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The role of osseointegration in patients with amputated limbs – clinical outcomes, safety issues and adverse events: A systematic review of the evidence

Running title: Osseointegration for amputated limbs

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Abstract

Background: Osseointegration, an approach for direct skeletal attachment of a prosthesis to an amputated limb, may address many of the socket-related problems associated with socket prosthesis. However, the safety issues and adverse events associated with osseointegration is uncertain. This study aimed to summarize evidence on functional and clinical outcomes, as well as adverse effects of osseointegration for patients with amputated limbs.

Methods: MEDLINE, EMBASE, Web of Science, and Cochrane Library were searched to April 2018. Eligible studies were observational, case, and qualitative studies, and randomized controlled trials (RCTs) conducted in patients with limb amputations, who were managed with osseointegrated prostheses, and had follow-up data.

Results: Twenty-two eligible articles comprising 13 unique studies were included. No RCT was identified. Sample sizes ranged from 11 to 100 participants. All relevant studies reported improvement in functional outcomes (walking ability, prosthetic use, and mobility), satisfaction, and quality of life following osseointegration compared with their preoperative status or when using conventional socket prosthesis. Infection rates (95% confidence intervals) ranged from 1.0% (0.2-5.4) to 76.7% (59.1-88.2). Majority of these infections were described as low-grade soft tissue or superficial infections related to the skin-implant interface, which were effectively treated with antibiotics. None of the studies reported additional amputation or death as a result of osseointegration.

Conclusion: Osseointegration of limb amputations confers increased prosthetic use, better sitting comfort, improved walking ability, mobility, gait, and quality of life. However, it is associated with an increased risk of soft tissue infections. Robust evidence from definitive trial designs are warranted.

Key words: osseointegrated prosthesis, limb amputation, function, quality of life, infection

Introduction

Following an extremity amputation, patients are usually provided with socket-suspended prostheses which represent the current standard of care. However, accumulating evidence suggests that these traditional sockets can be problematic due to residual volume changes, poor suspension, failure in load transfer and stability, and skin problems; thereby reducing the use of the prosthesis and overall quality of life.[1-5] Over the past two decades, osseointegration has emerged as a novel approach for the attachment of an externally fitted prosthesis to an amputated limb. It has been suggested this approach addresses many of the socket-related problems associated with socket prosthesis, as it involves direct attachment of the prosthesis to the residual bone. The concept of osseointegration emerged over five decades ago started by Swedish Professor Per-Ingvar Branemark and its principle is based on the ability of living bone cells to attach to metal surfaces.[6] After successful experimental studies in rabbit models, osseointegration was introduced in humans and employed in dental implants,[7] with progression to bone-anchored hearing aids and other implants.[8] Osseointegration usually involves two surgical procedures in which the metal implant is inserted into the bone of the arm or leg and this implant penetrates through the skin. The artificial limb or prosthesis is easily attached to this implant with a connector (**Fig. 1**). The technique of osseointegration has been reported to offer many advantages compared to socket prostheses and these include improved walking and joint movement, longer walking distances, increased stability, ability to quickly put on and off the prosthesis, better sitting comfort, and improved image and quality of life.[9-16] Though there are potential benefits of osseointegration as a result of direct skeletal attachment, the concept of a metal implant protruding through the skin and communicating with the external environment has raised substantial concerns about the risk of adverse events such as deep infection, osteomyelitis, other complications as well as their management.[17] The safety and adverse events associated with osseointegration is however uncertain because of limited and sparse clinical evidence. In this context, this study aimed to identify and summarize any evidence on clinical and functional outcomes as well as adverse effects and complications of osseointegration for people with limb amputations using a systematic review as well

as qualitative and quantitative synthesis of the literature. The review will cover all observational (prospective cohort, nested case-control, or case-control, retrospective cohort) studies, case reports, case studies, and interventional studies conducted in patients with upper and lower limb amputations who were managed with an osseointegrated implant system.

Methods

Data sources and search strategy

This review was conducted in accordance with PRISMA guidelines[18](**Supplementary Material 1**). Observational studies (prospective cohort, nested case-control, or case-control, retrospective cohort), case studies, case series, qualitative studies, non-randomised studies, and randomised controlled trials (RCTs) were searched in MEDLINE, EMBASE, Web of Science, Cochrane Library, and reference lists of relevant studies from inception to 23 April 2018. The computer-based searches combined free and MeSH search terms and combination of key words related to the intervention (e.g., "osseointegration", "bone regeneration") and population (e.g., "amputation", "artificial limbs"). Only articles published in English were considered and were restricted to humans. Reference lists of relevant articles were manually scanned for additional studies likely to have been missed by the electronic search. Details on the MEDLINE search strategy are provided in **Supplementary Material 2**.

Study selection

The following studies were included: those enrolling consecutive patients with upper or lower limb amputations who were managed with an osseointegration implant system, had follow-up durations, and have reported on clinical and functional outcomes, adverse events or complications associated with osseointegration. The intervention was any osseointegrated prosthesis, whether it was a single-staged or a two-staged procedure. Studies based on osseointegrated finger or digital prostheses were not included. The initial screening of titles and abstracts to retrieve potentially relevant articles was

performed by one reviewer. Detailed evaluation of the full texts of these relevant articles was conducted to determine whether they met all inclusion criteria, and this was conducted independently by two reviewers.

Data extraction and quality assessment

Using a standardized predesigned data collection form, data were extracted on study publication date, study design, geographical location, baseline mean or median age, percentage of males, type of amputation and indication for amputation, eligibility criteria for implantation, type of implantation, duration of follow-up, sample size, and outcomes. Methodological quality of non-randomised studies including cohort and case-control studies was assessed based on the nine-point Newcastle–Ottawa Scale (NOS).[19] It uses three pre-defined domains namely: selection of participants (population representativeness), comparability (adjustment for confounders), and ascertainment of outcomes of interest. The NOS assigns a maximum of four points for selection, two points for comparability, and three points for outcome. Nine points on the NOS reflects the highest study quality. Based on previously published evidence,[20, 21] we judged studies that received a score of nine points to be at low risk of bias, studies that scored seven or eight points to be at medium risk, and those that scored six or less to be at high risk of bias.

Outcome measures and definitions

Outcomes extracted were daily prosthetic use, implant survival rates, adverse events and complications as well as measures of function, mobility, satisfaction, and quality of life as assessed by validated outcome measures such as 6-minute walk test (6MWT),[22] Timed Up & Go (TUG) test,[23] K-levels,[24] Short Form-36 (SF-36) scores,[25] Questionnaire for Persons with Transfemoral Amputation (Q-TFA) scores,[26] the Amputation Mobility Predictor (AMPPRO),[27] life habits questionnaire (LIFE-H),[28] and the lower extremity scale (LEFS).[29] Majority of these outcome measures are based on self-report questionnaires. The SF-36 is a generic measure for the assessment of general health-related

quality of life. The results of this score are presented in eight subscales. The Q-TFA is a condition specific outcome measure used for transfemoral amputees and reflects current prosthetic use, prosthetic mobility, problems, and global health. Quality of life assessments are conducted using the SF-36 and the Q-TFA global score. Walking ability is evaluated using the 6MWT and the TUG test.

Data synthesis and analysis

Where possible, the proportions or rate of adverse events e.g., infections (estimated from the number of patients with adverse events within the period of follow-up/total number of participants) with 95% confidence intervals (CIs) were estimated across studies. The Freeman-Tukey variance stabilising double arcsine transformation [30] was used in estimating the rates because of the binary nature of the data and low rates associated with some of the data. Given the variety of measures reported for the outcomes and inconsistent reporting by the studies, a formal meta-analysis could not be performed; a narrative synthesis was rather conducted. The findings of such studies were summarised in tables that included the main characteristics of the study and the results in natural units as reported by the investigators. STATA release 14 (Stata Corp, College Station, Texas, USA) was used for all relevant statistical analyses.

