NHS England Evidence Review:

Direct skeletal fixation for transfemoral limb loss in adults

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Prepared by Solutions for Public Health (SPH) on behalf of NHS England Specialised Commissioning

Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of direct skeletal fixation (DSF) compared to no prosthetic use in adults with transfemoral limb loss[1] who are unable to tolerate conventional socket use.

DSF of limb prostheses using an intraosseous transcutaneous implant may be carried out in two separate operations or as a single operation. In the first stage, a metallic implant is inserted into the medullary cavity of the residual bone. The second stage of the procedure is undertaken either at the same operation or approximately 3 to 6 months later, after the stump wound has completely closed and has healed and osseointegration has taken place. The second stage involves surgically (re-exposing part of the implant and) connecting it to a small metal extension, known as an abutment. The wound is closed with the abutment penetrating the skin, allowing attachment of the external prosthesis to the intraosseous implant. A period of rehabilitation follows, during which a training prosthesis is used. The implant is inert and usually made of titanium.

The current treatments for transfemoral amputations are bespoke sockets for functional lower limb users or cosmetic limbs for non-functional lower limb amputees. The type of prosthetic limb that is recommended will depend on:

1. The type of amputation (level and length)
2. The amount of muscle strength in the remaining section of the limb
3. General health
4. Tasks the prosthetic limb will be expected to perform, whether the limb is to look as real as possible or be as functional as possible
5. If it is thought that there will be difficulty withstanding the strain of using a prosthetic limb, a cosmetic limb may be recommended.

Extensive physiotherapy and rehabilitation are required and therefore a prosthesis is not a suitable option for every patient. The current alternative for patients who are unable to manage a prosthetic limb is the use of mobility aids such as crutches or a wheelchair.

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from treatment with DSF more than others, as well as what rehabilitation programmes people who had DSF undertook within the included studies.

[1] Transfemoral limb loss includes congenital limb deficiency or amputation or disarticulation through knee or more proximal

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost effectiveness of direct skeletal fixation (DSF) compared to no prosthetic use in adults with transfemoral limb loss[2] who are unable to tolerate conventional socket use. The searches for evidence published since January 2012 were conducted on 23 September 2022 and identified 822 references. The titles and abstracts were screened and 57 full text papers were obtained and assessed for relevance.

Five papers were identified for inclusion, three prospective case series and two retrospective case series. The studies included between 50 and 111 patients. Follow-up ranged from 21.5 months to 15 years. Two studies were based in Sweden, one in Australia, one in the Netherlands and one in Australia and the Netherlands. No studies comparing DSF with no prosthetic use were identified.

In terms of clinical effectiveness:

- **Functional outcome measures (critical outcome).** One prospective case series provided very low certainty evidence of a statistically significant improvement in functional outcomes in patients with unilateral transfemoral amputation (TFA) and socket or prosthesis-fitting problems undergoing direct skeletal fixation (DSF) who had been prosthetic users pre-operatively as measured by the timed up and go (TUG)[3] test and 6-minute walk test (6MWT)[4] at a mean follow-up of 21.5 months. For those patients who had been wheelchair bound pre-operatively the authors reported that post-operative scores were comparable with those of the patients who had been walking pre-operatively.
- **Quality of life (critical outcome).** Two prospective case series provided very low certainty evidence of a statistically significant improvement in quality of life in patients with unilateral TFA and socket or prosthesis-fitting problems undergoing DSF as measured by the short-form-36 health survey (SF-36)[5] physical component, Q-TFA global score[6], Q-TFA problem score[7] and response to a single Q-TFA question on the patient's overall situation as an amputee[8] at 2, 5, 7 and 10 years follow-up.

[2] Transfemoral limb loss includes congenital limb deficiency or amputation or disarticulation through knee or more proximal

[3] A valid test for quantifying functional mobility. It measures the time a person takes to rise from a chair, walk 3 metres, walk back, and sit down. The TUG test is interpreted as follows: ≤ 10 seconds = normal; ≤ 20 seconds = good mobility, can go out alone, mobile without a gait aid; < 30 seconds = problems, cannot go outside alone, requires a gait aid

[4] Measures the distance a person can walk in a 6-minute period and has been shown to reliably measure functional capacity in various populations, including amputees

[5] The 36-Item Short Form Health Survey (SF-36) is a generic measure of quality of life. The tool has 8 subscales: 4 measure physical health (physical functioning, role functioning‑physical, bodily pain, general health) and 4 measure mental and psychological health (vitality, social functioning, role functioning‑emotional, mental health). The results are also captured in two summary measures: the physical component summary (PCS) and the mental component summary (MCS). In each scale, values run between 0 and 100. A higher score indicates better physical or mental health

[6] The Questionnaire for Persons with a Transfemoral Amputation (Q-TFA) is a self-report measure developed for nonelderly transfemoral amputees using a socket- or osseointegrated prosthesis to reflect use, mobility, problems, and global health, each in a separate score (0-100). Global health is defined as the perception of function and problems with the current prosthesis and the perception of the current overall amputation situation. The score is a summary of three questions to which answers are given on a 5-point Likert scale. A Global score of 100 indicates the best possible overall situation as measured by this instrument

[7] The Questionnaire for Persons with a Transfemoral Amputation (Q-TFA) is a self-report measure developed for nonelderly transfemoral amputees using a socket- or osseointegrated prosthesis to reflect use, mobility, problems, and global health, each in a separate score (0-100). Problems are defined as the extent of specific problems related to the amputation and the prosthesis and their impact on the quality of life. A higher score indicates more serious problems

[8] This is the third question of the Global health subdomain of the Q-TFA "How would you summarise your overall situation as an amputee?" Responses include Extremely poor (0) Poor (1) Average (2) Good (3) Extremely good (4)

- **Activities of daily living (critical outcome).** No evidence was identified for this outcome.
- **Mobility (important outcome).** Two prospective case series provided very low certainty evidence on mobility in patients with unilateral TFA and socket or prosthesis-fitting problems undergoing DSF as measured by Amputation Mobility Predictor Prothesis (AMPPRO)[9] scores presented as K-levels[10], Q-TFA mobility scores[11] and prosthetic activity grades[12] up to 15 years. One study reported a statistically significant improvement in mobility as measured by prosthetic activity grades at 2, 5, 7 and 10 years follow-up with an improvement also observed at 15 years but no statistical significance of this result reported. One study reported an improvement in mobility as measured by AMPPRO scores at a mean follow-up of 21.5 months but no statistical significance of this result was reported. Another study reported Q-TFA mobility scores at 7 years but no baseline result or statistical significance was reported.
- **Psychological impact (important outcome).** No evidence was identified for this outcome.
- **Wheelchair use (important outcome).** Two prospective case series provided very low certainty evidence that wheelchair use was reduced in patients with TFA and socket or prosthesis-fitting problems undergoing DSF up to a median follow-up of 34 months. One study reported that all patients who had been wheelchair bound pre-operatively became community ambulators after surgery and the other study reported that all patients who had been wheelchair bound pre-operatively had mobility scores comparable with patients who had been walking pre-operatively. No statistical comparisons over time were reported.
- **Frequency of implant replacement and/or re-fitting (important outcome).** Five case series (three prospective and two retrospective) provided very low certainty evidence that the percentage of implant replacement and/or re-fitting after DSF ranged between 3% to 4% at around 2 to 3 years to 34% at 5 years and 16% at 15 years in patients with TFA or a knee disarticulation and socket or prosthesis-fitting problems. One study reported that 10% of implants were extracted due to osteomyelitis at a mean follow-up of 7.9 years and another study reported that 6% were extracted due to infection at 15 years. One study reported a 10-year cumulative risk of implant extraction due to

[9] 21-item performance-based functional test designed specifically for people with lower limb loss to determine functional mobility by evaluating ability in transfers, sitting and standing balance, and gait skills

[10] A 5-level rating system used by the US Medicare health insurance program to indicate the extent of a person's disability and their potential for rehabilitation in individuals with lower-limb amputations. K-levels include: K0 – patient has no ability or potential to ambulate or transfer safely with or without assistance and a prosthesis does not enhance their quality of life or mobility; K1 - patient has the ability or potential to use a prosthesis for transfers or ambulation on level surfaces at fixed cadence - a typical limited or unlimited household ambulator; K2 - patient has the ability or potential for ambulation with the ability to traverse low level environmental barriers such as curbs, stairs, or uneven surfaces - a typical community ambulator; K3 - patient has the ability or potential for ambulation with variable cadence - a typical community ambulator with the ability to traverse most environmental barriers and may have therapeutic or exercise activity that demands prosthetic use beyond simple locomotion; K4 - patient has the ability or potential for prosthetic ambulation that exceeds basic ambulation skills, exhibiting high impact, stress, or energy levels - typical of the prosthetic demands of the child, active adult, or athlete

[11] The Questionnaire for Persons with a Transfemoral Amputation (Q-TFA) is a self-report measure developed for nonelderly transfemoral amputees using a socket- or osseointegrated prosthesis to reflect use, mobility, problems, and global health, each in a separate score (0-100). Prosthetic mobility is defined as the ability and performance of the amputee to move and change and maintain postures when using the prosthesis. The score consists of three sub scores, each with a range from 0 to 100: capability (12 items), use of walking aids (2 items), and walking habits (5 items). The average of these three sub scores generates the total mobility score. A higher score indicates better mobility

[12] The activity grade was assigned to each patient at each follow-up by the physiotherapist in the treating team. Activity is graded between 0 and 4 and combines the extent of prosthetic use, use of walking aids, outdoor walking habits, and other activities using the prosthesis, and is captured from Q-TFA items and medical records. 0 = Do not use prosthesis; no prosthetic activity; 1 (Low) = Limited use of prosthesis for standing/walking, use walking aid, no long walks; 2 (Average) = Use prosthesis most of the day, with or without walking aid at home, use walking aid outdoors; 3 (High) = Uses prosthesis for a full day, no walking aid except for longer distances, walks a lot, rarely performs other demanding or high-load activities in use of prosthesis; 4 (Very High) = Uses prosthesis for a full day, no walking aid, walks a lot and/or routinely performs other highly demanding or high-load activities involving the prosthesis (e.g. cycling, gym training)

osteomyelitis of 9%. One study reported that 5%of implants were extracted due to fractures at 15 years. One study reported that revision-free survival of the fixture ranged from 92% at 2 years to 72% at 15 years, and a survival of the fixture until the first event necessitating a change of the abutment and/or abutment screw ranging from 81% at 2 years to 14% at 15 years. Another study reported a cumulative implant survival probability after 9 years of 78% and a median implant survival time of 6 years.

In terms of safety:

- Three case series (two prospective and one retrospective) provided very low certainty evidence on adverse events in patients with TFA and socket or prosthesis-fitting problems undergoing DSF. One study reported that 54% of patients experienced an adverse event at a mean follow-up of 21.5 months. The percentage of patients experiencing infections reported by the studies included 42% at a mean follow-up of 21.5 months, 34% at a median follow-up of 34 months and 17% at a mean follow-up of 7.9 years. One study reported a 10-year cumulative risk of implant-associated osteomyelitis of 20% and a median time from implantation to osteomyelitis of 2.6 years. One study reported that 8% of patients sustained periprosthetic fractures at a mean follow-up of 21.5 months and another study reported that 3% had proximal femoral fractures at a median follow-up of 34 months. One study reported that 20% had stoma hypergranulation and 16% had redundant soft tissue at a median follow-up of 34 months.

In terms of cost effectiveness:

- No evidence was identified for cost effectiveness.

In terms of subgroups:

- No evidence was identified for subgroups.

Limitations

No comparative studies were identified that met the inclusion criteria for population and comparator. All studies that reported exclusion criteria, excluded patients with peripheral vascular disease and diabetes mellitus, and exposure to radiation in the affected limb or past or ongoing chemotherapy. None of the studies defined the criteria used to assess socket or prosthesis-fitting problems, and one study reported that approximately one-third of those assessed were found suitable for implant surgery but no further details were provided. It was therefore not possible to determine whether problems with sockets and suitability for surgery were assessed in a standard and reliable manner and therefore whether the studies included all patients with TFA who underwent DSF after being unable to tolerate socket prostheses. The largest and the longest study (Hagberg et al 2020) was conducted over an 18 year follow-up period and reported results for multiple timepoints (2, 5, 7, 10 and 15 years). However, the 15 year follow-up results were based on a small number of patients (n=14 patients) due to patients being recruited and different times throughout the study. All the studies were at high risk of bias and certainty about the evidence for all critical and important outcomes reported was very low when assessed using modified GRADE. Limitations reducing certainty for the outcomes included uncertainty about whether the inclusion of participants was complete and limited reporting of results, with some studies not conducting statistical tests and some reporting results only in graph form. None of the studies commented on what Minimum Clinically Important Difference thresholds would be for any of the outcomes reported.

Conclusion

The evidence included in this review is insufficient to draw conclusions about the clinical effectiveness and safety of DSF compared to no prosthetic use in people with transfemoral limb loss who are unable to tolerate conventional socket use. The key limitation to identifying evidence on the effectiveness of DSF compared to no prosthetic use in people who are unable to tolerate conventional socket use is the lack of studies comparing DSF with no prosthetic use in this group.

Five case series (three prospective and two retrospective) were identified ranging in size from 50 to 111 patients and reporting results at multiple time-points up to 15 years. This very low certainty, non-comparative evidence in people with transfemoral limb loss who are unable to tolerate conventional socket use suggests that DSF improves functional outcomes as measured by the TUG test and 6MWT at 2 years, quality of life as measured by the SF-36 and Q-TFA up to 10 years, mobility as measured by prosthetic activity grades up to 10 years and wheelchair use up to 3 years follow-up. Across the studies, at different time-points up to 15 years, rates of implant replacement and/or re-fitting ranged from 3% to 34%, and extraction due to infection ranged from 6% to 10%. Over half of patients experienced an adverse event as reported by one study at 2 years, and across the studies the percentage of patients experiencing infections at different time-points up to 8 years ranged from 17% to 42%.

No evidence was identified for activities of daily living and psychological impact outcomes.

No evidence was identified on the cost effectiveness of DSF compared to no prosthetic use in people with transfemoral limb loss who are unable to tolerate conventional socket use.

No evidence was identified for particular sub-groups of patients that would benefit more from DSF.

3. Methodology

Review questions

The review question(s) for this evidence review are:

1. In people with transfemoral limb loss who are unable to tolerate conventional socket use, what is the clinical effectiveness of direct skeletal fixation compared to no prosthetic use?
2. In people with transfemoral limb loss who are unable to tolerate conventional socket use, what is the safety of direct skeletal fixation compared to no prosthetic use?
3. In people with transfemoral limb loss who are unable to tolerate conventional socket use, what is the cost effectiveness of direct skeletal fixation compared to no prosthetic use?
4. From the evidence selected, are there any subgroups of patients that may benefit from direct skeletal fixation more than the wider population of interest?
5. From the evidence selected, what rehabilitation programmes did people who had direct skeletal fixation undertake?

See Appendix A for the full PICO document.

Review process

The methodology to undertake this review is specified by NHS England in its 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted 23 September 2022.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO document. Full text of potentially relevant studies were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE profiles.

4. Summary of included studies

Five papers were identified for inclusion (Al Muderis et al 2016a, Al Muderis et al 2016b, Hagberg et al 2020, Mohamed et al 2022, Tillander et al 2017). Table 1 provides a summary of these included studies and full details are given in Appendix E. Three were prospective case series (Al Muderis et al 2016a, Al Muderis et al 2016b, Hagberg et al 2020) and two were retrospective case series (Mohamed et al 2022, Tillander et al 2017). Some studies had overlapping patients (Hagberg et al 2020 & Tillander et al 2017; Al Muderis et al 2016a & Al Muderis et al 2016b; and & Al Muderis et al 2016b and Mohamed et al 2022).

No cost effectiveness studies were identified.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Al Muderis et al 2016a Prospective case series Single centre, Australia	50 adults with unilateral transfemoral amputation (TFA) and socket or prosthesis-fitting problems, excluding those with disabling psychiatric disorder, non-compliant behaviour, pregnancy, previous radiotherapy to the affected residual limb, chemotherapy, immunosuppression, diabetes, peripheral vascular disease diabetes and smokers No subgroups reported	**Intervention** Integral Leg Prosthesis (ILP) or the Osseointegrated Prosthetic Limb (OPL) implant system followed by a rehabilitation programme **Comparison** None	Mean follow-up = 21.5 months Results are reported pre and post operatively (minimum of one-year follow-up after stage one surgery) **Critical outcomes** Functional outcome measures • Timed up and go (TUG)[13] duration, mean seconds (SD) • 6-minute walk test (6MWT)[14] distance, mean metres (SD) Quality of life • Short-form-36 health survey (SF-36)[15] physical component summary, mean points (SD) • Q-TFA global score, mean points (SD) **Important outcomes** Mobility • Change in Amputation Mobility predictor prothesis (AMPPRO)[16] scores presented as K-levels[17]

[13] A valid test for quantifying functional mobility. It measures the time a person takes to rise from a chair, walk 3 metres, walk back, and sit down. The TUG test is interpreted as follows: ≤ 10 seconds = normal; ≤ 20 seconds = good mobility, can go out alone, mobile without a gait aid; < 30 seconds = problems, cannot go outside alone, requires a gait aid

[14] Measures the distance a person can walk in a 6-minute period and has been shown to reliably measure functional capacity in various populations, including amputees

[15] The 36-Item Short Form Health Survey (SF-36) is a generic measure of quality of life. The tool has 8 subscales: 4 measure physical health (physical functioning, role functioning‑physical, bodily pain, general health) and 4 measure mental and psychological health (vitality, social functioning, role functioning‑emotional, mental health). The results are also captured in two summary measures: the physical component summary (PCS) and the mental component summary (MCS). In each scale, values run between 0 and 100. A higher score indicates better physical or mental health

[16] 21-item performance-based functional test designed specifically for people with lower limb loss to determine functional mobility by evaluating ability in transfers, sitting and standing balance, and gait skills

[17] A 5-level rating system used by the US Medicare health insurance program to indicate the extent of a person's disability and their potential for rehabilitation in individuals with lower-limb amputations. K-levels include: K0 – patient has no ability or potential to ambulate or transfer safely with or without assistance and a prosthesis does not enhance their quality of life or mobility; K1 - patient has the ability or potential to use a prosthesis for transfers or ambulation on level surfaces at fixed cadence - a typical limited or unlimited household ambulator; K2 - patient has the ability or potential for ambulation with the ability to traverse low level environmental barriers such as curbs, stairs, or uneven surfaces - a typical community ambulator; K3 - patient has the ability or potential for ambulation with variable cadence - a typical community ambulator with the ability to traverse most environmental barriers and may have therapeutic or exercise activity that demands prosthetic use beyond simple locomotion; K4 - patient has the ability or potential for prosthetic ambulation that exceeds basic ambulation skills, exhibiting high impact, stress, or energy levels - typical of the prosthetic demands of the child, active adult, or athlete

