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. 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. Lack of comfort, skin ulcers, inadequate or fluctuating suspension, tissue irritation, excessive heat and perspiration, poor control due to the motion of the soft tissue within the socket, and low confidence with mobility 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. 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.

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. 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 or complications 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 by an additional information specialist. Search strategies from previous literature reviews 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. 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**

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

**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
<table>
<thead>
<tr>
<th>Study characteristics:</th>
<th>Study characteristics:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Randomized controlled trials</td>
<td>• Systematic review</td>
</tr>
<tr>
<td>• Controlled (clinical) trials</td>
<td>• Other literature reviews (scoping, rapid, mapping, narrative, and any others)</td>
</tr>
<tr>
<td>• Non-randomized controlled trials (such as single-arm trials, crossover designs, and others)</td>
<td>• Health Technology Assessments</td>
</tr>
<tr>
<td>• Observational studies</td>
<td>• Protocol only</td>
</tr>
<tr>
<td>• Cohort studies</td>
<td>• Case study</td>
</tr>
<tr>
<td>• Case series</td>
<td>• Editorials</td>
</tr>
<tr>
<td>• Cross-sectional studies</td>
<td>• Erratum</td>
</tr>
<tr>
<td>• Published in English, French, and Spanish</td>
<td>• Opinion pieces</td>
</tr>
<tr>
<td></td>
<td>• Thesis (reason: it is grey literature)</td>
</tr>
<tr>
<td></td>
<td>• Conference abstracts</td>
</tr>
<tr>
<td></td>
<td>• Conference papers</td>
</tr>
<tr>
<td></td>
<td>• Conference posters</td>
</tr>
</tbody>
</table>

Other:                                                                                   Other:
• None                                                                                  • 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 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
References


Appendix 1: Example of literature search in OVID MEDLINE All

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

Search Strategy:

<table>
<thead>
<tr>
<th>Search</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Osseointegration/ (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.</td>
<td>11191</td>
</tr>
<tr>
<td>2 Bone-Anchored Prosthesis/ (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 prosth*) or (bone? adj2 grow* adj2 prosth*) or (bone* adj2 implant* adj2 interface*) or (bone* adj2 prosth* 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 implamt*)).ti,ab,kf.</td>
<td>257</td>
</tr>
<tr>
<td>3 or/1-4 [Concept 1]</td>
<td>28179</td>
</tr>
<tr>
<td>4 exp Lower Extremity/</td>
<td>189904</td>
</tr>
<tr>
<td>5 exp &quot;Bones of Lower Extremity&quot;/</td>
<td>156054</td>
</tr>
<tr>
<td>6 Locomotion/</td>
<td>28946</td>
</tr>
<tr>
<td>7 exp walking/ (illa or lea or (low<em>2 adj4 limb?) or (low</em>2 adj4 extremit*) or leg? or Knee? or Thigh? or Transtibial or tibia* or Transfemoral* or femoral* or syme or femur*).ti,ab,kf.</td>
<td>69481</td>
</tr>
<tr>
<td>8 or/6-10 [Concept 2]</td>
<td>874610</td>
</tr>
<tr>
<td>9 Amputees/</td>
<td>4378</td>
</tr>
<tr>
<td>10 Amputation Stumps/</td>
<td>3248</td>
</tr>
<tr>
<td>11 Amputation, Traumatic/</td>
<td>5098</td>
</tr>
<tr>
<td>12 Artificial Limbs/</td>
<td>8264</td>
</tr>
<tr>
<td>13 exp Amputation, Surgical/</td>
<td>24721</td>
</tr>
<tr>
<td>14 Prosthesis Design/</td>
<td>61366</td>
</tr>
<tr>
<td>15 Prosthesis Implantation/</td>
<td>15650</td>
</tr>
<tr>
<td>16 Prosthesis Failure/</td>
<td>31813</td>
</tr>
<tr>
<td>17 (amputee* or amputat* or postamputat* or stump? or disarticulat* or (los# adj2 limb?) or (residual adj2 limb?) or artificial).ti,ab,kf.</td>
<td>320966</td>
</tr>
</tbody>
</table>
21 (prosthe* or periprosthe*).ti.
22 or/12-21 [Concept 3]
23 Military Personnel/
24 Military Health/
25 Military Medicine/
26 Veterans/
27 Veterans Health/
28 Veterans Health Services/
29 Veterans Disability Claims/
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.
31 or/23-30 [Concept 4]
32 Economics/
33 exp "Costs and Cost Analysis"/
34 Economics, Nursing/
35 Economics, Medical/
36 exp Economics, Hospital/
37 exp "Fees and Charges"/
38 exp Budgets/
39 budget*.ti,ab,kf.
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
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.
42 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.
43 (value adj2 (money or monetary)).ti,ab,kf.
44 exp models, economic/
45 economic model*.ab,kf.
46 markov chains/
47 markov.ti,ab,kf.
48 monte carlo method/
49  monte carlo.ti,ab,kf.
50  exp Decision Theory/
51  (decision* adj2 (tree* or analy* or model*)).ti,ab,kf.
52  or/32-51 [Filter CADTH: Economic Evaluations & Models]
53  "Value of Life"/
54  Quality of Life/
55  quality of life.ti,kf.
56  (instrument or instruments) adj3 quality of life).ab.
57  Quality-Adjusted Life Years/
58  quality adjusted life.ti,ab,kf.
59  (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kf.
60  Disability-Adjusted Life Years/
61  disability adjusted life.ti,ab,kf.
62  Healthy Life Expectancy/
63  (daly* or disability free life expectanc* or haly* or health* life expectanc*).ti,ab,kf.
64  (sf36 or sf 36 or short form 36 or shortform 36 or shortform36 or shortform thirty six or
65  sf thirtysix or sftwentysix or sfthirty six or sf thirty six or short form thirty six or short
66  form thirty six or short form thirty six or short form thirty six).ti,ab,kf.
67  (sf6 or sf 6 or short form 6 or shortform 6 or short form six or shortform 6 or shortform
68  six or short form six or short form six).ti,ab,kf.
69  (sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform8 or short form
70  eight or short form eight).ti,ab,kf.
71  (sf12 or sf 12 or short form 12 or shortform 12 or shortform 12 or
72  sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kf.
73  (sf16 or sf 16 or short form 16 or shortform 16 or shortform 16 or short form
74  sixteen or short form sixteen or shortform sixteen).ti,ab,kf.
75  (sf20 or sf 20 or short form 20 or shortform 20 or shortform 20 or
76  short form twenty or short form twenty).ti,ab,kf.
77  (hql or hqol or h qol or hrqol or hr qol).ti,ab,kf.
78  (hqe or hqes).ti,ab,kf.
79  (health* adj2 year* adj2 equivalent*).ti,ab,kf.
80  (pqol or qls).ti,ab,kf.
81  (quality of wellbeing or quality of well being or index of wellbeing or index of well
82  being or qwb).ti,ab,kf.
nottingham health profile*.ti,ab,kf.  
sickness impact profile.ti,ab,kf.  
exp health status indicators/  
(health adj3 (utilit* or status)).ti,ab,kf.  
(utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kf.  
(preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kf.  
disutilit*.ti,ab,kf.  
rosser.ti,ab,kf.  
willingness to pay.ti,ab,kf.  
standard gamble*.ti,ab,kf.  
(time trade off or time tradeoff).ti,ab,kf.  
tto.ti,ab,kf.  
(hui or hui1 or hui2 or hui3).ti,ab,kf.  
(eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kf.  
duke health profile.ti,ab,kf.  
functional status questionnaire.ti,ab,kf.  
dartmouth coop functional health assessment*.ti,ab,kf.  
or/53-91 [Filter CADTH: Economic - Health Utilities / Quality of Life]  
exp Attitude to Health/  
Patient-Centered Care/  
Patient Participation/  
Choice Behavior/  
Decision Making/  
exp Patient Satisfaction/  
((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*
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
103 not (exp Upper Extremity/ or (upper or thumb? or digit* or finger* or dental
104 or facial or craniofacial or arch).mp.) [Osseo and Amputation and 3 filters NOT 433
upper extrem. and others]
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.