Results

Study identification and selection

Fig. 2 shows the flow of studies through the review. The initial search of relevant databases and manual scanning of reference lists of relevant studies identified 177 potentially relevant citations. After the initial screening of which was based on titles and abstracts, 42 articles remained for full text evaluation. Following detailed evaluation, 20 articles were excluded because (i) they included populations not relevant to review (n=4); (ii) the outcomes reported were not relevant (n=4); (iii) populations were based on finger prostheses (n=4); (iv) articles were in German (n=4); however, the study patients overlapped with that of another study already included in the review;[31] and (v) was a

study protocol. The remaining 22 articles[9, 11-16, 31-45] comprising 13 unique studies met the inclusion criteria and were included in the review.

Study characteristics and quality

Table 1 summarises the characteristics of the studies included in the review. Studies were published between 2003 and 2017. Studies were conducted in Europe (Sweden, Netherlands, Austria, Germany, and the UK) and Australia. Majority of studies were however based on the prospective Osseointegrated Prostheses for the Rehabilitation of Amputees (OPRA) study conducted in Sweden. A variety of study designs were employed which included observational cohorts (prospective or retrospective cohorts), prospective case-control, case series or reports, and qualitative studies. Whiles majority of studies were before- and after-designs, two studies compared outcomes in patients using osseointegrated prosthesis with those using socket prosthesis.[11, 16] One retrospective cohort study split patients into two groups to compare outcomes between the first two previous designs and the final design of the osseointergrated implant system.[44] No RCT was identified. Methodological quality of included observational cohort and case-control studies using NOS criteria ranged from 4-8.

Baseline characteristics of study populations

Sample size of cohorts (excluding case reports or series) ranged from 11 to 100 participants (**Table 1**). Three studies were case series or reports comprising 1-5 patients.[33, 40, 41] Though the study populations varied and included patients with amputations of the lower and upper limbs, majority of studies were conducted in patients with transfemoral amputations (**Table 2**). Traumatic injury and tumours were the major indications for amputation. The mean baseline age of study participants at implantation ranged from 42 to 48 years. In a case series of 5 patients with peripheral vascular disease (PVD), age at implantation ranged from 56 to 84 years.[46] The mean interval between amputation and implantation and the mean duration of follow-up after implantation ranged from 9 to 19 years and 1 to 8 years respectively. Majority of studies used a two-stage procedure and the implant type used by studies

included the Integrated Leg Prosthesis (ILP) or Osseointegration Prosthesis (OIP), Osseointegrated Prosthetic Limb (OPL), OPRA, and the Endo-Exo-Femurprosthesis system which is now known as the ILP.[44] To be considered for an osseointegration prosthesis, common inclusion criteria reported by all studies were difficulties or problems with using conventional socket prosthesis, adequate bone quality, suitability for surgery based on medical and physical examinations, and motivation to comply with treatment and follow-up requirements. Except for the case series comprising of patients with PVD,[33] all studies considered PVD as an exclusion criterion for osseointegration surgery.

Functional Outcomes

Walking Ability Seven studies evaluated walking ability using one or two of the following measures: 6MWT, TUG, LIFE-H, LEFS, and subitems of the Q-TFA Mobility score (**Table 3**). However, majority of these studies used the 6MWT and TUG tests. All studies reported significant improvement in this domain at follow-up after having an osseointegrated prosthesis compared with baseline or pre-operative values when patients were using socket prosthesis or were wheelchair bound.

Prosthetic Use

Prosthetic use was assessed by the Q-TFA prosthetic use score and this was reported by five studies. The prosthetic use score after insertion of an osseointegrated implant improved compared with preoperative values. Daily prosthetic use was reported by about 89% of patients at two-year follow-up following insertion of an osseointegrated implant.[12, 14] In a case series of two patients which aimed to determine the effect of the osseointegrated implant together with a customized socket design compared with a conventional socket fitting on range of motion of the shoulder and prosthetic function, both patients reported daily prosthesis use at 2-year follow-up.[40] However, in a 2-year follow-up evaluation of 39 patients with transfemoral osseointergrated prosthesis; increased prosthetic use was reported by 26 patients compared with baseline values, whiles 11 patients reported the same amount of use at baseline and 2 reported less prosthesis use.[13] For studies that explicitly reported on

the number of patients still using their osseointegrated prosthesis at the end of follow-up period, estimates ranged from 68 to 100% over a mean follow-up period of 1 to 6 years (**Table 2**).

Mobility

Six studies evaluated mobility using one or two of the following measures: LIFE-H, LEFS, AMPPRO score, K-levels and the Q-TFA subitem prosthetic mobility score (**Table 3**). All studies reported improved mobility of patients during follow-up after osseointegration surgery. In a case series involving five patients with transtibial amputation and a history of PVD, of which three patients were wheelchair bound at baseline; all five patients were able to walk unaided at 12 months follow-up after receiving an osseointegration implant.[33] In a qualitative study involving 13 patients with upper or lower extremity amputation who had been using osseointegrated prosthesis for 3-5 years, patients reported improved function and freedom compared to when they used conventional socket prostheses.

Other Functional Outcomes

Hagberg and colleagues evaluated hip range of motion and sitting comfort comparing individuals with osseintegrated prostheses to those with a socket prosthesis.[11] The study results showed that none of the individuals with osseintegrated prosthesis reported restriction in hip motion and only one person reported discomfort when sitting. Gait patterns preoperatively, with the use of socket prosthesis and healthy controls were compared with those at two years following insertion of an osseointegrated implant in 19 patients with a unilateral transfemoral amputation; the findings showed that there was a significant increase of hip extension and reduction of the pelvic tilt in those with implants and these changes approached that of the healthy controls.[16] In the case series of two patients, both patients reported improved prosthetic function and a decrease in restriction of range of motion using the implant with customized sockets compared with conventional socket prosthesis.[40]

Pain

Except for one study which evaluated pain using the SF-36 Bodily Pain subscore and reported significant improvement in this domain at 2-years following osseointegration compared with the preoperative situation,[12] none of the other studies indicated having evaluated pain using validated questionnaires. However, several studies assessed pain as an adverse event or complication after osseointegration. In a case series involving five patients with transtibial amputation and a history of PVD who received an osseointegration implant, four of the patients were pain-free at one year post-operative follow-up.[33] In the case series of two patients, no pain was reported at the stump on wearing prosthesis at 2 years follow-up.[40] In a prospective follow-up (approximately 3 months -17.5 years) of 100 individuals with osseintegrated implants, severe phantom limb pain was reported as the main reason why two patients were not using their prostheses.[35] In the 2-year follow-up of 51 patients with osseointegrated implants by Branemark and colleagues, five patients reported episodic pain during rehabilitation and three patients reported pain on weight bearing and this was associated with loosening of their implants.[14] Two years after treatment with an osseointegrated implant in 39 patients with unilateral transfemoral amputation, one patient reported not using the prosthesis at all due to loading pain and this was associated with loosening of the implant.[13] In the same study, though patients showed substantial improvements in prosthetic function and physical quality of life, they reported no significant change in phantom limb pain and pain from the back, shoulders, and contralateral limb. In the 8 year median follow-up of 16 transhumeral amputees who received osseointegrated percutaneous implants, two patients reported pain on loading and three patients had phantom pain in their arm.[43] In the prospective follow-up of 86 patients with transfemoral amputation who were treated with an osseointegration implant, one patient was unable to load the residual limb due to severe pain and this led to the removal of the implant.[32]

Quality of Life

Eight studies assessed general and/or condition-specific health related quality of life using the following measures: LIFE-H, LEFS, SF-36 and Q-TFA global score. Studies compared these outcomes at follow-up following osseointegration with the preoperative status or when using socket prostheses. All studies reported considerable improvement in quality of life at a mean of 2 years follow-up (**Table 3**). In a qualitative study of 13 patients who had been using osseointergrated prosthesis for 3-15 years, all patients reported substantial improvement in their functional abilities as well as their quality of life.[15] However, participants expressed fear of sustaining fractures and developing infections which could curtail their improved function and freedom.

