMC8578080.
[44] Hagberg K, Brånemark R, Hägg O. Questionnaire for Persons with a Transfemoral Amputation (Q-TFA): initial validity and reliability of a new outcome measure. J Rehabil Res Dev 2004;41:695–706.
[45] Andrysek J, García D, Rozbaczylo C, Alvarez-Mitchell C, Valdebenito R, Rotter K, et al. Biomechanical responses of young adults with unilateral transfemoral amputation using two types of mechanical stance control prosthetic knee joints. Prosthet Orthot Int 2020;44:314–22. https://doi.org/10.1177/0309364620916385.
[46] Tranberg R, Zugner R and Karrholm J. Improvements in hipand pelvic motion for patients with osseointegrated transfemoral prostheses. Gait Posture 2011; 33: 165–168.
[47] Cutti AG, Verni G, Migliore GL, Amoresano A, Raggi M. Reference values for gait temporal and loading symmetry of lower-limb amputees can help in refocusing rehabilitation targets. J NeuroEngineering Rehabil 2018;15:61. https://doi.org/10.1186/s12984-018-0403-x.
[48] Andrysek J, Wright FV, Rotter K, et al. Long-term clinical evaluation of the automatic stance-phase lock-controlled prosthetic knee joint in young adults with unilateral aboveknee amputation. Disabil Rehabil Assist Technol 2017; 12: 378–384.

Bibliografia

[1] Marks LJ, Michael JW. Science, medicine, and the future: Artificial limbs. BMJ 2001;323:732–5. https://doi.org/10.1136/bmj.323.7315.732.

[2] Dillingham TR, Pezzin LE, MacKenzie EJ. Incidence, acute care length of stay, and discharge to rehabilitation of traumatic amputee patients: an epidemiologic study. Arch Phys Med Rehabil 1998;79:279–87. https://doi.org/10.1016/s0003-9993(98)90007-7.

[3] Kalbaugh CA, Strassle PD, Paul NJ, McGinigle KL, Kibbe MR, Marston WA. Trends in Surgical Indications for Major Lower Limb Amputation in the USA from 2000 to 2016. Eur J Vasc Endovasc Surg Off J Eur Soc Vasc Surg 2020;60:88–96. https://doi.org/10.1016/j.ejvs.2020.03.018.

[4] Lombardo FL, Maggini M, De Bellis A, Seghieri G, Anichini R. Lower extremity amputations in persons with and without diabetes in Italy: 2001-2010. PloS One 2014;9:e86405. https://doi.org/10.1371/journal.pone.0086405.

[5] Van de Meent H, Hopman MT, Frölke JP. Walking ability and quality of life in subjects with transfemoral amputation: a comparison of osseointegration with socket prostheses. Arch Phys Med Rehabil 2013;94:2174–8. https://doi.org/10.1016/j.apmr.2013.05.020.

[6] Hagberg K, Brånemark R. Consequences of non-vascular trans-femoral amputation: a survey of quality of life, prosthetic use and problems. Prosthet Orthot Int 2001;25:186–94. https://doi.org/10.1080/03093640108726601.

[7] Buikema KES, Meyerle JH. Amputation stump: Privileged harbor for infections, tumors, and immune disorders. Clin Dermatol 2014;32:670–7. https://doi.org/10.1016/j.clindermatol.2014.04.015.

[8] Dudek NL, Marks MB, Marshall SC, Chardon JP. Dermatologic conditions associated with use of a lower-extremity prosthesis. Arch Phys Med Rehabil 2005;86:659–63. https://doi.org/10.1016/j.apmr.2004.09.003.

[9] Meulenbelt HEJ, Geertzen JHB, Jonkman MF, Dijkstra PU. Skin problems of the stump in lower-limb amputees: 2. Influence on functioning in daily life. Acta Derm Venereol 2011;91:178–82. https://doi.org/10.2340/00015555-1023.

[10] Brånemark R, Berlin O, Hagberg K, Bergh P, Gunterberg B, Rydevik B. A novel osseointegrated percutaneous prosthetic system for the treatment of patients with transfemoral amputation: A prospective study of 51 patients. Bone Jt J 2014;96-B:106–13. https://doi.org/10.1302/0301-620X.96B1.31905.

[11] Hagberg K, Häggström E, Uden M, Brånemark R. Socket versus bone-anchored trans-femoral prostheses: hip range of motion and sitting comfort. Prosthet Orthot Int 2005;29:153–63. https://doi.org/10.1080/03093640500238014.

[12] Tranberg R, Zügner R, Kärrholm J. Improvements in hip- and pelvic motion for patients with osseointegrated trans-femoral prostheses. Gait Posture 2011;33:165–8. https://doi.org/10.1016/j.gaitpost.2010.11.004.

[13] Hagberg K, Hansson E, Brånemark R. Outcome of percutaneous osseointegrated prostheses for patients with unilateral transfemoral amputation at two-year follow-up. Arch Phys Med Rehabil 2014;95:2120–7. https://doi.org/10.1016/j.apmr.2014.07.009.