Study	Population	Intervention and comparison	Outcomes reported

			Wheelchair use
			• Change in K-levels in pre-operative wheelchair bound patients
			
			Frequency of implant replacement and/or re-fitting
			• Number of implant revisions
			
			Adverse events
			• Number of patients experiencing an adverse event
			• Number of patients experiencing one or more infections
			• Number of patients experiencing one or more infections and responding to:
			  ○ oral antibiotics alone
			  ○ intravenous antibiotics
			  ○ surgical soft tissue debridement
			• Number of patients sustaining periprosthetic fractures

Al Muderis et al 2016b
 	
Prospective case series
 	
2 centre, Australia & the Netherlands
	86 patients (91 implants) with a TFA experiencing socket-related problems or difficulties using a prosthesis, excluding those with limb exposure to radiation ongoing chemotherapy, growing/immature skeleton, diabetes, peripheral vascular disease, mental illness and an inability to comply with rehabilitation protocol and follow-up program
	
	No subgroups reported
		Intervention
		
		ILP, OPL or osseointegration prosthesis (OIP) implant system followed by a rehabilitation protocol
		
		Comparison
		
		None
			Median follow-up of 34 months (range 24 to 71)
			
			Important outcomes
			
			Wheelchair use
			• Number of patients wheelchair bound pre and post surgery
			
			Frequency of implant replacement and/or re-fitting
			• Number of patients requiring replacement due to:
			  ○ inadequate osseointegration
			  ○ breakage of intramedullary component
			  ○ breakage of pin
			
			Adverse events
			• Number of patients experiencing one or more infections
			• Number of patients experiencing other adverse events

Hagberg et al 2020 Prospective case series	111 patients with a unilateral TFA experiencing problems related to a socket suspended prosthesis and having mature	**Intervention** OPRA implant system followed by a rehabilitation protocol	**Critical outcome** Quality of life • Q-TFA global mean and median score at 7 years

Study	Population	Intervention and comparison	Outcomes reported
Single centre, Sweden	and sufficient residual skeleton dimensions No subgroups reported	**Comparison** None	• Q-TFA problem mean and median score[18] at 7 years • Response to the single Q-TFA question on the patient's overall situation as an amputee[19] at baseline, 2, 5, 7, 10 & 15 years • Change in response to the single Q-TFA question on the patient's overall situation as an amputee compared with baseline at 2, 5, 7, 10 & 15 years **Important outcomes** Mobility • Q-TFA mobility score[20] at 7 years • Prosthetic activity grade[21] at baseline, 2, 5, 7, 10 & 15 years • Change in prosthetic activity grade compared with baseline at 2, 5, 7, 10 & 15 years Frequency of implant replacement and/or re-fitting During 15-year follow-up • Number of implant failures • Revision-free survival of the fixture • Number of patients with at least one mechanical complication resulting in change of the abutment and/or abutment screw • Survival of fixture until the first event necessitating the change of the abutment and/or abutment screw

[18] The Questionnaire for Persons with a Transfemoral Amputation (Q-TFA) is a self-report measure developed for nonelderly transfemoral amputees using a socket- or osseointegrated prosthesis to reflect use, mobility, problems, and global health, each in a separate score (0-100). Problems are defined as the extent of specific problems related to the amputation and the prosthesis and their impact on the quality of life. A higher score indicates more serious problems

[19] This is the third question of the Global health subdomain of the Q-TFA "How would you summarise your overall situation as an amputee?" Responses include Very poor (0) Poor (1) Average (2) Good (3) Very good (4)

[20] The Questionnaire for Persons with a Transfemoral Amputation (Q-TFA) is a self-report measure developed for nonelderly transfemoral amputees using a socket- or osseointegrated prosthesis to reflect use, mobility, problems, and global health, each in a separate score (0-100). Prosthetic mobility is defined as the ability and performance of the amputee to move and change and maintain postures when using the prosthesis. The score consists of three sub scores, each with a range from 0 to 100: capability (12 items), use of walking aids (2 items), and walking habits (5 items). The average of these three sub scores generates the total mobility score

[21] The activity grade was assigned to each patient at each follow-up by the physiotherapist in the treating team. Activity is graded between 0 and 4 and combines the extent of prosthetic use, use of walking aids, outdoor walking habits, and other activities using the prosthesis, and is captured from Q-TFA items and medical records. 0 = Do not use prosthesis; no prosthetic activity; 1 (Low) = Limited use of prosthesis for standing/walking, use walking aid, no long walks; 2 (Average) = Use prosthesis most of the day, with or without walking aid at home, use walking aid outdoors; 3 (High) = Uses prosthesis for a full day, no walking aid except for longer distances, walks a lot, rarely performs other demanding or high-load activities in use of prosthesis; 4 (Very High) = Uses prosthesis for a full day, no walking aid, walks a lot and/or routinely performs other highly demanding or high-load activities involving the prosthesis (e.g. cycling, gym training)

Study	Population	Intervention and comparison	Outcomes reported

Mohamed et al 2022
 	
Retrospective case series
 	
Single centre, the Netherlands
	58 patients (59 implants) with a knee disarticulation or TFA who completed rehabilitation with their socket prosthesis and suffered from socket-related problems and were suitable for standard osseointegrated implant surgery
	
	No subgroups reported
		Intervention
		
		OPRA implant system followed by a rehabilitation protocol
		
		Comparison
		
		None
			Minimum of 5 years of follow-up
			
			Important outcomes
			
			Frequency of implant replacement and/or re-fitting
			• Number of patients undergoing revision surgery due to:
			  ○ Failed intramedullary stem
			  ○ Broken dual-cone adapter
			• Cumulative implant survival probability after 9 years
			• Median implant survival time

Tillander et al 2017 Retrospective case series Single centre, Sweden	96 patients (102 implants) with TFAs experiencing difficulty to use (socket complications) or be fitted with (stump malformation) a socket prosthesis, and found to be suitable for implant surgery No subgroups reported	**Intervention** OPRA implant system for majority of patients (72%). Remaining patients had their implants before the start of the OPRA protocol (no further details reported) **Comparison** None	Mean follow-up of 7.9 years (range 1.5 to 19.6 years) **Important outcomes** Frequency of implant replacement and/or re-fitting • Implants extracted due to osteomyelitis[22] • 10-year cumulative risk of implant extraction due to osteomyelitis Adverse events • Number of patients who developed osteomyelitis • 10-year cumulative risk of implant-associated osteomyelitis[23] • Median time from implantation to osteomyelitis

Abbreviations
6MWT: 6-Minute Walk Test; AMPPRO: Amputation Mobility Predictor Prothesis; ILP: Integral Leg Prosthesis; OIP: Osseointegration Prosthesis; OPL: Osseointegration Prosthetic Limb; OPRA: Osseointegrated Prostheses for the Rehabilitation of Amputees; Q-TFA: Questionnaire for Persons with a Transfemoral Amputation; SF-36: 36-Item Short Form Health Survey; TUG: Timed Up and Go Test; TFA: Transfemoral Amputation

[22] Indication for extraction was infection not responsive to conservative treatment or loosening evident in stability testing of the implant
[23] Evidence of infection involving implant-surrounding bone and/or bone marrow, supported by positive percutaneous bone biopsy or aspirated bone marrow cultures, and classified as definite, probable, or possible

5. Results

In adults with transfemoral limb loss, what is the clinical effectiveness and safety of DSF compared with no prosthetic use?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Functional outcome measures **Certainty of evidence:** Very low	Functional outcomes are important to patients as they quantify enablement, independence and active participation. In total, one prospective case series reported non-comparative evidence for functional outcomes at a minimum of one year follow-up after stage one direct skeletal fixation (DSF) surgery (mean follow-up of 21.5 months) in adults with unilateral transfemoral amputation (TFA) and socket or prosthesis-fitting problems. Outcomes reported included timed up and go (TUG)[24] test duration and 6-minute walk test (6MWT)[25] distance. The results were reported separately for pre-operative wheelchair bound patients and prosthetic user patients. At a mean follow-up of 21.5 months: • One prospective case series (Al Muderis et al 2016a) reported a mean TUG duration of 9 (0.56 SD) seconds for patients who had been wheelchair bound pre-operatively (n=14). These patients were not able to complete the TUG test before surgery but the authors reported that post-operative scores were comparable with those of the patients who had been walking pre-operatively. **(VERY LOW)** • Al Muderis et al (2016a) also reported a *statistically significant* (p<0.01) improvement in TUG duration for patients who had been prosthetic users pre-operatively (n=36) with a mean TUG duration of 14.59 (5.94 SD) seconds pre surgery and 8.74 (2.81 SD) seconds post surgery. **(VERY LOW)** • Al Muderis et al (2016a) also reported a mean 6MWT distance of 411 (31.44 SD) metres for patients who had been wheelchair bound pre-operatively (n=14). These patients were not able to complete the 6MWT before surgery but the authors reported that post-operative scores were comparable with those of the patients who had been walking pre-operatively. **(VERY LOW)** • Al Muderis et al (2016a) reported a *statistically significant* (p<0.001) improvement in 6MWT distance for patients who had been prosthetic users pre-operatively (n=36) with a mean 6MWT distance of 281 (93 SD) metres pre surgery and 419 (133 SD) metres post surgery. **(VERY LOW)** **This study provided very low certainty evidence that there is a statistically significant improvement in functional outcomes in patients with unilateral TFA and socket or prosthesis-fitting problems undergoing DSF who had been prosthetic users pre-operatively as measured by the TUG test and 6MWT at a mean follow-up of 21.5 months. For those patients who had been wheelchair bound pre-operatively, the authors reported that post-operative scores were comparable with those of the patients who had been walking pre-operatively.**
Quality of life **Certainty of evidence:** Very low	Quality of life is an important outcome to patients as it provides an indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. In total, two prospective case series reported non-comparative evidence for quality of life up to 15 years follow-up after DSF in patients with unilateral TFA and socket or prosthesis-fitting problems. Outcomes reported included the short-form-36 health

[24] A valid test for quantifying functional mobility. It measures the time a person takes to rise from a chair, walk 3 metres, walk back, and sit down. The TUG test is interpreted as follows: ≤ 10 seconds = normal; ≤ 20 seconds = good mobility, can go out alone, mobile without a gait aid; < 30 seconds = problems, cannot go outside alone, requires a gait aid

[25] Measures the distance a person can walk in a 6-minute period and has been shown to reliably measure functional capacity in various populations, including amputees

Outcome	Evidence statement
	survey (SF-36)[26] physical component, Q-TFA global score[27], Q-TFA problem score[28] and response to a single Q-TFA question on the patient's overall situation as an amputee[29]. At a mean follow-up of 21.5 months: • One prospective case series (Al Muderis et al 2016a) reported a *statistically significant* (p<0.001) improvement in mean SF-36 physical component summary score, from 37.09 (9.54 SD) pre surgery (n=46) to 47.29 (9.33 SD) post surgery (n=49). **(VERY LOW)** • Al Muderis et al (2016a) also reported a *statistically significant* (p<0.001) improvement in mean Q-TFA global score, from 47.82 (17.28 SD) pre surgery (n=46) to 83.52 (18.04 SD) post surgery (n=46). **(VERY LOW)** At 2 years: • One prospective case series (Hagberg et al 2020) reported on the response to a single Q-TFA question on patient's overall situation as an amputee with 0/83 (0%) patients responding "very poor", 7/83 (8%) patients responding "poor", 14/83 (17%) patients responding "average", 38/83 (46%) patients responding "good" and 24/83 (29%) patients responding "very good". At baseline 23/107 (21%) patients responded as "very poor", 29/107 (27%) patients as "poor", 34/107 (32%) patients as "average", 16/107 (15%) patients as "good" and 5/107 (5%) patients as "very good". **(VERY LOW)** • Hagberg et al (2020) also reported a *statistically significant* (p<0.001) improvement in response to a single Q-TFA question on the patient's overall situation as an amputee compared with baseline with 62/81 (77%) patients having a better score, 14/81 (17%) patients having an equal score and 5/81 (6%) patients having a worse score. **(VERY LOW)** At 5 years: • One prospective case series (Hagberg et al 2020) reported on the response to a single Q-TFA question on patient's overall situation as an amputee with 0/62 (0%) patients responding "very poor", 2/62 (3%) patients responding "poor", 14/62 (23%) patients responding "average", 25/62 (40%) patients responding "good" and 21/62 (34%) patients responding "very good". At baseline 23/107 (21%) patients responded as "very poor", 29/107 (27%) patients as "poor", 34/107 (32%) patients as "average", 16/107 (15%) patients as "good" and 5/107 (5%) patients as "very good". **(VERY LOW)** • Hagberg et al (2020) also reported a *statistically significant* (p<0.001) improvement in response to a single Q-TFA question on the patient's overall situation as an amputee compared with baseline with 47/60 (78%) patients having a better score, 10/60 (17%) patients having an equal score and 3/60 (5%) patients having a worse score. **(VERY LOW)** At 7 years: • One prospective case series (Hagberg et al 2020) reported on the response to a single Q-TFA question on patient's overall situation as an amputee with 0/54

[26] The 36-Item Short Form Health Survey (SF-36) is a generic measure of quality of life. The tool has 8 subscales: 4 measure physical health (physical functioning, role functioning‑physical, bodily pain, general health) and 4 measure mental and psychological health (vitality, social functioning, role functioning‑emotional, mental health). The results are also captured in two summary measures: the physical component summary (PCS) and the mental component summary (MCS). In each scale, values run between 0 and 100. A higher score indicates better physical or mental health

[27] The Questionnaire for Persons with a Transfemoral Amputation (Q-TFA) is a self-report measure developed for nonelderly transfemoral amputees using a socket- or osseointegrated prosthesis to reflect use, mobility, problems, and global health, each in a separate score (0-100). Global health is defined as the perception of function and problems with the current prosthesis and the perception of the current overall amputation situation. The score is a summary of three questions to which answers are given on a 5-point Likert scale. A Global score of 100 indicates the best possible overall situation as measured by this instrument

[28] The Questionnaire for Persons with a Transfemoral Amputation (Q-TFA) is a self-report measure developed for nonelderly transfemoral amputees using a socket- or osseointegrated prosthesis to reflect use, mobility, problems, and global health, each in a separate score (0-100). Problems are defined as the extent of specific problems related to the amputation and the prosthesis and their impact on the quality of life. A higher score indicates more serious problems.

[29] This is the third question of the Global health subdomain of the Q-TFA "How would you summarise your overall situation as an amputee?" Responses include Extremely poor (0) Poor (1) Average (2) Good (3) Extremely good (4)

Outcome	Evidence statement
	(0%) patients responding “very poor”, 1/54 (2%) patients responding “poor”, 12/54 (22%) patients responding “average”, 20/54 (37%) patients responding “good” and 21/54 (39%) patients responding “very good”. At baseline 23/107 (21%) patients responded as “very poor”, 29/107 (27%) patients as “poor”, 34/107 (32%) patients as “average”, 16/107 (15%) patients as “good” and 5/107 (5%) patients as “very good”. **(VERY LOW)** • Hagberg et al (2020) also reported a *statistically significant* (p<0.001) improvement in response to a single Q-TFA question on the patient’s overall situation as an amputee compared with baseline with 40/52 (77%) patients having a better score, 11/52 (21%) patients having an equal score and 1/52 (2%) patients having a worse score. **(VERY LOW)** • Hagberg et al (2020) also reported a mean Q-TFA global score of 74 (20.6 SD; 17 to 100 range) and a median score of 75 (58 to 92 IQR) (n=55). **(VERY LOW)** • One prospective case series (Hagberg et al 2020) reported a mean Q-TFA problem score of 17 (10.8 SD; 0 to 44 range) and a median score of 16 (8 to 25 IQR) (n=54). **(VERY LOW)** At 10 years: • One prospective case series (Hagberg et al 2020) reported on the response to a single Q-TFA question on patient’s overall situation as an amputee with 1/30 (3%) patients responding “very poor”, 4/30 (13%) patients responding “poor”, 4/30 (13%) patients responding “average”, 10/30 (33%) patients responding “good” and 11/30 (37%) patients responding “very good”. At baseline 23/107 (21%) patients responded as “very poor”, 29/107 (27%) patients as “poor”, 34/107 (32%) patients as “average”, 16/107 (15%) patients as “good” and 5/107 (5%) patients as “very good”. **(VERY LOW)** • Hagberg et al (2020) also reported a *statistically significant* (p<0.001) improvement in response to a single Q-TFA question on the patient’s overall situation as an amputee compared with baseline with 21/29 (72%) patients having a better score, 6/29 (21%) patients having an equal score and 2/29 (7%) patients having a worse score. **(VERY LOW)** At 15 years: • One prospective case series (Hagberg et al 2020) reported on the response to a single Q-TFA question on patient’s overall situation as an amputee with 1/11 (9%) patients responding “very poor”, 0/11 (0%) patients responding “poor”, 4/11 (36%) patients responding “average”, 3/11 (27%) patients responding “good” and 3/11 (27%) patients responding “very good”. At baseline 23/107 (21%) patients responded as “very poor”, 29/107 (27%) patients as “poor”, 34/107 (32%) patients as “average”, 16/107 (15%) patients as “good” and 5/107 (5%) patients as “very good”. **(VERY LOW)** • Hagberg et al (2020) also reported the change in response to a single Q-TFA question on the patient’s overall situation as an amputee compared with baseline with 7/11 (64%) patients having a better score, 3/11 (27%) patients having an equal score and 1/11 (9%) patients having a worse score. *Statistical significance* of change not reported. **(VERY LOW)** **These studies provided very low certainty evidence that there is a statistically significant improvement in quality of life in patients with unilateral TFA and socket or prosthesis-fitting problems undergoing DSF as measured by the SF-36 and Q-TFA at 2, 5, 7 and 10 years follow-up.**
Activities of daily living **Certainty of evidence:** Not applicable	This outcome is important to patients because it reflects daily functioning and how well people can engage in education, employment and recreational activities. **No evidence was identified for this outcome.**
Important outcomes	
Mobility **Certainty of evidence:** Very low	This outcome is important to patients as it is a useful measure of overall mobility and functional capability. This encompasses patients’ individual rehabilitation goals. In total, two prospective case series reported non-comparative evidence for mobility up to 15 years follow-up after DSF in patients with unilateral TFA and socket or prosthesis-fitting problems. Outcomes reported included Amputation Mobility

