

OSSEOINTEGRATION FOR LOWER-LIMB AMPUTATION

A Systematic Review of Clinical Outcomes

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Abstract

Background: Traditional socket prostheses are not a viable option for all lower-limb prosthetic users. Discomfort, pain in the residual limb, and problems related to the fit of the socket are common and have been shown to negatively impact quality of life and mobility. Osseointegrated or bone-anchored prosthetic implants have evolved over the past 2 decades as a promising alternative for patients who are experiencing substantial issues with socket prostheses.

Methods: A review of the literature was performed to identify studies focusing on the evolution, clinical outcomes, success rates, and complications of osseointegrated lower-limb prostheses. Articles were summarized according to the implant type, amputation level, and study characteristics, with rating of the Level of Evidence. Information on patient selection criteria, outcomes, and complications was extracted.

Results: Fourteen articles (with Level-II, III, or IV evidence) met the inclusion criteria. Infection and soft-tissue irritation at the stoma were the most common complications. It is evident that, over the years, changes in implant design, surgical technique, perioperative and postoperative care, and rehabilitation protocols have resulted in improvements in functional outcomes and health-related quality of life, and reduction in rates of complications.

Conclusions: Osseointegration for limb amputation has become an established clinical treatment option for persons with lower-limb amputation not tolerating traditional socket prostheses. Osseointegration could provide substantial benefits regarding function and quality of life for appropriately selected patients who accept the documented risks.

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

Limb amputation is a life-altering event, affecting mobility, quality of life, and participation in daily activities. The leading cause of lower-limb amputation in developed countries is atherosclerosis, often with

concomitant diabetes¹, whereas in developing countries, traumatic etiology related to industrial, traffic, and wartime injury predominates^{1,2}. In the United States Army, the reported amputation rate related to military conflicts ranged from 7.4% to

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19%^{3,4} of all major extremity injuries sustained, which has potentially shifted the prevalence of amputations to younger individuals, including a higher prevalence of multiple limb amputations⁵.

Prosthetic limbs have evolved, with substantial technological advancements in the past 2 decades, but there are still limitations to their use. The conventional method of attaching a prosthetic limb to the body is through a custom-designed socket⁶. The socket must fit securely to the residual limb to maximize comfort, to transmit the forces of the skeleton to the ground through the interposing soft tissues, and to allow the movement of the residual limb to control the artificial limb. The quality of the interface between the residual limb and the socket is one of the most critical aspects for the success of any prosthesis, complicated by the fact that the residual limb is a dynamic organ (i.e., it tends to atrophy over time, or may swell with heat or weight gain), which can lead to irritation and loss of socket fit¹. Discomfort and problems related to the fit of the socket are common and have been shown to negatively impact the quality of life and mobility of the user⁷⁻¹⁰. The

most commonly faced issues with socket prostheses reported in a survey of 97 individuals with transfemoral amputation included heat or sweating in the prosthetic socket (72%), sores or skin irritation from the socket (62%), inability to walk in woods and open fields (61%), inability to walk quickly (59%), and pain in the residual limb (51%)⁹. Other studies have shown that between one-fourth of 78 participants interviewed⁸ and one-third of 935 participants interviewed¹⁰ expressed dissatisfaction with their prosthesis; they reported problems with wounds, skin irritation, and pain and considered themselves to have a poor or extremely poor quality of life¹⁰.

These problems led to the development of new techniques of attaching prosthetic components directly to the skeleton of the residual limb, thereby bypassing the need for a socket interface. Osseointegration refers to the direct structural and functional connection between living bone and the surface of an artificial metal implant¹¹, providing stable fixation between remodeled biological tissues and a titanium implant without initiating rejection mechanisms¹². In the 1950s, Per-Ingvar

Brånemark used a titanium implant chamber to study blood flow in rabbit bone and noted that the chambers could not be removed at the end of the experiment¹³. Following this remarkable discovery that bone can integrate with titanium components, he coined the term *osseointegration*.

Direct skeletal fixation by osseointegration is currently used in total joint replacements, dental implants, the edentulous mandible, craniofacial deficiencies, maxillofacial reconstruction, orbital prostheses, bone-anchored hearing aids, and, since the 1990s, percutaneous implants for attachment of prosthetic limbs. The use of osseointegrated prosthetic implants for limb amputation is now being performed in several centers in the world, and recently, in the United States, clinical trials are under way with a U.S. Food and Drug Administration Humanitarian Use Device designation¹⁴. Various osseointegration approaches have emerged and have evolved over the past several years. This goal of this article was to present a comparative descriptive review of the use, safety, and reported outcomes of lower-limb osseointegrated prosthetic implants.

Fig. 1
Flow diagram of search results.