[14] Hagberg K, Brånemark R, Gunterberg B, Rydevik B. Osseointegrated trans-femoral amputation prostheses: prospective results of general and condition-specific quality of life in 18 patients at 2-year follow-up. Prosthet Orthot Int 2008;32:29–41. https://doi.org/10.1080/03093640701553922.
[15] Schalk SAF, Jonkergouw N, van der Meer F, Swaan WM, Aschoff H-H, van der Wurff P. The Evaluation of Daily Life Activities after Application of an Osseointegrated Prosthesis Fixation in a Bilateral Transfemoral Amputee: A Case Study. Medicine (Baltimore) 2015;94:e1416. https://doi.org/10.1097/MD.0000000000001416.
[16] Lundberg M, Hagberg K, Bullington J. My prosthesis as a part of me: a qualitative analysis of living with an osseointegrated prosthetic limb. Prosthet Orthot Int 2011;35:207–14. https://doi.org/10.1177/0309364611409795.
[17] Hobusch GM, Döring K, Brånemark R, Windhager R. Advanced techniques in amputation surgery and prosthetic technology in the lower extremity. EFORT Open Rev 2020;5:724–41. https://doi.org/10.1302/2058-5241.5.190070.
[18] Mastinu E, Engels LF, Clemente F, Dione M, Sassu P, Aszmann O, et al. Neural feedback strategies to improve grasping coordination in neuromusculoskeletal prostheses. Sci Rep 2020;10:11793. https://doi.org/10.1038/s41598-020-67985-5.
[19] Hebert JS, Rehani M, Stiegelmar R. Osseointegration for Lower-Limb Amputation: A Systematic Review of Clinical Outcomes. JBJS Rev 2017;5:e10. https://doi.org/10.2106/JBJS.RVW.17.00037.
[20] Li Y, Brånemark R. Osseointegrated prostheses for rehabilitation following amputation : The pioneering Swedish model. Unfallchirurg 2017;120:285–92. https://doi.org/10.1007/s00113-017-0331-4.
[21] Muderis MA, Tetsworth K, Khemka A, Wilmot S, Bosley B, Lord SJ, et al. The Osseointegration Group of Australia Accelerated Protocol (OGAAP-1) for two-stage osseointegrated reconstruction of amputated limbs. Bone Jt J 2016;98-B:952–60. https://doi.org/10.1302/0301-620X.98B7.37547.
[22] Leijendekkers RA, van Hinte G, Frölke JP, van de Meent H, Nijhuis-van der Sanden MWG, Staal JB. Comparison of bone-anchored prostheses and socket prostheses for patients with a lower extremity amputation: a systematic review. Disabil Rehabil 2017;39:1045–58. https://doi.org/10.1080/09638288.2016.1186752.
[23] Al Muderis M, Lu W, Li JJ. Osseointegrated Prosthetic Limb for the treatment of lower limb amputations : Experience and outcomes. Unfallchirurg 2017;120:306–11. https://doi.org/10.1007/s00113-016-0296-8.
[24] Stam HJ, Dommisse A-MV, Bussmann HJBJ. Prevalence of low back pain after transfemoral amputation related to physical activity and other prosthesis-related parameters. Disabil Rehabil 2004;26:794–7. https://doi.org/10.1080/09638280410001696683.
[25] Stenlund P, Trobos M, Lausmaa J, Brånemark R, Thomsen P, Palmquist A. Effect of load on the bone around bone-anchored amputation prostheses. J Orthop Res Off Publ Orthop Res Soc 2017;35:1113–22. https://doi.org/10.1002/jor.23352.
[26] Brånemark RP, Hagberg K, Kulbacka-Ortiz K, Berlin Ö, Rydevik B. Osseointegrated Percutaneous Prosthetic System for the Treatment of Patients With Transfemoral Amputation: A Prospective Five-year Follow-up of Patient-reported Outcomes and

