Osseointegrated Implants in Patients With Diabetes Mellitus: A Case Series of Eight Patients

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ABSTRACT

Background: Osseointegration is a novel approach to eliminate socket related problems experienced by amputees. Over 70% of amputations in developed countries are due to vascular causes with the prevalence of diabetes mellitus reaching pandemic status leading to more amputations. Traditionally, diabetic patients with amputations have been excluded from Osseointegrated reconstruction due to higher risks of complications. This is the first study reporting on the clinical outcomes of diabetic patients receiving an Osseointegration.

Method: this is a case series with one-year follow-up in ten diabetic patients with a trans-tibial or trans-femoral amputation, and has received Osseointegration implants between 2013 and 2016. Clinical and functional outcomes were assessed including pain, prostheses wearing time, mobility, walking ability and quality of life. Adverse events were monitored and recorded, including infection, fractures, implant failure, revision surgery, further amputation, and death.

Result: four trans-tibial and six trans-femoral amputees (aged 49-74 years) were included in this study. All patients were pain-free and still using the Osseointegrated prosthesis at 12-months post-surgery. The mobility of all patients improved at follow-up. Notably, Six of the ten patients were wheelchair-bound prior to surgery, but all were able to walk and perform daily activities at follow-up. Two patients experienced infection events which were treated by surgical debridement and antibiotics. One patient experienced per prosthetic fracture after a fall which was fixated by retrograde nail with a lag screw. No other adverse events were recorded.

Conclusions: Lower limb amputees with a history of diabetes mellitus have been traditionally excluded from Osseointegrated reconstruction. Here we report the initial results of treating diabetic amputees with osseointegration, demonstrating improvements in function, mobility, and quality of life. It can be expected that the improved function and mobility can serve a protective role in controlling the underlying diabetic conditions in these patients which make Osseointegration an attractive alternative to conventional socket prosthesis.

Level of evidence: Therapeutic Level IV.
BACKGROUND

Worldwide incidence of lower-limb amputation is highly variable with incidence rates ranging from 5.8 to 31 per 100,000 (Moxey, Gogalniceanu et al. 2011). In Australia, amputees represent 1 per 1,000 individuals with one Australian losing a lower limb every 3 hours as a direct result of diabetes-related disease ((AOPA) 2015)

Rehabilitation post-amputation will often aim to provide the patient with a prosthetic device that endeavours to substitute the function and appearance of the lost limb. (Sanders, Bell et al. 1998, Beil and Street 2004) These factors, in addition to comfort, have been confirmed as being important to improve their quality of life by improving their mobility (Warmuz, Szeliga et al. 2003). The quality of life for people with lower limb amputations is heavily dependent on their level of mobility and pain they feel in their residual limb (Dumbleton, Buis et al. 2009), thus impacting prosthetic use. Reciprocally, a poor prosthetic fit is associated with reduced adherence due to numerous pressure- associated sequelae. High pressures may lead to occlusion of the cutaneous blood flow and friction between the skin and the socket, which impede daily prosthetic use, and reduce the mobility of the amputee, and jeopardize vocation (Meulenbelt, Dijkstra et al. 2006). Approximately 86% of patients with a lower extremity amputation are fitted with a socket prosthesis (Rommers, Vos et al. 1997). A well-fitting prosthesis is essential to increasing mobility and reducing residual limb pain (Redfield 2013). However, around 34–63% of these patients have chronic skin problems and pain associated with the socket.[3, (Butler, Bowen et al. 2014) (Lyon, Kulkarni et al. 2000, Meulenbelt, Dijkstra et al. 2006) such as discomfort, pain, sweating and skin irritation or breakdown (Redfield 2013) These problems often have a severe impact on quality of life which related to problems at body function or structures (e.g., limited prosthesis use) and activity level (mobility restrictions) with as consequence limitations in participation. (Brânemark, Berlin et al. 2014) (Demet, Martinet et al. 2003). The consequent reduction in activity does not only influences physically on the patient’s life but may also have psychological impacts due to a decreased sense of achievement and frustration at their inability to complete activities of daily living independently [6](Klute, Glaister et al. 2010) (Sanders 1995).