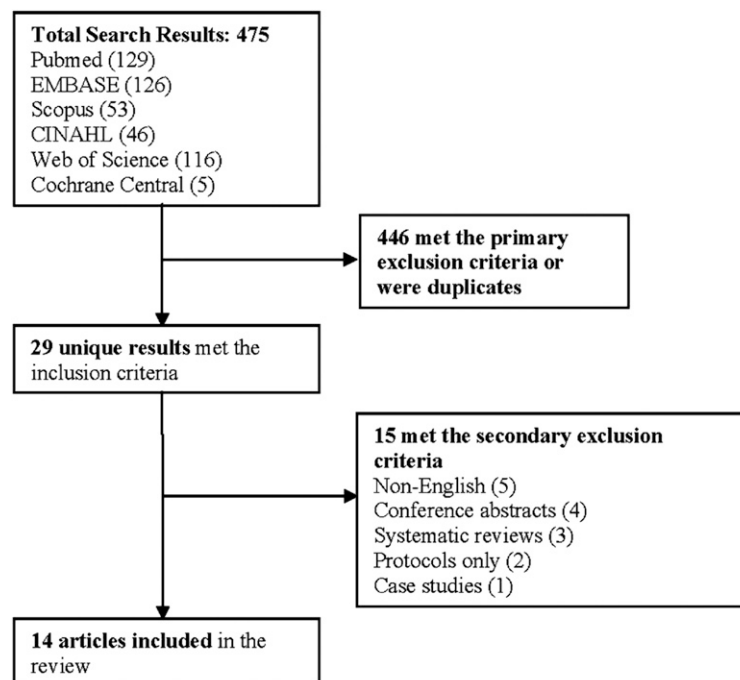


TABLE I Summary of Patient Selection Criteria and Contraindications in the Published Literature

Patient selection criteria

Problems with conventional socket prostheses^{18-20,23,25,28-30}Discomfort, pain, poor suspension, or an inability to use conventional socket prostheses at all^{19,20,23,25}Recurrent skin infections and ulceration, a short stump, soft-tissue scarring, volume fluctuation of the stump, extensive areas of skin grafting, socket retention problems due to excessive perspiration³⁰Expected to have problems with conventional prosthesis²⁰Have reached full skeletal maturity^{18-20,22,24,25,30}Normal skeletal anatomy^{18,20}Age criteria: <70 years^{18-20,30}, >18 years^{25,29}, or >20 years²⁰Be suitable for surgical procedure on the basis of medical history and physical examination^{18,20,30}Agree to comply with the treatment program and follow-up^{20,25,30}

Contraindications

Severe peripheral vascular disease^{18-20,22,24,25,28,29}Diabetes^{20,22,24,25,28,29}Current chemotherapy treatment^{18,19,22,24,25,28,29}, corticosteroid use¹⁹, or immunosuppressant drugs^{19,20,24,28,29}Limb exposure to radiation^{24,25,28,29}Pregnancy^{18,20,22,28,29}Mental illness or disabling psychiatric disorder^{22,25,28,29}Smoking^{24,25,28,29}, encouraged to quit or decreaseOsteoporosis³⁰, atrophic bone conditions²⁴Body weight in excess of 100 kg^{18,30}Infection²², not further specifiedSkin disease involving the amputated limb²⁰Noncompliant during preoperative screening and evaluation^{28,29}Satisfied with conventional socket technology²⁴**Materials and Methods**

A computer-based literature search was performed to identify studies focusing on osseointegrated lower-limb prostheses. Our search utilized the following databases from their inception to April 7, 2017: PubMed, Embase, Scopus, CINAHL, Web of Science, and Cochrane Central Register of Controlled Trials. The search terms used (truncation indicated with an asterisk) were: (osseointegrat* OR bone-anchored OR bone anchored) AND (prosth*) AND (leg OR lower limb* OR lower extremity* OR transfem* OR transtib*). The following MeSH keywords were also used if they were required by the database: Osseointegration, Prostheses and Implants, Artificial Limbs, Leg, Femur, and Tibia.

Inclusion criteria were articles pertaining to physical, functional, and health-related quality-of-life outcomes, implant survival rate, infections, and

complications. Primary exclusion criteria were articles pertaining to animal models; loading or stress evaluation; biomechanical, radiographic, microbiological, or histological evaluation; the upper limb; and myoelectric implants. Secondary exclusion criteria were study protocols, single-case studies, systematic reviews, conference abstracts, and articles in languages other than English.

Data on clinical outcomes, walking ability, quality of life, infections, and other complications were systematically extracted and were tabulated to illustrate the published evidence on efficacy and safety of lower-limb osseointegrated prostheses. Although the protocol for this review generally followed the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines¹⁵, meta-analysis was deemed infeasible because of heterogeneity in the surgical technique, implant design, study design, methodology, follow-up times, and

reported outcomes. Included studies were individually assessed with regard to the Level of Evidence as per the Centre for Evidence-Based Medicine¹⁶.

Results

Fourteen articles were included in this review (Fig. 1): with regard to Level of Evidence, 5 were Therapeutic Level II, 5 were Therapeutic Level III, and 4 were Therapeutic Level IV. All studies were evaluated as having a risk of bias inherent to nonrandomized prospective and retrospective cohort studies, with lack of blinding of participants or study personnel, and patient selection criteria including individuals currently having difficulties (and therefore more likely to show improvement).

Published patient selection criteria were relatively consistent across studies and are summarized in Table I. A tabulated descriptive summary of study characteristics is provided in Table II, reported clinical outcomes are provided