Infections

Fourteen articles reported on infection outcomes. Given that some of the studies were conducted in the same study setting, there was a possibility of patient overlap and therefore the pooled infection rate was not estimated across the studies. The infection rates with 95% confidence intervals ranged from 1.0 (0.2-5.4) to 76.7 (59.1-88.2) over mean follow-up periods of 5 months to 5 years (**Fig. 3**). The majority of infection types were reported as low-grade soft tissue or superficial infections, which were treated effectively with oral antibiotics for a few days. A few patients required prolonged treatment or parenteral antibiotic therapy. In the study that compared infection outcomes between the first two previous designs (Group 1) and the final design (Group 2) of the osseointergrated implant system, 77% of patients in Group 1 needed surgical interventions due to infections compared to Group 2 patients who remained infection-free.[44] Deep infections were reported in two studies - one study reported 4 of 51 patients developing deep infection which were successfully treated in 3 patients and one had the implant removed due to loosening;[14] the other study reported a deep implant infection in one patient about 3.5 years after stage 1 osseointegration surgery, but this resolved after 3 months of oral antibiotics.[43] Two studies reported the development of osteomyelitis in one patient.[35, 36] In a

long-term follow-up of 96 patients with transfemoral implants (majority who were part of the OPRA study), 16 (16.7%) patients developed implant-associated osteomyelitis.[45]

Other adverse events and complications

Apart from infection which accounted for majority of adverse events, other adverse events and complications reported on follow-up after osseointegration surgery included peri-prosthetic fracture, fractures of the implant (abutment), skin reactions, soft-tissue problems, stoma hypergranulation, implant failure and removal, loosening of the fixtures, mechanical complications of the abutment, and revision surgery (**Table 3**). Three articles reported one or two patients sustaining fractures of the prosthetic components or implant.[12, 39, 42] Five articles reported on periprosthetic fractures with rates ranging from 3.5 to 44.4%.[14, 31, 32, 34, 43] The cumulative survival of the implant reported in two articles ranged from 83 to 92% at two years.[14, 43] Implant removal rate ranged from 2.6 to 11.0% across six articles[13, 14, 31, 35-37, 39] and were mainly attributed to infections and loosening. Revision rates ranged from 0 to 54.1% across five articles.[31, 32, 34, 40, 43] A high complication rate and substantial number of adverse events following osseointegration surgery were reported by four articles during follow-up of patients. Branemark and colleagues in their 2 year follow-up of 51 patients reported a total of 101 complications, with 46 patients having one or more complications.[14] In 2 to19 years follow-up of 16 patients with transhumeral osseointegrated implants, a total of 43 adverse events were reported.[43] In another series of 86 patients who underwent transfemoral osseointegration and were followed for a median of 34 months, 26 patients developed one or more complications.[32] Infact, only 31 patients experienced no complications at all during the follow-up period. In a follow-up of 50 patients with transfemoral osseointegrated limbs, 27 patients experienced an adverse event.[34] It however appears that majority of these adverse events and complications reported in these studies were effectively managed using simple strategies. None of the studies reported additional amputation or death as a result of the osseointegrated implant.

Patient satisfaction

All studies reported that patients were generally satisfied with the improvement in functional outcomes and quality of life after insertion of the osseointegrated implant. Of 37 patients who had an Endo-Exo-Femur prosthesis implanted, 35 of them reported that they would choose to have the procedure again under similar circumstances.[31] However, a number of studies reported patients' concerns with slowness of rehabilitation after osseointegration surgery and fear of sustaining a fracture as a result of a fall or acquiring infections at the skin-implant interface.[15, 42]

Radiological findings

Three studies reported on radiological signs of bone remodelling during follow-up after osseointegration.[32, 37, 43] Common radiological findings reported by these studies included proximal trabecular streaming or buttressing, distal and endosteal bone resorption, cancellization, and cortical thinning; however, the extent of progression of these changes were inconsistent during the periods of follow-up in the studies. Furthermore, in the series of 86 patients who underwent transfemoral osseointegration, follow-up radiographs showed stable osseous growth and no implant migration in all but one patient, as well as hypertrophic bone formation in the distal part of the femur in 10% of the patients.[32]

Robustness of findings

Though the reported conclusions from the included studies generally suggest that osseointegrated prostheses for both upper and lower limb amputees is associated with improved function, mobility, and quality of life (**Table 3**); the findings should be interpreted with caution given some limitations in the study designs used (observational cohorts, case-control studies, and case series/reports), the low methodological quality of majority of the studies, lack of appropriate controls in some of the studies, self-reports of outcomes by study participants, and selective reporting of outcomes.

Discussion

Using a systematic review approach, this study has assessed evidence on functional outcomes, clinical outcomes, as well as adverse effects and complications of osseointegration for patients with amputated limbs. All relevant studies reported substantial improvement in walking ability, prosthetic use, mobility, satisfaction, or quality of life with an osseointegrated implant compared with their preoperative status or when using conventional socket prosthesis. Generally, only few patients reported pain as a complication after insertion of an osseointegrated implant and this was usually associated with loading or weight bearing. However, in one study, though patients showed significant improvements in prosthetic function and physical quality of life after osseointegration, they reported no significant change in phantom limb pain and pain from the back, shoulders, and contralateral limb. The infection rate ranged from as low as 1.0% to as high as 76.7% across studies, but majority were low-grade soft tissue or superficial infections at the skin-implant interface and were effectively treated with antibiotics. Two studies reported the development of deep implant infection, the rates which were low and majority were successfully treated;[14, 43] and one study reported implant-associated osteomyelitis in about 16% of patients after a mean of about 8 years following implantation.[45] A few studies reported a substantial number of adverse events after osseointegration surgery and these included peri-prosthetic fractures, skin reactions, soft-tissue problems, stoma hypergranulation, implant failure, loosening of the fixtures, mechanical complications of the abutment, and revision surgery. Events such as aseptic loosening, implant removal and implant fractures were however low in number. Nevertheless, majority of these complications were resolved nonoperatively or using simple measures. No study reported further amputation or death as a complication of osseointegration. Finally, two studies reported radiological changes after osseointegrative implantation[32, 43] which may suggest a predisposition to periprosthetic fracture; however, the clinical relevance is not certain given the absence of long-term follow-up evidence.

The consistent findings reported by the included studies suggest that osseointegrative implantation, which provides direct skeletal attachment of the prosthesis to the residual limb, indeed offers benefits

for both lower and upper limb amputees in the form of increased prosthetic use, improved mobility, range of motion, gait, comfort, and quality of life. The current findings are very relevant as it brings together the existing evidence and convincingly demonstrates the potential advantages of osseointegration for amputees. Socket-mounted prosthesis which have traditionally been the mainstay of treatment for patients with lower limb amputations are fraught with problems such as pain, skin conditions and ulcerations, heat, sweating, discomfort, failing in load transfer and skeletal control;[2, 17, 47, 48] which reduce the ability to walk and quality of life.[3, 9, 49] Over the last two decades, osseointegrated implantation has revolutionized the rehabilitation of patients with extremity amputations and has obviated problems associated with socket prostheses. Though the advantages of osseointegration are numerous, as demonstrated in our review, there are major concerns associated with the high risk of infections (up to about 77%) at the skin-implant interface. However, majority of these infections are low-grade, soft tissue, or superficial infections which are typically managed effectively with oral antibiotics and in some cases, parenteral antibiotics. In addition, with the changes in design of the osseointegration implant and surgical techniques over the past decade, it appears infection rates associated with this surgery are on the decrease. Indeed, in the recent study which compared infection outcomes between two previous versions with a newer version of the implant system which was designed to reduce the risk of infection at the skin-implant interface, all patients treated with the newer version remained infection free at follow-up.[44] Despite the benefits of osseointegration, it is not indicated for all amputees. It is usually reserved for patients with amputations who cannot tolerate or have problems using the conventional socket prosthesis and patients with motivation and emotional stability to comply with rehabilitation, treatment and follow-up requirements such as stomal wound care; as the whole process following osseointegration is a life-long and challenging one. Furthermore, amputation due to vascular disease has been regarded as a contraindication to osseointegration surgery.[9, 14, 32] However, in a case series of five transtibial amputees with PVD, osseointegration improved mobility, walking ability, and quality of life in these patients as well as reduced the prevalence of pain.[33] Given the small number of study participants and

short follow-up period, further evidence is required to confirm if osseointegrated implantation will be an acceptable treatment for amputees with PVD. Finally, though our review did not evaluate cost implications of osseointegration surgery for the patient and the healthcare system because of the limited evidence; it appears that the total costs associated with osseointegrated prosthesis are similar to that for socket prostheses as demonstrated in a recent cost analysis study.[50] Taking the overall evidence together, osseointegration may be a suitable and cost-effective alternative to traditional socket prosthesis in some patient populations. Further research is however required on long-term complications of osseointegrated surgery, how to prevent or reduce the high risk of infections, and identification of populations who will benefit most from this surgery.