Outcome	Evidence statement
	Predictor Prothesis (AMPPRO)[30] scores presented as K-levels[31], Q-TFA mobility scores[32] and prosthetic activity grades[33]. At a mean follow-up of 21.5 months: • One prospective case series (Al Muderis et al 2016a) (n=50) reported an improvement in K-levels post-operatively compared to pre-operatively in 30 patients (K0 to K2 in 2 patients; K0 to K3 in 12 patients; K0 to K4 in 1 patient; K1 to K3 in 1 patient; K2 to K3 in 11 patients; K3 to K4 in 3 patients) and no change in 20 patients (K2 in 2 patients; K3 in 13 patients; K4 in 5 patients). **(VERY LOW)** At 2 years: • One prospective case series (Hagberg et al 2020) reported on prosthetic activity grade with 1/86 (1%) patients graded "no prothesis", 13/86 (15%) patients graded "low", 30/86 (35%) patients graded "average", 24/86 (28%) patients graded "high" and 18/86 (21%) patients graded "very high". At baseline 26/110 (24%) patients were graded "no prothesis", 27/110 (25%) patients graded "low", 39/110 (35%) patients graded "average", 9/110 (8%) patients graded "high" and 9/110 (8%) patients graded "very high". **(VERY LOW)** • Hagberg et al (2020) also reported a *statistically significant* (p<0.001) improvement in prosthetic activity grade compared with baseline with 50/85 (59%) patients having a better score, 32/85 (38%) patients having an equal score and 3/85 (4%) patients having a worse score. **(VERY LOW)** At 5 years: • One prospective case series (Hagberg et al 2020) reported on prosthetic activity grade with 2/63 (3%) patients graded "no prothesis", 4/63 (6%) patients graded "low", 25/63 (40%) patients graded "average", 16/63 (25%) patients graded "high" and 16/63 (25%) patients graded "very high". At baseline 26/110 (24%) patients were graded "no prothesis", 27/110 (25%) patients graded "low", 39/110 (35%) patients graded "average", 9/110 (8%) patients graded "high" and 9/110 (8%) patients graded "very high". **(VERY LOW)** • Hagberg et al (2020) also reported a *statistically significant* (p<0.001) improvement in prosthetic activity grade compared with baseline with 42/62 (68%) patients having a better score, 19/62 (31%) patients having an equal score and 1/62 (2%) patients having a worse score. **(VERY LOW)** At 7 years:

[30] 21-item performance-based functional test designed specifically for people with lower limb loss to determine functional mobility by evaluating ability in transfers, sitting and standing balance, and gait skills

[31] A 5-level rating system used by the US Medicare health insurance program to indicate the extent of a person's disability and their potential for rehabilitation in individuals with lower-limb amputations. K-levels include: K0 – patient has no ability or potential to ambulate or transfer safely with or without assistance and a prosthesis does not enhance their quality of life or mobility; K1 - patient has the ability or potential to use a prosthesis for transfers or ambulation on level surfaces at fixed cadence - a typical limited or unlimited household ambulator; K2 - patient has the ability or potential for ambulation with the ability to traverse low level environmental barriers such as curbs, stairs, or uneven surfaces - a typical community ambulator; K3 - patient has the ability or potential for ambulation with variable cadence - a typical community ambulator with the ability to traverse most environmental barriers and may have therapeutic or exercise activity that demands prosthetic use beyond simple locomotion; K4 - patient has the ability or potential for prosthetic ambulation that exceeds basic ambulation skills, exhibiting high impact, stress, or energy levels - typical of the prosthetic demands of the child, active adult, or athlete

[32] The Questionnaire for Persons with a Transfemoral Amputation (Q-TFA) is a self-report measure developed for nonelderly transfemoral amputees using a socket- or osseointegrated prosthesis to reflect use, mobility, problems, and global health, each in a separate score (0-100). Prosthetic mobility is defined as the ability and performance of the amputee to move and change and maintain postures when using the prosthesis. The score consists of three sub scores, each with a range from 0 to 100: capability (12 items), use of walking aids (2 items), and walking habits (5 items). The average of these three sub scores generates the total mobility score. A higher score indicates better mobility

[33] The activity grade was assigned to each patient at each follow-up by the physiotherapist in the treating team. Activity is graded between 0 and 4 and combines the extent of prosthetic use, use of walking aids, outdoor walking habits, and other activities using the prosthesis, and is captured from Q-TFA items and medical records. 0 = Do not use prosthesis; no prosthetic activity; 1 (Low) = Limited use of prosthesis for standing/walking, use walking aid, no long walks; 2 (Average) = Use prosthesis most of the day, with or without walking aid at home, use walking aid outdoors; 3 (High) = Uses prosthesis for a full day, no walking aid except for longer distances, walks a lot, rarely performs other demanding or high-load activities in use of prosthesis; 4 (Very High) = Uses prosthesis for a full day, no walking aid, walks a lot and/or routinely performs other highly demanding or high-load activities involving the prosthesis (e.g. cycling, gym training)

Outcome	Evidence statement
	• One prospective case series (Hagberg et al 2020) reported on prosthetic activity grade with 0/55 (0%) patients graded “no prothesis”, 8/55 (11%) patients graded “low”, 18/55 (33%) patients graded “average”, 17/55 (31%) patients graded “high” and 14/55 (25%) patients graded “very high”. At baseline 26/110 (24%) patients were graded “no prothesis”, 27/110 (25%) patients graded “low”, 39/110 (35%) patients graded “average”, 9/110 (8%) patients graded “high” and 9/110 (8%) patients graded “very high”. **(VERY LOW)** • Hagberg et al (2020) also reported a *statistically significant* (p<0.001) improvement in prosthetic activity grade compared with baseline with 36/54 (67%) patients having a better score, 17/54 (31%) patients having an equal score and 1/54 (2%) patients having a worse score. **(VERY LOW)** • Hagberg et al (2020) also reported a mean Q-TFA mobility score of 67 (17.8 SD; 22 to 95 range) and a median score of 71 (58 to 79 IQR) (n=54). **(VERY LOW)** At 10 years: • One prospective case series (Hagberg et al 2020) reported on prosthetic activity grade with 3/32 (9%) patients graded “no prothesis”, 3/32 (9%) patients graded “low”, 8/32 (25%) patients graded “average”, 14/32 (44%) patients graded “high” and 4/32 (13%) patients graded “very high”. At baseline 26/110 (24%) patients were graded “no prothesis”, 27/110 (25%) patients graded “low”, 39/110 (35%) patients graded “average”, 9/110 (8%) patients graded “high” and 9/110 (8%) patients graded “very high”. **(VERY LOW)** • Hagberg et al (2020) also reported a *statistically significant* (p<0.001) improvement prosthetic activity grade compared with baseline with 22/32 (69%) patients having a better score, 6/32 (19%) patients having an equal score and 4/32 (13%) patients having a worse score. **(VERY LOW)** At 15 years: • One prospective case series (Hagberg et al 2020) reported on prosthetic activity grade with 0/11 (0%) patients graded “no prothesis”, 1/11 (9%) patients graded “low”, 1/11 (9%) patients graded “average”, 4/11 (36%) patients graded “high” and 5/11 (45%) patients graded “very high”. At baseline 26/110 (24%) patients were graded “no prothesis”, 27/110 (25%) patients graded “low”, 39/110 (35%) patients graded “average”, 9/110 (8%) patients graded “high” and 9/110 (8%) patients graded “very high”. **(VERY LOW)** • Hagberg et al (2020) also reported the change in prosthetic activity grade compared with baseline with 5/11 (45%) patients having a better score and 6/11 (55%) patients having an equal score. *Statistical significance* of change not reported. **(VERY LOW)** **One study provided very low certainty evidence that there is a statistically significant improvement in mobility in patients with unilateral TFA and socket or prosthesis-fitting problems undergoing DSF as measured by prosthetic activity grades at 2, 5, 7 and 10 years follow-up with an improvement also observed at 15 years but no statistical significance of this result reported. One study provided very low certainty evidence that there is an improvement in mobility as measured by AMPPRO scores at a mean follow-up of 21.5 months but no statistical significance of this result was reported. Another study reported Q-TFA mobility scores at 7 years but no baseline result or statistical significance was reported.**
Psychological impact **Certainty of evidence:** Not applicable	This outcome is important to patients because it considers the psychological impact of amputation and rehabilitation. It is important to consider in order to facilitate engagement in rehabilitation programmes. **No evidence was identified for this outcome.**
Wheelchair use	This outcome is important to patients as it may reflect issues with functional aspects of the prosthetic.

Outcome	Evidence statement
Certainty of evidence: Very low	In total, two prospective case series reported non-comparative evidence for wheelchair use at a mean follow-up of 21.5 months and a median follow-up of 34 months after DSF in patients with TFA and socket or prosthesis-fitting problems. At a mean follow-up of 21.5 months: • One prospective case series (Al Muderis et al 2016a) (n=50) reported that all 14 participants that had been wheelchair bound pre-operatively had post-operative K-level scores that were comparable with those of the patients who had been walking pre-operatively (K2 or better). It was not reported whether any participants who were walking pre-operatively became wheelchair bound after surgery. **(VERY LOW)** At a median follow-up of 34 months: • One prospective case series (Al Muderis et al 2016b) (n=86) reported that 25% of the study population was wheelchair-bound before osseointegration, and all of these patients became community ambulators after surgery. It was not reported whether any participants who were walking pre-operatively became wheelchair bound after surgery. **(VERY LOW)** **These studies provided very low certainty evidence that wheelchair use was reduced in patients with TFA and socket or prosthesis-fitting problems undergoing DSF up to a median follow-up of 34 months. One study reported that all patients who had been wheelchair bound pre-operatively became community ambulators after surgery and the other study reported that all patients who had been wheelchair bound pre-operatively had mobility scores comparable with patients who had been walking pre-operatively.**
Frequency of implant replacement and/or re-fitting **Certainty of evidence:** Very low	This outcome is important to patients as it impacts on user comfort and functional use. In total, five case series (three prospective and two retrospective) reported non-comparative evidence on the frequency of implant replacement and/or re-fitting up to 15 years follow-up after DSF in patients with TFA or a knee disarticulation (9% of participants in one study) and socket or prosthesis-fitting problems. At a mean follow-up of 21.5 months: • One prospective case series (Al Muderis et al 2016a) reported that 2/50 (4%) patients underwent revision of an implant. These were due to failure of osseointegration as a result of an undersized device in one patient and implant fatigue failure at 3.5 years in one patient. **(VERY LOW)** At 2 years: • One prospective case series (Hagberg et al 2020) (n=111) reported a revision-free survival of the fixture of 92% (95% confidence interval (CI) 85% to 96%). **(VERY LOW)** • Hagberg et al (2020) (n=111) also reported a survival of the fixture until the first event necessitating a change of the abutment and/or abutment screw of 81% (95% CI 71% to 88%). **(VERY LOW)** At a median follow-up of 34 months: • One prospective case series (Al Muderis et al 2016b) reported that 1/86 (1%) patient had inadequate osseointegration and underwent implant replacement, 2/86 (2%) patients experienced breakage of the intramedullary component at 42 and 47 months after surgery respectively leading to implant replacement and 25/86 (29%) patients experienced breakage of the pin used for safety in the dual-cone (extramedullary) component on a total of 30 occasions. **(VERY LOW)** At 5 years: • One prospective case series (Mohamed et al 2022) reported that 20/58 (34%) patients underwent revision surgery, 7/58 (12%) were due to a failed intramedullary stem due to breakages (n=6) or septic loosening (n=1) and 13/58 (22%) were due to a broken dual-cone adapter due to weak-point breakages (n=9), broken distal taper of the dual cone (n=3) or broken the weak-point and the distal taper (n=1). **(VERY LOW)**

Outcome	Evidence statement
	• Mohamed et al (2022) also reported a cumulative implant survival probability after 9 years (n=58) of 78% (95%CI 58% to 89%) and a median implant survival time of 6 years (IQR 4). **(VERY LOW)** At 7 years: • One prospective case series (Hagberg et al 2020) (n=111) reported a revision-free survival of the fixture of 89% (95% CI 80% to 94%). **(VERY LOW)** • Hagberg et al (2020) (n=111) also reported a survival of the fixture until the first event necessitating a change of the abutment and/or abutment screw of 32% (95% CI 22% to 43%). **(VERY LOW)** At a mean follow-up of 7.9 years: • One retrospective case series (Tillander et al 2017) reported that 10/102 (10%) implants were extracted due to osteomyelitis[34]. **(VERY LOW)** • Tillander et al (2017) (n=102) also reported a 10-year cumulative risk of implant extraction due to osteomyelitis of 9% (95% CI 4% to 20%). **(VERY LOW)** At 15 years: • One prospective case series (Hagberg et al 2020) reported that 18/111 (16%) had implant revisions, 7/111 (6%) due to infection, 6/111 (5%) due to aseptic loosening and 5/111 (5%) due to fractures. **(VERY LOW)** • Hagberg et al (2020) (n=111) also reported a revision-free survival of the fixture of 72% (95% CI 57% to 83%). **(VERY LOW)** • Hagberg et al (2020) also reported that 61/111 (55%) patients had at least one mechanical complication resulting in change of the abutment and/or abutment screw. **(VERY LOW)** • Hagberg et al (2020) (n=111) also reported a survival of the fixture until the first event necessitating a change of the abutment and/or abutment screw of 14% (95% CI 6% to 26%). **(VERY LOW)** **These studies provided very low certainty evidence that the percentage of implant replacement and/or re-fitting after DSF ranged between 3% to 4% at around 2 to 3 years to 34% at 5 years and 16% at 15 years in patients with TFA or a knee disarticulation and socket or prosthesis-fitting problems. One study reported that 10% of implants were extracted due to osteomyelitis at a mean follow-up of 7.9 years and another study reported that 6% were extracted due to infection at 15 years. One study reported a 10-year cumulative risk of implant extraction due to osteomyelitis of 9%. One study reported that 5%of implants were extracted due to fractures at 15 years. One study reported that revision-free survival of the fixture ranged from 92% at 2 years to 72% at 15 years, and a survival of the fixture until the first event necessitating a change of the abutment and/or abutment screw ranging from 81% at 2 years to 14% at 15 years. Another study reported a cumulative implant survival probability after 9 years of 78% and a median implant survival time of 6 years.**
Safety	
Adverse events **Certainty of evidence:** Very low	These outcomes are important to patients because they will impact on the patient's treatment choices, recovery and could have long term sequelae. In total, three case series (two prospective and one retrospective) reported non-comparative evidence on adverse events up to a mean follow-up of 7.9 years after DSF in patients with TFA and socket or prosthesis-fitting problems. At a mean follow-up of 21.5 months: • One prospective case series (Al Muderis et al 2016a) reported that 27/50 (54%) patients experienced an adverse event. **(VERY LOW)** • Al Muderis et al (2016a) also reported that 21/50 (42%) patients experienced one or more infections, 13 of which responded to oral antibiotics alone, 5 responded to intravenous antibiotics and 3 required surgical soft tissue debridement of infected soft tissues. **(VERY LOW)**

[34] Indication for extraction was infection not responsive to conservative treatment or loosening evident in stability testing of the implant

Outcome	Evidence statement
	• Al Muderis et al (2016a) also reported that 4/50 (8%) patients sustained periprosthetic fractures as a result of falls, three of whom were previously wheelchair bound with severe osteoporosis. All four fractures were managed by open reduction and internal fixation with a dynamic hip screw and cables as necessary, without interfering with the osseointegration of the implant. All fractures healed within three months. **(VERY LOW)** At a median follow-up of 34 months: • One prospective case series (Al Muderis et al 2016b) reported that 29/86 (34%) patients experienced one or more infections: 23/86 (27%) patients had Grade 1A[35] infection (low-grade soft-tissue infection cellulitis with signs of inflammation treated with oral antibiotics); 1/86 (1%) had Grade 1B infection (severe cellulitis and intense pain treated with parenteral antibiotics); 1/86 (1%) had Grade 1C infection (severe cellulitis and intense pain treated with parenteral antibiotics followed by local debridement); 4/86 (5%) had Grade 2C[36] infection (high-grade soft-tissue infection with abscess formation that needed surgical debridement). No patient developed a serious (grade 3[37] or 4[38]) infection. **(VERY LOW)** • Al Muderis et al (2016b) also reported that 17/86 (20%) had stoma hypergranulation (22 events). **(VERY LOW)** • Al Muderis et al (2016b) also reported that 14/86 (16%) had redundant soft tissue (23 events). **(VERY LOW)** • Al Muderis et al (2016b) also reported that 3/86 (3%) had a proximal femoral fracture (3 events. All patients underwent surgical stabilisation of the fracture without the need of implant removal. **(VERY LOW)** At a mean follow-up of 7.9 years: • One retrospective case series (Tillander et al 2017) reported that 16/96 (17%) patients developed osteomyelitis (12 definitive, 3 probable, 1 possible). The clinical presentation of osteomyelitis was subacute or acute in 8 patients and chronic with or without fistulas in 8 patients. The clinical outcome for patients with osteomyelitis was recovery[39] after antibiotics with or without minor debridement (n=4); recovery and later relapse (n=1); successful re-implantation (n=1); recovery after extraction (n=9); and chronic with fistula (n=1). The prosthetic use[40] at the time of diagnosis of osteomyelitis was reported to be unable to use prostheses (n=2); moderately restricted prosthetic use (n=6); no impairment (n=2); and not assessed as patient in the early rehabilitation phase (n=6). **(VERY LOW)** • Tillander et al (2017) (n=96) also reported a 10-year cumulative risk of implant-associated osteomyelitis[41] of 20% (95% CI 12 to 33). **(VERY LOW)** • Tillander et al (2017) (n=96) also reported a median time from implantation to osteomyelitis of 2.6 years (0.3 to 13.8 range). **(VERY LOW)** **These studies provided very low certainty evidence on adverse events after DSF in patients with TFA and socket or prosthesis-fitting problems undergoing DSF. One study reported that 54% of patients experienced an adverse event at a mean follow-up of 21.5 months. The percentage of patients experiencing infections reported by the studies included 42% at a mean follow-up of 21.5 months, 34% at a median follow-up of 34 months and 17% at a mean follow-up of 7.9 years. One study reported a 10-year cumulative risk of implant-associated osteomyelitis of 20% and a median time from implantation**

[35] Grade 1 - Low-grade soft-tissue infection cellulitis with signs of inflammation (redness, swelling, warmth, stinging pain, pain that increases on loading, tense) treated with oral antibiotics (Grade 1A), parenteral antibiotics (Grade 1B) or surgical intervention (Grade 1C)
[36] High-grade soft-tissue infection with pus collection, purulent discharge, raised level of C-reactive protein treated with oral antibiotics (Grade 2A), parenteral antibiotics (Grade 2B) or surgical intervention (Grade 2C)
[37] Bone infection with radiographic evidence of osteitis (periosteal bone reaction), radiographic evidence of osteomyelitis (sequestrum and involucrum)
[38] Implant failure with radiographic evidence of loosening
[39] Infections were considered resolved if patients were symptom-free 12 months or more after discontinuation of antibiotics
[40] Prosthetic use at the time of osteomyelitis was retrospectively assessed by a team physiotherapist and assigned a simple 1 to 3 score (unchanged = 1, impaired = 2, and no prosthetic use owing to infection = 3)
[41] Evidence of infection involving implant-surrounding bone and/or bone marrow, supported by positive percutaneous bone biopsy or aspirated bone marrow cultures, and classified as definite, probable, or possible

Outcome	Evidence statement
	to osteomyelitis of 2.6 years. One study reported that 8% of patients sustained periprosthetic fractures at a mean follow-up of 21.5 months and another study reported that 3% had proximal femoral fractures at a median follow-up of 34 months. One study reported that 20% had stoma hypergranulation and 16% had redundant soft tissue at a median follow-up of 34 months.
Abbreviations 6MWT: 6-Minute Walk Test; AMPPRO: Amputation Mobility Predictor Prothesis; CI: Confidence Interval; DSF: Direct Skeletal Fixation; IQR: Interquartile Range; Q-TFA: Questionnaire for Persons with a Transfemoral Amputation; SD: Standard Deviation; SF-36: 36-Item Short Form Health Survey; TUG: Timed Up and Go Test	

In adults with transfemoral limb loss, what is the cost effectiveness of DSF compared with no prosthetic use?