TABLE II Patient Characteristics per Article in the Published Literature*

Reference	Type of Implant	Study Design	LOE	Period of Follow-up	No. of Subjects
Sullivan (2003) ³⁰	OPRA 1997-2003	Retrospective, descriptive	III	NR	11
Hagberg (2008) ^{18†}	OPRA 1999-2004	Prospective cohort (i.e., consecutive patients)	II	2 yr	18
Hagberg (2009) ¹⁹	OPRA 1990-2008§	Retrospective	III	3 mo to 17.5 yr	100
Tillander (2010) ²¹	OPRA 2005	Retrospective	IV	3 yr	39
Brånemark (2014) ^{20#}	OPRA 1999-2007	Prospective cohort	II	2 yr	51
Hagberg (2014) ^{31**}	OPRA 1999-2007	Prospective cohort	II	2 yr	39
Aschoff (2010) ²²	ILP 1999-2009	Retrospective	III	NR	37
Van de Meent (2013) ²³	ILP 2009-2011	Prospective case-control	II	12 mo	22
Juhnke (2015) ²⁴	ILP 1999-2013	Retrospective comparative, treated over 15 yr with 3 types of implant design	III	Group 1: 74 mo (range, 6 to 144 mo); Group 2: 32 mo (range, 1 to 59 mo)	69: 30 in Group 1 (Design A or B) and 39 in Group 2 (Design C)
Al Muderis (2016) ²⁵	ILP 2009-2013	Prospective cohort	IV	Median, 34 mo	86
Khemka (2015) ²⁶	OPL (custom total knee replacement) 2012-2014	Case series	IV	1 to 3 yr	4
Khemka (2016) ²⁷	OPL (custom with total hip replacement) 2013-2014	Case series	IV	1.5 to 2.5 yr	3
Al Muderis (2016) ²⁸	ILP and OPL 2011-2014	Prospective cohort	II	Minimum, 1 yr; mean, 21.5 mo	50
Al Muderis (2017) ²⁹	OPL 2013-2014	Retrospective cohort	III	1 yr median (mean, 14 mo [range, 10 to 30 mo])	22

*LOE = Level of Evidence, and NR = not reported. †The values are given as the mean, with or without the standard deviation, in years, with or without the range in parentheses. ‡These data were subsequently reported by Brånemark et al. (2014)²⁰. §Note that the change in protocol occurred in 1999. #The preliminary report was by Hagberg et al. (2009)¹⁹. **This was the same cohort as that in the study by Brånemark et al. (2014)²⁰.

in Table III, and complications are presented in Table IV. Comparison across groups was challenging as not all centers reported the same outcomes; however, literature consistently reported improved functional mobility, physical performance, and physical health, as well as several domains of health-related quality of life after osseointegration. The most frequently used outcome measure was the Questionnaire for Persons with a Transfemoral Amputation (Q-TFA), designed and validated for evaluating

prosthetic use, mobility, problems, and global health of patients using lower-limb prostheses¹⁷, with demonstrated criterion validity relative to the Short Form-36 Health Survey (SF-36).

The most common complication was superficial skin infection at the stoma site¹⁸⁻²⁹, typically managed by local wound care and a course of oral antibiotics. Deep infections²⁰ and/or removal of the implant due to infection^{20,22,24,30} were reported less commonly. With subsequent iterations

of design and rehabilitation protocols, a reduction in the rates of complications was observed. In the earliest iteration of the Osseointegrated Prosthesis for the Rehabilitation of Amputees (OPRA), the infection rate was 66%²⁰ in a study with 51 subjects. In the most recent prospective cohort of 86 subjects using the Osseointegration Group of Australia Accelerated Protocol (OGAAP), the infection rate was 34%²⁵. This is consistent with the iterative comparison showing fewer infections with the most

TABLE II (continued)

Sex Ratio (M:F)	Level of Amputation	Age†		Cause of Amputation
		At Amputation	At Implantation	
NR	Transfemoral	NR	NR	NR
8:10	Transfemoral	31 (14 to 60)	45 (22 to 62)	Trauma (12), tumor (5), arterial embolus (1)
61:39	Transfemoral	32 (10 to 63)	NR	Trauma (67), tumor (21), vascular including arterial embolus (3), diabetes (2), infection (7)
21:18	Transfemoral (33), transtibial (1), transulnar (4), transradial (4), transhumeral (3)	NR	49 (28 to 74)	"Either trauma or neoplasia"
28:23	Transfemoral	32 (13 to 64)	44 (20 to 65)	"Trauma and malignant tumour"
17:22	Transfemoral	31 ± 14.8	44 ± 12.4	Trauma (23), tumor (11), other (5)
30:7	Transfemoral	33 (14 to 56)	44 (17 to 69)	Trauma (30), tumor (4), other (3)
18:4	Transfemoral	NR	46 (23 to 67)	Trauma (20), tumor (2)
56:13	Transfemoral	NR	Group 1: 46 (17 to 69); Group 2: 45 (24 to 76)	Trauma (51), tumor (7), infection (3), fourth-degree burn (1), other (7)
65:21	Transfemoral	32 ± 14	48 ± 14	Trauma (65), tumor (11), infection (8), congenital (1), other (1)
3:1	Transtibial with socket-related problems, arthritis, and/or a short residuum (<40 mm)	40 (23 to 69) (calculated)	55 (38 to 77)	Trauma (3), infection (1)
1:2	Transfemoral with short residuum (<10 cm) with socket-related problems, arthritis, with or without osteoporosis	38 (34 to 46) (calculated)	49 (35 to 65)	Trauma (2), tumor (1)
34:16	Transfemoral	NR	48.4	Trauma (32), tumor (8), infection (5), blast injury (3), congenital (2)
17:5	Transfemoral	NR	46 (20 to 67)	Trauma (16), tumor (4), infection (2)

recent Integral Leg Prosthesis (ILP) design²⁴. Encouragingly, the rate of severe infection (deep bone infection or infection of the implant) was nil in the most recent series^{24,25,29}. The safety study on the Australian protocol also identified specific patient risk factors for complications, namely, increased odds ratios for women, with a sixfold higher risk of severe infection; those with a body mass index of >25 kg/m², with a threefold higher risk of mild infection; and smokers, with a sevenfold higher risk of recurrent infection²⁵. Other noninfectious complications (Table IV) included fractures of the femur^{24,25,28}, implant

loosening^{19,20}, mechanical complications with the abutment^{20,30}, revision surgical procedures^{22,25,28}, soft-tissue refashioning^{25,28,29}, and implant breakage^{25,28}. Reports on phantom or other limb pain were inconsistently reported. Limited information on prosthetic components was provided¹⁹; however, most protocols mentioned the importance of a safety device to prevent excessive torque from being transmitted to the implant^{19,29,30}.

