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Advanced techniques in amputation surgery and prosthetic technology in the lower extremity

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- Bone-anchored implants give patients with unmanageable stump problems hope for drastic improvements in function and quality of life and are therefore increasingly considered a viable solution for lower-limb amputees and their orthopaedic surgeons, despite high infection rates.
- Regarding diversity and increasing numbers of implants worldwide, efforts are to be supported to arrange an international bone-anchored implant register to transparently overview pros and cons.
- Due to few, but high-quality, articles about the beneficial effects of targeted muscle innervation (TMR) and regenerative peripheral nerve interface (RPNI), these surgical techniques ought to be directly transferred into clinical protocols, observations and routines.
- Bionics of the lower extremity is an emerging cutting-edge technology. The main goal lies in the reduction of recognition and classification errors in changes of ambulant modes. Agonist–antagonist myoneuronal interfaces may be a most promising start in controlling of actively powered ankle joints.
- As advanced amputation surgical techniques are becoming part of clinical routine, the development of financing strategies besides medical strategies ought to be boosted, leading to cutting-edge technology at an affordable price.
- Microprocessor-controlled components are broadly available, and amputees do see benefits. Devices from different manufacturers differ in gait kinematics with huge inter-individual varieties between amputees that cannot be explained by age. Active microprocessor-controlled knees/ankles (A-MPK/As) might succeed in uneven ground-walking. Patients ought to be supported to receive appropriate prosthetic components to reach their everyday goals in a desirable way.
- Increased funding of research in the field of prosthetic technology could enhance more high-quality research in order to generate a high level of evidence and to identify individuals who can profit most from microprocessor-controlled prosthetic components.

Keywords: amputation surgery; bone-anchored prosthesis; prosthetic technology bionics; TMR; RPNI

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Introduction

Amputation surgery is often considered simple with predictable outcomes; nonetheless amputations are troubled with high risks of consequential complications.[1] Among traumatic amputees, 51% suffer from anatomical sequelae,[2] 63% of amputees suffer from one or more skin problems that lead to daily routine activity limitations in one third of these patients.[3] Around 70% of amputees develop phantom limb pain (PLP) or residual limb pain (RLP),[4] 14.5% of traumatic lower-limb amputees need to have revision surgery,[5] and 25–56% of amputees develop social problems.

Age-adjusted rates of lower-extremity amputations are in the range of 16.9–22.9 amputees/100,000 inhabitants/year in different countries.[6–8] Ninety percent of amputations are due to common aetiologies for amputations such as peripheral arterial occlusive disease and diabetic foot syndrome.[9] Although only 10% of amputations are performed for other diagnoses such as tumours, cutaneous diseases, musculoskeletal diseases or trauma, the prevalence of these amputees is high due to their younger age.[9]

Recent reviews about how to find the right time point and amputation level reflect further difficulties in determining an indication for amputation surgery. However, there is still low evidence to clearly decide whether to choose knee disarticulation (KDA) instead of transfemoral amputation (TFA) or transtibial amputation (TTA) instead of partial foot amputation (PFA) based on quality of life data.[10–13] There is not even a single reliable predictive score for the decision to amputate or salvage a limb in a mangled extremity.[12] Though decision making in amputation surgery can be challenging, for experienced surgeons success depends on thoughtful patient selection.[10]

In parallel, surgical improvements, new prosthetic solutions and personal demands for higher activity levels accompanied with modern measurement instruments such as gait analysis and patient-reported outcome measures (PROMs) blur the boundaries between two aspects of amputation: the best surgical option OR the best possible medical care strategy to improve functional outcome and quality of life after failed surgery for infection, tumours or certain congenital musculoskeletal anomalies.[1,14] The main objective of the present review is to identify all major studies dealing with amputation surgery and prosthetic technologies published between 1 January 2014 and 1 October 2019. The specific focus was on recent advances and novel concepts in amputation surgery and technique as well as prosthetic technology. Within the last five years, 381 studies have been published in journals dealing with amputation surgery and prosthetic technologies, 58 studies finally met the inclusion criteria to be included in this review. Most studies came from United States and Europe. The following review will explain the best of surgical techniques and prosthetic technology and its applicability.

