Bone-anchored implants for direct attachment of external prostheses for persons with transtibial amputation: Protocol for a systematic review of clinical effectiveness, complications, patient experiences, and cost-effectiveness

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Introduction

Rationale

Amputation of the lower limb has a severe impact on physical function, psychological well-being, and social participation.[1–8] Following an amputation, the conventional method of

attaching a prosthetic limb to the body is through a custom-designed socket-suspension system to which their prosthetic devices are connected (hereafter called “socket prosthesis”). About 86% of people with a major lower extremity amputation are fitted with a socket prosthesis.[9] Prosthetic limbs dependent on socket-suspension systems have evolved over the past few decades, with substantial technological advancements, but there still are limitations to their use. The socket is custom-designed for each individual user according to the condition and shape of their residual limb. They rely on suction or strapping of the prosthesis to the residual limb. The socket must fit securely to the residual limb to maximize comfort, to transmit the forces of the skeleton to the ground, and to allow the movement of the residual limb to control the prosthetic limb. The interface between the residual limb and the socket is one of the most crucial aspects for the success of any prosthesis and continues to be a major limiting factor in prosthetic use. Discomfort and problems related to the fit of the socket are common and have been shown to negatively affect the quality of life and mobility of the user.[10–13] Lack of comfort, skin ulcers,[14] inadequate or fluctuating suspension,[15] tissue irritation, excessive heat and perspiration,[14] poor control due to the motion of the soft tissue within the socket, and low confidence with mobility[12] are problems that plague many prosthetic users. Between 34% and 63% of socket prosthesis users have chronic skin problems and pain resulting from friction between the residual limb and the prosthesis which lead to reduced prosthetic use and function, reduced quality of life and detrimental body image.[12,16–19] The socket can also restrict the range of movement of the proximal joint leading to difficulties in sitting or participating in activities of daily living. These issues necessitate frequent refitting in up to three-quarters of socket prosthesis users.[11]

These problems spurred the development of new techniques of attaching prosthetic components directly to the bone of the residual limb, bypassing the need for a socket interface. This procedure, termed *osseointegration*, has become an established treatment option in several areas of the world. This technology which relies on anchoring the prosthetic devices directly to the bone of the residual limb involves the surgical insertion of a titanium implant into the centre of the residual femur, which extends percutaneously, i.e., through the skin, to allow a direct structural and functional connection to a prosthetic leg.[20,21] Titanium is naturally biocompatible (non-toxic and non-allergenic) and the titanium implant integrates with living bone tissue. A connector allows for proper attachment of the implant to the prosthesis.

Several types of implants exist and previous reviews on this topic often mix results clinical outcomes [22,23]or complications[24] from various levels of amputation. Also, there exist several reviews in the peer-reviewed literature on the transfemoral (above-knee) bone-anchored prostheses. To the best of our knowledge, there is no review of the outcomes of bone-anchored or osseointegrated prostheses at the transtibial (below-knee) level. This review aims to serve this need by providing a single resource to which clinicians and policymakers can refer if they need to

learn about the evidence on clinical efficacy, adverse events, patient experience, and cost-effectiveness of transtibial bone-anchored prostheses.

Objectives

The research question guiding this systematic review is: What is the (a) clinical-effectiveness, (b) complications and adverse events, (c) patient experience, and (d) cost-effectiveness of bone-anchored implants that enable attachment of prosthetic devices for persons with below-knee amputations?

Methods

Information sources

The following databases will be searched: MEDLINE All (Ovid), Embase (Ovid), APA PsycInfo (Ovid), CINAHL Complete (EBSCOhost), Cochrane Database of Systematic Reviews (Ovid), PEDro (https://pedro.org.au/), Health Technology Assessment (Ovid), NHS Economic Evaluation Database (Ovid)

Search strategy

Specific details regarding the initial search strategy in Ovid MEDLINE All is available in Appendix 1. An experienced knowledge synthesis specialist (MC) developed and tested the search strategies through an iterative process in consultation with four of the review authors (MR, NH, DZ, and JSH). The search strategy in MEDLINE has been peer-reviewed according to PRESS guidelines[25] by an additional information specialist. Search strategies from previous literature reviews[26–28] were consulted and some of the search terms used in their strategies were identified.