Over the last two decades, a technique has been advanced to preclude the socket related problems which allow the prosthetic limb to be rigidly attached to the residuum itself transcutaneously. This is accomplished by adhering to the principles of Osseointegration, which performs in a structural and functional connection between the macro-porous surface of a biocompatible metal implant and living bone (Al Muderis, Bosley et al. 2016). This technique has participated to a significant improvement in the quality of life, mobility of recipients, reducing the energetic cost of walking (Hagberg, Brânemark et al. 2008) In addition to formation Osseo-perception.

To date, diabetic patients with amputation have been an exclusion criterion for osseointegration. (Aschoff and McGough 2012). Diabetes is a common metabolic disorder that affects approximately 170 million people worldwide, including 20.8 million in the USA (Control and Prevention 2011) and by 2030 these numbers are projected to double, (Rathmann and Giani 2004) characterized by hyperglycaemia due to impaired insulin secretion, insufficient insulin action, or both. The vast majority of diabetic cases fall in one of the following categories type I (insulin dependent diabetes mellitus ) and type II (non-insulin dependent diabetes mellitus) (Association 2010).

Over 100 known physiologic factors contribute to wound healing deficiencies in individuals with diabetes These include decreased or impaired growth factor production (Falanga 2005, Galkowska, Wojewodzka et al. 2006, Goren, Müller et al. 2006), angiogenic response (Falanga
macrophage function (Lobmann, Ambrosch et al. 2002), collagen accumulation, epidermal barrier function, quantity of granulation tissue (Falanga 2005), keratinocyte and fibroblast migration and proliferation, number of epidermal nerves (Brem and Tomic-Canic 2007), bone healing (Lobmann, Ambrosch et al. 2002) and bone mass. The decrease in bone mass observed in diabetes is not necessarily due to insulin deficiency itself as diabetes is frequently associated with other risk factors for osteoporosis such as negative protein balance, reduced physical activity, or impaired gonadal function (Bouillon 1991).

The consequences of persistent and poorly controlled hyperglycaemia lead to neuropathic and vascular abnormalities that cause diabetic ulceration. 82% of all vascular-related lower extremity amputations in the USA are associated with diabetes (Moxey, Gogalniceanu et al. 2011) and patients with diabetes have a 30 times greater lifetime risk of having an amputation than patients without diabetes (Tentolouris, Al-Sabbagh et al. 2004).

The purpose of this paper is to examine the outcomes of Osseointegrated reconstruction in diabetic patients. Clinicians might be irresolute to prescribe Osseointegration therapy for the diabetic patient for a variety of reasons, including delayed wound healing, the prevalence of macro and micro-vascular disease, impaired response to infection and bone loss. The ability to treat this special group of patients with Osseointegration brings the potential of significantly improving their function and mobility level, which may have major impacts on their quality of life and even survival. It should be noted however that, up to date, there is a lack of well-designed, large-scale, epidemiological studies reporting on the incidence of complications during the osseous healing process in the population of diabetic patients (Retzepli and Donos 2010).
METHOD

Study design

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

Participants

Patients are diabetic with lower limb amputation treated with Osseointegrated implants between September 2013 and March 2016 in Sydney, Australia. The inclusion criteria were diabetic patients with trans-tibial and trans-femoral amputation. The exclusion criteria were smoking, psychological instability, limb exposure to radiation, ongoing chemotherapy, and inability to comply with the treatment program. This study was approved by the human research Ethics committee and all participants gave their informed consent (Sydney: 014153S)

Surgery and rehabilitation

The Osseointegration implant is press-fitted into the residual bone by single-stage or two stages surgery. Prospective candidates underwent an assessment by the multidisciplinary team; Candidate had a medical, psychological, physiotherapy and prosthetic assessment. A pre-osseointegration gait analysis is also included. Much of the pre-osseointegration assessment focuses on the candidate's current diabetes control. A computed tomography (CT) scan and standard radiographs were used for designing the customized 3D-printed titanium implant. The Human Research Ethics Committees approved the study. All subjects signed an informed consent form.