Material and methods

All studies published in PubMed between 1 January 2014 and 1 October 2019 were included in the review, after applying the specific search terms listed below. Original articles dealing with amputation surgery written in English language and listed in PubMed with an impact factor ranking (see Fig. 1) in the best 60% (top 20%, standard 20–60%) journals according to Journal Citation Report (JCR) in the categories orthopaedics, rehabilitation, surgery, health care science, biomedical engineering, multidisciplinary sciences, medicine research & experimental/general internal, neurosciences, and mathematical & computational biology were considered to be eligible (see Fig. 2). This number was calculated by dividing the total number of publications in the respective categories by the rank of the journal of interest. Literature research was performed up to 1 October 2019. The following search-fields were used to identify target studies: amputation, osseointegration/bone-anchored prosthesis, amputation, bridge synostosis, targeted muscle re-innervation, regenerative peripheral nerve interface, bionic, socket, microprocessor knee. Reviews, cadaver studies and duplicates were excluded manually. As amputation surgery is an emerging new field, articles with ‘case report’ in the title were excluded unless reporting novel promising techniques. Altogether, 381 original studies were identified based on the abovementioned search terms within the pre-defined time period. As a first step, 141 articles were excluded from further analyses with study titles not in the scope of the present review, leaving 240 articles potentially eligible. Following the review of the abstract, another 63 articles were excluded due to them not being within the scope of this review and 16 further articles due to duplication. From the remaining 118 articles, 52 had an impact factor ranking them in the best 60% either in the abovementioned categories. Three articles were included despite a lower than 40% ranking and three articles were included while not being classified within a category. Full-text articles were downloaded from the journal websites

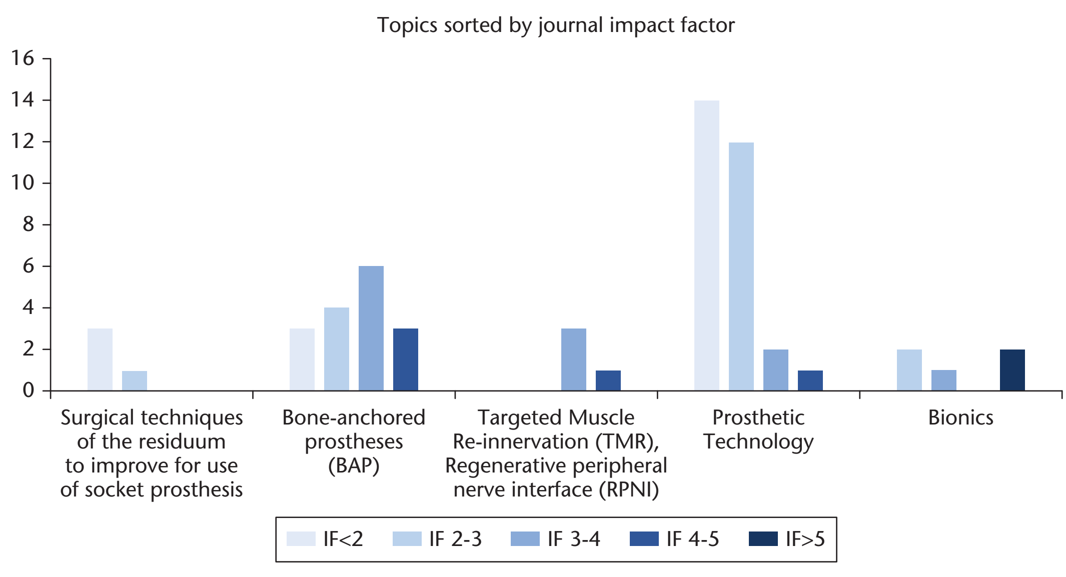

Fig. 1 Numbers of publications split by journal impact factor in presented five categories.