Outcome	Evidence statement
Cost effectiveness	**No evidence was identified for cost effectiveness.**

From the evidence selected, are there any subgroups of patients that may benefit from DSF more than the wider population of interest?

Outcome	Evidence statement
Subgroups	**No evidence was identified for subgroups.**

From the evidence selected, what rehabilitation programmes did people who had direct skeletal fixation undertake?

Outcome	Evidence statement
Rehabilitation programmes	Al Muderis et al 2016a reported that the first phase of rehabilitation was initiated while patients were still hospitalised. On day 3 after the second stage of surgery, patients applied a static axial load of 20 kg twice daily for 20 minutes. The load was increased each day by 5 kg until it reached 50 kg, or half of their body weight. The second phase of rehabilitation started when patients reached the recommended axial loading level and involved the fitting of a rehabilitation prosthesis incorporating a stable locked knee. Patients mobilised using parallel bars until they could balance and felt stable. The third phase started when the patients were safely mobilising with the rehabilitation prosthesis, and at approximately 14 days they were then fitted with their definitive prosthesis, including a hydraulic knee with safety mechanisms. A laser prosthetic alignment device was used to accurately adjust the prosthetic limb in the sagittal and coronal planes. Alignment was also carefully adjusted to reduce shear and torsional loading on the bone-implant interface. For the initial six weeks, patients were prescribed two crutches when weightbearing. A single crutch was used in the opposite hand for an additional six weeks and they were allowed unaided weightbearing thereafter. Afterwards, further gait training was prescribed that focused on fall prevention and management, balance, walking, and ascending and descending slopes. Al Muderis et al 2016b reported that at both centres the patients followed a gradual incremental axial loading program. The patients from the centre in Australia followed the Osseointegration Group of Australia Accelerated Protocol (OGAAP) for rehabilitation which is the protocol described above for Al Muderis et al 2016a. The patients from the centre in the Netherlands (Al Muderis et al 2016b & Mohamed et al

Outcome	Evidence statement
	2022) performed rehabilitation twice a week in group training sessions of two hours' duration and the average rehabilitation period was six to eight weeks. It began with weight-bearing exercises using a short pylon attached to the transcutaneous unit two weeks after the second operation. Weight feedback was provided by a scale. During the first week, participants were allowed to bear 50% of their body weight on the implant. This was gradually increased to full body weight-bearing during the second week. Four weeks after the second surgery, the prosthesis was attached to the transcutaneous unit using a click-safety adapter and a progressive loading rehabilitation program initiated. Rehabilitation consisted of gradually increasing the amount of weight-bearing on the implant and locomotion exercises. In two weeks, participants were allowed to bear their full body weight on the implant. Patients from Hagberg et al 2020 and Tillander et al 2017 from the centre in Sweden followed the OPRA rehabilitation protocol described in Hagberg et al 2009. The OPRA rehabilitation protocol aims to gradually increase loading of the bone-implant unit to prepare for unrestricted artificial limb use and includes an initial training period using a short training prosthesis and a later training period using the osseointegrated prosthesis. It is differentiated into two slightly different protocols: Normal-Speed (treated for about 12 months) and Half-Speed (treated for about 18 months). The Half-Speed Protocol is for patients with poorer skeletal conditions as judged by the surgeons. All patients begin training about two weeks after the second surgical procedure by performing gentle exercises (i.e., range of motion (ROM) exercises without full voluntary muscle contraction) to prevent development of hip joint contractures. At four to six weeks after surgery, when the skin penetration area and soft tissue are adequately healed, more active training begins. Initial training includes axial weight-bearing and weight shifting standing on a short training prosthesis. The patient can measure the amount of weight put on the short training prosthesis using a normal bathroom scale. In addition, the patient is given a general exercise program emphasising more active training of hip ROM and muscle strength. The general exercise program's aim is also to stimulate bone mineralisation by loading the bone-implant unit in additional directions other than axial. In the Normal-Speed Protocol, weight bearing on the short training prosthesis starts at 20 kg and is performed twice a day for 30 minutes. The patient is instructed to increase weight bearing by 10 kg each week until weight shifting to full body weight is achieved painlessly. Most patients report some pain during weight-bearing training, and pain recorded at visual analogue scale (VAS) level 2 to 3 is considered safe. However, pain reported above VAS 5 should be avoided and weight-bearing exercises should be decreased to a more pain-free level. For all patients, the protocol includes five to six weeks of training with the short training prosthesis before prosthetic gait training on the definitive prosthesis starts. Thus, prosthetic gait training starts at about 12 weeks after the second surgical procedure. During the first 2 weeks, the patient is instructed to use the prosthesis a maximum of two hours per day, only indoors, and with the support of two crutches for very limited weight-bearing on the prosthetic foot. The prosthesis wearing time, as well as prosthetic activity and weight-bearing, is gradually increased in the following weeks. The patient achieves full-day prosthetic use after four to six weeks. During the first three months of prosthetic use, walking should be done with double support (crutches or sticks). Based on X-rays and the clinical status six months after the second surgical procedure a decision is made by the team on walking without walking aid support both indoors and outdoors. Again, pain reported above VAS 5 should be avoided, and individual protocol progress should be slowed so as not to risk overloading the ongoing integration of bone structure.

Abbreviations
OGAAP: Osseointegration Group of Australia Accelerated Protocol; OPRA: Osseointegrated Prostheses for the Rehabilitation of Amputees; ROM: range of motion; VAS: visual analogue scale

6. Discussion

This evidence review considered the clinical effectiveness and safety of DSF compared to no prosthetic use in people with transfemoral limb loss who are unable to tolerate conventional socket use. The critical outcomes of interest were functional outcome measures, quality of life and activities of daily living. The important outcomes were mobility, psychological impact, wheelchair use, frequency of implant replacement and/or re-fitting and safety. Evidence on cost effectiveness was also sought.

No comparative studies were identified that met the inclusion criteria for population and comparator. Evidence was available from five case series, three prospective (Al Muderis et al 2016a, Al Muderis et al 2016b, Hagberg et al 2020) and two retrospective (Mohamed et al 2022 & Tillander et al 2017), including between 50 and 111 patients. Two studies were based in Gothenburg in Sweden (Tillander et al 2017 (n=96; recruitment period 1990 to 2010; 8 years follow-up) and Hagberg et al 2020 (n=111; recruitment period 1999 to 2017; 15 years follow-up)) and had overlapping recruitment periods and therefore will have included some of the same patients. However, these two studies reported on different outcomes with the exception of frequency of implant replacement and/or re-fitting which was reported by both studies. One study was based in a centre in Australia (Al Muderis et al 2016a (n=50; recruitment period 2011 to 2014; 21.5 months follow-up)), one in the Netherlands (Mohamed et al 2022 (n=58; recruitment period 2009 to 2015; 5 years follow-up)) and one study was a combined safety analysis of patients from these two centres (Al Muderis et al 2016b; (n=86; recruitment period 2009 to 2013; 34 months follow-up)). The majority of the studies were conducted in single centres and included some patients undergoing surgery around ten to thirty years ago. It is not clear to what extent the results of these studies might be generalisable to the UK population or to current practice.

All studies included adults with TFA with socket or prosthesis-fitting problems. Two studies (Al Muderis et al 2016a & Hagberg et al 2020) only included patients with unilateral amputations. The other three studies included some patients with bilateral amputations, but the numbers were too small to compare results between unilateral and bilateral amputees. Two studies included a small number of patients with congenital amputation (Al Muderis et al 2016a (n=2; 4% of study population) & Al Muderis et al 2016b (n=1; 1%). One study included patients with a knee disarticulation (Mohamed et al 2022 (n=5; 9% of study population). All studies that reported exclusion criteria, excluded patients with peripheral vascular disease and diabetes mellitus, and exposure to radiation in the affected limb or past or ongoing chemotherapy. None of the studies defined the criteria used to assess socket or prosthesis-fitting problems, and one study reported that approximately one-third of those assessed were found suitable for implant surgery but no further details were provided. It was therefore not possible to determine whether problems with sockets and suitability for surgery were assessed in a standard and reliable manner and therefore whether the studies included all patients with TFA who underwent DSF after being unable to tolerate socket prostheses.

All patients underwent two stage surgery using either the OPRA, ILP, OPL or OIP system followed by a rehabilitation programme. Rehabilitation programmes followed gradual incremental axial loading and varied between an average of 6 to 12 weeks for the centres in Australia and the Netherlands and 12 to 18 months in Sweden.

The follow-up periods ranged between 2 years and 18 years. The largest and the longest study (Hagberg et al 2020) was conducted over an 18 year follow-up period and reported results for multiple timepoints (2, 5, 7, 10 and 15 years). However, the 15 year follow-up results were based on a small number of patients (n=14 patients) due to patients being recruited at different times throughout the study.

All the studies were at high risk of bias and certainty about the evidence for all critical and important outcomes reported was very low when assessed using modified GRADE. Limitations reducing certainty for the outcomes included uncertainty about whether the inclusion of participants was complete and limited reporting of results, with some studies not conducting statistical tests and some reporting results only in graph form. None of the studies commented on what Minimum Clinically Important Difference thresholds would be for any of the outcomes reported.

No evidence was identified on activities of daily living (critical outcome) and psychological impact (important outcome). No evidence was identified for cost effectiveness. No evidence was identified on subgroups.

7. Conclusion

The evidence included in this review is insufficient to draw conclusions about the clinical effectiveness and safety of DSF compared to no prosthetic use in people with transfemoral limb loss who are unable to tolerate conventional socket use. The key limitation to identifying evidence on the effectiveness of DSF compared to no prosthetic use in people who are unable to tolerate conventional socket use is the lack of studies comparing DSF with no prosthetic use in this group.

Five case series (three prospective and two retrospective) were identified ranging in size from 50 to 111 patients and reporting results at multiple time-points up to 15 years. This very low certainty, non-comparative evidence in people with transfemoral limb loss who are unable to tolerate conventional socket use suggests that DSF improves functional outcomes as measured by the TUG test and 6MWT at 2 years, quality of life as measured by the SF-36 and Q-TFA up to 10 years, mobility as measured by prosthetic activity grades up to 10 years and wheelchair use up to 3 years follow-up. Across the studies, at different time-points up to 15 years, rates of implant replacement and/or re-fitting ranged from 3% to 34%, and extraction due to infection ranged from 6% to 10%. Over half of patients experienced an adverse event as reported by one study at 2 years, and across the studies the percentage of patients experiencing infections at different time-points up to 8 years ranged from 17% to 42%.

No evidence was identified for activities of daily living and psychological impact outcomes.

No evidence was identified on the cost effectiveness of DSF compared to no prosthetic use in people with transfemoral limb loss who are unable to tolerate conventional socket use.

No evidence was identified for particular sub-groups of patients that would benefit more from DSF.

Appendix A PICO document

The review questions for this evidence review are:

1. In people with transfemoral limb loss who are unable to tolerate conventional socket use, what is the clinical effectiveness of direct skeletal fixation compared to no prosthetic use?
2. In people with transfemoral limb loss who are unable to tolerate conventional socket use, what is the safety of direct skeletal fixation compared to no prosthetic use?
3. In people with transfemoral limb loss who are unable to tolerate conventional socket use, what is the cost effectiveness of direct skeletal fixation compared to no prosthetic use?
4. From the evidence selected, are there any subgroups of patients that may benefit from direct skeletal fixation more than the wider population of interest?
5. From the evidence selected, what rehabilitation programmes did people who had direct skeletal fixation undertake?

P –Population and Indication	Adult patients with transfemoral limb loss as the result of either acquired amputation or congenital absence (congenital deficiency) who are unable to tolerate conventional socket use. Subgroups of interest: • Surgical vs traumatic amputations • Congenital limb deficiency vs amputation • Unilateral vs bilateral • Single operation vs two operations [Transfemoral limb loss includes congenital limb deficiency or amputation or disarticulation through knee or more proximal. Patients who are unable to tolerate conventional socket use include those who use crutches or a wheelchair. Adult patients only as the femur needs to be mature prior to insertion of the implant to avoid disruption of the growth plate. Therefore, this policy proposition excludes children.]
I – Intervention	Direct skeletal fixation (DSF) with a rehabilitation programme [DSF is a surgical technique to treat transfemoral limb loss. It is a two-step procedure that may be carried out in a single operation or over two operations. The first step involves the insertion of a titanium implant into the medullary cavity of the residual bone. If being carried out over two operations, the stump wound is completely closed and allowed to heal. The second step of the procedure is undertaken either in the same operation or approximately 3-6 months later, once osseointegration has taken place. In this step the implant is connected to a metal extension (known as an abutment) which penetrates the skin, allowing attachment of the external prosthesis to the intraosseous implant. A failsafe mechanism joins the abutment to the prosthesis to reduce risk of bony or prosthetic damage. Implant manufacturers and inventors: 1. Osseointegrated Prostheses for the Rehabilitation of Amputees (OPRA), Integrum, Branemark

	2. Integral Leg Prosthesis (ILP, previously Endo-Exo Prosthesis), ESKA Orthopaedic, Grundei 3. Osseointegrated Prosthetic Limb (OPL), Osseointegration International/Permedica, Al-Muderis DSF is proposed as a treatment option for patients who fail to tolerate conventional socket use. It includes a minimum of 6 weeks rehabilitation programme.]
C – Comparator(s)	No prosthesis
O – Outcomes	**<u>Clinical Effectiveness</u>** *Unless stated for the outcome, minimum clinically important differences (MCIDs) are unknown. Outcomes ideally measured at 6, 12, 24 months as well as long-term outcomes.* *<u>Critical to decision-making:</u>* • **Functional outcome measures** *Functional outcomes are important to patients as they quantify enablement, independence and active participation.* - 2-or-6 minute walk test [This test assesses walking capacity for the duration of either 2 or 6 minutes. It is used to assess aerobic capacity and walking function through an evaluation of distance walked in the time frame.] - Timed up and go test [This test involves observation of the patient while rising from an armchair, walking 3m and returning to the chair. It is used to study the physical mobility of patients.] • **Quality of life** *Quality of life is an important outcome to patients as it provides an indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living.* - [Including but not limited to EQ-5D and The Short Form 36 (SF-36)] • **Activities of daily living** *This outcome is important to patients because it reflects daily functioning and how well people can engage in education, employment and recreational activities.* - [Including but not limited to the Reintegration to Normal Living Index (RNLI).] *<u>Important to decision-making:</u>* • **Mobility** *This outcome is important to patients as it is a useful measure of overall mobility and functional capability. This encompasses patients' individual rehabilitation goals.* - [Mobility scores including but not restricted to the Amputee Mobility Predictor with Prosthesis (AMPPro), the Locomotor Capabilities Index (LCI) and the Special

	Interest Group for Amputee Medicine (SIGAM) mobility grade] • **Psychological impact** *This outcome is important to patient because it considers the psychological impact of amputation and rehabilitation. It is important to consider in order to facilitate engagement in rehabilitation programmes.* - [Scores including but not restricted to the Patient Health Questionnaire (PHQ-9) and the Generalised Anxiety Disorder Questionnaire (GAD-7)] • **Wheelchair use** *This outcome is important to patients as it may reflect issues with functional aspects of the prosthetic.* • **Frequency of implant replacement and/or re-fitting** *This outcome is important to patients as it impacts on user comfort and functional use.* **<u>Safety</u>** • Adverse events *These outcomes are important to patients because they will impact on the patient's treatment choices, recovery and could have long term sequelae.* - [Including but not restricted to infection, number of courses of antibiotics, fracture, adverse events relating to the failsafe mechanism] **<u>Cost effectiveness</u>**
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	Adults
Date limits	2012-2022
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-publication prints and guidelines
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase and the Cochrane Library were searched limiting the search to papers published in English language in the last 10 years. Conference abstracts, commentaries, letters, editorials and case reports were excluded.