The discussion is presented in historical order according to implant type to illustrate the development and evolution of the technology.

Discussion

Osseointegrated Prosthesis for the Rehabilitation of Amputees

Carrying on the work of Per-Ingvar Brånemark, a group in Sweden at the University of Gothenburg led by Rickard Brånemark was the first to use percutaneous osseointegrated implants for lower-limb amputation in the 1990s. Their implant and protocol are known as OPRA (Integrum), involving a 2-stage surgical procedure. In the first stage, a threaded titanium implant is inserted into the medullary canal of the femur, and the soft tissue is closed around the end of the limb. The second

TABLE III Reported Clinical Outcomes per Article in the Published Literature

Reference	Reported Clinical Outcomes		
	Prosthetic Use	Walking	Quality of Life or Other
Sullivan (2003) ³⁰	9 of 11 patients using prosthesis daily, all day	Reduced perceived energy consumption; ability to walk further and do more work wearing the osseointegration prosthesis	Improved proprioception; osseoperception or improved sensory feedback; perceived ability to participate fully in activities of daily living; "no longer felt disabled"
Hagberg (2008) ^{18*}	17 of 18 using osseointegration prosthesis with no restrictions at 2-yr follow-up; Q-TFA showed improved prosthetic use (p = 0.013)	14 of 17 osseointegration prosthesis users reported that they normally used a walking aid outdoors; Q-TFA prosthetic mobility score significantly improved (p = 0.001); walking habit subscore significantly improved (p = 0.013)	SF-36 improved in physical component score (p = 0.001); Q-TFA significantly improved in problem score (p = 0.002) and global score (p = 0.002); overall improvements in general and condition specific health-related quality of life
Hagberg (2009) ¹⁹	68 of 100 patients (74 implants) using osseointegration prosthesis; mean 5-yr follow-up (3 mo to 17.5 yr); 3 case studies reported full day prosthetic use at 2-yr follow-up	Subcohort results reported ^{17,19} ; 3 case studies reported using walking aid outdoors, unaided indoors	Subcohort results reported ^{17,19} ; case study Q-TFA improved in prosthetic use, mobility, and global score (7-yr follow-up)
Tillander (2010) ²¹	Not reported	Not reported	Not reported
Brånemark (2014) ^{20†}	47 of 51 patients using osseointegration prosthesis at the time of follow-up; 92% (95% confidence interval, 80% to 97%) cumulative survival after 2 yr; 89% using prosthesis daily compared with 57% prior to osseointegration	Q-TFA prosthetic mobility score significantly improved (p < 0.001)	SF-36 showed significant improvement in general quality of life (p < 0.0001); Q-TFA scores improved (p < 0.0001): prosthetic use, prosthetic mobility, global situation, and fewer problems
Hagberg (2014) ^{31‡}	Of 39 patients, increased prosthetic use reported by 26, same use reported by 11, and less use reported by 2	Walking energy cost (Physiological Cost Index) significantly decreased at 2-yr follow-up (p < 0.0001); 21% reported walking 500 m without stopping several days per week at baseline; this increased to >50% at the time of follow-up; no significant change in use walking aids	6 of 7 Q-TFA scores improved compared with baseline (p < 0.0001); physical functioning, physical component scores improved (p < 0.0001); single index of health (Short Form-6 Dimensions) significantly improved (p = 0.007)
Aschoff (2010) ²²	Not reported	Not reported	35 of 37 patients stated they would choose to have the procedure again under similar circumstances
Van de Meent (2013) ²³	Prosthetic use significantly improved (p < 0.001) with osseointegration prosthesis compared with socket prosthesis	Significant improvements in 6-minute walk test (27%; p = 0.002) and Timed Up-and-Go test (44%, p = 0.002); subjects with osseointegration prosthesis were capable of walking further faster and with 18% less oxygen requirements (p = 0.001) compared with socket prosthesis	Significant improvements with osseointegration prosthesis compared with socket prosthesis in Q-TFA global score (p = 0.001) for prosthesis-related quality of life
Juhnke (2015) ²⁴	Not reported	Not reported	Not reported
Al Muderis (2016) ²⁵	Not reported	Not reported	Not reported
Khemka (2015) ²⁶	"Participants reported being able to use their prosthesis all through the day if needed"	All subjects improved ambulation and activity level, daily number of steps, and duration of physical activity (p = 0.1); 37 to 84 m improvement in 6-minute walk test (p = 0.07)	Improved SF-36 physical component and Q-TFA (p = 0.07); pain-free knee and no phantom-limb sensation at the time of follow-up, compared with preoperative phantom sensation and pain

continued

TABLE III (continued)

