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PHYSICAL ACTIVITY AND OSSEOINTEGRATION: "STEP FORWARD" TO IMPROVE THE QUALITY OF LIFE OF A TRANS-FEMORAL AMPUTEE PERSON

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ABSTRACT

Lower limb amputation is an event that inevitably changes the lifestyle of the person who suffers it, often restricting autonomy and movement and consequently having a significant impact on quality of life. People with a lower limb amputation who are able to use the prosthesis to walk and keep occupationally operative can be more physically active and this has been shown to improve the quality of life. The traditional socket-type prosthesis entails that the residual limb is in direct contact with the socket which often implies numerous disadvantages. In fact, 34-63% of patients using socket-type implants have chronic skin problems and pain that lead amputees to decide to limit or eliminate the use of the prosthesis. Osseointegrated prosthesis is a solution that avoids skin problems because not include the presence of the socket. In this type of prosthesis, in fact, a titanium stem is surgically inserted inside the medullary canal and connected with the external prosthetic limb. In Italy, the osteointegration of the lower limb is a recent and innovative technique and there are still many aspects to study and examine in depth.

Therefore, this thesis aims both to highlight and explore the main strengths and problems of treatment with osseointegrated prostheses and to examine the role physical activity, with attention on functional capacity and bone quality. The objectives of the thesis will be developed through 5 studies: (I) A gait analysis of a 44 years-old male patient who underwent surgery for the implantation of an osseointegrated prosthesis, with follow-up at the pre-operative phase and at 3- 6- and 12-month post-surgery; (II) A systematic review to investigate the state of stump bone quality in patients with limb amputations; (III) A systematic review of the technologies involved in such devices has been carried out to identify the most fruitful ones in improving bone quality; (IV) A systematic review investigating the topic of physical activity and bone turnover

biomarkers in the osteoporosis population; (V) A systematic review to investigate the effects of physical activity interventions combined with drug treatments on bone biomarkers in people with osteopenia and osteoporosis.

The case report study found progressive improvement, after the osseointegration, of the gait symmetry and a strong difference in terms of spatiotemporal parameters and joint kinematics between osseointegrated and socket-type prostheses. In patients with unilateral amputation, the amputated limb has lower bone mineral density (BMD) values than the non-amputated limb, moreover, a higher level of amputation was associated with a lower BMD level. Ultrasounds and laser arose to be the most studied technologies in the literature. However, it turned out that, nowadays, none prevails over the others in terms of its effect on bone quality. The systematic reviews on the role of physical activity on bone biomarkers demonstrate possible benefits in terms of improving bone formation and decreasing bone resorption biomarkers in case of low bone mineral density. However, only three randomized controlled trials matched the eligibility criteria and only one include a combined approach between physical activity and drugs.

The integrated prosthesis is a good solution for people with lower limb amputation who cannot use their traditional socket-type prosthesis. Although many objectives have already been achieved, there are still many aspects that we can improve. These include the creation of a multidisciplinary path that support patients along their path, with particular attention to the pre-surgery and the post-rehabilitation phase that is still lacking even if of fundamental impact in determining the quality of life. In the near future the Public Administration and all professionals in the field should encourage the development in Italy of this prosthetic technique that has proven to improve the quality of life in people with a lower limb amputation.

1 INTRODUCTION

1.1 QUALITY OF LIFE

Quality of life (QoL) is a concept that takes shape since the 1950s when the World Health Organization (WHO) defined health as "not merely the absence of disease or infirmity, but a state of complete psychical, mental and social well-being" (WHO, 1958). However, in the years, research has focused on the concept of QoL and pursuing this target increasingly (Staquet, 1996). Over the years, WHO itself has expanded the concept of QoL: "*An individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns*" (WHO, 1995). Nowadays, the quality of life has established itself and plays an important role in practice and research in the field of health and medicine (Fayers, 2016).

Knowing and better understanding QoL is extremely important when is related to fragile people and patient. An assessment of self-reported QoL may improving care and rehabilitation of patients or may underline strengths or weaknesses point of some therapies.

Understanding and analyzing QoL is especially important in people living with chronic medical condition, that may have problems even at the end of the specific treatments. In this regard, Qol has proven to be a predictor of survival (Fayers, 2016) stressing the need to highlight this element not only from an evaluative point of view but also interventional.

The greatest difficulty in understanding and defining QoL concerns the complexity of the domains that compose it, which includes elements that refer to physical, psychological, social, and spiritual aspects (Hiatt, 1986).

Given the complexity of the concept, it is necessary to isolate the aspect more linked to health and therefore more easily assessable, comparable, and modifiable with regard to people with chronic disabilities. Therefore, to date, an essential primary outcome to evaluate the impact of disease and the effects of medical intervention, must necessarily linked to health and is defined as health-related QoL (HRQoL), (Staquet, 1998). Mayo (Mayo 2015) define the HRQoL as: "*A term referring to the health aspects of quality of life, generally considered to reflect the impact of disease and treatment on disability and daily functioning; it has also been considered to reflect the impact of perceived health on an individual's ability to live a fulfilling life*". In this point of view, we can consider the health-related QoL as a multidimensional concept that includes physical, psychological, and social aspects that could be affected by the health condition.

As we have seen, QoL is a concept that crosses many different disciplines that can define and interpret it in different ways. Evaluation can also be different and include various tools closely related to a specific aspect. According to Gill (Gill, 1994), the best approach to assessing the quality of life of patients should start from the opinions of patients, integrating or replacing instruments that do not consider the purely personal aspect.

The tools used to measure QoL are divided into 3 subtypes: type of report, scores, and population. The latter is categorized into generic and condition-specific (Petersen-Ewert-2011). Normally, generic measurements are used to support more specific measurements and have the advantage of being able to compare different target populations; condition-specific measurements are the most widely used and appear to be clinically more relevant (Moher 2009). While the generic outcomes on QoL are more widespread and widely used, the specific outcomes turn out to be many as there is at least one for most conditions. For these reasons, it is important to choose the right tool according to the objectives of the study or treatment (Haraldstad, 2019).

The review conducted by Haraldstad et al. (Harastad 2019) found a strong interest in the effects of medical treatment on chronic conditions, not only clinically but also on QoL. However, although many studies consider and evaluate QoL, mostly use the outcome as secondary data, and just a few studies planning an intervention to improve it.

A program to improve the QoL of healthy subjects and HRQoL in subjects with chronic disabilities should include a variety of elements concerning both physical and psychological aspects, including physical exercises, relaxation, health education, stress, and self-management.

In summary, QoL is a very complex concept that has been studied for a long time. It is used in the evaluation of different types of populations, and HRQoL is important, in subjects who live a chronic disability condition, to evaluate the long-term effects of therapy. However, there are still few initiatives aimed at supplementing therapeutic treatment with actions aimed at improving the QoL.

1.1.1 QUALITY OF LIFE IN RELATION TO AMPUTEE

Despite the careful prevention of cardiovascular diseases and the improvement of medical-surgical knowledge, which are two main factors that can reduce cases of limb amputation, the number of amputees remains high in Italy and in the world. Moreover, the future prevalence is estimated may be double in the year 2050 (Ephraim, 2003; Lombardo, 2014; McDonald 2021; Ziegler-Graham, 2008).

Lower limb amputation is an event that inevitably changes the lifestyle of the person who undergoes it, often limiting autonomy and movement (Fatima, 2022). Given the estimated diffusion and the strong impact of amputation on life habits, including physical and mental aspect impairment, the evaluation and improvement of QoL plays a fundamental role also in the post-rehabilitation phase.

An amputation of the lower limb profoundly modifies the life of the amputees and their families in several aspects. Among the factors that determine the QoL, there is the presence of phantom pain and pain in the stump, movements, independence in daily activity, age, work, and access to rehabilitation (De Melo, 2021; Grzebien, 2017).

Walking is a factor that has a strong impact on autonomy. In this regard, it is important the level of amputation, in particular, a low level of transfemoral amputation or transtibial amputation, that spares the knee joint, allows to restore walking with a faster rehabilitation, and with less energy consumption (Mohanty, 2012). In addition, subjects with below-knee amputations have better walking performance and overall physical condition than those with above-knee amputations, who have a lower quality of life. (Knežević, 2015). Walking ability, influence the social integration on life of amputees patients. People who are well socially integrated walked with a fast gait and stronger the social integration, higher the quality of life (Hawkins 2016) After amputation it is very important to start active rehabilitation, which includes physical therapy and occupational therapy, encouraging the patient to use prosthesis and return to his routine social activities.

Phantom limb pain significantly contributes to ordinary life activity and has been shown to be decisive in the quality of life. People with phantom limb pain problems walk less than amputees without these symptoms (Van der Schans, 2002). There was also a relationship between phantom limb symptoms and emotional problems due to stress condition (Muraczyńska, 2003). Moreover, not only somatic symptoms such as pain have a negative influence on patients after amputation but also social dysfunction, insomnia, anxiety, and perception of the physical aspect (Whyte, 2011; Sinha, 2011). Pain also affects the work aspect, in fact, the index of job satisfaction has been shown to be lower in amputees with pain symptoms. Instead, no relationship has been found between pain type, its severity, and the return to the normal work rhythm. However, there does

not seem to be any relationship between the return time to work and the severity of the pain (Ide, 2001). Decreased walking, emotional status, and works satisfaction make phantom pain symptoms an important determinant in the quality of life of patients after limb amputation.

In addition to the factors inherent in amputation, the use or not of the external prosthesis seems to significantly affect the quality of life (Zidarov, 2009; Akarsu, 2013). For this reason, it is important in the post-operative period to assist patients to provide better safety and performance to the use of the prosthesis (Dillingham, 2013).

1.2 BENEFITS OF PHYSICAL ACTIVITY IN AMPUTEE

Physical Activity (PA) is defined as any movement of the body generated by skeletal muscles that required energy expenditure (WHO, 2018). PA can be classified into sports, occupational, conditioning, household, or other activities (Longobucco, 2022). Physical activity, therefore, includes all activities that involve human movement and burn calories; so, it includes also all daily activities such as gardening, cycling, or walking. In everyday life, walking is one of the main activities. Amputees who are able to use the prosthesis to walk and keep occupationally operative, can therefore be more physically active and this has been shown to improve the QoL; whereas, people with walking impairments present a significantly lower QoL (Napieracz-Trzosek, 2010). As well known in the literature, physical activity offers advantages in different aspects of life: physical, psychological, and social (Bragaru, 2011; Warburton, 2017; Peluso, 2005). People after amputation are forced to change their motor and kinematic patterns and thus unable to resume the previous activities they did before amputation (Grzebien, 2017). For this reason, it is important during and after rehabilitation to educate and encourage people to an active lifestyle (Langford, 2019). One of the most important aspects of rehabilitation procedures

following amputatio, is supporting amputated individuals to engage in the regular practice of physical activity (Bragaru, 2011). In addition, it would not be enough to provide amputees with the physical tools to return to activities, but it is important to act at the mental level, motivating them to wear the prosthesis and exercise in order to also improve mood and increase self-esteem (Warmuz, 2004).

1.3 OSSEOINTEGRATION

Walking rehabilitation, in subjects with lower limb amputation, is carried out through the use of a prosthesis. The traditional prosthetic system (currently the most used) entails that the residual limb is in direct contact with the socket which often implies the occurrence of skin problems. In fact, 34-63% of patients using socket type implants have chronic skin problems and pain. In this regard, the literature highlights how the socket-type prosthesis, presents numerous disadvantages mainly due to the contact between skin and prosthesis: excessive sweating, sores, abscesses or skin irritations (Van de Meent, 2013; Butler, 2014, Dudek, 2005; Lyon, 2000; Meulenbelt, 2009). To the above problematics, must be added the problems related to the increase in the body weight of the patient and those related to the emotional-relational sphere, such as not accepting their body shape (Warmuz, 2004). All these factors lead amputees to decide to limit or eliminate the use of the prosthesis (Van de Meent, 2013).

Since the amputation of a limb has a significant impact on the patient's functional abilities, the use of a prosthesis requires a long rehabilitation aimed at increasing motor skills and adapting the patient to the use of the same prosthesis. In addition, the higher the level of amputation, the more difficult it will be for the patient to restore functional capabilities and achieve an optimal level of comfort. (Warmuz, 2004; Ülger, 2018). Although new materials and patients' custom

socket designs have been developed, skin problems continue to represent a challenge, because the skin remains exposed to considerable pressure that leads to an annoying and continuous weakening of the skin during walking (Ontario Health, 2019). In the last twenty years, several research groups, assisted by experienced surgeons, have tried to find an implantation solution that avoids socket use and thus puts an end to all the problems related to it. One solution to treat transfemoral amputees is osseointegrated prostheses, which exploit the physiological process of osseointegration as a means of anchoring between endo-prostheses and residual limb (Ontario Health, 2019; Al Muderis, 2017; Gerzina, 2019). In this type of prosthesis, in fact, a titanium stem, surgically inserted inside the medullary canal of the residual limb and fixed to it by the surrounding bone accretion, ensures the connection between the amputated limb and the external prosthetic limb. Nowadays, this prosthetic system is diffused all over the world, accepted as a valid alternative to the traditional prosthesis, and recommended in young and active subjects, with transfemoral, transtibial, transomeral or transradial amputation, not due to vascular problems (Brånemark, 2014; Hebert, 2017).

1.3.1 OSSEOINTEGRATION AND OSTEOPOROSIS

Osteoporosis is an age-related systemic skeletal disease characterized by a decrease in mass and deterioration in bone microarchitecture. It is associated with increased risk of fracture with pain, decreased physical and social functioning capacity, and QoL (Buchner, 1992; Peck, 1993). The WHO defines the osteoporosis as a BMD T-score of 2.5 or lower or with a previous fragility fracture (Anonymous, 1993; Kanis, 1994).

Bone mineral density (BMD) is a biological parameter of bone quality usually related to the risk of fractures and at the prediction of bone fractures.

Studies have shown that BMD decreases rapidly after amputation, particularly in the amputated limb stump (Black, 2020; Bemben 2017; Flint, 2014). The risk of fractures following an osseointegrated prosthesis is uncommon, indeed, following an accidental fall, the presence of safety pins causes the loosening of the transcutaneous adapter without causing bone fractures and safeguarding the osseointegrated stem (Al Muderis, 2016). However, good bone quality is essential for successful osseointegration and evaluation is needed before surgery.

Assessing BMD changes in patients with limb amputations is a complex challenge. There are several factors to consider when evaluating the impact of lower limb amputations on BMD, including the level of amputation, time since amputation, and use of prostheses.

2. OSSEOINTEGRATION

2.1 INTRODUCTION

In 2005, there were approximately 1.6 million amputees in the United States, a prevalence of almost 1 in 200 people, and that number is expected to double by 2050 (Ziegler-Graham, 2008). The global amputee census is difficult to establish (Moxey, 2011).

The current accepted standard for rehabilitation and mobility following amputation is a socket-mounted prosthesis. Unfortunately, problems are common. Up to three-quarters of individuals with transfemoral amputation have chronic skin problems associated with the socket of their prosthesis (Lyon, 2000; Meulembelt, 2009; Hagberg, 2009), experience skin ulcers or intolerable perspiration (Koc, 2008) and require frequent refitting (Dillingham, 2001), or have prosthesis-fit issues due to residuum size fluctuation (Sanders, 2011); approximately 7% sustain a fracture in the residual limb(Nehler, 2003); and the majority have reported that they lack confidence with mobility (Hagberg, 2001). These skin problems often cause serious limitations in mobility and quality of life (Hagberg, 2009; Demet, 2008; Pezzin, 2004; Pezzin, 2000). Despite new materials and improved socket designs, skin problems remain an important burden because the skin in weight-bearing areas of the socket is not always resistant to the pressure and friction caused by the socket during ambulation. Bone anchorage of the artificial limb is an intervention that avoids these problems. With this technique, the prosthesis is transcutaneously attached to the human skeleton by osseointegration using an intramedullary implant into the femur.

Osseointegration (OI) is the direct anchorage of a metal implant into bone, allowing for the connection of an external prosthesis to the skeleton. This technique is developed by Professor P. I. Branemark from Gothenburg, Sweden which allows the anchorage of a prosthesis directly into

bone using titanium fixtures. Per-Ingvar Brånemark first coined the term “OI” in the early 1950s. (Branemark, 2017). This technique has gradually gained greater acceptance in the almost 30 years since the first osseointegration surgical procedure was performed in Sweden on May 15, 1990.

2.2 HISTORICAL ASPECTS

Despite the improvements in medical and surgical interventions for limb salvage procedures, the amputation numbers remain high in the world due to the aging population, civilian accidents, local wars, and terrorism attacks (Ephraim, 2003; Soboci 2005). Prostheses are aimed to enhance mobility, independence, safety, and quality of life for amputees (Millstein, 1985). Evidence of prosthesis usage can be dated back to ancient Egyptians. The earliest documented functional lower-limb prosthesis was unearthed in Italy, probably from 300 B.C. The weight-bearing part of the prosthesis was made of bronze and iron, combined with a wooden/leather socket for connecting the residual limb (Thurston, 2007]. The material and technique evolved over centuries, while the socket remains as a critical part for prosthesis connection. The socket design, however, frequently places the residual limb under excessive stresses and pistoning (vertical movements within the socket) and results in skin irritation and ulcers, which are often regarded as the major reasons for prosthesis rejection by amputees (Reiber, 1994).

In the early 1960s, the Swedish researcher Per-Ingvar Brånemark discovered in his microcirculation studies that his titanium chambers were firmly maintained in rabbit tibia without severe soft tissue reaction or loosening. When the experiments were finished, the titanium chambers could not be removed from the bone. These unexpected findings gave P.-I. Brånemark the idea that titanium implants could be used as a restoration option for tooth loss. After

successful animal experiments with intraosseous anchorage of dental prostheses (Brånemark, 1969), P.-I. Brånemark completed the first human trial in an edentulous patient in 1965. The long-term success of a series of clinical trials confirmed the advantage of the functional and structural connection between living bone and the titanium implant, which he later named "osseointegration" (Brånemark, 1977).

The application of osseointegration for amputee rehabilitation started in 1990s, mainly based on the dental and craniofacial osseointegration experience and the biomechanical studies of P.-I. Brånemark's son, Rickard Brånemark, who later became the Chief Surgeon and Director of the Center for Orthopedic Osseointegration (COO) at Sahlgrenska University Hospital in Gothenburg, Sweden. R. Brånemark and coworkers evaluated the biomechanics of bone-anchored implants during healing, after irradiation, in experimental arthritis, in rat, rabbit, dog, and human (Brånemark, 1996). This experimental work became the basis for implant designs and rehabilitation protocols for extremity osseointegrations.

The first osseointegration treatment in an amputee was on 15 May 1990 on a 25-year-old woman, who had undergone bilateral transfemoral amputation at the age of 15 due to a tram accident. A titanium fixture was installed in her right residual femur. Six months later, a titanium abutment was connected to the well-osseointegrated implant. In 1991, a similar two-stage procedure was done on her left femoral stump. After postoperative rehabilitation, the patient could walk with crutches and exercise with cycling. The clinical trials were continued with a few transfemoral amputees as well as thumb amputees and a series of transradial amputees (TRAs) in the early 1990s (Jonsson, 2011). These initial efforts provided valuable experience for the later standardization of the OPRA program.

2.2.1 IMPROVEMENTS DURING THE EARLY 1990S

The initial clinical trials of osseointegration for amputees were more or less an extended application of the dental implants to the extremities. However, unlike the relative stable situation for oral and craniofacial applications, the implant system in extremities were under higher and unknown and unpredictable stresses during movements and falls. On the other hand, the muscle contractions and relaxations in daily life made the edge of the skin opening under frequent traction and twisting stresses against the percutaneous abutments. Therefore, although there were apparent functional improvements, there were inflammation/infection problems. In addition, mechanical complications due to overload led to fractures of the abutment screws, abutments, and fixtures.

The surgical techniques were also improved in the 1990s. At the first osseointegration operation, the importance of direct attachment of the dermal flap to bone was not well established. Experience from osseointegrated bone anchored hearing aids (BAHA) was adapted (Holgers, 1989), which emphasized strict removal of all hair follicles in the skin in the 15 mm radius from the abutment opening and adequate soft tissue reduction at the end of the stump. This technique effectively reduced the risk of soft tissue problems by limiting soft tissue movement.

The early clinical trials also indicated that bone resorption could be problematic for long-term maintenance of the osseointegrated system. When placing the fixture flush with the distal end of the bone, resorption of the distal cortical bone was observed in some instances, which caused exposure of the threads of the fixture, and mobile soft tissues riding over the exposed threads led to inflammation. Therefore, a central position of the implant in the medullary canal and 20 mm embedment of the fixture end into the distal bone stump was later regarded as an optimal depth for fixture insertion.

2.3 SURGICAL TECHNIQUE

Several osseointegration implant systems are available on the market. There are several different osseointegrated implant designs, surgical techniques, and rehabilitation protocols with their own strengths and limitations. Some implants were designed for single-stage implantation, other for double stage.

The technique of osseointegration applied to prosthetic limbs is currently practiced by several orthopedic centers both in Europe and the rest of the world.

Thanks to the Me.Ta.COs research project, the result of a collaboration between the Rizzoli Orthopedic Institute, the University of Bologna and the INAIL Prosthesis Center in Vigorso di Budrio, this technique has recently been imported to Italy.

The surgical technique that we analyze is characterized by 2 surgical steps, spaced 2 months apart (Annex 1 – Surgical protocol of osseointegration technique applied to transfemoral amputation patient).

2.3.1 FIST STAGE

The goal of the first procedure is to press-fit implant inside the intramedullary bone. In brief, this is achieved by gently reaming the canal (Figure 1), working the intramedullary canal with rasps of increasing size (Figure 2), then perform of transosseous sutures for distal myodesis (Figure 3-5).

Subsequently, there is insertion of the implant using a press-fit technique (Figure 4) and a temporary plug inserted into the distal end of the implant (Figure 5). After inserting the implant, the incision is then fully closed (Figure 6). At the end the surgeon performs the compression bandage) and postoperative radiographic control (Figure 7).

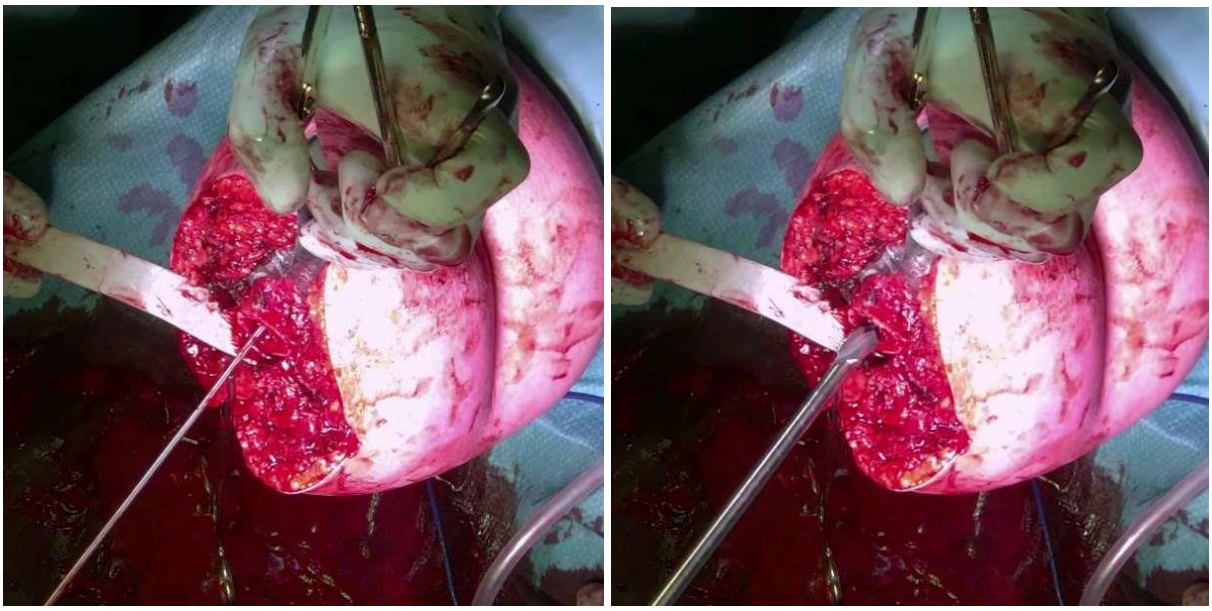


Figure 1 – Reaming the canal

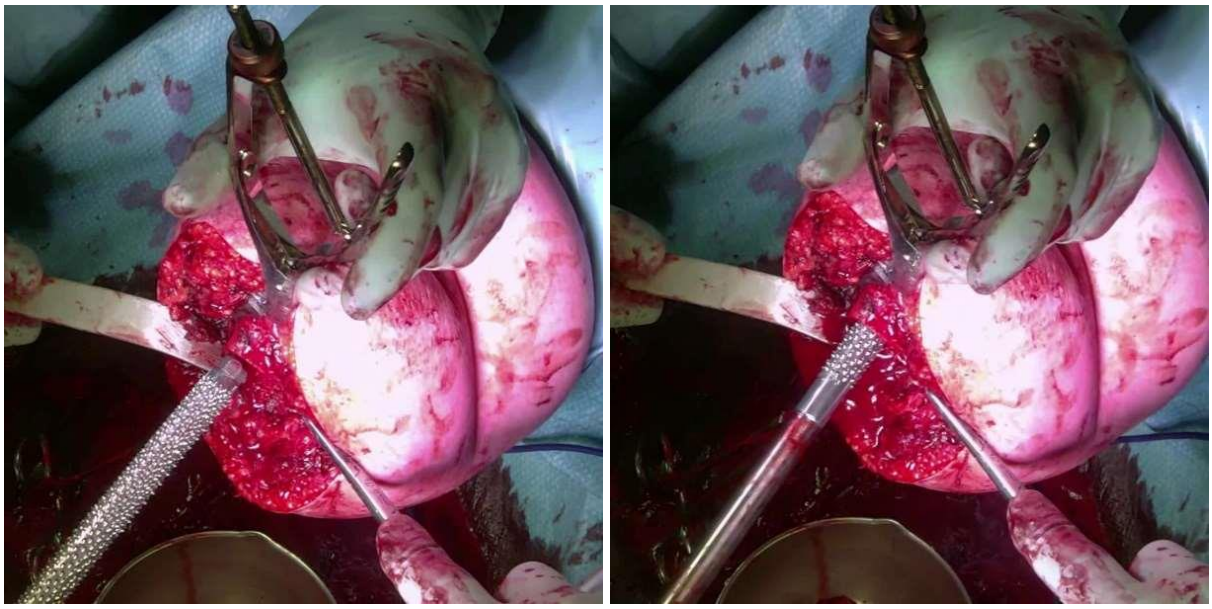


Figure 2 – Working of the intramedullary canal with rasps of increasing size

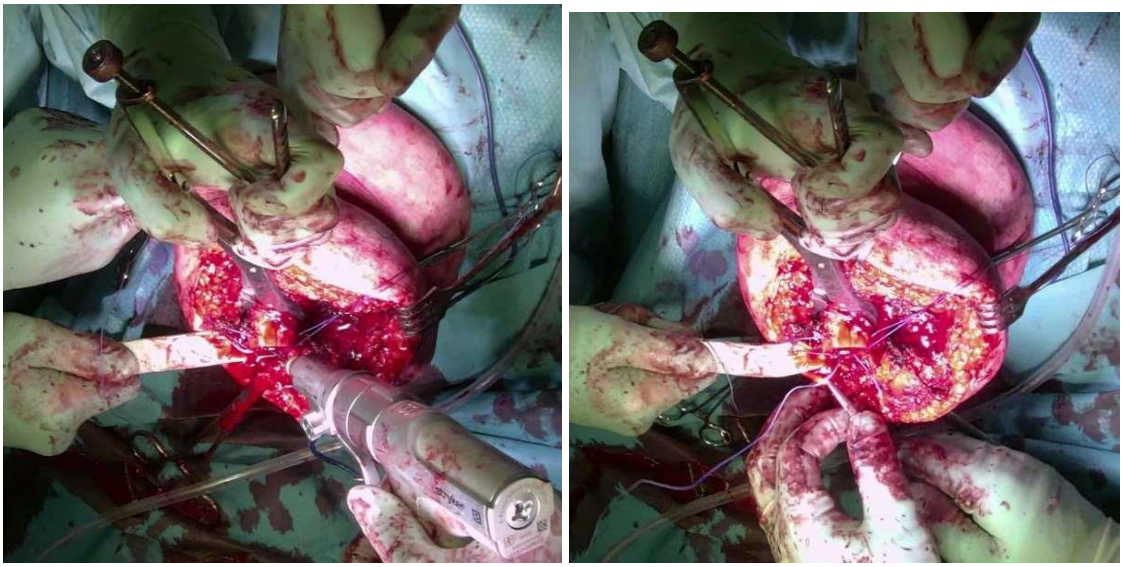


Figure 3 – Perform of transosseous sutures for distal myodesis

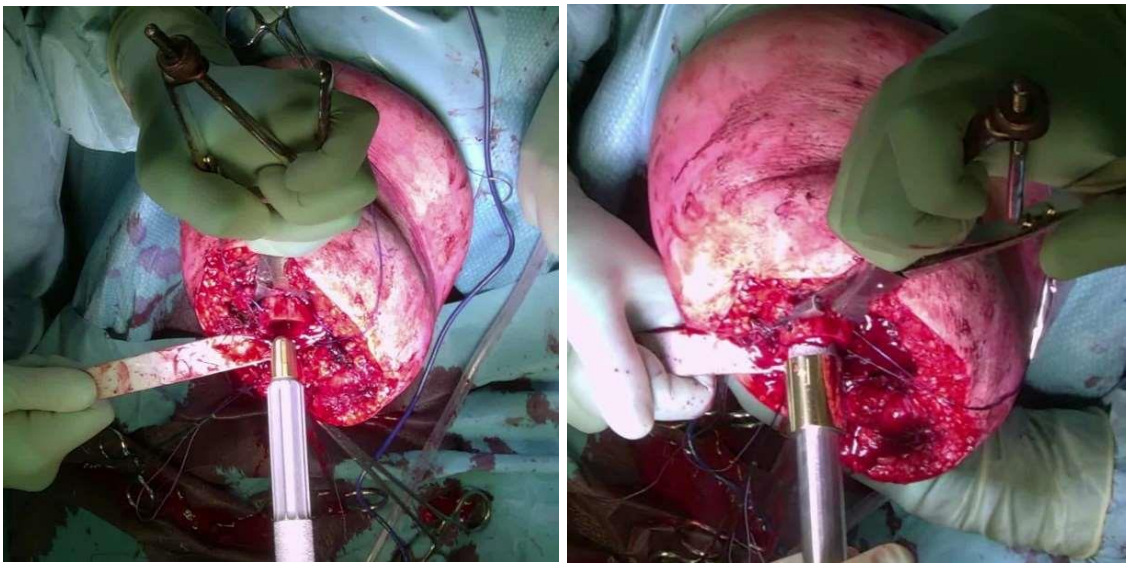


Figure 4 – Insertion of the implant using a press-fit technique

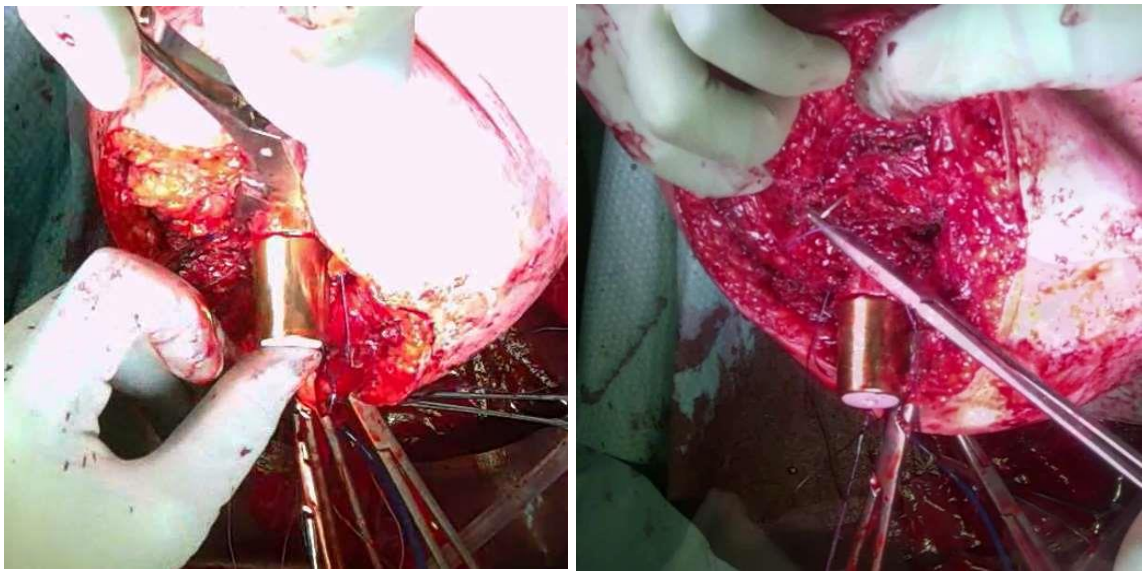


Figure 5 - Temporary plug inserted into the distal end of the implant

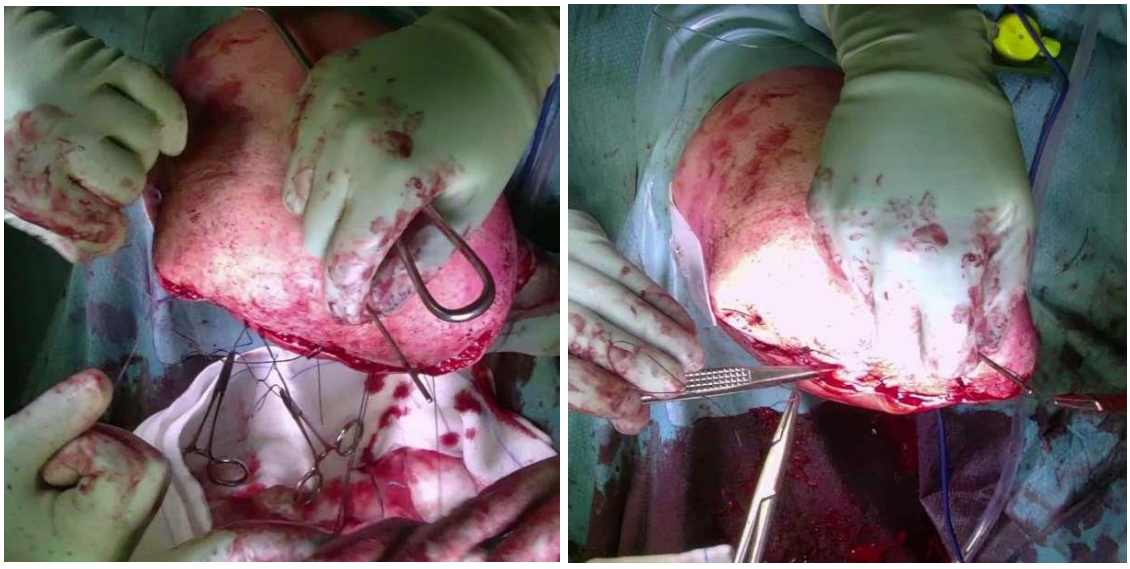


Figure 6 - The incision is then fully closed

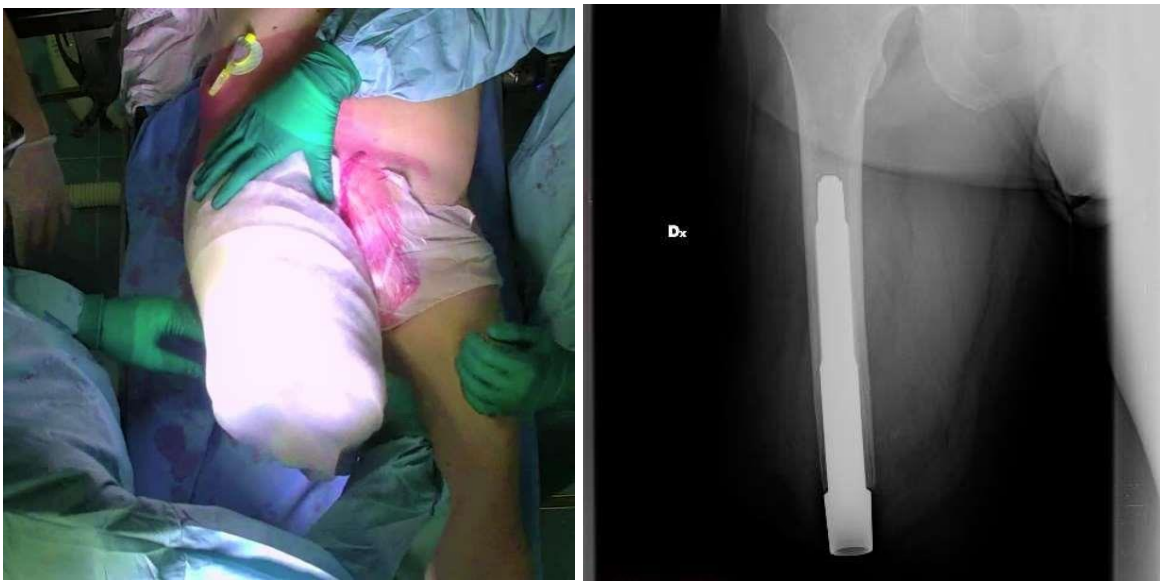


Figure 7 - The compression bandage (left) and postoperative radiographic control (right)

2.3.2 SECOND STAGE

Following an interval of 2 months, to allow the implant to integrate with the host bone, the second surgical step is undertaken. A circular corer is used to open the skin over the abutment to create a stoma (Figure 8). The implant plug is then removed (Figure 9), and a dual cone adapter is inserted percutaneously (Figure 10-11). At the end of the procedure, the double-cone adapter should protrude from the skin by at least 5 cm, and the ostomy should be tightly adhered to the implant but still free to move so as not to create pain on movement (Figure 11).

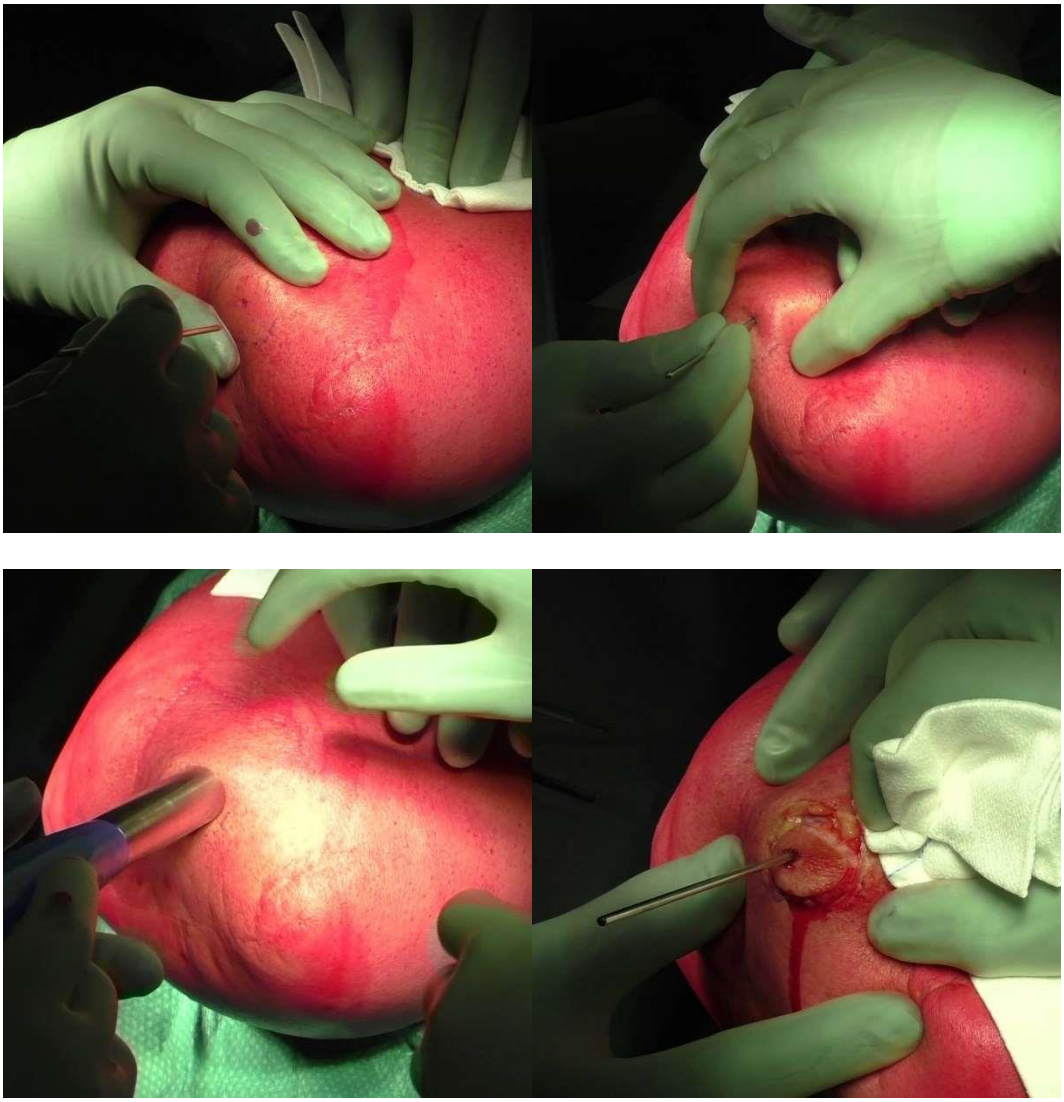


Figure 8 - A circular corer is used to open the skin over the abutment to create a stoma

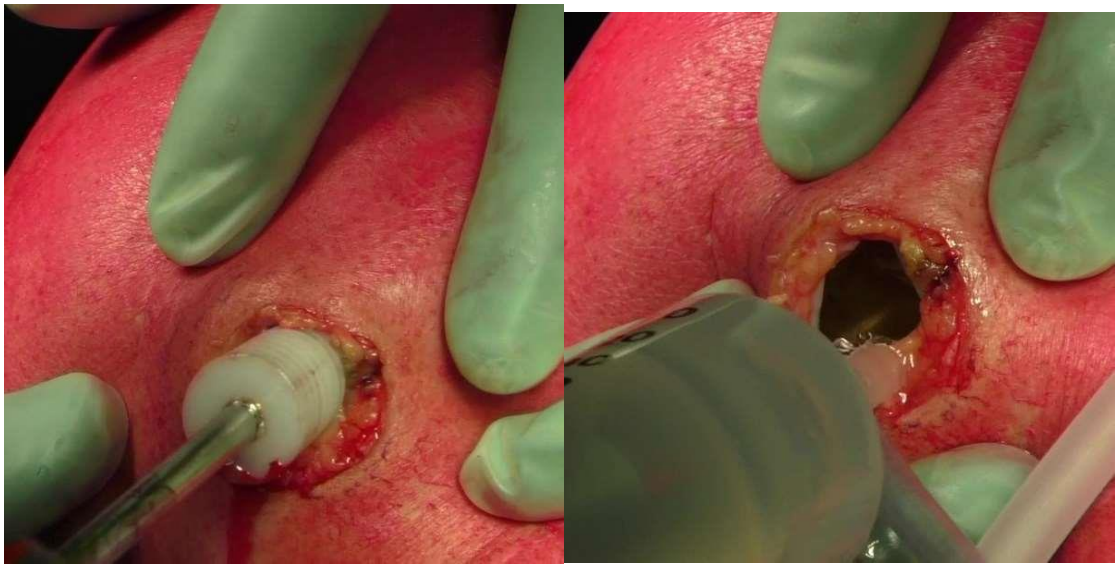


Figure 9 - Implant plus is removed

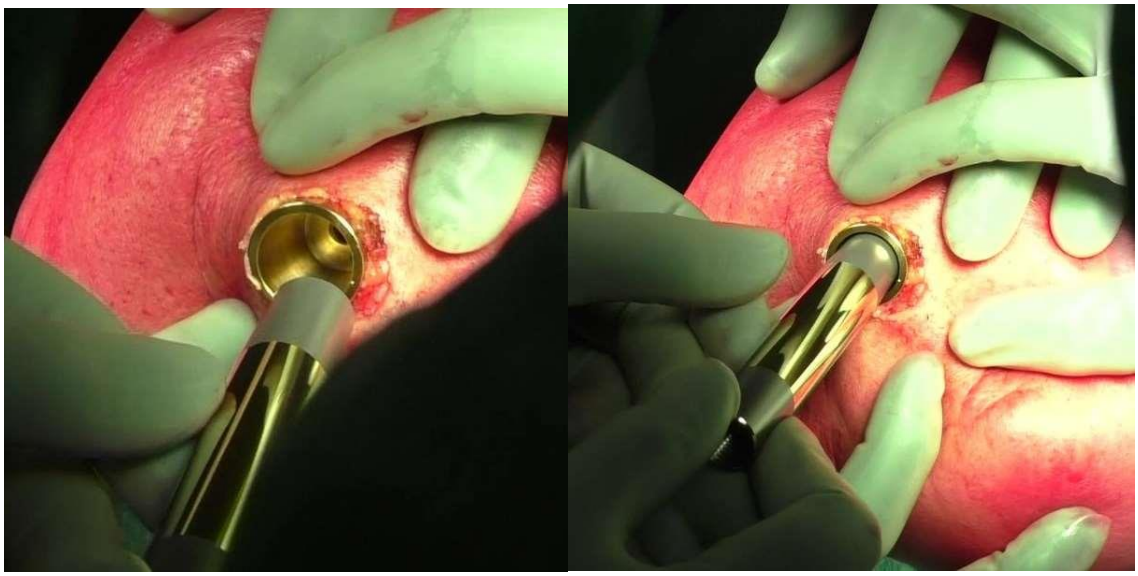


Figure 10 - Dual cone adapter is inserted

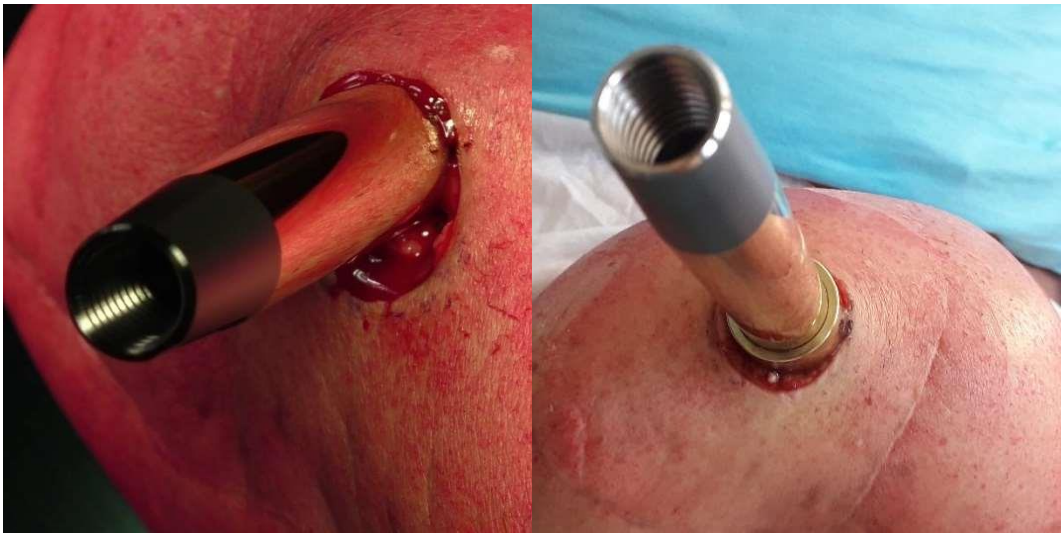


Figure 11 – Final results after post-operative

2.3.3 INCLUSION CRITERIA

Osseointegration is considered for trans-femoral amputees who have been unable to achieve a satisfactory level of rehabilitation using conventional socket techniques (Branemark, 2001). Reasons include recurrent skin infections and ulceration in the socket contact area, a short stump, volume fluctuation of the stump, soft tissue scarring, extensive areas of skin grafting or socket retention problems due to excessive perspiration. Indeed, early contraindications at the osseointegrated surgery, included peripheral vascular disease, diabetes, age of >70 years, ongoing chemotherapy, immunosuppressive medications, skeletal immaturity, irradiated limbs, pregnancy, and situations of questionable patient compliance or psychiatric stability (Hagberg, 2009; Al Muderis, 2017; Sullivan, 2003). On the basis of positive early experience, some surgeons have expanded indications or disproven supposed contraindications to osseointegration, improving the mobility of patients with peripheral vascular disease (Atallah, 2017), those who underwent total hip arthroplasty (Khemka, 2016) or total knee arthroplasty (Khemka, 2015), and elderly patients who underwent amputation decades ago (Leijendekkers, 2017).

Potential candidates must also fulfil other criteria:

1. Candidates must have tried conventional socket techniques;
2. Candidates must have reached full skeletal maturity and have normal skeletal anatomy;
3. Candidates should not be over 70 years of age;
4. Candidates' body mass must not be in excess of 100 kg;
5. Candidates must be suitable for surgery based upon medical history and physical examination;
6. Candidates should agree to comply with the programme.

As basic science understanding and clinical experience improve, it is likely that the indications will broaden and the contraindications will narrow. (Annex 2 – Patient Assessment Guide)

2.4 TECHNICAL MANAGEMENT OF THE PROSTHESIS

The role of the orthopedic technician is very important both in pre- and post-surgery phases, working closely with the patient, with doctors (surgeons and physiatrists) and with physiotherapists (Annex 3 - Prosthetic protocol for amputated limb treated with osseointegrated implant).

During the first medical examination, the orthopedic technician collects the data related to the external prosthesis, focusing his attention to the knee and foot components.

It is a good practice to ensure that the external prosthesis is equipped with performing prosthetic components, being the osseointegration designed for dynamic and active patients classified with a K level equal to K3 (Table 1).

Table 1 Lower limb extremity prosthesis medicare functional classification levels (K levels)

Level 0:	Does not have the ability or potential to ambulate or transfer safely with or without assistance and a prosthesis does not enhance their quality of life or mobility
Level 1:	Has the ability or potential to use a prosthesis for transfers or ambulation on level surfaces at fixed cadence. Typical of the limited and unlimited household ambulator.
Level 2:	Has the ability or potential for ambulation with the ability to traverse low level environmental barriers such as curbs, stairs, or uneven surfaces. Typical of the limited community ambulator.
Level 3:	Has the ability or potential for ambulation with variable cadence. Typical of the community ambulator who has the ability to traverse most environmental barriers and may have vocational, therapeutic, or exercise activity that demands prosthetic utilization beyond simple locomotion.
Level 4:	Has the ability or potential for prosthetic ambulation that exceeds basic ambulation skills, exhibiting high impact, stress, or energy levels. Typical of the prosthetic demands of the child, active adult, or athlete.

For this reason, a good choice is to equip the external prosthesis with a hydraulic multi-functional knee (for example, the 3R80 of Ottobock). Regarding to the foot component, the patient needs to be equipped with a foot that guarantee a good cushioning response in axial and rotational loading (for example, Pro-Flex XC Torsion of Ossür). In this way, it is possible to avoid excessive torsion loading and prevent the risk of loosening of the intramedullary femoral stem.

The orthopedic technician must be able to assess the encumbrance of the entire external prosthesis, from the connector to the prosthetic knee. The height of the connector may vary depending on the model chosen (for example, 75mm for Heli Connector of OTN Implants).

The pre-operative planning must allow the right height to prevent contact with soft tissues following their collapse which could lead to redness and infection.

The components of the osseointegration prosthesis of interest to the orthopedic technician are:

- The transcutaneous double-cone adapter, which is the connecting portion between the intramedullary implant and the external prosthesis. It crosses the skin at the level of the ostomy and interfaces in the distal portion with the connector for the external prosthesis (Figure 12);
- The connector for the external prosthesis (Figure 13).

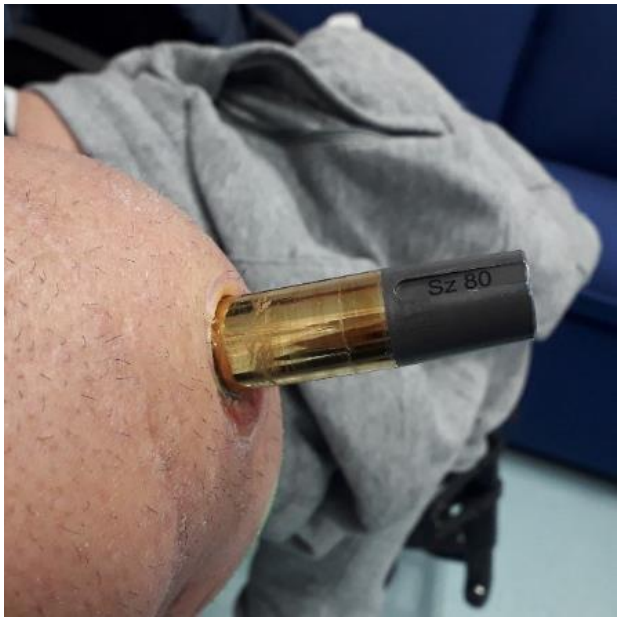


Figure 12 - Transcutaneous double-cone adapter

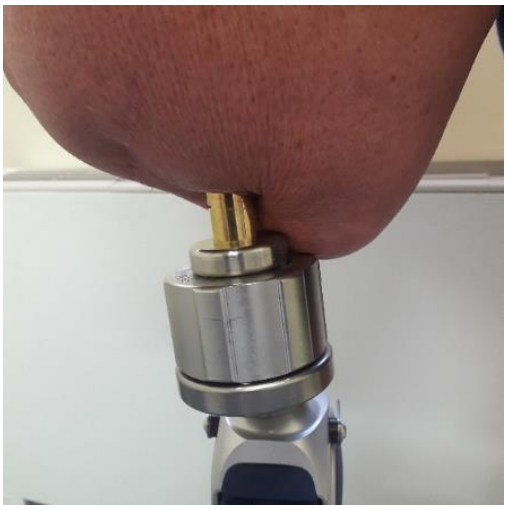
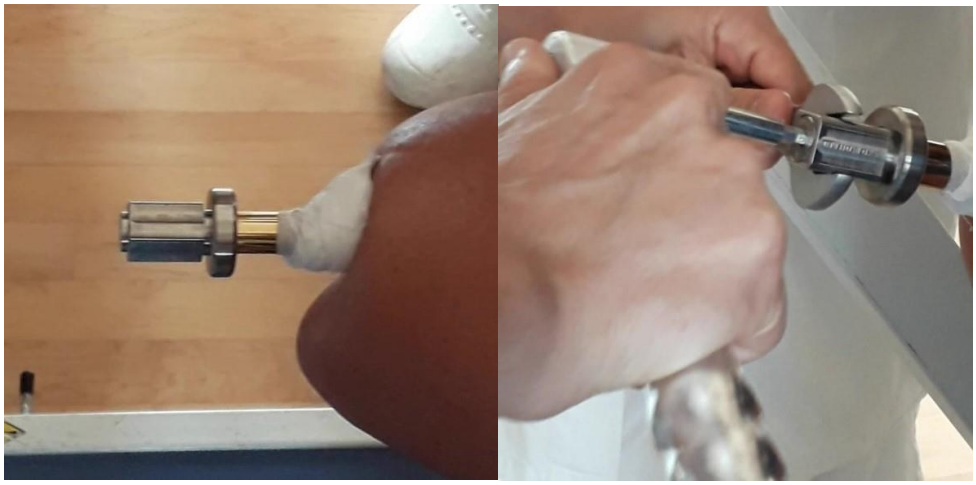


Figure 13 - Connector for the external prosthesis

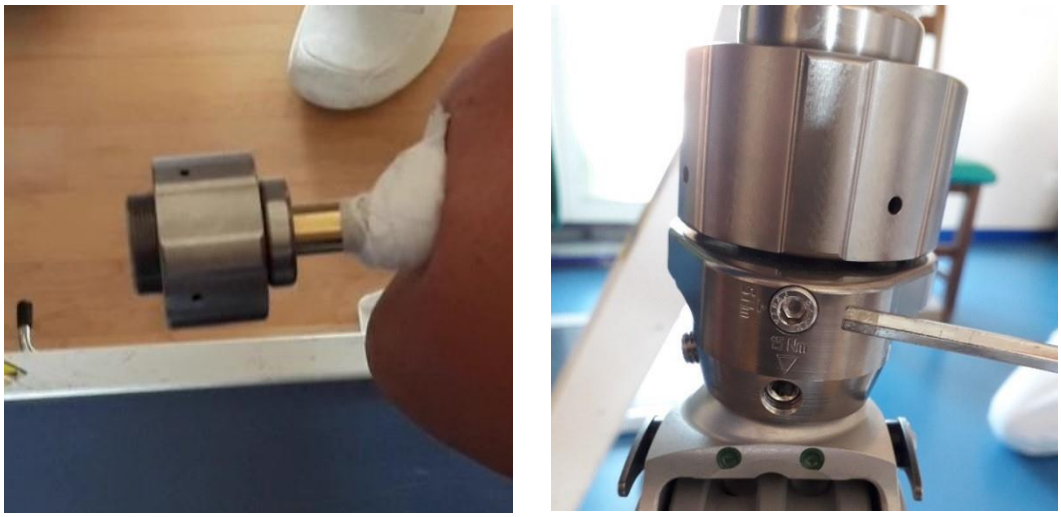
By means of the connector, the patient is able to quickly attach or detach the external prosthesis from the osseointegrated implant. During the setting phase by an orthopaedic technician. It is important to have adequate prosthetic components available and to carry out a correct optimization of the alignment in the static phase and in the dynamic phase of the step. The following point list represents a summary of the phases to attach the connector to the external prosthesis

1. Clean the distal part of the double cone adapter and fix the male connector on it with a locking screw (M14, OTNI) and stabilize the male connector. Make sure that the flat front surface of the male connector is aligned with the direction of travel (Figures 14a and 14b);



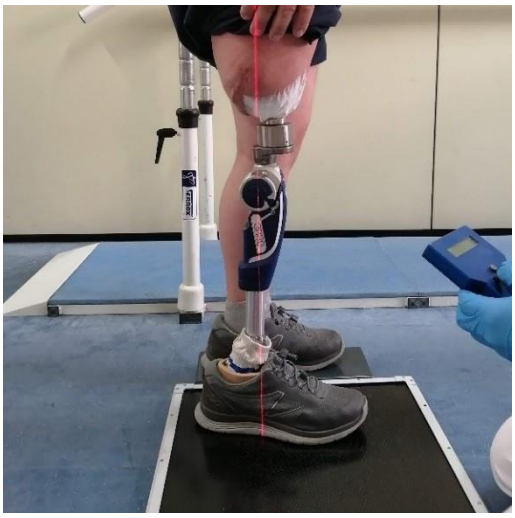
Figures 14 (a e b) – Screwing of the male connector

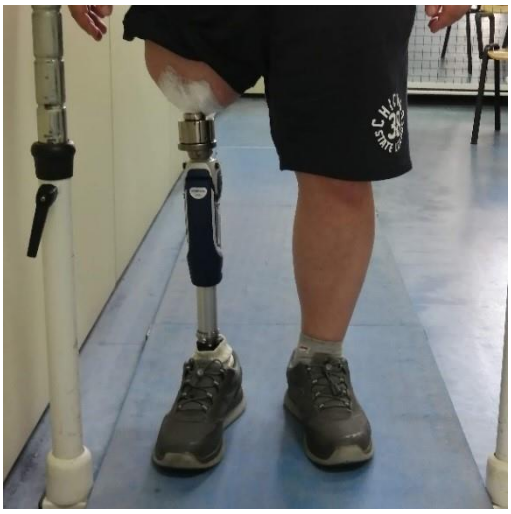
2. Insert the female connector and lock the two components by tightening the locking ring (Figures 15 and 16);



Figures 15 and 16 – Insert the female connector and M5 screw (right)

3. Screwing the offset plate onto the threaded portion of the female connector. If patient has mounted a prosthetic knee with electronic control of the flexion-extension angles, any small differences can always be balanced with a plate equal to 0, 10 or 20mm. The degree of compensation has consequences for walking: the lower the offset applied, the less energy the patient needs to flex the knee at the end of the stance phase. During the rehabilitation phase the muscles of the anterior compartment of the thigh gradually regain elasticity, eliminating the degree of flexion: in this way, the compensation applied can be gradually reduced, until an acceptable degree of flexion of the stump is reached. In patients with a transtibial osseointegration implant, the offset plate can also be used to correct the alignment of the prosthesis with respect to the frontal plane, compensating for any valgus or varus angles by means of a medial or lateral translation;
4. The grade of rotation of the prosthetic knee can be adjusted by rotating the offset plate with respect to the female connector, using the appropriate screw (M5, OTNI) (Figures 17a and 17b);





Figures 17 (a e b) – Static aligment and final result.