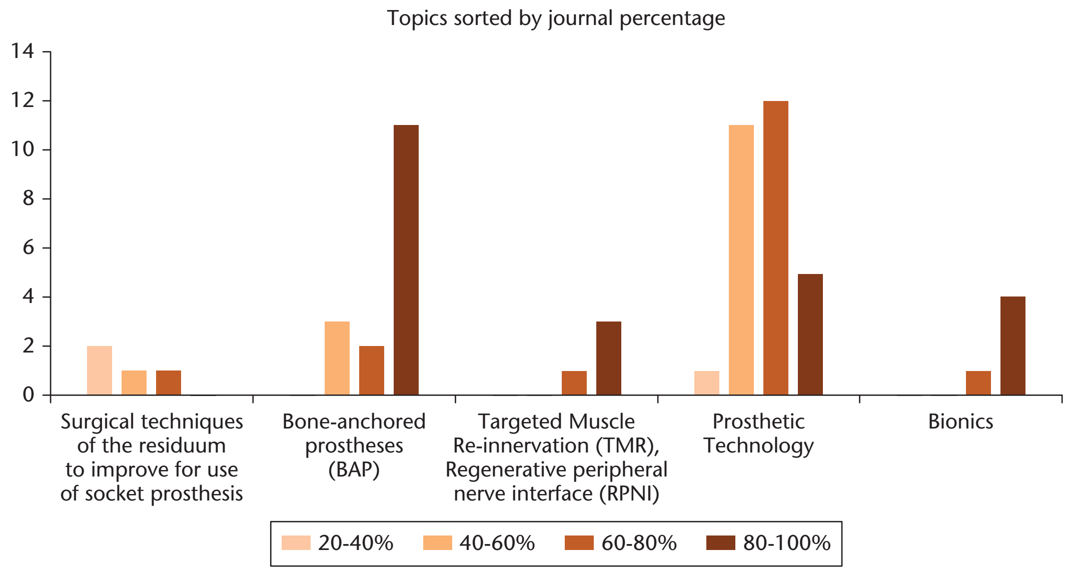

Fig. 2 Number of publications split by journal ranking (JCR) in presented five categories.

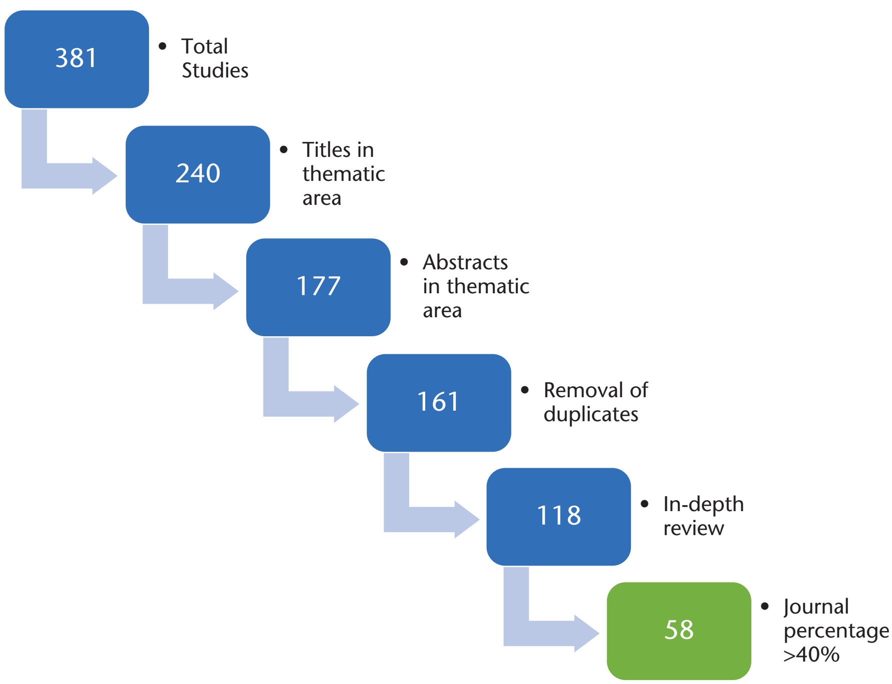

Fig. 3. Flow diagram showing the selection process of this review's articles.

of all included finally publications (see Fig. 3). Authors from specific studies were not personally contacted, all necessary information could be extracted from the full-text articles (see Tables 1 and 2). Most of the studies were retrospective comparative studies (level of evidence III), only some were non-randomized or prospective comparative studies (levels of evidence II). All articles finally eligible were grouped into the following fields: Surgical techniques of the residuum for improvement of socket prosthesis use (bridge synostosis/Ertl technique, adductor myodesis), bone-anchored prosthesis/osseointegration, targeted muscle innervation (TMR), regenerative peripheral nerve interface (RPNI), socket prostheses, bionics. Primary literature research was performed by the first and the second author

Table 1. Included studies in categories 'surgery', 'bone-anchored prostheses' and 'targeted muscle reinnervation (TMR), regenerative peripheral nerve interface (RPNI)'