Spinal anesthesia blockade was combined with general anesthesia. Prophylactic antibiotics using 2g of cephazolin was given on induction. Prepping was done using alcoholic chlorhexidine on the affected limb, followed by the application of a disposable fenestrated extremity drape. All patient but one (cases 6) an elliptical horizontal incision was made at the distal end of the stump, after which the soft tissues were reduced to a minimum. All vessels and nerves were ligated, and a flap of skin and subcutaneous tissue was created to the distal end of the stump. The subcutaneous tissue at the distal end of tibia or femur in trans-tibial and trans-femoral was removed respectively and the dermis was sutured circumferentially to the periosteum, after which the wound was closed.

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All patients but one (case 1) underwent a single-stage Osseointegration consequently the stoma was created at the level of the femur or tibia using a circular cutting device (Corer). The medullary canal was reamed, followed by press-fit implantation of the intramedullary component of the Osseointegration device under image intensifier guidance. The dual cone component of the Osseointegration device was then inserted into the intramedullary component and secured with an internal locking screw. One patient (case 6) underwent amputation with single stage osseointegration as mentioned previously. One patient (case 1) was performed in two stages with the first stage involving the reduction and reconstruction of soft tissues and implantation of the intramedullary component. The second stage was performed 6-8 weeks later as a guide wire is used to localize the center of the cannulated end –cap. A coring device is then passed over the guide wire, perforating the skin and subcutaneous tissue to create a stoma. A dual-cone component of appropriate length is then inserted into the intramedullary implant and secured with an internal locking screw. The wound care involved daily dressing changes with dry ribbon gauze and the Patients were instructed to wash the stoma with soap and warm tap water twice daily. Staples were removed within 3-4 weeks. Patients followed the Osseointegration Group of Australia Accelerated Protocol (OGAAP) for rehabilitation (Al Muderis, Tetsworth et al. 2016).
Study outcomes

**Descriptive statistics**: Patient demographics, the cause of amputation, age at amputation and previous medical history were recorded at baseline.

**Clinical outcomes**: Pain scores were assessed at the 12-month follow-up.

**Functional outcomes**: Functional outcomes were assessed at baseline and at the 12-month follow-up. Prosthesis wearing time was assessed using the Questionnaire for persons with a Trans-Femoral Amputation (Q-TFA) prosthetic use score (0-100 points). Mobility level was measured using K-levels (K0–K4, where K0 represents a non-ambulatory person and K4 represents an active, high-level prosthetic user). Walking ability was evaluated using the Six Minute Walking Test (6MWT)(Lin and Bose 2008) and the Timed Up and Go (TUG) test(Schoppen, Boonstra et al. 1999). the Quality of life assessments was conducted using the Short Form Health Survey-36 (SF-36) (0-100 points) and the Q-TFA global score (0-100 points). The SF-36 estimates physical and mental aspects of quality of life. (Ware Jr 2000) The Q-TFA was originally developed and validated to study amputees using trans-femoral socket prostheses, but could also be used for patients converting from socket to osseointegrated prostheses(Hagberg, Brånemark et al. 2004, Van de Meent, Hopman et al. 2013), (Hagberg, Hansson et al. 2014) It is validated for use by trans-femoral amputees, but also estimates aspects that are relevant for trans-tibial amputees(Hagberg, Brånemark et al. 2004)

**Adverse events**: Adverse events related to the Osseointegrated implant were observed, including infections, fractures, implant failure, the need for revision surgery, and further amputation. All adverse events and subsequent interventions were noted in the patient’s medical file. By default, plain radiographs were taken at baseline and follow-up. Cases of infection were managed by one of the following: administer conservative management (salt bath and topical antiseptic agent), visit the general practitioner, or visit the clinic for further evaluation. The severity of infection was graded into four levels based on clinical findings: (1) low-grade soft-tissue infection, (2) high-grade soft-tissue infection, (3) deep bone infection, and (4) septic implant failure (Al Muderis, Bosley et al. 2016).