Reference	Reported Clinical Outcomes		
	Prosthetic Use	Walking	Quality of Life or Other
Khemka (2016) ²⁷	Not reported	Two of 3 patients changed from being wheelchair-bound (K-level 0) to being community ambulators (K-level 3); all 3 patients were able to perform 6-minute walk test (>200 m) and Timed Up-and-Go test (<15 seconds) after osseointegration	Improved SF-36 (physical and mental components) and Q-TFA in all 3 patients (p = 0.11); phantom-limb sensation was reduced in all 3 patients; pain-free hip and normal hip range of motion at the time of follow-up
Al Muderis (2016) ²⁸	Not reported	Significant improvements in amputation mobility predictor, K-level (p = 0.001), Timed Up-and-Go test (p < 0.01), and 6-minute walk test (p < 0.001); 14 wheelchair-bound patients able to perform mobility tests postoperatively	Significant improvement in SF-36 physical component summary (p < 0.001) and Q-TFA global score (p < 0.001)
Al Muderis (2017) ²⁹	9 of 10 wheelchair-bound patients using osseointegration prosthesis and walking at 1-yr follow-up (1 died)	Significant improvements in 6-minute walk test (128%) and Timed Up-and-Go test (30%) (p < 0.05) at 1-yr follow-up	Q-TFA and SF-36 scores were significantly higher at the time of follow-up than preoperatively (p < 0.05)

*These data were subsequently reported by Brånemark et al. (2014)²⁰. †The preliminary report was by Hagberg et al. (2009)¹⁹. ‡This was the same cohort as that in the study by Brånemark et al. (2014)²⁰.

stage of the surgical procedure follows 6 months later, which includes the attachment of a titanium extension, known as an abutment, to the osseointegrated fixture. The soft tissues and skin are closed around the abutment, to which the prosthetic components can then be directly connected. Varying lengths of residual femur can be implanted, with the most recently reported series classifying the length of the residual limb as long in 4 patients (10%), medium in 27 patients (69%), and short in 8 patients (21%)³¹. A rehabilitation protocol following the second surgical procedure³² was developed in the late 1990s. The rehabilitation protocol involves gradual loading of the bone-implant interface over a period of 6 months to stimulate and facilitate the process of osseointegration. There is an initial training period using a short training prosthesis (4 to 6 weeks following the surgical procedure) and involving axial weight-bearing and gentle weight shifting, avoiding any rotation. This is followed by gradually increased prosthetic use using crutches (16 to 24 weeks following the surgical procedure) to prepare the user for eventual unrestricted prosthetic use.

To our knowledge, the first peer-reviewed, descriptive, retrospective report on osseointegrated implants for transfemoral amputees was published in 2003³⁰ by a group in the United Kingdom. They reported that, at the time of publication, 11 patients had undergone both stages of the surgical procedure and a comprehensive rehabilitation process. Of those patients, 9 were able to use their osseointegrated prostheses every day, and 2 required removal of the implant due to infection.

The Brånemark team's first prospective report on the outcome for individuals treated with OPRA implants was published in 2008¹⁸. Using 2 self-reporting questionnaires, SF-36 and the Q-TFA, the investigators reported that, at the 2-year follow-up, 17 of 18 patients were using the osseointegrated prostheses. Significant improvement was reported in physical functioning, bodily pain, prosthetic use, prosthetic mobility, overall health, and all components of the SF-36. The patients demonstrated a general improvement in health-related quality of life compared with their preoperative quality of life.

In 2009, Hagberg and Brånemark presented the results of 100 patients

treated with osseointegrated transfemoral prostheses between 1990 and 2008¹⁹. It was reported that the majority of treatment failures occurred in patients before a strict rehabilitation protocol was established in 1999. By 2009, 68 of 100 patients were still using their prostheses; superficial infections treated with oral antibiotics were the most common complication, but 11 patients had permanent removal of the implant. The implementation of graded rehabilitation was found to be most effective for improved results.

In a prospective study²⁰ of 51 patients treated with the OPRA protocol between 1999 and 2007, 92% (47 patients) were using the osseointegrated transfemoral prosthesis at the 2-year follow-up; 89% used it daily compared with 57% who had used the socket prosthesis prior to the surgical procedure. Improvement in physical function, prosthetic use, mobility, and overall situation was reported. Superficial infection was reported to be the most frequent complication, occurring 41 times in 28 patients. Four patients experienced deep infections, and 1 of them required removal of the implant due to loosening. Four patients experienced