Complications. J Am Acad Orthop Surg 2019;27:e743–51. https://doi.org/10.5435/JAAOS-D-17-00621.
[27] Tomaszewski PK, Verdonschot N, Bulstra SK, Rietman JS, Verkerke GJ. Simulated bone remodeling around two types of osseointegrated implants for direct fixation of upper-leg prostheses. J Mech Behav Biomed Mater 2012;15:167–75. https://doi.org/10.1016/j.jmbbm.2012.06.015.
[28] Tomaszewski PK, van Diest M, Bulstra SK, Verdonschot N, Verkerke GJ. Numerical analysis of an osseointegrated prosthesis fixation with reduced bone failure risk and periprosthetic bone loss. J Biomech 2012;45:1875–80. https://doi.org/10.1016/j.jbiomech.2012.05.032.
[29] Nebergall A, Bragdon C, Antonellis A, Kärrholm J, Brånemark R, Malchau H. Stable fixation of an osseointegated implant system for above-the-knee amputees: titel RSA and radiographic evaluation of migration and bone remodeling in 55 cases. Acta Orthop 2012;83:121–8. https://doi.org/10.3109/17453674.2012.678799.
[30] Frölke JPM, Leijendekkers RA, van de Meent H. Osseointegrated prosthesis for patients with an amputation : Multidisciplinary team approach in the Netherlands. Unfallchirurg 2017;120:293–9. https://doi.org/10.1007/s00113-016-0302-1.
[31] Juhnke D-L, Beck JP, Jeyapalina S, Aschoff HH. Fifteen years of experience with Integral-Leg-Prosthesis: Cohort study of artificial limb attachment system. J Rehabil Res Dev 2015;52:407–20. https://doi.org/10.1682/JRRD.2014.11.0280.
[32] Al Muderis M, Khemka A, Lord SJ, Van de Meent H, Frölke JPM. Safety of Osseointegrated Implants for Transfemoral Amputees: A Two-Center Prospective Cohort Study. J Bone Joint Surg Am 2016;98:900–9. https://doi.org/10.2106/JBJS.15.00808.
[33] Kunutsor SK, Gillatt D, Blom AW. Systematic review of the safety and efficacy of osseointegration prosthesis after limb amputation. Br J Surg 2018;105:1731–41. https://doi.org/10.1002/bjs.11005.
[34] Tillander J, Hagberg K, Berlin Ö, Hagberg L, Brånemark R. Osteomyelitis Risk in Patients With Transfemoral Amputations Treated With Osseointegration Prostheses. Clin Orthop 2017;475:3100–8. https://doi.org/10.1007/s11999-017-5507-2.
[35] Zaborowska M, Tillander J, Brånemark R, Hagberg L, Thomsen P, Trobos M. Biofilm formation and antimicrobial susceptibility of staphylococci and enterococci from osteomyelitis associated with percutaneous orthopaedic implants. J Biomed Mater Res B Appl Biomater 2017;105:2630–40. https://doi.org/10.1002/jbm.b.33803.
[36] Al Muderis M, Lu W, Tetsworth K, Bosley B, Li JJ. Single-stage osseointegrated reconstruction and rehabilitation of lower limb amputees: the Osseointegration Group of Australia Accelerated Protocol-2 (OGAAP-2) for a prospective cohort study. BMJ Open 2017;7:e013508. https://doi.org/10.1136/bmjopen-2016-013508.
[37] Resnik L, Borgia M. Reliability of outcome measures for people with lower-limb amputations: distinguishing true change from statistical error. Phys Ther 2011;91:555–65. https://doi.org/10.2522/ptj.20100287.
[38] Balestroni G, Bertolotti G. L'EuroQol-5D (EQ-5D): uno strumento per la misura della qualità della vita. Monaldi Arch Chest Dis - Card Ser 2012;78:155–9.

[39] Acquistapace F, Piepoli MF. [The walking test: use in clinical practice]. Monaldi Arch Chest Dis Arch Monaldi Mal Torace 2009;72:3–9. https://doi.org/10.4081/monaldi.2009.336.
[40] Gailey RS, Roach KE, Applegate EB, Cho B, Cunniffe B, Licht S, et al. The amputee mobility predictor: an instrument to assess determinants of the lower-limb amputee's ability to ambulate. Arch Phys Med Rehabil 2002;83:613–27. https://doi.org/10.1053/ampr.2002.32309.
[41] Bottner F, Su E, Nestor B, Azzis B, Sculco TP, Bostrom M. Radiostereometric Analysis: The Hip. HSS J 2005;1:94–9. https://doi.org/10.1007/s11420-005-0114-2.
[42] Ryd L, Yuan X, Löfgren H. Methods for determining the accuracy of radiostereometric analysis (RSA). Acta Orthop Scand 2000;71:403–8. https://doi.org/10.1080/000164700317393420.
[43] Aro E, Alm JJ, Moritz N, Mattila K, Aro HT. Good stability of a cementless, anatomically designed femoral stem in aging women: a 9-year RSA study of 32 patients. Acta Orthop 2018;89:490–5. https://doi.org/10.1080/17453674.2018.1490985.
[44] Finnilä S, Moritz N, SvedströM E, Alm JJ, Aro HT. Increased migration of uncemented acetabular cups in female total hip arthroplasty patients with low systemic bone mineral density. A 2-year RSA and 8-year radiographic follow-up study of 34 patients. Acta Orthop 2016;87:48–54. https://doi.org/10.3109/17453674.2015.1115312.
[45] Hagberg K, Brånemark R, Hägg O. Questionnaire for Persons with a Transfemoral Amputation (Q-TFA): initial validity and reliability of a new outcome measure. J Rehabil Res Dev 2004;41:695–706.
[46] Andrysek J, García D, Rozbaczylo C, Alvarez-Mitchell C, Valdebenito R, Rotter K, et al. Biomechanical responses of young adults with unilateral transfemoral amputation using two types of mechanical stance control prosthetic knee joints. Prosthet Orthot Int 2020;44:314–22. https://doi.org/10.1177/0309364620916385.
[47] Cutti AG, Verni G, Migliore GL, Amoresano A, Raggi M. Reference values for gait temporal and loading symmetry of lower-limb amputees can help in refocusing rehabilitation targets. J NeuroEngineering Rehabil 2018;15:61. https://doi.org/10.1186/s12984-018-0403-x.