5. Connect the universal male pyramidal attachment of the external prosthesis to the female pyramidal attachment of the offset plate and adjust its position by tightening the M8 set screws (OTNI), by means of a thread locker.

If necessary, it is possible to disassemble the connector using the appropriate removal tool supplied with the system:

1. Remove the female connector from the male connector;
2. Unscrew the M14 screw of the male connector, until it protrudes 2-4 mm beyond the apex of the connector. Avoid twisting the connector with respect to the osseointegrated implant (Figure 18);
3. Insert the extractor around the male connector (Figure 19). Continue by screwing the special screw applied distally to the extractor until hearing a click from the connector.
4. Remove the male connector from the double cone adapter, taking care to keep the tightening screw in a safe place.

Figure 18 - Unscrew the M14 screw of the male connector

Figure 19 - Insert the extractor around the male connector

It is important to always keep the system clean and dry. It is recommended to instruct the patient in daily cleaning of the product using a soft, damp cloth and drying it carefully. A daily inspection allows to investigate the possible presence of sand or dust in the connector, which must be carefully removed using fresh water (Annex 4 - Ostomy care and hygiene protocol for osseointegrated prosthesis).

The prosthesis can be used on the beach or in the shower, remembering, after contacting the prosthesis with salt or contaminated water, to rinse the prosthesis with clean fresh water and to dry everything.

The following point list represents a summary of the phases to clean the stoma:

1. Remove the gauze;
2. Rinse the stoma with the hand shower (Figure 20) or with a water jet (the water jet is recommended);
3. Remove any deposits (encrustations) from the system with a gauze pad, water and soap (Figure 21);
4. Make sure that the prosthetic implant is perfectly clean and free of dust;

5. Massage the skin and muscles during rinsing and make sure that no adhesions occur between the stoma and the implant;
6. After rinsing, proceed by removing any residual water.

Figures 20 and 21 – Cleaning the stoma with the hand shower (left) and cleaning the adapter with gauze (right)

2.5 REHABILITATION TREATMENT

2.5.1 INTRODUCTION

Rehabilitation of the patient with an osseointegrated transfemoral prosthesis (Annex 5 - Rehabilitation protocol of the patient with osseointegrated transfemoral prosthesis).

The rehabilitation course is structured in such a way as to allow a gradual load on the osseointegrated limb. Although recovery time may vary depending on the characteristics of the subject, clear and precise indications should be given on the type of exercises allowed depending on the stage of the rehabilitation course. These indications are designed in such a way that any

specialized physiotherapy center will have the necessary tools to allow proper rehabilitation of the osseointegrated patient.

2.5.2 GENERAL INDICATIONS

Rehabilitation treatment begins from 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 plan is drawn up, which may include muscle strengthening and stretching exercises for the patient to implement independently, either before surgery or during the break between the two surgical steps.

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 figures of the physical therapist and the orthopedic technician collaborate on the alignment of the prosthetic components during the duration of the rehabilitation phase, so that any necessary changes can be made in a timely manner, optimizing the rehabilitation time.

The rehabilitation course begins with the patient's intake by the physiatrist, who defines the goals to be achieved with the personalized rehabilitation project, sharing them with the person concerned. The physiatrist also intervenes whenever the subject complains of pain in the operated limb, in order to determine whether it is possible to continue with the course of the session or if, otherwise, the patient needs a day off. In this regard, it is useful to make use of the NRS

(Numerical Rate Scale) considering pain of an intensity of 5 out of 10 or more worthy of further investigation before beginning the performance of any exercise.

The rehabilitation course is divided into training sessions based on the functional/motor goals established.

The Italian outline of the Rehabilitation Protocol, appropriately adapted by the staff of the INAIL Prosthesis Center participating in the project from the outline used by the Radboud University Orthopedic Clinic in the Netherlands.

In the original Dutch version, the rehabilitation pathway of the transfemoral osseointegrated patient includes two hours of training twice a week, for a total of 22 sessions spread over 11 weeks. A break is planned after the tenth session, so that the patient can become familiar with the correct use of walking aids, maintaining a correct gait pattern while strengthening the muscles, pending the completion of the final rehabilitation phase; during the latter, the reduction or, if possible, the abandonment of aids while walking is planned.

The period of discontinuation from training may last 4 weeks, or extend up to 12 weeks, if the level of pain or limited muscle strength would not allow continued rehabilitation.

In the version adapted by the INAIL Rehabilitation Center staff, there are 44 sessions divided into two phases: the first one ending at the 20th session and the second one starting again from the 21st and ending on the 44th, which corresponds to the end of the rehabilitation course. Again, a suspension period (break) is to be inserted between the two phases.

Sessions are conducted every morning, with a total duration of about three hours, Monday through Friday. They can, also, be repeated in reduced sessions in the afternoon, provided the patient does not experience pain or excessive fatigue.

The scheme that is shown in detail can be considered a standard model, which often needs to be adapted and customized according to the characteristics and clinical conditions of the subject.

The patient recovers ambulation by gradually reducing the need for support during walking.

The physical therapist constantly follows the patient during the performance of each exercise, paying particular attention to the correct execution of the suggested tasks and the posture assumed by the subject.

2.5.3 PRE-SESSION WARM-UP EXERCISES

Each rehabilitation session begins with warm-up exercises. These exercises can be performed in combination or alternately at the discretion of the physical therapist and can also be performed during the session if muscle fatigue arises. In addition, they can be repeated during the defatigue phase.

Oscillation exercises

Consists of oscillation exercises of the amputee limb (Figure 22).

Starting position: patient in orthostatism, with prosthesis worn. The limb contralateral to the amputated limb is kept extended and in support, in an elevated position relative to the prosthetic limb (e.g., over a step).

Performance: perform free swings of the amputated limb along the sagittal plane.

Caution: during the exercise, the subject should maintain a correct pelvic position, thus avoiding anteversion or retroversion postures; the trunk should remain on axis with the rest of the body, without flexing, rotating or tilting.

Stationary exercise bike

Using an exercise bike for about 10 to 15 minutes is recommended (Figure 23).

Caution: its use should be limited to patients who do not experience stump discomfort that can be linked to soft tissue friction against the prosthesis.

Figure 22 – 23 - Oscillation exercises (left) and cyclette (right)

Muscle stretching exercises

Stretching exercises are aimed at recovering the joint range of motion of the stump (very often limited) and the elasticity of the residual muscles.

These exercises can be performed by the subject before each session or on their own, after being properly instructed by their physical therapist.

Muscle stretching exercises are performed without the prosthesis being worn.

2.5.4 FIRST REHABILITATION PHASE

First and second sessions (1-2)

It is appropriate, during the first few days of the rehabilitation phase, to educate the subject on hygiene and appropriate ostomy care according to the dedicated protocol (Annex 4 - Ostomy care and hygiene protocol osseointegrated prosthesis).

Next, the physical therapist and orthopedic technician explain and illustrate to the patient how to properly connect the prosthesis to the implant.

Before starting the rehabilitation phase, it is advisable to wait two weeks from a second surgery. At this point, if the subject reports no pain (or acceptable pain, less than 5/10 points on the NRS scale), one can start performing the planned exercises while wearing the prosthesis. Otherwise, the rehabilitation session can begin following the medical examination by the physiatrist specialist.

The first sessions are based exclusively on exercises in orthostatism, designed to improve balance and distribution of body weight on both lower limbs while remaining safely between the parallels. In this regard, it is helpful to use scales to evenly and evenly distribute body weight (50% and 50%) (Figure 24).

During these exercises the feet are resting on two different scales, placed parallel to each other.

Figure 24 - Distribute body weight (50% and 50%)

Third to sixth sessions (3-6)

In the next three rehabilitation sessions, exercises focusing on load distribution and support phase of the prosthetic limb during the gait cycle are performed.

Seventh - eighth sessions (7-8)

At this point in the rehabilitation process, the subject is ready to take the first steps safely, between the parallel bars, so as to partially unload the weight on the upper limbs. At the same time, the use of scales is abandoned.

Ninth - twelfth session (9-12)

From the ninth session, walking outside the parallels is allowed, adopting the necessary aids and gradually expanding the distance walked.

Thirteenth - sixteenth sessions (13-16)

At this point in rehabilitation, it is possible to increase the difficulty of gait training by inviting the patient to walk at different speeds and to tackle stairs and uneven surface terrain, as is often the case when walking outdoors (Figure 25).

Figure 25 - Uneven surface outdoors

Seventeenth to twentieth sessions (17-20.)

Step training with two two-point sticks.

Pitch training is continued by changing the type of aids, so as to allow more and more freedom of movement for the subject. If two canes are not available, crutches can be flipped so that forearm support is excluded.

*2.5.5 PAUSE (*break*)*

It is recommended to stop the rehabilitation phase at the end of the 20th session.

The break may last from 4 to 12 weeks depending on the pain and fatigue experienced by the patient.

Should the subject prove to be particularly fatigued during the previously described sessions, the break can be brought forward.

2.5.6 SECOND REHABILITATION PHASE

In the second phase, some exercises from the first phase are resumed, such as: training for postural symmetry, pelvic shift, active pelvic tilt, whole stance phase, and gait training with two sticks at two stance points at different speeds and on uneven surfaces.

Twenty-first to twenty-second sessions (21-22)

Stride training with nordic walking sticks

The rehabilitation course continues by changing the type of aids. You resume at the same time, step training exercises at different speeds and on uneven surfaces.

Please note: If you do not have Nordic Walking sticks, you are allowed to move on to the next exercise.

Stride training with a single point of support

You drop one of the two supports used, maintaining support on the non-prosthetic side (Figure 26).

Caution: pay special attention to the subject's posture, as abandoning only one of the support points could promote the creation of compensations during the implementation of the stride.

Figure 26 - A single point of support

Step training without aids

It is advisable, once the aids have been abandoned, to approach the first steps between the parallel bars, with the upper limbs free and without support; once the subject feels confident, the exercise can be continued outside the parallel bars (Figure 27).

Figure 27 - Training without aids

Twenty-third to thirtieth sessions (23-30)

Training in different walking modalities

The Physical Therapist prompts the subject to walk backward and sideways, stopping on command; he continues the session by having the patient perform slaloms around some obstacles and teaching him how to turn around himself safely.

Thirty-first to thirty-sixth sessions (31-36)

Climbing and descending stairs without aids

The patient resumes stair ascent and descent exercises in the same manner as described above, but without the aid of crutches or canes.

Step training on inclines

Starting position: patient in orthostatism, at the foot of an incline.

Performance: walking along a platform with an adjustable slope at various degrees of inclination, repeating the exercise both uphill and downhill.

Caution: if the prosthetic knee allows, the patient should be taught to walk up an incline either with the joint locked or free.

Step training with obstacles

Starting position: patient in orthostatism, facing the obstacle; the physical therapist stands to the side of the subject, supporting him/her in case of uncertainty.

Performance: walking past the obstacle interposed along the way; change the height of the obstacle to vary the difficulty of the exercise.

Strategies for falling down and getting back up

Teaching the strategy exercises for falling and getting up is essential in order to avoid any direct trauma at the level of the implant.

Starting position: patient in orthostatism, in front of a mat.

Performance: ask the patient to simulate a fall following the techniques previously explained by the physical therapist.

Thirty-seventh to thirty-eighth sessions (37-38)

Step training by performing another activity

The physical therapist invites the patient to walk while simultaneously performing other tasks, such as talking, carrying a tray or shopping bag.

Thirty-ninth to forty-fourth sessions (39-44)

Circuit training in outdoor and indoor environments

The patient concludes his or her rehabilitation by facing predetermined routes, with different types of terrain and obstacles to overcome, in order to integrate all the skills learned during the different sessions.

2.5.7 CONCLUSIONS

Six months after the intervention, the patient is able to walk indoors and outdoors and without the aid of any support. In case the patient presents, at the beginning of rehabilitation, with compromised muscle mass, bone density deficit, or other issues, it is possible that the rehabilitation course may be extended up to twelve months.

2.5.8 PSYCHOLOGICAL SUPPORT

It often appears necessary during the rehabilitation phase to have a course of psychological support from an appropriately trained figure.

It is also advisable to organize the training sessions in such a way that several patients treated with osseointegration are involved together, so that the members within the group can compare the course and the feelings experienced, which differ significantly from those resulting from the use of traditional socketed prosthesis.

2.6 BENEFIS, RISK AND POTENTIAL ADVERSE EFFECTS

The overwhelming majority of amputees who change from a traditional socket prosthesis to an osseointegrated prosthesis improve dramatically, both subjectively and objectively. One study showed that when amputees changed from a socket prosthesis to an osseointegrated prosthesis, there were improvements on the Questionnaire for Persons with Transfemoral Amputation (from 45.27 to 84.86 points), Short Form-36 Physical Component Summary (from 36.97 to 49.00 points), 6 Minute Walk Test (from 286.25 to 512.72 meters), and the Timed Up and Go test (from 13.86 to 9.12 seconds) (Al Muderis, 2018). Laboratory gait analysis revealed that cadence, duration of the gait cycle, and support phases are closer to normal in patients with osseointegrated prostheses than in patients with socketed prostheses (Frossard, 2010; Frossard, 2011).

2.6.1 PHYSICAL BENEFITS

- A full, unrestricted range of movement around the hip joint, unimpeded by a socket brim;
- Better body perception (Lundberg, 2011);
- Osseoperception. Osseoperception is defined as the mechanical stimulation of a bone-anchored prosthesis that is transduced by mechanoreceptors likely located in the muscles, joints, skin, and other bone-adjacent tissues that travel to the central nervous system to cause passive awareness of a patient's own sensorimotor position and function (Klineberg, 2005). There is improved sensory feedback as a result of the direct link with the skeletal system (Kumar, 2012; Hagberg, 2008; Branemark, 2001; Ysander, 2001).
- Reduced soft tissue problems;
- Maximum sitting confort (Hagberg, 2005):
- Increased walking ability (Frossard, 2010);

- Improved functional capacity (Frossard, 2008; Frossard, 2011);
- Overall increase in quality of life (Hagberg, 2008; Lundberg, 2011; Berlin 2012);

2.6.2 PROSTHETIC BENEFITS

- Improved suspension of the prosthesis, with no functional lengthening during swing phase and a direct transmission of movements;
- No fitting problems due to fluctuation of stump volume;
- No skin problems from the stump/socket interface;
- Direct prosthesis control:
- Improve stability;
- Better fixation;
- Prosthesis use is high (82% to 90% daily use) (van ECK, 2015);
- Ease of donning and doffing (Bergkvist, 1998; Hagberg, 2008; Hagberg, 2005).

As a result of these benefits, candidates experience functional improvements in their general activities of daily living. Examples include sitting comfortably on a low chair, fully flexing the hip to tie shoelaces and cycling.

2.6.3 RISK AND POTENTIAL ADVERSE EFFECTS

Several articles have been published in the literature reporting the risks and potential adverse effects associated with osseointegration surgery. These data have allowed optimization of patient inclusion criteria and preventive measures to be taken according to different risk categories (Al Muderis, 2016).

The most common adverse effects are at the ostomy, which is the circular opening in the skin that allows the transcutaneous adapter to pass through, enabling the connection between the intramedullary implant and the external prosthesis. Notably, there have been multiple cases of irritation (hypergranulations caused by redundant soft tissue rubbing) and superficial infections (Figure 28) (Li, 2017; Branemark, 2019). In general, the most common complication surrounding OI prosthetic implants is superficial infection. In these infections are staphylococcus aureus and coagulase-negative staphylococci species.

Superficial infections are often managed effectively with oral antibiotics alone and do not require surgical debridement. Superficial infections most commonly present with mild pain, erythema, swelling, or purulent discharge at the skin/abutment interface. In their series of transfemoral implants, a study (Brånemark, 2014) reported a superficial infection rate of 54.9%. Superficial infection occurred 41 times in 28 patients. The majority of these were successfully treated with a 10-day course of oral antibiotics and only four patients required prolonged antibiotic treatment. More importantly, none the patients who were treated for superficial infection developed a deep infection and none of these patients required implant removal.

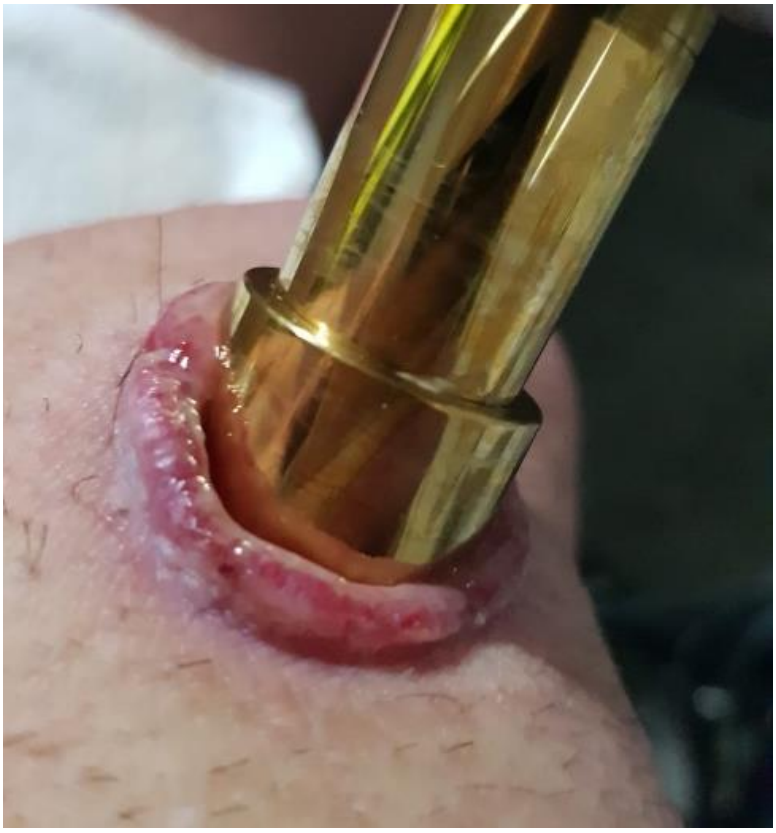


Figure 28 - Superficial Infection

Other adverse effects involve the osseointegrated implant and the amputated limb.

The most serious complications recorded 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 stem;
- Fracture and replacement of the double-cone adapter or clamping screw;
- Fractures of the proximal femur;
- Deep infections.

Deep infections are the most important complication, involving long-term treatment with one or more antibiotics in combination; in some cases, surgical treatment is necessary, but rarely is there

a need to remove the implant. Cases of implant failure due to infection have occurred in patients in whom infection was known to have occurred prior to osseointegration surgery (Brånemark, 2019). The deep infection leading to implant failure is infrequent, the risk of superficial infection with OI amputation implants may exceed 50%.

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, rupture 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 the transcutaneous adapter to loosen without causing bone fractures and safeguarding the osseointegrated stem (Al Muderis, 2018).

A Body Mass Index (BMI) greater than 25 and muscular hypotrophy of the residual limb are among the main underlying causes of soft tissue overgrowth around the ostomy. Proper management of soft tissue around the ostomy helps prevents 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 delayed osseointegration, leaving part of the stem uncovered and leading to an increased risk of stem failure (Al Muderis, 2018).

The impact on patients' quality of life following complications was investigated through questionnaires. It emerged that, in each case, such events were not a source of major problems (Brånemark 2014).

The fact that the number of serious adverse events is limited to a few cases confirms how the risk-benefit ratio is in favor of the intervention (Al Muderis, 2018).

As with all intramedullary implants, fractures can occur proximal to the implant or at the level of the implant, disrupting the bone-implant interface. Three periprosthetic fractures reported a study (Brånemark, 2014) were ipsilateral hip fractures, proximal to the implant. As with all implants,

failure/fracture can also occur through the implant itself secondary to fatigue or intense stress. In the same study nine implant failures were reported in four patients and included bending or fracture of the abutment or abutment screw. All were treated successfully with revision surgery and implant replacement. Six of the nine implant failures occurred in the same patient, indicating likely individual patient specific factors that overestimate the rate of overall implant failure in this study. In a more recent prospective series of 51 patients/55 limbs and 5-year clinical follow-up, mechanical complications with bent abutments or abutment screw failures remained common, including 16 bent abutments in nine patients (Brånemark, 2019). In both series, no implant failures occurred at the fixture itself (Brånemark, 2019).

It is possible, especially in the immediate postoperative period, that the patient may not be able to accept the appearance of the ostomy. In this case, psychological support and the opportunity to compare with other patients who have gone through the same process is helpful.

Of all those goals, perhaps the least certain is how to address the implant-skin interface. The transcutaneous nature of the implant and the exposure to the external environment represent the most clinically important and obvious risk. Generally, stable skin is less likely to become inflamed than skin that is moved or stretched (Al Muderis, 2016; Paleyx, 1990). Detailed research with regard to the ideal skin-implant interface is actively being pursued, and creative innovations may be necessary.

2.7 COST ANALYSIS

A study reports the incremental costs and heath gain as well as cost-effectiveness of bone-anchored prostheses compared to socket-suspended prostheses (Frossard, 2018). The provision of bone-anchored prostheses costed 21% ± 41% more but increased quality-adjusted life-years

by 17% ± 5% compared to socket-suspended prostheses. The incremental cost-effectiveness ratio ranged between -$25,700 per quality-adjusted life-year and $53,500 per quality-adjusted life-year with indicative incremental cost-effectiveness ratio of approximately $17,000 per quality-adjusted life-year. Bone-anchored prosthesis was cost-saving and cost-effective for 19% and 88% of the participants, respectively. This study indicated that bone-anchored prostheses might be an acceptable alternative to socket-suspended prostheses at least from a prosthetic care perspective in Australian context. Altogether, this initial evidence-based economic evaluation provided a working approach for decision makers responsible for policies around care of individuals with lower limb amputation worldwide. Clinical relevance for the first time, this study provided evidence-based health economic benefits of lower limb bone-anchored prostheses compared to typical socket-suspended prostheses from a prosthetic care perspective that is essential to clinicians and decision makers responsible for policies (Frossard, 2018).

While another study (Black, 2022) reported that the average cost of OI surgery was $54,463. Twenty percent of patients required preimplantation soft tissue revision surgery ($49,191). Complication rates per year and average costs were as follows: soft tissue infection (29%, $435), bone/implant infection (11%, $11,721), neuroma development (14%, $14,659), and mechanical failure (17%, $46,513). The incremental cost-effectiveness ratio (ICER) was $44,660. A cost-effectiveness acceptability curve demonstrated that OI was favored over SS in 78% of cases at a willingness-to-pay of $100,000 per quality-adjusted life year. In a 1-way sensitivity analysis, the ICER was most sensitive to the mechanical failure rate, mechanical failure cost, and prior socket-suspended prosthesis costs. The model shows that OI prostheses provide a higher quality of life at affordable costs when compared to poorly tolerated SS prostheses in patients with lower limb amputations in the United States. The cost-effectiveness is largely determined by the patient's previous SS prosthesis costs and is limited by the frequency and costs of OI mechanical failure.

More research must be done to understand the long-term benefits and risks of OI prostheses (Black, 2022).

There are few prosthetic cost analyses in the literature. Additional analyses are needed to determine the direct and indirect costs associated with prosthetic acquisition, fitting, and maintenance; the costs of amputee rehabilitation; and long-term economic and quality-of-life benefits. Such studies may guide future prosthetic and rehabilitative care, especially in resource-austere settings where prosthetic needs are greatest (Donnelley, 2021).

With the resultant increased implant production, the unit cost per implant should be reduced, and this would, in turn, permit greater access worldwide. This is especially important for patients who live in areas of the world where amputation is often the solution to relatively routine trauma, or where land mines and war injuries remain a devastating cause of limb loss (Ebrahimzadeh, 2007, McKinley, 2018).

3. JUSTIFICATION AND AIMS

The limb prosthesis is essential tool for the recovery of motor functions after a lower limb amputation. Over the years, technological progress has made it possible to customize the prostheses according to the needs of the subjects, reaching optimal levels of functionality. However, although prosthetic techniques have been refined over the years, many problems remain unresolved. Among these, the difficulties related to the realization and footwear of the socket are the most common among subjects with a lower limb amputation who wear a traditional socket type prosthesis. Osteointegration surgery, applied to the lower or upper limbs, is an innovative technique. It consists in replacing the socket of prosthesis with an endomedullary implant, inserted inside the bone stump of the amputated limb. This solution allows to connect the skeleton directly to the external prosthesis through an opening of the skin, solving all the problems related to the socket. This technique already known in some European orthopedic clinics and in some parts of the world, in Italy has been adopted only in recent years. With a project born at the Rizzoli Orthopedic Institute in collaboration with the University of Bologna and the Centro Protesi di Vigorso - INAIL it was possible to perform in 2019 the first osteointegration surgery in Italy.

Since the osteointegration of the lower limb is an innovative technique, there are still many aspects to study and examine in depth.

Kinematic patterns markedly change between a subject with amputated limb and a healthy subject; moreover, an amputated limb can also affect the sound limb (Jaegers, 1995; Boonstra, 1996; Vaughan, 1992; Genin, 2008; Harandi, 2020). Given the problems (Hagberg, 2001; Dudek, 2004; Meulenbelt, 2011) that can result from a traditional prosthesis with a socket, such

kinematic differences could also be found between a traditional prosthesis and an integrated prosthesis.

In subjects with amputation, that have also other comorbidities, the bone quality decreases rapidly, especially in the limb stump, leading to an increased fear of falling as well as actual falls among amputees (Bemben 2017; Miller 2001). Is therefore of crucial importance know and manage the modification bone quality, through the study of its biological parameters, to mitigate the morbidity progression in all subjects exposed to lose BMD (Black, 2020; Bemben 2017; Flint, 2014). Due to the number of people suffering from osteoporosis, several therapies have been proposed to improve bone quality and prevent resorption. Traditional therapy includes the intake of calcium and vitamins as well as the administration of drugs (Prestwood, 2003; Fink, 2019). However, there are also non-pharmacological approaches which are used as prevention or which are complementary to drug therapy. Through mechanical stimulation of bone, physical exercise is a method used to promote bone turnover and prevent bone resorption (Troy, 2018). There are also modern external devices that use technology to stimulate bone formation with a non-invasive approach and minimal discomfort for patients (Turner, 2006; Knothe, 2013; Mogil, 2016).

For these reasons, the present thesis aims to: (i) to provide a longitudinal functional assessment of a patients treated with an osseointegrated prosthesis for transfemoral amputation by means of wearable sensors; (ii) to investigate the state of stump bone quality in patients with limb amputations; (iii) to investigate which external devices are present in the literature that use state-of-the-art technology to improve bone quality; (iv) to evaluate and critically analyze, the available evidence on the effects of physical activity interventions and the combined therapeutic strategy based on pharmacological treatment and physical activity on bone biomarkers.

In the following chapters the objectives of the thesis will be developed through 5 studies:

- Study I: ***Longitudinal gait analysis of a trans-femoral amputee patient: form socket type to osseointegrated prosthesis;***
- Study II: ***The stump bone quality in amputee patients: a systematic review and meta-analysis of 561 lower limb amputees;***
- Study III: ***External devices increasing bone quality in animals: a systematic review;***
- Study IV: ***The Effect of Physical Activity on Bone Biomarkers in People With Osteoporosis: A Systematic Review;***
- Study V: ***Current Lack of Evidence for an Effect of Physical Activity Intervention Combined with Pharmacological Treatment on Bone Turnover Biomarkers in People with Osteopenia and Osteoporosis: A Systematic Review.***

4. STUDY I

LONGITUDINAL GAIT ANALYSIS OF A TRANS-FEMORAL AMPUTEE PATIENT: FORM SOCKET TYPE TO OSSEOINTEGRATED PROSTHESIS

4.1 ABSTRACT

The amputation of a limb is a life-changing event, limiting a person's independence, quality of life and participation in everyday activities. The osseointegration technique represents an alternative method of treatment for amputees with socket-related problems and low quality of life. The aim of the case report is to provide a longitudinal functional assessment of a patient treated with an osseointegrated prosthesis for transfemoral amputation.

The present is a case report study of a 44 years-old male patient who underwent surgery for the implantation of an osseointegrated prosthesis, 17 years after transfemoral amputation. The gait analysis was performed by 15 wearable inertial sensors, at the pre-operative phase and at 3- 6- and 12-month follow-ups post-surgery.

Gait speed was comparable among the follow-ups. Step width decreased by one-half between pre-op and all the follow-ups. The symmetry index was the highest in the pre-op (1.14) and the lowest in the last follow-up OI FU 1Y (1.04). Hip flexion-extension differed significantly between the pre-op and the last follow-up ($p<0.001$). In the amputee limb, hip abduction and hip internal rotation were also reduced from the preoperative to the 3- and 6-month follow-ups, while peak abduction and rotation between pre-op and 12-month follow-up during the swing phase were comparable.

This case report found a difference in terms of spatiotemporal parameters and joint kinematics during the gait of a transfemoral amputee patient after a surgical treatment of osseointegration compared to a standard socket-type prosthesis.

4.2 INTRODUCTION

The amputation of a limb is a life-changing event, limiting a person's independence, quality of life and participation in everyday activities.

In developed countries, the main cause of lower limb amputation is vascular disease, with diabetes mellitus accounting for two-thirds of all amputations, in contrast to developing countries, where traumatic aetiology related to occupational accidents, road trauma and blast trauma in war situations is the most common cause (Marks, 2001; Dillingham, 1998).

Another important cause, especially in young males, is musculoskeletal tumours (Kalbaugh, 2020).

Although technological progress has made it possible to make prostheses that are customised to individual needs, difficulties in the fabrication and daily use of the socket remain very common among patients with lower limb amputation and represent the main causes of dissatisfaction. Indeed, pressure sores, skin abrasions due to friction, excessive skin sweating, changes in stump volume, lack of balance and walking difficulties are very frequent problems among amputees, who abandon the use of the socket, reducing their overall quality of life (Van de Meent, 2013; Hagberg, 2001; Buikema, 2014; Dudek, 2004; Meulenbelt, 2011).

A subject with amputation must modulate his kinematic pattern according to the musculature of the residual limb (Jaegers, 1995; Boonstra, 1996; Vaughan, 1992; Genin, 2008). Indeed, the primary role of the healthy limb muscles leads to walking characterized by a poor hip flexion-

extension of the amputated limb during the ipsilateral and contralateral heel strike and contralateral toe-off phases. In addition, the healthy limb has a greater anterior pelvic tilt and abduction resulting in a limping gait (Harandi, 2020).

The osseointegration technique represents an alternative method of treatment for amputees with socket-related problems and a low quality of life. This technique involves implanting a stem within the medullary canal of the amputated skeletal segment that extends outside the amputation stump. A prosthesis is then attached to the metal extension using a quick-release coupling system.

These implants exploit the properties of the recipient's bone to grow within the macro-porosity present on their external surface, a process that leads to osseointegration within the amputated bone (Brånemark, 2014).

The possibility of attaching the external prosthesis directly to the amputated skeletal segment has many advantages for the patient, including the elimination of the socket with all its associated skin problems, increased skeletal proprioception and improved gait cycle efficiency, with increased walking speed and improved muscle control of the stump (Van de Meent, 2013; Hagberg, 2005; Tranberg, 2011; Hagberg, 2014; Hagberg, 2008; Shalk, 2015; Lundberg, 2011).

Therefore, interest in this technique has grown considerably in recent years, and more and more patient who are dissatisfied with their socket are asking to undergo this innovative intervention, in the hope of regaining the independence lost after the amputation.

The aim of the case report is to provide a longitudinal functional assessment of a patients treated with an osseointegrated prosthesis for transfemoral amputation by means of wearable sensors. The hypothesis is that gait with an osseointegrated prosthesis will have a greater range of motion balance between the hip, greater trunk stability and a reduce limping gait than a gait with a socket-type prosthesis.

4.3 METHODS

4.3.1 CASE REPORT

The patient is 44 years-old male who underwent a left transfemoral amputation following a motorbike accident in 2003. The patient had also suffered an amputation of the fifth finger of the left hand at the proximal interphalangeal level, a lacerated contusion wound in the volar region of the left hand and a traumatic injury to the extensor muscles of the left hand. Ipsilateral hip movements were complete and pain free. No other major comorbidities were present.

Despite the implementation of several prostheses, 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 when walking, with important limitation in the continuous and satisfactory use of the external prosthesis. He reported occasional paresthesias in the distal portion of the stump, in the absence of strength deficit.

After a preliminary evaluation by a multidisciplinary team composed of orthopaedist, physiatrist, prosthetic technician and psychologist, indication was given 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.

In March 2021, the patient then underwent the first surgical step of stump revision and implantation of the osseointegrated intramedullary stem (Figure 1). After 6 weeks, the second surgical step of creating the skin stoma and implanting the transcutaneous double-cone adapter was performed. After a convalescence period of 15 days, the patient started the 17-day rehabilitation program.

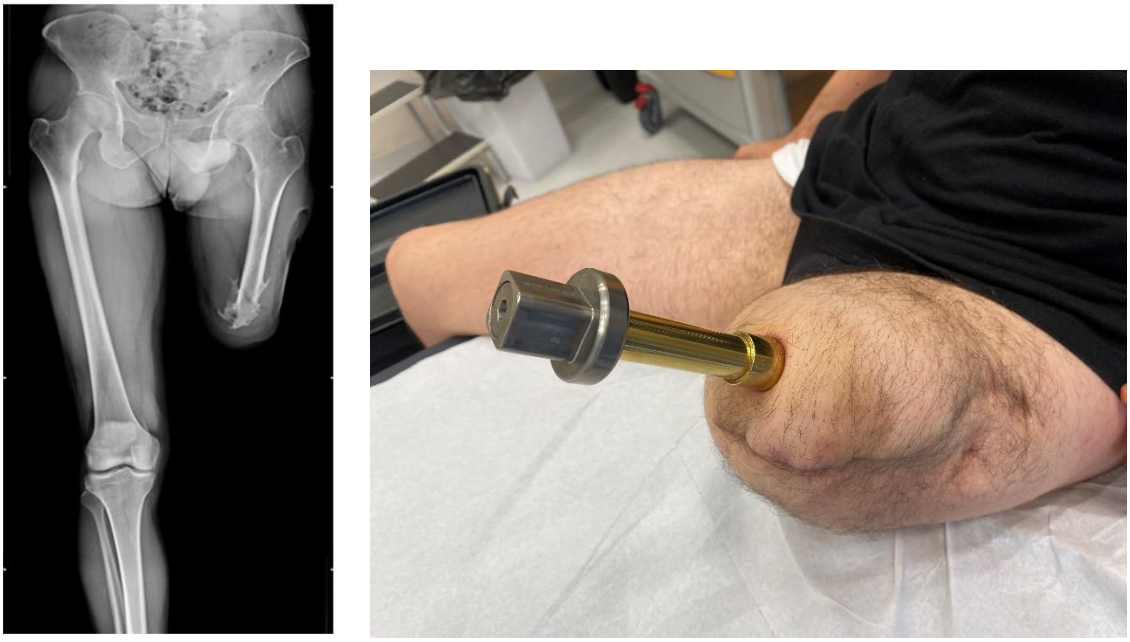


Figure 1 - *X-ray (left), bone-prosthesis connection after the second surgical step (right)*

4.3.2 DATA COLLECTION

Functional tests were submitted to the patient the day before osseointegration surgery, thus the last day of socket-type prosthesis (ST Pre-op) and 3 months (OI FU 3M), 6 months (OI FU 6M), and 12 months (OI FU 1Y) after the second osseointegration surgical step. The first follow-up coincided with the rehabilitation clearance by the physiotherapists team.

The gait analysis was performed using a set of 15 wearable inertial sensors (MTw Awinda, Xsens Technologies, Enschede, The Netherlands) placed bilaterally on: Head, shoulders, arms, forearms, trunk, pelvis (L5), upper legs, lower legs, and feets (Figure 2).

A 20-meter walk (roundtrip in a 10-meter path) was carried in the indoor hall of the hospital where the patient underwent the two surgical steps and the acute postoperative phase. out twice at self-selected speed and twice at the maximum speed possible.

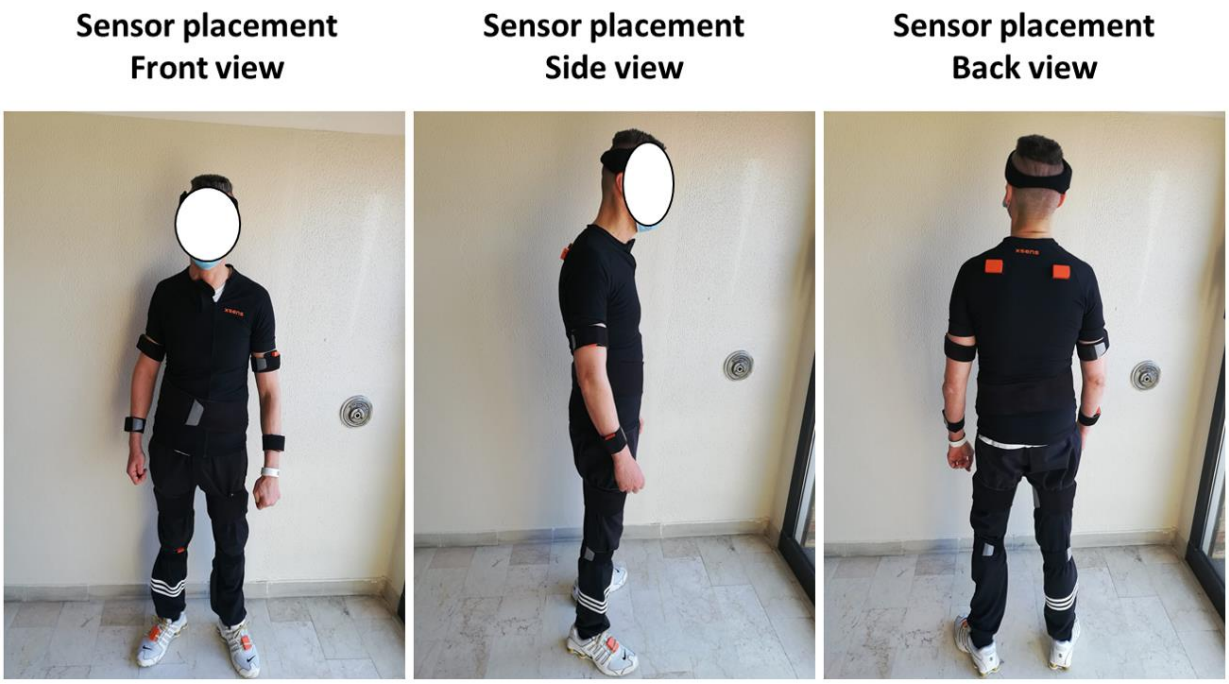


Figure 2 - Sensors placement. Full-body placement of inertial sensor units for gait analysis in front view (left), side view (middle), and back view (right). Note: the sensors on the thigh were placed on the residual stump for the amputee leg and symmetrically on the sound limb, according to the manufacturer instruction

4.3.4 DATA ANALYSIS

Wearable sensors data were processed in the Gait Analysis Report in the Xsens Motion Cloud (*https://www.xsens.com/motioncloud*). Joint angles were defined using the Euler sequence ZXY and further postprocessed in a customized script in Matlab (The MathWorks, Natick, Massachusetts, US). All parameters were investigated according to the normalized gait cycle (0-100%). The following spatial parameters were assessed: speed, cadence, step length, and step width. The temporal parameters under investigation were the gait cycle percentage of stance and swing phase, single and double support phase, symmetry index (assessed as the ratio between sound and amputee limb stance phase (Cutti, 2018), and coefficient of variation (assessed as the percentage of the ratio between standard deviation and average of the stride time). The symmetry

index decreased as the symmetry increased (symmetry index=1.00 means perfect symmetry (Cutti, 2018), and a threshold of 2.6% for the coefficient of variation was identified in the literature to describe the pathological gait (König, 2014). The 3D joint kinematics of hip (amputee and sound limb), knee and ankle (sound limb), and pelvis were investigated.

4.3.5 Statistical Analysis

Continuous variables were presented as mean and standard deviation, while categorical variables were presented as sample size and percentages over the total. The Repeated measures ANOVA was used to assess the differences between the follow-ups for the continuous kinematic variables through the Random Field Theory according to Pataky et al. in Statistical Parametric Mapping 1D (spm1D) (Pataky, 2011). The Student's t-test with Bonferroni correction for multiple comparisons was performed to compare each follow-up couple. For conciseness, the post-hoc differences between the preoperative gait analysis (ST pre-op) and the first (OI FU 3M) and last (OI FU 1Y) follow-ups were the only ones reported and further discussed. Statistical tests were performed in Matlab. Differences between the groups were considered statistically significant if $p < 0.05$.

4.4 RESULTS

Minimal differences in terms of speed and kinematics emerged between self-selected speed gait and fast gait. For conciseness, only fast gait results were presented.

4.4.1 *SPATIOTEMPORAL PARAMETERS*

Gait speed was comparable among the follow-ups. Cadence decreased from ST pre-op to all the follow-ups. Step width decreased by one half between ST pre-op and all the follow-ups for both the amputee and the sound limb (Table 1).

The side-to-side difference between amputee and sound limb in stance and swing phase progressively decreased from the ST pre-op through all the follow-ups. The symmetry index was the highest in the ST pre-op (1.14, lowest symmetry) and the lowest in the last follow-up OI FU 1Y (1.04, highest symmetry). The coefficient of variation was the lowest in the last follow-up OI FU 1Y for both the amputee and sound limb and was always below the pathological threshold (Table 1). The side-to-side difference between amputee and sound limb in single support phase progressively decreased over time and the total percentage of double support phase was up to double in the last follow-ups (highest in OI FU 6M) compared to the ST preo-op (Table 2).

Table 1 - *Spatial gait parameters for the pre-operative gait analysis (socket-type prosthesis, ST) and for the follow-up gait analyses (osseointegrated prosthesis, OI).*

Spatial parameters		**Pre-op**	**Follow-up 3M**	**Follow-up 6M**	**Follow-up 1Y**
Speed (m/s)		1.63	1.66	1.55	1.68
Cadence (steps/min)		131.67	127.67	125.97	130.43
Step Length (cm)	Amputee Limb	75.08 ± 2.72	71.42 ± 2.00	74.28 ± 1.59	69.23 ± 1.82
	Sound Limb	82.65 ± 1.83	88.20 ± 1.76	74.92 ± 1.42	86.11 ± 2.47
	Difference	-7.56	-16.78	-0.64	-16.88
Step Width (cm)	Amputee Limb	13.74 ± 1.81	8.28 ± 1.70	4.71 ± 1.35	6.66 ± 2.20
	Sound Limb	14.19 ± 1.10	8.84 ± 1.98	4.99 ± 1.27	7.31 ± 4.43
	Difference	-0.45	-0.56	-0.28	-0.66

Data are presented as mean ± standard deviation. Note: "Difference" means Sound limb – Amputee limb variable.

Table 2 - *Temporal gait parameters for the pre-operative gait analysis (socket-type prosthesis, ST) and for the follow-up gait analyses (osseointegrated prosthesis, OI).*

Temporal parameters (% of gait cycle)		**Pre-op**	**Follow-up 3M**	**Follow-up 6M**	**Follow-up 1Y**
Stance	Amputee Limb	51.00 ± 0.98	54.82 ± 1.30	57.13 ± 1.34	57.23 ± 0.77
	Sound Limb	58.15 ± 0.81	59.62 ± 0.97	60.53 ± 0.78	59.35 ± 1.25
	Difference	-7.15	-4.8	-3.4	-2.12
Swing	Amputee Limb	49.00 ± 0.98	45.18 ± 1.30	42.87 ± 1.34	42.77 ± 0.77
	Sound Limb	41.71 ± 1.14	40.27 ± 1.35	39.59 ± 1.29	40.92 ± 1.21
	Difference	7.3	4.91	3.28	1.85
Symmetry Index		1.14	1.09	1.06	1.04
Coefficient of Variation	Amputee Limb	1.97	2.48	1.78	1.13
	Sound Limb	1.50	1.79	1.29	1.19
	Difference	-0.47	-0.70	-0.48	0.06
Single Support	Amputee Limb	41.90 ± 1.27	40.27 ± 1.06	39.43 ± 1.06	40.82 ± 1.12
	Sound Limb	48.79 ± 1.38	45.17 ± 0.97	43.04 ± 1.25	42.88 ± 1.17
	Difference	-6.89	-4.9	-3.61	-2.06
Double Support	Amputee Limb	3.03 ± 1.13	7.60 ± 1.18	9.08 ± 0.99	9.74 ± 0.50
	Sound Limb	6.04 ± 1.14	6.96 ± 0.90	8.66 ± 0.97	6.68 ± 1.20
	Difference	-3.01	0.64	0.43	3.06
	Total	9.07 ± 1.82	14.56 ± 1.61	17.74 ± 1.65	16.42 ± 1.16

Data are presented as mean ± standard deviation in percentage of gait cycle. Note: "Difference" means Sound limb – Amputee limb variable; symmetry index=1.00 means perfect symmetry between stance phases of the two limbs.

4.4.2 *JOINT KINEMATICS*

Hip flexion-extension differed significantly between the ST pre-op and the OI follow-up ($p<0.001$): after 6 months from the surgery, a reduced flexion peak at foot contact and an increased extension peak at toe-off were noted both at the amputee and sound limb (Figures 3 and 4). In the amputee limb, hip abduction and hip internal rotation were also reduced from the preoperative to the 3M and 6M follow-ups, while peak abduction and rotation between pre-op and 1Y follow-up during the swing phase were comparable (Figure 3).

Pelvis kinematics significantly changed over time on the three planes: reduced anteversion during the entire gait cycle and reduced rotation and obliquity at amputee limb foot contact were noted (Figures 5 and 6). Lower pelvis rotation at toe-off was also noted during the 1Y follow-up compared to the preoperative phase ($p<0.001$).