Searches are planned to be conducted on Friday, March 1st, 2024. The strategies will utilize a combination of controlled vocabulary (e.g., "Bone-Anchored Prosthesis", "Osseointegration", "Bones of Lower Extremity") and keywords (e.g., " OPRA", "osseo-anchor", "tibia"). Vocabulary and syntax will be adjusted across the databases, and no language or date restrictions will be imposed, although animal-only records will be removed where possible. Results will be uploaded and deduplicated using Covidence[29]. Reference lists of previous pertinent systematic reviews and of the articles selected for full-text or included in this review will also be searched for additional sources. Forward citation searching will be done with Web of Science SCI-EXPANDED for articles included in this review.

PICOTS

Population: Adults (≥18 years) with a unilateral or bilateral transtibial (below-knee) amputation. Participants include users and non-users of a prosthesis. There are no age limitations for adults.

Intervention: Osseointegrated/bone-anchored implants to which prosthetic legs are attached

Comparator: Socket-suspension systems to which prosthetic legs are attached or no prosthesis

Outcome: Health-related quality of life, mobility, prosthesis usage, complications and adverse events, patient experiences, health economic outcomes

Time: No restriction (since inception of database to February 29, 2024)

Studies: Randomised controlled trials and controlled (clinical) trials, observational studies, cohort studies, cross-sectional studies, non-randomised controlled trials published in English or French.

Inclusion/exclusion criteria

Inclusion	Exclusion
Population: • Humans only • Adults (age ≥18 years) • Unilateral or bilateral • Transtibial (below-knee) amputation • Users and non-users of a prosthesis • No age limitations for adults	Population: • Animal models • Non-adults (age < 18 years)
Intervention: • Osseointegrated/bone-anchored implants to which prosthetic legs are attached • Screw-fit type or press-fit type • OPRA (Osseointegrated Prostheses for the Rehabilitation of Amputees) • ILP (Integral Leg Prosthesis) • OPL (Osseointegrated Prosthetic Limb) • EEP (Endo-Exo Prosthesis) • TOPS (Transcutaneous Osseointegrated Prosthetic Systems) • POP (Percutaneous Osseointegrated Prosthesis)	Intervention: • Comparison between two socket prostheses but NOT osseointegrated prosthesis • Hip replacement • Hip implants • Hip arthroplasty • Knee replacement • Knee implants • Tooth implants • Maxillofacial implants • Edentulous jaw • Hearing implants

• OTN • BADAL X • ITAP (Intraosseous Transcutaneous Amputation Prosthesis)	• Cochlear implants • Implants for any other body part which is not a below-knee amputation
Comparator: • Socket-suspended prosthesis • Transtibial socket • No prosthesis • Wheelchair-bound	Comparator: • Those that do not meet the inclusion criteria
Outcome: • Patient-reported outcome measures • Patient-reported experience measures • Clinician-reported outcome measures • Performance-based outcome measures • Functional tests/outcome measures • Self-reported mobility (PLUS-M, others) • Health-related quality of life (SF-36, SF-6D, Q-TFA, EQ-5D, HUI, others) • Mobility (2MWT, 6MWT, 10 MWT, Physiological cost Index, TUG, L-test, and others) • Prosthesis usage • Don/doff time • Complications (relating to surgery like infection, deep infection or mechanical complications, and others) • Adverse events (infection, deep infection, falls, periprosthetic fracture, implant breakage, implant loosening, implant removal), • Qualitative literature outlining patient experiences of participants who do undergo osseointegration • Health economic outcomes (cost-utility studies, cost-comparison	Outcome: • Gait parameters (temporal-spatial, kinematic, kinetic, and electromyography data) • Loading or loading characteristics • Imaging (DEXA, BMD, CT scans) • Biomarkers (bone density, blood-based biomarkers) • Histological findings