Search dates: 1 January 2012 to 23 September 2022

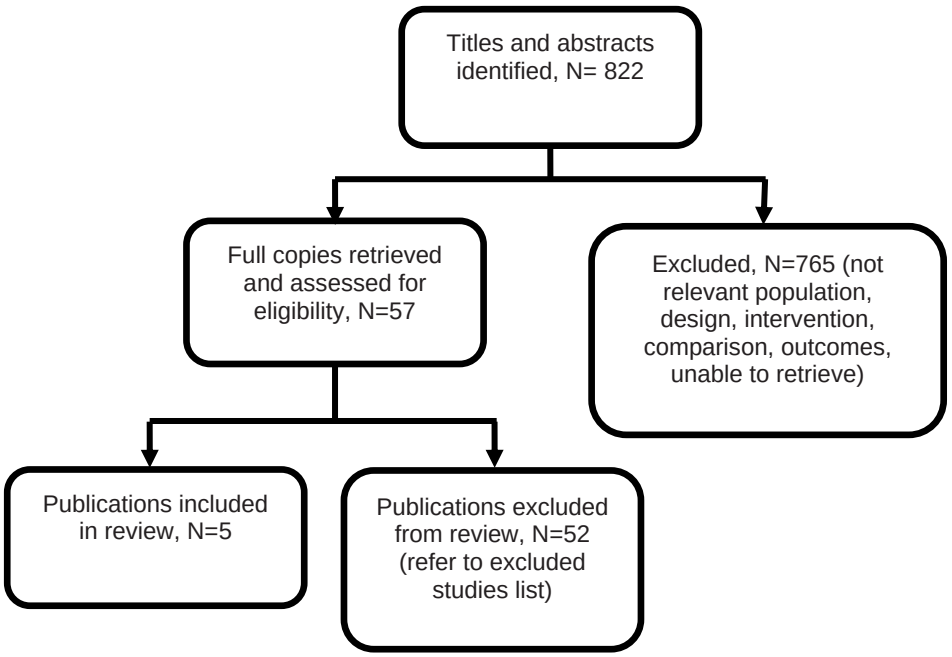
Medline search strategy:

1	Amputees/
2	Amputation/ or Amputation Stumps/
3	Artificial Limbs/
4	limb deformities, congenital/ or exp lower extremity deformities, congenital/
5	(amputat* or amputee?).ti,ab,kf.
6	((congenital adj2 (limb? or lower extremit* or leg? or foot or feet or tibia? or fibia? or fibula? or femur? or femoral or transfemoral)) and (deformit* or deficien* or malformation?)).ti,ab,kf.
7	((limb? or lower extremit* or leg? or foot or feet or tibia? or fibia? or fibula? or femur? or femoral or transfemoral) adj2 loss).ti,ab,kf.
8	(knee? adj2 disarticulat*).ti,ab,kf.
9	(((limb? or lower extremit* or leg? or foot or feet or tibia? or fibia? or fibula? or femur? or femoral or transfemoral) adj2 (prosthe* or implant*)) or artificial limb? or artificial leg?).ti,ab,kf.
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	Osseointegration/
12	(direct skelet* adj2 (fix* or attach*)).ti,ab,kf.
13	(osseointegrat* or osseo-integrat* or osseousintegrat* or osseous-integrat*).ti,ab,kf.
14	((intraosseous or intra-osseous) adj3 (implant* or prosthe*)).ti,ab,kf.
15	((integrated adj (limb? or lower extremit* or leg? or foot or feet or tibia? or fibia? or fibula? or femur? or femoral)) and (prosthe* or implant*)).ti,ab,kf.
16	bone anchored.ti,ab,kf.
17	11 or 12 or 13 or 14 or 15 or 16
18	10 and 17
19	exp animals/ not humans.sh.
20	18 not 19
21	limit 20 to (english language and yr="2012 - Current")
22	limit 21 to ("systematic review" or "reviews (maximizes specificity)")
23	(comment or editorial or letter or review).pt.
24	21 not 23
25	22 or 24

Appendix C Evidence selection

The literature searches identified 822 references. These were screened using their titles and abstracts and 57 references were obtained in full text and assessed for relevance. Of these, 5 references are included in the evidence summary. The remaining 52 references were excluded and are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection - decision and rationale if excluded
McMenemy L, Ramasamy A, Sherman K, Mistlin A, Phillip R, Evriviades D, et al. Direct Skeletal Fixation in bilateral above knee amputees following blast: 2 year follow up results from the initial cohort of UK service personnel. Injury. 2020;51(3):735-43.	Outcomes in this case series are reported in larger case series which are included in this review
Matthews DJ, Arastu M, Uden M, Sullivan JP, Bolsakova K, Robinson K, et al. UK trial of the Osseointegrated Prosthesis for the Rehabilitation for Amputees: 1995-2018. Prosthet Orthot Int. 2019;43(1):112-22.	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis
Kunutsor SK, Gillatt D, Blom AW. Systematic review of the safety and efficacy of osseointegration prosthesis after limb amputation. Br J Surg. 2018;105(13):1731-41.	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis

Appendix D Excluded studies table

Study reference	Reason for exclusion
Akhtar MA, Hoellwarth JS, Al-Jawazneh S, Lu W, Roberts C, Al Muderis M. Transtibial Osseointegration for Patients with Peripheral Vascular Disease: A Case Series of 6 Patients with Minimum 3-Year Follow-up. JB JS Open Access. 2021;6(2):Apr-Jun.	Population out of scope - Transtibial amputations
Akhtar MA, Hoellwarth JS, Tetsworth K, Oomatia A, Al Muderis M. Osseointegration Following Transfemoral Amputation After Infected Total Knee Replacement: A Case Series of 10 Patients With a Mean Follow-up of 5 Years. Arthroplasty Today. 2022;16:21-30.	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis
Al Muderis M, Lu W, Li JJ. Osseointegrated Prosthetic Limb for the treatment of lower limb amputations : Experience and outcomes. Unfallchirurg. 2017;120(4):306-11.	Outcomes in this case series are reported in larger case series which are included in this review
Al Muderis MM, Lu WY, Li JJ, Kaufman K, Orendurff M, Highsmith MJ, et al. Clinically Relevant Outcome Measures Following Limb Osseointegration; Systematic Review of the Literature. J Orthop Trauma. 2018;32(2):e64-e75.	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis
Atallah R, Leijendekkers RA, Hoogeboom TJ, Frolke JP. Complications of bone-anchored prostheses for individuals with an extremity amputation: A systematic review. PLoS ONE. 2018;13(8):e0201821.	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis
Atallah R, van de Meent H, Verhamme L, Frolke JP, Leijendekkers RA. Safety, prosthesis wearing time and health-related quality of life of lower extremity bone-anchored prostheses using a press-fit titanium osseointegration implant: A prospective one-year follow-up cohort study. PLoS ONE. 2020;15(3):e0230027.	Only a subgroup of study population is in scope. Outcomes in this case series are reported in case series with a total population in scope which are included in this review
Black GG, Jung W, Wu X, Rozbruch SR, Otterburn DM. A Cost-Benefit Analysis of Osseointegrated Prostheses for Lower Limb Amputees in the US Health Care System. Ann Plast Surg. 2022;88(3 Suppl 3):S224-S8.	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis
Branemark R, Berlin O, Hagberg K, Bergh P, Gunterberg B, Rydevik B. A novel osseointegrated percutaneous prosthetic system for the treatment of patients with transfemoral amputation: A prospective study of 51 patients. Bone Joint J. 2014;96-B(1):106-13.	Patients in this case series are included in Hagberg et al 2020 which has a larger sample size and longer follow-up and is included in this review
Branemark RP, Hagberg K, Kulbacka-Ortiz K, Berlin O, Rydevik B. Osseointegrated Percutaneous Prosthetic System for the Treatment of Patients With Transfemoral Amputation: A Prospective Five-year Follow-up of Patient-reported Outcomes and Complications. J Am Acad Orthop Surg. 2019;27(16):e743-e51.	Patients in this case series are included in Hagberg et al 2020 which has a larger sample size and longer follow-up and is included in this review
Diaz Balzani L, Ciuffreda M, Vadala G, Di Pino G, Papalia R, Denaro V. Osseointegration for lower and upper-limb amputation a systematic review of clinical outcomes and complications. J Biol Regul Homeost Agents. 2020;34(4 Suppl. 3):315-26. Congress of the Italian Orthopaedic Research Society.	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis

Study reference	Reason for exclusion
Dickinson AS, Steer JW, Worsley PR. Finite element analysis of the amputated lower limb: A systematic review and recommendations. Med Eng Phys. 2017;43:1-18.	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis
Donnelley CA, Shirley C, von Kaeppler EP, Hetherington A, Albright PD, Morshed S, et al. Cost Analyses of Prosthetic Devices: A Systematic Review. Arch Phys Med Rehabil. 2021;102(7):1404-15.e2.	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis
Dumoulin Q, Sabau S, Goetzmann T, Jacquot A, Sirveaux F, Mole D, et al. Assessment of a press-fit proximal femoral modular reconstruction implant (PFMR^R) at 14.5 years. A 48-case series with a disturbing rate of implant fracture. Orthop Traumatol Surg Res. 2018;104(3):317-23.	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis
Frossard L, Ferrada L, Berg D. Survey data on the quality of life of consumers fitted with osseointegrated fixation and bone-anchored limb prostheses provided by government organization. Data Brief. 2019;26:104536.	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis
Frossard L, Merlo G, Quincey T, Burkett B, Berg D. Development of a Procedure for the Government Provision of Bone-Anchored Prosthesis Using Osseointegration in Australia. Pharmacoeconom Open. 2017;1(4):301-14.	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis
Frossard LA, Merlo G, Burkett B, Quincey T, Berg D. Cost-effectiveness of bone-anchored prostheses using osseointegrated fixation: Myth or reality? Prosthet Orthot Int. 2018;42(3):318-27.	Comparator out of scope. - socket prosthesis (not no prothesis)
Gerzina C, Potter E, Haleem AM, Dabash S. The future of the amputees with osseointegration: A systematic review of literature. J. 2020;11(Suppl 1):S142-S8.	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis
Gholizadeh H, Abu Osman NA, Eshraghi A, Ali S. Transfemoral prosthesis suspension systems: a systematic review of the literature. Am J Phys Med Rehabil. 2014;93(9):809-23.	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis
Groundland J, Brown JM, Monument M, Bernthal N, Jones KB, Randall RL. What Are the Long-term Surgical Outcomes of Compressive Endoprosthetic Osseointegration of the Femur with a Minimum 10-year Follow-up Period? Clin Orthop. 2022;480(3):539-48.	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis
Guirao L, Samitier CB, Costea M, Camos JM, Majo M, Pleguezuelos E. Improvement in walking abilities in transfemoral amputees with a distal weight bearing implant. Prosthet Orthot Int. 2017;41(1):26-32.	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis
Hagberg K, Brodtkorb TH. Patient-reported benefits of bone-anchored transfemoral prostheses as assessed by MedTech20: A general outcome measure for medical products. Prosthet Orthot Int. 2021;45(4):355-61.	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis
Hagberg K, Hansson E, Branemark R. Outcome of percutaneous osseointegrated prostheses for patients with unilateral transfemoral amputation at two-year follow-up. Arch Phys Med Rehabil. 2014;95(11):2120-7.	Patients in this case series are included in Hagberg et al 2020 which has a larger sample size and longer follow-up and is included in this review
Hagberg K. Bone-anchored prostheses in patients with traumatic bilateral transfemoral amputations: rehabilitation description and outcome in 12 cases	Outcomes in this case series are reported in larger case series which are included in this review

Study reference	Reason for exclusion
treated with the OPRA implant system. Disabil. 2019;14(4):346-53.	
Haggstrom EE, Hansson E, Hagberg K. Comparison of prosthetic costs and service between osseointegrated and conventional suspended transfemoral prostheses. Prosthet Orthot Int. 2013;37(2):152-60.	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis
Hansen CH, Hansen RL, Jorgensen PH, Petersen KK, Norlyk A. The process of becoming a user of an osseointegrated prosthesis following transfemoral amputation: a qualitative study. Disabil Rehabil. 2019;41(3):276-83.	Qualitative description of the process of becoming a user, not reporting quantitatively on outcomes that are in scope of the PICO specification for this review
Hansen RL, Langdahl BL, Jorgensen PH, Petersen KK, Soballe K, Stilling M. Does migration of osseointegrated implants for transfemoral amputees predict later revision? A prospective 2-year radiostereometric analysis with 5-years clinical follow-up. Orthop Traumatol Surg Res. 2019;105(5):1013-20.	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis
Hansson E, Hagberg K, Cawson M, Brodtkorb TH. Patients with unilateral transfemoral amputation treated with a percutaneous osseointegrated prosthesis: a cost-effectiveness analysis. Bone Joint J. 2018;100-B(4):527-34.	Comparator out of scope - socket prosthesis (not no prothesis)
Hebert JS, Rehani M, Stiegelmar R. Osseointegration for Lower-Limb Amputation: A Systematic Review of Clinical Outcomes. JBJS rev. 2017;5(10):e10.	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis
Hoellwarth JS, Tetsworth K, Kendrew J, Kang NV, van Waes O, Al-Maawi Q, et al. Periprosthetic osseointegration fractures are infrequent and management is familiar. Bone Joint J. 2020;102-B(2):162-9.	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis
J P M Frölke RALHvdM. Osseointegrated prosthesis for patients with an amputation: Multidisciplinary team approach in the Netherlands. Der Unfallchirurg. 2017;120:293-9.	General non-systematic review
Juhnke DL, Beck JP, Jeyapalina S, Aschoff HH. Fifteen years of experience with Integral-Leg-Prosthesis: Cohort study of artificial limb attachment system. J Rehabil Res Dev. 2015;52(4):407-20.	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis
Kagan R, Adams J, Schulman C, Laursen R, Espana K, Yoo J, et al. What Factors Are Associated With Failure of Compressive Osseointegration Fixation? Clin Orthop. 2017;475(3):698-704.	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis
Kunutsor SK, Gillatt D, Blom AW. Systematic review of the safety and efficacy of osseointegration prosthesis after limb amputation. Br J Surg. 2018;105(13):1731-41.	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis
Leijendekkers RA, van Hinte G, Frolke JP, van de Meent H, Atsma F, Nijhuis-van der Sanden MW, et al. Functional performance and safety of bone-anchored prostheses in persons with a transfemoral or transtibial amputation: a prospective one-year follow-up cohort study. Clin Rehabil. 2019;33(3):450-64.	Only a subgroup of study population is in scope. Outcomes in this case series are reported in case series with a total population in scope which are included in this review
Leijendekkers RA, van Hinte G, Frolke JP, van de Meent H, Nijhuis-van der Sanden MW, Staal JB. Comparison of bone-anchored prostheses and socket prostheses for	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis

Study reference	Reason for exclusion
patients with a lower extremity amputation: a systematic review. Disabil Rehabil. 2017;39(11):1045-58.	
Li Y, Lindeque B. Percutaneous Osseointegrated Prostheses for Transfemoral Amputations. Orthopedics. 2018;41(2):75-80.	General non-systematic review
Marano AA, Modiri O, Rozbruch SR, Otterburn DM. Soft Tissue Contouring at the Time of Osseointegrated Implant Reconstruction for Lower Extremity Amputation. Ann Plast Surg. 2020;85(S1 Suppl 1):S33-S6.	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis
Matthews DJ, Arastu M, Uden M, Sullivan JP, Bolsakova K, Robinson K, et al. UK trial of the Osseointegrated Prosthesis for the Rehabilitation for Amputees: 1995-2018. Prosthet Orthot Int. 2019;43(1):112-22.	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis
McMenemy L, Ramasamy A, Sherman K, Mistlin A, Phillip R, Evriviades D, et al. Direct Skeletal Fixation in bilateral above knee amputees following blast: 2 year follow up results from the initial cohort of UK service personnel. Injury. 2020;51(3):735-43.	Outcomes in this case series are reported in larger case series which are included in this review
Muderis MA, Lu W, Glatt V, Tetsworth K. Two-Stage Osseointegrated Reconstruction of Post-traumatic Unilateral Transfemoral Amputees. Mil Med. 2018;183(suppl_1):496-502.	Outcomes in this case series are reported in larger case series which are included in this review
Ontario H. Osseointegrated Prosthetic Implants for People With Lower-Limb Amputation: A Health Technology Assessment. Ont Health Technol Assess Ser. 2019;19(7):1-126.	Systematic review in scope but it is a systematic review of case series with no meta-analysis. Individual studies included instead. The comparator used in the cost-effectiveness analysis is not in scope (conventional socket prosthesis, not no prosthesis)
Orgel M, Schwarze F, Graulich T, Krettek C, Weidemann F, Aschoff HH, et al. Comparison of functional outcome and patient satisfaction between patients with socket prosthesis and patients treated with transcutaneous osseointegrated prosthetic systems (TOPS) after transfemoral amputation. Eur. 2022;18:18.	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis
Osseointegrated Prosthetic Implants for Lower Limb Amputation: A Review of Clinical Effectiveness, Cost-Effectiveness and Guidelines. CADTH - Health Technology Review. 2017.	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis
Pospiech PT, Wendlandt R, Aschoff HH, Ziegert S, Schulz AP. Quality of life of persons with transfemoral amputation: Comparison of socket prostheses and osseointegrated prostheses. Prosthet Orthot Int. 2020:309364620948649.	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis
Reetz D, Atallah R, Mohamed J, van de Meent H, Frolke JPM, Leijendekkers R. Safety and Performance of Bone-Anchored Prostheses in Persons with a Transfemoral Amputation: A 5-Year Follow-up Study. J Bone Joint Surg Am. 2020;102(15):1329-35.	Outcomes in this case series are reported in larger case series which are included in this review
Reif TJ, Khabyeh-Hasbani N, Jaime KM, Sheridan GA, Otterburn DM, Rozbruch SR. Early Experience with Femoral and Tibial Bone-Anchored Osseointegration Prostheses. JB JS Open Access. 2021;6(3):Jul-Sep.	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis
Sinclair S, Beck JP, Webster J, Agarwal J, Gillespie B, Stevens P, et al. The First FDA Approved Early Feasibility Study of a Novel Percutaneous Bone	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis

Study reference	Reason for exclusion
Anchored Prosthesis for Transfemoral Amputees: A Prospective One-year Follow-up Cohort Study. Arch Phys Med Rehabil. 2022;28:28.	
Thomson S, Lu W, Zreiqat H, Li JJ, Tetsworth K, Al Muderis M. Proximal Bone Remodeling in Lower Limb Amputees Reconstructed With an Osseointegrated Prosthesis. J Orthop Res. 2019;37(12):2524-30.	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis
Van de Meent H, Hopman MT, Frolke JP. Walking ability and quality of life in subjects with transfemoral amputation: a comparison of osseointegration with socket prostheses. Arch Phys Med Rehabil. 2013;94(11):2174-8.	Outcomes in this case series are reported in larger case series which are included in this review
Van Eck CF, McGough RL. Clinical outcome of osseointegrated prostheses for lower extremity amputations: A systematic review of the literature. Current Orthopaedic Practice. 2015;26(4):349-57.	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis
Wood P, Small C, Mahoney P. Perioperative and early rehabilitation outcomes following osseointegration in UK military amputees. BMJ Mil Health. 2020;166(5):294-301.	Population out of scope - No requirement for patients to be unable to tolerate socket prosthesis
Yan Li RB. Osseointegrated prostheses for rehabilitation following amputation: The pioneering Swedish model. Der Unfallchirurg. 2017;120:285-92.	General non-systematic review