Several strengths and limitations of this review deserve consideration. This study systematically examines the clinical outcomes, safety issues, and adverse effects associated with osseointegrated implantation in patients with lower and upper limb amputations. The literature search was detailed, spanned several databases, and included a diversity of study designs such as observational cohorts, case-control studies, qualitative studies, and case series or reports. The review was limited by the potential for biases in the study designs employed. However, these study designs were included because of the limited evidence on the topic. A meta-analysis of the results could not be performed because of the heterogeneous nature of study designs and methods, overlapping participants, and inconsistent outcome measures reported by eligible studies. Given the inability to pool the findings, analyses taking into consideration the methodological quality of the studies could not be conducted. Another limitation was that the protocol for this review could not be registered.

On the basis of available mixed observational evidence, patients with osseointegration of limb amputations have increased prosthetic use, better sitting comfort, improved walking ability, mobility, gait, and quality of life. The rates of events such as aseptic loosening, implant removal and implant fractures are acceptably low. However, osseointegrative implantation is associated with an increased risk of infections, majority of which are low-grade soft tissue infections and respond well to antibiotics. Nevertheless, given the limitations associated with some of the study designs and their

low methodological quality, these findings need to be interpreted with caution. Robust evidence from definitive clinical trials are urgently warranted. Future studies should aim to recruit adequate sample sizes, include appropriate controls in their study designs, consistently report validated outcome measures, ensure participants are followed up for appropriate durations for the ascertainment of outcomes, and not selectively report outcomes.

Competing interests

The authors declare they have no competing interests.

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References

1. Dillingham TR, Pezzin LE, MacKenzie EJ, Burgess AR. Use and satisfaction with prosthetic devices among persons with trauma-related amputations: a long-term outcome study. *Am J Phys Med Rehabil* 2001;**80**(8): 563-571.

2. Lyon CC, Kulkarni J, Zimerson E, Van Ross E, Beck MH. Skin disorders in amputees. *J Am Acad Dermatol* 2000;**42**(3): 501-507.

3. Hagberg K, Branemark R. Consequences of non-vascular trans-femoral amputation: a survey of quality of life, prosthetic use and problems. *Prosthet Orthot Int* 2001;**25**(3): 186-194.

4. Smith DG, Horn P, Malchow D, Boone DA, Reiber GE, Hansen ST, Jr. Prosthetic history, prosthetic charges, and functional outcome of the isolated, traumatic below-knee amputee. *J Trauma* 1995;**38**(1): 44-47.

5. Nair A, Hanspal RS, Zahedi MS, Saif M, Fisher K. Analyses of prosthetic episodes in lower limb amputees. *Prosthet Orthot Int* 2008;**32**(1): 42-49.

6. GlaxoSmithKline. Investigate the Efficacy and Safety of GSK1070806 in Obese Subjects with T2DM. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2012 Dec 12]. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01648153?term=IL-18&rank=9 NLM Identifier: NCT01648153.

7. Adell R, Lekholm U, Rockler B, Branemark PI. A 15-year study of osseointegrated implants in the treatment of the edentulous jaw. *Int J Oral Surg* 1981;**10**(6): 387-416.

8. Tjellstrom A, Rosenhall U, Lindstrom J, Hallen O, Albrektsson T, Branemark PI. Five-year experience with skin-penetrating bone-anchored implants in the temporal bone. *Acta Otolaryngol* 1983;**95**(5-6): 568-575.

9. Van de Meent H, Hopman MT, Frolke JP. Walking ability and quality of life in subjects with transfemoral amputation: a comparison of osseointegration with socket prostheses. *Arch Phys Med Rehabil* 2013;**94**(11): 2174-2178.

10. Haggstrom E, Hagberg K, Rydevik B, Branemark R. Vibrotactile evaluation: osseointegrated versus socket-suspended transfemoral prostheses. *J Rehabil Res Dev* 2013;**50**(10): 1423-1434.

11. Hagberg K, Haggstrom E, Uden M, Branemark R. Socket versus bone-anchored trans-femoral prostheses: hip range of motion and sitting comfort. *Prosthet Orthot Int* 2005;**29**(2): 153-163.

12. Hagberg K, Branemark R, Gunterberg B, Rydevik B. Osseointegrated trans-femoral amputation prostheses: prospective results of general and condition-specific quality of life in 18 patients at 2-year follow-up. *Prosthet Orthot Int* 2008;**32**(1): 29-41.

13. Hagberg K, Hansson E, Branemark R. Outcome of percutaneous osseointegrated prostheses for patients with unilateral transfemoral amputation at two-year follow-up. *Arch Phys Med Rehabil* 2014;**95**(11): 2120-2127.

14. Branemark R, Berlin O, Hagberg K, Bergh P, Gunterberg B, Rydevik B. A novel osseointegrated percutaneous prosthetic system for the treatment of patients with transfemoral amputation: A prospective study of 51 patients. *Bone Joint J* 2014;**96-B**(1): 106-113.

15. Lundberg M, Hagberg K, Bullington J. My prosthesis as a part of me: a qualitative analysis of living with an osseointegrated prosthetic limb. *Prosthet Orthot Int* 2011;**35**(2): 207-214.

16. Tranberg R, Zugner R, Karrholm J. Improvements in hip- and pelvic motion for patients with osseointegrated trans-femoral prostheses. *Gait Posture* 2011;**33**(2): 165-168.

17. Dougherty PJ, Smith DG. One Step Forward, But a Need for Caution: Commentary on an article by Munjed Al Muderis, MB ChB, FRACS, FAOrthA, et al.: "Safety of Osseointegrated Implants for Transfemoral Amputees. A Two-Center Prospective Cohort Study". *J Bone Joint Surg Am* 2016;**98**(11): e48.

18. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;**6**(7): e1000097.

19. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp [10 March 2015.

20. Chowdhury R, Kunutsor S, Vitezova A, Oliver-Williams C, Chowdhury S, Kiefte-de-Jong JC, et al. Vitamin D and risk of cause specific death: systematic review and meta-analysis of observational cohort and randomised intervention studies. *BMJ* 2014;**348**: g1903.

21. Chowdhury R, Warnakula S, Kunutsor S, Crowe F, Ward HA, Johnson L, et al. Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis. *Ann Intern Med* 2014;**160**(6): 398-406.

22. Lin SJ, Bose NH. Six-minute walk test in persons with transtibial amputation. *Arch Phys Med Rehabil* 2008;**89**(12): 2354-2359.

23. Schoppen T, Boonstra A, Groothoff JW, de Vries J, Goeken LN, Eisma WH. The Timed "up and go" test: reliability and validity in persons with unilateral lower limb amputation. *Arch Phys Med Rehabil* 1999;**80**(7): 825-828.

24. Adams LA, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology* 2005;**129**(1): 113-121.

25. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical care* 1992;**30**(6): 473-483.

26. Hagberg K, Branemark R, Hagg O. Questionnaire for Persons with a Transfemoral Amputation (Q-TFA): initial validity and reliability of a new outcome measure. *J Rehabil Res Dev* 2004;**41**(5): 695-706.

27. Gailey RS, Roach KE, Applegate EB, Cho B, Cunniffe B, Licht S, et al. The amputee mobility predictor: an instrument to assess determinants of the lower-limb amputee's ability to ambulate. *Arch Phys Med Rehabil* 2002;**83**(5): 613-627.

28. Fougeyrollas P, Noreau L, Bergeron H, Cloutier R, Dion SA, St-Michel G. Social consequences of long term impairments and disabilities: conceptual approach and assessment of handicap. *Int J Rehabil Res* 1998;**21**(2): 127-141.