**Data analysis**

Differences in functional outcome measures between baseline and follow-up were calculated in measurement units and compared. Analyses were conducted using Systat SPSS v.22.0 (IBM Corp., Armonk, NY, USA).
RESULTS

Patient characteristics

Ten patients (8 males and 2 females, aged 49–74 years) were included. All patients were diabetic and 9 of them had trans-tibial or trans-femoral amputation while one had Charcot disease.

Five patients had an amputation due to infection, three patients due to trauma, and one due to a gunshot. One patient (case 6) underwent amputation with Osseointegration surgery due to Charcot disease with Left foot ulcer which was not healing and was struggling for the last four years before the operation. Two of this group underwent soft tissue infection which was (case 1 and case 4) which were successfully treated by surgical debridement and antibiotics. One patient of this group (case 1) had left femur peri-prosthetic fracture which was fixed by femoral neck lag screw added to his implant.

All patients but one (case 6) underwent amputation months to years prior to Osseointegration surgery. All patients but one (case 6) attempted to use socket prostheses, which resulted in excessive amounts of phantom limb pain, socket-interface problems, and subsequent failure in utilizing the prosthesis.

Clinical outcome

At follow-up, all patients were pain-free and no patients experienced phantom limb sensations.

Functional outcomes

Clinical follow-up was performed and radiographs were made at three and six months, at one year, five patients were wheelchair-bound at baseline. At follow-up, all ten patients were able to walk unaided and were still using the Osseointegrated prosthesis. The mobility level (K-level) of all patients increased at follow-up compared to baseline. The three ambulatory patients showed improvements in TUG results and improvements in 6MWT results. The originally non-ambulatory patients were able to perform walking tests post-surgery. All patients showed improvements in the SF-36 physical score at follow-up, while the SF-36 mental score remained unchanged, possibly due to the small sample size. The Q-TFA was only assessed in ambulatory individuals that were able to utilize a socket. At follow-up, the Q-TFA global score of all the ambulatory patients increased, while that of the non-ambulatory patients reported results similar to earlier investigations (Al Muderis, Tetsworth et al. 2016).

Adverse events

Radiographs showed stable and well-aligned implants in all patients, with evidence of osseointegration between the bone and implant. All patients achieved complete healing of the stoma and experienced minimal discharge at follow-up. No one presented with stoma irritation or excessive granulation. Cases 1 and 4 each experienced one episode of soft-tissue infection, which were successfully treated with surgical debridement and antibiotics. No patients experienced deep infection osteomyelitis, implant loosening or other complications, and above level amputation.
DISCUSSION

This study is the first case series presenting the outcomes of osseointegration surgery in transtibial or trans-femoral in diabetic amputees. This group of patients would normally be precluded from osseointegration surgery, while the treatment resulted in a low incidence of pain at one-year follow-up and improvements in prosthesis wearing time, mobility level, walking ability, and quality of life. The radiographs were regular at follow-up. Two cases of soft tissue infections in the skin-penetration area of the OIP were presented successfully managed with debridement and/or antibiotics. However, we did not observe deep infections/osteomyelitis. Overall; osseointegration resulted in multiple benefits in this group of patients, as well as convenient severity and rate of adverse events.

Diabetic-related risk factors for lower extremity amputation include prolonged duration of disease, poor glycemic control, high blood pressure and treatment with insulin (Rawdaree, Ngarmukos et al. 2006). Patients with diabetes are more likely to progress to a higher level of amputation (Davis, Brown et al. 2010). Subsequent amputation, diabetes can result in soft tissue infection, skin lesions and ulcers of the lower extremity. Concomitant neuropathy with sensory loss also occurs frequently in diabetics (Cawley 1987, Clayton and Elasy 2009). Such patients have a less favorable environment for wound recovery and high risks of infections development. Increasing the mobilization through osseointegrated reconstruction can play an important protective role. (Batty 2002, Clayton and Elasy 2009) Studies have shown an inverse association between level of physical activity and the incidence of any stroke (Batty 2002). Therefore, the osseointegrated implant may confer benefits beyond the functional and quality of life improvements in diabetic patients through ambulating of these patients after amputation and improve their cardio-respiratory fitness, Osseointegrated reconstruction may play a vital role in their overall survival.