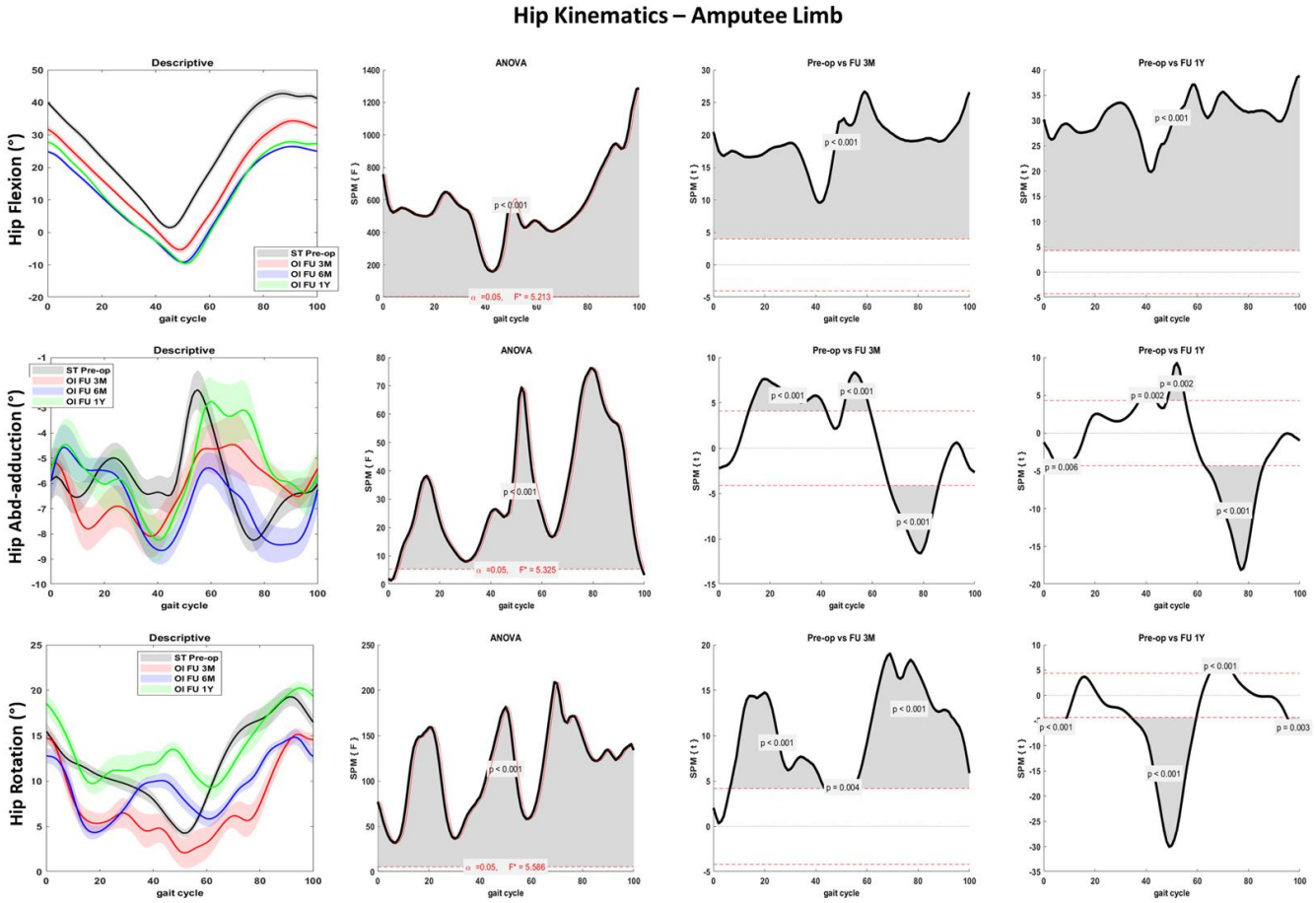


Figure 3 - Hip joint kinematics for the amputee limb over the percentage of gait cycle in sagittal (first row), frontal (second row), and transverse (third row) planes. Descriptive data (first column) was expressed as mean (solid line) and standard deviation (dashed line). The gray line represents pre-operative gait analysis with socket-type prosthesis (ST pre-op), the red line represents gait analysis at 3 months follow-up with osseointegrated prosthesis (OI FU 3M), the blue line represents gait analysis at 6 months follow-up with osseointegrated prosthesis (OI FU 6M), the green line represents gait analysis at 1 year follow-up with osseointegrated prosthesis (OI FU 1Y). The results of the spm1D repeated-measure ANOVA were presented in the second column. Gray areas represent statistically significant differences ($p<0.05$) among the groups. The differences between pre-operative phase and either 3 months follow-up (third column) or 1 year follow-up (fourth column) were assessed through t-test with Bonferroni correction

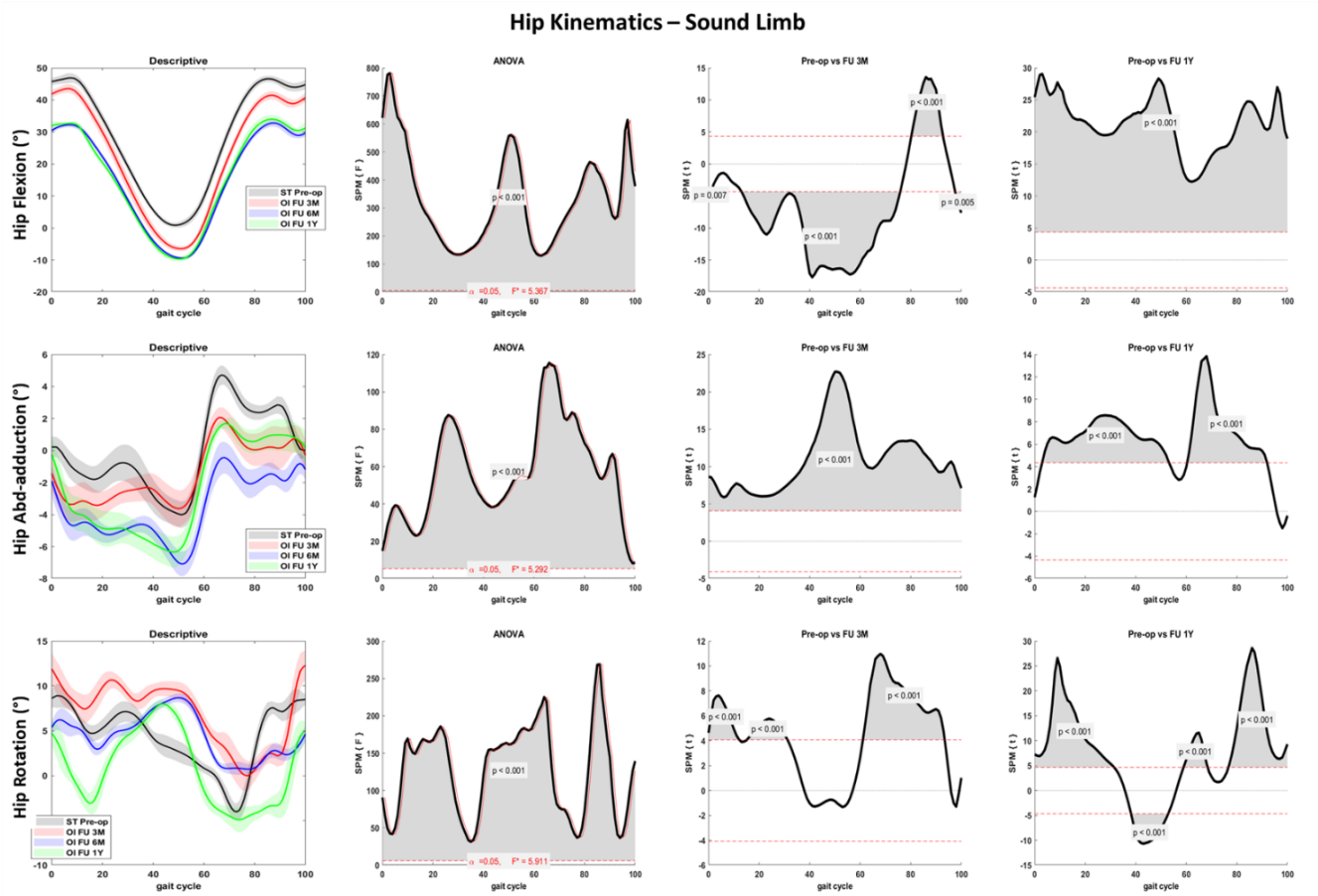


Figure 4 - Hip joint kinematics for the sound limb over the percentage of gait cycle in sagittal (first row), frontal (second row), and transverse (third row) planes. Descriptive data (first column) was expressed as mean (solid line) and standard deviation (dashed line). The gray line represents pre-operative gait analysis with socket-type prosthesis (ST pre-op), the red line represents gait analysis at 3 months follow-up with osseointegrated prosthesis (OI FU 3M), the blue line represents gait analysis at 6 months follow-up with osseointegrated prosthesis (OI FU 6M), the green line represents gait analysis at 1 year follow-up with osseointegrated prosthesis (OI FU 1Y). The results of the spm1D repeated-measure ANOVA were presented in the second column. Gray areas represent statistically significant differences ($p<0.05$) among the groups. The differences between pre-operative phase and either 3 months follow-up (third column) or 1 year follow-up (fourth column) were assessed through t-test with Bonferroni correction

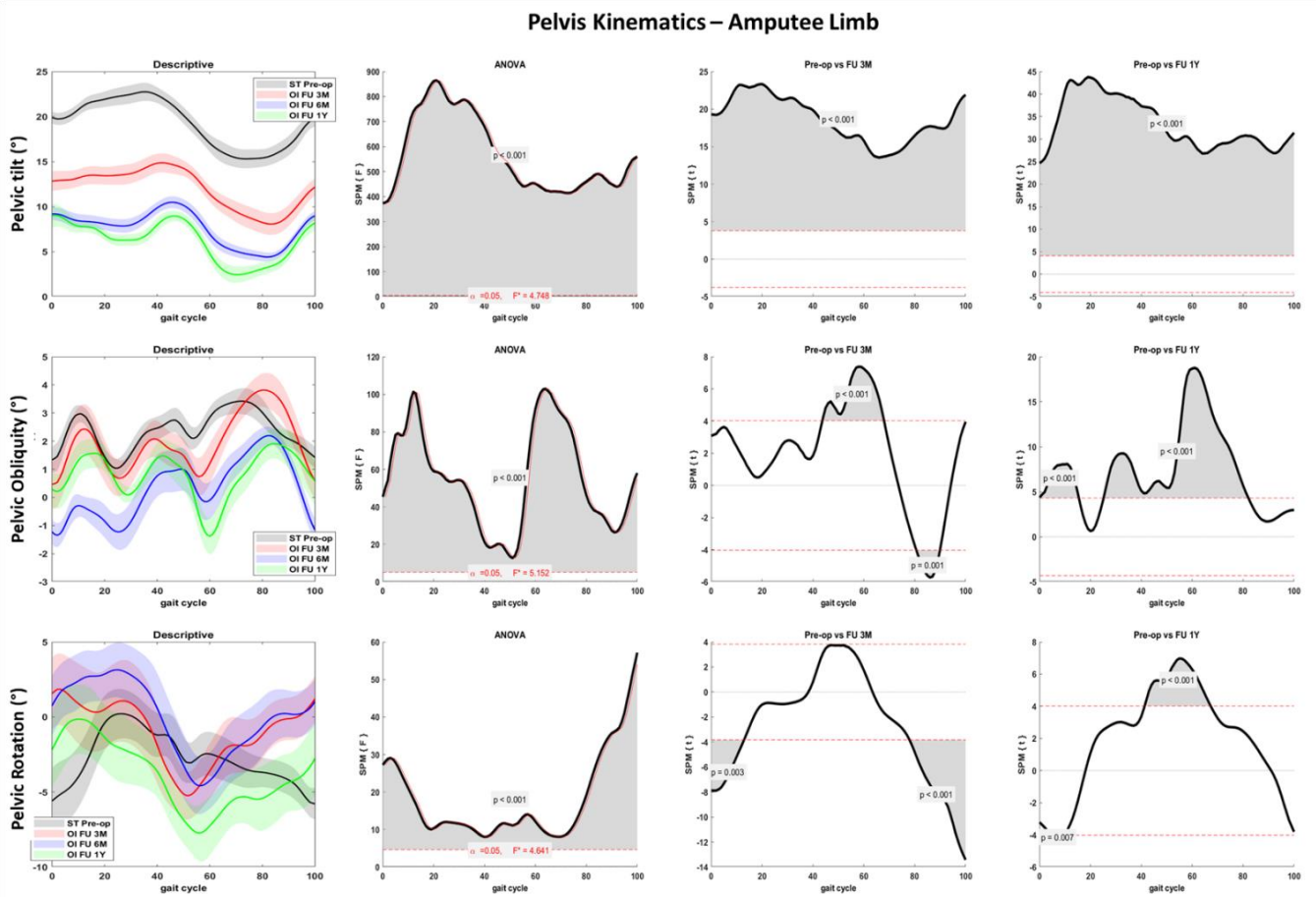


Figure 5 - Pelvis joint kinematics during over the percentage of gait cycle performed with the amputee limb in sagittal (first row), frontal (second row), and transverse (third row) planes. Descriptive data (first column) was expressed as mean (solid line) and standard deviation (dashed line). The gray line represents pre-operative gait analysis with socket-type prosthesis (ST pre-op), the red line represents gait analysis at 3 months follow-up with osseointegrated prosthesis (OI FU 3M), the blue line represents gait analysis at 6 months follow-up with osseointegrated prosthesis (OI FU 6M), the green line represents gait analysis at 1 year follow-up with osseointegrated prosthesis (OI FU 1Y). The results of the spm1D repeated-measure ANOVA were presented in the second column. Gray areas represent statistically significant differences ($p<0.05$) among the groups. The differences between pre-operative phase and either 3 months follow-up (third column) or 1 year follow-up (fourth column) were assessed through t-test with Bonferroni correction

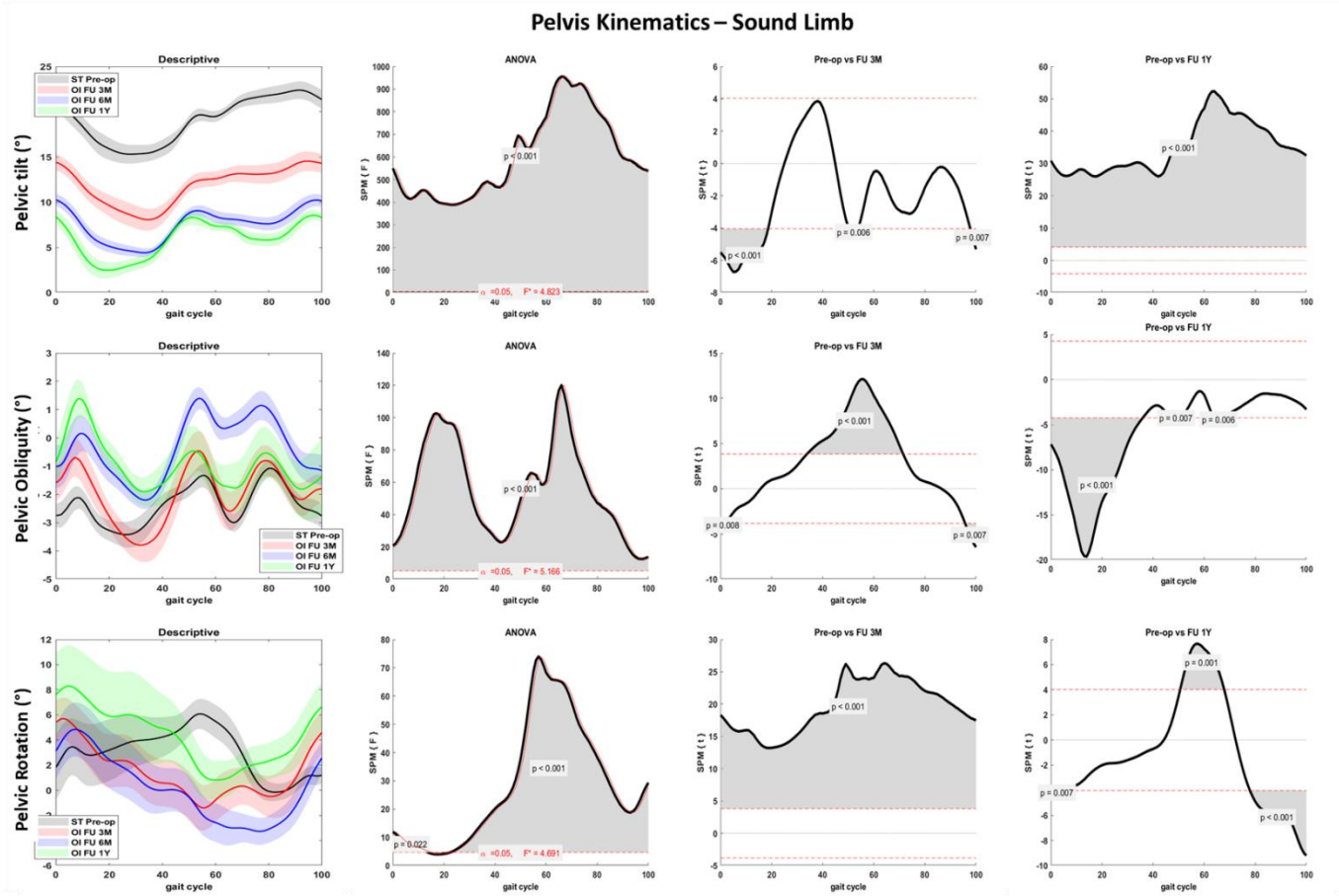


Figure 6 - Pelvis joint kinematics during over the percentage of gait cycle performed with the sound limb in sagittal (first row), frontal (second row), and transverse (third row) planes. Descriptive data (first column) was expressed as mean (solid line) and standard deviation (dashed line). The gray line represents pre-operative gait analysis with socket-type prosthesis (ST pre-op), the red line represents gait analysis at 3 months follow-up with osseointegrated prosthesis (OI FU 3M), the blue line represents gait analysis at 6 months follow-up with osseointegrated prosthesis (OI FU 6M), the green line represents gait analysis at 1 year follow-up with osseointegrated prosthesis (OI FU 1Y). The results of the spm1D repeated-measure ANOVA were presented in the second column. Gray areas represent statistically significant differences ($p<0.05$) among the groups. The differences between pre-operative phase and either 3 months follow-up (third column) or 1 year follow-up (fourth column) were assessed through t-test with Bonferroni correction

4.5 DISCUSSION

Better gait parameters were found in the patient with the osseointegrated prosthesis than in the standard socket-type prosthesis. In particular, findings underline a strong difference in terms of spatiotemporal parameters and joint kinematics.

Speed gait and step cadence are greater respect the references values reported by the current literature (Cutti, 2018; Andrysek, 2020; Gaunaurd, 2020). Half step width in the follow-ups compared to the pre-op is less than half. A wide support base is a common strategy used to keep or increase the walking medio-lateral stability when there is a poor motor control (Skiadopoulos, 2020). However, excessive step width is an important predictor of risk of fall (Nordin, 2010). During the follow-ups, patient strongly decreases the step width to increase walking speed, strong index of more confidence, sensorimotor control and great strategy to reduce the risk of fall.

Asymmetry observed in the present study, between sound and amputee limb, in particular a shorter support phase and extended swing time on the amputated limb, find several comparable results in literature (Nolan, 2003; de Castro, 2014; Aslani, 2016; Agrawal, 2013). Reduced difference between amputee and sound limbs both in stance and swing phases indicate an increased simmetry during walking, which is an important factor in reducing the risks associated with asymmetric gate (Gailey, 2008). Moreover, reduced difference in single support between amputee and sound limbs is an indication of greater confidence in amputee limb that spent more time on load. Symmetry index and coefficient of variation closer to normality especially at the last follow-up, better than socket type in literature and closer to normal gait or transtibial (Cutti, 2018).

People with transfemoral amputation generally adopt a kinematic gait strategy to compensate for deficits in muscle strength and joint mobility. Compensatory movements increase the risks of

lowe back pain, which is one of the main concerns for individuals with lower limb amputations, and degenerative changes in intact joints, in particular hip osteoarthritis of the sound limb (Devan, 2012; Ehde, 2001; Gailey, 2008; Zhang, 2020). In this study, the gait kinematics analysis showed an improvement of the quality of movement after the osseointegration treatment that imply a reduced risk of comorbidities usually associated at the trasfemoral amputee condition.

Previous studies showed a reduced hip flexion and extension in the residual limb and a large hip abduction and rotation as compensatory movement during walking (Harandi, 2020; Armannsdottir, 2018; Bowker, 1992). Hip kinematics of amputee limb, in this study, show an increased extension during toe-off and a decrease of abduction and rotation which are characteristic of the limping attitude.

Amputees' compensatory movement, also include a poor hip muscle control and insufficient ankle dorsiflexion; these mechanism affects the stabilization of the pelvis during walking stance phase and increase pelvic obliquity (Armannsdottir, 2018; Cruz, 2009; Lee, 2010). Osseintegrated prosthesis demonstrates a strongly reduced pelvic motion during the entire gait, in particular neutral pelvic position on sagittal plane and limited movement on frontal and trasversal plane.

During the lastest follow-up, the hip kinematic shows an increase of abduction in response to a greater hip extension. However, the pelvic balance was not compromised, and the compensatory movement strategies results overall declined, decreasing secondary joints risk.

4.6 CONCLUSION

The most important finding of the present case report study was the strong difference in terms of spatiotemporal parameters and joint kinematics during the gait of a transfemoral amputee patient

after a surgical treatment of osseointegration compared to a standard socket-type prosthesis. The patient exhibited a progressive improvement of the gait parameters over time and reached symmetry indices standard close to non-pathological gait. The present case report study represents the first longitudinal functional assessment of a transfemoral amputee patient treated with osseointegration during the first year after surgery. Future studies could evaluate the gait analysis in a wider cohort of patients, integrating other devices such as pressure sensors inside footwear or dedicated questionnaire to have a global vision of the benefits of an osseointegrated prosthesis.

5. STUDY II

THE STUMP BONE QUALITY IN AMPUTEE PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF 561 LOWER LIMB AMPUTEES

5.1 ABSTRACT

The aim of this systematic review was to investigate the state of stump bone quality in patients with limb amputations. The eligibility criteria were: adults, total upper- and- lower-limb amputation, healthy limb or recent amputation, and bone quality outcomes. The research was conducted on Pubmed, Embase, Scopus, Cochrane, and Web of Science. The Newcastle-Ottawa Scale (NOS) was used to assess the risk of bias. The pooled effect size estimates were presented as forest plots for each comparison. Statistical significance was set at $p<0.05$. After the screening 16 studies were included in the analysis which involved 561 participants (443 men, 47 women, and 71 not defined) with at least one lower limb amputation and 61 health control. No randomized control trials and intervention studies were included.

Dual-energy X-ray absorptiometry was the most used tool for the bone mineral density (BMD) evaluation and areal BMD and volumetric BMD were the most reported outcomes. A higher level of amputation was associated with a lower BMD level (SMD=2.11; $p=0.009$). In patients with unilateral amputation, the amputated limb (AL) has lower BMD values than non-amputated limb (nAL) (SMD=-1.23; $p<0.001$). In patients with recent amputation (≤12 months from the evaluation), the mean BMD (SMD=-0.66; $p=0.003$) was lower than in patients with late amputation (>12 months from evaluation) (SMD=-1.26; $p<0.001$). Limitations included small

sample size, wide age –range, and unclear gender distribution. The mechanical bone stimulation given by the physical activity is the main factors influencing the bone quality in patients with lower limb amputation. Such findings could help future researchers to define strategies to investigate the risk of fractures in amputee patients and could back patients and clinicians interested in normative BMD data for amputee patients.

5.2 INTRODUCTION

Bone fractures are associated with a dramatic economic burden for the healthcare systems (Barron, 2020) especially when considering older adults, women with osteoporosis, and patients with limb amputations. The prediction of bone fractures is therefore of crucial importance to mitigate the costs and morbidity progression. Bone mineral density (BMD) is a biological parameter of bone quality usually related to the risk of fractures (Barron, 2020; Black, 2020). Indeed, changes in BMD, commonly assessed through Dual-energy X-ray absorptiometry (DXA), are widely used to track the effectiveness of a treatment in clinical trials (Black, 2020).

The assessment of BMD changes in patients with limb amputation represents a complex challenge. Limb amputation primarily occurs due to trauma and significantly influences all aspects of the person's life (McDonald 2021). It is suggested that the level of BMD decreases rapidly after amputation, especially in the amputated limb stump (Black, 2020; Bemben 2017; Flint, 2014). Furthermore, amputee patients present psychological (Ramirez 2011) and functional impairments such as knee osteoarthritis in non-amputated limb (nAL) (Kulkarni 1998), muscle atrophy (Hansen 2018), weakness, and loss of proprioceptive feedback (Tugcu 2009) in the amputated limb (AL). Such comorbidities lead to an increased fear of falling as well as actual falls among amputees (Bemben 2017; Miller 2001).

There are different factors worthy of consideration when concerning the influence of lower limb amputations on BMD: unilateral or bilateral amputations, level of amputation (transtibial amputation, TTA; transfemoral amputation, TFA), time from amputation, and use of prostheses. However, most of the studies that evaluated the BMD in amputee patients (Bemben, 2017; Tugcu, 2009; Sherk 2008; Smith, 2011; Royer, 2005) were limited in small sample size or did consider a single anatomical site (e.g., femoral neck only).

Therefore, the aim of this systematic review was to investigate the state of stump bone quality in patients with limb amputations. A detailed literature search of BMD loss according to anatomical parts, level of amputation, and unilateral or bilateral amputations was provided. The most used diagnostic instruments were identified. A meta-analysis of BMD loss was also conducted.

5.3 MATERIALS AND METHODS

The present systematic review has been registered on Prospero (ID = CRD42021270597). The PECO framework (Patients, Exposure, Comparators and Outcomes), a variant of PICO framework (Patients, Intervention, Comparators and Outcomes) for non-interventional studies, was used to identify the primary question of this review and the eligibility criteria for the study selection. Eligibility criteria were: (P) adults; (E) total upper- and- lower-limb amputation; (C) healthy limb or recent amputation; (O) bone quality outcomes. Other eligibility criteria were published articles written in English and human studies. Moreover, randomized controlled trials (RCT), quasi-experimental studies, and observational studies were included. Studies that did not report outcomes evaluating the bone quality (e.g., bone mineral density, bone biomarker etc…) and/or articles that did not meet inclusion criteria (review, protocols, case report, case series, books, etc...) were excluded.

The research was conducted on five electronic databases: Pubmed, Embase, Scopus, Cochrane, and Web of Science. The search was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Guidelines (Moher, 2009). In this screening phase, no article type, language, or publication year filters were used. Moreover, hand searches using snowball technique were conducted using the included studies' references.

For each database, the complete list of items found was imported to EndNote (EndNote X9.3.3) and duplicates were removed; then, five authors (G.B., R.Z., E.P., S.D.P., and A.I.M.) reviewed independently each record (article's title and abstract). Any disagreements during the selection process were solved via a discussion between the reviewers. In case of necessity, a sixth reviewer (L.B.) was consulted to solve the disagreement.

Four authors (R.Z., E.P., S.D.P. and A.I.M) extracted data and eventual disagreement was discussed with a fifth author (G.B.). A Microsoft Excel form was agreed upon by all the authors and used to standardize the data collection.

The main outcomes domains included: a) Authors and publication year; b) Study design; c) Population; d) Unilateral or bilateral amputation; e) Outcome of the study (referred to bone quality); f) Evaluation tools; g) Results. Secondary outcomes include the type of amputation (e.g., tibia or femur) for each patient. Only outcomes and connected results relating to bone quality were collected in the data extraction table, in order to focus the data extraction on the objective of the study. The results of the present systematic review are showed in alphabetic order in table 1 (Table 1)

5.3.1 Risk of Bias and Quality Assessment

The risk of bias was assessed for each included study using the Newcastle-Ottawa Scale (NOS) for case-control or cohort studies (Wells, 2000). The NOS checklist includes three categories to

evaluate the studies' quality: (i)selection, (ii)comparability and (iii)exposure/outcomes. The categories have a total of 8 items and each study was assigned a score from 0 (lowest quality) to 9 (highest quality). The studies scored greater than or equal to 7 were considered as high-quality articles (Tab. 2). Two authors (G.B. and L.B.) separately assessed the NOS in all selected studies and any disagreement was solved by the third blind reviewer (S.D.P.).

5.3.2 STATISTICAL ANALYSES

The primary outcome was the BMD. An Excel spreadsheet (Microsoft Corporation, Redmond, WA, USA) was used to retrieve data from the studies. In all the studies, the BMD was reported as a continuous variable with mean and standard deviation (SD).

To assess the difference between the height of lower limb amputation, it was assumed that TFA was a high amputation and TTA was a low amputation. To further evaluate differences in BMD between nAL and AL, three anatomic sites, femoral neck, trochanter, and total hip were separately investigated. To assess the effect of amputation on BMD level, the BMD of healthy patients was compared with both healthy limb (nAL) and amputated limb (AL) of amputee patients. To assess the effect of the time elapsed between amputation and evaluation on amputee patients' BMD, a threshold of 12 months was considered.

A pooled mean, weighted over the number of patients in each group, was estimated for BMD values referring to the same anatomical sites and amputation level. The maximum and minimum BMD retrieved among all the studies were also reported. The standardized mean difference (SMD) and 95% confidence interval (CI) were calculated, and the Higgins' I2 statistics was computed to determine the heterogeneity of the meta-analysis comparisons. The pooled estimates of the effect size were presented as forest plots for each comparison. The Mantel–Haenszel random-effects model was used to pool the data if statistically significant heterogeneity was

reached; the fixed-effects model was used otherwise. Statistical significance was set at $p < 0.05$. For each analysis, the funnel plot was reported to evaluate the publication bias. All the meta-analyses were conducted in MedCalc (version 19.2.6, MedCalc Software Ltd, Ostend, Belgium).

5.4 RESULTS

5.4. 1 FLOW CHART

A total of 2133 studies were found after consultation of the five databases. After the duplicates removal, the abstracts of 1400 articles were screened. A total of 107 articles were selected for full-text assessment. At this stage, 91 studies were excluded for the following reasons: a) did not report amputee patients (n=21); b) did not report outcome of bone quality or density (n=16); c) studies design did not meet the inclusion criteria (n=22); d) studies did not involving human (n=5); e) studies not in English (n=7); f) full-text not available (n=20). In the end, 16 studies met the inclusion criteria and were selected for the data extraction and quality assessment (Figure. 1).

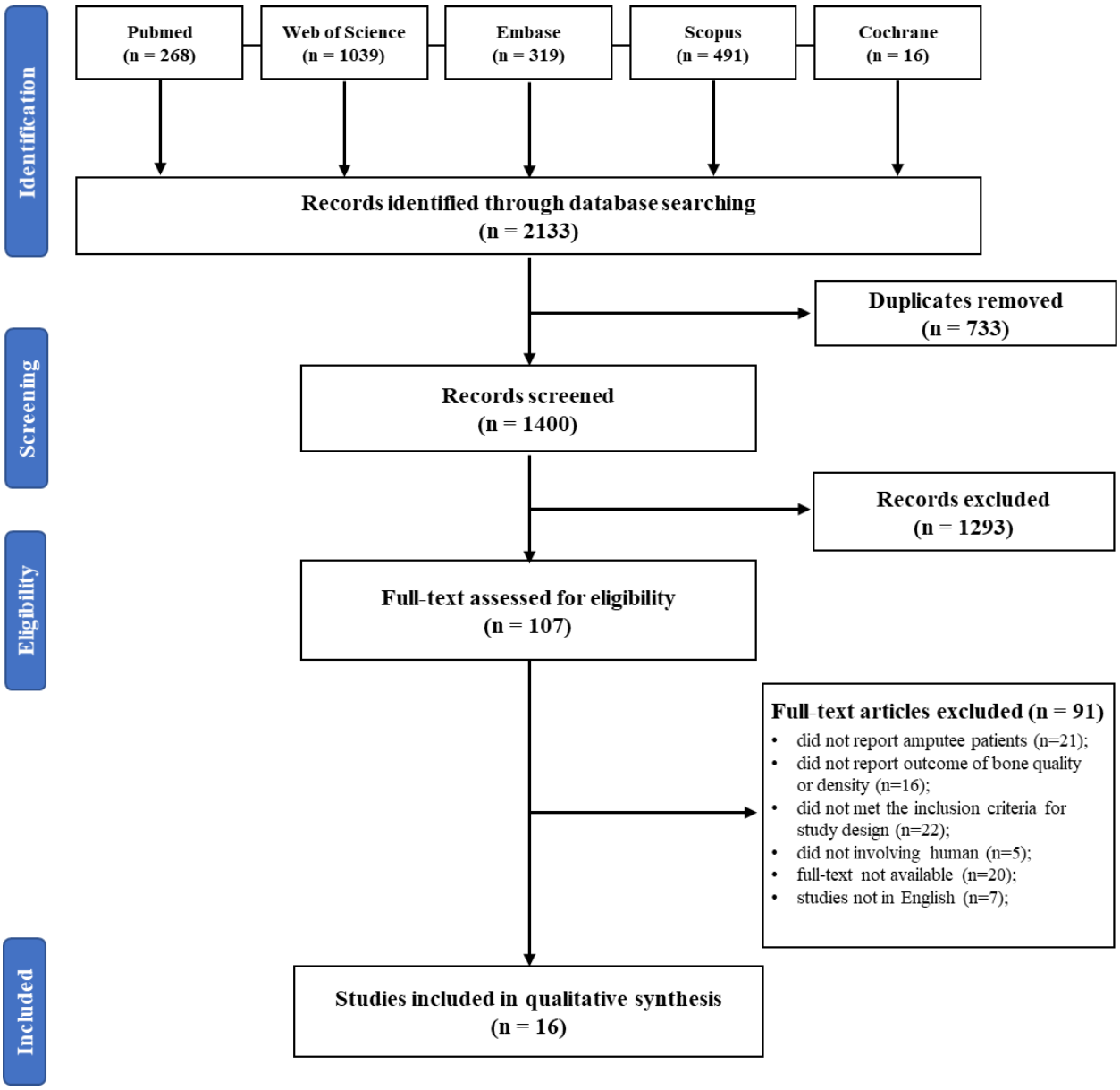


Figure 1 Flow diagram, describing the number of studies identified, included, and excluded

The included articles were published between 1994 (Rush, 1994) and 2021(Hoyt 2021; Cavedon, 2021) (Table 1). Concerning the study design, no RCT and intervention studies were found. Overall, the studies recruited 561 participants (443 men, 47 women, and 71 not defined) with at least one lower limb amputation and 61 health control. The studies analysed a total of 242 TFA, 266 TTA, 13 disarticulations, and 52 no specified amputation type. Specifically, three studies

reported data of TFA only (Ramirez, 2011; Thomson, 2019; Hansen, 2019), three included TTA only (Bemben 2017; Tugcu, 2009; Yazicioglu, 2008), and seven studies reported both TFA and TTA (Flint, 2014; Kulkarni, 1998; Sherk, 2008; Hoyt, 2021; Smith, 2011; Cavedon, 2021; Thomson, 2019). No studies reporting upper-limb amputations were found.

The included studies analysed 443 patients with unilateral amputation, 47 with bilateral amputations, and 274 not indicated. In particular, findings from 11 studies showed bone mineral density of patients with unilateral amputation only (Bemben, 2017; Ramirez, 2011; Kulkarni, 1998; Tugcu, 2009; Thomson, 2019; Sherk, 2008; Royer, 2005; Smith, 2011; Rush, 1994; Cavedon, 2021; Yazicioglu, 2008; Thomson b, 2019), three studies included both unilateral and bilateral amputees (Flint, 2014; Hoyt, 2021; Smith, 2011), and no studies reported patients with bilateral amputations only.

The most used outcome of the included studies was the areal BMD (aBMD) (Bemben, 2017; Flint, 2014; Kulkarni, 1998; Tugcu, 2009; Thomson a, 2019; Sherk, 2008; Smith, 2011; Rush, 1991; Cavedon, 2021; Hansen, 2019; Yazicioglu, 2008; Thomson b, 2019), among them three reported also the volumetric BMD (vBMD) (Bemben, 2017; Sherk, 2008; Cavedon, 2021). Four studies evaluated both the Z-score and the T-score (Kulkarni, 1998; Sherk, 2008; Smith, 2011; Yazicioglu, 2008), while two studies used Z-score only (Flint, 2014; Thomson b, 2019) and one used the T-score only (Tugcu, 2009). Finally, one study reported the Hounsfield units (HU's) (Hoyt, 2021) and one the Youngs's module (Ramirez, 2011).

Ten studies reported data of amputee patients after trauma (Bemben, 2017; Flint, 2014; Kulkarni, 1998; Tugcu, 2009; Thomson a,2019; Sherk, 2008; Hoyt, 2021; Smith, 2009; Smith, 2011; Yazicioglu, 2008) while six studies did not report such information (Ramirez, 2011; Thomson a, 2019; Smith, 2011; Rush, 1994; Cavedon, 2021; Hansen, 2019).

One study performed the aBMD and Hus evaluations through DXA and CT respectively (Hoyt, 2021), while one study used both DXA and peripheral Quantitative Computed Tomography (pQCT) (Sherk, 2008). Twelve studies utilized the DXA only (Bemben, 2017; Flint, 2014; Kulkarni, 1998; Tugcu, 2009; Thomson a, 2019; Smith, 2011; Smith, 2009; Royer, 2005; Rush, 1994; Cavedon, 2021; Hansen, 2019), while one study used the CT (Ramirez, 2011) and one used the X-ray (Thomson b, 2019).

Ten studies reported the information about the time elapsed between surgery and evaluation (Bemben, 2017; Flint, 2014; Ramirez, 2011; Tugcu, 2009; Hoyt, 2021; Smith, 2011; Smith, 2009; Royer, 2005; Rush, 1994; Yazicioglu, 2008), while six studies did not report such data (Kulkarni, 1998; Miller, 2001; Sherk, 2008; Cavedon, 2021; Hansen, 2019; Thomson b, 2019). One study performed the BMD evaluation early after amputation (Bemben, 2017), three studies performed the assessment between 3 and 6 months after surgery (Bemben, 2017; Flint, 2014; Hoyt, 2021), five studies reported data between 7 to 12 months (Bemben, 2017; Ramirez, 2011; Smith, 2011, Smith, 2009; Royer, 2005), and three studies performed the evaluation more than 12 months after surgery (Tugcu, 2009; Rush, 1994, Yazicioglu, 2008).

Only two reported data of patients with osseointegrated prosthesis for the ambulation (Thomson a, 2019; Thomson b, 2019).

Table 1. Data extraction

Authors Years	Study design	Population (Type of amputation) n° (TFA, TTA)	Bilateral/ Unilateral (n°)	Outcomes	Evaluation tools	Results
Bemben et al. 2017	Prospective study - Cohort Study	8 (0, 8)	UNI (8) BIL (0)	aBMD vBMD	DXA	**BMD (g/cm2)** **0 month** **6 months** **12 months** Total body 1.271 ± 0.010 1.279 ± 0.111 1.271 ± 0.106 Spine (L1-L4) 1.266 ± 0.200 1.244 ± 0.177 1.257 ± 0.200 **AL** Total hip 1.098 ± 0.089 0.957 ± 0.106 0.972 ± 0.111 Femoral neck 1.087 ± 0.104 0.966 ± 0.080 0.984 ± 0.075 Trochanter

							0.862 ± 0.081	0.734 ± 0.092	0.739 ± 0.108
						nAL			
						Total hip	1.134 ± 0.098	1.125 ± 0.099	1.126 ± 0.101
						Femoral neck	1.119 ± 0.092	1.087 ± 0.094	1.095 ± 0.096
						Trochanter	0.904 ± 0.079	0.911 ± 0.086	0.912 ± 0.092
Cavedon et al. 2021	Cross-sectional study	18 (11, 7)	UNI (18) BIL (0)	aBMD vBMD	DXA	**BMD (g/cm2)**	**TFA (n=11)**		**TTA (n=7)**
						Total body	1.15 ± 0.07		1.20 ± 0.08
						Trunk	0.87 ± 0.09		0.91 ± 0.06
						Arms	0.81 ± 0.08		0.86 ± 0.07
						Femoral neck AL	1.00 ± 0.16		1.11 ± 0.12
						Femoral neck nAL	1.25 ± 0.09		1.30 ± 0.15
						BMC (g)			

						Total body	2,141.21 ± 260.64 2,605.00 ± 196.36
						Trunk	591.74 ± 97.96 702.89 ± 68.56
						Arms	388.74 ± 69.16 439.19 ± 76.35
						AL	64.39 ± 38.67 249.91 ± 68.87
						nAL	496.21 ± 51.34 541.79 ± 67.61
Flint et al. 2014	Retrospective case– control comparison	156 (58, 86, 12 others)	UNI (121) BIL (35)	aBMD Z-Score	DXA	**BMD (g/cm2)**	**AL nAL UNI BIL (35) (121)**
						Femoral neck	0.86 ± 0.18 0.98 ± 0.18
						Total hip	0.95 ± 0.16 1.11 ± 0.17
						Z-Score	
						Total hip	-0.6 ± 1.1 0.4 ± 0.8 -0.6 ± 1.1 -1.2 ± 1.0

Hansen et al. 2019	Prospective control cohort study	19 (19, 0) - 38 health control	UNI (n.i.) BIL (n.i.)	aBMD	DXA	**BMD (g/cm2)**	**0 m**	**30 m (RI)**	**30 m (NRI)**
						Spine L1-L4	1.13 ± 0.23	1.09	1.15
						Proximal femur **AL**	0.66 ± 0.23	0.55	0.68
						Proximal femur **nAL**	1.03 ± 0.17	0.97	1.03
						Control			
						Spine L1-L4	1.18 ± 0.15		
						Proximal femur **AL**			
						Proximal femur **nAL**	- 1.04 ± 0.15		
Hoyt et al. 2021	Retrospective cohort study	26 (13, 17)	UNI (22) BIL (4)	T-Score HUs	DXA CT	**T-Score**		**6 months**	

						Femoral neck		-0.6 ± 1.5
						CT Hounsfield units		193 ± 87
Kulkarni et al. 1998	Retrospective cohort study	44 (15, 29)	UNI (44) BIL (0)	aBMD Z-Score T-Score	DXA	**BMD (g/cm2)**	**AL**	**nAL**
						Femoral neck	0.79 ± 0.15	0.93 ± 0.15
						Ward's triangle	0.65 ± 0.16	0.78 ± 0.15
						Trochanter	0.75 ± 0.16	0.94 ± 0.14
						T-Score		
						Femoral neck	-2.26	-1.10
						Ward's triangle	-3.37	-1.37
						Trochanter	-1.52	0.22

						Z-Score		
						Femoral neck	-0.85	0.31
						Ward's triangle	-0.43	0.57
						Trochanter	-0.93	0.81
Ramirez et al. 2011	Cohort study	20 (20, 0)	UNI (20) BIL (0)	Young's module	CT	**GPa**	**AL**	**nAL**
						Femoral neck	4.31 ± 2.83	5.63 ± 1.93
						Metaphysis	7.32 ± 5.61	11.52 ± 2.80
						Diaphysis	14.65 ± 21.35	17.39 ± 2.18
Royer et al. 2005	Cohort study - control group	9 (0, 9) 9 health control	UNI (9) BIL (0)	aBMD	DXA	**BMD (g/cm2)**	Medial limb	Femoral neck
						AL	0.78 ± 0.5	0.84 ± 0.5

						nAL	1.09 ± 0.8	0.91 ± 0.5
						Control	0.97 ± 0.5	0.91 ± 0.7
Rush et al. 1994	Cohort study - control group	16 (16, 0)	UNI (16) BIL (0)	aBMD	DXA	**BMD (g/cm2)** Femoral neck	**AL** 0.68 ± 0.14	**nAL** 1.01 ± 0.14
Sherk et al. 2008	Cross-sectional independent group	14 (7, 7) 14 health control	UNI (14) BIL (0)	aBMD vBMD Z-Score T-Score	DXA pQCT	**BMD (g/cm2)** Total body	**TTA** 1.272 ± 0.044	**TFA** 1.227 ± 0.069
						Spine L1 - L4	1.267 ± 0.089	1.241 ± 0.102
						Spine L2 - L4	1.296 ± 0.094	1.277 ± 0.102
						AL		
						Total hip	1.044 ± 0.096	0.680 ± 0.069

Femoral neck	1.015 ± 0.071	0.704 ± 0.070
Trochanter	0.817 ± 0.084	0.527 ± 0.075
nAL		
Total hip	1.142 ± 0.071	1.108 ± 0.101
Femoral neck	1.077 ± 0.049	1.064 ± 0.092
Trochanter	0.930 ± 0.061	0.937 ± 0.084
Control patients	**Tibia**	**Femur**
Total body	1.275 ± 0.044	1.264 ± 0.043
Spine L1-L4	1.311 ± 0.070	1.398 ± 0.078
Spine L2-L4	1.336 ± 0.071	1.441 ± 0.080

						AL		
						Total hip	1.093 ± 0.068	1.143 ± 0.098
						Femoral neck	1.078 ± 0.068	1.158 ± 0.105
						Trochanter	0.897 ± 0.073	0.914 ± 0.074
						nAL		
						Total hip	1.104 ± 0.075	1.130 ± 0.089
						Femoral neck	1.072 ± 0.075	1.146 ± 0.089
						Trochanter	0.915 ± 0.074	0.904 ± 0.070
						vBMD (mg/cm2)	**TTA**	**TFA**
						AL		
						Total bone	512.3 ± 62.1	462.7 ± 68.0

						Trabecular bone	259.4 ± 45.2	190.0 ± 45.6
						Cortical bone	930.2 ± 44.2	953.8 ± 45.0
						nAL		
						Total bone	757.3 ± 48.4	812.3 ± 104.3
						Trabecular bone	173.1 ± 22.6	151.7 ± 10.3
						Cortical bone	1120.5 ± 16.4	1189.9 ± 19.2
						Control patients		
						AL		
						Total bone	739.5 ± 29.6	921.2 ± 18.6
						Trabecular bone	149.4 ± 14.3	151.5 ± 9.9
						Cortical bone	1154.9 ± 10.9	1163.9 ± 11.2

						nAL		
						Total bone	749.7 ± 28.8	927.7 ± 25.0
						Trabecular bone	134.1 ± 15.2	150.2 ± 15.8
						Cortical bone	1157.0 ± 8.5	1169.1 ± 15.3
Smith et al. 2009	Cross-sectional study	255 (52 n.i.)	UNI (n.i.) BIL (n.i.)	aBMD	DXA	**BMD (g/cm2)**	**AL**	
						Total lumbar spine	0.994 ± 0.201	
						Femoral neck	0.724 ± 0.141	
						Total proximal femur	0.897 ± 0.190	
Smith et al. 2011	Cross-sectional study	52 (22, 37, 1 other)	UNI (44) BIL (8)	aBMD Z-Score T-Score	DXA	**BMD (g/cm2)**		
						Total lumbar spine	M 1.039 ± 0.202	

							F 0.865 ± 0.137	
							AL	**nAL**
						Femoral neck	M 0.672 ± 0.160	M 0.753 ± 0.137
							F 0.556 ± 0.148	F 0.865 ± 0.137
						Total proximal femur	M 0.807 ± 0.213	M 0.753 ± 0.137
							F 0.617 ± 0.174	F 0.865 ± 0.137
						T-Score		
						Total lumbar spine	M -0.33 ± 1.89	
							F -1.65 ± 1.26	
							AL	**nAL**

						Femoral neck	M -1.91 ± 1.17 F -2.63 ± 1.34	M -1.30 ± 1.00 F -1.96 ± 1.05
						Total proximal femur	M -1.38 ± 1.53 F -2.65 ± 1.43	M -0.57 ± 1.15 F -1.68 ± 1.25
						Z-Score		
						Total lumbar spine	M 0.11 ± 1.96 F 0.63 ± 1.46	
							AL	**nAL**
						Femoral neck	M -1.01 ± 1.26 F -0.48 ± 1.25	M -0.38 ± 1.05 F 0.19 ± 0.87

						Total proximal femur	M -1.06 ± 1.47 F -0.80 ± 1.34	M -0.11 ± 1.19 F 0.24 ± 0.92
Thomson et al., 2019, a	Prospective cohort study	48 (33 (22 TFAL, 11 TFAS), 15)	UNI (48) BIL (0)	aBMD	DXA	**BMD (g/cm2)**	**TTA**	**TFAL**	**TFAS**
						Spine (L2–L4)	1.316 ± 0.164	1.268 ± 0.124	1.173 ± 0.198
						Femoral neck **AL**	0.975 ± 0.099	0.709 ± 0.143	0.672 ± 0.203
						Femoral neck **nAL**	1.072 ± 0.134	1.016 ± 0.138	1.010 ± 0.247
						Z-score			
						Spine (L2–L4)	0.466 ± 1.555	0.190 ± 0.186	-0.300 ± 1.295
						Femoral neck **AL**	-0.320 ± 0.829	-2.309 ± 0.915	-2.291 ± 1.278
						Femoral neck **nAL**			

						0.443 ± 0.934	0.047 ± 0.748	0.327 ± 1.606
Thomson et al., 2019, b	Retrospective cohort study	28 (28, 0)	UNI (28) BIL (0)	aBMD Z-Score	X-rays	**BMD (g/cm2)**		
						ILP	Larger decrease in bone density than OPL, except in zone 4	
						OPL	Largest mean difference between BL and FU: zone 4, -18.9%	
						ILP	Largest mean difference between BL and FU: zone 5, -20.4%	
						Bone Coverage		
						ILP	Changes in bone coverage BL - FU: -2.3% medial - 4.1% lateral	
						Bone Thickness		
						OPL	Increases in all zones	
						ILP	Decreased in zone 7	

						OPL	Differences BL vs FU in zone 3 (5.0%) and zone 5 (9.3%)	
Tugcu et al., 2009	Prospective cohort study	15 (0, 15)	UNI (15) BIL (0)	aBMD T-Score	DXA	**BMD (g/cm2)**	**AL**	**nAL**
						Femoral neck	1.01 ± 0.12	1.15 ± 0.15
						Ward's triangle	1.01 ± 0.13	1.15 ± 0.22
						Total Hip	1.01 ± 0.13	1.19 ± 0.14
						Tibia		0.86 ± 0.33
						T-Score		
						Femoral neck	-0.4 ± 0.8	0.8 ± 1.1
						Ward's triangle	0.3 ± 1.1	1.5 ± 1.7
						Total Hip	-0.5 ± 1.1	1.1 ± 1.2
		36 (0, 36)	UNI (36)	aBMD	DXA	**BMD (g/cm2)**	**AL**	**nAL**

Yazicioglu et al. 2008	Prospective cohort study - control group		BIL (0)	Z-Score T-Score		Femoral neck Ward's triangle Total hip Tibia **T-Score** Femoral neck Ward's triangle Total hip **Z-Score** Femoral neck Ward's triangle	0.97 ± 0.12 0.94 ± 0.15 0.96 ± 0.12 0.60 ± 0.26 -0.69 ± 0.91 -0.12 ± 1.14 -0.88 ± 1.02 -0.62 -1.59	1.11 ± 0.14 1.06 ± 0.18 1.14 ± 0.13 0.95 ± 0.38 -0.69 ± 0.91 0.84 ± 1.40 0.59 ± 1.02

						Total hip	-0.84
						Tibia	-2.23

Acronysm: Male (M); Female (F); Transtibial amputation (TTA); Transfemoral amputation (TFA); Unilateral (UNI); Bilateral (BIL); Not indicated (n.i.); Amputated limb (AL); Non-amputated limb (nAL); Areal bone mineral density (aBMD); Volumetric bone mineral density (vBMD); Bone mineral density (BMD); Bone mineral content (BMC); Dual energy X-ray absorptiometry (DXA); Removed implant (RI); Non-removed implant (NRI); Transfemoral amputation long (TFAL); Transfemoral amputation short (TFAS); Integral limb prosthesis (ILP); Osseointegrated prosthetic limb (OPL); Peripheral Quantitative Computed Tomography (pQCT); Young's modulus (Gpa).

5.4.2 QUALITY ASSESSMENT

The results of the risk of bias assessment are shown in table 2 (Table 2). Mean NOS score for all included studies was 6.37: nine studies obtain at least a score of seven or more(Bemben, 2017; Flint, 2014; Tugcu, 2009; Thomson a, 2019; Sherk, 2008;Smith, 2011; Rush, 1994; Hansen, 2019; Yazicioglu, 2008) and were considered high-quality, while seven studies received a score of 6 or less (Ramirez, 2011; Kulkarni, 1998; Hoyt, 2021; Smith, 2009; Royer, 2005;Cavedon, 2021; Thomson b, 2019).

Table 2. Quality assessment

		Bemben et al.2017	Cavedon et al. 2021	Flint et al. 2014	Hansen et al. 2019	Hoyt et al. 2021	Kulkarni et al. 1998	Ramirez et al. 2011	Royer et al. 2005	Rush et al. 1994	Sherk et al. 2008	Smith et al. 2009	Smith et al. 2011	Thomson et al. 2019, a	Thomson et al. 2019, b	Tugcu et al. 2009	Yazicioglu et al. 2008
Selection	**REC**	d	**a**	**a**	**a**	**a**	**a**	**a**	**a**	**a**	**a**	**a**	**a**	**a**	**a**	**a**	**a**
	SNEC	**a**	**a**	**a**	**a**	**a**	**a**	b	b	**a**	b	**a**	**a**	**a**	**a**	b	b
	AE	**a**	**a**	b	b	**a**	**a**	**a**	c	**a**	**a**	**a**	**a**	**a**	**a**	**a**	**a**
	ONP	**a**	b	**a**	**a**	b	**a**	b	**a**	**a**	**a**	**a**	**a**	**a**	b	**a**	**a**
Comparability		**a**	**a**	**	**	*	*	*	/	*	*	/	**	*	*	*	**
Outcome/ exposure	**AO**	**a**	**a**	**a**	**a**	**a**	**a**	**a**	**a**	**a**	**a**	**a**	**a**	**a**	**a**	**a**	**a**
	LF	**a**	**a**	**a**	**a**	b	b	**a**	**a**	**a**	**a**	b	b	**a**	**a**	**a**	**a**
	AF	b	b	b	b	d	d	b	b	**a**	**a**	d	d	d	d	**a**	**a**
Total		7	6	7	7	5	6	5	4	8	7	5	7	7	6	7	8

Acronyms: Representativeness of exposed cohort (REC); Selection of nonexposed cohort (SNEC); Ascertainment of exposure (AE); Outcome not present at the start of the study (ONP); Assessment of outcomes (AO); Length of follow-up (LF); Adequacy of follow-up (AF).

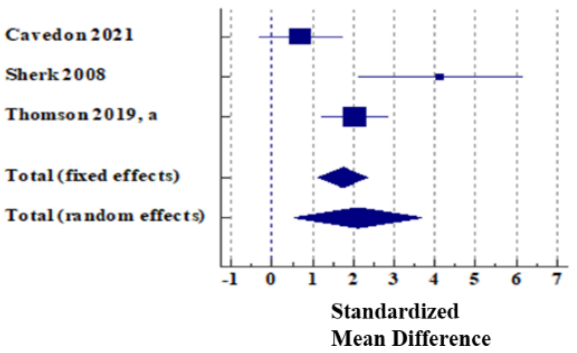
5.4.3 META-ANALYSIS

The pooled means for all the outcomes are reported in Table 3. An effect of the amputation height on BMD was observed (Figure 2). On the femoral neck the BMD values were 24.8% lower in patient with TFA (SMD = 2.11, p = 0.009).

Figure 2. Comparison of BMD measured at femoral neck between TTA and TFA

TTA vs TFA

Studies / year	N. of patients			SMD	SE	95% CI	t	P	Weight (%)	
	TTA	TFA	Total						Fixed	Random
Cavedon 2021	7	11	18	0.72	0.48	-0.29 to 1.72			37.82	36.15
Sherk 2008	7	7	14	4.13	0.93	2.11 to 6.15			9.96	26.31
Thomson 2019, a	15	22	37	2.05	0.41	1.22 to 2.87			52.22	37.53
Total (fixed effects)	29	40	69	1.75	0.29	1.17 to 2.33	5.98	<0.001	100.00	100.00
Total (random effects)	**29**	**40**	**69**	**2.11**	**0.78**	**0.55 to 3.67**	**2.70**	**0.009**	**100.00**	**100.00**



Acronysm: Transtibial amputation (TTA); Transfemoral amputation (TFA); Standardized Mean Difference (SMD); Standard error (SE); Confidence interval (CI).

Differences in BMD measured at three different regions were observed between the AL and nAL of the same TFA patients (Figure 3). AL shows lower BMD measured in femoral neck (SMD = -1.23, $p = 0.009$), trochanter (SMD = -1.64, $p = 0.003$), and total hip (SMD = -1.27, $p < 0.001$).

Figure 3. Comparison of BMD between AL and nAL measured at femoral neck, trochanter, and total hip

AL vs nAL - Femoral neck

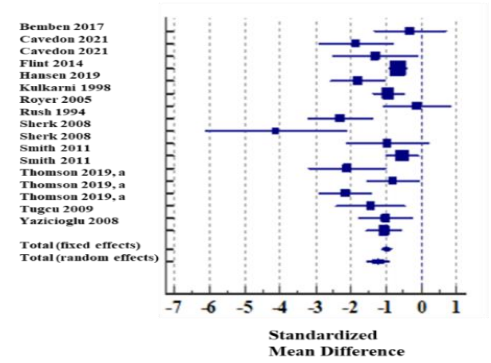
Studies / year	N. of patients			SMD	SE	95% CI	t	P	Weight (%)	
	AL	nAL	Total						Fixed	Random
Bemben 2017, TTA	8	8	16	-0.31	0.48	-1.33 to 0.71			2.53	5.21
Cavedon 2021, TFA	11	11	22	-1.85	0.50	-2.89 to -0.82			2.32	5.02
Cavedon 2021, TTA	7	7	14	-1.31	0.56	-2.53 to -0.09			1.84	4.47
Flint 2014, mixed	121	121	242	-0.67	0.13	-0.92 to -0.41			33.01	8.78
Hansen 2019, TFA	19	19	38	-1.79	0.38	-2.56 to -1.02			4.00	6.22
Kulkarni 1998, mixed	44	44	88	-0.93	0.22	-1.37 to -0.48			11.56	7.95
Royer 2005, TTA	9	9	18	-0.13	0.45	-1.09 to 0.82			2.83	5.47
Rush 1994, TFA	16	16	32	-2.30	0.45	-3.21 to -1.38			2.84	5.48
Sherk 2008, TFA	7	7	14	-4.12	0.93	-6.14 to -2.11			0.67	2.34
Sherk 2008, TTA	7	7	14	-0.95	0.53	-2.11 to 0.21			2.03	4.70
Smith 2011, mixed	34	38	72	-0.54	0.24	-1.02 to -0.07			10.12	7.78
Smith 2011, mixed	10	12	22	-2.09	0.52	-3.18 to -1.01			2.13	4.81
Thomson 2019, a, TTA	15	15	30	-0.80	0.37	-1.56 to -0.04			4.18	6.31
Thomson 2019, a, TFAL	22	22	44	-2.15	0.37	-2.90 to -1.39			4.09	6.26
Thomson 2019, a, TFAS	11	11	22	-1.44	0.46	-2.40 to -0.47			2.66	5.33
Tugcu 2009, TTA	15	15	30	-1.00	0.38	-1.78 to -0.23			4.00	6.22
Yazicioglu 2008, TTA	36	36	72	-1.06	0.25	-1.56 to -0.57			9.20	7.66
Total (fixed effects)	392	398	790	-0.99	0.08	-1.13 to 0.83	-13.02	<0.001	100.00	100.00
Total (random effects)	**392**	**398**	**790**	**-1.23**	**0.16**	**-1.55 to 0.91**	**-7.54**	**<0.001**	**100.00**	**100.00**

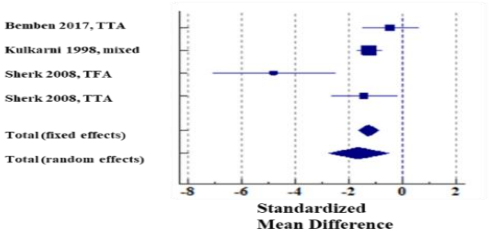
AL vs nAL - Trochanter

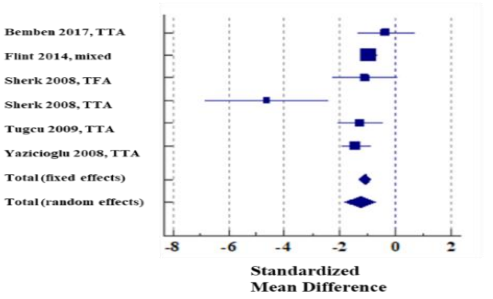
Studies / year	N. of patients			SMD	SE	95% CI	t	P	Weight (%)	
	AL	nAL	Total						Fixed	Random
Bemben 2017, TTA	8	8	16	-0.47	0.48	-1.50 to 0.56			16.07	27.19
Kulkarni 1998, mixed	44	44	88	-1.25	0.23	-1.71 to -0.79			69.09	32.32
Sherk 2008, TFA	7	7	14	-4.82	1.04	-7.08 to -2.56			3.43	15.43
Sherk 2008, TTA	7	7	14	-1.44	0.57	-2.68 to -0.20			11.41	25.07
Total (fixed effects)	66	66	132	-1.27	0.19	-1.65 to -0.89	-6.61	<0.001	100.00	100.00
Total (random effects)	**66**	**66**	**132**	**-1.64**	**0.55**	**-2.73 to -0.55**	**-2.98**	**0.003**	**100.00**	**100.00**

AL vs nAL - Total Hip

Studies / year	N. of patients			SMD	SE	95% CI	t	P	Weight (%)	
	AL	nAL	Total						Fixed	Random
Bemben 2017, TTA	8	8	16	-0.36	0.48	-1.39 to 0.66			5.21	15.07
Flint 2014, mixed	121	121	242	-0.97	0.14	-1.23 to -0.70			64.57	25.97
Sherk 2008, TFA	7	7	14	-1.09	0.54	-2.27 to 0.09			4.05	13.33
Sherk 2008, TTA	7	7	14	-4.63	1.01	-6.83 to -2.44			1.17	5.83
Tugcu 2009, TTA	15	15	30	-1.30	0.39	-2.10 to -0.49			7.68	17.67
Yazicioglu 2008, TTA	36	36	72	-1.42	0.26	-1.95 to -0.90			17.32	22.14
Total (fixed effects)	194	194	388	-1.09	0.11	-1.30 to -0.87	-9.99	<0.001	100.00	100.00
Total (random effects)	**194**	**194**	**388**	**-1.27**	**0.27**	**-1.80 to -0.73**	**-4.62**	**<0.001**	**100.00**	**100.00**







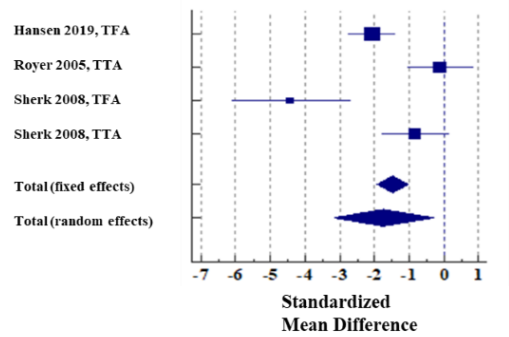
Note: Mixed is composed of TTA and TFA. Acronysm: Transtibial amputation (TTA); Transfemoral amputation (TFA); Amputated limb (AL); Non-amputated limb (nAL); Standardized Mean Difference (SMD); Standard error (SE); Confidence interval (CI).

At femoral neck, the healthy control group showed higher BMD levels than TFA AL (SMD= -1.74, p = 0.017), while were no statistically significant differences with nAL (SMD = -0.18, p = 0.352) (Figure 4).