29. Binkley JM, Stratford PW, Lott SA, Riddle DL. The Lower Extremity Functional Scale (LEFS): scale development, measurement properties, and clinical application. North American Orthopaedic Rehabilitation Research Network. *Phys Ther* 1999;**79**(4): 371-383.

30. Freeman MF, Tukey JW. Transformations Related to the Angular and the Square Root. *Ann Math Statist* 1950: 607-611.

31. Aschoff HH, Kennon RE, Keggi JM, Rubin LE. Transcutaneous, distal femoral, intramedullary attachment for above-the-knee prostheses: an endo-exo device. *J Bone Joint Surg Am* 2010;**92 Suppl 2**: 180-186.

32. Al Muderis M, Khemka A, Lord SJ, Van de Meent H, Frolke JP. Safety of Osseointegrated Implants for Transfemoral Amputees: A Two-Center Prospective Cohort Study. *J Bone Joint Surg Am* 2016;**98**(11): 900-909.

33. Atallah R, Li JJ, Lu W, Leijendekkers R, Frolke JP, Al Muderis M. Osseointegrated Transtibial Implants in Patients with Peripheral Vascular Disease: A Multicenter Case Series of 5 Patients with 1-Year Follow-up. *J Bone Joint Surg Am* 2017;**99**(18): 1516-1523.

34. Muderis MA, Tetsworth K, Khemka A, Wilmot S, Bosley B, Lord SJ, et al. The Osseointegration Group of Australia Accelerated Protocol (OGAAP-1) for two-stage osseointegrated reconstruction of amputated limbs. *Bone Joint J* 2016;**98-B**(7): 952-960.

35. Hagberg K, Branemark R. One hundred patients treated with osseointegrated transfemoral amputation prostheses--rehabilitation perspective. *J Rehabil Res Dev* 2009;**46**(3): 331-344.

36. Tillander J, Hagberg K, Hagberg L, Branemark R. Osseointegrated titanium implants for limb prostheses attachments: infectious complications. *Clin Orthop Relat Res* 2010;**468**(10): 2781-2788.

37. Nebergall A, Bragdon C, Antonellis A, Karrholm J, Branemark R, Malchau H. Stable fixation of an osseointegated implant system for above-the-knee amputees: titel RSA and radiographic evaluation of migration and bone remodeling in 55 cases. *Acta Orthop* 2012;**83**(2): 121-128.

38. Al Muderis M, Lu W, Li JJ. Osseointegrated Prosthetic Limb for the treatment of lower limb amputations : Experience and outcomes. *Unfallchirurg* 2017;**120**(4): 306-311.

39. Jonsson S, Caine-Winterberger K, Branemark R. Osseointegration amputation prostheses on the upper limbs: methods, prosthetics and rehabilitation. *Prosthet Orthot Int* 2011;**35**(2): 190-200.

40. Salminger S, Gradischar A, Skiera R, Roche AD, Sturma A, Hofer C, et al. Attachment of upper arm prostheses with a subcutaneous osseointegrated implant in transhumeral amputees. *Prosthet Orthot Int* 2016.

41. Schalk SA, Jonkergouw N, van der Meer F, Swaan WM, Aschoff HH, van der Wurff P. The Evaluation of Daily Life Activities after Application of an Osseointegrated Prosthesis Fixation in a Bilateral Transfemoral Amputee: A Case Study. *Medicine (Baltimore)* 2015;**94**(36): e1416.

42. Sullivan J, Uden M, Robinson KP, Sooriakumaran S. Rehabilitation of the trans-femoral amputee with an osseointegrated prosthesis: the United Kingdom experience. *Prosthet Orthot Int* 2003;**27**(2): 114-120.

43. Tsikandylakis G, Berlin O, Branemark R. Implant survival, adverse events, and bone remodeling of osseointegrated percutaneous implants for transhumeral amputees. *Clin Orthop Relat Res* 2014;**472**(10): 2947-2956.

44. Juhnke DL, Beck JP, Jeyapalina S, Aschoff HH. Fifteen years of experience with Integral-Leg-Prosthesis: Cohort study of artificial limb attachment system. *Journal of Rehabilitation Research & Development* 2015;**52**(4): 407-420.

45. Tillander J, Hagberg K, Berlin O, Hagberg L, Branemark R. Osteomyelitis Risk in Patients With Transfemoral Amputations Treated With Osseointegration Prostheses. *Clin Orthop Relat Res* 2017;**475**(12): 3100-3108.

46. Atallah R, Li JJ, Lu W, Leijendekkers R, Frolke JP, Al Muderis M. Osseointegrated Transtibial Implants in Patients with Peripheral Vascular Disease: A Multicenter Case Series of 5 Patients with 1-Year Follow-up. *Journal of Bone & Joint Surgery - American Volume* 2017;**99**(18): 1516-1523.

47. Dudek NL, Marks MB, Marshall SC, Chardon JP. Dermatologic conditions associated with use of a lower-extremity prosthesis. *Arch Phys Med Rehabil* 2005;**86**(4): 659-663.

48. Ghoseiri K, Safari MR. Prevalence of heat and perspiration discomfort inside prostheses: literature review. *J Rehabil Res Dev* 2014;**51**(6): 855-868.

49. Demet K, Martinet N, Guillemin F, Paysant J, Andre JM. Health related quality of life and related factors in 539 persons with amputation of upper and lower limb. *Disabil Rehabil* 2003;**25**(9): 480-486.

50. Haggstrom EE, Hansson E, Hagberg K. Comparison of prosthetic costs and service between osseointegrated and conventional suspended transfemoral prostheses. *Prosthet Orthot Int* 2013;**37**(2): 152-160.

Supporting information

S1 file

Figure legends

Fig. 1 Osseointegration prosthesis

A, Radiograph of a transfemoral osseointegration prosthesis; B, Radiograph of a patient with bilateral transtibial osseointegration prostheses; C, Patient sitting with a transfemoral osseointegration prosthesis

Fig. 2 PRISMA flow diagram

Fig. 3 Rates of infection across studies

CI, confidence interval (bars)

Table 1. Summary characteristics of studies included in the review

Lead author, publication date	Location	Baseline year	Study design	Further details on study design	Population	Population source (name of study)	Eligibility criteria for osseointegration / entry into study	Males (%)	Number of patients with osseointegration (no. of implants)	Drop-out rate	Mean/median duration of follow-up (years)	Study quality
Sullivan, 2003	UK	NR	Cohort study	Report experiences and outcomes of patients who have completed osseointegration surgery	Transfemoral amputees	Healthcare setting	Transfemoral amputees unable to achieve a satisfactory level of rehabilitation using conventional socket techniques	NR	11	NR	5.5	5
Hagberg, 2005	Sweden and UK	NR	Case-control	Individuals with osseointegrated implant compared with those with a socket prosthesis	Transfemoral amputees	Healthcare setting (OPRA)	To have a unilateral transfemoral amputation, for at least 2 years, for reasons other than vascular disease; to be between 20 and 70 years old; and to be a prosthetic user, with the ability to walk continuously for at least 100 m	75.0	20	NR	5.0	5
Hagberg, 2008	Sweden	1999-2004	Prospective cohort	Prospective follow-up of individuals with osseintegrated implants and outcomes compared with pre-operative situation	Transfemoral amputees	Healthcare setting (OPRA)	Transfemoral amputees with problems using a conventional socket prosthesis, completed maturation of the skeleton as well as normal skeletal anatomy, age below 70 years and to be suitable for surgery based upon the medical and physical examinations.	44.4	18	NR	2.0	5