studies, cost-effectiveness study, cost-benefit analysis, cost-minimization analysis, and others)	
Study characteristics: • Randomized controlled trials • Controlled (clinical) trials • Non-randomized controlled trials (such as single-arm trials, crossover designs, and others) • Observational studies • Cohort studies • Case series • Cross-sectional studies • Published in English, French, and Spanish	Study characteristics: • Systematic review • Other literature reviews (scoping, rapid, mapping, narrative, and any others) • Health Technology Assessments • Protocol only • Case study • Editorials • Erratum • Opinion pieces • Thesis (reason: it is grey literature) • Conference abstracts • Conference papers • Conference posters
Other: • None	Other: • Device design

Data management

Covidence will be used to manage the data and carry out the screening procedures for this study.

Selection process

Title and abstract screening will be carried out independently by two of three reviewers (MR, PMB, and SG). A full-text review will be carried out independently by two reviewers (MR and PMB). Any conflicts at these stages will be handled by consensus (between MR and PMB). A third reviewer (DZ) will serve as arbiter when needed.

Data collection process

A data extraction template will be developed through discussion between six reviewers (MR, PMB, SG, DZ, NH, JSH) and trialed with two included articles by two reviewers (MR and PMB). Following this, three reviewers (MR, PMB, and SG) will carry out data extraction, which will be validated by discussion with other reviewers (NH and JSH) who are subject matter experts on amputation, osseointegration, and prosthesis research.

Data items

Essential characteristics of the studies, including study type, country of the centre publishing the study, funding source, number of patients, sex ratio, laterality, age of participants at treatment, time since amputation, etiology of the patients, length of follow-up, external prosthesis components in addition to the outcomes of interest, will be extracted.

Outcomes

Outcomes on clinical efficacy including health-related quality of life, mobility, prosthesis usage, disability, prosthesis satisfaction will be extracted depending on what is available in the literature. Complications and adverse events data will be extracted including types and incidence of complications/adverse events, and odds of complications. Patient experiences, changes in lived experience and challenges with bone-anchored implants that enable prosthetic fixation will be extracted from the qualitative literature. Heath economic variables including study type, costs, outcomes, ICER will be extracted. The above noted variables may change based on what's available in the literature.

Quality assessment and risk of bias in individual studies

Quality assessment and risk of bias will be evaluated by two reviewers (among MR, PMB, SG, and DZ) using appropriate tools based on the study design of the articles included in the final review. Risk of bias of individual studies will be assessed using the Cochrane risk-of-bias tool (RoB 2) for randomized controlled trials (RCTs) and the modified Downs and Black scale for non-RCTs. Two reviewers (among MR, PMB, SG, and DZ) will independently assess the quality of the included studies and any disagreement will be resolved by consensus.

Analysis and synthesis

Data synthesis

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[30] will be used to describe the search process and results. The quality of the included studies and information relevant to the research question, including detailed information on the studied population and outcomes reported, will be summarized in tables for descriptive analysis. The statistical outcome from original reviews will be retrieved and compared for each outcome. Data will be presented in a tabular format for evidence on clinical efficacy, complications, patient experiences, and health economic data. A meta-analysis will be carried out if possible. If methodologically not feasible, a narrative summary will be presented. Data synthesis will occur at the level of individual outcome measure or complication.

Confidence in cumulative evidence

Confidence in the cumulative evidence will be determined based on the available literature, the quality of the literature, and the risk of bias assessments.

Analysis of subgroups or subsets

Analysis of subgroups will be considered according to the available data. Factors that will be considered for the sub-group analysis will include gender and cause of amputation.