Figure 4. Comparison of BMD between healthy control and AL or nAL measured at femoral neck

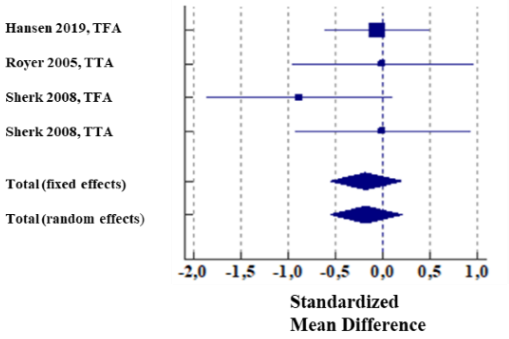
AL vs Health

Studies / year	N. of patients			SMD	SE	95% CI	t	P	Weight (%)	
	AL	Control	Total						Fixed	Random
Hansen 2019, TFA	19	38	57	-2.08	0.34	-2.76 to -1.40			43.90	27.14
Royer 2005, TTA	9	9	18	-0.11	0.45	-1.06 to 0.84			24.96	25.96
Sherk 2008, TFA	7	14	21	-4.42	0.81	-6.11 to -2.71			7.61	21.10
Sherk 2008, TTA	7	14	21	-0.84	0.46	-1.81 to 0.13			23.52	25.80
Total (fixed effects)	42	75	117	-1.47	0.22	-1.92 to -1.03	-6.57	<0.001	100.00	100.00
Total (random effects)	**42**	**75**	**117**	**-1.74**	**0.72**	**-3.17 to -0.32**	**-2.42**	**0.017**	**100.00**	**100.00**



nAL vs Health

Studies / year	N. of patients			SMD	SE	95% CI	t	P	Weight (%)	
	nAL	Control	Total						Fixed	Random
Hansen 2019, TFA	19	38	57	-0.063	0.28	-0.62 to 0.49			47.04	47.04
Royer 2005, TTA	9	9	18	0.000	0.45	-0.95 to 0.95			17.93	17.93
Sherk 2008, TFA	7	14	21	-0.89	0.47	-1.86 to 0.088			16.72	16.72
Sherk 2008, TTA	7	14	21	0.000	0.44	-0.93 to 0.93			18.30	18.30
Total (fixed effects)	**42**	**75**	**117**	**-0.18**	**0.19**	**-0.55 to 0.20**	**-0.93**	**0.352**	**100.00**	**100.00**
Total (random effects)	42	75	117	-0.18	0.19	-0.55 to 0.120	-0.93	0.352	100.00	100.00



Acronysm: Transtibial amputation (TTA); Transfemoral amputation (TFA); Amputated limb (AL); Non-amputated limb (nAL); Standardized Mean Difference (SMD); Standard error (SE); Confidence interval (CI).

In terms of time elapsed between amputation and evaluation (Figure 5), lower BMD levels on TFA AL compared to nAL were observed both before 12 months (SMD = -0.66, $p = 0.03$) and after 12 months (SMD = -1.26, $p < 0.001$) from amputation.

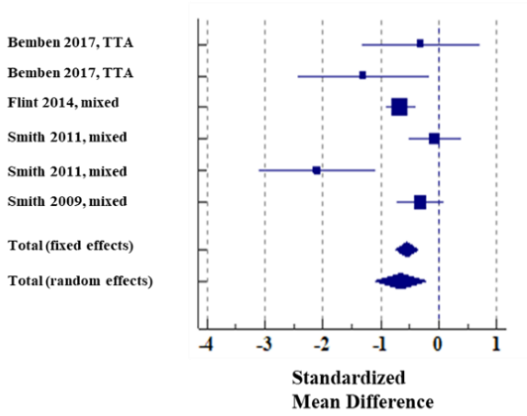
Figure 5. Comparison of BMD between AL and nAL within and over 12 months from amputation measured at femoral neck

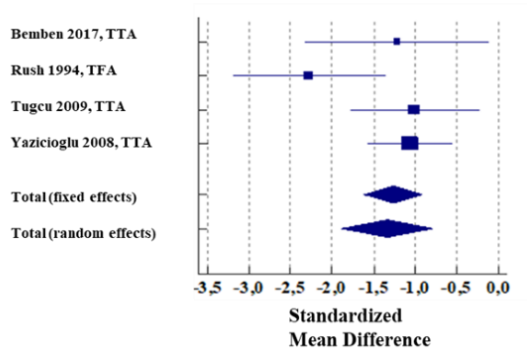
BMD < 12

Studies / year	N. of patients			SMD	SE	95% CI	t	P	Weight (%)	
	AL	nAL	Total						Fixed	Random
Bemben 2017, TTA	8	8	16	-0.31	0.48	-1.33 to 0.71			3.81	11.81
Bemben 2017, TTA	8	8	16	-1.31	0.53	-2.44 to -0.18			3.11	10.52
Flint 2014, mixed	121	121	242	-0.67	0.13	-0.92 to -0.41			49.71	23.81
Smith 2011, mixed	39	39	78	-0.07	0.22	-0.52 to 0.38			17.13	20.52
Smith 2011, mixed	13	13	26	-2.10	0.48	-3.09 to -1.11			3.76	11.74
Smith 2009, mixed	52	52	104	-0.31	0.20	-0.70 to 0.078			22.47	21.60
Total (fixed effects)	241	241	482	-0.54	0.09	-0.73 to -0.36	-5.86	<0.001	100.00	100.00
Total (random effects)	**241**	**241**	**482**	**-0.66**	**0.22**	**-1.10 to -0.23**	**-2.98**	**0.003**	**100.00**	**100.00**

BMD > 12

Studies / year	N. of patients			SMD	SE	95% CI	t	P	Weight (%)	
	AL	nAL	Total						Fixed	Random
Bemben 2017, TTA	8	8	16	-1.22	0.52	-2.33 to -0.10			11.67	18.03
Rush 1994, TFA	16	16	32	-2.28	0.45	-3.20 to -1.37			15.71	21.51
Tugcu 2009, TTA	15	15	30	-1.00	0.38	-1.78 to -0.23			22.02	25.58
Yazicioglu 2008, TTA	36	36	72	-1.06	0.25	-1.56 to -0.57			50.60	34.89
Total (fixed effects)	**75**	**75**	**150**	**-1.26**	**0.18**	**-1.61 to -0.91**	**-7.10**	**<0.001**	**100.00**	**100.00**
Total (random effects)	75	75	150	-1.34	0.28	-1.89 to -0.79	-4.81	<0.001	100.00	100.00





Note: Mixed is composed of TTA and TFA.

Acronysm: Transtibial amputation (TTA); Transfemoral amputation (TFA); Amputated limb (AL); Non-amputated limb (nAL); Bone mineral density (BMD); Standardized Mean Difference (SMD); Standard error (SE); Confidence interval (CI).

5.5 DISCUSSION

The purpose of the present study was to review state of the art on stump bone quality in patients with limb amputation. First, the present review underlined that despite the great number of articles found focusing on the relationship between bone quality and amputee patients, there is a lack of observational and interventional studies. Moreover, most of the included studies had a limited sample size, lower limb amputees only were included. These aspects suggested that, in spite of the great interest in bone quality assessment in amputee patients, the enrolment of adequately powered cohorts in such studies is a major challenge.

Multiple factors influencing the BMD in amputee patients emerged from this review. It has been reported that the height of the lower limb amputation and single or double amputations have a sensitive impact on BMD. In addition, the tools and the anatomical site of the evaluation provided different BMD values that can be hardly compared with other tools and sites of measurement. Time from amputation and type of prosthesis (i.e., socket type, osseointegrated etc..) were also shown to affect the BMD.

The BMD varied according to the level of amputation. A higher level of amputation was associated with low BMD levels both in AL and nAL. Cavedon et al. (Cavedon, 2021), Thomson et al.(Thomson a, 2019), and Sherk et al.(Sherk, 2008) reported that the BMD values of TFA were lower than the TTA. Differences in BMD between TTA and TFA were smaller at lumbar spine and total body than femoral neck, trochanter, and total hip (Thomson a, 2019; Sherk, 2008; Cavedon, 2021). Several studies confirmed that TFA has lower femoral neck BMD and more severe bone loss compared to TTA ones (Flint, 2014; Kulkarni, 1998; Tugcu, 2009; Thomson, 2019; Rush, 1994; Yazicioglu, 2008). The present meta-analysis confirmed this statement over more than 160 patients (67 TFA and 97 TTA, Tab. 3). Such findings suggest a substantially

increased risk of hip fractures in TFA patients, endorsing the need to save as much bone as possible (and, preferably, the knee joint) during amputation surgery.

Only one study (Flint, 2014) directly compared BMD values of unilateral and bilateral amputations, reporting lower BMD levels in patients with bilateral amputations. This finding could be related to the rehabilitation time, since patients with bilateral amputations need longer times to return to weight-bearing (Flint, 2014; Ostojić, 2001) activities, and that the duration of disability negatively correlates with hip BMD on the amputated side (Smith, 2011).

The present review confirmed that DXA is broadly considered the gold standard for the evaluation of BMD, probably due to its non-invasive nature, low radiation dose, and relatively low costs (Barron, 2020). Furthermore, the most reported outcomes were aBMD and vBMD. On the other hand, the relative values Z-score and T-score are not often used for amputee patients. However, Z-score and T-score are primarily used as diagnostic values on different population targets, such as osteoporosis and osteopenia.

Lower BMD values for AL with respect to nAL was found at hip level, with a percentage difference between 15% and 20% according to the different anatomical sites (Tab. 3). The main cause of such differences could be the weight-bearing distribution between the AL and nAL during the daily life activities. Indeed, amputee patients avoids loading the AL resulting in abnormal movements, since they rely more on ischiatic muscles (Van de Meent, 2013). This reduced load on AL might lead to a reduction of BMD in time. However, a recent treatment procedure for amputee patients, the osseointegrated prosthesis, allows reconstructing the anatomical axis of the femur,

providing a better and more physiological load distribution and, consequently, improving the bone response (Thomson a, 2019; Thomson b, 2019; Mirulla, 2021) compared to the socket-type prosthesis.

In addition, the AL presents muscle atrophy, weakness, and loss of proprioceptive feedback (Tugcu, 2009) due to underuse during walking or standing and removal of joint structures. Furthermore, nAL shows higher strength than the amputated one (Tugcu, 2009; Pedrinelli, 2002), especially, in hamstrings and quadriceps (Tugcu, 2009). However, muscle strength seems not toinfluence BMD in TTA (Tugcu, 2009). Moreover, the abnormal gait and the altered weight-bearing distribution could negatively affect the nAL, increasing the prevalence of osteoarthritis (Royer, 2005; Melzer, 2001).

A 30% BMD difference between unilateral amputee patients' AL and healthy controls was found, while no differences were found between patients' nAL and healthy patients (Tab. 3). The BMD difference emerged between AL and nAL (20%) and between the AL and healthy controls (30%) could be considered as reference thresholds when assessing bone quality in clinical trials on amputee patients.

The influence of time from the amputation on BMD is another debated factor in the current literature. Sherk et al., Rush et al. (Sherk, 2008; Rush, 1994) suggested that time from the amputation does not seem to influence the BMD. In the present study, (Bemben, 2017; Flint, 2014; Tugcu, 2009; Smith, 2011; Smith, 2009; Rush, 1994; Yazicioglu, 2008), the mean BMD was lower for patients with a recent amputation (≤ 12 months) than for those with a late amputation (> 12 months) (Bemben, 2017; Flint, 2014; Tugcu, 2009; Smith, 2011; Smith, 2009; Rush, 1994; Yazicioglu, 2008). Hence, these results suggested that BMD strongly decreases immediately after the surgery, probably due to the bed rest time (Bemben, 2017), and then partially recovers in the following months, by to rehabilitation and return to walking.

Rush et al. suggested that the young age of patients also may influence the level of BMD. Indeed, their results showed that younger patients have more osteopenia than older ones, caused by amputations occurred before reaching the peak bone mass (Rush, 1994). In contrast, Sherk et al., Yazicioglu et al., Flint et al. (Flint, 2014; Sherk, 2008; Yazicioglu, 2008) did not find a correlation between BMD and age at the time of amputation.

In summary, the present review showed that the decrease in bone mass derived mainly by the behaviours that the amputation brings in, rather than resulting from amputation itself. Indeed, among the consequences of amputation there are rest periods (absence of movement, especially for the AL) and altered biomechanical patterns that can result in altered bone remodelling. A surgical procedure and rehabilitation aimed at soliciting the amputated limb with more physiological loads could reduce the losses of bone density, significantly improving the quality of the bone.

To the best of authors knowledge, the present systematic review represents the most extensive description of a critical bone quality marker such as BMD in the amputee population. Given the limited possibility to perform adequately powered clinical studies with homogeneous populations because of the complexity of the amputee condition, the present review might be of crucial importance for those interested in assessing bone quality status and risk of falling in amputee patients. Practical guidelines for surgical and rehabilitation therapies (which surgery adopt – standard or osseointegrated, what to expect from the early rehab or from different amputation levels) could be also drowned out.

This systematic review presents some limitations. Many of the included studies did not report the gender of the cohort. Moreover, the patients' age range was wide with respect to the sample size, which was small in most of the studies. Such elements might increase data heterogeneity among the studies.

5.5.1 RISK OF BIAS

Based on NOS, 56.25% of the included articles' results as high quality whereas 43.75% had a low-quality evaluation. “Adequacy of follow-up" has been the item with the worse score, only 4 (Tugcu, 2009; Sherk, 2008; Rush, 1994; Yazicioglu, 2008) studies satisfied this criterion, instead the other studies found difficulties in follow-up losses.

5.6 CONCLUSION

The present systematic review with meta-analysis provided an overview of the current knowledge regarding bone quality in patients with limb amputations. The comprehensive results of the present study reported BMD differences between AL and nAL in lower limb amputee patients for different anatomical sites, time from amputation, and with respect to healthy controls. Such findings could help future researchers to define high-methodological quality studies to investigate the risk of fractures in amputee patients, overcoming the limits of the current literature. Moreover, it could be useful to patients and clinicians interested in normative BMD data for amputee patients.

6. STUDY III

EXTERNAL DEVICES INCREASING BONE QUALITY IN ANIMALS: A SYSTEMATIC REVIEW

6.1 ABSTRACT

Background: Osteoporosis can reduce bone quality and increase the risk of fractures. This condition is highly correlated to bone mineral density, which decreases due to imbalances in bone turnover. External devices are detected in the literature alongside pharmaceutical approaches, physical activity, and implanted devices as effective solutions for strengthening bones.

Methods: A systematic review of the technologies involved in such devices has been carried out to identify the most fruitful ones in improving bone quality. Studies involving uniquely pharmaceutical approaches have been excluded. This review, carried out according to the PRISMA Statement, focuses on studies involving animals and is preparatory for a subsequent investigation of human trials.

Findings: The exploited devices, their settings, interventions, and measured effect on bone quality are reported for each detected technology. Ultrasounds and laser arose to be the most studied technologies in the literature. However, it turned out that, nowadays, none prevails over the others in terms of its effect on bone quality.

Interpretation: External devices are promising as they offer a non-invasive approach, causing minimum discomfort to the patient. This review aimed to detect the technologies in the current state-of-the-art devices significantly affecting bone quality. Such technologies have been identified, but the variety of the outcomes measured, measurement methods, device settings, and

interventions, as well as the few articles found for some technologies do not enable quantitative comparisons.

6.2 INTRODUCTION

The skeleton fulfils several fundamental tasks, ranging from enabling motion, protecting vital organs, and providing calcium reserves (Turner, 2006). Promoting bone health should be paramount for preserving good quality of life and, in particular, in old age when bone health naturally tends to diminish. Ageing leads to an increased exposure to the risk of osteoporotic fragility fracture. Indeed, in the US only, more than 10 million people aged 50 and over suffer from osteoporosis, and approximately 1,5 million people suffer fragility fractures each year (Wright, 2014; Fink, 2019; Clynes, 2020). It was estimated that more than 200 million peopleworldwide had an osteoporotic hip fracture (Sözen, 2017). In addition to ageing, also steroid deficiency (e.g., during menopause) can be associated with an increased risk of osteoporosis-related fractures.

Osteoporosis is a skeletal disease characterized by the microarchitectural deterioration of the bone tissue and loss of bone mass, which rapidly degrades bone quality and strength, and increases fragility and the risk of fractures (Clynes, 2020; Sözen, 2017; Christodoulou, 2003; Noh, 2020). The bone tissue, primarily composed of collagen and mineral, is continuously lost through resorption and rebuilt by formation. Osteoporosis occurs due to an imbalance in the bone turnover in which the resorption rate is higher than the formation one (Sözen, 2017; Noh, 2020). Menopause and advancing age may cause such an imbalance, but several other factors can lead to osteoporotic fractures, e.g., physical inactivity, smoking, alcohol consumption, nutrition,

genetic actors, use of glucocorticoids, and endocrine disorders (Sözen, 2017; Christodoulou, 2003).

Bone Mineral Density (BMD) is a significant (but not the only) predictor of osteoporosis. As the World Health Organization (WHO) defined, osteoporosis is related to a BMD T-score equal to or less than -2.5, using standard deviation scores of BMD depending on peak bone mass in healthy young women (Sözen, 2017; Christodoulou, 2003; Noh, 2020). So, higher BMD leads to a lower risk of complications from osteoporosis (Christodoulou, 2003). Besides, such a disease makes difficult any prosthesis implantation. Indeed, some modern prostheses are bone anchored by osseointegration, thus avoiding debilitating problems related to soft tissues, providing physiological weight-bearing, improving range of motion, and sensory feedback (Li, 2017; Haque, 2020). For these systems, bones play the critical role of anchor site, and implant stability has been found to be correlated to the BMD (Merheb, 2018).

Due to the number of people suffering from osteoporosis, several therapies have been proposed to improve bone quality and prevent resorption. A traditional therapy prescribes vitamin D and, eventually, calcium supplements, while different pharmaceutical approaches involve hormonal (Prestwood, 2003) or other drug treatments (Fink, 2019). Although these therapies look promising (Fink, 2019), they are not the only options available. It has been shown that mechanical loading, for example, during weight-bearing exercises, promotes bone formation, especially in the most stressed regions (Turner, 2006; Augat, 2021). For this reason, physical exercise is prescribed for bone resorption prevention or skeletal improvements (Troy, 2018), usually accompanied by correct eating habits and limited use of alcohol, cigarettes, and coffee (Sözen, 2017). Other modern studies tested some implanted devices for bone healing: (Zhang, 2009) implanted polymeric membrane materials around the fracture that can induce effective negative pressure to achieve both membraneand negative pressure-induced bone regeneration; (Dolkart,

2021) implanted a miniaturized electromagnetic device generating Pulsed ElectroMagnetic Fields (PEMFs) therapy, while the effect on BMD of vagus nerve stimulator in epileptic patient, used for treating refractory seizures in adults and children, have been investigate in (Tamini, 2021). However, the aforementioned methods can involve side effects, such as reliance on longterm patient commitment or invasive surgical procedures, that may be dangerous for other bodily functions (Fink, 2019).

Also, studies exploiting external devices for bone stimulation with different operating technologies have been detected in the literature, showing interesting results. These have the potential to promote bone healing and growth with a non-invasive approach, and minimum discomfort for the patients, avoiding the pharmacological therapy. Some mechanisms through which the strengthening is achieved may be bone mechanical loading, promoting bone growth where the stresses are more significant (Turner, 2006), microfracture provocation and healing (Knothe, 2013), metabolism stimulation, stem cell biasing toward bone formation (Mogil, 2016), or their combinations.

Given these premises, in this article, a review of the emerging literature that particularly focuses on stimulation from external devices will be conducted to understand if technologies resulting in a better effect on bone quality exist and, in case, which they are. Specifically, the bone structure has been considered to understand if there are technologies that can influence the bone turnover, and thus the BMD, and how they operate. Only external devices and the technologies employed were considered in this review, but no other therapies were taken into account. Indeed, they represent an interesting solution for improving bone quality, enabling to avoid invasive approach (e.g., surgical approach for implanted devices), and the pharmacological one, not always usable for the patients involved due to other diseases they suffer from. Future treatments may consist of the use of an external device that stimulates the bone, or maybe the technology involved may be

integrated in developing devices or prosthesis for the same result. Thus, the following research questions will be addressed: “Which external devices or technologies have been tested for bone quality improvement without pharmacological interventions? Which effects do these have on bone structure?” Several technologies have been tested for bone stimulation, including ultrasounds, laser, and magnetic field applications. Experiments were performed in many different settings: indeed, simulations, and studies in vitro, on animal and human subjects can be found. For a full overview on the topic, this review is focused on animal studies, while in the near future a systematic review on human studies will be conducted. Amplitudes, frequencies, and other settings are different between devices and studies; nonetheless, trends can be analyzed by considering the measured bone characteristics and observations in each paper.

6.3 METHODS

6.3.1 DATA SOURCE AND SEARCH TERMS

This systematic review has been conducted by searching articles in four databases (Web Of Science, PubMed, Embase, and IEEXplore) and using the PRISMA Statement checklist (Liberati, 2009). The research was performed on 11 October 2021. The reviewhas been registered in Prospero beforehand (ID number: CRD42022303286). The query string (adapted according to the requirements of each database) used for the research has been “((Bone Mass) OR (Bone Turnover) OR (Bone Metabolism) OR (Bone Density) OR (Bone Loss) OR (Bone Losses) OR (Bone Densities) OR (Bone MineralDensity) OR (Bone Mineral Densities) OR (Bone Mineral Content) OR (Bone Mineral Contents) OR (Bone Resorption)) AND ((Biomedical Technologies) OR (Health Technology) OR (Health Care Technology) OR (Supplies) OR (Inventor*) OR

(Device*) OR (Equipment) OR (Instrument*) OR (Apparatus) OR (Appliance*)). Terms and keywords were located within the title and/or abstract and/or keywords.

The following criteria were used to define our research: only original full-text articles published in English in the last 20 years about devices that directly improve the bone quality on animals, which were not reviews or meta-analysis, were included in this review.

6.3.2 INCLUSION AND EXCLUSION CRITERIA, AND STUDY SELECTION

Among the ones identified from the database search, duplicate articles were excluded using EndNote functionalities and then manually.

The remaining articles have been screened by reading their title and abstract firstly and then the full text of only the selected papers. Studies were included if they met the following criteria: i) written in English, ii) not reviews or metanalysis, and iii) full text available. Papers were excluded if: i) presented in-vitro studies; ii) presented human studies; iii) employed only pharmacological therapies; iv) described only lifestyle interventions (physical activity and/or dieting); v) described only measurement instruments and methods; vi) did not provide bone quality assessment; vii) did not apply external devices (not implanted through surgery) or technology.

6.3.3 DATA EXTRACTION

The authors (W.S., N.S., C.B., A.I.M., L.B.) extracted the following information from the full-text papers of the eligible studies: the first author and publication year for identification, the device used, its settings, the interventions, and study results about the treatment effect on bone quality, referring to bone structure parameters. Moreover, data extracted have been organized

through the physical actions detected: hyperbaric oxygenation, ultraviolet irradiation, mechanical vibrations, magnetic fields, ultrasounds, and laser.

6.3.4 QUALITY ASSESSMENT

The quality assessment of the selected articles has been performed independently by two authors (A.I.M., G.B.) following the SIRCLE'S tool guidelines for assessing the risk of bias (Hooijmans, 2014). Specifically, this tool covers six types of bias (selection, performance, detection, attrition, reporting bias, and other), and ten domains: sequence generation, base- line characteristics, allocation concealment, random housing, caregivers/investigators blinding, random outcome assessment, outcomes assessor blinding, incomplete outcome data, selective outcome data, and other sources of bias. As reported in Table 1, the authors provided an answer to each question (yes, no, or unclear), a correlated risk of bias (low, high, or unclear), and a motivation for each item and article. Disagreements were solved through consensus- oriented discussion. Furthermore, a third reviewer (L.B.) took the final decision if no consensus was reached.

Table1 Devices for increasing bone quality in animals

Risk of Bias in animal studies according to SYRCLE's Risk of Bias tool										
Study	A			B		C		D	E	F
	1	2	3	4	5	6	7	8	9	10
Arai et al. (2020)				HR	HR					LR
Clark et al. (2006)				HR	HR			LR		LR
Do Nascimento et al. (2013)		LR		HR	HR	LR				LR
Fazilat et al. (2014)	HR		HR	HR	LR		LR			LR
Figueiredo et al. (2012)	HR		HR	HR	HR					HR
Franzen et al. (2015)		LR		LR				LR	LR	LR
Freddo et al. (2012)	HR	LR	HR	HR	HR					LR
Heybeli et al. (2002)	HR		HR							LR
Huang et al. (2017)				LR			LR	LR	LR	LR
Jing et al. (2014)		LR		LR			LR	LR	LR	LR
Knothe et al. (2013)	HR	LR	HR							LR
Li et al. (2020)		LR							LR	LR
Liu et al. (2007)		LR		LR				LR	LR	LR
Machado et al. (2019)				LR						LR
Morita et al. (2016)	HR		HR		LR					LR
Qian et al. (2020)		LR					LR			LR
Tobita et al. (2011)	LR	LR			LR	LR	LR			LR
Wenger et al. (2010)	HR	LR	HR	LR						LR
Wenger et al. (2021)	HR	LR	HR							LR
Yao et al. (2019)		HR								LR
Zhang et al. (2018)	LR	LR	HR	LR	LR		LR			LR

Note. SYRCLE's RoB tool. The type of bias are distinguished as: A) Selection Bias, B) Performance Bias, C) Detection Bias, D) Attrition Bias, E) Reporting Bias, F) Other. The domains are indicated with numbers from 1 to 10: 1) Sequence Generation,

2) Baseline Characteristics, 3) Allocation Concealment, 4) Random Housing, 5) Caregivers/investigators Blinding, 6) Random Outcome Assessment, 7) Outcomes Assessor Blinding, 8) Incomplete Outcome Data, 9) Selective Outcome Data, 10) Other Bias Sources. The correlated risk of bias can be high (HR) or low (LR); the cell is empty if the risk is unclear.

6.4 RESULTS

The selection of the included papers has been performed as shown in the PRISMA flow diagram (Figure. 1).

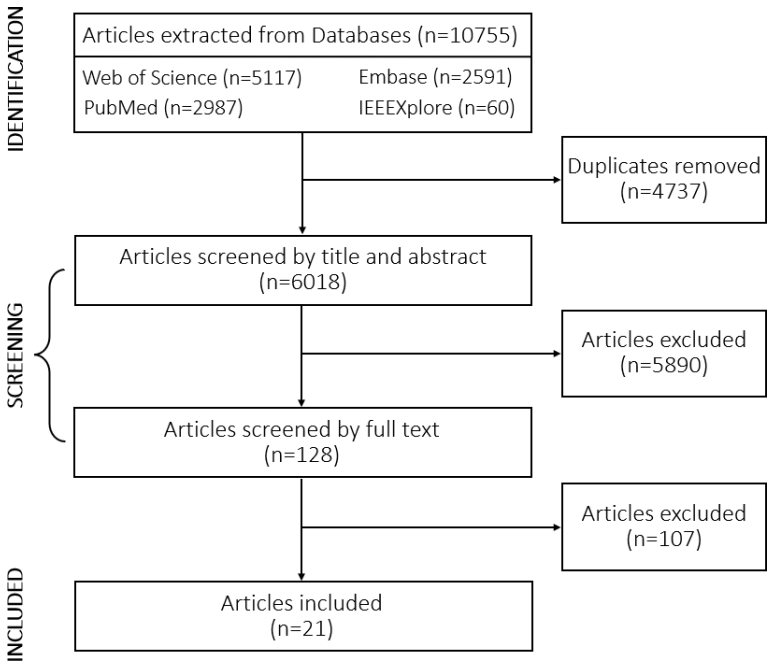


Figure 1: PRISMA flow diagram for studies selection

According to the abovementioned research string, 10755 articles have been identified for this

systematic review from the four databases queried (Web Of Science, PubMed, Embase, and IEEEXplore). 6018 papers have been included after removing duplicates (n=4737) using Endnote, and manually. Subsequently, 5890 articles were excluded after screening by reading their title and abstract, while 107 articles were excluded after reading the full text of the remaining ones. Finally, 21 papers have been included to extract information about the effect of stimulation from external devices on bone quality. Data extracted are reported in this review in Table 2 and Table 3 below.

First, a general overview is presented through the main subject area, animals involved, parameters employed for bone quality evaluation, and results from primary studies. Afterward, each technology is described in more detail in a specific section. As expected, the included papers are mainly published in medical journals (11 out of 21). There is only one engineering-related paper (Huang, 2017), one in the physics (Machado, 2019), and two in biology/biochemistry (Wenger, 2010; Wenger, 2021) areas. The animal subjects are split almost evenly among the included papers between mice (tested in five papers), rats (tested in eight papers), and rabbits (tested in seven papers), while only one experiment was performed on sheep. The mainly outcomes employed for bone quality evaluation are Bone Mineral Content (BMC) or BMD, Bone Volume (BV), Bone and Tissue Volume Rate (BV/TV), Bone-Specific Surface (BS/BV), trabecular thickness, number, and separation (Tb.Th, Tb.N, Tb.Sp), cortical thickness and area (Ct.Th, Ct.Ar), the mean value of the osteoclast numbers (N.Oc/BS), and Mineral Apposition Rate (MAR). These are measured primarily through Computed Tomography (CT), ʻCT, Cone Beam CT (CBCT) and Dual-Energy X-ray Absorptiometry (DEXA), combined in some studies with histological and histomorphometric analysis (Knothe, 2013; Clark, 2006; Fazilat, 2014; Franzen, 2015; Jing, 2014; Li, 2020; Quian, 2020; Yao, 2019). Figure 2. shows how many analysed papers employ each outcome, while Figure 3. highlights the adopted measurement methods.

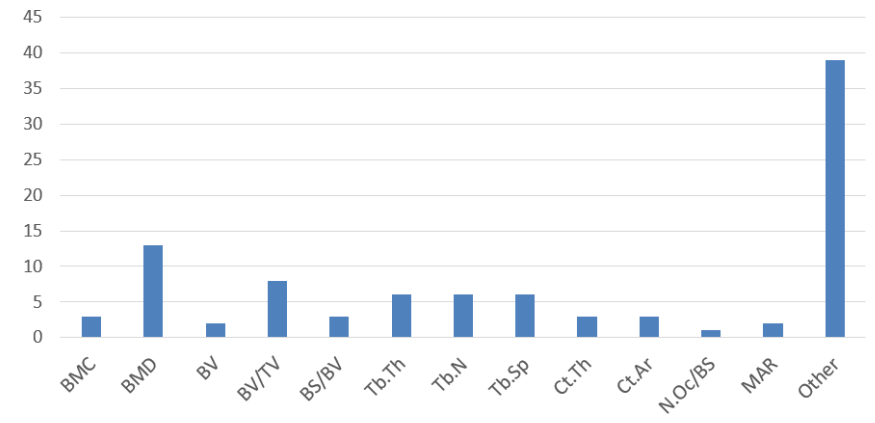


Figure 2: Outcomes measured in the included papers and in how many papers each outcome was measured. The "Other" column includes all the parameters detected only once among the selected papers

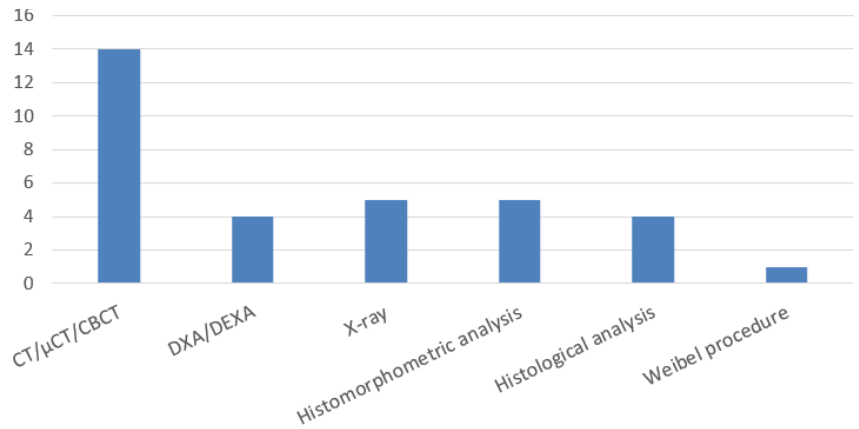


Figure 3: Measurement methods adopted in the investigated studies and in how many studies each measurement method was exploited

Going on to details of greater interest for the paper research questions, six different technologies tested for bone improvement have been identified in the literature, as reported in Figure 4: ultra-sounds (six papers out of 21), laser (six), magnetic fields (four), mechanical vibrations (four), hyperbaric oxygenation (one), and ultraviolet irradiation (one).

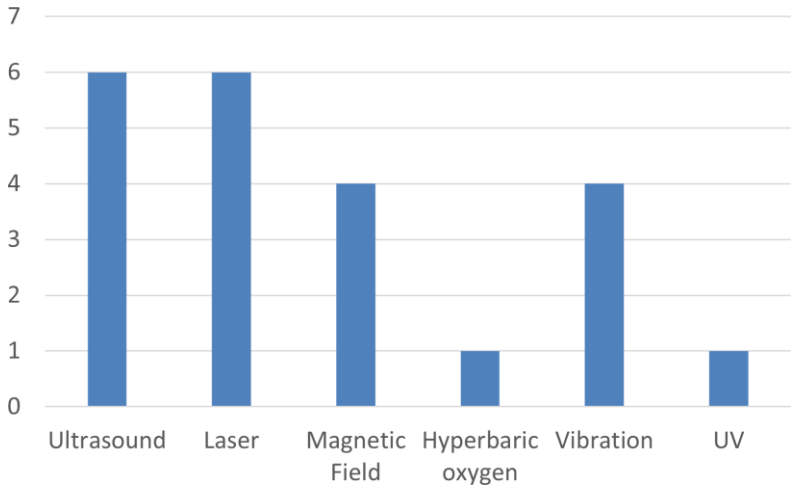


Figure 4: Technologies identified in the included papers and in how many papers they have been exploited.

Looking at the reported effects as a result of the application of the described devices (Table 4), most papers (nine out of 21) declare an increased effect on bone structure, describing bone quality improvement (Clark, 2006; do Nascimento, 2013; Heybeli, 2002; Qian, 2020; Liu, 2007; Qian, 2020; Tobita, 2011; Wanger, 2010; Yao, 2019). It is worth noting that do Nascimento (do Nascimento, 2013) proposes a comparison between devices exploiting two different technologies, both resulting in an increased effect on bone quality, as reported in Table 4. Besides, seven papers report no notable changes to a control group (Arai, 2020; Franzen, 2015; Jing, 2014; Machado, 2019; Morita, 2016; Wanger, 2021; Zhang, 2018). The five remaining papers (Knothe, 2013; Fazilat, 2014; Figueiredo, 2012; Freddo, 2012; Huang, 2017) report mixed results, meaning that improvement is conditional on some extra constraints, e.g., the reported improvement was limited to a specific time frame, the technology was applied in conjunction with other devices, or neither an improvement nor a worsening of bone quality was recorded in the treated group compared to the worsening of the control group. These papers will be further analyzed in each

technology section below. Table 4. specifically shows how many papers belong to these resulting groups for each technology studied.

Table 2 - HBO, UV, Mechanical Vibrations, and MFs: technologies, devices, settings, interventions, and reported effect on bone quality

N°	References	Technology	Device	Settings	Interventions	Bone quality
1	Clark et al. (2006) [22]	HBO	Provided by the Hyperbaric Oxygen Service, Eisenhower Army Medical Center	Pressure: 2.4 atm	90 min per day, 20 sessions before and 10 after surgery	Increased
2	Morita et al. (2016) [34]	UV	UV lamps of the LED system from Nikkiso Co ltd (Japan)	Wavelength: 268, 282, 290, 305, and 316 nm, Radiation irradiance: 0.54 mW/cm^2, UV irradiation dose: 1 kJ/m^2	185 s, 2 days per week, 4 weeks	No notable changes wrt the control group
3	Huang et al. (2017) [29]	Mechanical Vibrations	Custom device for passive exercise and local vibration on hindlimbs	Frequency: 35 Hz, Amplitude: 1 mm	200 s, 2 times per day, 21 days, 20 bouts in 2 s each time with 8s intervals	Not reduced
4	Wenger et al. (2021) [38]	Mechanical Vibrations	Custom: vibration powered by a servomotor (Mavilor BLT-055, Barcelona, Spain) connected to a polycarbonate platform	Frequency: 30 Hz, Acceleration: 0.3 g	20 min per day, 21 days	No notable changes wrt the control group
5	Wenger et al. (2010) [37]	Mechanical Vibrations	Custom vibration platform	Frequency: 32 Hz, Acceleration: 0.5 or 1.5 g	30 min per day, 5 days per week, 3 months	Increased
6	Yao et al. (2019) [39]	Mechanical Vibrations	Custom comprising: a shaking device (NX-25D) and a vibration device (SK-40-D1) by Nissin Scientific Corporation (Japan)	Frequency: 40 Hz, Amplitude: 5 mm, Shaking: 2.5 Hz, 50 mm	30 min per day, 6 days per week, 10 weeks	Increased
7	Jing et al. (2014) [30]	MFs	CRSMART-C, Chaoruishi Medical Supplies Co. (China)	Rotating MF, Maximum magnetic flux: 400 mT, Magnetic flux distribution in cage: 0.38-0.60 T, Rotation frequency: 7 Hz	2 h per day, 4 weeks	No notable changes wrt the control group
8	Li et al. (2020) [31]	MFs	PS30, Orthofix Medical Inc. (USA)	PEMF, Frequency: 15 Hz, Magnetic field: 30 T/s	3 h per day from day 7 to 1, 3 or 4 weeks after distraction	Increased
9	Qian et al. (2020) [35]	MFs	TY-PEMF-B, Tianjin Tongye Technology (China)	PEMF, Frequency: 15 Hz, Magnetic field: 3.8 mT	40 min per day, 5 days per week, 8 weeks	Increased
10	Zhang et al. (2018) [40]	MFs	Custom 16 T superconductive magnet (Japan)	Static MF, Magnetic field: 0.2 T	Continuously exposed for 30 days	No notable changes wrt the control groups

Table - 3 Ultrasounds and Laser: technologies, devices, settings, interventions, and reported effect on bone quality.

N°	References	Technology	Device	Settings	Interventions	Bone quality
11	Arai et al. (2020) [21]	Ultrasounds	Osteotron D2 ITO (Japan)	Frequency: 1.5 MHz, Intensity: 30 mW/cm^2, Pulse repetition frequency: 1 kHz	20 min per day, 14 days	No notable changes wrt the control group
12	Do Nascimento et al. (2013) [23]	Ultrasounds	Sonopulse III Indústria Brasileira de Equipamentos Médicos (Brazil)	Frequency: 1 MHz, Intensity: 2 W/cm^2	6 min per day, 24 days	Increased
13	Heybeli et al. (2002) [28]	Ultrasounds	Diagnostic sonographic equipment - AU3 Partner, Esaote (Italy)	Frequency: 7.5 MHz, Intensity: 11.8 mW/cm^2, Pulse duration: 1 ms, Pulse repetition frequency: 1 Hz	10 min every 5 days, 1, 5, 8 times	Increased
14	Knothe Tate et al. (2013) [17]	Ultrasounds	Modulith SLX lithotripter Storz Medical AG (Switzerland)	Frequency: 2 GHz, Energy density: 0.46, 1.06 mJ/mm^2, Shock waves: 500, 1500	One-time treatment	Increased in case of 1500 shock waves
15	Machado et al. (2019) [33]	Ultrasounds	EXOGEN Bioventus (USA)	Frequency: 1.5 MHz, Intensity: 30 mW/cm^2, Pulse duration: 200 ms, Pulse repetition frequency: 1 kHz	20 min per day, 18 days	No notable changes wrt the control group
16	Tobita et al. (2011) [36]	Ultrasounds	SAFHS 2000J Teijin Pharma (Japan)	Frequency: 1.5 MHz, Intensity: 30 mW/cm^2, Pulse duration: 200 μs, Pulse repetition frequency: 1 kHz	20 min, 6 times per week, 4, 6, 8 weeks	Increased
12	Do Nascimento et al. (2013) [23]	Laser	Flash Lase III, DMC, Sao Carlos (Brazil)	Wavelength: 808 nm, Output power: 100 mW, Energy density: 6 J/cm^2	6 min per day, 24 days	Increased
17	Fazilat et al. (2014) [24]	Laser	THOR Photomedicine Ltd	GaAlAs Wavelength: 810 nm, Power: 200 mW, irradiation mode, continuous wave, Energy density: 3 J/cm^2, Power density: 400 mW/cm^2	7.5 severy other day, 14 days	Increased in early stages
18	Figueiredo et al. (2012) [25]	Laser	Low Level diode laser- MMOptics, São Carlos (Brazil)	Wavelength: 780 nm, continuous, Power: 40 mW, Energy density: 10 J/cm^2	10 s on alternate days, 15 days	No notable changes with LLLT alone, increased values if combined with MPA
19	Franzen et al. (2015) [26]	Laser	GaAlAs diode laser device - Rønvig Dental AS, Daugaard (Denmark)	GaAlAs Continous wavelength: 830 nm, Power: 75 mW, Power density: 550 mW/cm^2, Energy density: 23 J/cm^2, 3 J per session	17 s, every second or third day for 1, 3, 5, 7, 14, 21 days receiving 1, 2, 3, 4, 5, 7 doses of irradiation, respectively	No notable changes wrt the control group
20	Freddo et al. (2012) [27]	Laser	Thera Laser - DMC, São Carlos (Brazil)	GaAlAs Wavelength: 830 nm, Energy density: 5 J/cm^2 at 3 points (15 J/cm2 total), Power: 50 mW, continuous wave	1.41 min immediately after the last activation and then every 48 h, for 8 sessions	Increased in consolidation period
21	Liu et al. (2007) [32]	Laser	Low-energy laser apparatus - Phototherapy, San Diego, (USA)	Wavelength: 830 nm, Energy density: 10 J/cm^2, Power density: 200 mW/cm2	50 s at 4 points, daily, 20 days	Increased

Table 4 The number of papers reporting increased, mixed, or not significant effect on bone quality, divided on the basis of the applied technology among the ones found in the reviewed literature

Technology/Effect	Increased	Mixed	Not significant
Ultrasounds	3	1	2
Laser	2	3	1
Magnetic Fields	2	0	2
Hyperbaric Oxygenation	1	0	0
Mechanical Vibrations	2	1	1
Ultraviolet Irradiation	0	0	1
Total	10 (one paper double-counted)	5	7

6.4.1 HYPERBARIC OXYGENATION

In Clark (Clark, 2006), the research team tests HyperBaric Oxygenation (HBO) to increase bone density. Rabbits have been treated with 2.4 atm HBO, but no further detail is provided on the device since therapy was performed in a military medical center. HBO is reported to increase bone quality in the first 20 sessions before distraction, having measured a significantly increased BMD following the treatment (Table 2.). CT measures are not reliable after surgery due to scatteringartifacts.

6.4.2 ULTRAVIOLET IRRADIATION

In Morita (Morita, 2016), the effect of multiple UltraViolet (UV) wave- lengths, namely 268,

282, 290, 305, and 316 nm lengths with 0.54 mW/cm2 irradiance, is tested on different groups. No statistically significant bone quality variation could be identified (Table 2); however, several wavelengths are tested, and the main trabecular and cortical bone volume parameters tended to be higher (Morita, 2016) for the 316 nm group.

6.4.3 MECHANICAL VIBRATIONS

All the devices exploiting vibration stimulation employ custom-made devices with displacement amplitudes ranging from 1 to 5 mm, accelerations from 0.3 to 1.5 g, and frequencies from 30 to 40 Hz. Additionally, Yao (Yao, 2019) applies a 50-mm, 2.5-Hz rotational shaking. No device-limb strict coupling is performed. Instead, the stimulus is delivered through the cage's platforms as Whole-Body Vibration (WBV). The only exception is Huang (Huang, 2017), where rats' feet are fixed to the footplates with medical tape. Specific settings, interventions, and results are reported in (Table 2). As regards the reported effects on bone quality, two articles claim an increasing effect (Wenger, 2010; Yao, 2019), resulting from higher values of BV, BV/TV in (Wenger, 2010), and N.Ob, N.Ob/TV, BS/TV, Tb.N in Yao (Yao, 2019), both related to the non-stimulated control group. It is worth highlighting that in Wenger (Wenger, 2010) [37] the different acceleration values tested produced varied effects regionally, still always significant on bone quality. Specifically, a 0.5-g-vibration level is reported to be more effective for increasing bone density in the femur than 1.5 g, instead resulting in a more significant improvement in the radius. Besides, one article shows no significant change by observing the trend of BV and bone density spectrum (Wenger, 2021), and another one reports a conditional effect over two different control groups (Huang, 2017), thus considered among the articles with mixed results. In particular, in this last paper (Huang, 2017), a control group consisted of rats suspended by their tails to generate osteoporosis and simulate space conditions by reducing loadings on weight-

bearing bones, while in the other, rats were not suspended. BMD decreased in the non- stimulated but suspended group compared to the suspended and stimulated group, but this one had no statistically significant variation with the third non-suspended and non- stimulated group.

6.4.4 MAGNETIC FIELDS

Regarding Magnetic Fields (MFs), three subgroups can be identified: in Jing (Jing, 2014), a rotating MF with 0.38-0.60 T flux and a 7-Hz magnet rotation creating a non-uniform field is applied through a commercial device; commerical devices are also exploited in Li (Li, 2020) and Qian (Qian, 2020) to apply PEMFs with 30 T/s and 3.8 mT, respectively, both at 15 Hz of frequency; finally, in Zhang (Zhang, 2018) a custom 16 T superconductive magnet is used to enforce an incage static MF of 0.2 T. Specific devices, set- tings, and interventions are detectable in Table 2). As well as vibrating devices, MFs are reported to have diverse effects. Two research groups (Li, 2020; Qian, 2020) declare an increased effect on bone quality, evaluating BMD and BV/TV in Li (Li, 2020) and also trabecular bone parameters in Qian (Qian, 2020). Instead, no statistically significant difference has been detected in comparison with a control group in Jing (Jing, 2014) and with a control and a hypomagnetic field (500 nT) group in [40] by measuring BMD, BV/TV, and trabecular and cortical bone parameters. The papers reporting an increased effect employed PEMF, while the others used rotating or static fields. In Li (Li, 2020), the MF positive effect is observable only in the group terminated after four weeks.

6.4.5 ULTRASOUNDS

According to the article screening, ultrasounds are one of the most adopted technologies due to six papers included. In the experiments, commercial and custom equipment was used. Therapies were performed with sinusoidal waves ranging from 1 to 7.5 MHz, with intensity

between 11.8 mW/cm2 and 2 W/cm2, delivered in bursts at a pulse repetition frequency of 1 kHz (Arai, 2020; Machado, 2019; Tobita, 2011), with different pulse duration (200 ms in Machado (Machado, 2019), 200 ʻsec in Tobita (Tobita, 2011)) or with a 1 ms pulse at 1 Hz (Heybeli, 2002). Knothe et al. (Knothe, 2013) used ultrasounds to deliver 500 or 1500 shock waves at 2 GHz and different power levels to bring controlled microdamage on rats' bones and promote appositional growth. Devices, settings, and interventions are specified in Table 3.

Among the screened articles, three included studies report an increased bone quality shown by the BMD measurement do Nascimento, Heybeli, Tobita (do Nascimento, 2013; Heybeli, 2002; Tobita, 2011), while Knothe (Knothe, 2013) has constrained results, thus assigned to the mixed group. Indeed, bone apposition was significantly higher in bones treated with 1500 shock waves compared to the contralateral control bones, while no significant increase in new bone formation is observed in the group treated with 500 shocks by exploiting the same power levels. Finally, in Arai and Machado (Arai, 2020; Machado, 2019), no statistically significant variation in BMC or BMD value was found over the control group.

6.4.6 LASER

Laser is the second most studied technology, with as many included papers as ultrasounds. All authors use commercial devices operating in the infrared spectrum (700 nm – 1 mm), from 780 nm to 830 nm. Output power ranges from 40 to 200 mW. Specifically, devices, settings, and interventions are shown in Table 3. The papers report overall varied results on bone quality improvements. Two experiments show an increased bone quality after the laser therapy application (do Nascimento, 2013; Liu, 2007), while no statistically significant difference is found in Franzen (Franzen, 2015) by comparing BMD values measured in the group undergoing Low-Level Laser Therapy (LLLT) and in a control group. The results of the remaining three

articles (Fazilat, 2014; Figueiredo, 2012; Freddo, 2012) were considered mixed. Indeed, (Figueiredo, 2012) reports no significant effect on bone mass treated with LLLT except for an increased bone quality if combined with applying a mandibular propulsive appliance (MPA) to rats.

Freddo et al. (Freddo, 2012) reports an improvement in bone quality only if the laser therapy is applied during the consolidation period (thus, the last period of the distraction osteogenesis protocol, preceded by the latency and activation ones). Instead, such values tend to decrease in the case of laser application during the latency/activation period regardless of the distraction device usage period, with a consequent delay in bone healing. Finally, an increase in bone formation is visible in Fazilat (Fazilat, 2014) through histological analysis only in the early stages of the treatment, while an inflammation response is active.

6.5 DISCUSSION

The present systematic review investigates the studies available in literature where external devices and different technologies have been tested on animals to improve bone quality. Based on this review's database analysis, there is no prevailing technology employed for bone quality enhancement in the literature as of 11 October 2021. Laser and ultrasounds result the most studied technologies due to their six papers each out of the 21 included. The latter is reported as effective in more studies (three) compared to laser applications (two) without considering constraints, while also including mixed results, the former prevails over the latter. However, no definitive conclusion can be drawn. The same goes for the device parameters, interventions, and their influence on bones. It should be noted that an important advantage of the devices that exploit these technologies is due to their ability to target specific bone regions. Besides, none of the

included studies report any undesired side effects.

In more detail, HBO (Table 2) has been tested only in one of the included papers (Clark, 2006). Although this reports an increased bone density, no conclusion can be drawn, and more experiments are needed. No limb-device coupling is described, and no specific section stimulation is performed. UV irradiation (Table 2) has been studied in just one included paper (Morita, 2016). However, several wavelengths (268, 282, 290, 305, 316 nm) are tested with the same irradiance power on different groups. Although none of the examined settings led to a statistically significant result, the 316 nm group tends to have higher trabecular volume and cortical parameters, implying a positive effect on bone quality.

The reported effects of vibrating devices are various (Table 2). Two studies (Wanger, 2010; Yao, 2019) declare an increase in bone quality; one (Wenger, 2010) reports no notable difference from a control group, and one (Huang, 2017) a non-reduction in bone quality, unlike the control group. (Wenger, 2010; Wenger, 2021) employ analogous devices with similar vibrating frequencies (30-32 Hz) and accelerations (0.3, 0.5, and 1.5 g), finding positive effects only at the two highest accelerations, with the most remarkable bone density improvement at 0.5 g (Wenger, 2010). It is worth highlighting also the different intervention duration, which is two months longer in (Wenger, 2010) than in (Wenger, 2021). In all four studies, vibrations at 30-40 Hz are applied for 30 min or less, which comply with the 30-50 Hz for less than 30 min recommended in (Duan, 2018) for preventing harmful WBV. However, no trend in the device settings and interventions can be identified. Moreover, in the same way as HBO devices, no limb-specific stimulation is applied except for (Huang, 2017).

MFs (Table 2) also have different effects on bone quality: two studies report an increase (Li, 2020; Qian, 2020), and two have no statistically significant results (Jing, 2014; Zhang, 2018). Three different kinds of stimulation are performed by applying rotating (Jing, 2014), pulsed (Li,

2020; Qian, 2020), or static (Zhang, 2018) electromagnetic fields. Both papers employing PEMF (at the same frequency of 15 Hz, but with different magnetic fields and interventions) describe a better bone quality coherently with a previous review on extremely low-frequency PEMF (ELF-PEMF) (Ehnert, 2019). Rotating (Jing, 2014) and static (Zhang, 2018) MF had no significant results compared to the control group. Thus, no trend can be underlined in session and therapy duration.

Ultrasound devices (Table 3) are the most studied, along with lasers, in the included articles (six out of 21). Three papers describe an increased effect on bone quality (do Nascimento, 2013; Heybeli, 2002; Tobita, 2011), while only two have found no statistically significant variation with a control group (Arai, 2020; Machado, 2019). Finally, Knothe (Knothe, 2013) reports mixed results. Five studies apply sinusoidal waves through peri- odic short bursts, with different frequencies and intensities, stimulating bone formation similarly to mechanical loading (Perry, 2009; Ramas, 2009). In the remaining article (Knothe, 2013), bone strengthening is achieved by causing controlled microfractures on the bones through shock waves and letting them heal. It should be noted that the two studies with no statistically significant results (Arai, 2020; Machado, 2019) work with analogous frequency, intensity, and pulse repetition frequency (1.5 MHz, 30 mW/cm2, 1 kHz) for the lowest therapy duration, except for Knothe (Knothe, 2013), which exploits a different approach. The same settings but a more extended period of intervention in comparison with Arai and Machado (Arai, 2020; Machado, 2019) are exploited in Tobita (Tobita, 2011), reporting, instead, an increased effect on bone quality. However, no other conclusions can be drawn since, in the remaining articles (Knothe, 2013; do Nascimento, 2013; Heybeli, 2002), positive and negative results were reached with no common device settings and interventions.

Laser (Table 3) is the other most studied technology with six included papers but have more uncertain effects than ultrasounds. Two articles report an increased effect on bone quality (do

Nascimento, 2013; Liu, 2007), only one has no statistically significant difference with a control group (Franzen, 2015), while three belong to the mixed category (Fazilat, 2014; Figueiredo, 2012; Freddo, 2012). More specifically, Fazilatat (Fazilat, 2014) describes a bone quality improvement only in the early application stage, during the inflammation period, explaining it through the influence of infrared laser over redox mechanisms, subsequently affecting pH levels. On the contrary, in Freddo (Freddo, 2012), in which a slightly higher wavelength and energy density but lower power density are exploited compared to Fazilat (Fazilat, 2014), significant results are postponed to the consolidation period, while bone quality tends to worsen during the latency/activation period. Do Nascimento (do Nascimento, 2013) also reports a bone quality improvement while adopting a similar wavelength but lower power and longer sessions and therapy duration than Fazilat (Fazilat, 2014).

Figuiredo (Figueiredo, 2012) found no statistical significance for laser stimulation alone but an increased bone mass when applied with a mandibular propulsive appliance. No trend for wavelengths, power intensities, or interventions can be pointed out.

In one especially compelling paper (do Nascimento, 2013), ultrasound and laser technologies are compared in a randomized control trial. Two groups undergo Low-Intensity UltraSound (LIUS) and Laser (LIL) irradiation, respectively, while a third group is treated with each one on a different mandible side. A distraction device is applied to all rabbits. As reported in Table 3, both therapies resulted in an increased effect on BMD recuperation compared to the control group. Data extracted from do Nascimento (do Nascimento, 2013) show a more remarkable improvement in the LIUS group than the LIL group.

The results obtained from this review highlighted the absence of a shared protocol or methodology for assessing bone quality variations. Specifically, having no common measurement method, devices, and outcomes makes com- paring results from different

experiments complex. In the same way, different device settings (e.g., frequency and power) and interventions make it difficult to obtain comparable results on bone quality for the same technology used and detect the appropriate stimulation mechanism. Only do Nascimento (do Nascimento, 2013) compares the outcomes achieved by applying two different technologies, but this is not enough to draw any conclusion.

6.6 CONCLUSION

The questions addressed in this review were: “Which external devices or technologies have been tested for bone quality improvement without pharmacological interventions? Which effects do these have on bone structure?” The technologies for bone quality improvement in animals identified in this literature review are ultrasounds, laser, ultraviolet irradiation, magnetic fields, mechanical vibrations, and hyperbaric oxygenation. The analyzed data show that ultrasounds and laser devices are the most studied. However, not enough papers have been found to draw a definitive conclusion on the technologies or devices that significantly affect bone quality. Furthermore, different out- comes measured, measurement methods, and interventions do not enable direct and quantitative comparison between effects on bone quality for each technology and the outcomes themselves. In conclusion, further studies are needed to evaluate external devices’ short- and long-term effects on bone quality, even after treatment termination. In the light of this investigation, the authors believe that a common approach for carrying out experiments could help deepen the understanding of these devices’ influence on bones. In particular, standard measurement methods, guidelines on interventions, and device settings could be followed to compare outcomes achieved by exploiting different technologies.

7. STUDY IV

THE EFFECT OF PHYSICAL ACTIVITY ON BONE BIOMARKERS IN PEOPLE WITH OSTEOPOROSIS: A SYSTEMATIC REVIEW

7.1 ABSTRACT

Background: Bone imbalance between anabolic and catabolic processes at the level of remodeling unit due to the prevalence of resorbing activity, represents a health problem of aging. The consequence is the negative balance of bone turnover that can lead to osteoporosis. Physical activity (PA) can play a central role in the comprehensive management of osteoporosis, since it induces the anabolism of bone tissue. Bone turnover biomarkers, reflecting the cellular activity linked to bone metabolism, can represent an evaluation tool to assess the efficacy of PA in the osteoporotic population. The aim of this systematic review, conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, was to investigate the effects of PA interventions on bone biomarkers in people with osteoporosis.