Author	Year	Title	Findings	IF
Surgical techniques of the residuum to improve for use of socket prosthesis				
Chillale et al[20]	2019	Mechanical and finite element analysis of an innovative orthopedic implant designed to increase the weight carrying ability of the femur and reduce frictional forces on an amputee's stump	Level IV, experimental study. Hypothesis testing both by mechanically testing on an Amputee Simulation Device (ASD) and through Finite Element Analysis (FEA) modelling software. With the implant attached to the femur, the FEA and ASD demonstrated that the femur carried 90% and 93% respectively of the force of walking. Without the implant, the FEA model and ASD femur carried only 35% and 77%, respectively, of the force of walking. FEA modelling demonstrates that the normal contact forces and shear forces are pushed the distal weight-bearing area of the amputee stump, relieving the lateral stump of frictional forces.	0.853
Ferris et al[16]	2017	Ertl and Non-Ertl amputees exhibit functional biomechanical differences during the sit-to-stand task	Level II, prospective comparative study. Two groups Ertl ($n = 11$) and Non-Ertl ($n = 7$) participants, performing the five-time sit-to-stand task sat on a chair with each foot on separate force plates, outcome symmetry index (intact vs. affected limbs), peak ground reaction forces; Ertl group performed the task significantly faster (9.33 s (2.66) vs. 13.27 s (2.83)). Symmetry index (23.33% [23.83%] Ertl, 36.53% [13.51%] Non-Ertl) indicated the intact limb for both groups produced more force than the affected limb. Ertl affected limb peak ground reaction forces were significantly larger than the Non-Ertl affected limb. Peak knee power and net work of the affected limb were smaller than their respective intact limb for both groups. The Ertl intact limb produced significantly greater peak knee power and net work than the Non-Ertl intact knee.	1.863
Guirao et al[19]	2017	Improvement in walking abilities in transfemoral amputees with a distal weight bearing implant	Level IV case series with 10 transfemoral amputees with titanium implant. Two-min walk-test score prior to implant 98.4 ± 19.5 m, post implant 122.5 ± 26.1 m at 14 months, gait speed prior 0.82 ± 0.16 and post implant	1.103
Bone-anchored prostheses (BAP)				
Chimutengwende-Gordon et al[40]	2017	The in vivo effect of a porous titanium alloy flange with hydroxyapatite, silver and fibronectin coatings on soft-tissue integration of intraosseous transcutaneous amputation prostheses	Level IV animal study. The porous titanium alloy flange reduced epithelial downgrowth and increased soft-tissue integration compared with the current drilled flange.	3.581
Frossard et al[92]	2017	Cost-effectiveness of bone-anchored prostheses using osseointegrated fixation: myth or reality?	Level III, retrospective individual case-controlled observations and systematic review. Actual costs were extracted from financial records and completed by typical costs when needed over six-year time horizon for a cohort of 16 individuals. The provision of bone-anchored prostheses costed 21% ± 41% more but increased quality-adjusted life-years by 17% ± 5% compared to socket-suspended prostheses. The incremental cost-effectiveness ratio ranged between –Australian Dollar (AUD)25,700 per quality-adjusted life-year and AUD 53,500 per quality-adjusted life-year with indicative incremental cost-effectiveness ratio of approximately AUD 17,000 per quality-adjusted life-year.	1.482
Frossard et al[93]	2017	Development of a procedure for the government provision of bone-anchored prosthesis using osseointegration in Australia	Level IV action research study aimed at providing a working plan for stakeholders and a procedure for provision. Included 18 amputees. The procedure included seven processes involving fixed expenses during treatment and five processes regulating ongoing prosthetic care expenses. Prosthetic care required 22 hours of labour, corresponding to AUD$3300 per patient, during rehabilitation. Prosthetists spend 64% and 36% of their time focusing on prosthetic care and other activities, respectively. Approximately 41%[7] and 59%[10] of obstacles were within or outside stakeholders, lack of a definitive rehabilitation programme.	3.705
Hagberg et al[27]	2014	Outcome of percutaneous osseointegrated prostheses for patients with unilateral transfemoral amputation at two-year follow-up	Level III prospective two-year case-control study with 39 unilateral transfemoral amputees. Six of seven Q-TFA scores improved ($P < .0001$) . The walking aid subscore did not improve ($P = .327$). The PF, PCS, and SF-6D improved by a mean of 24.1 ± 21.4 ($P < .0001$), 8.5 ± 9.7 ($P < .0001$), and 0.039 ± 0.11 ($P = .007$) points; walking energy cost decreased ($P < .0001$).	2.565
Haket et al[41]	2017	Periprosthetic cortical bone remodeling in patients with an osseointegrated leg prosthesis	Level III, retrospective comparative study. 27 patients with a transfemoral ILP (integrated leg prosthesis). Periprosthetic cortical thickness analysed from standard anteroposterior (AP) radiographs taken immediately and at both 12 and 24 months post implantation. The BMD femoral hip neck on both sides, measured pre-operatively with Dual X-ray absorptiometry (DXA) and at 12 and 24 months, cortical thickness increased significantly by 9.6% ($p = 0.020$) and 8.9% ($p < 0.001$) at 12 and 24 months, BMD of hip neck on both sides was not significant, data indicate good prospects for implant survival.	3.414