Collaborators

Virginie Paquet, Health sciences information specialist, Université de Montréal

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Appendix 1: Example of literature search in OVID MEDLINE All

Database(s): Ovid MEDLINE(R) ALL 1946 to February 29, 2024
Search Strategy:

#	Searches	Results
1	Osseointegration/	11191
2	(os#eointegrat* or os#eointegrat* or postos#eointegrat* or (os#eo* adj2 integrat*) or os#eoanchor* or os#eo-anchor* or (peri* adj5 implant* adj5 endosseo* adj5 heal*)).ti,ab,kf.	15361
3	Bone-Anchored Prosthesis/	257
4	(bone? anchor* or boneanchor* or endo exo* or endoexo* or (bone? adj2 format* adj2 implant*) or (bone? adj2 ongrow* adj2 implant*) or (bone? adj2 grow* adj2 implant*) or (bone? adj2 ongrow* adj2 prosthe*) or (bone? adj2 grow* adj2 prosthe*) or (bone? adj2 implant* adj2 interface*) or (bone? adj2 prosthes* adj2 interface*) or (skelet* adj2 fixat*) or (skelet* adj2 fixture*) or (bone* adj3 fixture*) or (bone* adj3 fixture*) or (screw* adj2 implant*) or (press fit* adj2 implant*)).ti,ab,kf.	10113
5	or/1-4 [Concept 1]	28179
6	exp Lower Extremity/	189904
7	exp "Bones of Lower Extremity"/	156054
8	Locomotion/	28946
9	exp walking/	69481
10	(lla or lea or (low*2 adj4 limb?) or (low*2 adj4 extremit*) or leg? or Knee? or Thigh? or Transtibial or tibia* or Transfemoral* or femoral* or syme or femur*).ti,ab,kf.	660123
11	or/6-10 [Concept 2]	874610
12	Amputees/	4378
13	Amputation Stumps/	3248
14	Amputation, Traumatic/	5098
15	Artificial Limbs/	8264
16	exp Amputation, Surgical/	24721
17	Prosthesis Design/	61366
18	Prosthesis Implantation/	15650
19	Prosthesis Failure/	31813
20	(amputee* or amputat* or postamputat* or stump? or disarticulat* or (los# adj2 limb?) or (residual adj2 limb?) or artificial).ti,ab,kf.	320966

21	(prosthe* or periprosthe*).ti.	63201
22	or/12-21 [Concept 3]	462408
23	Military Personnel/	45318
24	Military Health/	125
25	Military Medicine/	30200
26	Veterans/	22756
27	Veterans Health/	2044
28	Veterans Health Services/	263
29	Veterans Disability Claims/	304
30	(veteran* or air* force* or armed force* or land force* or ground force* or special force* or marines or militar* or army or armies or navy or navies or soldier* or sailor* or warfare* or battle* or war? or conflict or conflicts).ti,ab,kf.	381165
31	or/23-30 [Concept 4]	401595
32	Economics/	27525
33	exp "Costs and Cost Analysis"/	268902
34	Economics, Nursing/	4013
35	Economics, Medical/	9272
36	exp Economics, Hospital/	25798
37	exp "Fees and Charges"/	31456
38	exp Budgets/	14190
39	budget*.ti,ab,kf.	37425
40	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2	399463
41	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.	291763
42	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.	220406
43	(value adj2 (money or monetary)).ti,ab,kf.	3167
44	exp models, economic/	16264
45	economic model*.ab,kf.	4390
46	markov chains/	16087
47	markov.ti,ab,kf.	30321
48	monte carlo method/	32684