Methods: A comprehensive literature search of electronic databases was conducted through PubMed, Cochrane, Cinahl, Embase, Trip, to find randomized controlled trials (RCTs) investigating the topic of PA and bone turnover biomarkers in the osteoporosis population. In accordance with the Cochrane risk-of-bias tool, the quality of each study was assessed.

Results: Out of 992 identified articles, 136 full texts were screened. Only three RTCs matched the eligibility criteria. In one study, sub-maximal aerobic exercise improved Bone-specific

alkaline phosphatase (bone formation biomarker) and Amino-terminal Crosslinked Telopeptide of type 1 collagen (bone resorption biomarker) in osteoporotic women. The other two studies showed a positive effect on total alkaline phosphatase (a non-specific bone formation biomarker) in women with osteoporosis.

Conclusion: The systematic review revealed possible exercise benefits in terms of improving bone formation and decreasing bone resorption biomarkers in the osteoporotic population. However, these results should be interpreted with caution, especially due to the limited number and poor quality of the studies included. Further research is needed to estimate the influence of PA on bone biomarkers in the osteoporosis management.

7.2 INTRODUCTION

Bone is hard tissue that is in a constant state of flux, being built up by bone-forming cells called osteoblasts while also being broken down or resorbed by cells known as osteoclasts (WHO, 2003). The assessment of bone quality can involve several parameters, including the extent of mineralization, the number and distribution of micro fractures, the rate of osteocyte apoptosis, and changes in the collagenous bone matrix. The status of bone mass is usually measured using a densitometry method (Leeming, 2009). However, it is more difficult to accurately examine bone structure and strength in live tissue only by Dual X-ray Absorptiometry (DXA) (Seibel, 2005). Some blood and urinary molecules have been identified as biomarkers to detect the dynamics of bone turn-over (Kuo, 2017). They are ideal tools to evaluate the actual metabolic status of the bone, as well as a well-established result of abnormal metabolism (Banfi, 2010). Table 1 shows the most reviewed bone biomarkers to assess the different phases of bone

metabolism process (Kuo, 2017; Vasikaran, 2011; Nagy, 2020; Park a, 2018; Liu, 2019; Glendenning, 2019; Drake, 2017).

Table 1 Summary of bone turnover biomarkers currently available and their characteristics

Biomarkers	Assay method	Characteristics	Reference
Bone formation markers			
Alkaline phosphatase (ALP)	Serum Standard Auto-analyzer technique	Widely used but non-specific for bone turnover	Vasikaran, 2011 Kuo, 2017
Bone alkaline phosphatase (BALP)	Serum EIA-CLEIA	Applied for the monitoring of osteoporosis.	Kuo, 2017 Nagy, 2020 Park, 2018
Osteocalcin (OC)	Serum IRMA-ECLIA	No significant utility for the assessment of osteoporosis. Promising for the investigation of osteoporosis therapy efficacy	Liu, 2019 Kuo, 2017 Nagy, 2020
Procollagen type 1 C-terminal propeptide (P1CP)	Serum Radioimmunoassay	Limited study in literature.	Kuo, 2017 Nagy, 2020

		Promising for the investigation of bone formation	
Procollagen type 1 N-terminal propeptide (P1NP)	Serum RIA-ECLIA	The most sensitive marker to measure the bone formation rate the most accepted marker for monitoring drug therapy.	Kuo, 2017 Glendenning, 2018 Nagy,2020
Bone resorption markers			
Amino-terminal crosslinked telopeptide of type 1 collagen (NTX-1)	Urine EIA-CLEIA	Stable and not affected by food intake. Promising marker for osteoporosis management	Kuo, 2017 Nagy, 2020
Bone sialoprotein (BSP)	Serum immunoassay	Potential biomarker for osteoporosis assessment	Kuo, 2017
Carboxy-terminal crosslinked	Serum/plasma/urine EIA-CLEIA	Specific and sensitive biomarker	Kuo, 2017 Glendenning, 2018

telopeptide of type 1 collagen (CTX-1)		for osteoporosis management. Useful marker for monitoring drug therapy	Nagy, 2020
Cathepsin K (CTSK)	Serum ELISA	Potential marker for monitoring drug therapy	Kuo, 2017 Drake, 2017
Deoxypyridinoline (DPD)	Urine HPLC-EIA-CLEIA	Not very sensitive for osteoporosis management	Kuo, 2017 Nagy, 2020
Hydroxylysine (HYL)	Urine HPLC	Limited application due to the lack of a simple routine method	Kuo, 2017
Hydroxyproline (HYP)	Urine Spectrophotometric technique	Not very sensitive for osteoporosis management, it has been replaced by more specific markers	Kuo, 2017
Osteopontin (OP)	Plasma ELISA	Promising biomarker to	Kuo, 2017; Glendenning, 2018

		monitor the parathyroid hormone treatment in menopausal osteoporosis	Nagy, 2020
Pyridinoline (PYD)	Urine HPLC	Non-specific for diagnosis and treatment of osteoporosis	Kuo, 2017 Nagy, 2020
Tartrate-resistant acid phosphatase 5b (TRAP 5b)	Serum/plasma EIA	Good specificity and high sensitivity for monitoring drug therapy	Kuo, 2017 Nagy, 2020
Regulators of bone turnover			
Dickkopf-1 (DDK-1)	Serum ELISA	Insufficient clinical data for osteoporosis management	Kuo, 2017 Nagy, 2020
Osteoprotegerin (OPG),	Serum ELISA	Insufficient data for clinical management of osteoporosis	Kuo, 2017

Receptor activator of NF-kB ligand (RANKL)	Serum ELISA	Insufficient data for diagnosis and treatment of osteoporosis	Kuo, 2017
Sclerostin	Serum ELISA	Insufficient clinical data for osteoporosis assessment	Kuo, 2017 Nagy, 2020

The negative balance of bone turnover, due to the absolute (increase in osteoclastic function) or relative (inadequacy of osteoblastic function) prevalence, represents a health problem. The most common cause of this process is aging, but it can also result from other conditions such as immobilization, cortisone therapy, or estrogen deficiency. The most common metabolic bone disease is osteoporosis, which is characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased susceptibility to fractures (Prentice, 1997). Currently, it has been estimated that more than 200 million people are suffering from OP, and this number is increasing due to the aging population and the change in lifestyles. According to recent statistics from the International Osteoporosis Foundation, OP affects one in three women and one in five men over the age of 50 years worldwide (IOF, 2018). Estrogen deficiency is the main etiopathogenic factor in postmenopausal OP. Indeed, throughout the menopausal transition, serum estradiol and estrone levels decrease, with an increase in bone resorption leading to OP (Lupsa, 2015; Consensus Development Conference, 1993).

Nowadays, osteoporosis is a major public health concern worldwide due to its healthcare cost and requires a multi-modal care approach including both pharmacological and PA interventions

(Kendler, 2016). In Europe, the most commonly administered agents involved in OP drug therapy are raloxifene, BP, agents derived from parathyroid hormone, and denosumab (Kanis., 2019; Choi, 2013). The guidelines for the prevention and treatment of OP recommend regular physical exercise. A low level of PA represents an important risk factor for OP due to the reduced mechanical stimulation of osteoblasts. For these reasons, PA should be part of the comprehensive management of osteoporotic patients since it can reduce disability, improve physical function, lower the risk of subsequent falls, and act on bone structure (Cosman, 2014; Howe, 2011).

It is likely that PA induces an anabolic or homeostatic effect on bone *via* mechanotransduction (McMillan, 2017). Although the mechanism underlying the effects of exercise on bone remodeling is not yet fully understood, some hypotheses seem more probable. One is the piezoelectric effect: when the mechanical impulse transmitted to the bone is converted by hydroxyapatite crystals into an electrical impulse that leads to greater bone mineralization. Another is the vascular effect: when the increase in muscle activity leads to a positive variation in the bone blood flow, improving the local metabolism (Tong, 2019). In particular, exercise carried out under conditions of weight-bearing determines the most significant benefits, as the mechanical stress is more intense. Also, the bone response to exercise is greater in districts where more mechanical stress is exerted. Furthermore, aerobic exercise seems to be particularly effective in the enzymatic activation of the osteoblasts (Benedetti, 2018).

Nowadays bone metabolic biomarkers have become useful clinical parameters in the management of osteoporosis and their use continues to expand (Nishizawa, 2013), as the possible variation in their concentrations may indicate an anabolism status or a bone catabolism (Vincent, 2002). The monitoring of bone turnover biomarkers could be a useful assessment tool to understand the physiological mechanism deriving from the osteogenic effect of PA (Cadore, 2005) and to assess the impact of exercise on osteoporotic bone (Brown, 2009; Maimoun, 2011).

This highlights the need for an investigation of the influence of exercise on biomarkers linked to bone turnover in the osteoporotic population. In this scenario, the purpose of the present systematic review was to evaluate and critically analyze, for the first time, the available evidence on the effects of PA interventions on bone biomarkers in people with OP.

7.3 METHODS

7.3.1 SEARCH STRATEGY AND DATA SOURCES

We conducted this current Systematic Review following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Moher, 2009). Beforehand, we registered the protocol in the International Prospective Register of Systematic Reviews (PROSPERO).

The following PICO (Patients, Interventions, Comparators and Outcomes) question was developed, addressing the primary search objective, through the following search terms: (P) Osteoporotic people, aged 45–80+; (I) Physical activity; (C) Standard care or no exercise treatment; (O) The effect of physical activity interventions on bone biomarkers.

We searched electronic databases, with a 10-year time limit on the publication date because we were interested in recent pharmacologic treatments and approaches. The primary search was performed on 20 October 2019 and was updated on 14 May 2020. In all data bases we applied the following criteria to define the research: we included only Clinical Trial, Clinical Study, Comparative Study, Observational Study, Randomized Controlled Trial with Full text available, published in the last 10 years; with Human subjects. We defined a range of population aged 80 and over: 80+ years, Middle Aged + Aged: 45+ years, Middle Aged: 45–64 years, Aged: 65+ years.

The databases searched were: MEDLINE (PubMed); Embase (Ovid); Cochrane Central Register of Controlled Trials (Central); CINAHL (EBSCO); TRIP Medical. The search terms were adapted when necessary to fit the specific search requirements of each database.

Search strategies (strings adapted to the different databases) used the following Boolean expression: keywords and terms: "((((((((((((((((((((Osteoporoses) OR Osteoporosis, Post-Traumatic) OR Osteoporosis, Post Traumatic) OR Post-Traumatic Osteoporoses) OR Post-Traumatic Osteoporosis) OR Osteoporosis, Senile) OR Osteoporoses, Senile) OR Senile Osteoporoses) OR Osteoporosis, Involutional) OR Senile Osteoporosis) OR Osteoporosis, Age-Related) OR Osteoporosis, Age Related) OR Bone Loss, Age-Related) OR Age-Related Bone Loss) OR Age-Related Bone Losses) OR Bone Loss, Age Related) OR Bone Losses, Age-Related) OR Age-Related Osteoporosis) OR Age Related Osteoporosis) OR Age-Related Osteoporoses) OR Osteoporoses, Age-Related) AND ((((((((((((((((((((Exercises) OR Physical Activity) OR Activities, Physical) OR Activity, Physical) OR Physical Activities) OR Exercise, Physical) OR Exercises, Physical) OR Physical Exercise) OR Physical Exercises) OR Acute Exercise) OR Acute Exercises) OR Exercise, Acute) OR Exercises, Acute) OR Exercise, Isometric) OR Exercises, Isometric) OR Isometric Exercises) OR Isometric Exercise) OR Exercise, Aerobic) OR Aerobic Exercise) OR Aerobic Exercises) OR Exercises, Aerobic) OR Exercise Training) OR Exercise Trainings) OR Training, Exercise) OR Trainings, Exercise) AND ((((((((((((((((Bones and Bone Tissue) OR Bones and Bone) OR Bone Tissue) OR Bone Tissues) OR Tissue, Bone) OR Tissues, Bone) OR Bony Apophyses) OR Apophyses, Bony) OR Bony Apophysis) OR Apophysis, Bony) OR Condyle) OR Condyles) OR Bones) OR Bone) OR Bone Biomarker) OR Bone Biomarkers) OR Biomarker, Bone) OR Biomarkers, Bone)". After exporting articles, duplicates were removed. Moreover, we conducted a gray literature search of other papers and hand searches of key conference proceedings, journals, professional

organizations' websites and guideline clearing houses. In accordance with the snowball technique, we examined references cited in the primary papers to identify additional papers.

7.3.2 INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria:

1. Articles written in English;
2. Population with a diagnosis of osteoporosis (T score ≤−2.5);
3. Physical activity intervention;
4. Bone Biomarker evaluation, bone biomarkers measured at least one time during the study;
5. Additional physical performance measured outcomes, or other indices of physical performance described in each study for example walking, balance, dexterity;
6. All the additional outcomes measured at least one time during the study;
7. Original primary data.

Exclusion criteria:

1. Articles not pertinent for the research topic;
2. Population with osteopenia, absence of osteoporosis diagnosis, different diseases;
3. Absence of physical activity intervention, physiotherapy, reported physical activity, other therapy;
4. Study protocol or other papers without original data.

7.3.3 DATA EXTRACTION AND QUALITY ASSESSMENT

Four independent and blind investigators (SM, AM, GB, YL) screened and checked all the titles and abstracts retrieved in order to select pertinent items and to extract data following the inclusion

criteria, using a pre-tested data extraction form. In case of doubts about the pertinence, the investigators assessed the eligibility of the study by reading the full text of the article.

The studies thus selected were independently and blindly assessed for the risk of bias by three researchers (SM, AM, GB), using the "Cochrane risk-of-bias tool for randomized trials" (Sterne, 2019). Any disagreement between the quality scores separately assigned by the blind reviewers was resolved through discussion and, if necessary, a fourth blind reviewer (YL) was involved as tiebreaker. The evaluation of risk of bias was made on the basis of the primary outcome of our interest, namely bone turnover biomarkers. This methodological choice was supported by the PRISMA guidelines (Moher, 2009).

The Cochrane risk-of-bias tool for randomized trials analyses seven bias categories for studies classified as a randomized controlled trial (RCT): (1) random sequence generation and (2) allocation concealment (concerning bias of selection and allocation), (3) selective reporting for reporting bias, (4) blinding of participants and personnel (performance bias due to knowledge of the allocated intervention), (5) blinding of outcome assessment for detection bias, (6) incomplete outcomes data for bias in attrition, and another domain (7) called "other bias" based on the probable bias not covered in the other categories. Each category results in a value of high, low or unclear (when the authors did not provide enough evidence about the bias category) risk of bias. According to the Cochrane RoB Tool we converted the score to AHRQ (Agency for Healthcare Research and Quality) standards (Good, Fair and Poor). The threshold to provide the final score are the following: Good quality correspond to all criteria met (*i.e.* low risk of bias for each domain); Fair quality, only one criterion not met (*i.e.* high risk of bias for one domain) or two criteria unclear; Poor quality two or more criteria listed as high or unclear risk of bias.

The investigators extracted data independently, following the standardized norms for literature collection. We conducted a descriptive analysis of the studies by searching and extracting the

following information from the articles: name of the first author, publication year, country, study design, population study with ages and number of experimental (EG) and control (CG) groups, sample size, type intensity and frequency of intervention, primary and secondary outcomes, results stratifying the studies for the different outcomes. Results were tabulated as mean ± SD where possible.

Any disagreement was resolved by consensus (LD, LB, FM). The study authors or investigators were contacted when additional information was necessary (Greenhalgh, 2005).

7.4 RESULTS

7.4.1 STUDY SELECTION AND CHARACTERISTICS

As shown in Figure 1, a total of 992 articles were identified in the databases browsed and through hand search. Papers were published from 2012 to 2018; 374 studies were excluded because duplicated, 482 studies were excluded following abstract and/or title review. After this step, we judged 136 records as pertinent, 133 of which were subsequently excluded after a detailed full-text reading. The main causes of exclusion were related to the non-relevance and coherence with the aim of this study: the effects of PA interventions on bone biomarkers in people with OP. Furthermore, the majority of the articles were excluded due to the samples that did not match our inclusion criteria (people with osteopenia and not osteoporosis). As a result, only three papers (Arazi, 2018; Roghani, 2013; El-Mekawy, 2012) were finally included in the systematic review, fully meeting the eligibility criteria (Figure 1).

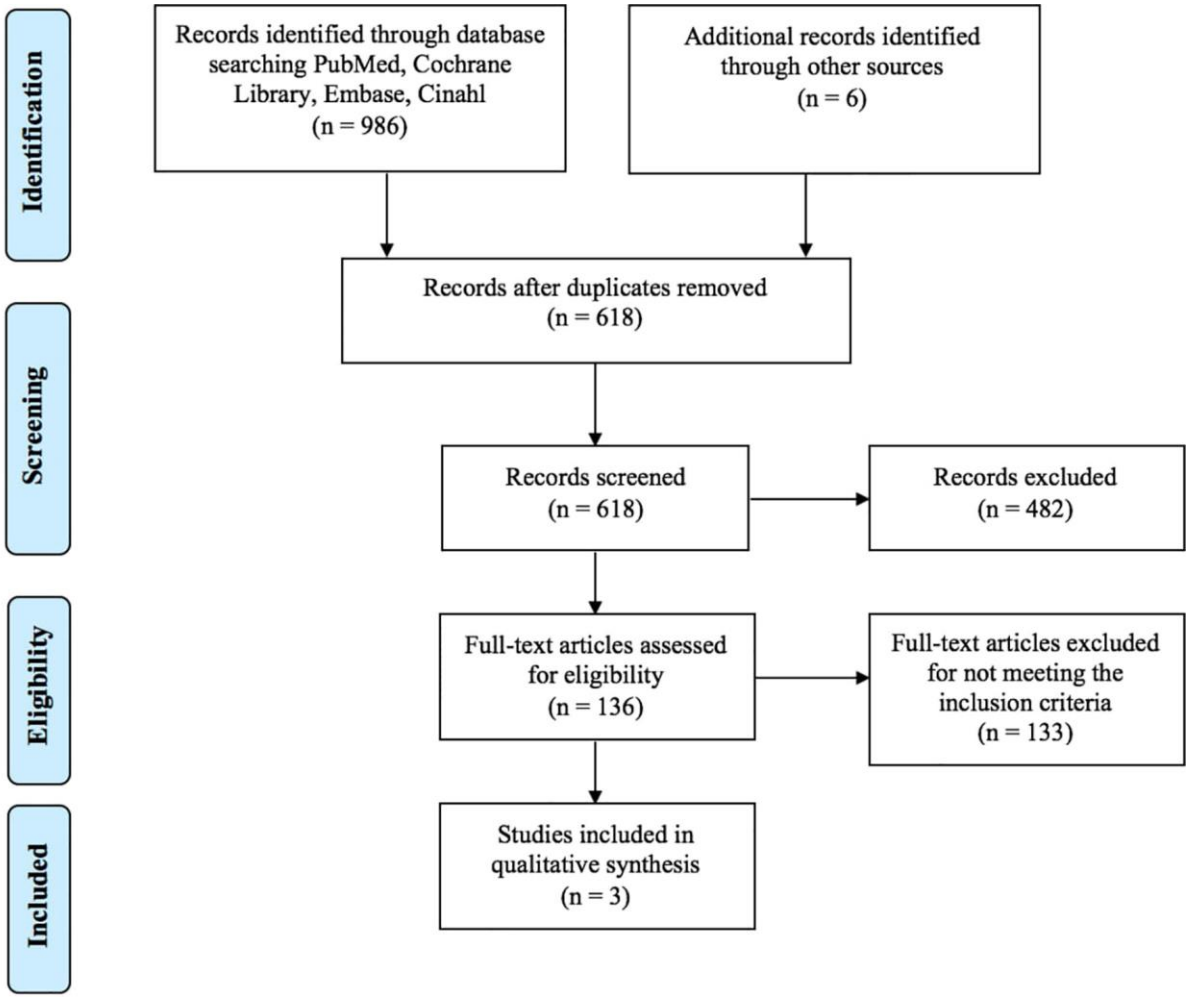


Figure 1- PRISMA diagram of the study selection

7.4.2 RISK OF BIAS

Following the descriptive analysis, we assessed the quality of each RCT study.

In accordance with the Cochrane risk-of-bias tool for randomized trials we assessed the quality based on biomarkers outcome (Table 2). The three RCTs do not explain in detail the randomization methods or allocation of participants (items #1 and #2), and none of them had a research protocol registered; due to this, the selective reporting was assessed as unclear (item#3). There was no blinding of participants (item #4), but the review authors judge that the biomarker outcome is not likely to be influenced by lack of blinding of participants. Regarding the blinding

of outcome assessment (item #5) Roghani et al. was the only one that described and used techniques and methods that ensure the sensitivity of outcome assessment (Roghani, 2013); the studies by Arazi et al. (Arazi, 2018) and El-Mekawy et al. (El-Mekawy, 2012) were not clear in describing the methodology used to guarantee no risk of bias of outcome assessors. Overall, each RCT had one or more criteria unclear. For these reasons, the risk of bias was scored as "Poor quality".

Table 2 Risk of bias evaluation

Studies	Random sequence	Allocation concealment	Selective reporting	Other bias	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data	Quality
Arazi et al. 2018 (27)								Poor
El-Mekawy et al. 2012 (28)								Poor
Roghani et al. 2013 (26)								Poor

green: criterion met, yellow: criterion unclear, red: criterion not met

7.4.3 DATA EXTRACTION

According to our aim focused on assessing the effects of PA on biomarkers, we extracted the data considering the bone biomarkers analysis and other hematological parameters as primary outcome; bone mineral density (BMD) assessment and physical performance tests as secondary outcome. Table 3 shows the main characteristics and results of the included studies evaluating the effects of PA interventions on bone biomarkers, in people with OP. The geographic origin of the studies was: Iran (n = 2, 66%) and Egypt. Study characteristics were heterogeneous. The sample size varied from 26 to 60 people. Ages ranged from 30–45 to 60–65 years. Concerning

the subject's inclusion/exclusion criteria, in both Roghani et al. and El-Mekawy et al. studies, subjects were excluded if they were taking any drugs that affected bone metabolism or were receiving hormone replacement therapy. In Arazi et al. an inclusion criterion was not using low-fat dairy (milk, yogurt, cheese) as a source of vitamin D. The duration of the intervention varied from 6–10 weeks to 6 months with a common frequency of three times a week. The type of exercise training was, in all three studies (Cadore, 2005; Brown, 2009; Maimoun, 2011), aerobic such as walking on a treadmill or resistance weighted exercise, administered in more than one group. In both Roghani et al. and Arazi et al. were enrolled other experimental groups performing weighted aerobic exercise and aerobic-resistance training, respectively, while only the study by El-Mekawy included an outdoor walking intervention. The El-Mekawy et al. study did not have a control group, while the other two envisaged a standard care control group. In Arazi et al. two intervention groups (concurrent training and milk; only milk supplementation) received a supplementation of 500 ml daily milk for ten weeks.

Table 3. Studies included in the review

Study	Study design	Sample	Intervention	Outcomes	Results	Quality (RoB Tool)
Arazi et al., 2018 Rasht, Iran	RCT	N:40 age:30-45 EG-training:10 EG-training +milk:10 EG-milk:10 CG:10	**Duration:** 10 weeks **Type of intervention:** EG-training: aerobic exercises 10 weeks x 3 sessions/week, 90-110 min x session EG-training+milk: aerobic exercises 10 weeks x 3 sessions/week, 90-110 min x session +500 ml daily milk for 10 weeks immediately (250 ml) and 1 hour after	**Primary outcome**: ALP and 25OHD **Secondary outcome**: BMD hip values (right and left) and BMD lumbar spine (L2-L4)	**Primary outcome results** **Statistically significant improvement in ALP:** EG-training+milk p<0.001; EG-training p<0.001; EG-milk p=0.01. **Statistically significant improvement in 25OHD:** EG-training+milk p<0.001; EG-training p<0.001; EG-milk p=0.03. **Secondary outcome results** **Statistically significant improvement in BMD hip** EG-training+milk: right hip: p<0.001; left hip: p<0.001;	**Poor**

			training (250 ml). EG-milk: 500 ml daily milk for 10 weeks, milk immediately (250 ml) and one 1 hour after training (250 ml), CG: standard care.		EG-training: right hip: p=0.01; left hip: p<0.001; EG-milk: right hip: p=0.15; left hip: p=0.09. **Statistically significant improvement in BMD lumbar spine** EG-training+milk p=0.02; EG-training p<0.001 EG-milk p=0.10.	
El-Mekawy et al., 2012 Cairo, Egypt	RCT	N: 60 women age:59.03±2.67 EG-A:20 EG-B:20 EG-C:20	**Duration:** 6 months **Frequency:** 3 times a week **Type of intervention:** EG-A: walk daily in the morning in fresh air, 30 min. EG-B: aerobic exercise training for hip and lumbar	**Primary outcome**: ALP and calcium (Ca)	**Primary outcome results** **Pre-post change in ALP**: EG-A= pre: 175.68±33.48 vs post: 173.00±32.95, change pre:1.53%, p value<0.91; EG-B= pre: 157.00±35.23 vs post: 154.44±35.92, change:1.63%, p value<0.33; EG-C= pre: 153.48±36.44 vs post: 150.96±35.92, change:1.64%, p value<0.05.	**Poor**

	spine. Sustained muscle contraction for each specific exercise was maintained for 5 seconds followed by 10 seconds of relaxation. EG-C: treadmill program for 30 min consisted of 5 min warm up which involved walking with no resistance and no inclination at the walk way of the treadmill followed by 20 min of walking with 15º inclination at the	**Secondary outcome**: Response of BMD neck and BMD lumbar spine to exercise	**Pre-post change in Ca**: EG-A= pre: 8.48±0.31 vs post: 8.66±0.3, change: 2.12%, p-value<0.81; EG-B= pre: 8.45±0.36 vs post: 8.66±0.37, change: 2.49%, p value<0.44; EG-C= pre: 8.48±0.34 vs post: 8.73 ±0.37, change: 2.95%, p-value<0.66. **Secondary outcome results** **Pre-post change in BMD neck**: EG-A= pre: -2.97± 0.64 vs post: -2.66 ±0.59, change:10.44%, p value<0.05; EG-B= pre: -2.87±0.67 vs post: -2.55±0.65, change: 11.15%, p-value<0.004; EG-C= pre:2.71±0.30 vs post: -2.38±0.32, change: 12.18%, p value<0.002.

			walk way of the treadmill at 60-75% of the training heart rate and ended by 5 min cool down.		**Pre-post change in BMD lumbar spine**: EG-A= pre: -3.59±0.90 vs post: -3.26±0.88, change: 9.19%, p-value<0.01; EG-B= pre: -3.64±0.65 vs post: -3.29±0.74, change: 9.62%, p value<0.002; EG-C= pre: -3.44±0.83 vs post: -3.08±0.79, change: 10.47%, p-value<0.001.	
Roghani et al., 2013 Thran, Iran	RCT	N:27 age:45-65 CG:9 EG-aerobic:9 EG-weight:9	**Duration:** 6 weeks, 18 sessions **Frequency:** 3 times a week, 30 min each session **Type of intervention:** EG-Aerobic: treadmill submaximal, increasing the intensity every 2	**Primary outcome**: (tALP), BALP, and NTX levels, calcium (Ca), phosphorus (P).	**Primary outcome results** **Pre-Post change in tALP (U/L)**: EG-Aerobic= pre: 218.00±68.32 vs post: 226.12±72.11, change: +8.12, NS; EG-Weighted= pre: 222.44±60.96 vs post: 221.55±80.04, change: -0.89, NS; CG= pre: 181.50±83.36 vs post:186.70 ±80.04, change: +5.2, NS. **Pre-Post change in BALP (U/L)**: EG-Aerobic= pre: 156.12±38.08 vs post: 173.37±51.20, change: +10.25%, p=0.03;	**Poor**

	weeks; EG-Weighted: Aerobic + wearing a vest 4–8 % of body weight; CG: usual care	EG-Weighted= pre: 154.22±33.73 vs post: 166.44±43.92, change: +7.31%, p=0.05; CG= pre: 139.70±59.55 vs post: 136.60±57.37, change: -1.93%. **Pre-Post change in NTX (nM)**: EG- Aerobic= pre: 20.80±2.37 vs post:19.51±1.88, change: -5.99%, p=0.001; EG-Weighted**=** pre: 21.10±2.33vs post: 19.72±1.91, change: -6.34%, p=0.002; CG= pre: 21.08±2.32 vs post:21.20±2.38, change: +0.60%, p=0.6. **Pre-Post change in P(mg/dL):** EG-Aerobic= pre: 3.86±0.40 vs post: 3.84±0.3, change: - 0.02, NS; EG-Weighted= pre: 3.33±0.43 vs post: 3.53±0.26, change: +0.2, NS; CG= pre: 3.79±0.42 vs post: 3.83±0.66, change: +0.4, NS.

		Pre-Post change in Ca (mg/dL): EG-Aerobic=pre: 9.10±0.11 vs post: 9.16±0.25, change: +0.06, NS; EG-Weighted= pre: 8.91±0.16 vs post: 9.23 ± 0.23, change: +0.32, p-value< 0.07; CG= pre: 9.06±0.38 vs post: 9.07 ± 0.20, change: +0.01, NS.
	Secondary outcome: Balance: near tandem stand (NTS) and star-excursion (SE) test	**Secondary Outcome Results** **Pre-post change in SE test (cm):** EG-Aerobic= +10.72%, p-value<0.05; EG-Weighted= +13.43%, p-value<0.05; CG= -10.43%, p-value<0.05. **Pre-post change in Near Tandem Stand (NTS) test (s)** EG-Aerobic= +49.68 %, EG-Weighted= +104.66%, CG= -28.96%.

In the study by Arazi et al. the aim was to investigate the effects of concurrent training and milk, only training and daily milk consumption, on bone biomarkers and BMD. The exercise protocol for the concurrent training was performed by groups in 10 weeks, with three sessions of 90–110 min each week. Aerobic training included three sets of 5 min, running with 55–75% of heart rate maximum (HRmax) of the target and exercise intensity gradually increased for 5% HRmax and 3–5 min every two weeks (rest period of approximately 3 min between each set). Resistance training involved performing two sets of bench press, leg extension, wide grip pull-down, and leg curls, which were circular with 10 RM, and training intensity was gradually increased every two weeks for new 10 RM. At the end of 10 weeks, Arazi et al. reported a significant improvement in blood levels of 25-hydroxyvitamin D (25OHD) and ALP in all the experimental groups (concurrent training-milk, training group, milk group) compared to the control group (standard care), with a higher increase in the concurrent training-milk group ($p < 0.05$).

The study by El-Mekawy et al. conducted to determine the ideal type of exercise for the treatment of osteoporosis, foresaw three types of exercise (brisk walking in fresh air, specific exercise program for hip and lumbar spine, and weight-bearing exercise program on treadmill). The results obtained after 6 months showed a significant increase in all the primary and secondary tested parameters (pre-post change in ALP, BMD neck and BMD lumbar spine) in the three exercise groups.

Roghani et al. evaluated the effect of submaximal aerobic exercise with and without external loading, in three groups: aerobic group, weighted-vest group and control group. The exercise program performed by both the aerobic and weighted-vest group, consisted of 18 sessions of submaximal aerobic walking exercise on a treadmill three times a week, every other day, with each session lasting 30 min. The intensity of the exercise was increased gradually during the 6 weeks; specifically, 50% heart rate reserve (HRR) during the first 2 weeks, 55% HRR during the

second 2 weeks, and 60% HRR during the last 2 weeks. Heart rate, blood pressure, and electrocardiogram (ECG) were monitored throughout the course of the exercise program. In the weighted-vest group the initial inner weight of the vest was 4% of the individual's body weight and was gradually increased by 2% every 2 weeks based on the tolerance level of each subject. The control group was requested not to change their daily PA or dietary patterns during the 6 weeks. As a result, BALP and NTX decreased significantly in both exercise groups ($p < 0.05$). The changes in bone biomarker levels were significant between each exercise group compared to the control group, except for the ALP pre-post changes. Concerning the secondary outcome of balance assessed through the near tandem stand (NTS) and star-excursion (SE) test, the exercise groups increased significantly while the control group decreased ($p < 0.05$).

7.5 DISCUSSION

The present systematic review evaluates the effects of PA on bone biomarkers in the osteoporotic population and provides an outlook of their application to set up exercise programs.

Most of the articles included in the preliminary full text analysis from the database research involved osteopenic people without osteoporosis, and they did not meet the established inclusion criteria. For this reason, our findings focused on data from only three studies (Arazi, 2018; El-Mekawy, 2012; Roghani, 2012). Regarding the bone biomarkers assessment, all the studies investigated the serum ALP. Roghani et al. and El-Mekawy et al. both included serum calcium as an additional parameter, while Arazi et al. analyzed the 25-hydroxyvitamin D (25OHD).

All three studies included in our review reported a significant improvement in terms of bone biomarkers value in osteoporotic people participating in exercise interventions. The best effect in bone turnover was obtained with two different PA interventions including both aerobic and

weighted-vest aerobic training in the study by Roghani et al. In particular, the study showed that short term submaximal walking training wearing a weighted vest is effective for stimulating bone formation and decreasing bone resorption in postmenopausal women with OP.

According to more recent literature (Kuo, 2017; Nagy, 2020; Park, 2018) the most specific and sensitive biomarkers for osteoporosis management and the most accepted for monitoring drug therapy are CTX-1(bone resorption) and P1NP (bone formation). These two biomarkers were not investigated in any of the three studies analyzed. Roghani et al. evaluated BALP, a widely-used bone formation biomarker, and NTX, a promising marker of bone resorption. On the other hand, both El-Mekawy et al. and Arazi et al. investigated ALP, a non-specific bone turnover marker, even though widely applied in clinical diagnosis. These data hamper a robust evaluation of the findings.

Regarding quality assessment, the studies analyzed present further limitations due to the low quality. All three RCTs were scored as “Poor quality” according to the Cochrane Tool for Quality Assessment. In all the included studies, it was not possible to understand the methodology used for randomization and allocation concealment. Moreover, the three studies did not register the study protocol. Only Roghani et al. described specific methods to guarantee the sensitivity of outcomes assessment. Despite these limitations, Roghani et al. could be considered the most appropriate study with a lesser number of risks of bias.

As already mentioned in the *Introduction* of this article, OP has been increasingly studied over the years as it is a skeletal disease leading to structural deterioration of bone tissue and especially when related fractures occur, it significantly interferes with the QoL (Karlsson, 2020). Besides, concern has grown to identify effective strategies for managing OP.

Evidence has consistently proven the importance of regular participation in specific exercise programs to prevent and minimize the osteoporotic bone deterioration and its consequences on

health (Cosman, 2014; Choi, 2012; Todd, 2004). In this review BMD assessment and physical performance tests have been evaluated as secondary outcome. Roghani et al. showed that weighed-vest aerobic exercise is more effective for improving the balance of participants than simple aerobic training. The other two studies evaluated the effect of PA on BMD estimated with DXA. El-Mekawy et al. reported an increase in BMD at neck and lumbar spine with the highest score for the weight bearing exercise group, and the lowest recorded in the brisk walking group. Arazi et al. showed that the concurrent training-milk intervention significantly improved the BMD measured at lumbar spine and hips.

To date, no optimal exercise training for osteoporotic people has been established, but there is growing evidence supporting a multimodal approach that includes different types of exercise and training (Bonaiuti, 2002; Daly, 2019). Resistance training and weight-bearing impact exercises seem to be the most suitable and specific to reduce the risk of fracture, acting on the musculoskeletal system; however, the benefits depend on the frequency and intensity of training (Daly, 2019). Balance and mobility exercises are also widely used to increase functionality and reduce the risk of falls (Greenway, 2012). On the other hand, aerobic PA that does not include impact (*e.g.* cycling or swimming) has a weak effect on prevention related to bone loss, due to the low impact on the musculoskeletal apparatus, inadequate to gain a bone adaptation (Greenway, 2012). In spite of this, aerobic exercises have great benefits on the cardiovascular and metabolic apparatus and body composition of osteoporotic patients. In addition, exercise can help to achieve beneficial and significant effects on quality of life, balance, and functional mobility also in patients with osteoporosis-related vertebral fractures (Stanghelle, 2019; Marini, 2019). However, there is still no agreement on which type of exercise, in terms of intensity, frequency, duration, type and setting, is optimal and can affect bone metabolism in people with OP (Gibbs, 2019; Shojaa, 2020; Bragonzoni, 2020).

Biomarkers of bone metabolism, reflecting the cellular activity linked to the bone turnover process, could be a valid tool to assess the efficacy of PA and exercise programs in the osteoporotic population. Of note, some studies, which we excluded after our preliminary full-test analysis because they include non-osteoporotic study groups, monitored the benefits of physical activity on bone metabolism by the evaluation of P1NP and CTX, the two biomarkers considered specific for bone turnover (Manfrini, 2019; Dionello, 2016). Interestingly, an improvement in bone metabolism was induced by different types of exercise, for example a football training intervention (Bowtell, 2016; Skoradal, 2018). Moreover, Moreira et al. found a positive effect of high-intensity aquatic exercise on P1NP and CTX among people with osteoporosis and osteopenia on P1NP and CTX (Moreira, 2013). On the other hand, Wochna et al. did not obtain effects on CTX in healthy post-menopausal women performing aqua fitness activities in deep water (Wochna, 2019).

On the whole, the available scientific evidence points to a gap of knowledge regarding the potential of PA to influence biomarkers and does not allow an unequivocal conclusion about exercise programs suitable for people with OP. Despite the limitations reported in terms of the small sample size of the studies included and their quality and design, to our knowledge this systematic review is the first that investigates the effects of PA on bone biomarkers in the osteoporotic population. Hopefully, our findings can serve to summarize the existing literature on this topic and highlight the need for additional studies in this field.

Further research is required with a special focus on osteoporotic people, investigating the most specific bone biomarkers (CTX, P1NP) and following the guidelines on quality evidence to adopt more rigorous methodologies. In the future, bone turnover biomarkers could prove highly promising in the design and evaluation of exercise programs for OP interventions.

7.6 CONCLUSION

For the understanding of the physical activity role in osteoporosis management, a desired goal is to correlate the effects of exercise on bone turn-over biomarkers. Despite our comprehensive literature search, the level of available evidence does not allow us to establish a clear conclusion since the limit number of the studies and their poor quality according to Risk of Bias tool.

Although the results should be interpreted with caution, the reported data indicate the beneficial effect of exercise especially weighted and aerobic, in terms of improving bone formation biomarkers such as ALP and BALP, and decreasing bone resorption biomarkers such as NTX in the osteoporotic population. These findings could pave the way for planning future research to better assess the effectiveness of PA on bone metabolism. Further study population, performed with rigorous methodology, is needed to identify the most useful exercise able to modulate bone turnover biomarkers in people with osteoporosis.

8. STUDY V

CURRENT LACK OF EVIDENCE FOR AN EFFECT OF PHYSICAL ACTIVITY INTERVENTION COMBINED WITH PHARMACOLOGICAL TREATMENT ON BONE TURNOVER BIOMARKERS IN PEOPLE WITH OSTEOPENIA AND OSTEOPOROSIS: A SYSTEMATIC REVIEW

8.1 ABSTRACT

The process of bone loss occurs silently and progressively with age, often appearing as osteopenia or osteoporosis or related fractures. Given the rapid raise in disease burden and socio-economic costs of these conditions worldwide, drug therapy combined with physical activity can be a useful strategy and bone biomarkers, can represent a useful evaluation tool to assess their effects. The objective of this systematic review, conducted according to PRISMA statement, was to investigate the effects of physical activity interventions combined with drug treatments on bone biomarkers in people with osteopenia and osteoporosis. Through PubMed, Cochrane, Cinahl, Embase, Trip, a comprehensive literature search was performed. Each study's quality was assessed according to the Cochrane risk-of-bias tool. Out of 582 identified articles, 50 full texts were screened. Only one matched the eligibility criteria. The study, scored as high quality, showed, in both experimental and control groups, an increase of CTX and P1NP bone biomarkers, without statistically significant differences. Based on available evidence, no exhaustive conclusion can be drawn. However, this systematic review

critically analyses the literature, highlighting the knowledge gap on combined treatments efficacy assessed by bone biomarkers. Moreover, an outlook is provided for the planning of future studies.

8.2 INTRODUCTION

Undeniably, a gradual loss of bone mineral density (BMD) can lead to osteopenia and osteoporosis (OP). The World Health Organization (WHO) establish OP as a BMD T-score of 2.5 or lower at any one location or presenting a previous fragility fracture (Anonymous, 1993; Kanis, 1994). Whereas, according to the WHO criteria for assessment of dual X-ray absorptiometry (DXA) measurements, osteopenia is defined as a BMD between 1.0 and 2.5 SD below that of a "young normal" adult (Kanis, 1994; Karaguzel, 2010). Although the main burden of diseases occurs in post-menopausal women, bone loss represents an inevitable implication of aging in both women and men (Orwoll, 2013). The loss of BMD is due to an alteration of bone remodelling cycle. The balance between bone resorption and bone formation is determined by the process carried out by two cell types: osteoclast (responsible for secretion of proteolytic enzymes which digest bone matrix) and osteoblast (responsible for bone matrix synthesis). Generally, the process of bone loss occurs silently and progressively, besides there are no symptoms until the first fracture happens (Cooper, 2019). The risk of fracture increases with decreases in BMD, albeit most of osteoporotic fractures occur in osteopenic patients. Since, even though fracture risk is lower in osteopenia compared to OP, the osteopenic range present a higher number of subjects at risk (Eriksen, 2012). For these reasons, prevent the development of OP and related fractures is the main goal of screening and treating for osteopenia. Indeed, valid fracture prevention would have a great influence on patient's morbidity and a fundamental impact

on mortality. Worldwide in 2010, the number of individuals aged 50 years at high risk of osteoporotic fracture, was estimated at 158 million additionally, it is expected to double over the next 40 years (Odén, 2015). It is estimated that 75 million people in Europe, USA and Japan are affected by OP (Kanis, 2007). Given that, the economic burden of OP including long-term fracture care and pharmacological prevention represent an urgent issue worldwide bound to frightfully increase, a reasonable goal of treatment should be focused on reducing fractures (Hernlund, 2013; Pavone, 2017).

In view of this, multiple strategies are generally applied. Certainly, the first line is represented by pharmacological treatments which are prescribed to reduce the risk of fragility fractures. Another strategy can be represented by physical activity (PA), useful in prevention and treatment of bone loss and its consequences.

Many drugs with distinct mechanisms of action have been approved for the prevention and treatment of OP and are effective and available globally. Pharmacological therapy should be initiated also in patients with osteopenia (Pavone, 2017). These treatments must be prescribed in conjunction with calcium and vitamin D supplements, adequate lifestyle changes, appropriate nutrition and physical activity. As showed in Table 1, pharmacological treatments can be divided into two main categories: Anti-resorptive drugs, which reduce bone resorption preserving BMD, and Anabolic drugs aimed to stimulate bone formation, thereby increasing BMD (Cooper, 2019; Pavone, 207). Currently, alendronate, ibandronate, risedronate and zoledronic acid are the most common Bisphosphonates used for the treatment of OP worldwide (Bilezikian, 2018). Medications can have oral (daily, weekly, monthly dosing) or parental administration, dosing intervals of 6 months or longer, convenient for many patients improving short-term persistence with therapy. Among selective estrogen receptor modulators, raloxifene is widely used due to its favourable overall risk-benefit ratio (Kanis,

2003; Kanis, 2019), while teriparatide is the first approved anabolic drug for the treatment of OP (Pavone, 2017; IOF, 2020).

Table 1 Summary of pharmacological treatments currently available and their characteristics

Drug Class	Mechanism of Action	Characteristics	References
Anti-Resorptive			
Biphosphonates	Interaction with specific intracellular pathways in osteoclasts, resulting in cellular toxicity	First-line pharmacological therapy for most post-menopausal women at risk for fractures. Efficacy in reducing the risk of vertebral, non-vertebral and hip	Compston 2019; Pavone, 2017; Kanis, 2019; IOF, 2020
Denosumab	Inactivation of osteoclasts, reduction of osteoclasts' differentiation	Strong efficacy in reducing spine and hip fractures. First-line therapy in patients intolerant to oral BP or having renal failure	Compston 2019; Pavone, 2017; Kanis, 2019
Menopausal Hormone Therapy /Hormone Replacement Therapy	Increase of bone mineral density at all skeletal sites in early and late postmenopausal women	Therapy to prevent bone loss and reduce fracture risk in women at high risk of fracture when alternate therapies are not appropriate	Pavone, 2017; Kanis, 2019; IOF 2020

Selective Estrogen Receptor Modulators	Interaction with bone estrogen receptors, increasing trabecular bone mass	Contraindicated for prevention or treatment of OP in premenopausal women. Option treatment for younger postmenopausal women with osteopenia and osteoporosis without pronounced vasomotor menopausal symptoms, who are at risk for vertebral but not hip fractures	Pavone, 2017; Kanis, 2019; IOF, 2020.
Anabolic			
Teriparatide	Activation of osteoblasts by binding the parathyroid hormone receptor; stimulation of bone formation on active remodelling sites, particularly in the trabecular compartment	Daily administration of subcutaneous injection for 18–24 months reduces the risk of vertebral and non-vertebral fracture in osteoporotic women	Pavone, 2017; Kanis, 2019; IOF, 2020
Abaloparatide	Selective activation of the parathyroid hormone receptor	Increase of BMD at the lumbar spine, femoral neck, and total hip; reduced risk	Compston, 2019; IOF, 2020

		of new vertebral fractures in postmenopausal patients with osteoporosis. It has been approved only in the USA	
Romosozumab	Inhibition of sclerostin; Increase of bone formation and decrease of bone resorption	A starting treatment in women with high risk of fracture reduces the incidence of new vertebral fractures. The effects are reversible when the treatment is stopped, hence the therapy will need to be administered in sequence with an anti-resorptive drug	IOF, 2020

Note: BMD: Bone mineral density; OP: Osteoporosis.

PA plays a fundamental role in the prevention and treatment of many diseases, including OP (HHS, 2018; WHO, 2020). Indeed, PA can increase bone health during childhood and adolescence, while in the adulthood attenuate bone loss, improve or preserve muscle mass, strength, and power, overall reducing the risk of falls. However, not all exercise types are effective at attenuating all fracture risk factors (Bilezikian, 2018). As stated in the new WHO Guidelines on "Physical Activity and Sedentary Behaviour", there is high certainty evidence that higher levels of PA that combines balance, strength, gait, and functional training (e.g., multicomponent physical activity) are associated with a reduced rate of falls and risk of injury from falls in older adults. Furthermore, there is moderate certainty evidence that programmes involving multiple exercises may have significant effects on bone health and OP prevention (WHO, 2020). Also, whole-body vibration therapy (WBVT) is a form of passive activity that has demonstrated positive outcomes for a range of musculoskeletal disorders such as OP, although the evidence remains unclear due to the relatively limited and conflicting interventional studies in older adults with OP (McMillan, 2017). Just like an exercise program, WBVT has different applications methods. A review conducted by Weber-Rajek et al. shows that the vibration frequency set on whole-body vibration changes from 12 Hz to 90 Hz between different analysed studies (Weber-Rajek, 2015). Moreover, even if evidence suggested that WBVT might be a valid tool to improve the body composition, the results do not show significant differences due to different frequency levels, making it difficult to determine which frequency is most effective (Klarner, 2011).

Concerning the effects of exercise on BMD, research showed that free-living PA is associated with significant but modest improvements in BMD and, at least, seems to generate homeostatic influences on BMD during ageing (McMillan, 2017). Indeed, PA that enhances muscle strength also improve bone mass (in terms of BMD and content) and bone strength of the specific bones

stressed and may serve as a valuable measure to prevent, slow, or reverse the loss of bone mass (Agostini, 2018). In particular, PA contributes to bone mineralization not only via mechanotransduction but also inducing anabolic vascular effect, overall improving local tissue metabolism (Tong, 2019). For these reasons, PA interventions are recommended in the prevention and treatment of OP, also to decrease the risk of future bone fractures by being able to increase BMD, during all stages of life (Xu, 2016; Daly, 2017). The constant and balanced activityof both osteoblasts and osteoclasts plays a crucial role in regulating the bone remodelling process (IOF, 2020). The structural integrity of bone is maintained throughout life, so that most of the adult skeleton is replaced about every 10 years (Cooper, 2019).

At present, the diagnosis of health bone is generally based on quantitative analysis of BMD by DXA. Besides imaging technique, bone turnover biomarkers are measured as a helpful or complementary diagnostic data (Nagy, 2020; Brown, 2009). Currently, biomarkers represent products of bone proteins linked to bone formation and bone resorption, and they can reflect the physiological or pathological status of bone remodelling (Nagy, 2020; Kuo, 2017; Glendenning, 2018). OP is a silent disease characterized by bone fragility; thus, biomarkers have been proposed as indicators of the integrity of the whole skeleton to assess the early diagnosis of OP (Nagy, 2020; Brown, 2009; Kuo, 2017). For their ability to provide specific and dynamic indications on bone turn-over metabolism, biomarkers may also be powerful parameters for monitoring the effect of drug therapy in OP patients (Nagy, 2020; Migliorini, 2021). The benefits of exercise are recognized to reduce the impact of bone ageing, thus PA is considered a non-pharmacologic strategy for OP (Faienza, 2020). In the last decade, some studies have reported the capability of PA to influence the bone biomarker in osteoporotic patients (Arazi, 2018; Roghani, 2013; El-Mekawy, 2012). Recently, a crisis in the treatment of osteoporosis havebeen identified by researchers in this field, since both prescription and

compliance to pharmacological treatments have decreased in the last years (Khosla, 2016) . Similar trends have been observed for non-pharmacological treatment. The critical point lies in the need of finding ways to ensure that patients who need appropriate treatment for OP are not only prescribed effective medications but are also equipped with the information they need to make informed choices regarding their condition (Khosla, 2016). Therefore, multicomponent interventions may represent the key factor to improving prescription and compliance rates for OP management (McMillna, 2017).

The recent clinical guidelines for the prevention and treatment of osteopenia and OP stated that a global approach is needed in this scenario (Kanis, 2019; Tarantino, 2017; Compston, 2017). The basic components of a combined approach are behavioural interventions, PA program, pharmacological treatment and nutritional guidelines in individuals at high risk for fractures (Yates, 2015).

Nowadays, given the global burden of osteopenia and OP consequences, there is a growing interest in the field of combined treatment strategy to prevent and treat people suffering from these conditions. It has been a while since the situation has been assessed in this regard (Vestergaard, 2011). This would therefore appear to be a good time to take stock of the situation. Current evidence supports the potential for bone turnover markers to provide clinically useful information for OP management (Morris, 2017). Consequently, a focus to expand knowledge on the application of biomarkers to monitor the efficacy of OP multicomponent interventions is of great scientific interest. Moreover, in spite of the fact that drugs and physical activity efficacy has been widely confirmed, they are generally applied separately, not combined (Fischbacher, 2019).

In such a scenario, the goal of the present systematic review is to investigate and critically analyse, for the first time, the existing evidence on the effects of combined therapeutic

strategy based on pharmacological treatment and PA interventions measured by bone biomarkers in people with osteopenia and OP.

8.3 MATERIALS AND METHODS

8.3.1 Search Strategy and Data Sources

This systematic review was conducted in accordance with PRISMA recommendations and the criteria of the reporting of meta-analysis guidelines (Moher, 2009). The systematic review's protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration Number CRD42021230809 available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021230809 (accessed on 2 August 2021).

The following Patients, Interventions, Comparators and Outcomes (PICO) question was developed, addressing the primary search objective, through the following search terms: (P) Osteoporotic or osteopenic people, aged 45–80+; (I) Physical activity; (C) Standard pharmacological treatment and no exercise intervention; (O) The effect of physical activity interventions combined with pharmacological treatment on bone biomarkers.

A systematic literature search of MEDLINE (PubMed), Embase (Ovid), Cochrane Central Register of Controlled Trials (Central), and CINAHL (EBSCO) up to January 2021 was conducted to identify all published articles about the effect of physical activity combined with pharmacological treatment on bone biomarkers in people with osteopenia and OP.

We searched electronic databases, with a 10-year publication date limit, because we were interested in recent pharmacologic treatments and approaches. The following criteria were used to define our research: we included only Randomized Controlled Trial, Clinical Trial, Clinical Study, Comparative Study and Observational Study, with Full text available and conducted on

Human subjects. We defined a range of population aged 80 and over: 80+ years, Middle Aged + Aged: 45+ years, Middle Aged: 45–64 years, Aged: 65+ years.

Search strategies (strings adapted when necessary to fit the specific search requirements of each database) used the following Boolean expression: keywords and terms: ((Osteoporosis OR Osteoporoses OR Osteoporosis Post-Traumatic OR Osteoporosis Post Traumatic OR Post-Traumatic Osteoporoses OR Post-Traumatic Osteoporosis OR Osteo- porosis Senile OR Osteoporoses Senile OR Senile Osteoporoses OR Osteoporosis Involu- tional OR Senile Osteoporosis OR Osteoporosis Age-Related OR Osteoporosis Age Related OR Bone Loss Age-Related OR Age-Related Bone Loss OR Age-Related Bone Losses OR Bone Loss Age Related OR Bone Losses Age-Related OR Age-Related Osteoporosis OR Age Related Osteoporosis OR Age-Related Osteoporoses OR Osteoporoses Age-Related OR Osteopenia OR Osteopenias OR Low Bone Density OR Bone Density Low OR Low Bone Densities OR Low Bone Mineral Density) AND (Exercise OR Exercises OR Physical Activity OR Activities Physical OR Activity Physical OR Physical Activities OR Exercise Physical OR Exercises Physical OR Physical Exercise OR Physical Exercises OR Acute Exercise OR Acute Exercises OR Exercise Acute OR Exercises Acute OR Exercise Isometric OR Exercises Isometric OR Isometric Exercises OR Isometric Exercise OR Exercise Aerobic OR Aerobic Exercise OR Aerobic Exercises OR Exercises Aerobic OR Exercise Training OR Exercise Trainings OR Training Exercise OR Trainings Exercise) AND (anti resorptive therapy OR anti-resorptive therapies OR Therapy Drug OR Drug Therapies OR Therapies Drug OR Pharmacotherapy OR Pharmacotherapies) AND (Bone Biomarker OR Bone Biomarkers OR Remodeling Bone OR Bone Turnover OR Bone Turnovers OR Turnover Bone OR Turnovers Bone OR Bones and Bone Tissue OR Bones and Bone OR Bone Tissue OR Bone Tissues OR Tissue Bone OR Tissues Bone OR Bony Apophyses OR Apophyses Bony OR Bony Apophysis OR Apophysis Bony OR Condyle OR Condyles OR

Bones OR Bone OR Bone Resorptions OR Resorption Bone OR Resorptions Bone OR Osteoclastic Bone Loss OR Bone Loss Osteoclastic OR Bone Losses Osteoclastic OR Loss Osteoclastic Bone OR Losses Osteoclastic Bone OR Osteoclastic Bone Losses OR Bone Formation OR Osteogenesis)).

Moreover, we conducted a grey literature search of other papers, using Proquest and Medrxiv, and hand searches of key conference proceedings, journals, professional organizations' websites and guideline clearing houses. In accordance with the snowball technique, we examined references cited in the primary papers to identify additional papers.

8.3.2 INCLUSION AND EXCLUSION CRITERIA

The inclusion and exclusion criteria are described in Table 2.

Table 2 PICOST eligibility criteria.

Parameter	Inclusion Criteria	Exclusion Criteria
Population	OP people (T-score ≤ 2.5) Osteopenic people (1 < T-score < 2.5) Aged 45–80+	Population with secondary OP Absence of OP diagnosis Different diseases
Intervention	PA combined with pharmacological treatment	Absence of PA and pharmacological treatment
Comparator	Standard pharmacological treatment No exercise intervention	Participants receiving different PA
Outcome	Bone biomarkers evaluation, physical performance or other indices of physical performance	No information about bone biomarkers and PA
Study design	Experimental or observational study with original primary data	Study Protocol or other papers without original data
Timing	English Language 10-year publication date limit (January 2011)	Not in English Language Published before January 2011

NOTE: OP: osteoporosis; PA: Physical activity.

8.3.3DATA EXTRACTION AND QUALITY ASSESSMENT

On the basis of the above criteria (Table 2), reviewers screened the title and abstracts and selecting the eligible articles. Subsequently, potentially eligible full-text articles were

downloaded and, after duplicates were removed, extracted and reviewed independently by the four reviewers (SM, AM, GB, YL) using a pre-tested data extraction form following the methods provided by the Cochrane Reviewers' Handbook (Higgins, 2008). Finally, researchers extracted the data of the included studies. The details retrieved included: name of the first author, publication year, country, study design, population study with ages and number of experimental (EG) and control (CG) groups, sample size, type intensity and frequency of intervention, primary and secondary outcomes, results stratifying the studies for the different outcomes. Results were tabulated as mean SD where possible.