Appendix E Evidence table

For abbreviations see list after table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Al Muderis MA, Tetsworth K, Khemka A, Wilmot S, Bosley B, Lord SJ, et al. The Osseointegration Group of Australia Accelerated Protocol (OGAAP-1) for two-stage osseointegrated reconstruction of amputated limbs. Bone Joint J. 2016;98-B(7):952-60. **Study location** University of Notre Dame, Sydney, Australia **Study type** Prospective case series **Study aim** To describe the Osseointegration Group of Australia Accelerated Protocol-1 (OGAAP-1) protocol and to assess its outcomes in a cohort of 50	**Inclusion criteria** Patients aged over 18 years with unilateral transfemoral amputation (TFA) and socket or prosthesis-fitting problems **Exclusion criteria** Smoking, disabling psychiatric disorder, non-compliant behaviour, pregnancy, previous radiotherapy to the affected residual limb, chemotherapy, immunosuppression, diabetes and peripheral vascular disease **Total sample size** n=50 **No. of participants in each treatment group** n/a	**Interventions** Osseointegrated reconstruction using either the Integral Leg Prosthesis (ILP; Orthodynamic GmbH; Lübeck, Germany) or the Osseointegrated Prosthetic Limb (OPL; Permedica s.p.a; Milan, Italy) Insertion of the press-fit implant involved two surgical stages (surgery 1 & surgery 2[42]), approximately 4 to 8 weeks apart followed by a rehabilitation programme **Comparators** n/a	Mean follow-up = 21.5 months Post-operative results are at a minimum of one-year follow-up after stage one surgery **Critical outcomes** **Functional outcome measures** Timed up and go (TUG)[43] duration, mean seconds (SD) for: Wheelchair bound (n=14) • Pre-operative: Not assessed • Post-operative: 9 (0.56) Prosthetic user (n=36) • Pre-operative: 14.59 (5.94) • Post-operative: 8.74 (2.81) Statistically significant difference, p<0.01 6-minute walk test (6MWT)[44] distance, mean metres (SD) for: Wheelchair bound (n=14) • Pre-operative: Not assessed • Post-operative: 411 (31.44) Prosthetic user (n=36) • Pre-operative: 281 (93) • Post-operative: 419 (133) Statistically significant difference, p<0.001	This study was appraised using the JBI Critical Appraisal Checklist for Case Series 1. YES 2. UNCLEAR 3. UNCLEAR 4. YES 5. YES 6. YES 7. YES 8. YES 9. NO 10. NO **Other comments:** As a case series this study does not include a comparator group. Clear inclusion and exclusion criteria were reported for the participants. However insufficient detail was provided on the criteria for defining

[42] The first stage of surgery involves implantation of the intramedullary part, preparing the soft tissues with refashioning of the stump and excision of excess subcutaneous fat. The second stage of surgery involves creation of the skin opening and insertion of the transcutaneous dual cone adaptor

[43] A valid test for quantifying functional mobility. It measures the time a person takes to rise from a chair, walk 3 metres, walk back, and sit down. The TUG test is interpreted as follows: ≤ 10 seconds = normal; ≤ 20 seconds = good mobility, can go out alone, mobile without a gait aid; < 30 seconds = problems, cannot go outside alone, requires a gait aid

[44] Measures the distance a person can walk in a 6-minute period and has been shown to reliably measure functional capacity in various populations, including amputees

Study details	Population	Interventions	Study outcomes	Appraisal and funding
unilateral trans-femoral amputees. **Study dates** March 2011 to June 2014	**Baseline characteristics** Male, n (%): 34 (68) Mean age, years (range): 48.4 (24 to 73) Amputation side, n (%): Right: 25 (50) Left: 25 (50) Amputation cause, n (%): • Trauma: 32 (64) • Blast injury: 3 (6) • Infection: 5 (10) • Oncology: 8 (16) • Congenital: 2 (4) Time between amputation and surgery, n (%): • < 2 years: 11 (22) • > 2 to 10 years: 12 (24) • > 10 to 20 years: 13 (26) • > 20 to 30 years: 8 (16) • > 30 to 40 years: 3 (6) • > 40 to 65 years: 3 (6)		**Quality of life** Short-form-36 health survey (SF-36)[45] physical component summary, mean points (SD): • Pre-operative (n=46): 37.09 (9.54) • Post-operative (n=49): 47.29 (9.33) Statistically significant difference, p<0.001 Questionnaire for Persons with a Transfemoral Amputation Q-TFA global score[46], mean points (SD): • Pre-operative (n=46): 47.82 (17.28) • Post-operative (n=46): 83.52 (18.04) Statistically significant difference, p<0.001 **Important outcomes** **Mobility**	participants as having problems related to socket suspended prosthesis and therefore it was not possible to determine whether this was assessed in a standard and reliable manner. The study was conducted over a short follow-up period (mean 21.5 months). No patients were lost to follow-up. Valid tools were used to assess functional outcomes, quality of life and mobility. Limited reporting of mobility results with no summary statistic or statistical significance reported. The study reported findings for a single institution, and it is not clear how generalisable these findings are to the NHS. **Source of funding:** Source of funding not reported. The first author declared receiving royalties for design contributions and sales for the implants from Orthodynamic GmbH; Lübeck, Germany) and the Osseointegrated Prosthetic Limb (OPL; Permedica s.p.a; Milan, Italy). In addition, the

[45] The 36-Item Short Form Health Survey (SF-36) is a generic measure of quality of life. The tool has 8 subscales: 4 measure physical health (physical functioning, role functioning‑physical, bodily pain, general health) and 4 measure mental and psychological health (vitality, social functioning, role functioning‑emotional, mental health). The results are also captured in two summary measures: the physical component summary (PCS) and the mental component summary (MCS). In each scale, values run between 0 and 100. A higher score indicates better physical or mental health.

[46] The Questionnaire for Persons with a Transfemoral Amputation (Q-TFA) is a self-report measure developed for nonelderly transfemoral amputees using a socket- or osseointegrated prosthesis to reflect use, mobility problems, and global health, each in a separate score (0-100). Global health is defined as the perception of function and problems with the current prosthesis and the perception of the current overall amputation situation. The score is a summary of three questions to which answers are given on a 5-point Likert scale. A Global score of 100 indicates the best possible overall situation as measured by this instrument.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Wheelchair-bound pre-operatively, n (%): 14 (28): • Direct conversion to osseointegrated implant (n=5) • Short stump and poor socket fit (n=4) • Poor socket fit (n=4) • Socket interface issues (pistoning and skin breakdown, pressure on soft tissues) (n=1) Socket prosthesis users pre-operatively, n (%): 36 (72): • Socket interface issue (n=21) • Socket interface issue (pistoning and skin breakdown, pressure on soft tissues) and poor fit (n=8) • Short stump and poor fit (n=6) • Donning and doffing problems related to upper limb injury (n=1)		Change in Amputation Mobility Predictor Prothesis (AMPPRO)[47] scores presented as K-levels[48] pre- and post-operatively: Improvement: 30 patients • K0 to K2: 2 patients • K0 to K3: 12 patients • K0 to K4: 1 patient • K1 to K3: 1 patient • K2 to K3: 11 patients • K3 to K4: 3 patients Unchanged: 20 patients • K2: 2 patients • K3: 13 patients • K4: 5 patients Reduced: 0 patients **Wheelchair use** All 14 participants who had been wheelchair bound pre-operatively had post-operative K-level scores that were comparable with those of the patients who had been walking pre-operatively (K2 or better). Baseline K-level scores were not reported for this group. It was not reported whether any participants who were walking pre-operatively became wheelchair bound after surgery	paper states that one or more of the authors have received or will receive benefits for personal or professional use from a commercial party related directly or indirectly to the subject of this article.

[47] 21-item performance-based functional test designed specifically for people with lower limb loss to determine functional mobility by evaluating ability in transfers, sitting and standing balance, and gait skills

[48] A 5-level rating system used by the US Medicare health insurance program to indicate the extent of a person's disability and their potential for rehabilitation in individuals with lower-limb amputations. K-levels include: K0 – patient has no ability or potential to ambulate or transfer safely with or without assistance and a prosthesis does not enhance their quality of life or mobility; K1 - patient has the ability or potential to use a prosthesis for transfers or ambulation on level surfaces at fixed cadence - a typical limited or unlimited household ambulator; K2 - patient has the ability or potential for ambulation with the ability to traverse low level environmental barriers such as curbs, stairs, or uneven surfaces - a typical community ambulator; K3 - patient has the ability or potential for ambulation with variable cadence - a typical community ambulator with the ability to traverse most environmental barriers and may have therapeutic or exercise activity that demands prosthetic use beyond simple locomotion; K4 - patient has the ability or potential for prosthetic ambulation that exceeds basic ambulation skills, exhibiting high impact, stress, or energy levels - typical of the prosthetic demands of the child, active adult, or athlete

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Frequency of implant replacement and/or re-fitting Revision of implant: n=2, due to: • failure of osseointegration as a result of an undersized device (n=1) • implant fatigue failure at 3.5 years (n=1) **Adverse events** 27 (54%) patients experienced an adverse event 21 (42%) patients experienced one or more infections • 13 responded to oral antibiotics alone • 5 responded to intravenous antibiotics • 3 required surgical soft tissue debridement of infected soft tissues 4 (8%) patients sustained periprosthetic fractures as a result of falls, three of whom were previously wheelchair bound with severe osteoporosis. All 4 fractures were managed by open reduction and internal fixation with a dynamic hip screw and cables as necessary, without interfering with the osseointegration of the implant. All fractures healed within 3 months. No further details reported. No results for PICO subgroups reported	
Al Muderis M, Khemka A, Lord SJ, Van de Meent H, Frolke JP. Safety of osseointegrated implants	**Inclusion criteria** Individuals with a TFA experiencing socket-related problems or	**Interventions** Australian centre patients: The Osseointegration Group of Australia Accelerated Protocol	Median follow-up, months (range): 34 months (24 to 71) **Wheelchair use**	This study was appraised using the JBI Critical Appraisal Checklist for Case Series

Study details	Population	Interventions	Study outcomes	Appraisal and funding
for transfemoral amputees: a two-center prospective cohort study. J Bone Joint Surg Am. 2016;98(11):900-9. **Study location** 2 centres: Norwest Private Hospital, Sydney, Australia & the Department of Surgery, Radboud University Medical Centre, Nijmegen, the Netherlands **Study type** Prospective case series **Study aim** To report on the safety of press-fit osseointegrated implants currently used in Australia and the Netherlands **Study dates** May 2009 to May 2013	difficulties using a prosthesis (ambulatory with assistive devices or non-ambulatory) **Exclusion criteria** • Limb exposure to radiation • Ongoing chemotherapy • Growing/immature skeleton • Diabetes • Peripheral vascular disease • Mental illness • Inability to comply with rehabilitation protocol and follow-up program **Total sample size** n=86 (91 implants) **No. of participants in each treatment group** n/a **Baseline characteristics** Male, n (%): 65 (76) Mean age at amputation, years (SD): 32 (14) Mean age at implantation, years (SD): 48 (14)	1 (OGAAP-1), 2-stage surgery (surgery 1 & surgery 2) using either the Integral Leg Prosthesis (ILP; Orthdynamics GmbH, Lübeck, Germany) or the Osseointegrated Prosthetic Limb (OPL; Permedica s.p.a, Milan, Italy) followed by a rehabilitation protocol The Netherlands centre patients: osseointegration prosthesis (OIP), 2-step surgery, followed by a rehabilitation programme **Comparators** n/a	25% of the study population was wheelchair-bound before osseointegration, and all of these patients became community ambulators after surgery It was not reported whether any participants who were walking pre-operatively became wheelchair bound after surgery **Frequency of implant replacement and/or re-fitting** 1 (1%) patient had inadequate osseointegration and underwent implant replacement 2 (2%) patients experienced breakage of intramedullary component at 42 and 47 months after surgery, leading to implant replacement 25 (29%) patients experienced breakage of pin used for safety in dual-cone (extramedullary) component on a total of 30 occasions **Adverse events** Patients experiencing one or more infections, n (%): 29 (34) • Grade 1A[49] infection: 23 (27) • Grade 1B: 1 (1); severe cellulitis and intense pain treated with parenteral antibiotics • Grade 1C: 1 (1); severe cellulitis and intense pain treated with parenteral antibiotics followed by local debridement	1. YES 2. UNCLEAR 3. UNCLEAR 4. YES 5. YES 6. YES 7. YES 8. YES 9. NO 10. YES **Other comments:** As a case series this study does not include a comparator group. Clear inclusion and exclusion criteria were reported for the participants. However insufficient detail was provided on the criteria for defining participants as having problems related to socket suspended prosthesis and therefore it was not possible to determine whether this was assessed in a standard and reliable manner. The recruitment period and the centres included in this study overlap with Al Muderis et al 2016a (patients recruited in 2011 to 2014 from the same centre Australia) and Mohamed et al 2022 (patients recruited in 2009

[49] Grade 1 - Low-grade soft-tissue infection cellulitis with signs of inflammation (redness, swelling, warmth, stinging pain, pain that increases on loading, tense) treated with oral antibiotics (Grade 1A), parenteral antibiotics (Grade 1B) or surgical intervention (Grade 1C).

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Mean interval between amputation and implantation, years (SD): 16 (14) Smoker: 6 (7%) Mean BMI, kg/m^2 (SD): 26 (4) Amputation side, n (%): Left: 47 (55) Right: 29 (33) Bilateral: 5 (6) Amputation cause, n (%): • Trauma: 65 (76) • Tumour: 11 (13) 6 • Infection: 8 (9) • Congenital: 1 (1) • Other 1 (1) Mean length of residuum, cm (SD): 26 (7) Patients having problems with the socket-skin interface while walking, n (%): 65 (76) Patients wheelchair bound, n (%): 21 (24)		• Grade 2C[50]: 4 (5); high-grade soft-tissue infection with abscess formation that needed surgical debridement • No patient developed a serious (grade 3[51] or 4[52]) infection Other adverse events, n (%): • Stoma hypergranulation 17 (20); 22 events • Redundant soft tissue: 14 (16); 23 events • Proximal femoral fracture: 3 (3); 3 events; all underwent surgical stabilisation of the fracture without the need of implant removal No results for PICO subgroups reported	to 2015 from the same centre in the Netherlands). No patients were lost to follow-up. The study reported findings for two institutions, and it is not clear how generalisable these findings are to the NHS. **Source of funding:** No external funding was received for this study. The first author declared that he has current financial consultant agreements with Orthodynamics (the manufacturer of the prosthesis that is the subject of this study), Endo-Exo Pty Ltd. and Permedica.

[50] High-grade soft-tissue infection with pus collection, purulent discharge, raised level of C-reactive protein treated with oral antibiotics (Grade 2A), parenteral antibiotics (Grade 2B) or surgical intervention (Grade 2C).
[51] Bone infection with radiographic evidence of osteitis (periosteal bone reaction), radiographic evidence of osteomyelitis (sequestrum and involucrum)
[52] Implant failure with radiographic evidence of loosening

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Hagberg K, Ghassemi Jahani SA, Kulbacka-Ortiz K, Thomsen P, Malchau H, Reinholdt C. A 15-year follow-up of transfemoral amputees with bone-anchored transcutaneous prostheses. Bone Joint J. 2020;102-B(1):55-63. **Study location** Sahlgrenska University Hospital, Gothenburg, Sweden **Study type** Prospective case series **Study aim** To describe implant and patient-reported outcome in patients with a unilateral TFA treated with a bone-anchored, transcutaneous prosthesis. **Study dates** January 1999 to December 2017	**Inclusion criteria** Patients with a unilateral TFA experiencing problems related to a socket suspended prosthesis and having mature and sufficient residual skeleton dimensions **Exclusion criteria** Patients with TFA due to severe peripheral vascular disease (including diabetes mellitus) or having other concurrent diseases or using drugs (e.g. chemotherapy) that could negatively affect the treatment **Total sample size** n=111 **No. of participants in each treatment group** n/a **Baseline characteristics** Male, n (%): 78 (70)	**Interventions** OPRA implant system Surgery in two stages (surgery 1 & surgery 2) about 6 months apart, followed by a rehabilitation protocol **Comparators** n/a	**Critical outcomes** **Quality of life** Q-TFA global score (0 to 100) at 7 years (n=55) • Mean (SD; range): 74 (20.6; 17 to 100) • Median (IQR): 75 (58 to 92) Q-TFA problem score[53] (100 to 0) at 7 years (n=54) • Mean (SD; range): 17 (10.8; 0 to 44) • Median (IQR): 16 (8 to 25) Change in Q-TFA global score and Q-TFA problem score from baseline at 2, 5, 7, 10 and 15 years were presented as boxplots and therefore results could not be extracted Response to the single Q-TFA question on the patient's overall situation as an amputee[54], n (%): • At baseline (n=107): 23 (21) very poor; 29 (27) poor; 34 (32) average; 16 (15) good; 5 (5) very good • At 2 years (n=83): 0 (0) very poor; 7 (8) poor; 14 (17) average; 38 (46) good; 24 (29) very good • At 5 years (n=62): 0 (0) very poor; 2 (3) poor; 14 (23) average; 25 (40) good; 21 (34) very good	This study was appraised using the JBI Critical Appraisal Checklist for Case Series 1. YES 2. UNCLEAR 3. UNCLEAR 4. YES 5. NO 6. YES 7. YES 8. NO 9. NO 10. YES **Other comments:** As a case series this study does not include a comparator group. Clear inclusion and exclusion criteria were reported for the participants. However insufficient detail was provided on the criteria for defining participants as having problems related to socket suspended prosthesis and therefore it was not possible to determine whether this was assessed in a standard and reliable manner.

[53] The Questionnaire for Persons with a Transfemoral Amputation (Q-TFA) is a self-report measure developed for nonelderly transfemoral amputees using a socket- or osseointegrated prosthesis to reflect use, mobility, problems, and global health, each in a separate score (0-100). Problems are defined as the extent of specific problems related to the amputation and the prosthesis and their impact on the quality of life. A higher score indicates more serious problems.
[54] This is the third question of the Global health subdomain of the Q-TFA "How would you summarise your overall situation as an amputee?" Responses include Very poor (0) Poor (1) Average (2) Good (3) Very good (4).