TABLE IV Reported Complications per Article in the Published Literature

Reference	Reported Complications	
	Infections	Other Complications
Sullivan (2003) ³⁰	Two of 11 had internal fixture removed due to infection	Five of 11 abutments replaced due to mechanical deformation with falls; 2 abutments fractured
Hagberg (2008) ^{18*}	Two of 18 patients had superficial infection at the skin penetration area	One implant loosening with pain during weight-bearing; unable to wear the prosthesis
Hagberg (2009) ¹⁹	Three case studies discussed as illustration of complications, including 2 with superficial infections treated with oral antibiotics	Of 100 patients, 20 had implants removed, 11 permanently (not replaced); 4 patients with implant not using prosthetic limb due to phantom pain, osteomyelitis, or contralateral limb problems
Tillander (2010) ²¹	Of 39 patients, 2 had implant infection at inclusion (at least 3 mo after osseointegration) and 7 had experienced implant infections at 3-yr follow-up; 7 had local infection in the 6-mo period preceding inclusion, 4 were treated with oral antibiotics; 11 had a history of local infection at the stoma during the 6-mo period before follow-up, 6 were treated with short-term oral antibiotics	One implant extracted due to mechanical loosening in a previously irradiated femur; 1 abutment removal due to chronic skin infection (not included in follow-up)
Brånemark (2014) ^{20,†}	Superficial infection occurred 41 times in 28 of 51 patients; deep infection occurred in 4 patients (immediately after first stage to 42 days after second stage), 3 treated with antibiotics and 1 with removal of implant at 6 mo	Total of 46 of 51 patients had ≥ 1 complications; total of 101 complications, 49 classified as "serious" complications in 39 patients; implant removed in 4 patients (1 infection, 3 aseptic loosening); 5 patients had episodic pain during rehabilitation, without loosening; 4 patients with 5 fractures, 3 in the ipsilateral hip, 1 below the elbow, and 1 vertebral compression; no peri-implant fractures reported; 9 mechanical abutment complications in 4 patients (6 in same patient), replaced with no long-term effect
Hagberg (2014) ^{31‡}	Not reported	No significant change in phantom-limb pain or bodily pain; other complications reported elsewhere ¹⁹
Aschoff (2010) ²²	Fourteen of 37 subjects underwent minor revision due to stoma; 2 of these 14 were due to severe infection (but no deep infection)	Of 37 patients, 17 had no complications or minor complications and 20 had ≥ 1 revisions; of these 20 patients, 4 required explantation (1 due to intramedullary infection, 2 due to chronic soft-tissue problems, 1 due to failure 7 yr after surgery), 2 successfully reimplanted; 14 of 37 patients had minor revision due to stoma, 12 of which were exchange of coupler
Van de Meent (2013) ²³	Eight of 22 mild infections of soft tissue	Not reported
Juhnke (2015) ²⁴	Group 1 (first 2 ILP iterations): soft-tissue infections occurred in 13 of 31 early and 10 of 18 at the time of follow-up (late); Group 2 (most recent ILP iteration): no soft-tissue infections in 38 patients	Group 1: 1 structural failure of implant, 4 explanations, 3 fractures, 77% had intervention due to soft-tissue stoma and 80% due to "any unplanned intervention"; Group 2: no structural failures or explantations, 2 peri-implant fractures (did not require implant removal), and 1 intervention due to soft-tissue stoma
Al Muderis (2016) ²⁵	Of 86 patients, 29 had infections; of these 29 patients, 25 were low-grade soft-tissue infections: 23 were treated with oral antibiotics, 1 was treated with parenteral antibiotics, and 1 required surgical intervention; 4 were high-grade soft-tissue infections that required surgical intervention	Of 86 patients, 31 had no complications or adverse events; 26 did not develop infections but had ≥ 1 other complications requiring intervention: stoma hypergranulation (17 patients); soft-tissue redundancy (14 patients); proximal femoral fracture (3 patients); implant replacement due to inadequate osseointegration (1 patient); implant breakage (2 patients)
Khemka (2015) ²⁶	One case of superficial infection (of 4 patients), treated with oral antibiotics; no deep infections	No major complications or adverse events
Khemka (2016) ²⁷	Superficial infection in 1 patient (of 3 cases); treated with oral antibiotics	No major complications or adverse events
Al Muderis (2016) ²⁸	Of 50 patients, 21 experienced ≥ 1 soft-tissue infections: 13 were treated with oral antibiotics, 5 were treated with intravenous antibiotics, and 3 required surgical soft-tissue debridement; no intramedullary (deep) bone infections	Of 50 patients, 23 had no complications or adverse events and 27 patients experienced at least 1 adverse event; 10 patients underwent soft-tissue refashioning; 4 patients sustained peri-implant fractures as a result of falls and all 4 were managed without interfering with the osseointegration of the implant; 2 patients required implant revision
Al Muderis (2017) ²⁹	Of a total of 22 patients, 15 cases of minor infection in 12 patients; of these cases, 12 resolved with oral antibiotics and 3 resolved with intravenous antibiotics	Six of 22 patients underwent elective soft-tissue refashioning; no cases of revision surgery, fracture, or implant failure

*These data were subsequently reported by Brånemark et al. (2014)²⁰. †The preliminary report was by Hagberg et al. (2009)¹⁹. ‡This was the same cohort as that in the study by Brånemark et al. (2014)²⁰.

falls and 5 fractures; however, there was no fracture involving the implant.

The authors reported on physical health-related quality of life and walking energy cost in a subset of 39 unilateral transfemoral amputees who received the OPRA prostheses and reported significant improvements in prosthetic use, mobility, walking habits, and overall amputation situation³¹ at the 2-year follow-up. Twenty-six patients reported increased prosthetic use, and walking energy cost was also significantly reduced ($p < 0.0001$).

Integral Leg Prosthesis

The success of the osseointegrated prostheses in Sweden spurred design of implants in Germany in the late 1990s. The German implant design diverted from screw-type fixation to intramedullary press-fit, porous-coated, alloy devices similar to those used in joint arthroplasty. This group, led by Horst Aschoff, termed their implant the Integral Leg Prosthesis (ILP) (ESKA Orthopaedic), although, in the first few design iterations, it was known as the Endo-Exo Femur Prosthesis. The intramedullary implant had a porous patented Spongiosa-Metal II surface (Orthodynamics) for osseointegration implantation without cement, which was directly implanted into the residual femur in a retrograde fashion during the first stage of the surgical procedure. It was reported that 12 to 15 cm of the distal part of the femur was needed for successful ILP implant-stem placement²². The initial design also utilized a bone-stabilizing bracket attachment that was deemed necessary to prevent fatigue failure of the implant. Approximately 6 to 8 weeks later, a stoma was created in the second-stage surgical procedure to expose the distal aspect of the implant and to attach a dual cone adaptor for fixation of the prosthetic components²².