Any disagreement was settled by consensus (LD, LB, FM). When further information was needed, researchers contacted study authors by email (Greenhalgh, 2005).

Three researchers (SM, AM, GB) separately and blindly evaluated the selected studies for the risk of bias using the "Cochrane risk-of-bias tool for randomized trials" (Sterne, 2019). In order to resolve any quality score dispute, a fourth blind reviewer (YL) was involved as tiebreaker, when necessary. Risk of bias evaluation was made based on the primary outcome of our interest: bone turnover biomarkers, according to PRISMA guidelines (Moher, 2009). The Cochrane risk-of-bias tool for randomized controlled trials analyses seven bias categories: (1) random sequence generation and (2) allocation concealment (regarding bias of selection and allocation), (3) selective reporting for reporting bias, (4) blinding of participants and personal (performance bias due to knowledge of the allocated intervention), (5) blinding of outcome assessment for detection bias, (6) incomplete outcomes data for bias in attrition, and another category (7) named "other bias" based on the probable bias not covered in the other domains. Each category results in a value of high, low or unclear (when the authors did not provide enough evidence about the bias category) risk of bias. We supplied a score to convert the Cochrane risk of bias tool to AHRQ (Agency for Healthcare Research and Quality) standards

(Good, Fair and Poor).

8.4 RESULTS

8.4.1 STUDY SELECTION AND CHARACTERISTICS

Through databases browsed and hand search a total of 561 articles were identified (Figure 1). Additionally, 21 records were identified through other sources such as Proquest and medRxiv. As a result, the total number of records identified was 582. Papers were published from 2010 to 2020; 71 studies were excluded because duplicated, 461 studies were excluded following abstract and/or title review. Subsequently, we judged 50 records as relevant, 49 of which were subsequently excluded after a detailed full-text reading. The main causes of exclusion were related to the non-coherence with the aim of this study: the combined effect of pharmacological treatment and PA interventions on bone biomarkers in people with osteopenia and OP. In addition, most of the records (24%) were excluded due to the samples that did not match our inclusion criteria (population without primary OP). As a result, only one paper fully meeting the eligibility criteria, was finally included in the systematic review (Figure 1).

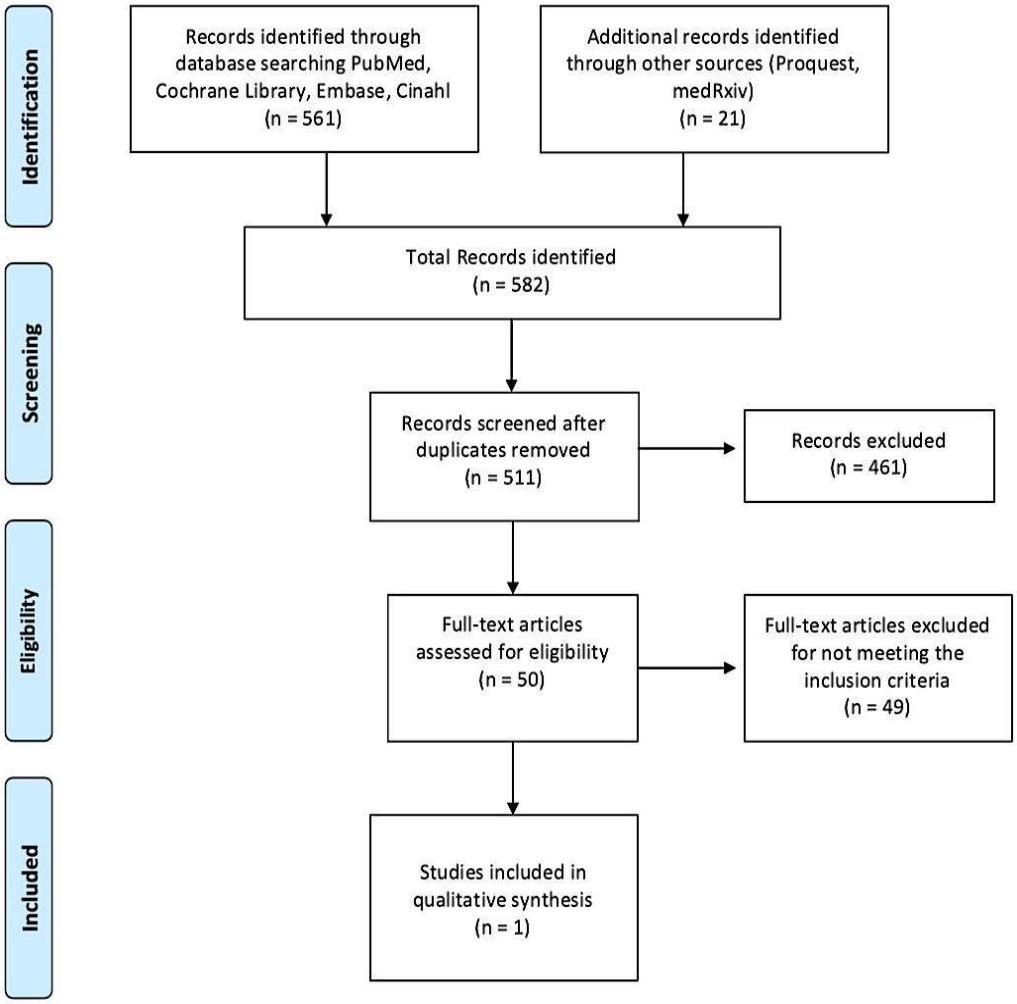


Figure 1 PRISMA flow diagram of the study selection.

8.4.2 RISK OF BIAS

Randomized controlled trial's quality was evaluated following the descriptive analysis. According to the Cochrane risk-of-bias tool for RCT we assessed the quality based on biomarkers outcome (Table 3). The RCT explained in detail the computer-generated web- based block-randomization methods used to assign eligible participants to the intervention or control group (item #1) and allocation of participants after baseline evaluation (item #2).

The selective reporting bias was assessed as clear due to availability of the study protocol

previously registered (item#3).

Table 3 - Quality assessment according to Cochrane Risk of Bias Tool for RCT

Studies	Random sequence	Allocation concealment	Selective reporting	Other bias	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data	Quality
Jepsen et al., 2019								Good

Note: green: criterion met, yellow: criterion unclear, red: criterion not met.

Since the intervention consisted in PA there was no blinding of participants (item #4), however, considering primary outcome of the presents systematic review, we judged that the biomarkers outcome, is not likely to be influenced by lack of blinding of participants. Concerning the blinding of outcome assessment (item #5), Jepsen et al. described methods and techniques used to ensure the sensitivity of outcome assessment (Jepsen, 2019). Regarding incomplete outcome data (item #6), we assessed low risk of bias because Jepsen et al. (Jepsen, 2019) reported all the outcomes data. Overall, the RCT included had no unclear criteria. Therefore, the risk of bias was scored as "Good quality".

8.4.3 DATA EXTRACTION

Table 4 shows the main characteristics and results of the included study, evaluating the effects of whole-body vibration (WBV) combined with teriparatide on bone biomarkers, BMD and bone mineral content (BMC) in postmenopausal women with severe OP. All participants received subcutaneous teriparatide treatment (20 µg/day) and were advised to take supplements with calcium and vitamin D according to Danish osteoporosis treatment guidelines. The type of

exercise training administered only to the experimental group was 12-min WBV training protocol previously tested in older population as safe, feasible and anabolic (Corrie, 2015). Since our aim was to assess the combined effects of pharmacological treatment and PA on bone biomarkers, we extracted the data considering the bone biomarkers analysis and other haematological parameters as primary outcome, whereas bone mineral density and bone microarchitecture assessment as secondary outcome. Regarding the bone biomarkers assessment, the study investigated the Procollagen type 1 N-terminal propeptide (P1NP), carboxy-terminal crosslinked telopeptide of type 1 collagen (CTX-1) which respectively reflect the anabolic and anti-resorptive metabolic effects and finally scerostin, a regulator of bone turnover.

Concerning the secondary outcomes, Jepsen et al. evaluated the response of bone mineral density estimated with DXA on the lumbar spine and total hip. Moreover, bone microarchitecture of non-dominant distal radius and tibia were included using HR-pQCT (XtremeCT; Scanco Medical, Zurich, Switzerland). After three and six months both groups showed a significant increase in CTX and P1NP but with no statically significant differences between groups.

Table 4 Study included in the review

Study	Study Design	Sample	Intervention	Outcomes	Results
Jepsen et al., 2019, Odense, Denmark	RCT	N:35 age:53–81 EG:17 CG:18	**Duration:** 12 weeks **Type of intervention:** EG: Whole-body vibration (WBV) training protocol 12 min x 3 session/week, rest ratio 1:1 min with a frequency of 30 Hz and amplitude of 1 mm + Teriparatide (20 μg/day) CG: Teriparatide (20 μg/day)	**Primary outcome**: CTX, P1NP Sclerostin **Secondary outcome**: BMD lumbar spine (L1-L4) and total hip, bone microarchitecture distal radius and tibia	**Primary outcome results** **Statistically significant improvement in CTX:** EG: $p < 0.05$ CG: $p < 0.05$ **Statistically significant improvement in P1NP:** EG: $p < 0.05$ CG: $p < 0.05$ **No statistically significant improvement in Sclerostin** **Secondary outcome results** **Statistically significant improvement in BMD lumbar spine of both group at 6 and 12 months** EG: 6.47% ± 3.40; 8.90% ± 5.48 CG: 3.48% ± 4.39; 6.65% ± 5.57 **No statistically significant improvement in BMD total hip** **No statistically significant improvement in bone microarchitecture**

8.5 DISCUSSION

Osteoporosis is a widespread bone illness considered as a more severe form of osteopenia. Nevertheless, osteopenia can be just as dangerous as OP especially when combined with other risk factors, such as smoking, a low-calcium diet, lack of vitamin D, hormonal changes due to age (especially menopause), and the presence of autoimmune conditions, such as rheumatoid arthritis (Bilezikian, 2018). The main consequences of these conditions are osteo- porotic fractures, which lead to a substantial raise in mortality and morbidity of patients, with an enormous and heavy impact on both the quality of life of people and the economy of the health care system (Sözen, 2017; Ensrud, 2000; Johnell, 2004). Moreover, pharmaco-economic considerations also play arole in this regard (Eriksen, 2012). Worse still, albeit the advances in pharmacotherapy, most of patients with osteopenia and OP are still not treated, and for whom begin to take medication, compliance to therapy is commonly below 50% at 1 to 2 years (Gillespie, 2009; Forsén, 2021). Furthermore, independently of bone tissue status, falls also represent a primary risk factor for osteoporotic fracture (Kistler-Fischbacher, 2021; Berry, 2008). Certainly, anabolic and antiresorptive bone drugs increase BMD reducing fracture risk, yet without preventing falls (Kistler-Fischbacher, 2021). Hence, in addition to pharmacological treatment, exercise can play a fundamental role since, alongside the strength effects on bone, it has the potential to improve muscle strength and balance, thus, also reducing the risk of falling (Sherrington, 2019). Overall, the combined treatment of both pharmacological therapy and PA intervention might represent a viable strategy. In this context, bone turnover biomarkers can be evaluated to monitor the benefits of combined therapy in patients with OP or osteopenia. Based on increasing professional and public awareness about chronic bone diseases, more scientific research to assess the combined treatment effects regarding OP or osteopenia, which are

silently disabling and causing detrimental effects on all the life components, would be expected, yet to date there still a huge gap in this field. This is demonstrated by the fact that only one study, published in the last 10 years, has been included in our systematic review with the aim to investigate the effects of combined therapeutic strategy based on pharmacological treatment and PA interventions on bone biomarkers in people with osteopenia or OP. Although we are aware that very strict inclusion/exclusion criteria have been established for the present systematic review, this was suitably planned to avoid any possible misinterpretation of the results. Moreover, the very strict PICOST methodology used was crucial in guaranteeing the quality of the review. A case in point is represented by the years range established. Though some trials in early 2000s has been conducted in this regard, they could not be included in our systematic review, due to the study design used which did not met our inclusion criteria (Uusi-Rasi, 2003; Newstead, 2004). Surprisingly, one of the main reasons for the records exclusion was related to the fact that, although most of the studies were based on osteoporotic population samples, the absence of any pharmacological treatment stood out among the inclusion criteria. This could be partly due to the differences among countries in terms of healthcare systems and therapeutic strategies in this regard. Considering the existing evidence, it can be postulated that, although the guidelines for management and treatment of osteopenia and OP are widely accepted and recommended (Kendler, 2016), there are certain difficulties associated with the implementation of pharmacological plans.

To note, in the RCT included in the review, the current standard recommended bone biomarkers CTX (resorption marker) and P1NP (formation marker) have been evaluated to investigate the combined effect of twelve-months WBV and teriparatide compared to teriparatide alone in postmenopausal women with severe OP. The findings have indicated an improvement during the study follow-up, but no additional effect of the combined

treatment emerged. Interestingly, the authors have shown a similar improvement in BMD lumbar spine detected by DXA, which represents a secondary outcome result of our review. This can be considered an encouraging finding to understand the ability of bone biomarkers to monitor the effects of the strategies to treat OP and osteopenia.

Nowadays, OP has become a major public health issue worldwide given its healthcare cost, and there is a growing interest in multimodal care approaches including not only drug treatments but also exercise (Kendler, 2016). Indeed, PA interventions are a cost-effective, feasible and effective way to ameliorate these conditions, but to date, they are still not enough applied and evaluated (Kistler-Fischbacher, 2021). Indeed, even though it is well known that exercise-induced mechanical load on the skeleton can improve bone strength by inducing adaptations in bone mass, a strong conclusion regarding the effects of exercise, in terms of intensity- duration-frequency of training, on bone tissue in osteoporotic people, has not yet been established (Kistler-Fischbacher, 2021). Also, the only study included in our review, albeit of high quality, applied a combined intervention including teriparatide and WBV which envisages the use of a tool instead of a proper PA program (Jepsen, 2019). Based on the available evidence analysed in the review, it seems that the combined strategies are scarcely applied to treat OP and osteopenia and worse still, poorly evaluated. Consistent with this, the challenge can be related to the limitations of currently available tools for monitoring these bone diseases.

A case in point is represented by bone turnover biomarkers. As already stated above in the "introduction" section, biomarkers are suitable tools to assess the dynamic metabolic bone status. Therefore, bone turnover biomarkers have become promising clinical parameters in the drug monitoring and management of OP (Nagy, 2020). In the meantime, data on the utility of biomarkers to assess the effects of exercise, alone or combined with drugs, on the

bone tissue in patients with OP are still insufficient. In this scenario, our PICOST question might have been pretentious. However, we believe that our findings can be useful to highlight the gap in the literature, which needs to be bridged to understand the potential of biomarkers in the planning and evaluation of PA intervention for osteoporosis treatment. The identification of effective multiple intervention strategies can improve the quality of life of people affected by osteopenia and osteoporosis and reduce the burden of socio-economic costs associated with their treatment.

8.6 CONCLUSION

The possibility of estimating the effectiveness of therapeutic strategies aimed at treating OP is a pressing need for public health. Bone turnover biomarkers are being usedfor the diagnosis and management of OP and osteopenia. Our review aimed to evaluate the ability of bone biomarkers to assess not only the effects of drug therapy but also of PA interventions which are increasingly included as a positive additional strategy for the prevention and treatment of osteopenia and osteoporosis. Our analysis of the available literature has not reached a conclusion related to the review question. However, despite this, the article meeting the inclusion criteria was of high quality according to the Risk of Bias tool. For this reason, these findings may help to speculate considering bone biomarkers as a possible strategy to assess the combined effects of both drug therapy and PA treatments, albeit the result should be undoubtedly interpreted with caution. In addition, our review reveals the difficulty in assessing an interaction of drug therapy and PA, as most of the bone-target exercise intervention studies did not included patients taking pharmacological treatment. Future research is needed to fill this knowledge gap. The study of bone biomarkers to assess the effects of combined treatment (drug and PA) on bone tissue status

is in its infancy. The study design of future RCTs should divide patients with OP or osteopenia into different experimental groups to evaluate the efficacy of the administration of drugs, PA or combined therapy. Moreover, in the planning of further studies the choice of the exercise training, in terms of intensity, duration and frequency, should have a key role, because the applied PA should be able to develop an adaptive response in bone. The availability of robust and clear evidence on applications of biomarkers will help healthcare professionals in their decision-making processes to plan interventions and guidelines for the treatment of OP and osteopenia. Overall, given the novel and unexplored features of this topic, as showed by the present systematic review, further investigations in this field are crucial to reduce the burden of socio-economic costs and to improve the health status and quality of life in people with osteopenia and OP.

9. CONCLUSION AND FUTURE DIRECTIONS

The field of osseointegration has existed for almost 30 years and now appears to be on the verge of greater acceptance and widespread implementation. Beyond providing an excellent mobility solution for an expanding spectrum of long bone amputees, some patients with a hip disarticulation, hemipelvectomy, or flail arm due to brachial plexus avulsion have already had their mobility or quality of life improved by relatively simple technical improvisations to the established fundamentals of osseointegration

The osseointegration seems ready to improve the lives of millions of amputees dramatically around the world.

Osseointegration for the reconstruction of the amputated limb appears to now be poised to follow a trajectory similar to that demonstrated by total joint arthroplasty, which gained universal acceptance and then underwent widespread adoption globally. As the concepts and principles guiding surgical techniques and implant technology become further established and more uniform, the surgeons and other clinicians providing care and the patients benefiting most from this procedure can become even more diverse.

The present thesis aimed to investigate in depth the main strengths and problems of an osseointegrated prosthesis and the role that physical activity, and movement in general, have on a patient with an osseointegrated prosthesis. For this reason, a kinematic gait analysis was performed on a patient before and after osseointegration, and a literature review on bone density changes in subjects with amputation was performed. Then, identify the possibilities for improving bone quality through a review of the literature on currently existing external devices that provide bone mechanical stimulation, and on the influence of physical activity on bone biomarkers.

The case report study found a strong difference in terms of spatiotemporal parameters and joint kinematics between osseointegrated and socket-type prostheses. In particular, after the surgery, patient showed a progressive improvement in the gait with a symmetry between the amputated and sound limb, close to non-pathological gait. An analysis of the literature shows that amputation can have consequences on bone quality in an amputated person, considering both the comparison with a healthy person and the comparison between the healthy limb and the amputated limb. The study also suggests focusing future research on possible mechanical bone stimulation to influence bone quality in patients with lower limb amputation. Such technologies which affect bone quality have been identified, in particular ultrasounds and lasers are the most studied in the literature. These devices are promising as they offer a non-invasive approach but these fields should be still studied to provide a gold-standard approach to the use of external devices for the quality of bone improvements. Physical activity demonstrates possible benefits in terms of improving bone formation and decreasing bone resorption biomarkers in case of low bone mineral density. However, the literature highlights the knowledge gap on combined treatments of physical activity and pharmacological therapy.

Future studies could incorporate new evaluations to provide a comprehensive understanding of osseointegration technique. The use of kinetic data in the evaluation of gait analysis may be an important contribution. For example, the use of computerized underfoot baropodometry could be used outdoors on different natural paths, thus excluding the biases given by a laboratory baropodometric system.

The kinematic and kinetic data could give indications about:

- Physical activity programs before surgery, with the aim to improve the range of motion of the hip and the functionality of the residual muscles;

- Physical activity programs after the rehabilitation phase, with the aim to allow a rapid recovery and prosthesis use, improve body control and, in general, provide the benefits that physical activity produces;
- The possibility of improving prosthetic components, materials, etc.

An interesting aspect is the analysis of the costs and economic impact that the osseointegration technique may have on the Italian health care system and the comparison with European countries that have been implementing this technique for some years. In this regard, given the impact of osseointegration on the quality of life and the possibility of an increase in the number of eligible patients, it is essential for the Public Administration to prepare a DRG "Diagnosis Related Group" to make the intervention available to all those who can benefit from it. Finally, future goals will be the promotion of physical activity for individuals with lower limb amputation, both invasive and osseointegrated, to be administered even at the end of rehabilitation treatment. Such promotion should be aimed not only at those directly affected but also at the sports community, decision makers, and all stakeholders in health care.

One aspect that should not be underestimated is the importance of communication between health and non-health professionals in terms of information and advice given to patients. To improve these interactions, it is suggested that physicians and other health care professionals provide clear and simple explanations of the potentials of osseointegration treatment as well as its disadvantages. Increased awareness could encourage people with amputation to consider this new treatment as an alternative in case of serious dissatisfaction with the traditional prosthetic system.

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ANNEX

Annex 1 – Surgical protocol of osseointegration technique; applied to transfemoral amputation patient;

Annex 2 – Patient Assessment Guide;

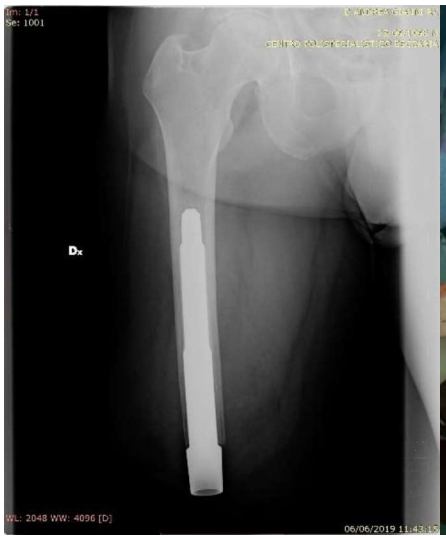
Annex 3 - Prosthetic protocol for amputated limb treated with osseointegrated implant;

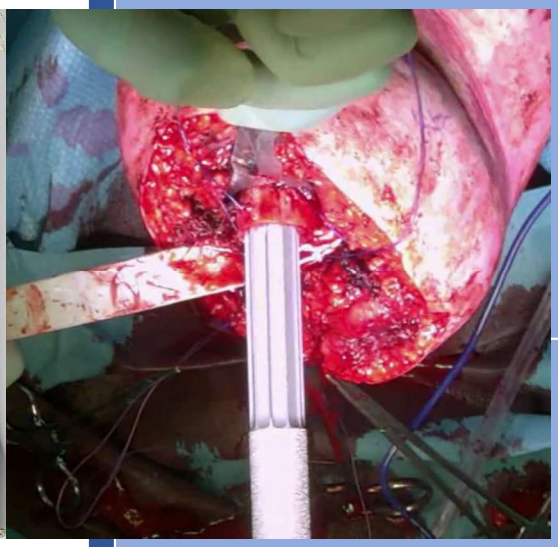
Annex 4 - Ostomy care and hygiene protocol for osseointegrated prosthesis;

Annex 5 - Rehabilitation protocol of the patient with osseointegrated transfemoral prosthesis

ANNEX 1

PROTOCOLLO CHIRURGICO DELLA TECNICA DI OSTEOINTEGRAZIONE APPLICATA AL PAZIENTE CON AMPUTAZIONE TRANSFEMORALE





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SOMMARIO

INTRODUZIONE

La protesi femorale per osteointegrazione è un sistema modulare di fissazione ossea endomidollare che permette la connessione, mediante un apposito adattatore transcutaneo, di una protesi d'arto inferiore direttamente all'osso femorale residuo di pazienti con amputazione transfemorale.

La protesi femorale per osteointegrazione comprende i seguenti componenti (Figura 1):

1. Stelo femorale (di tipo *press-fit*, nella fattispecie utilizzata nel progetto di ricerca METACOS) dotato di vite prossimale (diametri disponibili da 15 a 22 mm; lunghezza 140 mm);
2. Tappo di guarigione;
3. Adattatore transcutaneo a doppio cono, o *dual cone adapter* (lunghezze disponibili da 70 mm a 110 mm, step di 10 mm);
4. Vite di bloccaggio.

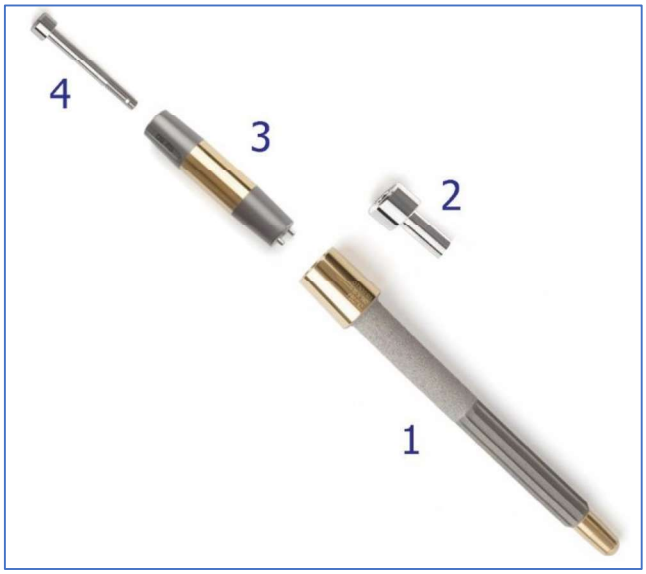


Figura 1 – La protesi femorale osteointegrata.
Dall'alto verso il basso: *vite di bloccaggio (4), adattatore transcutaneo a doppio cono (3), stelo femorale press-fit dotato di vite prossimale (1).* A fianco: *tappo di guarigione (2).*

PLANNING PRE-OPERATORIO

Lo scopo della pianificazione preoperatoria è quello di ricavare le misure necessarie al fine di poter scegliere il diametro dello stelo femorale e la lunghezza dell'adattatore a doppio cono che meglio si adattano al paziente. In tal modo, è possibile far coincidere l'asse di flessione del ginocchio della protesi esterna con il centro rotazionale del ginocchio dell'arto controlaterale, garantendo un risultato funzionale ed estetico ottimale.

SCELTA DEL DIAMETRO DELLO STELO FEMORALE

Il diametro dello stelo femorale da impiantare viene pianificato su una radiografia panoramica degli arti inferiori in ortostatismo (con calibrazione e con protesi esterna indossata), mediante software per visualizzazioni immagini DICOM. In particolare, viene misurato il diametro del canale endomidollare su due proiezioni ortogonali a livello del suo punto più stretto. Viene inoltre valutato lo spessore dell'osso corticale per stimare la quantità di bone stock residuo dopo la raspatura del canale. Tali misurazioni permettono di prevedere, con un margine di errore di ± 1 taglia, il diametro dello stelo da impiantare. In ogni caso è opportuno che tutte le taglie dello stelo femorale siano disponibili al momento dell'intervento chirurgico, nel caso in cui il diametro stimato nel planning non garantisca la fissazione primaria ottimale del dispositivo press-fit. La misurazione del canale endomidollare può anche essere eseguita con maggiore accuratezza sulla TC, ma data la maggior esposizione alle radiazioni, tale metodica viene utilizzata solamente nei monconi corti che necessitino di impianto custom o in caso di particolari alterazioni anatomiche.

REGOLARIZZAZIONE DEL MONCONE FEMORALE DISTALE

Dalla radiografia è possibile, inoltre, pianificare un'eventuale regolarizzazione del femore distale, che si rende necessaria in due casi: nel caso in cui il profilo osseo distale sia irregolare (condizione frequente, data dalla formazione del callo osseo a seguito dell'amputazione) e/o in alcuni casi di amputazione distale (terzo medio distale) in cui la lunghezza del moncone osseo sia tale da non consentire il corretto posizionamento del centro di rotazione del ginocchio protesico anche utilizzando un adattatore transcutaneo di lunghezza minima. Nel

primo caso si rende necessario solamente regolarizzare l'apice del moncone, senza alterarne drasticamente la lunghezza.

La regolarizzazione del femore residuo è consigliata qualora la distanza tra l'apice distale del moncone osseo e la joint line del ginocchio controlaterale non risulti sufficiente per potere ospitare le componenti protesiche esterne che si interpongono tra moncone e centro articolare del ginocchio, ovvero: la porzione esterna dell'adattatore a doppio cono, il connettore (*Heli connector,* nella fattispecie utilizzata) e la parte prossimale del ginocchio protesico.

Secondo le istruzioni per l'uso dell'impianto protesico utilizzato all'interno del progetto (OTN Implants BV, Arnhem, Netherlands), il femore deve essere regolarizzato in modo tale da garantire una distanza compresa tra 140 e 180 mm dall'estremità distale del moncone osseo alla rima articolare del ginocchio controlaterale. In base a tale distanza, viene scelta la lunghezza idonea dell'adattatore a doppio cono [consultare il paragrafo "*Pianificazione e scelta della misura dell'adattatore a doppio cono*"]. Nella scelta dell'adattatore a doppio cono, è da tenere in considerazione anche lo spessore del tessuto adiposo sottocutaneo, per garantire spazio sufficiente all'aggancio dell'*Heli connector* senza decubiti sulla cute.

Infine, bisogna conoscere il modello, le misure e il funzionamento del ginocchio protesico in uso al paziente avvalendosi di un Tecnico Ortopedico con esperienza nel settore.

PIANIFICAZIONE E SCELTA DELLA MISURA DELL'ADATTATORE A DOPPIO CONO

La pianificazione della lunghezza dell'adattatore a doppio cono viene eseguita su una radiografia panoramica degli arti inferiori in ortostatismo (con protesi esterna indossata e con calibrazione) (Figura 2). Per una corretta pianificazione bisogna accettarsi che il bacino non sia inclinato sul piano frontale: per ridurre il rischio di dismetrie è preferibile, se possibile, far indossare al paziente la protesi esterna personale durante l'esecuzione della radiografia.

Figura 2 – Pianificazione pre-chirurgica mediante calibrazione e software specifico ortopedico.

Le lunghezze disponibili dell'adattatore a doppio cono sono pari a 70, 80, 90, 100 e 110 mm.

La misura dell'adattatore a doppio cono dev'essere stimata tenendo in considerazione 1) lo spessore del tessuto adiposo sottocutaneo, consentendo un adeguato distanziamento delle componenti protesiche esterne dalla la cute del moncone (la frizione ripetuta dei tessuti molli sulla protesi potrebbe infatti provocare abrasioni e lesioni da decubito), e 2) le misure delle componenti esterne di aggancio fino, al centro di rotazione dello specifico ginocchio protesico, in riferimento al centro di rotazione del ginocchio controlaterale l'amputazione.

Le estremità distali dell'adattatore a doppio cono si inseriscono a:

- Livello dell'estremità distale dello stelo per una profondità di circa 25 mm;
- Livello della porzione prossimale dell'*Heli connector*, per una profondità di circa 35 mm.

L'*Heli connector* è disponibile in una sola lunghezza (75 mm).

A seconda del ginocchio protesico in uso al paziente, l'ingombro della parte prossimale (da intendere come porzione al di sopra del centro articolare) può variare.

In conclusione, è necessario pianificare la scelta dell'adattatore a doppio cono tenendo in considerazione tutte le variabili sopra riportate, al fine di garantire il massimo comfort del paziente e uno schema del passo corretto.

INDICAZIONI PER PROTESI DI TIPO *CUSTOM*

Quando il femore risulta essere più corto di 140 mm dall'estremità distale del moncone osseo al piccolo trocantere è opportuno utilizzare una protesi di tipo *custom* (personalizzata sul paziente), composta da uno stelo femorale più corto e da una vite cefalica che si inserisce nel collo del femore. L'utilizzo di uno stelo femorale standard (da 140 mm) nei monconi corti potrebbe comportare la limitazione dell'osteosintesi in caso di future fratture del collo del femore e l'impossibilità di eseguire un'artroprotesi d'anca in caso di osteoartrosi dell'articolazione coxo-femorale.

TECNICA CHIRURGICA

INTRODUZIONE

L'intervento di impianto della protesi per osteointegrazione prevede due tempi chirurgici distinti (chiamati "step"), tra i quali intercorre un tempo di circa 60 giorni: tale intervallo permette la completa guarigione delle cicatrici chirurgiche e dei tessuti molli e l'iniziale osteointegrazione dello stelo femorale (di tipo *press-fit*) ed è fondamentale per potere intraprendere il percorso riabilitativo in maniera sicura.

È consigliato evitare di prolungare l'intervallo tra i due tempi chirurgici più del necessario, perché i processi fibrotici che si interpongono tra l'apice del moncone e la cute potrebbero rendere difficoltoso individuare il punto di repere per creare la stomia.

È opportuno, altresì, istruire il paziente sull'esecuzione di esercizi di stretching e rinforzo muscolare da svolgere a casa, in autonomia, nelle settimane che precedono l'operazione. Ciò permette di mantenere un moncone adeguatamente tonico, facilitando la ripresa funzionale nel post-operatorio.

STEP 1 (S1)

L'intervento di osteointegrazione viene eseguito in anestesia generale o spinale, associando una profilassi antibiotica per via endovenosa all'induzione (Cefazolina 2g o Clindamicina 600 mg). Il paziente viene posto in posizione supina sul tavolo operatorio. Si allestisce il campo sterile.

In seguito, vengono elencati i passaggi dell'intervento chirurgico:

1) Incidere la pelle e la fascia ed esporre la porzione distale del femore (Figura 3a e 3b);

2) Asportare il tessuto cicatriziale, identificare il nervo sciatico, asportare l'eventuale neuroma e accorciare il nervo (Figura 4a e 4b);

3) Regolarizzare il femore con una sega oscillante secondo quanto stabilito nel planning preoperatorio e rimuovere cute e tessuti molli ridondanti (Figura 5a e 5b);

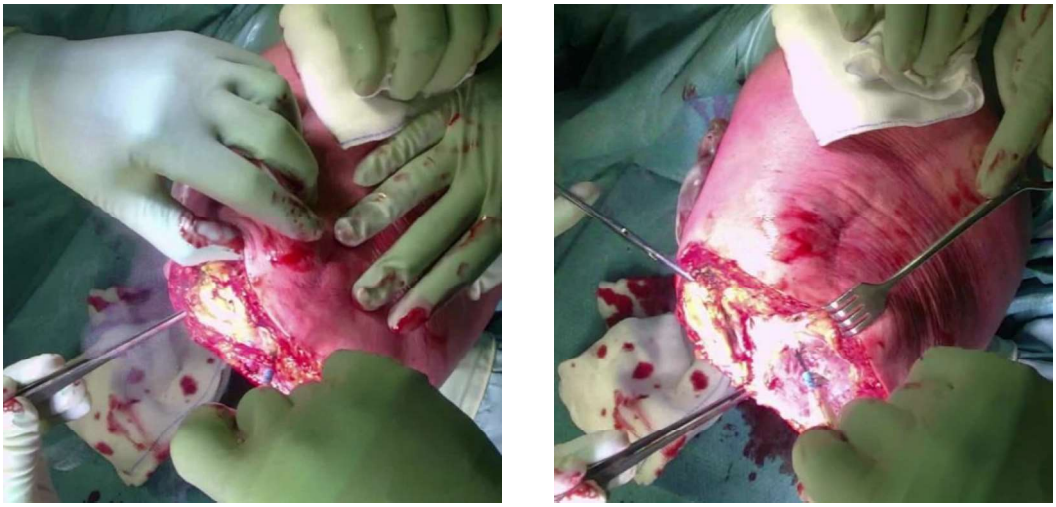


Figura 3 (a e b) – Incisione della cute e dei tessuti molli.

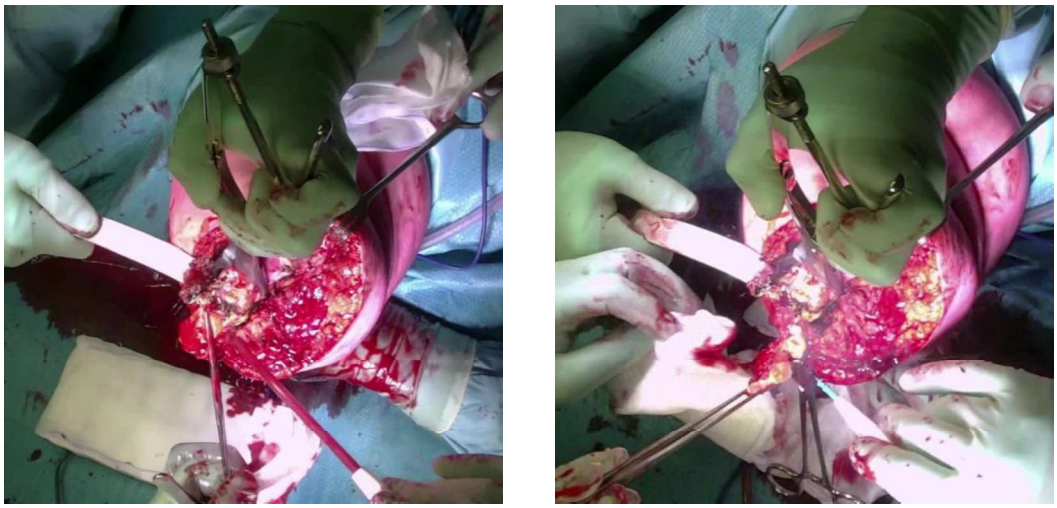


Figura 4 (a e b) – Identificazione e accorciamento del nervo sciatico.

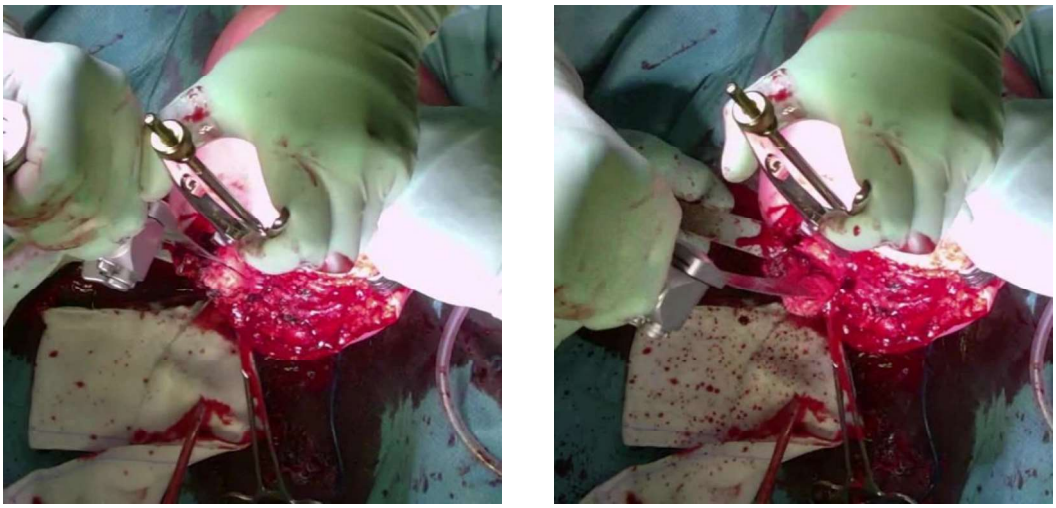


Figura 5 (a e b) – Regolarizzazione del moncone.

4) Inserire un filo guida con punta a sfera nella diafisi femorale. Alesare il canale midollare con alesatori standard flessibili non taglienti, sotto controllo ampliscopico. Conservare il tessuto osteo-midollare ottenuto con l'alesatura. Verrà applicato successivamente come innesto osseo. L'ultimo diametro dell'alesatore flessibile deve essere di 1mm inferiore rispetto al diametro dello stelo femorale pianificato (Figura 6a e 6b);

5) Raspare il canale endomidollare con le apposite raspe ricurve. Utilizzare le proiezioni laterali dell'ampliscopio per controllare il posizionamento della raspa ricurva rispetto all'ante-curvatura del femore. Raspare fino al raggiungimento del diametro pianificato dello stelo femorale (Figura 7a e 7b);

6) Utilizzare la fresa a tazza per creare un piano distale del femore esattamente perpendicolare al suo asse longitudinale.

   La dimensione della fresa a tazza viene scelta in base al diametro endomidollare femorale creato;

7) Contrassegnare sul moncone femorale la rotazione finale della raspa ricurva mediante l'apposito dispositivo di puntamento;

   Nota 1: la posizione della raspa ricurva deve corrispondere esattamente a quella dello stelo femorale che viene impiantato;

8) Realizzare quattro fori da 1,25 mm con filo di *Kirschner* per la successiva miodesi distale e, a tal fine, inserire le suture trans-ossee con filo riassorbibile del 4.0 (Figura 8a e 8b);

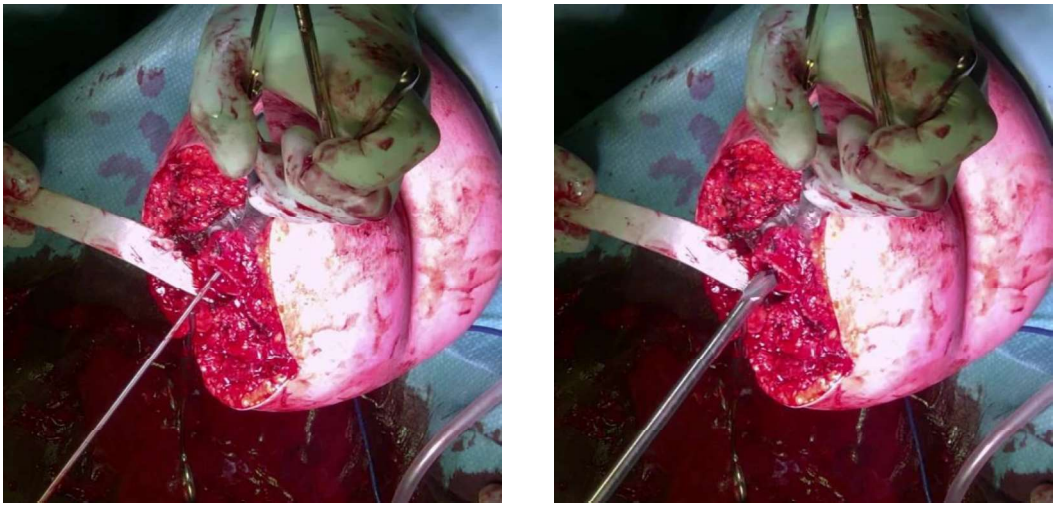


Figura 6 (a e b) – Alesatura del canale su filo guida.

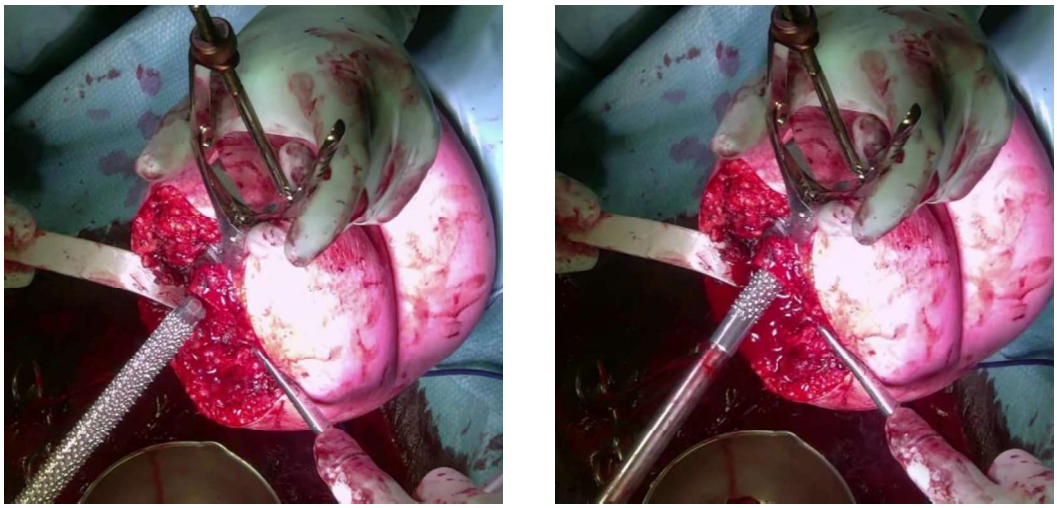


Figura 7 (a e b) – Lavorazione del canale endomidollare con raspe di misura crescente.

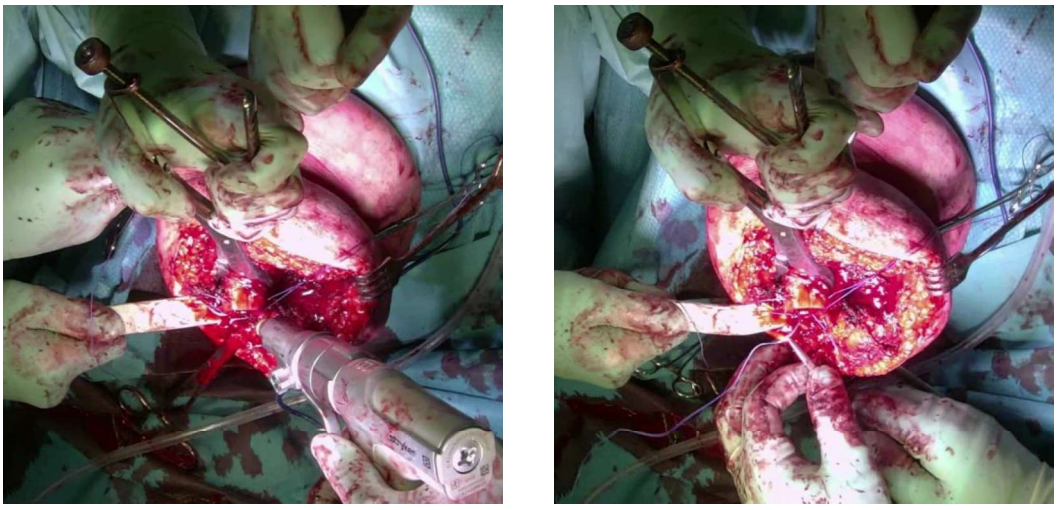


Figura 8 (a e b) – Realizzazione di suture transossee per la miodesi distale.

9) Serrare la vite sul cono morse prossimale dello stelo femorale con l'apposito cacciavite esagonale da 4.0 mm;

10) Inserire lo stelo femorale utilizzando l'apposito strumentario, assicurandosi di mantenere la corretta rotazione (Figura 9a e 9b). Applicare il tessuto osteo-midollare ottenuto dall'alesatura del canale come innesto osseo attorno alla zona di contatto distale tra lo stelo e la corticale ossea femorale;

Nota 2: il diametro dello stelo femorale selezionato deve corrispondere all'ultimo diametro della raspa ricurva utilizzata, al fine di poter ottenere una fissazione ottimale dell'impianto *press-fit*; il sottodimensionamento può portare a una mancata integrazione e il sovradimensionamento può portare a una frattura intraoperatoria del femore distale.

Nota 3: in caso di difficoltà nel posizionamento dell'impianto *press-fit* (ad esempio in caso di osso corticale eccessivamente rigido) può essere utilizzato l'installatore conico per facilitare l'avanzamento dello stelo.

Nota 4: evitare i contatti inutili con lo stelo femorale definitivo, compreso quello con guanti dell'operatore, che devono essere sostituiti prima dell'impianto.

11) Posizionare il tappo di guarigione all'interno del cono distale dello stelo femorale (Figura 10);

12) Effettuare abbondanti lavaggi con soluzione fisiologica;

13) Eseguire una miodesi distale suturando i gruppi muscolari all'osso utilizzando le suture trans-ossee precedentemente predisposte (Figura 11);

14) Identificare il sito in cui verrà eseguita la stomia e rimuovere il tessuto sottocutaneo in eccesso (Figura 12a e 12b);

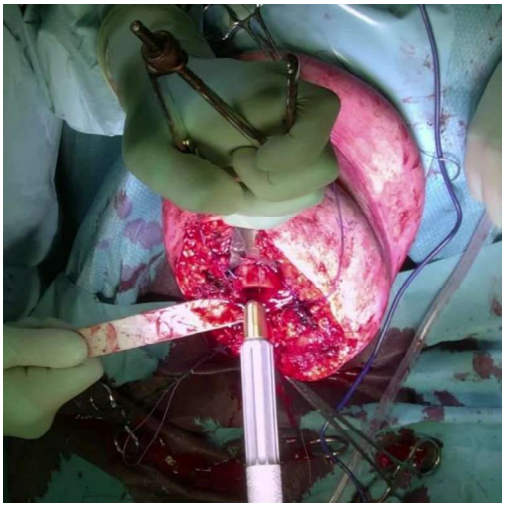
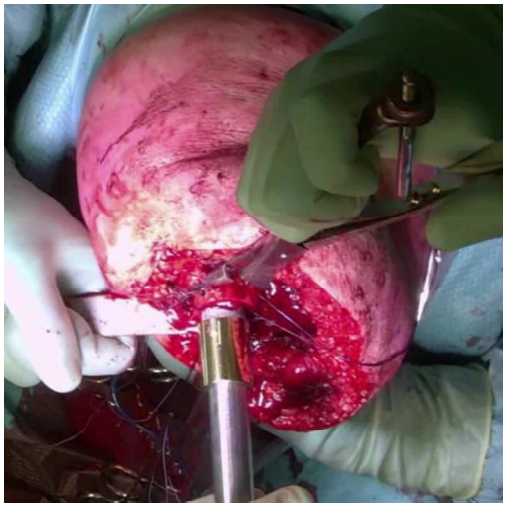



Figura 9 (a e b) – Impianto dello stelo femorale con tecnica *press-fit*.

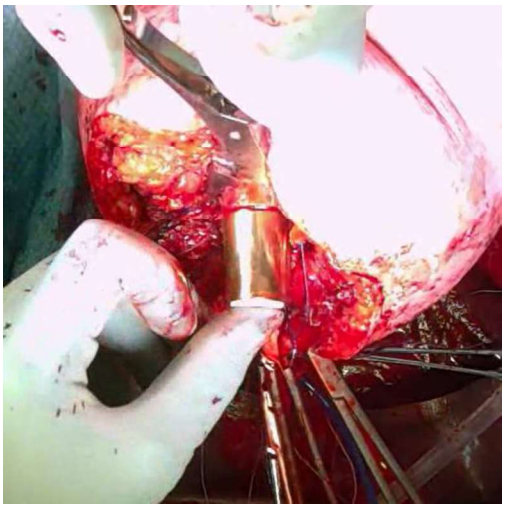
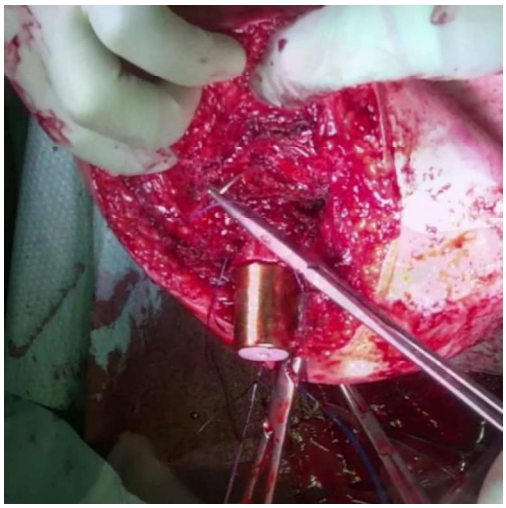



Figure 10 e 11 – Posizionamento del tappo di guarigione (a sinistra). Miodesi distale (a destra): i muscoli sono reinseriti sulla porzione distale del moncone osseo, attorno allo stelo.

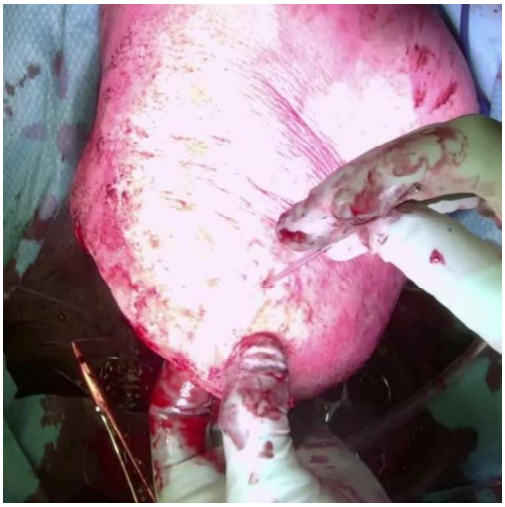
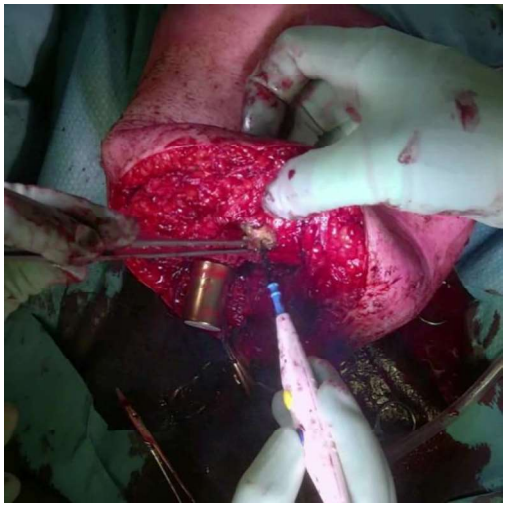



Figura 12 (a e b) – Individuazione della sede della stomia e rimozione del tessuto sottocutaneo in eccesso.

15) Inserire un catetere perinervoso per l'anestesia locale post-operatoria a livello del nervo sciatico (Figura 13a e 13b);

16) Suturare la ferita per piani secondo la tecnica standard del chirurgo (Figura 14a e 14b);

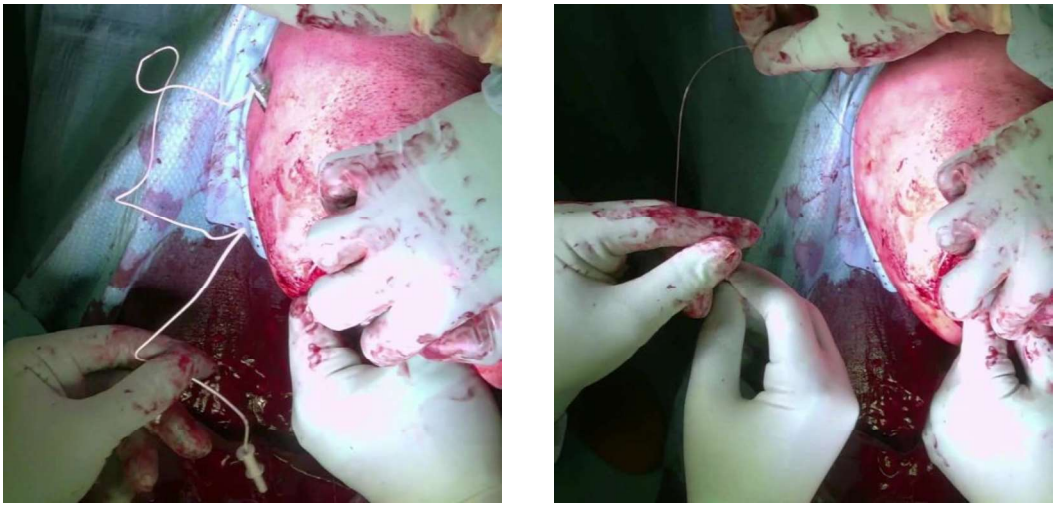


Figura 13 (a e b) – Inserimento di catetere perinervoso sciatico per il controllo del dolore post-operatorio.

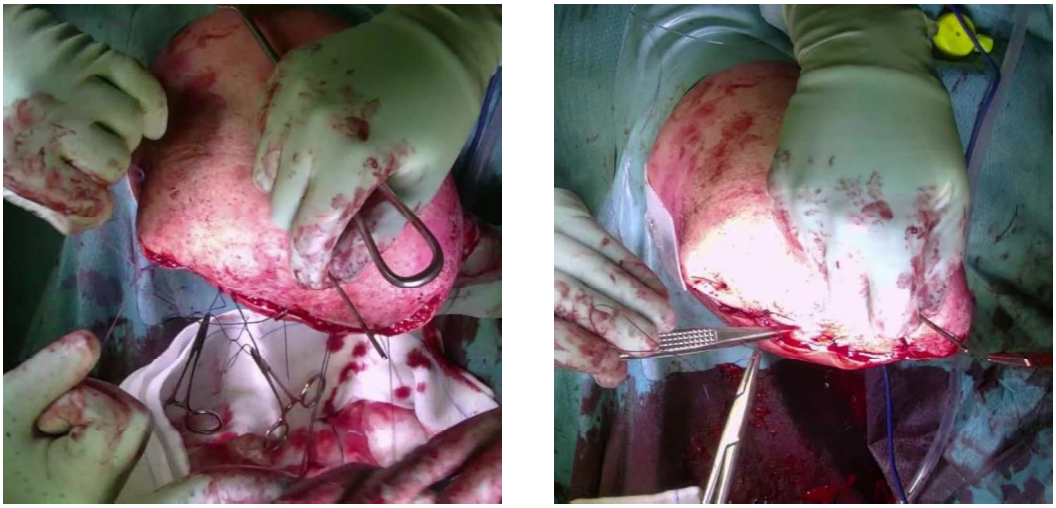
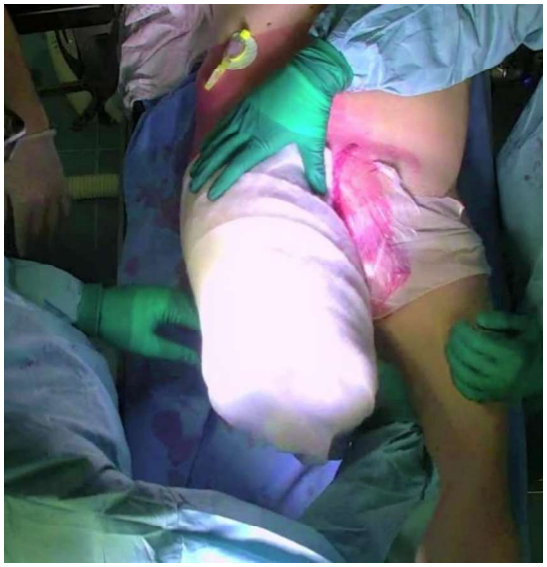


Figura 14 (a e b) – Sutura per piani.