Rehabilitation of this group of patients by using Osseointegration surgery has a significant impact on healthcare systems and society. Diabetes without concomitant vascular disease accounts for up to 53% of amputations in Australia. Therefore, it is worthwhile to endeavour Osseointegration in similar but larger patient groups, considering the positive results of this study and the presented advantages of Osseointegrated reconstruction (Hagberg, Brånemark et al. 2008, Hagberg, Hansson et al. 2014, Leijendekkers, van Hinte et al. 2016).

Osseointegration surgery has predominantly been performed in trans-femoral amputees with an exclusion of diabetic patients. Multiple studies have been completed to compare the outcomes of the socket and osseointegrated prostheses in amputees (Van de Meent, Hopman et al. 2013, Khemka, Frossard et al. 2015, Leijendekkers, van Hinte et al. 2016). No similar studies have been performed in diabetic amputees to date.

All patients in this case series have well-controlled diabetes mellitus and showed significant improvements in all outcome measures following Osseointegration surgery. In this case series, all patients but one (case 1) underwent single-stage Osseointegration. One out of ten patients performed the amputation with single stage Osseointegration who has Charcot disease. Three out of ten patients had trauma which was the cause of amputation, one of ten had gunshot injury which led to amputation while the rest of cases due to infection. Four out of ten patients have below knee amputation while the rest of them are above knee amputation. Despite one of the standard indications for osseointegration surgery being the inability to use socket prostheses. For these three patients with a skin flap adequate for wearing socket-mounted prostheses was not possible. Osseointegration was therefore offered as a solution to preserve the knee joint.
In this case series, K-levels and SF-36 were chosen as outcome measures which could be completed by all patients at both baseline and follow-up. Improvements in K-levels (average 2 levels) and the SF-36 physical component score (range 8.7–30.3 points). In addition to Q-TFA for assessing health-related quality of life. This is considered one of our limitations in this study. This tool is validated for use in non-elderly trans-femoral amputees, not in trans-tibial amputees (Hagberg, Brånemark et al. 2004). The outcome measure was chosen as it covered most aspects of health-related quality of life which were also relevant for trans-tibial amputees. Regrettably, we don’t have a particular design tool to use in trans-tibial amputees. To have an accurate assessment of outcomes of trans-tibial amputees, substitution validated assessments such as the Patient-Reported Outcomes Measurement Information System (PROMIS), Short Musculoskeletal Function Assessment Questionnaire (SMFA), or Prosthetic Limb Users Survey of Mobility (PLUS-M) questionnaires should be considered (Cella, Riley et al. 2010, Hafner, Morgan et al. 2016).

Larger prospective case-control studies with longer follow-up duration will be necessary to accurately inspect the adverse events such as technical failures and infection rates of Osseointegration surgery in this patient group.

In conclusion, based on these observations we think that a bone anchorage prosthesis is a safe and satisfactory alternative treatment and it may be concluded that is not contraindicated in amputees suffering from diabetes mellitus with a good metabolic control (serum glycemic level and HbA1c in the normal range). It can result in benefits including improved function, mobility, quality of life. Thus control of diabetes and treatment of soft tissue infections should be an important part of the overall management of diabetic patients and consequently could play an important role in successful Osseointegration. Furthermore, Glycaemic control is an essential parameter for the success of Osseointegration in individuals with diabetes. Nevertheless, larger studies with longer follow-up duration are required to substantiate the feasibility of implementing osseointegration surgery as the standard of care for amputees with diabetes mellitus. In a subsequent study, we plan to investigate adverse events of Osseointegration in a larger population with longer follow-up.
REFERENCES