Thirty-seven transfemoral amputees were reported to have undergone treatment with the ILP between 1999 and 2009²². Twenty of 37 patients underwent ≥ 1 revisions, with 4

undergoing removal of the implant (2 of these were subsequently successfully replaced). Fourteen of the 37 patients underwent minor revisions due to problems at the stoma, typically as a result of soft-tissue irritation. It was determined that the porous surface of the transdermal coupler caused hypergranulation tissue, which was uncomfortable for the patient and necessitated soft-tissue debridement procedures. This led to subsequent design iterations of the implant.

The next iteration of the ILP implant in 2009 saw the incorporation of a smoothly polished (nonporous) surface for the coupler to reduce soft-tissue irritation, elimination of the bone-stabilizing bracket attachment, shortening of the bridging connector to adjust to the deep soft-tissue channel, and coating of the connector and bone-capping portion of the osseointegrated implant with a nonabrasive titanium niobium oxynitride ceramic. Between 2009 and 2013, 39 patients were treated with the final iteration of the ILP implant²⁴ and the results of these patients were compared with 30 patients who received the prior implant design. There was a significant reduction in the rate of stoma-associated infections, with a 77% absolute risk reduction ($p < 0.001$) of any interventions due to soft-tissue problems at the stoma. All patients remained infection-free using a simple defined wound-hygiene protocol (cleaning the site with mild soap and water twice a day). The implant did not have to be removed in any patient with the final design of the ILP. For physical rehabilitation, patients were engaged in partial weight-bearing (crutch walking, initially 5 to 10 kg) and a vertical posture immediately after the second surgical procedure and progressed to full weight-bearing without crutches at 4 to 6 weeks after the second surgical procedure.

In a prospective study, Van de Meent et al.²³ assessed walking ability and quality of life of 22 transfemoral amputees with ILP implants, compared with their performance at baseline with socket prostheses. At the 12-month

follow-up, overall, participants had significantly improved prosthetic use ($p < 0.001$) and prosthesis-related quality of life. The Q-TFA global score with the osseointegrated prosthesis was significantly higher at 68% ($p < 0.005$). Prosthetic use improved by 45%, from 56 hours per week with the socket prosthesis to 101 hours per week with the osseointegrated prosthesis. Participants with the osseointegrated prosthesis walked significantly faster, by 44% ($p < 0.005$), and, at the preferred walking speed, they used 18% less oxygen ($p < 0.005$). During the 12-month follow-up period, 8 participants had mild infections of the soft tissue at the stoma site. Overall, the participants in this study experienced substantial improvement in their ability to walk and prosthesis-related quality of life with osseointegrated prostheses.

Al Muderis et al. reported on the safety of press-fit ILP implants²⁵ used in Australia and the Netherlands. In a prospective study, they examined adverse events in all patients with transfemoral amputation who were managed with a press-fit implant between 2009 and 2013 at the 2 centers. Eighty-six patients (some bilateral, for a total of 91 implants) were included in the study and were followed for a median of 34 months. Thirty-one patients (36%) had no complications, 29 developed an infection (most resolving with oral antibiotics), and 26 did not develop an infection but had 1 or more other complications that required intervention. Five infections required surgical debridement with revision of the stoma. Four patients had high-grade soft-tissue infection with abscess formation that needed surgical debridement. No patient experienced deep peri-implant infection or implant failure due to infection. Importantly, this article outlined a standard classification system for infectious complications based on clinical and radiographic findings²⁵.

Osseointegrated Prosthetic Limb

The next development in the field occurred in 2011 when Munjed Al

Muderis at the Macquarie University in Sydney, New South Wales, Australia, introduced the Osseointegrated Prosthetic Limb (OPL) (Permedica). The design of this implant is similar to the ILP with a highly polished smooth transcutaneous dual cone adaptor coated with titanium oxide to minimize soft-tissue friction, but also includes a distal flare within the intramedullary portion to assist with bone anchorage²⁵ and an option for inserting top cross-screws for short residual limbs. Insertion of the press-fit implant involves 2 surgical stages, approximately 4 to 8 weeks apart. In the first stage, the soft tissues are prepared with refashioning of the stump, excess subcutaneous fat is excised, neuromas are removed, and the bone is prepared to accept the implant (excision of irregular distal bone, reaming of the medullary canal, and use of locally obtained autologous bone graft when needed). The intramedullary component of the prosthesis is then inserted to achieve mechanically stable press-fit fixation. The second stage involves the creation of the skin opening and insertion of the transcutaneous dual-cone adaptor. Externally, the adaptor is fixed to a torque control safety device, which then connects to the prosthetic limb²⁶.

The Australian group developed a well-defined rehabilitation and outcomes tracking protocol, the OGAAP-1. In a prospective study of 50 consecutive unilateral transfemoral amputees followed for a minimum of 1 year post-surgery²⁸, adverse events were tracked and were analyzed. These patients were fitted with either the ILP or the OPL; therefore, this study evaluated both press-fit implants with the same rehabilitation and surgical protocol. It was reported that a cross-screw was inserted through the femoral neck if the residuum was shorter than 16 cm. A total of 23 patients (46%) did not experience any adverse events, 18 patients (36%) had superficial infections that resolved with antibiotics, and 3 patients (6%) underwent surgical debridement. Infections were confined to soft tissue,

and no deep bone infection was reported. Refashioning of the soft-tissue residuum was performed on 10 patients because of redundancy, and 4 patients experienced periprosthetic fractures. There was 1 implant fatigue failure and 1 failure of osseointegration related to an undersized implant, both of which were revised successfully.