Lead author, publication date	Location	Baseline year	Study design	Further details on study design	Population	Population source (name of study)	Eligibility criteria for osseointegration / entry into study	Males (%)	Number of patients with osseointegration (no. of implants)	Drop-out rate	Mean/median duration of follow-up (years)	Study quality
Hagberg, 2009	Sweden	1990-2008	Prospective cohort	Prospective follow-up of individuals with osseintegrated implants and brief overview of outcomes	Transfemoral, transtibial, transulnar, transradial, and transhumeral amputees	Healthcare setting (included participants of the OPRA study)	Patients with socket-related problems (i.e., discomfort, pain, poor suspension,) or an inability to use a conventional prosthesis at all.	61.0	100 (106)	None	5	5
Aschoff, 2010	Germany	1999-2009	Prospective cohort	Follow-up of patients who underwent osseointegration surgery	Transfemoral (above-knee) amputees	Healthcare setting	Persistent difficulties with socket prosthesis	81.1	37 (39)	None	NR	5
Tillander, 2010	Sweden	2005	Prospective cohort	Prospective follow-up of individuals with osseintegrated implants for infectious complications	Transfemoral, transtibial, transulnar, transradial, transhumeral amputees	Healthcare setting	Patients with severe discomfort when using conventional socket prostheses or poor stump conditions	53.8	39 (45)	4 patients lost to follow-up	3.0	5
Lundberg, 2011	Sweden	1992-2005	Qualitative study	Interviews to evaluate experience of people living with an osseointegrated prosthesis	Transfemoral, transhumeral, transradial amputees	NR	Patients with unilateral upper or lower limb amputation, having been treated with osseointegrated prostheses at least three years ago; and currently using the prosthesis	53.8	13	NA	3-15	N/A
Tranberg, 2011	Sweden	1999-2007	Prospective case-control	Patients with osseointegrated implants were compared with preoperative status, with the use of socket prosthesis, and healthy controls	Transfemoral amputees	Healthcare setting (OPRA)	Same as OPRA study	47.4	19	NR	2.0	8

Lead author, publication date	Location	Baseline year	Study design	Further details on study design	Population	Population source (name of study)	Eligibility criteria for osseointegration / entry into study	Males (%)	Number of patients with osseointegration (no. of implants)	Drop-out rate	Mean/median duration of follow-up (years)	Study quality
Jonsson, 2011	Sweden	1990-2010	Cohort study	Follow-up of individuals with osseintegrated implants	Thumb, partial hand, transradial, and transhumeral amputees	Healthcare setting	Difficult to fit with a conventional prosthesis or problems with socket prosthesis; adequate bone quality assessed by X-ray; no contraindicated illness; highly motivated patient	83.8	37 (48)	NR	0.3-20.0	5
Nebergall, 2012	Sweden	1999-2007	Prospective cohort	Follow-up of individuals with osseintegrated implants	Transfemoral	Healthcare setting (OPRA)	Same as OPRA study	54.9	51 (55)	1 lost to follow-up	Up to 10 years	5
Van de Meent, 2013	Netherlands	2009-2011	Prospective case-control	Compare outcomes of patients with osseointegrated implants with those of socket prosthesis in the same individuals	Transfemoral amputees	Healthcare setting	Patients having problems with socket prosthesis	81.8	22	None	1.0	5
Branemark, 2014	Sweden	1999-2007	Prospective cohort	Follow-up of individuals with osseointegrated implants	Transfemoral amputees	Healthcare setting (OPRA)	Problems with socket prosthesis or inability to use it; full skeletal maturity; suitability for surgery based on medical and physical examinations, and motivation to comply with treatment and follow-up requirements	55.0	51 (55)	3 patients withdrawn from study due to reasons unrelated to implant	2.0	5
Hagberg, 2014	Sweden	1999-2007	Prospective case-control	Compare outcomes of patients with osseointegrated implants with those of socket prosthesis in the same individuals	Transfemoral amputees	Healthcare setting (OPRA)	Same as OPRA study	43.6	45	6 patients not followed for 2 years	2.0	4

Lead author, publication date	Location	Baseline year	Study design	Further details on study design	Population	Population source (name of study)	Eligibility criteria for osseointegration / entry into study	Males (%)	Number of patients with osseointegration (no. of implants)	Drop-out rate	Mean/median duration of follow-up (years)	Study quality
Tsikandylakis, 2014	Sweden	1995-2010	Retrospective cohort	Follow-up of individuals with osseointegrated implants	Transhumeral amputees	NR	Inability to wear or severe problems wearing a conventional socket prosthesis and compliant patients	88.9	18	NR	8.0	5
Juhnke, 2015	Germany	1999-2013	Retrospective cohort	Patients were divided into two groups to compare outcomes between the first two previous designs (group 1) and a final design (group 2) of the osseointergrated implant system.	Transfemoral amputees	Healthcare setting	Traumatic amputations and the emotional stability and intelligence to undergo rehabilitation	Group 1 – 83.0 Group 2- 80.0	Group 1 – 30 (31) Group 2 – 39 (42)	NR	Group 1 – 6.2 Group 2 – 2.7	6
Schalk, 2015	Netherlands	2010	Case study	Case report evaluating the level of daily life activities of a patient before and after the application of an osseointegrated implant	Transfemoral amputee	Healthcare setting	Problems with socket prosthesis	NR	1	NA	Approximately 3.0	NA
Salminger, 2016	Austria	NR	Case series	Case series to determine the effect of an osseointegrated implant	Transhumeral amputees	NR	Minimal length of the humeral bone of 10 cm, sufficient skin and soft tissue quality especially at the distal third of the stump, and healthy bone quality in x-ray	100.0	2	NA	3.0-4.0	N/A

Lead author, publication date	Location	Baseline year	Study design	Further details on study design	Population	Population source (name of study)	Eligibility criteria for osseointegration / entry into study	Males (%)	Number of patients with osseointegration (no. of implants)	Drop-out rate	Mean/median duration of follow-up (years)	Study quality
Muderis, 2016	Australia and Netherlands	2009-2013	Prospective cohort	Follow-up of individuals with osseointegrated implants to determine safety outcomes	Transfemoral amputees	Healthcare setting	Experiencing socket-related problems or difficulties using a prosthesis	76.0	86	None	2.8	5
Muderis, 2016 (b)	Australia	2011-2014	Prospective cohort	Follow-up of individuals with osseointegrated implants to determine outcomes	Transfemoral amputees	Healthcare setting (OGAAP-1)	Unilateral trans-femoral amputation and socket or prosthesis-fitting problems	68.0	50	None	1.8	5
Muderis, 2017	Australia	2013-2014	Retrospective cohort	Retrospective analysis of patients with osseointegrated implants to compare outcomes pre-and post-operatively	Transfemoral amputees	Healthcare setting	Unilateral trans-femoral amputation and socket or prosthesis-fitting problems	77.3	22	NR	1.2	5
Atallah, 2017	Australia and Netherlands	2014-2015	Case series	Case series to determine the outcomes of patients with an osseointegrated implant	Transtibial amputees with PVD	Healthcare setting	Age over 18 years, unilateral transtibial amputation, and a history of PVD	40.0	5	None	1	N/A

N/A, not applicable; NR, not reported; OGAAP-1, Osseointegration Group of Australia's Accelerated Protocol two-stage strategy (OGAAP-1); OPRA, Osseointegrated Prostheses for the Rehabilitation of Amputees; PVD, peripheral vascular disease

Table 2. Key characteristics of osseointegration surgery in studies included in review and results of studies reporting patients still using osseointegrated prosthesis at end of follow-up

Lead author, publication date	Population	Indications for amputation	Mean age at amputation (years)	Mean age at implantation (years)	Mean interval between amputation and implantation (years)	Implant type	Surgery type	Number of patients with osseointegration implants	Number still using the prosthesis at end of follow-up period
Sullivan, 2003	Transfemoral amputees	NR	NR	NR	NR	ITAP	Two-stage	11	9
Hagberg, 2005	Transfemoral amputees	Trauma, tumour, and others	27.0	46.0 is age at study entry	19.0	OPRA	Two-stage	20	NR
Hagberg, 2008	Transfemoral amputees	Trauma and tumour	31.0	45.0	15.0	OPRA	Two-stage	18	17 at 2 years
Hagberg, 2009	Transfemoral, transtibial, transulnar, transradial, and transhumeral amputees	Trauma, tumour, and others	32.0	43.0	11.5	OPRA	Two-stage	100	68 at a mean of 5 years follow-up
Aschoff, 2010	Transfemoral (above-knee) amputees	Trauma, tumour, and others	33.0	44.0	NR	Endo-Exo-Femurprosthesis	Two-stage	37.0	NR
Tillander, 2010	Transfemoral, transtibial, transulnar, transradial, transhumeral amputees	Trauma and tumour	NR	49.3 is age at study entry	NR	OPRA	Two-stage	39	NR
Lundberg, 2011	Transfemoral, transhumeral, transradial amputees	Trauma, tumour, and infection	14-45	NR	NR	OPRA	Two-stage	13	NR
Tranberg, 2011	Transfemoral amputees	Trauma, tumour, and infection	NR	44.2	15.4	OPRA	Two-stage	19	NR
Jonsson, 2011	Thumb, partial hand, transradial, and transhumeral amputees	Trauma, tumour, and congenital	NR	40.9	8.3	NR	Two-stage	37	30