17) Applicare una medicazione con bendaggio compressivo sul moncone (Figura 15);

18) Eseguire un controllo radiografico finale (Figura 16).



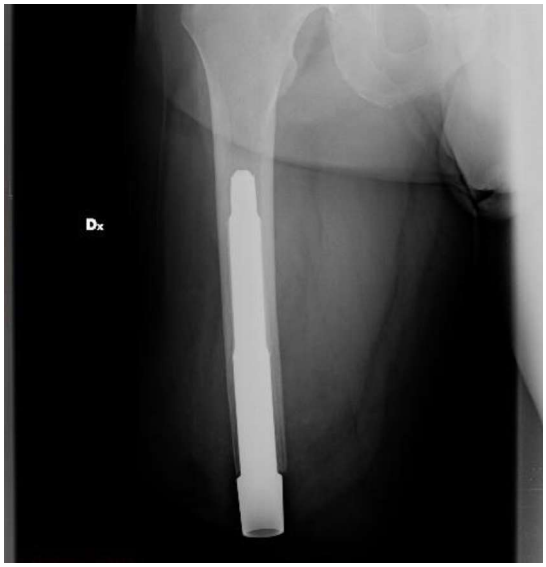


Figure 15 e 16 – Bendaggio compressivo e controllo radiografico post-operatorio.

STEP 2 (S2)

In seguito, vengono elencati i passaggi chirurgici del secondo step:

1. Localizzare il centro del tappo di guarigione tramite palpazione e posizionare per via percutanea un filo di *Kirschner* (K) nel tappo stesso (Figura17a e 17b);
2. Creare la stomia incidendo la cute utilizzando l'apposito *Corer* ed il filo di *Kirschner* come guida (Figura 18a e 18b);
3. Rimuovere il tappo di guarigione e lavare accuratamente la ferita e l'interno del cono morse, per rimuovere eventuale tessuto cicatriziale presente al suo interno (Figura 19a e 19b);
4. Verificare la dimensione dell'adattatore scelto in pianificazione rispetto allo spessore dei tessuti molli.

   Nota 5: è necessario che l'adattatore a doppio cono protruda per almeno 50 mm al di fuori della stomia cutanea;

5. Inserire l'adattatore e serrare la vite di bloccaggio utilizzando la chiave di controcoppia e l'apposita chiave a testa esagonale (Figura 20a e 20b).

   Nota 6: la chiave di controcoppia è uno strumento che previene le forze rotazionali sullo stelo durante il serraggio della vite di bloccaggio;

6. Per creare una connessione a cono morse stabile tra lo stelo femorale e l'adattatore, quest'ultimo è fissato all'interno del cono morse dello stelo femorale utilizzando il battitore e il martello (Figura 21a e 21b). Successivamente, la vite di bloccaggio viene serrata alla coppia di 19 Nm mediante la chiave dinamometrica e innesto a testa esagonale, utilizzando sempre la chiave di controcoppia.

EVENTUALE SOSTITUZIONE DELL'ADATTATORE A DOPPIO CONO

Nel caso in cui l'adattatore debba essere sostituito, può essere rimosso dal cono morse con l'apposito dispositivo di rimozione (estrattore) e i cilindri da 10 mm. A questo punto il nuovo adattatore viene inserito ripetendo i punti 5 e 6 descritti nel secondo step chirurgico.

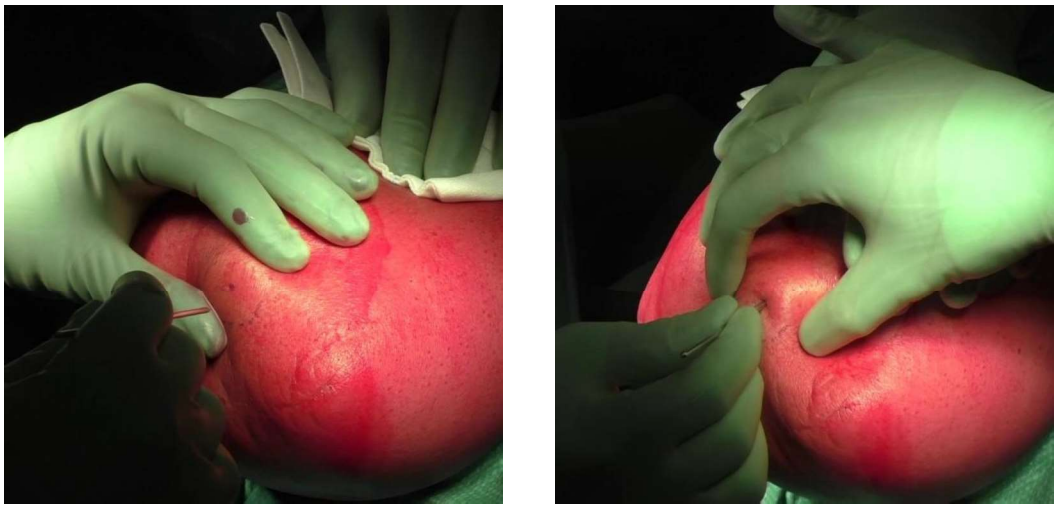


Figura 17 (a e b) – Localizzazione del tappo di guarigione posizionamento di un filo di *Kirschner*.

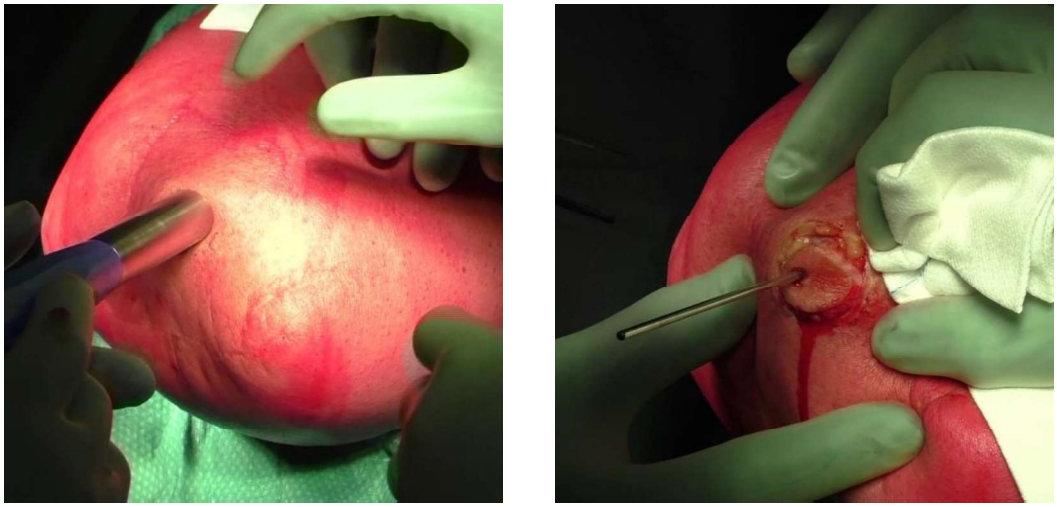


Figura 18 (a e b) – Creazione della stomia tramite apposito *Corer*.

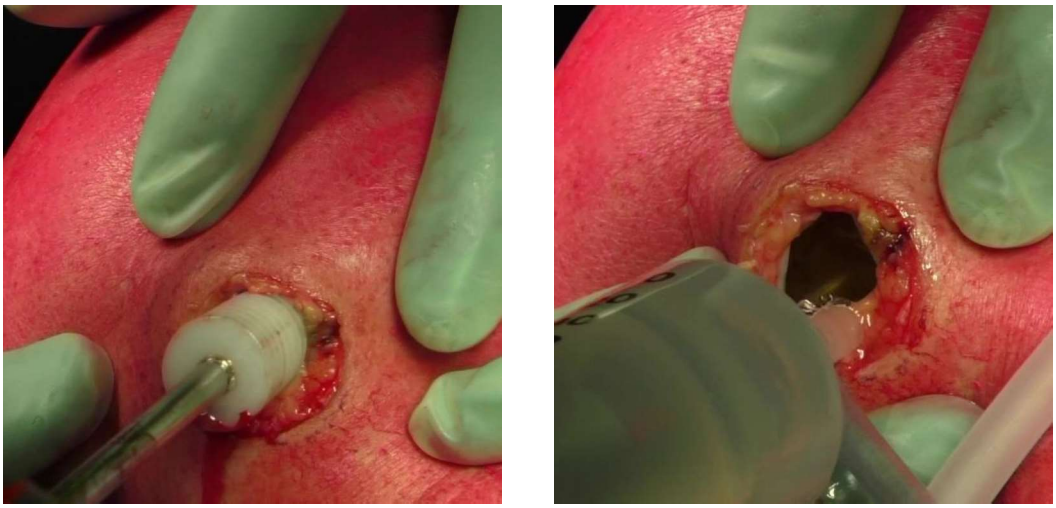


Figura 19 (a e b) – Rimozione del tappo di guarigione e lavaggio accurato della ferita.

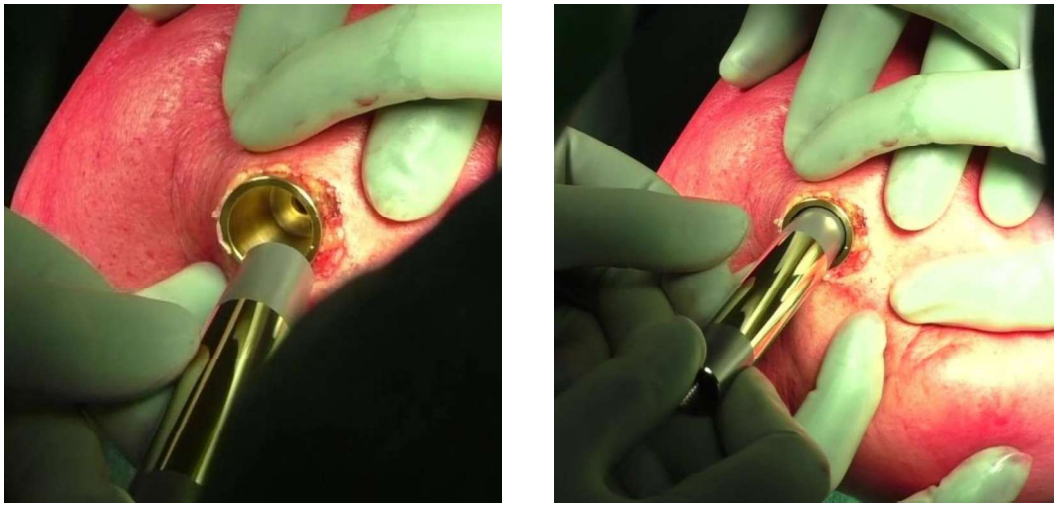


Figura 20 (a e b) – Impianto dell'adattatore a doppio cono (assicurandosi che sporga all'esterno per 50mm).

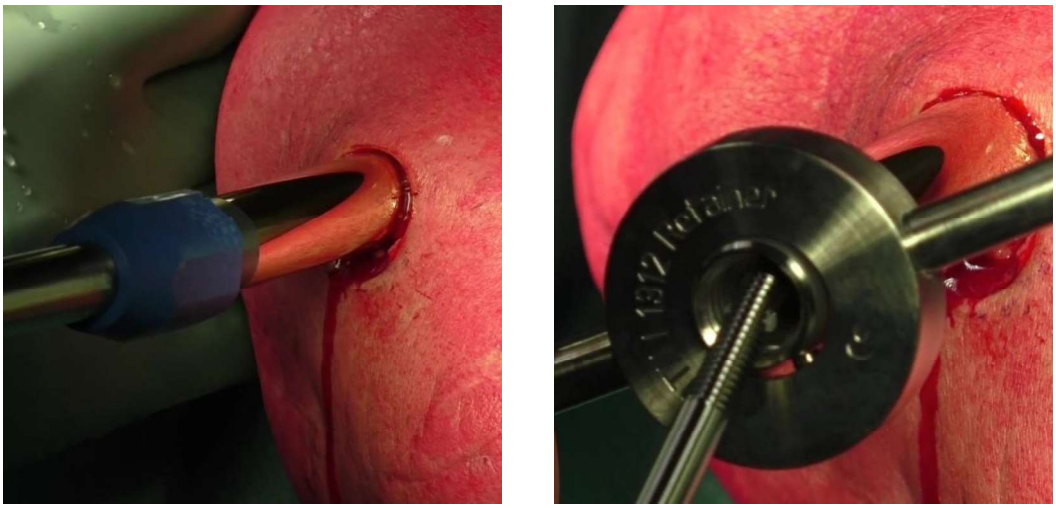
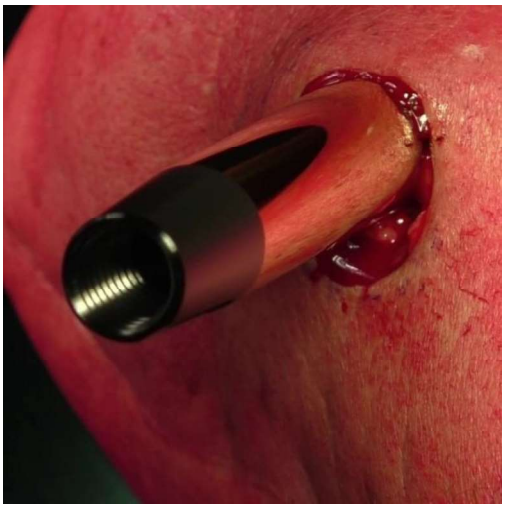
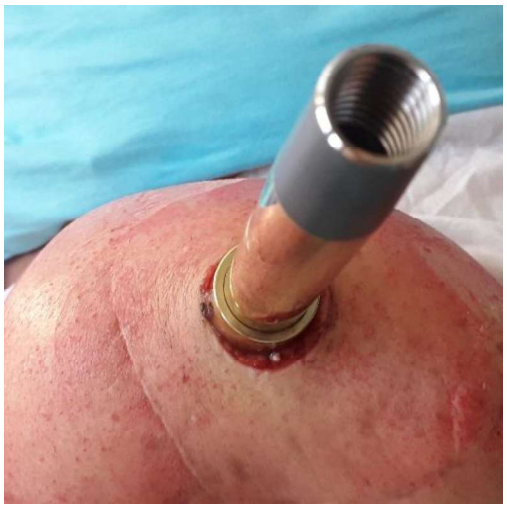


Figura 21 (a e b) – Fissaggio dell'adattatore con battitore e cacciavite utilizzando la chiave di controcoppia.

Risultato finale post-operatorio.





STRUMENTI CHIRURGICI

STRUMENTI CHIRURGICI UTILIZZATI NELLO STEP 1

STRUMENTAZIONE GENERALE

- Strumenti chirurgici di base per la chirurgia ortopedica (pinze, forbici, bisturi, bisturi monopolare e bipolare etc.);
- Sega oscillante;
- Trapano elettrico;
- Set di alesatori flessibili con filo guida a sfera;
- Martello da 1 Kg.

STRUMENTAZIONE RACCOMANDATA (FIGURA 23)

- Raspa ricurva taglia 15-22 (con incremento di 1 mm);
- Fresa a tazza taglia 13-21 (con incremento di 2 mm);
- Installatore;
- Installatore conico;
- Cacciavite Hexa 4 (cacciavite esagonale da 4.0mm);
- Dispositivo di regolazione.

STRUMENTI CHIRURGICI UTILIZZATI NELLO STEP 2

STRUMENTAZIONE GENERALE

- Fili di K. 2 mm;
- Martello da 1 Kg.

STRUMENTAZIONE RACCOMANDATA (FIGURA 24)

- *Corer* diametro 20 mm;
- Cacciavite *Hexa* 4 (cacciavite esagonale da 4.0mm);
- Punzone;

- Fermo;
- Dispositivo di rimozione;
- Cilindro;
- Chiave dinamometrica.

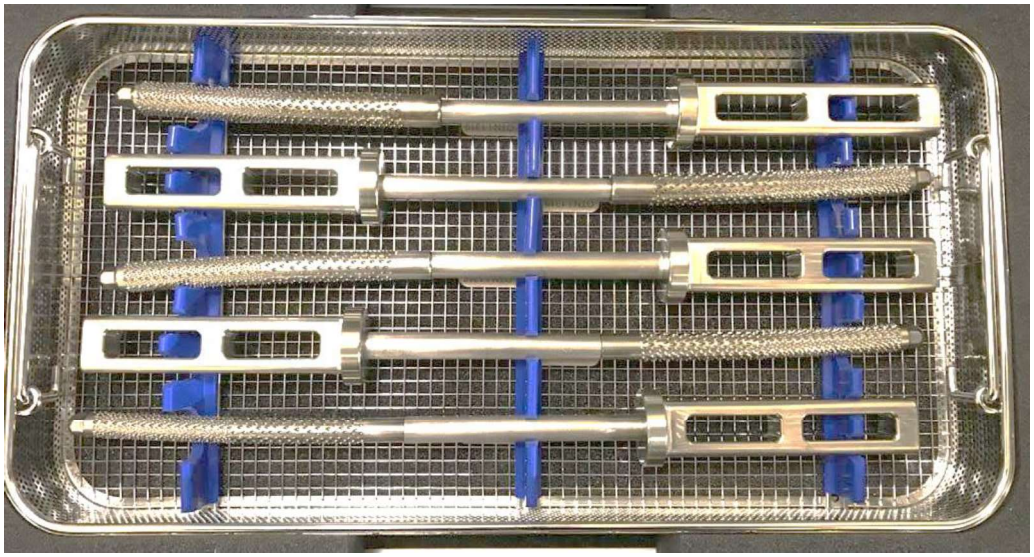


Figure 23 e 24 – Strumentario chirurgico utilizzato nei due interventi: raspe di misura crescente (sopra) e strumentario dedicato utilizzato sia nello Step 1 che nello Step 2 (sotto).

Si ringraziano della collaborazione

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ANNEX 2

Valutazione dei pazienti candidati all'intervento di osteointegrazione

Data, _____ / _____ / _____

- Prima dell'inizio della visita si consiglia di far compilare al paziente il questionario Q-TFA in allegato.

GENERALITÀ

Nome e cognome del paziente: _____

Data di nascita: _____ / _____ / _____

Luogo di nascita (città, nazione): _____

E-mail: _____@_____

Residente a _____

In Via _____

Recapito telefonico: _____

Data dell'amputazione: _____ / _____ / _____

Assistito: ☐ ASL ☐ Inail

Causa dell'amputazione:

- Trauma ☐
- Tumore ☐
- Infezione ☐
- Patologia vascolare ☐
- Diabete ☐
- Altro: _____

Altezza: _____ cm Peso: _____ kg

BMI _____

- Se si è selezionata come causa dell'amputazione "patologia vascolare" o "diabete", l'intervento di osteointegrazione è controindicato.

- Se si è selezionata come causa dell'amputazione "trauma" o "infezione", è possibile procedere con l'intervento sincerandosi prima che non ci sia ancora un episodio infettivo in atto.

- Se si è selezionata come causa dell'amputazione "tumore", l'intervento è indicato solamente se non ci sono cure chemioterapiche in corso e se non è stata eseguita radioterapia sull'arto amputato.

- Se il BMI risulta essere >25, è indicato perdere peso prima di sottoporsi all'intervento.

ANAMNESI FAMILIARE

- Allergie Sì: ☐ No: ☐ _____
- Diabete Sì: ☐ No: ☐ _____
- Malattie cardiovascolari Sì: ☐ No: ☐ _____
- Patologie ematologiche/coagulative Sì: ☐ No: ☐ _____
- Malattie ereditarie Sì: ☐ No: ☐ _____
- Malattie neoplastiche Sì: ☐ No: ☐ _____

- Il contenuto dell'anamnesi familiare non rappresenta, di per sé, un elemento di esclusione dall'intervento. È importante, tuttavia, prendere atto delle possibili patologie alle quali il paziente potrebbe andare incontro, al fine di adottare misure preventive, ove possibile.

ANAMNESI FISIOLOGICA

- Età: _____ anni
- Nascita da parto distocico Sì: ☐ No: ☐ _____
- Sviluppo psicofisico regolare Sì: ☐ No: ☐ _____
- Menarca Sì: ☐ No: ☐ _____
- Gravidanza Sì: ☐ No: ☐ _____
- Menopausa Sì: ☐ No: ☐ _____
- Alvo regolare Sì: ☐ No: ☐ _____
- Fumatore Sì: ☐ No: ☐ _____
- Uso di droghe Sì: ☐ No: ☐ _____
- Uso di alcool Sì: ☐ No: ☐ _____

- Se risulta una gravidanza in corso, l'intervento è momentaneamente sconsigliato.
- L'intervento di osteointegrazione è controindicato se:
  - l'età risulta <18 anni o non è ancora stata raggiunta la maturità ossea;
  - l'età risulta >70 anni;
  - risultano esserci problemi cognitivi che non permetterebbero una buona compliance;
  - vi è l'incapacità da parte del soggetto di astenersi dal fumo di sigaretta o dall'utilizzo di stupefacenti.

ANAMNESI PATOLOGICA REMOTA

- Malattie comuni dell'infanzia Sì: ☐ No: ☐ _____
- Malattie ereditarie Sì: ☐ No: ☐ _____
- Precedenti allergici Sì: ☐ No: ☐ _____
- Malattie respiratorie Sì: ☐ No: ☐ _____
- Malattie cardiocircolatorie Sì: ☐ No: ☐ _____
- Malattie vascolari (agli arti inferiori) Sì: ☐ No: ☐ _____
- Malattie ematologiche/coagulative Sì: ☐ No: ☐ _____
- Precedenti TVP/TEP Sì: ☐ No: ☐ _____
- Malattie dell'apparato digerente Sì: ☐ No: ☐ _____
- Malattie renali o vie urinarie Sì: ☐ No: ☐ _____
- Malattie metaboliche Sì: ☐ No: ☐ _____
- Diabete Sì: ☐ No: ☐
  Se sì: tipo 1 ☐ tipo 2 ☐
- Malattie neoplastiche Sì: ☐ No: ☐ _____
- Malattie infettive Sì: ☐ No: ☐ _____
- Malattie neurologiche Sì: ☐ No: ☐ _____
- Malattie dell'apparato locomotore Sì: ☐ No: ☐ _____
- Malattie cutanee (agli arti inferiori) Sì: ☐ No: ☐ _____
- Malattie del sistema immunitario Sì: ☐ No: ☐ _____
- Malattie psichiatriche Sì: ☐ No: ☐ _____
- Alterazioni dell'umore o depressione Sì: ☐ No: ☐ _____

- L'intervento di osteointegrazione è controindicato se:

  - sono presenti malattie vascolari agli arti inferiori;
  - vi sono gravi malattie coagulative;
  - è presente un diabete mellito non controllato adeguatamente;
  - sono presenti malattie cutanee che interessano l'arto amputato;
  - è presente immunosoppressione;
  - sono presenti malattie psichiatriche che non permetterebbero una buona compliance;
  - sono presenti alterazioni d'umore o depressione che non permetterebbero una buona compliance. Per tale ragione è utile ricorrere ad un consulto psicologico.

Interventi pregressi *(tipologia e data)*:

_____

_____

_____

_____

_____

ANAMNESI PATOLOGICA RECENTE

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

TERAPIA FARMACOLOGICA IN CORSO

_____

_____

_____

_____

_____

_____

_____

_____

- L'intervento di osteointegrazione è controindicato se:
  - è in corso un trattamento con corticosteroidi o altri farmaci che possono compromettere la buona riuscita dell'intervento e/o della riabilitazione;
  - è in corso un trattamento chemioterapico;
  - è presente in anamnesi un trattamento radioterapico sull'arto amputato.

MOTIVAZIONI ESPRESSE DAL SOGGETTO

- È utile sottoporre al paziente il questionario Q-TFA.
- Chiedere al soggetto se:
  - ☐ trova difficoltà a indossare la protesi per almeno 50 ore la settimana;
  - ☐ non è capace di percorrere 2 chilometri o più al giorno;
  - ☐ percepisce la protesi come inaffidabile, per cui si sente insicuro mentre la indossa;
  - ☐ avverte fastidio nel sedersi indossando la protesi;
  - ☐ lamenta la presenza di irritazioni, sfregamenti o ulcere cutanee legate all'utilizzo della protesi;
  - ☐ riscontra spesso problemi legati alla sudorazione o alla sensazione di calore del moncone;
  - ☐ giudica tali problemi, correlati all'utilizzo della protesi con invasatura, di considerevole impatto sulla qualità di vita.
- Se il soggetto risponde affermativamente ad almeno quattro risposte su sette, il paziente è un buon candidato all'intervento di osteointegrazione.
- Oltre ai criteri già visti, si aggiungono altri due aspetti che non precludono l'intervento, ma che sono da tenere in considerazione:
  - ☐ dubbi da parte del paziente sul sottoporsi all'intervento;
  - ☐ dolore da arto fantasma, per cui l'intervento di osteointegrazione non porterebbe alla risoluzione.
- È consigliato, infine, sottoporre sempre il paziente a un consulto psicologico.

ESAME OBIETTIVO

Tipo di amputazione:

☐ Sinistra

☐ TT ☐ TF ☐ Altro: _____

☐ Destra

☐ TT ☐ TF ☐ Altro: _____

Possibile osteointegrazione all'arto:

☐ Sinistro ☐ Destro

Lunghezza del moncone:

Sinistro ☐prossimale ☐mediale ☐distale

Destro ☐prossimale ☐mediale ☐distale

Eccesso di tessuti molli:

Sinistro Sì ☐ No ☐ Destro Sì ☐ No ☐

Neuroma, punti dolorosi nell'apice del moncone:

Sinistro Sì ☐ No ☐ Destro Sì ☐ No ☐

Valutazione sensitiva/termodolorifica/vibratoria e presenza di discromie:

_____

_____

Problematiche vascolari: _____

_____

_____

Forza muscolare del moncone:

Arto sinistro ☐ I° ☐ II° ☐ III° ☐ IV° ☐ V°

Arto destro ☐ I° ☐ II° ☐ III° ☐ IV° ☐ V°

Stato del moncone:

_____

_____

_____

_____

_____

L'intervento di osteointegrazione è controindicato se:

- il moncone osseo risulta più corto di 8 cm (misurazione radiografica);
- risultano essere presenti malattie vascolari;
- risultano essere presenti malattie cutanee che coinvolgono l'arto amputato.

AMPUTAZIONE TRANSFEMORALE

☐ Arto sinistro		☐ Arto destro	
Estensione dell'anca	_____°	Estensione dell'anca	_____°
Flessione dell'anca	_____°	Flessione dell'anca	_____°
Abduzione dell'anca	_____°	Abduzione dell'anca	_____°
Adduzione dell'anca	_____°	Adduzione dell'anca	_____°
Polso femorale palpabile:	Sì ☐ No ☐	Polso femorale palpabile:	Sì ☐ No ☐

AMPUTAZIONE TRANSTIBIALE

☐ Arto sinistro		☐ Arto destro	
Flessione del ginocchio	_____°	Flessione del ginocchio	_____°
Estensione del ginocchio	_____°	Estensione del ginocchio	_____°
Stabilità varo/valgo	_____	Stabilità varo/valgo	_____
Stabilità antero/posteriore	_____	Stabilità antero/posteriore	_____
Polso popliteo palpabile:	Sì ☐ No ☐	Polso popliteo palpabile:	Sì ☐ No ☐

- Se sono presenti ipotrofia del moncone o restrizioni del ROM, è consigliato intraprendere un programma fisioterapico dedicato che permetta al soggetto di riacquisire una buona mobilità e trofia dell'arto amputato prima dell'intervento e della riabilitazione.

ESAME RADIOLOGICO

Radiografia del moncone

(panoramica degli arti inferiori in ortostatismo (con protesi indossata), con calibrazione e con il segmento osseo controlaterale visibile)

Sì ☐ No ☐ data ____/_____/_____

TAC

(con calibrazione e con il segmento osseo controlaterale visibile)

Sì ☐ No ☐ data ____/_____/_____

RMN

Sì ☐ No ☐ data ____/_____/_____

Ecodoppler venoso/arterioso moncone

Sì ☐ No ☐ data ____/_____/_____

Densitometria ossea

Sì ☐ No ☐ data ____/_____/_____

Si riscontra:

- Deformità ossee: Sì ☐ No ☐ _____
- Osteoporosi: ☐Assente ☐Moderata ☐Severa (T-Score _____)
- Osteoartrosi dell'anca: Sì ☐ No ☐
- Osteoartrosi del ginocchio: Sì ☐ No ☐

PLANNING PRE-OPERATORIO

Transfemorale

Lunghezza dall'apice del moncone al piccolo trocantere: _____ cm

Lunghezza dell'apice del moncone alla joint-line del ginocchio controlaterale ____ cm

Transtibiale

Lunghezza dall'apice del moncone al piatto tibiale: _____ cm

_____

_____

_____

Soluzione protesica consigliata:

_____

_____

_____

Modello Ginocchio protesico: _____

Modello Piede protesico: _____

- **IDONEO ALL'INTERVENTO DI OSTEOINTEGRAZIONE?** Sì ☐ No ☐

Conclusioni

_____

_____

_____

_____

Progetto clinico/riabilitativo consigliato:

_____

_____

_____

_____

Data: _____/_____/_____

Nome e cognome del valutatore _____

ANNEX 3

PROTOCOLLO PROTESICO PER ARTO AMPUTATO TRATTATO CON IMPIANTO OSTEOINTEGRATO

Università degli Studi di Bologna

Istituto Ortopedico Rizzoli, Bologna

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A cura di

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SOMMARIO

INTRODUZIONE

La tecnica dell'osteointegrazione nelle protesi d'arto inferiore trova applicazione nei soggetti amputati che riscontrano problemi legati all'invasatura. Quando tali problemi non trovano soluzioni, limitando la persona nelle sue attività quotidiane o costringendola all'utilizzo della carrozzina o delle stampelle, è possibile proporre al soggetto l'intervento di osteointegrazione come valida alternativa.

COMPONENTI DELL'IMPIANTO PER OSTEOINTEGRAZIONE E PROCEDURA CHIRURGICA

Le componenti dell'impianto per osteointegrazione sono (Figura 1):

1. Stelo endomidollare, che rappresenta la porzione di impianto che subisce l'osteointegrazione con il moncone osseo. Ne esistono diverse tipologie a seconda del livello di amputazione alla quale viene applicata (in figura: impianto OTN Implants di tipo *press-fit* per amputazione transfemorale, nella fattispecie utilizzata nel progetto di ricerca METACOS);
2. Tappo di guarigione, che protegge la porzione distale dello stelo femorale tra le due fasi chirurgiche;
3. Adattatore transcutaneo a doppio cono, o *dual cone adapter* (lunghezze disponibili da 70 mm a 110 mm), che permette di collegare l'impianto interno alla protesi esterna;
4. Vite di bloccaggio, che fissa l'adattatore allo stelo endomidollare.

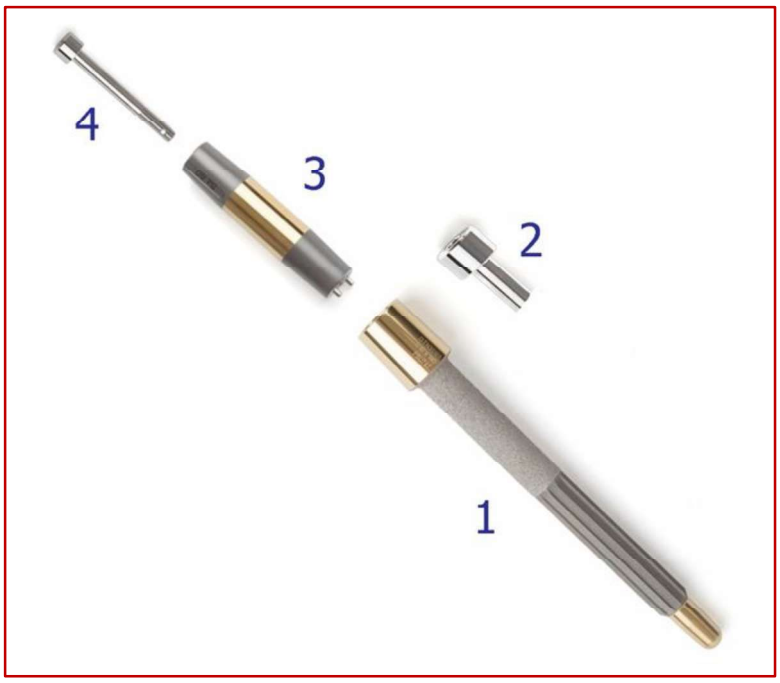

Figura 1 – Impianto per osteointegrazione per amputazione transfemorale della OTN Implants. Dall'alto verso il basso: vite di bloccaggio (4), adattatore transcutaneo a doppio cono (3), stelo femorale press-fit dotato di vite prossimale (1). A fianco: tappo di guarigione (2).

L'intervento chirurgico è diviso in due fasi (o "step").

1) Il primo *step* chirurgico include una plastica dei tessuti molli e l'eventuale accorciamento del moncone osseo, a seconda delle esigenze del caso. Procedendo, si accede al canale endomidollare, alesando e raspando con appositi strumenti fino a ottenere un diametro idoneo ad accogliere lo stelo del sistema di osteointegrazione. I gruppi muscolari vengono suturati alla corticale dell'apice del moncone osseo. Si individua il futuro sito di stomia e si procede rimuovendo il tessuto sottocutaneo e il tessuto adiposo in eccesso. A questo punto si applica il tappo di guarigione alla porzione distale dello stelo endomidollare e si sutura la cute per piani. Il paziente viene dimesso dopo una settimana dall'intervento.
2) Dopo 5/6 settimane si procede con il secondo *step* chirurgico: si crea una stomia circolare a livello della cute che copre la porzione distale dello stelo endomidollare.

A questo punto si collega l'adattatore a doppio cono allo stelo endomidollare, fissandolo con l'apposita vite.

Il periodo tra i due *step* chirurgici è di fondamentale importanza affinché avvenga l'osteointegrazione dell'impianto endomidollare. È vietato l'utilizzo della protesi e i movimenti sono permessi solo tramite l'uso di stampelle o della carrozzina.

Il paziente è libero di iniziare la fase di riabilitazione già nell'immediato post-operatorio, generalmente 2/3 giorni dopo il secondo *step* chirurgico.

RUOLO DEL TECNICO ORTOPEDICO

Il tecnico ortopedico interviene sia nel preoperatorio, sia nel post-operatorio, lavorando a stretto contatto con il paziente, i medici (ortopedici e fisiatri) e i fisioterapisti.

PRIMA VISITA

Durante la prima visita del paziente amputato, il tecnico ortopedico raccoglie i dati relativi alla protesi di normale dotazione utilizzata dal soggetto, prestando particolare attenzione al modello di ginocchio e di piede protesici.

È preferibile, infatti, disporre di componenti protesiche adeguatamente performanti, essendo l'osteointegrazione pensata per soggetti dinamici appartenenti a una classe K3 o superiore (secondo la *K classification level*), in buone condizioni generali e attivi dal punto di vista motorio. Di conseguenza, anche la soluzione protesica che si propone deve avere caratteristiche che si adeguino al livello di performance del paziente.

Per quanto riguarda la scelta del ginocchio protesico si consiglia, per la prima fornitura a seguito dell'intervento di osteointegrazione, di partire almeno da un ginocchio polifunzionale idraulico (ad esempio, il ginocchio 3R80 della Ottobock). Rispetto alla scelta del piede protesico, è consigliabile un modello che garantisca una buona ammortizzazione e capacità rotazionali (ad esempio, il piede *Pro-Flex XC Torsion* della Ossür), in modo tale da scongiurare torsioni a livello dell'arto protesico e prevenire eventuali movimentazioni dell'impianto femorale intramidollare.

Attenzione

Attualmente la protesi esterna può essere collegata alle componenti di una protesi per osteointegrazione solo tramite un attacco *piramidale*.
È buona norma sincerarsi se il paziente con amputazione transfemorale abbia eventualmente in dotazione un ginocchio con un attacco filettato: in questo caso è necessario disporre in officina di un apposito adattatore (ad esempio, l'adattatore piramidale per connettore filettato 4R50 della Ottobock).

PIANIFICAZIONE PREOPERATORIA

Nel caso di un paziente transfemorale il tecnico ortopedico deve saper fornire al medico ortopedico una stima dell'ingombro della protesi esterna, dall'inizio del connettore per protesi osteointegrate al centro articolare del ginocchio protesico in dotazione al paziente.

Per quanto concerne il connettore, l'altezza potrebbe variare a seconda del modello scelto: ad esempio, lo spazio totale occupato dal modello *Heli Connector 14* della OTN Implants (BV, Arnhem, Netherlands) è di 75 mm, dei quali 35 mm risultano sovrapposti all'adattatore a doppio cono degli impianti OTN, mentre 14 mm risultano sovrapposti all'adattatore piramidale della protesi.

La misura relativa al ginocchio protesico è disponibile nel manuale d'istruzione del ginocchio stesso, oppure, consultando il catalogo della ditta produttrice.

Attenzione

Nel caso in cui il moncone transfemorale risultasse particolarmente corto, è necessario considerare la differenza di altezza con il femore controlaterale e calcolare se è possibile colmare tale distanza con un modulo protesico idoneo. A tal scopo, ad esempio, sono fruibili degli adattatori a doppia piramide, che possono essere inseriti tra il connettore e il ginocchio protesico. Sono disponibili misure limitate: ad esempio, per il 4R72 della Ottobock sono disponibili quattro diverse lunghezze, rispettivamente di 69, 82, 97 e 112 mm. Essendo misure aventi un considerevole impatto sulla lunghezza finale della protesi, è doveroso informare il chirurgo sulle diverse soluzioni disponibili durante la pianificazione dell'intervento.

La pianificazione preoperatoria deve permettere una corretta altezza finale della protesi e deve prevenire, altresì, che i tessuti molli non entrino a contatto con le componenti protesiche esterne, al fine di evitare sfregamenti fastidiosi per il paziente.

MONTAGGIO DELLA PROTESI ESTERNA

Il tecnico ortopedico, adeguatamente formato, procede con il montaggio della protesi esterna e con il suo allineamento, seguendo le istruzioni fornite insieme alle varie componenti.

PROTESI PER OSTEOINTEGRAZIONE: COMPONENTI E MONTAGGIO

COMPONENTI PROTESICHE

Le componenti della protesi per osteointegrazione di interesse del tecnico ortopedico sono:

- *L'adattatore transcutaneo a doppio cono*, che rappresenta la porzione di collegamento tra l'impianto intramidollare e la protesi esterna. Attraversa la cute a livello della stomia e si interfaccia nella porzione distale con il connettore per la protesi esterna (Figura 1 e 2);
- Il *connettore per la protesi esterna* (Figura 3).

Se necessario anche:

- Un *adattatore a doppia piramide* (o altre soluzioni assimilabili), che può essere eventualmente inserito tra il connettore e il ginocchio protesico nel caso in cui la porzione femorale della protesi esterna risulti corta [per ulteriori informazioni consultare il paragrafo "*Pianificazione preoperatoria*"];
- Un *adattatore piramidale per connettore filettato*, qualora non fosse possibile un collegamento diretto tra il connettore e il ginocchio protesico in dotazione al paziente [per ulteriori informazioni consultare il paragrafo "*Prima visita*"].

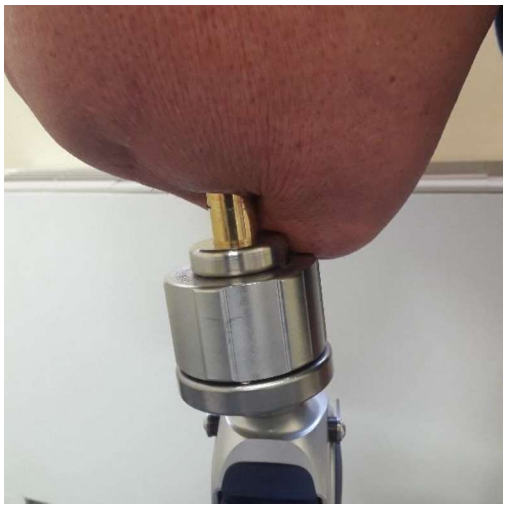

Figure 2 e 3 – Porzione distale dell'adattatore a doppio cono (modello OTN Implants, a sinistra). Connettore per protesi esterna (*Heli Connector*, OTNI) montato su protesi transfemorale (a destra).

CONNETTORE PER PROTESI ESTERNA

Il connettore è formato da tre componenti fondamentali (Figura 4):

1. Il connettore maschio, che si interfaccia con la porzione distale dell'adattatore a doppio cono, fissandosi con la rispettiva vite di serraggio;
2. Il connettore femmina, collegato alla protesi esterna, che permette l'aggancio tra l'arto amputato e il connettore maschio;
3. La piastra *offset* ("di compenso"), disponibile con diversi disassamenti, finalizzata a posteriorizzare la linea di carico e mettere così in sicurezza il ginocchio protesico quando esteso.

Figura 4 – Esempio di connettore per protesi esterna (*Heli Connector 14*, OTNI).

In alto, da sinistra: connettore montato; connettore maschio e connettore femmina.
In basso: piastra *offset*.

Attenzione

La componentistica protesica riportata nella descrizione e nelle immagini è utilizzata a scopo di esempio per fornire una panoramica generale; a tal proposito è preso come esempio il sistema di connessione *Heli connector 14* proposto dalla OTN Implants (BV, Arnhem, Netherlands). Le istruzioni per l'uso dei singoli moduli protesici selezionati per il paziente contengono informazioni dettagliate che devono essere utilizzate durante il montaggio della protesi.

MONTAGGIO DEL CONNETTORE E DELLA PROTESI ESTERNA

Attraverso il connettore per la protesi esterna, il soggetto può collegare rapidamente la propria protesi all'impianto di osteointegrazione. È importante avere a disposizione componenti protesiche adeguate ed effettuare una corretta ottimizzazione dell'allineamento nella fase statica e nella fase dinamica del passo.

Attenzione

Durante il primo utilizzo del connettore è necessario eseguire, durante il montaggio, i passaggi indicati nel paragrafo "*Manutenzione del connettore per protesi esterna*".

1) Pulire il cono distale dell'adattatore a doppio cono e fissare su di esso il connettore maschio tramite la vite di bloccaggio (M14, OTNI), utilizzando una coppia di serraggio di 25 Nm e aiutandosi, se necessario, con un prodotto frena filetti. Per stabilizzare il connettore maschio è consigliato l'utilizzo di una chiave inglese N. 20. Assicurarsi che la superficie piana anteriore del connettore maschio sia allineata con la direzione di marcia (Figura 5a e 5b);
2) Applicare il connettore femmina e bloccare i due componenti serrando l'anello di bloccaggio. Per garantire la sicurezza della chiusura del connettore ruotare l'anello in senso orario fino a quando lo stesso non si bloccherà compiendo un piccolo scatto [in caso di problemi consultare il paragrafo "*Manutenzione del connettore per protesi esterna*"] (Figura 6);
3) Procedere avvitando la piastra *offset* sulla porzione filettata del connettore femmina. Accertarsi che l'anello possa muoversi liberamente sulla piastra *offset*. Tra la piastra offset e l'anello di serraggio del connettore femmina deve essere lasciato uno spazio pari a 1 mm circa.

Attenzione

Le piastre *offset* della OTNI sono disponibili in diverse misure, in modo tale da adattarsi alle esigenze. Nei pazienti con un impianto di osteointegrazione transfemorale, il grado compenso della piastra corrisponde al grado di flessione dell'anca dell'arto amputato. Si può scegliere una piastra *offset* con disassamento pari a 20, 40 e 60 mm a seconda del bisogno. Si consiglia di iniziare montando sempre una piastra con disassamento pari a 20mm e di valutare in seguito, al momento dell'allineamento in fase dinamica del passo, se il paziente necessita di una misura maggiore (40 o 60 mm).

Nel caso in cui il paziente abbia montato un ginocchio protesico con controllo elettronico degli angoli di flesso-estensione, eventuali piccole differenze possono sempre essere bilanciate con una piastra pari a 0, 10 o 20mm.

Il grado di compenso ha delle conseguenze a livello del cammino: minore è il disassamento applicato, minore è l'energia necessaria al paziente per flettere il ginocchio alla fine della fase di appoggio. Durante la fase riabilitativa i muscoli del compartimento anteriore della coscia riacquisiscono progressivamente elasticità, annullando il grado di flessione: in tal modo, il compenso applicato può essere gradualmente ridotto, fino a raggiungere un grado di flessione accettabile del moncone.

Nei pazienti con un impianto di osteointegrazione transtibiale, la piastra *offset* può essere utilizzata anche per correggere l'allineamento della protesi rispetto al piano frontale, compensando mediante una traslazione mediale o laterale eventuali angoli di valgismo o varismo;

4) Il livello di rotazione del ginocchio protesico può essere regolato ruotando la piastra *offset* rispetto al connettore femmina, tramite l'apposita vite (M5, OTNI) (Figura 7). Una volta stabilita la rotazione corretta, la vite di bloccaggio della piastra *offset* può essere assicurata con una coppia di serraggio pari a 5 Nm.
5) Collegare la protesi fornita di un attacco piramidale universale maschio all'attacco piramidale femmina della piastra *offset* e regolarne la posizione serrando le viti di fermo M8 (OTNI), applicando loro un frenafiletti. La coppia di serraggio delle viti di fermo M8 è di 15 Nm.

Attenzione

Si consiglia, per i pazienti aventi un'osteointegrazione transfemorale, di applicare un angolo fisiologico pari a 7° di valgismo. Nei pazienti con un'osteointegrazione transtibiale, l'allineamento in valgismo/varismo permette di raggiungere il corretto carico a livello del plateau tibiale mediale o laterale.


Figura 5 (a e b) – Montaggio del connettore maschio e serraggio con chiave dinamometrica.

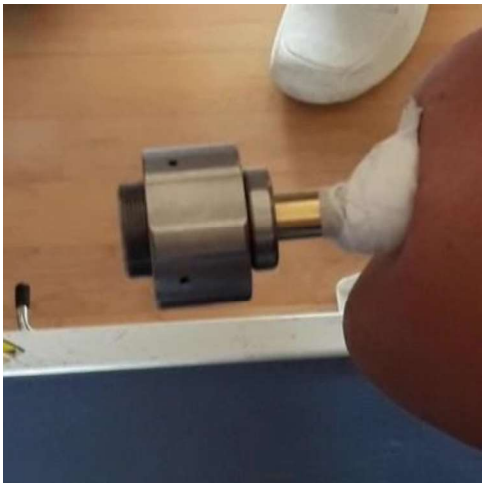


Figure 6 e 7 – Inserimento del connettore femmina (a sinistra) e dettaglio della vite M5 (a destra).

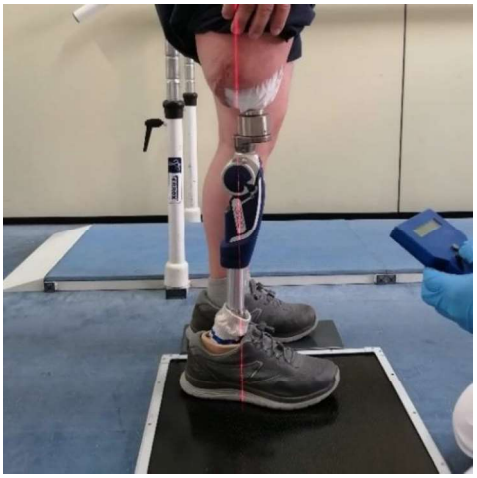


Figura 8 (a e b) – Completamento della statica (a sinistra) e risultato finale (a destra).

OTTIMIZZAZIONE DELLA PROTESI NELLA FASE STATICA

Eseguire l'allineamento statico della protesi rispettando le istruzioni d'uso dei prodotti che si stanno utilizzando. È consigliabile eseguire l'allineamento con la protesi montata sul paziente, aiutandosi con una pedana laser baropodometrica, in modo tale da ottenere una corretta visualizzazione del carico (Figura 8a e 8b).

Nei pazienti con un'osteointegrazione transfemorale è consigliato impostare un angolo pari a 7° di valgismo attraverso le viti di fermo dell'attacco piramidale posto tra la piastra *offset* e il resto della protesi.

Nei pazienti con un'osteointegrazione transtibiale è possibile, se necessario, regolare l'angolo di varismo/valgismo attraverso le viti di fermo dell'attacco piramidale.

Per i pazienti con un'osteointegrazione transfemorale utilizzare le varie misure delle piastre *offset* a seconda del grado di flessione dell'anca. Le piastre *offset* possono essere utilizzate anche nei pazienti con osteointegrazione transtibiale con lo scopo di raggiungere una certa traslazione in una determinata direzione.

OTTIMIZZAZIONE DELLA PROTESI NELLA FASE DINAMICA DEL PASSO

Testare e ottimizzare la protesi e i suoi vari componenti protesici distali al connettore mentre si invita il paziente a camminare con la protesi, osservando la dinamica del passo e recependo dal paziente medesimo le sensazioni di disequilibrio.

APPLICAZIONE DELLA COPERTURA COSMETICA

Realizzare la copertura cosmetica in modo tale che lo sgancio rapido della protesi possa funzionare correttamente; è consigliato applicare la copertura cosmetica esclusivamente dal ginocchio in giù.

RIFINITURA DELLA PROTESI

Quando l'allineamento della protesi e la riabilitazione del soggetto si sono conclusi, tutti i collegamenti a vite devono essere serrati ad una specifica coppia. Il frenafiletti può essere utilizzato come indicato nelle istruzioni delle singole componenti protesiche.

Attenzione

La vite M5 applicata alla piastra *offset*, che permette la rotazione del ginocchio durante l'allineamento, può essere serrata con la chiave dinamometrica non più di cinque volte, limite oltre il quale deve essere sostituita.

REALIZZAZIONE DELLA COVER IN SILICONE

Durante il periodo in cui il paziente decide di non indossare la protesi, il connettore maschio risulta scoperto. Al fine di garantire una condizione di maggior sicurezza e un maggiore comfort per il paziente è utile realizzare una cuffia in silicone su misura, affinché si possa coprire la porzione distale della protesi (Figura 9a e 9b).

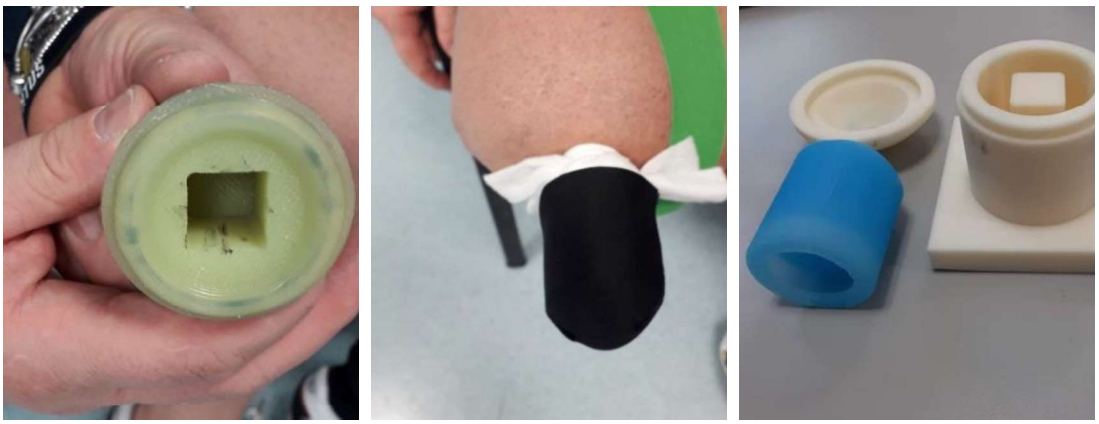

Figura 9 (a, b e c) – Esempio di cuffia in silicone (sinistra e centro) e stampo del connettore maschio utilizzato per la realizzazione.

SMONTAGGIO DEL CONNETTORE

Qualora risulti necessario, è possibile smontare il connettore utilizzando l'apposito strumento di rimozione fornito in dotazione insieme all'impianto.

1) Rimuovere il connettore femmina dal connettore maschio;
2) Svitare la vite M14 del connettore maschio tramite una vite a brugola da 6 mm, fino a farla sporgere di 2-4 mm oltre l'apice del connettore. Servirsi di una chiave inglese da 20 mm per evitare torsioni del connettore rispetto all'impianto osteointegrato (Figura 10);
3) Inserire l'estrattore attorno al connettore maschio (Figura 11). Proseguire avvitando l'apposita vite applicata distalmente all'estrattore, aiutandosi in caso di bisogno con una chiave inglese da 16 mm, fino a che non si avverte uno scatto da parte del connettore.

   Onde evitare che la vite M14 del connettore maschio si avviti nuovamente durante l'operazione, è utile porre in mezzo alla testa della vite stessa e l'estrattore una moneta da 10 centesimi;
4) Sfilare il connettore maschio dall'adattatore a doppio cono, avendo cura di conservare la vite di serraggio in un luogo sicuro.

Figure 10 e 11 – Svitare la vite M14 del connettore maschio (a sinistra) e rimuovere il connettore attraverso l'apposito estrattore (a destra).

MANUTENZIONE DEL CONNETTORE PER PROTESI ESTERNA *HELI CONNECTOR 14* OTNI

È raccomandabile eseguire un'ispezione visiva e un controllo funzionale dopo i primi 30 giorni di utilizzo della protesi. Si consiglia di eseguire un controllo di manutenzione una volta all'anno, prestando attenzione alla perdita di funzionalità, all'usura, ai collegamenti a vite e alla presenza di rumore durante il cammino.

MANUTENZIONE DEL CONNETTORE DURANTE IL PRIMO UTILIZZO

Le operazioni suggerite di seguito sono necessarie durante il primo utilizzo dell'*Heli connector 14* fornito dalla OTN Implants e durante i controlli, se necessario.

- Applicare il frenafiletti attorno al foro di ingresso della vite M14 (OTNI), posto alla base della porzione cava del connettore femmina, avendo cura di pulire gli eccessi (Figura 12). È consigliabile utilizzare un agente di bloccaggio apposito per filetti sottili (ad esempio, la LOCTITE 221);
- Applicare il frenafiletti anche a livello delle madreviti delle due viti laterali M2 (OTNI), a livello dell'anello di bloccaggio del connettore femmina, pulendo gli eccessi (Figura 13). È consigliabile utilizzare un agente di bloccaggio apposito per filetti sottili (ad esempio, la LOCTITE 221).

Attenzione

Prima di poter utilizzare il connettore, attendere un paio d'ore per far fissare bene il frenafiletti.


Figure 12 e 13 – Visione dell'interno del connettore femmina con frenafiletti applicato attorno al foro di ingresso della vite M14 (a sinistra) e visione dei fori laterali che accolgono le viti M2 (a destra).

SERRAGGIO DEL CONNETTORE

Prima di utilizzare la protesi, verificare che l'anello del connettore sia stato serrato e che si sia avvertito un leggero scatto. Se tale scatto non dovesse verificarsi, smontare l'anello del connettore femmina tramite l'apposita vite e sincerarsi che non ci siano dei residui o della polvere al suo interno che non permettono una corretta rotazione tra le due componenti (Figura 14).

Figura 14 – Componenti del connettore femmina dell'*Heli connector 14*: a sinistra l'anello di serraggio e a destra il meccanismo interno che ne permette lo scorrimento.

RISOLUZIONE DI MOVIMENTI ASSIALI/LATERALI DEL CONNETTORE

- Per quanto concerne eventuali movimenti anomali del connettore in senso assiale, sistemare con cautela la vite M14 all'interno del connettore femmina con una chiave a brugola N. 6 (da sotto), oppure con un cacciavite a punta piatta (da sopra) fino a che il movimento lungo l'asse non sia scomparso (Figura 15);

> ***Attenzione***
>
> Procedere lentamente mentre si regola la vite M14; se la vite fosse stretta eccessivamente non sarebbe possibile riaprire l'anello di bloccaggio. Può essere normale, all'inizio, riscontrare una resistenza maggiore mentre si serra l'anello di bloccaggio attorno al connettore maschio.