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Mean age, years (SD; range): • At amputation: 33.8 (14.6; 11.0 to 69.0) • At surgery 1: 44.6 (12.6; 17.0 to 70.0) Amputation side, n (%): Right: 59 (53) Left: 52 (47) Amputation cause, n (%): • Trauma: 75 (68) • Tumour: 23 (21) • Emboli: 3 (3) • Infection: 10 (9) Mean BMI, kg/m^2 (SD; range): 25.8 (4.3; 15.6 to 38.0) Mean time between amputation and surgery, years (SD; range): 11.1 (10.8; 0.0 to 43.0) Mean residual limb length after surgery 2, cm (SD, range): 21.3 (5.7, 8.3 to 34.9) Smoker at surgery 1, n (%): 18 (16) Smoker at latest follow-up, n (%): 9 (8)		• At 7 years (n=54): 0 (0) very poor; 1 (2) poor; 12 (22) average; 20 (37) good; 21 (39) very good • At 10 years (n=30): 1 (3) very poor; 4 (13) poor; 4 (13) average; 10 (33) good; 11 (37) very good • At 15 years (n=11): 1 (9) very poor; 0 (0) poor; 4 (36) average; 3 (27) good; 3 (27) very good Change in response to the single Q-TFA question on the patient's overall situation as an amputee compared with baseline, n (%): • At 2 years (n=81): 62 (77) better score; 14 (17) equal score; 5 (6) worse score; p<0.001 • At 5 years (n=60): 47 (78) better score; 10 (17) equal score; 3 (5) worse score; p<0.001 • At 7 years (n=52): 40 (77) better score; 11 (21) equal score; 1 (2) worse score; p<0.001 • At 10 years (n=29): 21 (72) better score; 6 (21) equal score; 2 (7%) worse score; p<0.001 • At 15 years (n=11): 7 (64) better score; 3 (27) equal score; 1 (9) worse score; p not reported **Important outcomes** **Mobility** Q-TFA mobility score[55] (0 to 100) at 7 years (n=54)	The recruitment period of this study (1999 to 2017) overlaps with the recruitment period of Tillander et al 2017 (1990 to 2010) which was also conducted in Sweden. Therefore, it is likely that that some of the same patients will be included in both studies. The study was conducted over a long follow-up period, 18 years reporting on 2, 5, 7, 10 and 15 year timepoints. However, as patients were enrolled at different timepoints during the study, the sample size reduces from 111 at baseline to 14 patients at 15 years. Furthermore, patients were excluded from the study due to death (n=3), lost to follow-up (n=6) and implant failures (n=18). The reasons for excluding patients with implant failures were not explained and it is likely that this exclusion will introduce bias as these patients are likely to have worse outcomes. A valid tool was used to assess quality of life and mobility. Some results were only reported graphically, and it was therefore not possible to extract this data. The study reported findings for a single institution over a 18 year period

[55] The Questionnaire for Persons with a Transfemoral Amputation (Q-TFA) is a self-report measure developed for nonelderly transfemoral amputees using a socket- or osseointegrated prosthesis to reflect use, mobility, problems, and global health, each in a separate score (0-100). Prosthetic mobility is defined as the ability and performance of the amputee to move and change and maintain postures when using the prosthesis. The score consists of three sub scores, each with a range from 0 to 100: capability (12 items), use of walking aids (2 items), and walking habits (5 items). The average of these three sub scores generates the total mobility score. A higher score indicates better mobility.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			• Mean (SD; range): 67 (17.8; 22 to 95) • Median (IQR): 71 (58 to 79) Prosthetic activity grade[56], n (%): • At baseline (n=110): 26 (24) no prosthesis; 27 (25) low grade; 39 (35) average grade; 9 (8) high grade; 9 (8) very high grade • At 2 years (n=86): 1 (1) no prosthesis; 13 (15) low grade; 30 (35) average grade; 24 (28) high grade; 18 (21) very high grade • At 5 years (n=63): 2 (3) no prosthesis; 4 (6) low grade; 25 (40) average grade; 16 (25) high grade; 16 (25) very high grade • At 7 years (n=55): 0 (0) no prosthesis; 8 (11) low grade; 18 (33) average grade; 17 (31) high grade; 14 (25) very high grade • At 10 years (n=32): 3 (9) no prosthesis; 3 (9) low grade; 8 (25) average grade; 14 (44) high grade; 4 (13) very high grade • At 15 years (n=11): 0 (0) no prosthesis; 1 (9) low grade; 1 (9) average grade; 4 (36) high grade; 5 (45) very high grade Change in prosthetic activity grade compared with baseline, n (%): • At 2 years (n=85): 50 (59) better score; 32 (38) equal score; 3 (4) worse score; p< 0.001	and it is not clear how generalisable these findings are to the NHS. **Source of funding:** None. The paper states that no benefits in any form were received or will be received from a commercial party related directly or indirectly to the subject of this article. Two authors declared a conflict of interest.

[56] The activity grade was assigned to each patient at each follow-up by the physiotherapist in the treating team. Activity is graded between 0 and 4 and combines the extent of prosthetic use, use of walking aids, outdoor walking habits, and other activities using the prosthesis, and is captured from Q-TFA items and medical records. 0 = Do not use prosthesis; no prosthetic activity; 1 (Low) = Limited use of prosthesis for standing/walking, use walking aid, no long walks; 2 (Average) = Use prosthesis most of the day, with or without walking aid at home, use walking aid outdoors; 3 (High) = Uses prosthesis for a full day, no walking aid except for longer distances, walks a lot, rarely performs other demanding or high-load activities in use of prosthesis; 4 (Very High) = Uses prosthesis for a full day, no walking aid, walks a lot and/or routinely performs other highly demanding or high-load activities involving the prosthesis (e.g. cycling, gym training).

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			• At 5 years (n=62): 42 (68) better score; 19 (31) equal score; 1 (2) worse score; p<0.001 • At 7 years (n=54): 36 (67) better score; 17 (31) equal score; 1 (2) worse score; p<0.001 • At 10 years (n=32): 22 (69) better score; 6 (19) equal score; 4 (13) worse score; p<0.001 • At 15 years (n=11): 5 (45) better score; 6 (55) equal score; p not reported **Frequency of implant replacement and/or re-fitting** (n=111) Follow-up = up to 15 years Implant revisions, n (%): 18 (16); 7 (6) due to infection, 6 (5) due to aseptic loosening and 5 (5) due to fractures Revision-free survival of the fixture: • At 2 years (n=90): 92% (95% confidence interval (CI) 85% to 96%) • At 7 years (n=55): 89% (95% CI 80% to 94%) • At 15 years (n=14): 72% (95% CI 57% to 83%) Follow-up = up to 15 years Number of mechanical complications resulting in a change of abutment and/or abutment screw: Mean (SD; range): 3.3 (5.76; 0 to 26) Median (IQR): 1 (0 to 3) 0 complications, n (%): 50 (45.0%) 1 complication, n (%): 15 (13.5%) 2 to 5 complications, n (%): 25 (22.5)	

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			6 to 10 complications, n (%): 10 (9.0%) >10 complications, n (%): 11 (10.0%) At least one complication n (%): 61 (55) Survival of the fixture until the first event necessitating a change of the abutment and/or abutment screw: • At 2 years (n=90): 81% (95% CI 71% to 88%) • At 7 years (n=55): 32% (95% CI 22% to 43%) • At 15 years (n=14): 14% (95% CI 6% to 26%) No results for PICO subgroups reported	
Mohamed J, Reetz D, van de Meent H, Schreuder H, Frolke JP, Leijendekkers R. What are the risk factors for mechanical failure and loosening of a transfemoral osseointegrated implant system in patients with a lower-limb amputation? Clin Orthop. 2022;480(4):722-31. **Study location** Radboud University Medical Center, Nijmegen, the Netherlands **Study type**	**Inclusion criteria** Patients with a knee disarticulation or TFA who completed rehabilitation with their socket prosthesis and suffered from socket-related problems and were suitable for standard osseointegrated implant surgery. The selection procedure included an assessment of the prosthesis use, mobility, prosthetic problems, and health-related quality of life (as demonstrated with a Q-	**Interventions** Press-fit standard CoCrMb transfemoral osseointegrated implant. performed as a 2-stage procedure, with a period of 6 to 8 weeks in between, and followed by a rehabilitation programme **Comparators** n/a	Minimum of 5 years of follow-up **Important outcomes** **Frequency of implant replacement and/or re-fitting** Cumulative implant survival probability after 9 years (n=58)[57]: 78% (95%CI 58% to 89%) Median implant survival time (n=58), years (IQR): 6 (4) Patients undergoing revision surgery, n (%): 20 (34) of patients • Failed intramedullary stem, n (%): 7 (12) due to breakages (n=6) and septic loosening (=1) • Broken dual-cone adapter, n (%): 13 (22) due to weak-point	This study was appraised using the JBI Critical Appraisal Checklist for Case Series 1. YES 2. UNCLEAR 3. UNCLEAR 4. YES 5. YES 6. YES 7. YES 8. YES 9. NO

[57] The survival rate was calculated by using a Kaplan-Meier analysis with time until osseointegrated implant breakage and septic loosening as the endpoints. No further details reported

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Retrospective case series **Study aim** To identify (1) the proportion of patients who received an osseointegrated implant after transfemoral amputation who underwent revision surgery, and the causes of those revisions (2) factors associated with revision surgery when stratified by the location of the mechanical failure and (septic) loosening (intramedullary stem versus dual cone adapter) **Study dates** May 2009 and July 2015	TFA) and radiographic assessment. **Exclusion criteria** None reported **Total sample size** n=58 (59 implants) **No. of participants in each treatment group** n/a **Baseline characteristics** Male, n (%): 71% (41) Mean age at implantation, years (SD): 51 (13) Level of amputation, n (%): • Knee disarticulation: 5 (9) • Transfemoral: 53 (91) Cause of amputation, n (%): • Trauma: 37 (64) • Oncology: 9 (16) • Vascular: 3 (5) • Infection: 7 (12) • Unknown: 2 (3) Median time between amputation and implantation, years (IQR): 11 (24)		breakages (n=9), broken distal taper of the dual cone (n=3), broken the weak-point and the distal taper (n=1) Time to revision surgery for patients with failed intramedullary stems, months (n=7): 7 to 11 after failure Time to revision surgery not reported for patients with broken dual-cone adapter No results for PICO subgroups reported	10. YES **Other comments:** As a case series this study does not include a comparator group. Clear inclusion criteria were reported for the participants. However insufficient detail was provided on the criteria for defining participants as having problems related to socket suspended prosthesis and therefore it was not possible to determine whether this was assessed in a standard and reliable manner. Patients were retrospectively followed up for a minimum of 5 years but the mean time of follow up was not reported. The study reported findings of a single institution and it is not clear how generalisable these findings are to the NHS. **Source of funding:** One of the authors certified receipt of personal payments or benefits, during the study period, in an amount of USD 10,000 to USD 100,000 from OTN Implants.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Mean BMI, kg/m^2: 26.5 (3.8)			
Tillander J, Hagberg K, Berlin O, Hagberg L, Branemark R. Osteomyelitis risk in patients with transfemoral amputations treated with osseointegration prostheses. Clin Orthop. 2017;475(12):3100-8. **Study location** Gothenburg, Sweden (centre not reported) **Study type** Retrospective case series **Study aim** (1) To quantify the risk of osteomyelitis, (2) to characterize the clinical effect of osteomyelitis (including risk of implant extraction and impairments to function), and (3) to determine whether common patient factors (age, sex, body weight, diabetes, and implant component replacements) are associated with osteomyelitis in patients with transfemoral amputations	**Inclusion criteria** Patients with TFAs experiencing difficulty to use (socket complications) or be fitted with (stump malformation) a socket prosthesis, and found to be suitable for implant surgery in team evaluation **Exclusion criteria** None reported **Total sample size** n=96 (102 implants) **No. of participants in each treatment group** n/a **Baseline characteristics** Male, n (%): 60 (63) Mean age, years (range): 43.5 (19 to 65) Number of implants (bilateral implants): 102 (6)	**Interventions** Osseointegrated Prostheses for the Rehabilitation of Amputees (OPRA) for majority of patients (72%). 27 (28%) had their implants before the start of the OPRA protocol (no further details reported) **Comparators** n/a	Mean follow-up: 7.9 years (median, 6.2 years; range, 1.5 to 19.6 years) **Important outcomes** **Frequency of implant replacement and/or re-fitting** Implants extracted due to osteomyelitis[59], n (%): 10 (10) 10-year cumulative risk of implant extraction due to osteomyelitis[60]: 9% (95% CI 4 to 20) **Adverse events** Osteomyelitis Patients developing osteomyelitis, n (%): 16 (17) (12 definitive, 3 probable, 1 possible) Clinical presentation of osteomyelitis: • Subacute or acute (n=8), • Chronic with or without fistulas (n=8) 10-year cumulative risk of implant-associated osteomyelitis[61] 20% (95% CI 12 to 33) Median time from implantation to osteomyelitis, years (range): 2.6 (0.3 to 13.8)	This study was appraised using the JBI Critical Appraisal Checklist for Case Series 1. YES 2. UNCLEAR 3. UNCLEAR 4. YES 5. YES 6. YES 7. YES 8. YES 9. NO 10. YES **Other comments:** As a case series this study does not include a comparator group. Clear inclusion criteria were reported for the participants. However, insufficient detail was provided on the criteria used to assess suitability of patients for an implant, with approximately one-third of the patients reported to be found suitable

[59] Indication for extraction was infection not responsive to conservative treatment or loosening evident in stability testing of the implant
[60] The Kaplan-Meier estimator was used to calculate the risk of osteomyelitis and extraction with time. No further details provided

.
[61] Evidence of infection involving implant-surrounding bone and/or bone marrow, supported by positive percutaneous bone biopsy or aspirated bone marrow cultures, and classified as definite, probable, or possible

Study details	Population	Interventions	Study outcomes	Appraisal and funding
treated with osseointegrated titanium implants **Study dates** May 1990 to January 2010	Reasons for amputation, n (%): • Tumour: 20 (21) • Trauma: 71 (74) • Ischemia: 5 (5) • Infection: 5 (5) • Other: 1 (1) Mean time since amputation, years (range): 11.5 (<1 to 44) Mean BMI, kg/m^2 (range): 26 (16 to 43) Smokers: 22 (23) Patients with diabetes (insulin dependent): 6 (6) (3 (3)) Residual limb lengths[58], n (%): • Short: 34 (35) • Normal: 60 (63) • Long: 8 (8)		Prosthetic use[62] at the time of diagnosis of osteomyelitis: • Unable to use prostheses (n=2) • Moderately restricted prosthetic use (n=6) • No impairment (n=2) • Not assessed as patient in the early rehabilitation phase (n=6) Clinical outcome for patients with osteomyelitis, n: • Recovery[63] after antibiotics with or without minor debridement (n=4) • Recovery and later relapse (n=1) • Successful re-implantation (n=1) • Recovery after extraction (n=9) • Chronic with fistula (n=1) No results for PICO subgroups reported	for implant surgery, and therefore it was not possible to determine whether this was assessed in a standard and reliable manner. Furthermore, insufficient detail was provided on the criteria for defining participants as having problems related to socket suspended prosthesis and therefore it was not possible to determine whether this was assessed in a standard and reliable manner The recruitment period of this study (1990 to 2010) overlaps with the recruitment period of Hagberg et al 2020 (1999 to 2017) which was also conducted in Sweden. Therefore, it is likely that that some of the same patients will be included in both studies. 28% of the study population had their implants before the start of the OPRA protocol and no further details were reported on the protocol followed for these patients. The study followed patients up retrospectively over a long period of time (10 years). For the implant survival analyses, 8 patients were right censored for reasons other than study completion (5 for non-infected implant extractions, 1 lost to follow-up; 1 with a retained fixture and sealed

[58] No cut-offs provided for short, normal and long residual limb lengths
[62] Prosthetic use at the time of osteomyelitis was retrospectively assessed by a team physiotherapist and assigned a simple 1 to 3 score (unchanged = 1, impaired = 2, and no prosthetic use owing to infection = 3)
[63] Infections were considered resolved if patients were symptom-free 12 months or more after discontinuation of antibiotics

Study details	Population	Interventions	Study outcomes	Appraisal and funding
				skin; and 1 death not related to the implant). The study reported findings for a single institution, and it is not clear how generalisable these findings are to the NHS. **Source of funding:** The study was supported by government research grants. One author was reported to be a co-owner of Integrum AB which supplied implant components used in the study

Abbreviations

6MWT: 6-Minute Walk Test; AMPPRO: Amputation Mobility Predictor Prothesis; CI: Confidence Interval; IQR: Interquartile Range; ILP: Integral Leg Prosthesis; OGAAP: Osseointegration Group of Australia Accelerated Protocol; OIP: Osseointegration Prosthesis; OPL: Osseointegration Prosthetic Limb; OPRA: Osseointegrated Prostheses for the Rehabilitation of Amputees; Q-TFA: Questionnaire for Persons with a Transfemoral Amputation; SD: Standard Deviation; SF-36: 36-Item Short Form Health Survey; TUG: Timed Up and Go Test; TFA: Transfemoral Amputation

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for Case Series

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series
3. Were valid methods used for the identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
10. Was statistical analysis appropriate?

Appendix G GRADE profiles

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**DSF**	**Comparator**	**Result**		
Functional outcome measures									
Timed up and go (TUG) duration (seconds, mean (SD)) at a mean follow-up of 21.5 months (benefit indicated by lower score)									
1 case series Al Muderis et al 2016a	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	50	None	In wheelchair bound patients (n=14): Pre-operative: Not assessed Post-operative: 9 (0.56) In prosthetic users (n=36): Pre-operative: 14.59 (5.94) Post-operative: 8.74 (2.81) Statistically significant difference, p<0.01	Critical	Very low
6-minute walk test (6MWT) distance (metres, mean (SD)) at a mean follow-up of 21.5 months (benefit indicated by higher score)									
1 case series Al Muderis et al 2016a	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	50	None	In wheelchair bound patients (n=14): Pre-operative: Not assessed Post-operative: 411 (31.44) In prosthetic users (n=36): Pre-operative: 281 (93) Post-operative: 419 (133) Statistically significant difference, p<0.001	Critical	Very low
Quality of life									
Short-form-36 health survey (SF-36) physical component summary (mean (SD)) at a mean follow-up of 21.5 months (benefit indicated by higher score)									
1 case series Al Muderis et al 2016a	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	BL: 46 F/up: 49	None	Pre-operative: 37.09 (9.54) Post-operative: 47.29 (9.33) Statistically significant difference, p<0.001	Critical	Very low

Q-TFA global score (mean (SD)) at a mean follow-up of 21.5 months (benefit indicated by higher score)									
1 case series Al Muderis et al 2016a	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	BL: 46 F/up: 46	None	Pre-operative: 47.82 (17.28) Post-operative: 83.52 (18.04) Statistically significant difference, p<0.001	Critical	Very low
Q-TFA global score (mean (SD; range) or median (IQR)) at 7 years (benefit indicated by higher score)									
1 case series Hagberg et al 2020	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	55	None	Mean (SD; range): 74 (20.6; 17 to 100) Median (IQR): 75 (58 to 92)	Critical	Very low
Q-TFA problem score (mean (SD; range) or median (IQR)) at 7 years (benefit indicated by lower score)									
1 case series Hagberg et al 2020	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	54	None	Mean (SD; range): 17 (10.8; 0 to 44) Median (IQR): 16 (8 to 25)	Critical	Very low
Response to the single Q-TFA question on the patient's overall situation as an amputee (n (%)) at 2 years									
1 case series Hagberg et al 2020	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	BL: 107 F/up: 83	None	BL: 23 (21) very poor; 29 (27) poor; 34 (32) average; 16 (15) good; 5 (5) very good F/up: 0 (0) very poor; 7 (8) poor; 14 (17) average; 38 (46) good; 24 (29) very good	Critical	Very low
Response to the single Q-TFA question on the patient's overall situation as an amputee (n (%)) at 5 years									
1 case series Hagberg et al 2020	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	BL: 107 F/up: 62	None	BL: 23 (21) very poor; 29 (27) poor; 34 (32) average; 16 (15) good; 5 (5) very good F/up: 0 (0) very poor; 2 (3) poor; 14 (23) average; 25 (40) good; 21 (34) very good	Critical	Very low
Response to the single Q-TFA question on the patient's overall situation as an amputee (n (%)) at 7 years									
1 case series Hagberg et al 2020	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	BL: 107 F/up: 54	None	BL: 23 (21) very poor; 29 (27) poor; 34 (32) average; 16 (15) good; 5 (5) very good F/up: 0 (0) very poor; 1 (2) poor; 12 (22) average; 20 (37) good; 21 (39) very good	Critical	Very low