Lead author, publication date	Population	Indications for amputation	Mean age at amputation (years)	Mean age at implantation (years)	Mean interval between amputation and implantation (years)	Implant type	Surgery type	Number of patients with osseointegration implants	Number still using the prosthesis at end of follow-up period
Nebergall, 2012	Transfemoral	Trauma and tumour	NR	45.0	NR	OPRA	Two-stage	51	NR
Van de Meent, 2013	Transfemoral amputees	Trauma and tumour	NR	46.5	16.4	Integrated Leg Prosthesis or Osseointegration Prosthesis	Two-stage	22	NR
Branemark, 2014	Transfemoral amputees	Trauma and tumour	32.0	44.0	12.0	OPRA	Two-stage	51	40 of 45 at 2 years
Hagberg, 2014	Transfemoral amputees	Trauma and tumour	31.0	44.0	NR	OPRA	Two-stage	45	38 of 39 at 2 years
Tsikandylakis, 2014	Transhumeral amputees	Trauma and tumour	NR	42.0	9.0	NR	Two-stage	18	NR
Juhnke, 2015	Transfemoral amputees	Trauma, tumour, infection, burns, and others	NR	Group 1 - 46.0 Group 2 – 45.0	NR	ILP	Two-stage	Group 1 – 30 Group 2 – 39	NR
Schalk, 2015	Transfemoral amputees	Trauma	21.0	NR	NR	NR	Two-stage	1	NR
Salminger, 2016	Transhumeral amputees	Trauma	23 years and 9 months prior to study	30 and 50 years	23 years and 9 months	Subcutaneous implant-supported attachment	One-stage	2	NR
Muderis, 2016	Transfemoral amputees	Trauma and tumour	32.0	48.0	16.0	Osseointegration Prosthesis	Two-stage	86	NR
Muderis, 2016 (b)	Transfemoral amputees	Trauma, tumour, and others	NR	48.4	NR	ILP or OPL	Two-stage	50	50 at 21.5 months
Muderis, 2017	Transfemoral amputees	Trauma, tumour, and infection	NR	46.2	NR	OPL	One-stage	22	22 at 14 months
Atallah, 2017	Transtibial amputees with PVD	PVD	NR	56-84	4.0-25.0	NR	One- or two-stage	5	5 at 1 year

ILP, Integrated Leg Prosthesis (ILP); ITAP, intraosseous transcutaneous amputation prosthesis; NR, not reported; OIP, Osseointegration Prosthesis; OPL, Osseointegrated Prosthetic Limb; OPRA, Osseointegrated Prosthesis for the Rehabilitation of Amputees; PVD, peripheral vascular disease

Table 3. Other relevant outcomes reported by eligible studies

Lead author, publication date	Walking ability	Prosthetic use	Mobility	Quality of life	Infections	Fractures	Implant failure/removal or revision surgery	Pain associated with implant	Other outcomes
Sullivan, 2003	Patients felt they were able to walk further and do more work wearing the osseointegrated prosthesis	NR	NR	NR	2 of 11 after one year	2 of 11 suffered fractures of the abutment	None	NR	NR
Hagberg, 2005	NR	NR	NR	NR	NR	NR	NR	NR	Participants with an osseointegrated implant had substantially larger hip motion in all movements when using the prosthesis and reported few problems with sitting discomfort compared to individuals with socket prosthesis
Hagberg, 2008	Evaluated with the Q-TFA Mobility score subscores: Mean walking-aid subscore improved from 70 to 76 points Mean walking habit sub-score improved from 39 to 57 points	Evaluated with Q-TFA subitem prosthetic use: Prosthetic use score improved by a mean of 32 score points from baseline. 16 of 18 reported daily prosthesis use at 2-year follow-up; 1 reported prosthesis use for 6 days a week	Evaluated with Q-TFA subitem prosthetic mobility: Improvement in mobility score by 17 score points from baseline	Compared general and condition-specific health related quality of life at 2-year follow-up with the preoperative situation using Q-TFA and SF-36: All four scores of Q-TFA and four scales of SF-36 improved significantly at follow-up	2 patients abstained from wearing the prosthesis for 1-3 days due to superficial infection	1 had broken prosthetic components	NR	Evaluated with SF-36 Bodily Pain subscore: Significant improvement in bodily pain subscore. 1 reported no prosthetic use due to pain and implant loosening	NR

Lead author, publication date	Walking ability	Prosthetic use	Mobility	Quality of life	Infections	Fractures	Implant failure/removal or revision surgery	Pain associated with implant	Other outcomes
Hagberg, 2009	NR	NR	NR	NR	1 patient developed osteomyelitis	NR	11 of 100 patients have no implant system at follow-up 13 of 100 retreated; 9 were successful and 4 unsuccessful	2 patients not using artificial limb because of severe phantom limb pain	NR
Aschoff, 2010	NR	NR	NR	NR	1 intramedullary infection	2 had pertrochanteric fracture	20 of 37 patients had one or more revisions 4 had removal of implant 1 had implant failure	NR	14 patients had minor revision due to problems at stoma 35 of 37 patients stated they would have the surgery again under similar circumstances
Tillander, 2010	NR	NR	NR	NR	7 of 39 patients at a mean of 3 years and were mostly of low infectious activity: 2 affected prosthetic use and 5 did not; 2 developed chronic skin fistulas 1 had the implant extracted 1 recovered with antibiotics	NR	1 had implant removed due to infection	NR	NR

Lead author, publication date	Walking ability	Prosthetic use	Mobility	Quality of life	Infections	Fractures	Implant failure/removal or revision surgery	Pain associated with implant	Other outcomes
					1 patient developed acute osteomyelitis				
Lundberg, 2011	NR	NR	Patients reported improved function and freedom	NR	Patients expressed the fear of acquiring infections at the skin-implant interface	NR	NR	NR	Patients expressed a fear of falling that could cause fracture
Tranberg, 2011	NR	NR	NR	NR	NR	NR	NR	NR	Improvement in walking pattern by an increase of hip extension and reduction of the pelvic tilt
Jonsson, 2011	NR	NR	NR	NR	1 of 37 patients developed an infection at 5 months after the surgery	1 patient experienced a fracture of the implant after an overload accident	1 had implant removed due to infection	NR	2 patients experienced loosening of fixtures
Nebergall, 2012	NR	NR	NR	NR	Reported that 1 implant was removed due to infection	NR	4 had implant removed due to loosening or infection	NR	Cortical thinning, cancellization, proximal trabecular streaming, and distal and endosteal resorption
Van de Meent, 2013	Measured with 6MWT and TUG tests: In 6 minutes participants with the implant walked significantly further (27%) than with the socket prosthesis	Evaluated with Q-TFA subitem prosthetic use: Prosthesis use significantly improved by 45%, from 56hrs/week with the socket prosthesis to 101 hrs/week with the implant	NR	Evaluated with Q-TFA: Q-TFA global score with implant was significantly higher (68%) than with a socket prosthesis at 1-year follow-up.	8 of 22 patients developed mild infections of the soft tissue at the skin-implant interface during the 12-month follow-up period	NR	NR	NR	NR