- Per quanto riguarda eventuali movimenti laterali anomali del connettore, collegare il connettore maschio al connettore femmina e sistemare le viti M2 presenti nell'anello esterno (in posizione aperta) con una chiave a brugola di 2 mm (Figura 16). Una volta collegata la protesi è possibile stringere ulteriormente le viti laterali se ritenuto necessario.

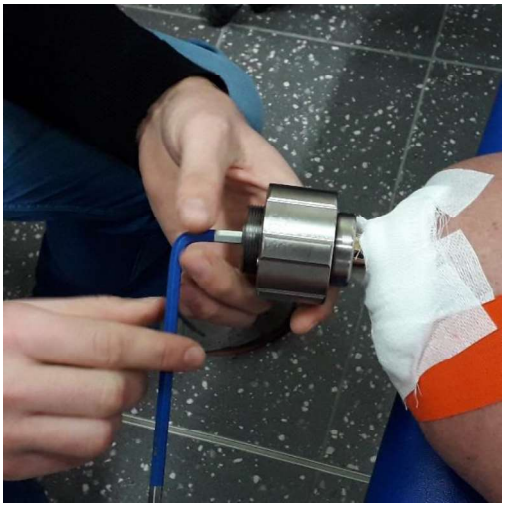

Figure 15 e 16 – Risoluzione dei movimenti anomali assiali (a sinistra) e laterali (a destra).

PULIZIA DEL CONNETTORE

Mantenere sempre pulito e asciutto l'impianto. È raccomandato istruire il paziente nella pulizia quotidiana del prodotto utilizzando un panno umido e morbido e asciugandolo con cura. Un'ispezione quotidiana permette di indagare l'eventuale presenza di sabbia o polvere nel connettore, che devono essere rimosse con cura utilizzando dell'acqua dolce.

La protesi può essere utilizzata in spiaggia o sotto la doccia, ricordandosi, dopo il contatto della protesi con acqua salata o contaminata, di sciacquare la protesi con acqua dolce pulita e di asciugare il tutto.

Si ringraziano della collaborazione

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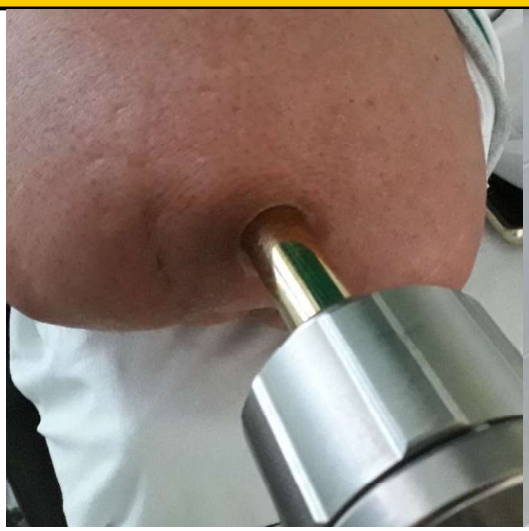
ANNEX 4

PROTOCOLLO DI CURA E IGIENE DELLA STOMIA PER PROTESI OSTEOINTEGRATA



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INDICE

PROTOCOLLO DI CURA DELLA STOMIA PER LA PROTESI OSTEOINTEGRATA DI ARTO INFERIORE

La stomia è l'apertura della cute attraverso la quale la porzione distale dell'impianto protesico (adattatore) protrude all'esterno. Nella fase del post-operatorio (Figura 1a e 1b) va trattata come una ferita chirurgica; nel corso delle settimane, la parete interna viene rivestita da un tessuto assimilabile all'epitelio di una mucosa. Tuttavia, nelle prime settimane la stomia rappresenta un sito particolarmente vulnerabile e sensibile: è possibile, quindi, che sanguini o che sia soggetta a infezioni. Una volta che l'epitelio si è formato il rischio di sanguinamenti, irritazioni e infezioni dei tessuti molli diminuisce.

È necessario istruire il paziente sulla corretta gestione della stomia e sul riconoscimento tempestivo di cambiamenti della stessa che necessitano di essere gestiti da personale medico-infermieristico.

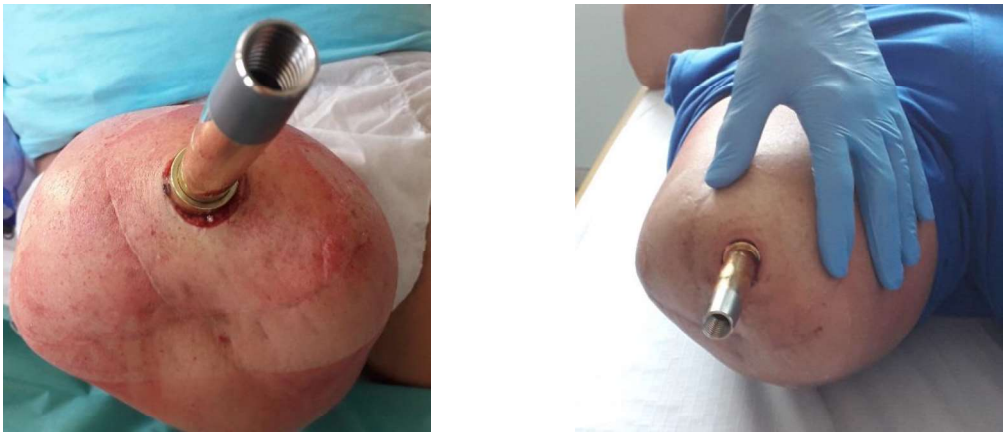

Figura 1 (a e b) – Presentazione della stomia a un giorno (sinistra) e a tre giorni (destra) dall'intervento.

La stomia deve essere pulita due volte al giorno per prevenire eventuali irritazioni o infezioni della pelle e dei tessuti molli. La cura inizia dal giorno successivo all'intervento chirurgico; nelle prime settimane la stomia deve essere accuratamente irrigata con il semplice getto di acqua del doccino. È consentito l'utilizzo di saponi neutri, tuttavia un lavaggio abbondante con acqua risulta sufficiente.

Quando la stomia continua a sanguinare si consiglia di risciacquare con acqua fredda, applicare una serie di garze ed effettuare una compressione. In caso di sanguinamento ricorrente, ridurre le attività e mantenere il moncone in scarico.

Attenzione

I tamponi di garza non sono da considerare sterili.

GESTIONE DELLA STOMIA

ISTRUZIONI PER LA CORRETTA PULIZIA DELLA STOMIA

1. Rimuovere il tampone di garza;
2. Irrigare la stomia con il doccino (Figura 2a) o con un idropulsore (si consiglia l'idropulsore). Per comodità, si consiglia di acquistare un idropulsore con livelli di getto d'acqua regolabili e con un serbatoio dell'acqua integrato;
3. Rimuovere eventuali depositi (incrostazioni) dall'impianto con un tampone di garza, acqua e sapone (Figura 2b);
4. Assicurarsi che l'impianto protesico sia perfettamente pulito e privo di detriti;
5. Massaggiare la pelle e i muscoli durante il risciacquo e assicurarsi che non si verifichino aderenze tra il rivestimento interno della stomia e l'impianto;
6. Dopo il risciacquo, procedere eliminando i residui di acqua con un asciugamano. Se necessario, coprire la stomia con una garza da 10x10 cm, adeguatamente ripiegata sul lato lungo e bloccata attorno all'impianto con un nodo.

Attenzione

Coprire la stomia con una garza solo quando c'è una secrezione importante. Lo scopo dell'uso di una garza è impedire semplicemente che si formino macchie sui vestiti: la copertura per stomia non ha lo scopo di mantenere la zona sterile. La stomia va pulita accuratamente anche dopo tutte le attività.

Figura 2 (a e b) – Pulizia della stomia con il doccino (sinistra) e pulizia dell'adattatore con una garza (destra).

CURA DELLA STOMIA

Uno dei primi segni di irritazione della stomia è il rossore, che può essere accompagnato da gonfiore dei tessuti molli, calore e dolore.

Va ricordato che la presenza di irritazioni o infezioni ripetute nello stesso soggetto può essere ricondotta a una scarsa o insufficiente igiene del moncone, a uno strato adiposo sottocutaneo sovrabbondante attorno all'area della stomia e/o alle abitudini tabagiche del soggetto.

Attenzione

Attenersi sempre alle indicazioni di un medico opportunamente formato.

INFIAMMAZIONE O INFEZIONE DELLA STOMIA

L'infezione si presenta come dolore attorno e all'interno della stomia, accompagnato da secrezioni purulente giallo-verdi, rossore, gonfiore, cute calda al tatto e rialzo della proteina C-reattiva.

In caso di infiammazione (Figura 3b) o infezione (Figura 3c) procedere nel modo seguente:

- Pulire frequentemente la stomia con acqua e sapone neutro;
- Disinfettare con clorexidina gluconato 0,5% + etanolo 70% (SANITAS) due volte al giorno, dopo aver pulito la stomia con acqua; in alternativa, irrigare la stomia con 4 mL di perossido di idrogeno (acqua ossigenata) per 5 minuti prima di sciacquare con acqua, ripetendo l'operazione due volte al giorno per due settimane. Per facilitare l'operazione è possibile aiutarsi con una siringa;
- I pazienti che soffrono di infezioni ripetute a livello della stomia traggono, talvolta, beneficio da un trattamento a lungo termine con un unguento idrofilo a base di acido

fusidico (Fucidin 20 mg/g unguento) da applicare attorno e all'interno della stomia due volte al giorno. In alternativa può essere applicata una pomata dermatologica a base di idrocortisone/oxitetraciclina cloridrato/polimixina B, che però in Italia viene commercializzata per l'applicazione auricolare o oculare (Terra-Cortril, Pfizer);

- Se, nonostante tutto, l'infezione si protrae oltre il mese di trattamento (con dolore, arrossamento e formazione di secreto purulento) chiedere al medico di famiglia di prescrivere un antibiotico per almeno 10 giorni. Oltre il 90% delle infezioni della stomia sono causate dallo Stafilococco Aureus, per questo motivo sono consigliati antibiotici mirati;

Qualora il soggetto presentasse una ridondanza di tessuto adiposo nello strato sottocutaneo attorno la stomia, sarebbe opportuno valutare la soluzione chirurgica. Rimuovendo il più possibile il tessuto adiposo, lo spessore del canale della stomia viene ridotto, creando il cosiddetto "short" o "dry stoma", che presenta il vantaggio di poter essere mantenuto pulito più facilmente; inoltre, rappresenta spesso la soluzione agli eccessivi sfregamenti dei tessuti molli attorno all'impianto protesico, riducendo gli episodi di irritazione e di infiammazione della stomia.

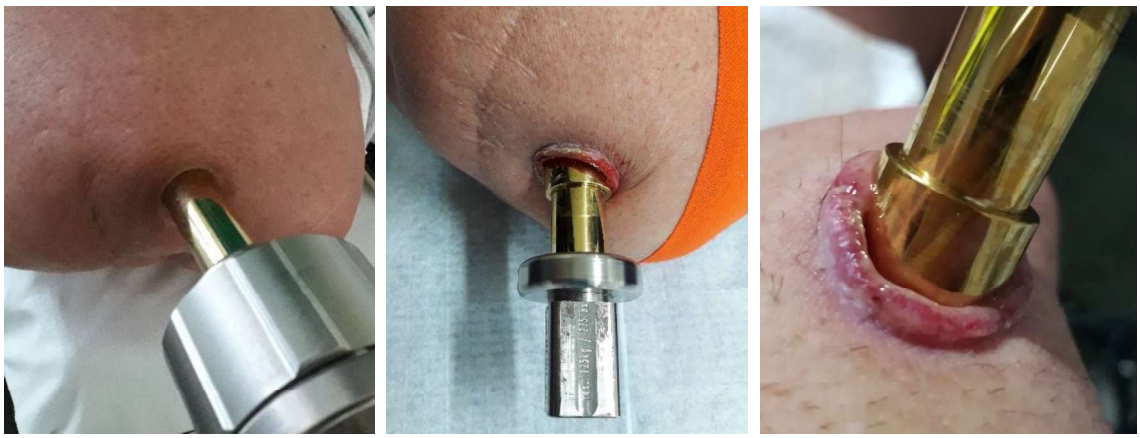

Figura 3 (a e b) – Confronto tra stomia sana (sinistra) e stomia infiammata (centro) e con infezione (destra).

IRRITAZIONE E/O SECCHEZZA DELLA STOMIA

L'irritazione (Figura 4) si presenta come dolore o sensazione di bruciore attorno e all'interno della stomia, potenzialmente accompagnato da un cambiamento della qualità delle secrezioni. Non devono essere presenti rossore, gonfiore, calore al tatto o rialzo della proteina C-reattiva.

Spesso l'irritazione è causata dal continuo sfregamento tra i tessuti molli attorno alla stomia e la parte dell'impianto protesico che la attraversa. Nei casi di "dry stoma", la parete interna della stomia può risultare più sensibile.

È possibile ricorrere all'Instillagel, un gel lubrificante sterile che contiene 0,23 g di lidocaina cloridrato e 0,0057 g di clorexidina gluconato che funge, quindi, da anestetico locale e antibatterico. È disponibile in siringhe da 11mL, solo su prescrizione medica. Applicare da 1 a 2 mL ogni ora del giorno, arrivando in profondità. Essendo il farmaco assorbito dalla cute in maniera molto limitata, è possibile utilizzare il gel cronicamente in caso di stomia secca e adesa alla componente protesica. In alternativa, nei casi meno gravi, è possibile applicare della vaselina sulla stomia e sull'impianto.

Figura 4 – Confronto tra stomia sana (sinistra) e stomia irritata (destra).

PRESENZA DI TESSUTO CICATRIZIALE E/O IPERGRANULAZIONE AI MARGINI DELLA STOMIA

Applicare Terra-Cortril due volte al giorno dopo aver pulito la stomia. Cessarne l'utilizzo una volta che la situazione è risolta. È altamente sconsigliato l'utilizzo per più di quattro settimane consecutive.

GESTIONE DEL DOLORE DELL'ARTO OSTEOINTEGRATO

È comune riscontrare dolore a livello di un arto osteointegrato. Le cause possono essere diverse: le più comuni si verificano durante la fase riabilitativa del soggetto neo-osteointegrato e sono, in gran parte, trattabili.

È importante, al fine di una corretta gestione, identificarne l'origine e trattarla in maniera specifica. Gran parte del dolore deriva dalla stomia e dal tessuto osseo in via di guarigione, oltre che dai tessuti molli presenti a livello dell'arto amputato (tendini, muscoli, articolazioni). La maggior parte dei tessuti molli risente dell'inutilizzo prolungato conseguente all'amputazione e/o all'impiego di una protesi con invasatura; con l'adozione di una protesi osteointegrata si assiste a una riattivazione dei gruppi muscolari e ciò, all'inizio, può essere causa di dolore.

È necessario spiegare l'eventualità al soggetto e tranquillizzarlo. Normalmente, adottando uno stile di vita attivo, controllando il peso corporeo ed evitando il fumo, il soggetto può riscontrare un beneficio sia a livello dell'arto amputato che globale.

In qualche caso, invece, è necessario integrare altri trattamenti medici.

DOLORE MUSCOLARE (MIALGIA) A LIVELLO DELL'ARTO AMPUTATO

È la tipologia di dolore di più comune riscontro durante il periodo di riabilitazione post-chirurgico. L'inattività prolungata dei gruppi muscolari è causata sia dall'utilizzo della carrozzina, sia dalla protesi tradizionale con invasatura. Di conseguenza il soggetto presenta spesso perdita di tono e forza muscolare a livello dell'arto amputato.

Dopo un intervento di plastica del moncone ed impianto di protesi osteointegrata i tessuti molli e le articolazioni sono portati a riacquisire gli schemi motori di un soggetto non amputato, motivo per cui il moncone accusa velocemente fatica e impotenza funzionale. Una volta che il tono e la trofia dell'arto vengono recuperati, il dolore e la fatica muscolare diminuiscono; la velocità con il quale questo avviene dipende dai ritmi e dalle attività intraprese durante la riabilitazione del soggetto, oltre che dalla durata del periodo di inattività conseguente all'amputazione prima di sottoporsi all'intervento di osteointegrazione.

È utile seguire alcuni accorgimenti:

- Allenarsi quotidianamente e con costanza, senza eccedere, soprattutto all'inizio;
- Proseguire la riabilitazione alleggerendo il carico di lavoro. È possibile, eventualmente, prolungare l'utilizzo delle stampelle. La sospensione degli esercizi non rappresenta una soluzione, in quanto rallenterebbe solo la formazione della struttura tendinea;
- Nel caso in cui il dolore all'arto diventi insostenibile è possibile l'impiego di un antidolorifico, dopo valutazione medica.

DOLORE ALL'APICE DELLA STOMIA

Si tratta di un dolore che insorge soprattutto nell'amputazione transfemorale e coinvolge i tessuti molli dell'apice distale della stomia, soprattutto nella parte anteriore. È causato dal sovraccarico dei muscoli che sono stati suturati alla corticale dell'osso femorale durante il primo *step* chirurgico (miodesi); tale ancoraggio, all'inizio, è debole e solo l'esercizio fisico e la deambulazione permettono la formazione di una giunzione tendinea solida tra la superficie corticale dell'osso e la porzione distale della muscolatura del moncone.

Il soggetto lamenta una sensazione di calore e bruciore all'apice della stomia, con un'insorgenza collegabile alle attività svolte durante la seduta di riabilitazione e accompagnata, talvolta, da sanguinamento.

Il dolore potrebbe peggiorare nel momento in cui si passa a caricare totalmente il peso corporeo sull'impianto, ovvero, in occasione dell'abbandono degli ausili (bastoni o stampelle).

DOLORE ALL'ARTICOLAZIONE COXO-FEMORALE

Il dolore all'anca (coxalgia) è la conseguenza del sovraccarico dell'articolazione coxo-femorale. Indossando una protesi transfemorale con invasatura l'articolazione viene privata del carico fisiologico, in quanto questo viene scaricato direttamente sulla pelvi; ciò comporta un assottigliamento della cartilagine articolare, dovuto al disuso. Nel caso di una protesi osteointegrata, il peso viene ridistribuito lungo l'asse fisiologico e l'anca potrebbe diventare dolente.

La coxalgia è un'indicazione a limitare il livello di carico o di attività, avendo cura di utilizzare sempre un ausilio per il cammino. Se la condizione dovesse peggiorare, sarebbe opportuno indagare lo stato di degenerazione articolare tramite una radiografia. Nel caso di una severa osteoartrosi resistente ai trattamenti conservativi, bisognerebbe valutare la necessità di ricorrere all'impianto di un'artroprotesi di anca.

NEUROMA E DOLORE DA ARTO FANTASMA

Il dolore di tipo neurologico nell'arto amputato è causato spesso dalla formazione di un neuroma a livello del nervo amputato. L'ipersensibilità della cute del moncone ne può rappresentare una manifestazione.

Il dolore può essere controllato attraverso farmaci inibenti la trasmissione del segnale nervoso (ad esempio: gabapentin, pregabalin o amitriptillina); essendo, comunque, causa di sonnolenza è opportuno limitarne l'utilizzo alla sera, al fine di garantire un corretto riposo del soggetto ed evitare sonnolenza e spossatezza durante il giorno. Se il paziente necessita di un dosaggio maggiore, è consigliabile somministrare dei dosaggi contenuti durante le ore diurne. Distrazioni quali lo sport, il lavoro o le attività di socializzazione possono essere uno strumento efficace per combattere questo tipo di dolore, che risente enormemente dello stato emotivo del soggetto.

L'utilizzo della Tecar terapia o un semplice massaggio locale possono essere di sollievo al paziente.

Attenzione: l'utilizzo di un catetere perinervoso collegato a un infusore esterno rappresenta una soluzione applicabile solo nell'immediato post-operatorio, ma trova difficoltà di utilizzo durante le sedute di riabilitazione, in quanto può essere mobilizzato dopo movimenti incauti o trazioni sul catetere.

Si ringraziano della collaborazione

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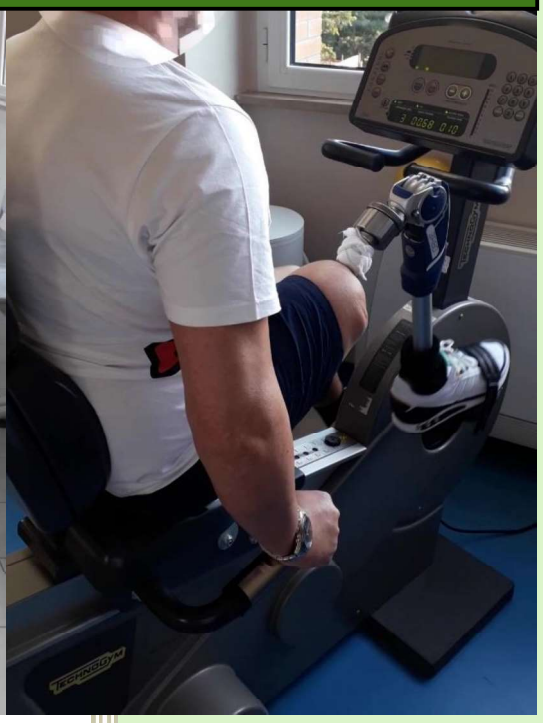
ANNEX 5

PROTOCOLLO RIABILITATIVO DEL PAZIENTE CON PROTESI TRANSFEMORALE OSTEOINTEGRATA



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INDICE

INTRODUZIONE

La tecnica dell'osteointegrazione nelle protesi d'arto inferiore trova applicazione nei soggetti amputati che riscontrano problemi legati all'invasatura. Quando tali problemi non trovano soluzioni, limitando la persona nelle sue attività quotidiane o costringendola all'utilizzo della carrozzina o delle stampelle, è possibile proporre al soggetto l'intervento di osteointegrazione come valida alternativa.

COMPONENTI DELL'IMPIANTO PER OSTEOINTEGRAZIONE E PROCEDURA CHIRURGICA

Le componenti dell'impianto per osteointegrazione sono:

- Stelo endomidollare, che rappresenta la porzione di impianto che subisce l'osteointegrazione con il moncone osseo. Ne esistono diverse tipologie a seconda del livello di amputazione sulla quale viene applicata (in figura: impianto OTN Implants di tipo *press-fit* per amputazione transfemorale, nella fattispecie utilizzata nel progetto di ricerca METACOS);
- Tappo di guarigione, che protegge la porzione distale dello stelo femorale tra le due fasi chirurgiche;
- Adattatore transcutaneo a doppio cono, o *dual cone adapter* (lunghezze disponibili da 70 mm a 110 mm), che permette di collegare l'impianto interno alla protesi esterna;
- Vite di bloccaggio, che fissa l'adattatore a doppio cono allo stelo endomidollare.

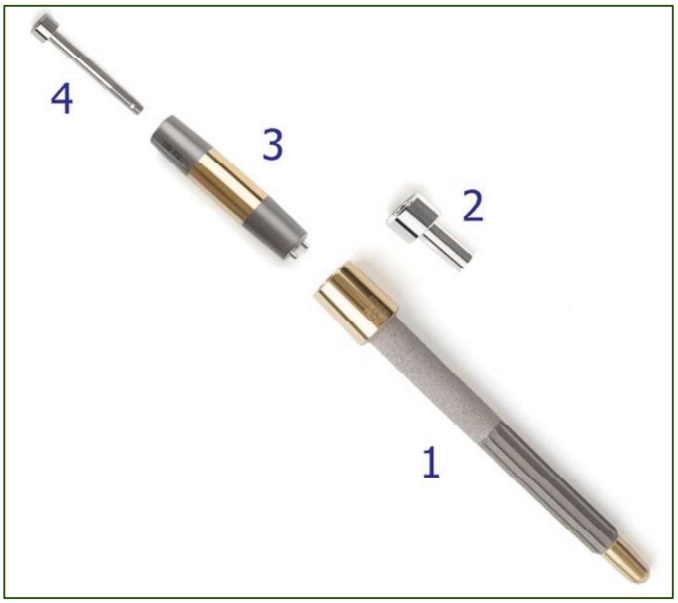

Figura 1 – Impianto per osteointegrazione per amputazione transfemorale della OTN Implants. Dall'alto verso il basso: vite di bloccaggio (4), adattatore transcutaneo a doppio cono (3), stelo femorale press-fit dotato di vite prossimale (1). A fianco: tappo di guarigione (2).

FASI DELL'INTERVENTO

L'intervento chirurgico è diviso in due fasi (o "step").

1) Il primo *step* chirurgico include una plastica dei tessuti molli e l'eventuale accorciamento del moncone osseo, a seconda delle esigenze del caso. Procedendo, si accede al canale endomidollare, alesando e raspando con appositi strumenti fino a ottenere un diametro idoneo ad accogliere lo stelo del sistema di osteointegrazione. I gruppi muscolari vengono suturati alla corticale dell'apice del moncone osseo. Si individua il futuro sito di stomia e si procede rimuovendo il tessuto sottocutaneo e il tessuto adiposo in eccesso. A questo punto si applica il tappo di guarigione alla porzione distale dello stelo endomidollare e si sutura la cute per piani. Il paziente viene dimesso dopo circa una settimana dall'intervento.
2) Dopo 5/6 settimane si procede con il secondo *step* chirurgico: si crea una stomia circolare a livello della cute che copre la porzione distale dello stelo endomidollare. A questo punto si collega l'adattatore a doppio cono allo stelo endomidollare, fissandolo con l'apposita vite.

Il periodo tra i due *step* chirurgici è di fondamentale importanza affinché avvenga l'osteointegrazione dell'impianto endomidollare. È vietato l'utilizzo della protesi esterna e i movimenti sono permessi solo tramite l'uso di stampelle o della carrozzina.

Il paziente è libero di iniziare la fase di riabilitazione già nell'immediato post-operatorio, generalmente 2/3 giorni dopo il secondo *step* chirurgico.

PERCORSO RIABILITATIVO

Il trattamento riabilitativo comincia dal periodo preoperatorio, quando si valutano le condizioni generali del paziente, lo stato del moncone e dell'arto controlaterale in termini di forza muscolare e di *range of motion* (ROM). Nel caso in cui fossero presenti limitazioni o deficit si elabora un progetto riabilitativo personalizzato, che può comprendere esercizi di rinforzo muscolare e di stretching da far attuare al paziente in autonomia, sia prima dell'intervento, che durante la pausa tra i due step chirurgici.

Un'analisi biomeccanica, ad esempio, della camminata a diverse cadenze del soggetto tramite sensori inerziali dovrebbe essere effettuato sia nella fase pre-operatoria che sia nella fase post-riabilitativa. Nella fase pre-operatoria ha lo scopo di impostare correttamente un protocollo di esercizi fisici mirati al ripristino dello stato funzionale prima dell'intervento e di definire una parte del protocollo riabilitativo, mentre nella fase post-riabilitativa per confrontare i dati con quella pre-operatoria.

La riabilitazione è preceduta dalla fase di assemblaggio della protesi esterna a cura di un Tecnico Ortopedico, che si occupa del montaggio del connettore protesico (nell'esempio l'*Heli*) e dell'allineamento della protesi [consultare il "*Protocollo protesico per arto amputato trattato con impianto osteointegrato*"].

È consigliabile che le figure del fisioterapista e del tecnico ortopedico collaborino all'allineamento delle componenti protesiche durante tutta la durata della fase riabilitativa, in modo tale da poter apportare tempestivamente le eventuali modifiche necessarie, ottimizzando i tempi della riabilitazione.

Il percorso riabilitativo comincia dalla presa in carico del paziente da parte del medico fisiatra che definisce gli obiettivi da raggiungere con il progetto riabilitativo personalizzato, condividendoli con il diretto interessato. Il fisiatra, inoltre, interviene ogni qual volta il soggetto lamenta dolore all'arto operato, al fine di stabilire se sia possibile continuare con lo svolgimento della sessione o se, altrimenti, il paziente necessiti di riposo. A tal proposito è utile servirsi della scala NRS (*Numerical Rate Scale*) considerando un dolore di intensità pari o superiore a 5 su 10 meritevole di essere approfondito prima di cominciare l'esecuzione di qualsiasi esercizio [consultare il "*Protocollo di cura e igiene della stomia per protesi osteointegrata*"].

Il percorso riabilitativo viene suddiviso in sessioni di *training* in base agli obiettivi funzionali/motori stabiliti.

In Figura 2 viene mostrato lo schema italiano del Protocollo Riabilitativo, opportunatamente adattato dallo staff del Centro Protesi Inail partecipante al progetto a partire dallo schema utilizzato dalla Clinica Ortopedica Universitaria Radboud, in Olanda.

Nella versione originale olandese il percorso riabilitativo del paziente osteointegrato transfemorale prevede due ore di allenamento due volte a settimana, per un totale di 22 sessioni distribuite in 11 settimane. È prevista una pausa dopo la decima sessione, in modo tale da consentire al paziente di familiarizzare con l'utilizzo corretto degli ausili per la deambulazione, mantenendo uno schema corretto del passo e rinforzando al contempo la muscolatura, in attesa del compimento della fase finale riabilitativa; durante quest'ultima è prevista la riduzione o, se possibile, l'abbandono degli ausili durante il cammino.

Il periodo di sospensione dall'allenamento può durare 4 settimane, o prolungarsi fino a 12 settimane, qualora il livello del dolore o la limitata forza muscolare non consentissero lo svolgimento della riabilitazione.

Nella versione adattata dallo staff del Centro Protesi Inail sono previste 44 sessioni suddivise in due fasi: la prima (Figura 2a), che si conclude alla ventesima sessione e la seconda (Figura 2b), che ricomincia dalla ventunesima e si conclude la quarantaquattresima, alla quale corrisponde la fine del percorso riabilitativo. Anche in questo caso, tra le due fasi, è previsto un periodo di sospensione (*break*).

Le sessioni vengono effettuate ogni mattina, con una durata complessiva di tre ore circa, dal lunedì al venerdì. Possono, altresì, ripetersi in sessioni ridotte nel pomeriggio, sempre che il paziente non provi dolore o eccessivo affaticamento.

Lo schema che viene illustrato nel dettaglio è considerabile un modello standard, che necessita spesso di essere adattato e personalizzato a seconda delle caratteristiche e delle condizioni cliniche del soggetto.

Il paziente recupera la deambulazione riducendo progressivamente la necessità di appoggi durante la deambulazione.

Il fisioterapista segue costantemente il paziente durante l'esecuzione di ogni singolo esercizio, prestando particolare cura alla corretta esecuzione dei compiti suggeriti e alla postura assunta dal soggetto.

Sessione di training (con supervisione)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	PAUSA
1) Cura della stomia secondo il protocollo	1	2																			
2) Mobilità/rinforzo dell'anca e *core stability*	1																			20	
3) Montaggio corretto della protesi	1	2																			
4) *Training* per la simmetria posturale	1																			20	
5) *Shift* pelvico	1																			20	
6) *Tilt* pelvico attivo			3																	20	
7) Intera fase di appoggio			3													16					
8) Fase di *swing* del passo							7									16					
9) *Training* del passo (TdP) tra le barre parallele							7									16					
10) TdP con 2 stampelle a 3 punti d'appoggio									9									18			
11) TdP con 2 stampelle a 2 punti d'appoggio													13							20	
12) TdP con 2 bastoni a 2 punti d'appoggio																	17			20	
13) TdP con bastoni da Nordic Walking																					
14) TdP senza ausili																					
15) Salita e discesa delle scale													13			16					
16) TdP a differenti velocità													13							20	
17) TdP su superfici irregolari													13							20	
18) Diverse modalità di cammino: di lato, all'indietro, fermarsi, girarsi e slalom																					
19) Strategie per cadere e rialzarsi																					
20) TdP su pendenze																					
21) TdP con ostacoli																					
22) TdP svolgendo un'altra attività																					
23) *Circuit training* in ambienti interni ed esterni																					
24) Bicicletta																					
25) Esercizi pendolari	1																			20	
26) Cyclette	1																			20	
27) Analisi video					5					10					15					20	

Sessione di training (con supervisione)	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
1) Cura della stomia secondo il protocollo																								
2) Mobilità/rinforzo dell'anca e *core stability*	21																							44
3) Montaggio corretto della protesi																								
4) *Training* per la simmetria posturale	21																							44
5) *Shift* pelvico	21																							44
6) *Tilt* pelvico attivo	21																							44
7) Intera fase di appoggio	21																							44
8) Fase di *swing* del passo																								
9) *Training* del passo (TdP) tra le barre parallele																								
10) TdP con 2 stampelle a 3 punti d'appoggio																								
11) TdP con 2 stampelle a 2 punti d'appoggio																								
12) TdP con 2 bastoni a 2 punti d'appoggio	21									30														
13) TdP con bastoni da Nordic Walking	21									30														
14) TdP senza ausili	21																							44
15) Salita e discesa delle scale											31							38						
16) TdP a differenti velocità	21																			40				
17) TdP su superfici irregolari	21																			40				
18) Diverse modalità di cammino: di lato, all'indietro, fermarsi, girarsi e slalom			23																	40				
19) Strategie per cadere e rialzarsi											31	32												
20) TdP su pendenze											31							38						
21) TdP con ostacoli											31							38						
22) TdP svolgendo un'altra attività																	37							44
23) *Circuit training* in ambienti interni ed esterni																			39					44
24) Bicicletta																							43	44
25) Esercizi pendolari	21																							44
26) Cyclette	21																							44
27) Analisi video	21					26						32						38						44

Figura 2 (a, b) - Schema riassuntivo relativo al programma riabilitativo di un paziente osteointegrato con amputazione transfemorale.

ESERCIZI DI RISCALDAMENTO PRE-SEDUTA

Ogni seduta di riabilitazione inizia con gli esercizi di riscaldamento. Questi esercizi possono essere effettuati in combinazione o alternati a discrezione del fisioterapista e sono eseguibili anche durante la seduta, in caso sopraggiunga fatica muscolare. Inoltre, è possibile ripeterli durante la fase di defaticamento.

ESERCIZI PENDOLARI

Consiste in esercizi di oscillazione dell'arto amputato (Figura 3).

Posizione di partenza: paziente in ortostatismo, con protesi indossata. L'arto controlaterale all'arto amputato è mantenuto esteso e in appoggio, in posizione sopraelevata rispetto all'arto protesizzato (ad esempio, sopra uno *step*).

Esecuzione: effettuare delle oscillazioni libere dell'arto amputato lungo il piano sagittale.

Attenzione: durate l'esercizio è opportuno che il soggetto mantenga una corretta posizione del bacino, evitando così di assumere atteggiamenti in antiversione o retroversione; il tronco deve rimanere in asse con il resto del corpo, senza flettersi, ruotarsi o inclinarsi.

CYCLETTE

È raccomandato l'utilizzo della cyclette per circa 10-15 minuti (Figura 4).

Attenzione: è opportuno limitarne l'uso ai soli pazienti che non avvertono fastidi al moncone collegabili a frizioni dei tessuti molli contro la protesi.


Figure 3 e 4 – Esercizi pendolari (sinistra) e cyclette (destra).

ESERCIZI DI STRETCHING MUSCOLARE

Gli esercizi di stretching sono finalizzati a recuperare l'escursione articolare del moncone (molto spesso limitata) e l'elasticità della muscolatura residua.

Tali esercizi possono essere eseguiti dal soggetto prima di ogni sessione o in autonomia, dopo essere stato adeguatamente istruito dal proprio fisioterapista.

Gli esercizi di stretching muscolare sono effettuati senza che venga indossata la protesi.

MOBILIZZAZIONE/RINFORZO DELL'ARTICOLAZIONE COXO-FEMORALE E *CORE STABILITY*

Posizione di partenza: paziente in decubito supino o prono.

Esecuzione: effettuare movimenti di

- Flessione ed estensione dell'articolazione coxo-femorale.
- Abduzione dell'articolazione coxo-femorale.
- Rotazione completa, interna ed esterna dell'articolazione coxo-femorale.

Per quanto riguarda la core stability, sono previste anche sedute quotidiane di riabilitazione robotica con feedback visivo

MOBILIZZAZIONE DEL TRONCO E DELLE SPALLE

Posizione di partenza: paziente seduto con il piede in appoggio al suolo.

Esecuzione: ripetere gli esercizi in serie, controllando la respirazione durante la loro attuazione;

- Torsione del busto, da entrambi i lati;
- Flessione delle spalle fino a 180°;
- Abduzione delle spalle fino a 180°;
- Estensione delle spalle, mantenendo il gomito in flessione;
- Rotazione esterna della spalla, con il gomito flesso a 90°.

PRIMA FASE RIABILITATIVA

PRIMA E SECONDA SESSIONE (1-2)

È opportuno, durante le prime giornate della fase riabilitativa, educare il soggetto all'igiene e all'appropriata cura della stomia, secondo quanto riportato dal protocollo dedicato [consultare il "*Protocollo di cura e igiene della stomia per protesi osteointegrata*"].

A seguire, il fisioterapista e il tecnico ortopedico spiegano ed illustrano al paziente come collegare correttamente la protesi all'impianto.

Prima di iniziare la fase riabilitativa è consigliabile aspettare due settimane da a secondo intervento.

A questo punto, se il soggetto riferisce di non aver dolore (o di aver un dolore accettabile, inferiore a 5/10 punti nella scala NRS), si può iniziare ad effettuare gli esercizi previsti indossando la protesi. In caso contrario, la seduta di riabilitazione potrà cominciare in seguito alla visita medica da parte dello specialista fisiatra.

Le prime sessioni si basano esclusivamente su esercizi in ortostatismo, atti a migliorare l'equilibrio e la distribuzione del peso corporeo su entrambi gli arti inferiori, rimanendo in sicurezza tra le parallele. A tal proposito è utile utilizzare delle bilance per distribuire in modo uniforme ed equilibrato il peso corporeo (50% e 50%).

Durante questi esercizi i piedi sono in appoggio su due diverse bilance, poste in parallelo fra loro.

TRAINING PER LA SIMMETRIA POSTURALE

Posizione di partenza: paziente in ortostatismo tra le parallele con le mani in appoggio.

Esecuzione: è possibile variare la tipologia di esercizi, servendosi di strumenti diversi.

- Impugnare un bastone o una stampella e flettere le spalle a 90°, cercando di rimanere in equilibrio;

- Mantenendo la stessa posizione, il fisioterapista applica dall'esterno delle forze, spingendo o tirando il bastone per provocare delle perturbazioni dell'equilibrio.

SHIFT PELVICO

Posizione di partenza: paziente in ortostatismo, con i piedi in appoggio su due bilance e il peso distribuito in modo equo su entrambi gli arti.

Esecuzione: spostare il peso a destra e sinistra e in avanti e indietro, senza sollevare i piedi.

Il soggetto deve mantenere l'equilibrio mentre:

- Flette a 180° ed estende le spalle in maniera alternata;
- Il fisioterapista, trattenendo i capi di una banda elastica che ha posto a livello della vita del soggetto, effettua delle trazioni (Figura 5a);
- Il fisioterapista, ponendosi ad una distanza di circa 1 metro dal soggetto, passa una palla al soggetto, che deve prenderla con entrambe le mani;
- Il soggetto porta una spalla flessa a 90° con il gomito esteso e la radio-carpica in estensione e il fisioterapista spinge la sua mano su quella del soggetto (Figura 5b);
- Il soggetto porta le spalle flesse a 90° con il gomito esteso, le radio-carpiche in flesso-estensione intermedia e i palmi in opposizione uno contro l'altro. Il fisioterapista spinge contro le mani del soggetto, prima verso l'alto, poi verso il basso, a destra e a sinistra (Figura 5c).

Figura 5 (a, b e c) – Trazioni con banda elastica (sinistra) e perturbamento dell'equilibrio (centro e destra).

TERZA – SESTA SESSIONE (3-6)

Nelle tre successive sessioni di riabilitazione si effettuano esercizi incentrati sulla distribuzione del carico e sulla fase di appoggio dell'arto protesico durante il ciclo del passo.

TILT PELVICO

Posizione di partenza: paziente in ortostatismo, con le mani appoggiate alle parallele e i piedi posti su due bilance.

Esecuzione:

- Effettuare un semipasso con l'arto non protesizzato, appoggiandolo su uno *step* posto davanti alle bilance (Figura 6);
- Sollevare l'arto protesico mantenendo la gamba in estensione, controllando il movimento con la muscolatura del bacino.

ESERCIZIO PROPEDEUTICO ALLA FASE DI APPOGGIO DEL PASSO

Posizione di partenza: in ortostatismo, con le mani appoggiate alle parallele e poste davanti al tronco; i piedi sono in appoggio su due differenti bilance poste una davanti all'altra, in maniera sfalsata tra loro.

Esecuzione:

- Spostare in maniera graduale il peso sull'arto protesico, rimanendo in appoggio con entrambi i piedi;
- Effettuare con l'arto non protesizzato una flessione plantare, spostando progressivamente il peso sull'arto protesizzato. Successivamente si ritorna alla posizione di partenza e si ripete l'esercizio (Figura 7a e 7b).

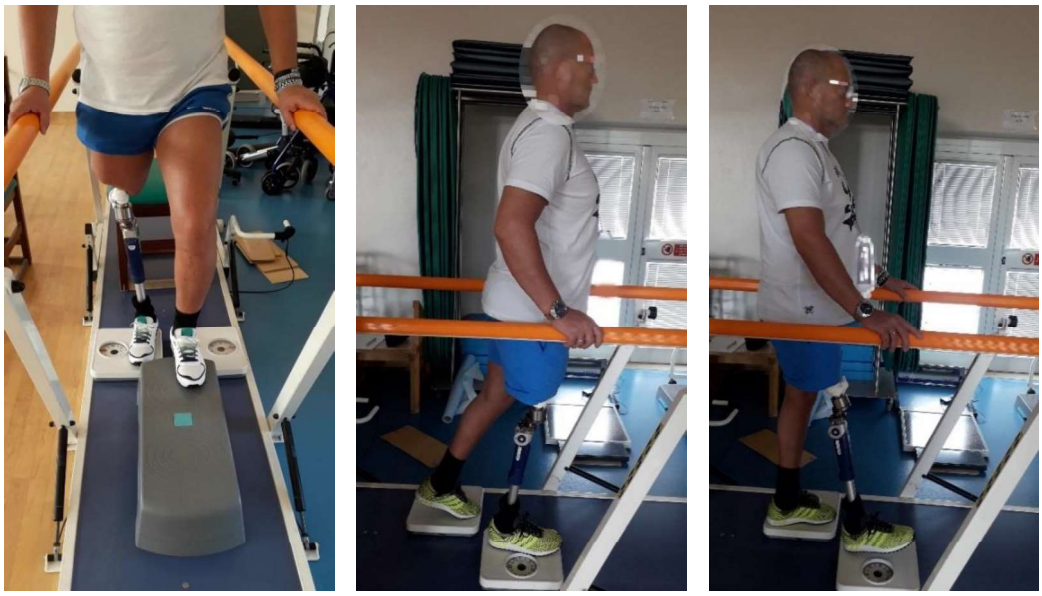

Figure 6 e 7 (a e b) – Semipasso sullo *step* (sinistra) e esercizi di carico sulla protesi (centro e destra).

INTERA FASE DI APPOGGIO

Posizione di partenza: paziente in ortostatismo, con le mani sulle parallele, poste davanti al tronco. Si posizionano tre bilance a terra: due dal lato non protesizzato e una, in mezzo, dal lato con la protesi; i piedi sono in appoggio sulle prime due.

Esecuzione: effettuare con l'arto non protesizzato la fase di oscillazione completa, mentre la protesi accoglie il peso del corpo senza staccarsi mai dal suolo (Figura 8a, 8b, 8c).

Figura 8 (a, b e c) – Fase d'appoggio dell'arto protesizzato.

SETTIMA – OTTAVA SESSIONE (7-8)

A questo punto del percorso riabilitativo, il soggetto è pronto ad affrontare i primi passi in sicurezza, tra le parallele, in modo tale da scaricare parzialmente il peso sugli arti superiori. Contemporaneamente si abbandona l'utilizzo delle bilance.

FASE DI SWING

Posizione di partenza: paziente in ortostatismo, tra le parallele.

Esecuzione: compiere un'intera fase di oscillazione ("swing") con l'arto protesizzato (Figura 9a, 9b, 9c).

Attenzione: le mani, all'inizio dell'esercizio, sono appoggiate davanti al tronco, in modo tale da trovarsi allineate al busto alla fine della fase di *swing*; il busto deve rimanere in asse, senza subire sbilanciamenti.

Figura 9 (a, b e c) – Fase di oscillazione dell'arto protesizzato.

TRAINING DEL PASSO TRA LE PARALLELE

Posizione di partenza: paziente in ortostatismo, tra le parallele.

Esecuzione: invitare il paziente a camminare lungo le parallele.

Attenzione: le mani seguono l'alternarsi dei passi durante il cammino e si muovono in maniera contrapposta rispetto agli arti inferiori (schema crociato).

NONA – DODICESIMA SESSIONE (9-12)

Dalla nona sessione è consentito camminare al di fuori delle parallele, adottando gli ausili necessari e ampliando gradualmente la distanza percorsa.

TRAINING DEL PASSO CON DUE STAMPELLE A TRE PUNTI DI APPOGGIO

Posizione di partenza: paziente in ortostatismo, il fisioterapista segue l'assistito nei movimenti.

Esecuzione: camminare con l'ausilio delle stampelle canadesi.

Attenzione: le stampelle si muovono contemporaneamente all'arto protesizzato. È possibile interporre una fase con la mano dalla parte dell'arto protesico appoggiata alla parallela e la controlaterale appoggiata alla stampella (Figura 10).

TREDICESIMA – SEDICESIMA SESSIONE (13-16)

A questo punto della riabilitazione è possibile incrementare la difficoltà del *training* del passo, invitando il paziente a camminare a differenti velocità e ad affrontare le scale e i terreni con superficie irregolare, come spesso succede camminando all'aperto.

TRAINING DEL PASSO CON DUE STAMPELLE A DUE PUNTI DI APPOGGIO

Si ripete la dinamica dell'esercizio precedente, ma con le stampelle che avanzano in maniera opposta agli arti inferiori, consentendo la fisiologica torsione del busto durante il cammino (Figura 11).

Figure 10 e 11 – Training del passo a due punti di appoggio.

TRAINING DEL PASSO A DIFFERENTI VELOCITÀ

Il paziente è invitato a camminare con due stampelle a due punti di appoggio variando la velocità del passo, sia in accelerazione, che in decelerazione.

TRAINING DEL PASSO SU SUPERFICI IRREGOLARI

Se la situazione lo permette, il fisioterapista accompagna il paziente a camminare con due stampelle all'aperto, saggiando diverse tipologie di terreno (prato, marciapiede, terreno sconnesso) (Figura 12a, 12b).

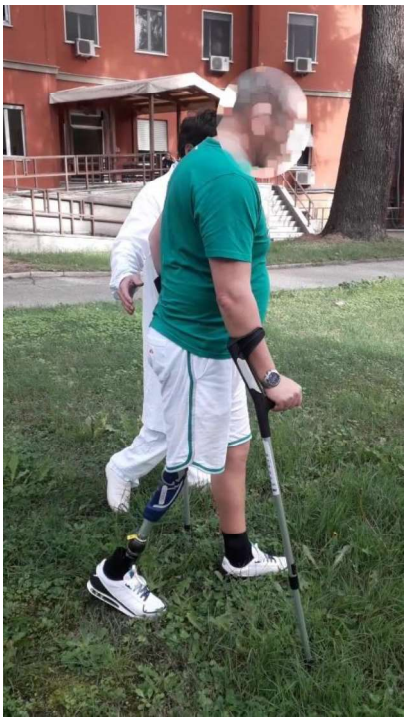

Figura 12 (a e b) – Training del passo all'aperto.

SALITA E DISCESA DELLE SCALE

Posizione di partenza: paziente in ortostatismo, davanti a una rampa di scale; il fisioterapista segue l'assistito garantendone la sicurezza. Si comincia autandosi con il corrimano e una stampella e, raggiunta una certa sicurezza da parte del soggetto, si passa all'utilizzo di due stampelle.

Esecuzione:

- salire le scale, caricando sempre sull'arto protesico e affrontando lo scalino con l'arto controlaterale (Figura 13a);
- scendere le scale, all'inizio flettendo sempre l'arto non protesizzato e scendendo con il controlaterale, per poi passare alla discesa a passo alternato (Figura 13b)

Attenzione: l'esercizio può subire alcune variazioni a seconda del modello di ginocchio protesico in dotazione al soggetto. È consigliabile istruire il paziente su diverse strategie per scendere le scale in maniera sicura, qualora le condizioni lo necessitino (ad esempio: scale disconnesse, folla) (Figura 13c).

Figura 13 (a, b e c) – Salita (sinistra) e discesa (centro) delle scale e discesa in sicurezza (destra).

DICIASSETTESIMA – VENTESIMA SESSIONE (17-20)

TRAINING DEL PASSO CON DUE BASTONI A DUE PUNTI DI APPOGGIO

Si continua il training del passo cambiando la tipologia di ausili, in modo tale da consentire sempre più libertà di movimento al soggetto. Se non sono disponibili due bastoni è possibile capovolgere le stampelle, in modo tale da escludere l'appoggio dell'avambraccio.

PAUSA (*BREAK*)

Si consiglia di interrompere la fase riabilitativa alla fine della ventesima sessione.

La pausa può durare da 4 a 12 settimane a seconda del dolore e dell'affaticamento avvertiti dal paziente.

Qualora il soggetto si dimostrasse particolarmente affaticato durante le sessioni precedentemente descritte, è possibile anticipare la pausa.

SECONDA FASE RIABILITATIVA

Nella seconda fase si riprendono alcuni esercizi della prima fase, quali: *training* per la simmetria posturale, *shift* pelvico, *tilt* pelvico attivo, intera fase di appoggio e *training* del passo con due bastoni a due punti di appoggio a differenti velocità e su superfici irregolari.

VENTUNESIMA – VENTIDUESIMA SESSIONE (21-22)

TRAINING DEL PASSO CON BASTONI DA NORDIC WALKING

Il percorso riabilitativo prosegue cambiando tipologia di ausili. Si riprendono contemporaneamente, gli esercizi di training del passo a differenti velocità e su superfici irregolari.

Attenzione: se non si dispone dei bastoni da Nordic Walking, è consentito il passaggio all'esercizio successivo.

TRAINING DEL PASSO CON UN SOLO PUNTO D'APPOGGIO

Si abbandona uno dei due sostegni utilizzati, mantenendo l'appoggio dal lato non protesizzato (Figura 14).

Attenzione: porre particolare attenzione alla postura del soggetto, in quanto l'abbandono di uno solo dei punti di appoggio potrebbe favorire la creazione di compensi durante l'attuazione del passo.

TRAINING DEL PASSO SENZA AUSILI

È consigliabile, una volta abbandonati gli ausili, affrontare i primi passi tra le parallele, con gli arti superiori liberi e senza appoggi; una volta che il soggetto si sente sicuro si può continuare l'esercizio al di fuori delle parallele (Figura 15).

Figure 14 e 15 – Training del passo con un punto d'appoggio (sinistra) e senza punti d'appoggio (destra).

VENTITREESIMA – TRENTESIMA SESSIONE (23-30)

TRAINING IN DIVERSE MODALITÀ DI CAMMINO

Il Fisioterapista invita il soggetto a camminare all'indietro e lateralmente, fermandosi al comando; continua la sessione facendo effettuare al paziente degli slalom attorno ad alcuni ostacoli e insegnandogli come girarsi su sé stesso in sicurezza.

TRENTUNESIMA – TRENTASEIESIMA SESSIONE (31-36)

SALITA E DISCESA DELLE SCALE SENZA AUSILI

Il paziente riprende gli esercizi di salita e discesa delle scale, nelle stesse modalità già descritte, ma senza l'ausilio delle stampelle o dei bastoni.

TRAINING DEL PASSO SU PENDENZE

Posizione di partenza: paziente in ortostatismo, ai piedi di una pendenza.

Esecuzione: camminare lungo una pedana con una pendenza regolabile a vari gradi di inclinazione, ripetendo l'esercizio sia in salita, che in discesa.

Attenzione: se il ginocchio protesico lo consente, è opportuno insegnare al paziente ad affrontare una pendenza sia con l'articolazione bloccata, sia libera.

TRAINING DEL PASSO CON OSTACOLI

Posizione di partenza: paziente in ortostatismo, davanti all'ostacolo; il fisioterapista si pone a lato del soggetto, sorreggendolo in caso di incertezza.

Esecuzione: camminare oltrepassando l'ostacolo interposto lungo il cammino; modificare l'altezza dell'ostacolo per variare la difficoltà dell'esercizio.

STRATEGIE PER CADERE E RIALZARSI

Insegnare gli esercizi di strategia per cadere e rialzarsi è indispensabile al fine di evitare qualsiasi trauma diretto a livello dell'impianto.

Posizione di partenza: paziente in ortostatismo, davanti un tappetino.

Esecuzione: chiedere al paziente di simulare una caduta seguendo le tecniche precedentemente illustrate dal fisioterapista.

TRENTASETTESIMA – TRENTOTTESIMA SESSIONE (37-38)

TRAINING DEL PASSO SVOLGENDO UN'ALTRA ATTIVITÀ

Il fisioterapista invita il paziente a camminare eseguendo, contemporaneamente, altri compiti, come parlare, portare un vassoio o la busta della spesa.

TRENTANOVESIMA – QUARANTAQUATTRESIMA SESSIONE (39-44)

CIRCUIT TRAINING IN AMBIENTI ESTERNI ED INTERNI

Il paziente conclude il suo percorso riabilitativo affrontando dei percorsi prestabiliti, con diversi tipi di terreno e ostacoli da superare, al fine di integrare tutte le abilità apprese nel corso delle diverse sessioni (Figura 16).

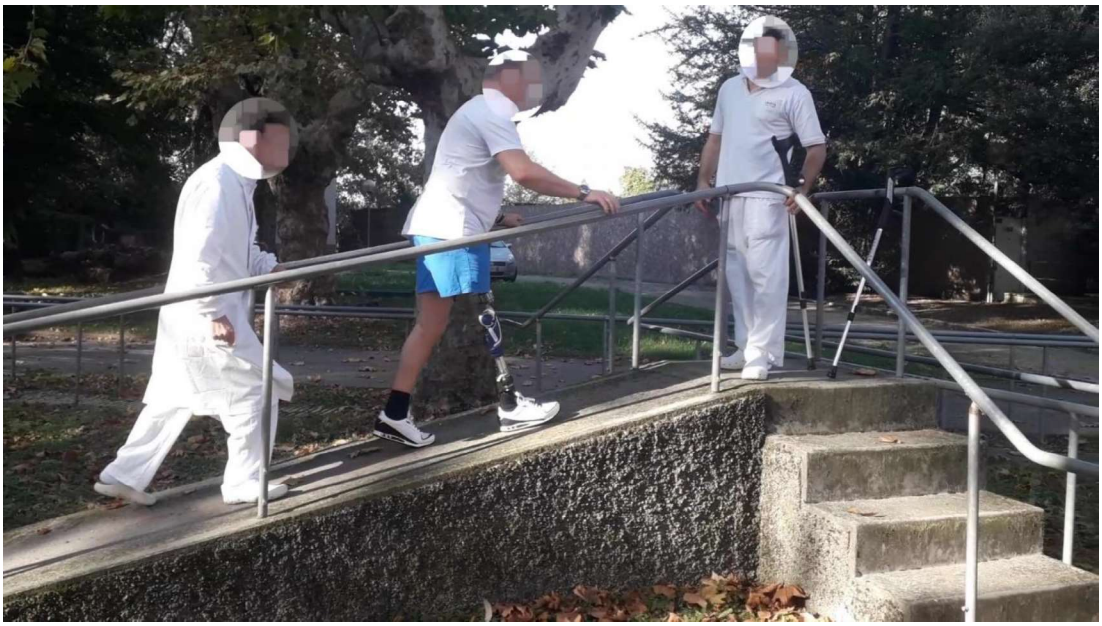

Figura 16 – Circuit training in ambiente esterno.

CONCLUSIONI

A sei mesi dall'intervento, il paziente è in grado di camminare in ambienti interni ed esterni e senza l'ausilio di alcun supporto. Nel caso in cui il paziente si presenti, all'inizio della riabilitazione, con una massa muscolare compromessa, un deficit di densità ossea, o altre problematiche è possibile che il percorso riabilitativo venga prolungato fino a dodici mesi.

SUPPORTO PSICOLOGICO

Appare spesso necessario, durante la fase riabilitativa, disporre di un percorso di sostegno psicologico da parte di una figura opportunatamente formata.

È consigliabile, inoltre, organizzare le sessioni di *training* in modo tale da coinvolgere insieme diversi pazienti trattati con osteointegrazione, per far sì che i membri all'interno del gruppo si possano confrontare sul percorso e sulle sensazioni provate, che differiscono sensibilmente da quelle conseguenti l'utilizzo di protesi tradizionale con invasatura.

ANALISI VIDEO

È consigliabile, qualora possibile, effettuare delle riprese video libere o dei test sulla qualità del cammino (in media, una volta ogni cinque sedute). Tale accorgimento permette di verificare i miglioramenti del paziente e discutere direttamente con l'interessato in merito a errori di postura o di esecuzione degli esercizi.

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