Response to the single Q-TFA question on the patient's overall situation as an amputee (n (%)) at 10 years									
1 case series Hagberg et al 2020	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	BL: 107 F/up: 30	None	BL: 23 (21) very poor; 29 (27) poor; 34 (32) average; 16 (15) good; 5 (5) very good F/up: 1 (3) very poor; 4 (13) poor; 4 (13) average; 10 (33) good; 11 (37) very good	Critical	Very low
Response to the single Q-TFA question on the patient's overall situation as an amputee (n (%)) at 15 years									
1 case series Hagberg et al 2020	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	BL: 107 F/up: 11	None	BL: 23 (21) very poor; 29 (27) poor; 34 (32) average; 16 (15) good; 5 (5) very good F/up: 1 (9) very poor; 0 (0) poor; 4 (36) average; 3 (27) good; 3 (27) very good	Critical	Very low
Change in response to the single Q-TFA question on the patient's overall situation as an amputee compared with baseline (n (%)) at 2 years									
1 case series Hagberg et al 2020	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	BL: 107 F/up: 81	None	62 (77) better score; 14 (17) equal score; 5 (6) worse score; p< 0.001	Critical	Very low
Change in response to the single Q-TFA question on the patient's overall situation as an amputee compared with baseline (n (%)) at 5 years									
1 case series Hagberg et al 2020	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	BL: 107 F/up: 60	None	47 (78) better score; 10 (17) equal score; 3 (5) worse score; p<0.001	Critical	Very low
Change in response to the single Q-TFA question on the patient's overall situation as an amputee compared with baseline (n (%)) at 7 years									
1 case series Hagberg et al 2020	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	BL: 107 F/up: 52	None	40 (77) better score; 11 (21) equal score; 1 (2) worse score; p<0.001	Critical	Very low
Change in response to the single Q-TFA question on the patient's overall situation as an amputee compared with baseline (n (%)) at 10 years									
1 case series Hagberg et al 2020	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	BL: 107 F/up: 29	None	21 (72) better score; 6 (21) equal score; 2 (7%) worse score; p<0.001	Critical	Very low

Change in response to the single Q-TFA question on the patient's overall situation as an amputee compared with baseline (n (%)) at 15 years									
1 case series Hagberg et al 2020	Very serious limitations[4]	Serious limitations[2]	Not applicable	Not calculable	BL: 107 F/up: 11	None	7 (64) better score; 3 (27) equal score; 1 (9) worse score; p not reported	Critical	Very low
Mobility									
Change in amputation mobility predictor prothesis (AMPPRO) score (number of patients at each K-level) at a mean follow-up of 21.5 months (benefit indicated by a higher K-level score)									
1 case series Al Muderis et al 2016a	Very serious limitations[5]	Serious limitations[2]	Not applicable	Not calculable	50	None	Improvement: 30 patients • K0 to K2: 2 patients • K0 to K3: 12 patients • K0 to K4: 1 patient • K1 to K3: 1 patient • K2 to K3: 11 patients • K3 to K4: 3 patients Unchanged: 20 patients • K2: 2 patients • K3: 13 patients • K4: 5 patients Reduced: 0 patients	Important	Very low
Q-TFA mobility score (mean (SD; range) or median (IQR)) at 7 years (benefit indicated by higher score)									
1 case series Hagberg et al 2020	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	54	None	Mean (SD; range): 67 (17.8; 22 to 95) Median (IQR):71 (58 to 79)	Important	Very low
Prosthetic activity grade (n (%)) at 2 years (benefit indicated by a higher grade)									
1 case series Hagberg et al 2020	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	BL: 110 F/up: 86	None	BL: 26 (24) no prosthesis; 27 (25) low grade; 39 (35) average grade; 9 (8) high grade; 9 (8) very high grade F/up: 1 (1) no prosthesis; 13 (15) low grade; 30 (35) average grade; 24 (28) high grade; 18 (21) very high grade	Important	Very low
Prosthetic activity grade (n (%)) at 5 years (benefit indicated by a higher grade)									
1 case series	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	BL: 110 F/up: 63	None	BL: 26 (24) no prosthesis; 27 (25) low grade; 39 (35) average grade;	Important	Very low

Hagberg et al 2020							9 (8) high grade; 9 (8) very high grade F/up: 2 (3) no prosthesis; 4 (6) low grade; 25 (40) average grade; 16 (25) high grade; 16 (25) very high grade		
Prosthetic activity grade (n (%)) at 7 years (benefit indicated by a higher grade)									
1 case series Hagberg et al 2020	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	BL: 110 F/up: 55	None	BL: 26 (24) no prosthesis; 27 (25) low grade; 39 (35) average grade; 9 (8) high grade; 9 (8) very high grade F/up: 0 (0) no prosthesis; 8 (11) low grade; 18 (33) average grade; 17 (31) high grade; 14 (25) very high grade	Important	Very low
Prosthetic activity grade (n (%)) at 10 years (benefit indicated by a higher grade)									
1 case series Hagberg et al 2020	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	BL: 110 F/up: 32	None	BL: 26 (24) no prosthesis; 27 (25) low grade; 39 (35) average grade; 9 (8) high grade; 9 (8) very high grade F/up: 3 (9) no prosthesis; 3 (9) low grade; 8 (25) average grade; 14 (44) high grade; 4 (13) very high grade	Important	Very low
Prosthetic activity grade (n (%)) at 15 years (benefit indicated by a higher grade)									
1 case series Hagberg et al 2020	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	BL: 110 F/up: 11	None	BL: 26 (24) no prosthesis; 27 (25) low grade; 39 (35) average grade; 9 (8) high grade; 9 (8) very high grade F/up: 0 (0) no prosthesis; 1 (9) low grade; 1 (9) average grade; 4 (36) high grade; 5 (45) very high grade	Important	Very low
Change in prosthetic activity grade compared with baseline (n (%)) at 2 years									
1 case series Hagberg et al 2020	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	BL: 110 F/up: 85	None	50 (59) better score; 32 (38) equal score; 3 (4) worse score; p< 0.001	Important	Very low

Change in prosthetic activity grade compared with baseline (n (%)) at 5 years									
1 case series Hagberg et al 2020	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	BL: 110 F/up: 62	None	42 (68) better score; 19 (31) equal score; 1 (2) worse score; p<0.001	Important	Very low
Change in prosthetic activity grade compared with baseline (n (%)) at 7 years									
1 case series Hagberg et al 2020	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	BL: 110 F/up: 54	None	36 (67) better score; 17 (31) equal score; 1 (2) worse score; p<0.001	Important	Very low
Change in prosthetic activity grade compared with baseline (n (%)) at 10 years									
1 case series Hagberg et al 2020	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	BL: 110 F/up: 32	None	22 (69) better score; 6 (19) equal score; 4 (13) worse score; p<0.001	Important	Very low
Change in prosthetic activity grade compared with baseline (n (%)) at 15 years									
1 case series Hagberg et al 2020	Very serious limitations[3]	Serious limitations[2]	Not applicable	Not calculable	BL: 110 F/up: 11	None	5 (45) better score; 6 (55) equal score; p not reported	Important	Very low
Wheelchair use									
Wheelchair bound (n) at a mean follow-up of 21.5 months									
1 case series Al Muderis et al 2016a	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	BL: 14 F/up: 14	None	All 14 participants that were wheelchair bound pre-operatively had post-operative K-level scores that were comparable with those of the patients who had been walking pre-operatively (K2 or better)	Important	Very low
Wheelchair bound (%) at a median follow-up of 34 months									
1 case series Al Muderis et al 2016b	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	86	None	25% of the study population was wheelchair-bound before osseointegration, and all of these patients became community ambulators after surgery[64]	Important	Very low

[64] It was not reported whether any participants who were walking pre-operatively became wheelchair bound after surgery

Frequency of implant replacement and/or re-fitting									
Revision of implant (n) at a mean follow-up of 21.5 months									
1 case series Al Muderis et al 2016a	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	50	None	2	Important	Very low
Patient having an inadequate osseointegration and undergoing implant replacement (n (%)) at a median follow-up of 34 months									
1 case series Al Muderis et al 2016b	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	86	None	1 (1)	Important	Very low
Patients experiencing breakage of intramedullary component leading to implant replacement (n (%)) at a median follow-up of 34 months									
1 case series Al Muderis et al 2016b	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	86	None	2 (2)	Important	Very low
Patients experienced breakage of pin used for safety in dual-cone (extramedullary) component (n (%)) at a median follow-up of 34 months									
1 case series Al Muderis et al 2016b	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	86	None	25 (29)	Important	Very low
Implant revisions (n (%)) at 15 years									
1 case series Hagberg et al 2020	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	111	None	18 (16)	Important	Very low
Implant revisions due to infection (n (%)) at 15 years									
1 case series Hagberg et al 2020	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	111	None	7 (6)	Important	Very low

Implant revisions due to aseptic loosening (n (%)) at 15 years									
1 case series Hagberg et al 2020	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	111	None	6 (5)	Important	Very low
Implant revisions due to fractures (n (%)) at 15 years									
1 case series Hagberg et al 2020	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	111	None	5 (5)	Important	Very low
Revision-free survival of the fixture (%) at 2 years									
1 case series Hagberg et al 2020	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	90	None	92 (95% confidence interval (CI) 85 to 96)	Important	Very low
Revision-free survival of the fixture at 7 years									
1 case series Hagberg et al 2020	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	55	None	89% (95% CI 80 to 94)	Important	Very low
Revision-free survival of the fixture (%) at 15 years									
1 case series Hagberg et al 2020	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	14	None	72 (95% CI 57 to 83)	Important	Very low
At least one mechanical complication resulting in change of the abutment and/or abutment screw (n (%)) at 15 years									
1 case series Hagberg et al 2020	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	111	None	61 (55)	Important	Very low
Survival of the fixture until the first event necessitating the change of the abutment and/or abutment screw (%) at 2 years									
1 case series Hagberg et al 2020	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	111	None	81 (95% CI 71 to 88)	Important	Very low

Survival of the fixture until the first event necessitating the change of the abutment and/or abutment screw (%) at 7 years									
1 case series Hagberg et al 2020	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	111	None	32 (95% CI 22 to 43)	Important	Very low
Survival of the fixture until the first event necessitating the change of the abutment and/or abutment screw (%) at 15 years									
1 case series Hagberg et al 2020	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	111	None	14 (95% CI 0.06 to 0.26)	Important	Very low
Patients undergoing revision surgery (n (%)) at a minimum of 5 years of follow-up									
1 case series Mohamed et al 2022	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	58	None	20 (34), due to: failed intramedullary stem:7 (12) broken dual-cone adapter:13 (22)	Important	Very low
Cumulative survival implant probability (%) after 9 years									
1 case series Mohamed et al 2022	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	58	None	78 (95% CI 58 to 89)	Important	Very low
Median implant survival time (years (IQR)) at a minimum of 5 years of follow-up									
1 case series Mohamed et al 2022	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	58	None	6 (4)	Important	Very low
Implants extracted due to osteomyelitis (n (%)) at a mean follow-up of 7.9 years									
1 case series Tillander et al 2017	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	102	None	10 (10)	Important	Very low
10-year cumulative risk of implant extraction due to osteomyelitis (%)									
1 case series Tillander et al 2017	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	102	None	9 (95% CI 0.04 to 0.20)	Important	Very low

Adverse events									
Patients experiencing an adverse event (n (%)) at a mean follow-up of 21.5 months									
1 case series Al Muderis et al 2016a	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	50	None	27 (54%)	Important	Very low
Patients experiencing one or more infections (n (%)) at a mean follow-up of 21.5 months									
1 case series Al Muderis et al 2016a	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	50	None	21 (42%) • 13 responded to oral antibiotics alone • 5 responded to intravenous antibiotics • 3 required surgical soft tissue debridement of infected soft tissues	Important	Very low
Patients experiencing one or more infections (n (%)) at a median follow-up of 34 months									
1 case series Al Muderis et al 2016b	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	86	None	29 (34) • Grade 1A[65] infection: 23 (27) • Grade 1B: 1 (1); severe cellulitis and intense pain treated with parenteral antibiotics • Grade 1C: 1 (1); severe cellulitis and intense pain treated with parenteral antibiotics followed by local debridement • Grade 2C[66]: 4 (5); high-grade soft-tissue infection with abscess formation that needed surgical debridement • No patient developed a serious (grade 3[67] or 4[68]) infection	Important	Very low

[65] Grade 1 - Low-grade soft-tissue infection cellulitis with signs of inflammation (redness, swelling, warmth, stinging pain, pain that increases on loading, tense) treated with oral antibiotics (Grade 1A), parenteral antibiotics (Grade 1B) or surgical intervention (Grade 1C).
[66] High-grade soft-tissue infection with pus collection, purulent discharge, raised level of C-reactive protein treated with oral antibiotics (Grade 2A), parenteral antibiotics (Grade 2B) or surgical intervention (Grade 2C).
[67] Bone infection with radiographic evidence of osteitis (periosteal bone reaction), radiographic evidence of osteomyelitis (sequestrum and involucrum)
[68] Implant failure with radiographic evidence of loosening

Patients sustaining periprosthetic fractures (n (%)) at a mean follow-up of 21.5 months									
1 case series Al Muderis et al 2016a	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	50	None	4 (8%)	Important	Very low
Patients experiencing stoma hypergranulation (n (%)) at a median follow-up of 34 months									
1 case series Al Muderis et al 2016b	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	86	None	17 (20)	Important	Very low
Patients experiencing redundant soft tissue (n (%)) at a median follow-up of 34 months									
1 case series Al Muderis et al 2016b	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	86	None	14 (16)	Important	Very low
Patients experiencing proximal femoral fracture (n (%)) at a median follow-up of 34 months									
1 case series Al Muderis et al 2016b	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	86	None	3 (3)	Important	Very low
Patients developing osteomyelitis (n (%)) at a mean follow-up of 7.9 years									
1 case series Tillander et al 2017	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	96	None	16 (17)	Important	Very low
10-year cumulative risk of implant-associated osteomyelitis (%)									
1 case series Tillander et al 2017	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	102	None	20 (95% CI 0.12 to 0.33)	Important	Very low
Median time from implantation to osteomyelitis (years (range)) at a mean follow-up of 7.9 years									
1 case series	Serious limitations[1]	Serious limitations[2]	Not applicable	Not calculable	102	None	2.6 (0.3 to 13.8)	Important	Very low

Tillander et al 2017									
Abbreviations 6MWT: 6-Minute Walk Test; AMPPRO: Amputation Mobility Predictor Prothesis; BL: Baseline; CI: Confidence Interval; DSF: Direct Skeletal Fixation; F/up: Follow-up; IQR: Interquartile Range; Q-TFA: Questionnaire for Persons with a Transfemoral Amputation; SD: Standard Deviation; SF-36: 36-Item Short Form Health Survey; TUG: Timed Up and Go Test									

GRADE table footnotes
1 Risk of bias: serious limitations due to lack of clarity on patient selection criteria
2 Indirectness: serious indirectness due to lack of comparator group
3 Risk of bias: very serious limitations due to lack of clarity on patient selection criteria and incomplete inclusion of participants
4 Risk of bias: very serious limitations due to lack of clarity on patient selection criteria, incomplete inclusion of participants and limited reporting of results with statistical significance of results not reported
5 Risk of bias: very serious limitations due to lack of clarity on patient selection criteria and limited reporting of results with statistical significance of results not reported

Glossary

Term	Definition
Adverse event	Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether or not the event is suspected to be related to or caused by the drug, treatment or intervention.
Baseline	The set of measurements at the beginning of a study (after any initial 'run-in' period with no intervention), with which subsequent results are compared.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted.
Case series	Reports of several patients with a given condition, usually covering the course of the condition and the response to treatment. There is no comparison (control) group of patients.
Clinical importance	A benefit from treatment that relates to an important outcome such as length of life and is large enough to be important to patients and health professionals.
Confidence interval (CI)	A way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).
Control group	A group of people in a study who do not have the intervention or test being studied. Instead, they may have the standard intervention. The results for the control group are compared with those for a group having the intervention being tested. The aim is to check for any differences. Ideally, the people in the control group should be as similar as possible to those in the intervention group, to make it as easy as possible to detect any effects due to the intervention.
Cost effectiveness study	An analysis that assesses the cost of achieving a benefit by different means. The benefits are expressed in non-monetary terms related to health, such as life years gained (that is, the number of years by which life is extended as a result of the intervention). Options are often compared on the cost incurred to achieve 1 outcome (for example, cost per life year gained).
GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.
Meta-analysis	A method often used in systematic reviews to combine results from several studies of the same test, treatment or other intervention to estimate the overall effect of the treatment.
Minimal clinically important difference	The smallest change in a treatment outcome that people with the condition would identify as important (either beneficial or harmful), and that would lead a person or their clinician to consider a change in treatment.
PICO (population, intervention, comparison and outcome) framework	A structured approach for developing review questions that divides each question into 4 components: the population (the population being studied); the interventions (what is being done); the comparators (other main

	treatment options); and the outcomes (measures of how effective the interventions have been).
Prospective study	A research study in which the health or other characteristic of patients is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
P-value (p)	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Standard deviation (SD)	A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data.
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance.

References

Included studies

- Al Muderis MA, Tetsworth K, Khemka A, Wilmot S, Bosley B, Lord SJ, et al. The Osseointegration Group of Australia Accelerated Protocol (OGAAP-1) for two-stage osseointegrated reconstruction of amputated limbs. Bone Joint J. 2016a;98-B(7):952-60.
- Al Muderis M, Khemka A, Lord SJ, Van de Meent H, Frolke JP. Safety of osseointegrated implants for transfemoral amputees: A two-center prospective cohort study. J Bone Joint Surg Am. 2016b;98(11):900-9.
- Hagberg K, Ghassemi Jahani SA, Kulbacka-Ortiz K, Thomsen P, Malchau H, Reinholdt C. A 15-year follow-up of transfemoral amputees with bone-anchored transcutaneous prostheses. Bone Joint J. 2020;102-B(1):55-63.
- Mohamed J, Reetz D, van de Meent H, Schreuder H, Frolke JP, Leijendekkers R. What are the risk factors for mechanical failure and loosening of a transfemoral osseointegrated implant system in patients with a lower-limb amputation? Clin Orthop. 2022;480(4):722-31.
- Tillander J, Hagberg K, Berlin O, Hagberg L, Branemark R. Osteomyelitis risk in patients with transfemoral amputations treated with osseointegration prostheses. Clin Orthop. 2017;475(12):3100-8.

Other references

- Hagberg K, Brånemark R. One hundred patients treated with osseointegrated transfemoral amputation prostheses - rehabilitation perspective. J Rehabil Res Dev. 2009;46(3):331-44.

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