Lead author, publication date	Walking ability	Prosthetic use	Mobility	Quality of life	Infections	Fractures	Implant failure/removal or revision surgery	Pain associated with implant	Other outcomes
	In the TUG test, participants with the implant were significantly faster (44%) than with the socket prosthesis								
Branemark, 2014	NR	Evaluated with Q-TFA subitem prosthetic use: 40 of 45 patients (89%) reported daily prosthetic use at 2-year follow-up. Mean prosthetic use score improved from 47 preoperatively to 79 at 2 years postoperatively	Evaluated with Q-TFA subitem prosthetic mobility: Improvement in mobility score by 18 score points from baseline to 2 years at follow-up	Evaluated with Q-TFA and SF-36: All four scores of Q-TFA and physical function scores of SF-36 improved significantly at 2-year follow-up	28 of 51 patients developed superficial infections. There were 41 infection episodes. Majority were treated effectively with antibiotics. 4 patients developed deep infection.	4 patients suffered bone fractures	4 patients had implant removed because of loosening Cumulative survival at two years follow-up was 92%	5 patients reported episodic pain during rehabilitation 3 patients reported pain on weight bearing which was associated with loosening of the implants	A total of 101 complications were reported. 46 patients reported one or more complications. 4 patients had mechanical complications with the abutment but these were fixed.
Hagberg, 2014	Evaluated with Q-TFA subitem walking habits: Improved walking habits at follow-up	Evaluated with Q-TFA subitem prosthetic use: Increased prosthetic use by 26 of 39 patients; 11 reported same amount of use as baseline; 2 reported less prosthesis use	Evaluated with Q-TFA subitem prosthetic mobility: Improved mobility at follow-up	Evaluated with Q-TFA and SF-36: All Q-TFA scores improved at 2-year follow-up except the Q-TFA walking aid subscore.	NR	NR	3 patients had implant removed due to complications	1 reported no prosthetic use due to loading pain Patients reported no significant change in phantom limb pain and pain from the back, shoulders, and contralateral limb	NR

Lead author, publication date	Walking ability	Prosthetic use	Mobility	Quality of life	Infections	Fractures	Implant failure/removal or revision surgery	Pain associated with implant	Other outcomes
Tsikandylakis, 2014	NR	NR	NR	NR	5 of 16 patients developed superficial infections of skin penetration site at 5-year follow-up; 15 episodes of infection 1 deep implant infection	8 patients had incomplete distal fracture of the residual bone at stage 1 surgery	3 patients had implant failure. Implant survival of 83% and 80% at 2 and 5 years respectively. 2 patients underwent two-stage revision surgery	2 patients reported pain on loading 3 patients had phantom pain in their arm	Total of 43 adverse events recorded. 8 patients developed skin reactions at skin penetration site; 3 patients - defective bony canal; 3 patients - avascular skin flap necrosis
Juhnke, 2015	NR	NR	NR	NR	Group 1 – 23 out of 30 patients had surgical interventions secondary to infection Group 2 – No infections reported at last follow-up	NR	Group 1 – 4 patients had implant removed Group 2 – No implants removed	NR	6 out of 30 patients in Group 1 and 34 out 39 patients in Group 2 have not had any unplanned interventions at all
Schalk, 2015	Evaluated with LIFE-H and LEFS: Improved walking ability	NR	Evaluated with LIFE-H and LEFS: Improved mobility	Evaluated with LIFE-H and LEFS: Improved quality of life at 3 years follow-up	NR	NR	NR	NR	NR

Lead author, publication date	Walking ability	Prosthetic use	Mobility	Quality of life	Infections	Fractures	Implant failure/removal or revision surgery	Pain associated with implant	Other outcomes
Salminger, 2016	NR	Both patients reported daily prosthesis use at 2 years	NR	NR	NR	NR	Implant survival of 100% at 4 years None had revision surgery	No pain at stump on wearing prosthesis at 2-year follow-up	Improved prosthetic function and decrease in restriction of range of motion.
Al Muderis, 2016	NR	NR	NR	NR	29 of 86 patients developed grade 1 or 2 infections over median follow-up of 34 months. 47 infection episodes	3 patients sustained proximal femoral fracture	2 patients had implant replacement due to inadequate osseointegration and severe pain	1 patient was unable to load the residual limb because of severe pain	26 patients developed one or more complications – e.g. stoma hypergranulation, soft-tissue redundancy, implant breakage etc.
Al Muderis, 2016 (b)	Measured with 6MWT and TUG tests: Significant improvement compared with preoperative values	NR	Evaluated with AMPPRO scores presented as K-levels: Significant improvement compared with preoperative values	Evaluated with Q-TFA and SF-36: Significant improvement compared with preoperative values at 21.5 months	21 of 50 patients experienced one or more infections	4 patients sustained periprosthetic fractures	2 patients had revision implant	NR	27 patients experienced an adverse event.
Al Muderis, 2017	Measured with 6MWT and TUG tests: Significant improvement compared with preoperative values	NR	NR	Evaluated with Q-TFA and SF-36: Significant improvement compared with preoperative values at 12 months	12 of 22 patients developed minor infections at 14 months follow-up; there were 15 infection episodes	None	None	None	Refashioning surgery was performed electively in 6 patients. No other adverse events recorded.

Lead author, publication date	Walking ability	Prosthetic use	Mobility	Quality of life	Infections	Fractures	Implant failure/removal or revision surgery	Pain associated with implant	Other outcomes
Atallah, 2017	Measured with 6MWT and TUG tests:	Evaluated with Q-TFA subitem prosthetic use:	Evaluated according to K-levels:	Evaluated with Q-TFA and SF-36:	2 of 5 patients had a single episode of superficial soft-tissue infection	None	None	4 of 5 patients were pain free at 12 months postoperatively	None reported phantom limb sensations.
	Improvement compared with baseline	Improvement compared with baseline	Mobility levels of all patients increased by 1 or 2 from baseline to follow-up	Improvement compared with baseline at 12 months					No reports of implant loosening, additional amputation, or death

AMPRO, Amputation Mobility Predictor; LEFS, lower extremity scale; LIFE-H, life habits questionnaire; NR, not reported; 6MWT, 6-minute walk test; OPRA, Osseointegrated Prosthesis for the Rehabilitation of Amputees; Q-TFA, Questionnaire for Persons with Transfemoral Amputation; SF-36, Short Form-36; TUG, Timed Up & Go

Supplementary Material

Supplementary Material 1	PRISMA checklist
Supplementary Material 2	Literature search strategy

Supplementary Material 1. PRISMA checklist

Section/topic	Item No	Checklist item	Reported on page No
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	Title page
Abstract			
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number	2; Abstract
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	3-4; Introduction
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	3-4; Introduction
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number	Not registered
Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale	4; Study selection
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	4; Data sources and search strategy
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	Supplementary Material 2
Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	4-5; Study selection
Data collection process	10	Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	5; Data extraction and quality assessment
Data items	11	List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made	5; Data extraction and quality assessment
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	5; Data extraction and quality assessment
Summary measures	13	State the principal summary measures (such as risk ratio, difference in means).	Not applicable

Section/topic	Item No	Checklist item	Reported on page No
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I^2 statistic) for each meta-analysis	Not applicable
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies)	Table 1
Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	Not applicable
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	6 and Fig. 1
Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations	7 and Table1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	7-14, Table 2-3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	Not applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	Table 1; Study characteristics and quality
Additional analysis	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression) (see item 16)	Not applicable
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, users, and policy makers)	13-16
Limitations	25	Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias)	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	16
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review	17

Supplementary Material 2. Literature search strategy

Relevant studies, published before 23 April 2018 (date last searched), were identified through electronic searches limited to the English language using MEDLINE, EMBASE, Web of Science, and Cochrane Library. Electronic searches were supplemented by scanning reference lists of articles identified for all relevant studies (including review articles) and by hand searching of relevant journals. The computer-based searches combined search terms related to osseointegration and amputation.

1 exp Osseointegration/ (9065)

2 exp Amputation/ (20451)

3 exp Amputees/ (3196)

4 exp Artificial Limbs/ (6598)

5 2 or 3 or 4 (26008)

6 1 and 5 (97)

7 limit 6 to (english language and humans) (74)

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Each part was specifically translated for searching the other databases (EMBASE, Web of Science, and Cochrane databases)