The patients reported significant improvements ($p < 0.001$) in their global amputation situation (Q-TFA), physical health-related quality of life (SF-36), and walking mobility. This included 14 patients who were wheelchair-bound preoperatively and were able to walk postoperatively. Patients were mobilizing with crutches or a forearm support frame on the third day and were discharged home 5 to 7 days following the first surgical procedure. After the second surgical procedure, the rehabilitation protocol began with limited weight-bearing on day 3, and patients were discharged from the hospital in 5 to 10 days, followed by outpatient therapy. Patients progressed from the surgical procedure to unaided walking in approximately 4.5 months, contrasting with the 9 to 12 months seen with previous screw-fit implants^{18,31}. Press-fit fixation appeared to provide adequate, immediate stability to allow more rapid rehabilitation, mobilization, and ambulation.

More recently, a single-stage procedure has been introduced by the Osseointegration Group of Australia, using a prospective cohort study, which began in April 2014³³. Retrospective preoperative and postoperative clinical data on 22 patients receiving the OPL implant in 1 stage with 1-year follow-up²⁹ showed significant improvement in functional walking tests and global scores ($p < 0.05$), with main complications of superficial infection (15 cases in 12 patients) and soft-tissue refashioning surgical procedures (in 6 of 22 patients) but no implant failures. Nine of 10 patients who were wheelchair-bound were able to perform walking tests at the 1-year follow-up. Further comment will need to be

reserved until publication of the prospective 2-year follow-up data.

Khemka et al.²⁶ also reported on the feasibility of combining total knee replacement with an osseointegrated fixation to the residual tibia in a case series of 4 transtibial cases, and on the feasibility of combining total hip replacement with an osseointegrated transfemoral implant in 3 cases²⁷. These procedures utilized custom implants integrated modularly to the joint replacement components. Clinical outcomes were assessed at baseline and after 1 to 3 years of follow-up. All patients showed improved clinical outcomes, including 2 of the transfemoral patients who were wheelchair-bound at baseline becoming community ambulatory. Khemka et al. reported superficial infection in 1 patient in each case series and no other major complications.

Additional Outcomes

To enhance understanding of the experience of living with an osseointegrated prosthesis, Lundberg et al. conducted a qualitative in-depth interview study on patients using bone-anchored prosthetic limbs³⁴. All participants described living with an osseointegrated prosthesis as a revolutionary change in their lives. All of them described drastic functional changes and being able to sit comfortably and not needing to spend as much time managing the prosthesis, which contributed to an improvement in their quality of life. Many participants reported feeling that the osseointegrated prosthesis became an integrated part of their body; it had strengthened the feeling of having a “whole body,” which influenced their way of looking at and experiencing the world. This impact on their sense of self had been so profound that the patients believed that they could be more the people who they were before the amputation. Osseoperception is the term used to describe the ability of patients with osseointegrated fixtures to identify sensory thresholds transmitted through their prostheses³⁵, and it is thought that this phenomenon contributes to enhancing patients’

subjective sense of integrating the osseointegrated prosthesis into their body schema.

In contrast to the substantial evidence on functional and quality-of-life benefits of osseointegration^{18,20,23,26-29,31,34}, there is limited evidence on cost-effectiveness. One study showed that, compared with socket prostheses, users of osseointegrated prostheses made fewer follow-up visits to the hospital or workshop, and the mean total annual cost of new prostheses, services, repairs, and adjustments was 14% lower for osseointegrated prostheses than for socket-suspended prostheses³⁶. Overall, there is insufficient evidence to address the cost-effectiveness of osseointegrated prostheses, and further longitudinal study is required.

In conclusion, osseointegration for limb amputation has become an established treatment option in several areas of the world, with specific patient selection criteria, rehabilitation protocols, and follow-up. Major clinical benefits from osseointegrated prosthesis include improved quality of life^{18,20,23,26-29,31,34}, prosthetic use^{18,34}, body image³⁴, range of movement at the hip³⁷, comfort when sitting³⁸, ease of fitting and removing prostheses¹⁸, osseoperception^{35,39}, and walking ability^{19,23,26-31}. Additional considerations beyond the scope of this review are the potential changes in bone mass due to increased loading through the skeletal tissues.

Considerations include the requirement for rehabilitation that can take between 4 months²⁸ and 18 months¹⁹, although the most recent approach utilizes a single-stage procedure with rapid rehabilitation and immediate weight-bearing, as per the principles of joint replacement surgical procedures²⁹. The skin area surrounding the abutment requires daily hygiene, with skin irritation and mild infection being the most commonly reported adverse events. There are less common risks of deeper soft-tissue infection, fractures from falls, and loosening of the implant. Users of osseointegrated

prosthetic devices are advised to avoid high-impact activities such as running or jumping and the use of public swimming pools to prevent infection³⁰.

Lastly, a permanent abutment may be considered less than desirable by some patients for cosmetic reasons³².

Osseointegration appears to have become an established treatment option for a selected group of patients with limb amputation not tolerating traditional socket fittings. There is sufficient evidence to fully inform patients as to the possible risks and complications compared with the benefits. Osseointegration could provide substantial benefits to function and quality of life for appropriate patients who accept the documented risks. As with any new technology, ongoing incremental iteration to optimize outcomes is expected through this clinical evolutionary phase. Adopting a standard classification system for tracking outcomes and complications would greatly assist in ongoing and future evaluation of implant techniques.

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