49	monte carlo.ti,ab,kf.	62277
50	exp Decision Theory/	13572
51	(decision* adj2 (tree* or analy* or model*)).ti,ab,kf.	41232
52	or/32-51 [Filter CADTH: Economic Evaluations & Models]	931079
53	"Value of Life"/	5821
54	Quality of Life/	282706
55	quality of life.ti,kf.	122366
56	((instrument or instruments) adj3 quality of life).ab.	4017
57	Quality-Adjusted Life Years/	16166
58	quality adjusted life.ti,ab,kf.	18284
59	(qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kf.	29755
60	Disability-Adjusted Life Years/	232
61	disability adjusted life.ti,ab,kf.	5900
62	Healthy Life Expectancy/	73
63	(daly* or disability free life expectanc* or haly* or health* life expectanc*).ti,ab,kf.	7026
64	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kf.	31559
65	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab,kf.	2731
66	(sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kf.	640
67	(sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kf.	7990
68	(sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kf.	41
69	(sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kf.	468
70	(hql or hqol or h qol or hrqol or hr qol).ti,ab,kf.	25471
71	(hye or hyes).ti,ab,kf.	78
72	(health* adj2 year* adj2 equivalent*).ti,ab,kf.	48
73	(pqol or qls).ti,ab,kf.	480
74	(quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kf.	741

75	nottingham health profile*.ti,ab,kf.	1251
76	sickness impact profile.ti,ab,kf.	1101
77	exp health status indicators/	344895
78	(health adj3 (utilit* or status)).ti,ab,kf.	96076
79	(utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kf.	16688
80	(preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kf.	15124
81	disutilit*.ti,ab,kf.	661
82	rosser.ti,ab,kf.	109
83	willingness to pay.ti,ab,kf.	9202
84	standard gamble*.ti,ab,kf.	919
85	(time trade off or time tradeoff).ti,ab,kf.	1702
86	tto.ti,ab,kf.	1462
87	(hui or hui1 or hui2 or hui3).ti,ab,kf.	2062
88	(eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kf.	24062
89	duke health profile.ti,ab,kf.	94
90	functional status questionnaire.ti,ab,kf.	133
91	dartmouth coop functional health assessment*.ti,ab,kf.	14
92	or/53-91 [Filter CADTH: Economic - Health Utilities / Quality of Life]	778354
93	exp Attitude to Health/	475026
94	Patient-Centered Care/	23343
95	Patient Participation/	29779
96	Choice Behavior/	35124
97	Decision Making/	105590
98	exp Patient Satisfaction/	100471
99	((patient* or user* or client* or individual* or customer* or participant* or consumer* or inpatient* or outpatient* or person* or people*) adj3 (participa* or preference* or satisfaction or accept or acceptability or acceptable or acceptance or accepted or activation or adherence or adoption or advisor? or attitude* or awareness or barrier* or facilit* or belie* or centered or centred or choice* or choose or collaboration or compliance or consent* or concern* or contribution or decision* or desire* or dissatisfact* or empower* or engag* or expectation* or experienc* or expert* or feedback or feeling* or focus* or goal* or hope* or input* or involve* or issue* or leader* or need* or nonadheren* or opinion* or participation or partner* or perception* or perspective* or perceiv*	2231640

	or view? or preference* or preferred or prefers or priorities or team* or values or voice* or wish* or willing)).ti,ab,kf.	
100	or/93-99 [Adapted filter FMD3S: Perspective Patient]	2599321
101	5 and 11 and 22 [Osseo and Lower extremity and Amputation]	2009
102	5 and 11 and (52 or 92 or 100) [Osseo and Lower extremity and 3 filters]	488
103	5 and 22 and (52 or 92 or 100)	687
104	103 not (exp Upper Extremity/ or (upper or thumb? or digit* or finger* or dental or facial or craniofacial or arch).mp.) [Osseo and Amputation and 3 filters NOT upper extrem. and others]	433
105	5 and 31 and (52 or 92 or 100) [Osseo and Military and 3 filters]	23
106	or/101-102,104-105	2445
107	Animals/ not (Humans/ and Animals/)	5164263
108	106 not 107	2076

ti=title, ab=abstract, kf=keyword heading word. ADJ# = words next to each other, in any order, up to # word.s. in between. *= retrieves all possible suffix variations of the root word indicated, ?= substitute for one or no characters. Terms ending with / are MeSH subject headings. Exp = the subject heading and all narrower terms are "OR'd" together. The Advanced mode in Ovid Medline All was used for this search.