(continued)

Table 1 (continued)

Author	Year	Title	Findings	IF
Hansen et al[30]	2019	The process of becoming a user of an osseointegrated prosthesis following transfemoral amputation: a qualitative study	Level V, qualitative study, based on the descriptive phenomenological framework Reflective Lifeworld Research. Data were collected through in-depth interviews with seven participants who had undergone transfemoral OPRA implant surgery and currently used their osseointegrated prosthesis. When familiar with the prosthesis, participants begin to experience radical improvements in their everyday lives, compared to with the socket-suspended prosthesis. The essential meaning is elaborated on in four constituents: determination to achieve rehabilitation results with the short training prosthesis, struggling to get familiar with the osseointegrated prosthesis, experiencing improvements in everyday life and reconnecting with one's prior self-perception. All the participants experienced increased action space and a more positive outlook on life; however, it took determination and stamina to become a user of an osseointegrated prosthesis.	2.054
Hansson et al[94]	2018	Patients with unilateral transfemoral amputation treated with a percutaneous osseointegrated prosthesis: a cost-effectiveness analysis	Level III comparative cost effectiveness study with 39 transfemoral amputees with OPRA implant and a socket-suspended (S) prosthesis; osseointegrated (OI) prostheses had an incremental cost per QALY gained of €83,374 compared with S prostheses. The clinical improvement seen with OI prostheses was reflected in QALYs gained. The impact of an annual decline in utility values of 1%, 2%, and 3%, for patients with S prostheses resulted in a cost per QALY gained of €37,020, €24,662, and €18,952, respectively, over 20 years.	4.301
Juhnke et al[35]	2015	Fifteen years of experience with Integral-Leg-Prosthesis: cohort study of artificial limb attachment system	Level III, therapeutic study, retrospective comparative study with 69 transfemoral amputees receiving ILP bone-anchored prostheses, two groups: group 1 with design A (n = 21) or B (n = 9) and group 2 with design C (n = 39), no infection, two periprosthetic fractures, one intervention due to soft-tissue problems with design C after a mean of 32 ± 18 months, high infection rate with designs A and B of 42% and implant explantation rate of 13%, periprosthetic fracture rate of 10%.	1.043
Leijendekkers et al[28]	2019	Functional performance and safety of bone-anchored prostheses in persons with a transfemoral or transtibial amputation: a prospective one-year follow-up cohort study	Level IV; 31 consecutive transfemoral amputees with osseointegrated implants. Strength, prosthetic use, walking distance, HRQol and satisfaction level increased at 12-month follow-up compared to baseline ($p < 0.002$) TUG changed after 12 months ($p < 0.005$).	2.738
Lennerås et al[38]	2017	The clinical, radiological, microbiological, and molecular profile of the skin-penetration site of transfemoral amputees treated with bone-anchored prostheses	Level IV, experimental study. Thirty TFA patients scheduled for abutment exchange or removal were consecutively enrolled. A positive correlation between TNF-a expression and the detection of S. aureus. S. aureus together with other bacterial species revealed a positive relationship with MMP-8 expression. A negative correlation between the length of the residual femur bone and the detection of a granulation ring and E. faecalis. A positive correlation between fixture loosening and pain and the radiological detection of endosteal bone resorption. Fixture loosening was also correlated with the reduced expression of interleukin-10 and osteocalcin. It is concluded that several relationships exist between clinical, radiological, microbiological, and molecular assessments of the percutaneous area of TFAs.	3.231
Matthews et al[34]	2019	UK trial of the osseointegrated prosthesis for the rehabilitation for amputees: 1995–2018	Level III, retrospective comparative study reporting outcome data for the UK trial of the OPRA Implant System of 18 transfemoral amputees. Minimum follow-up of 9-years, cumulative implant survivorship 40% before standardized protocol for the rehabilitation of amputees, and 80.21% for the OPR protocol. Five implants (28%) removed due to infection, two patients (11%) with peri-implant infections suppressed with oral antibiotics. Eleven patients (61%) with superficial infection were successfully treated with antibiotics. Significant improvements in SF-36 and Q-TFA-Item short-form health survey and Questionnaire for Persons with a Transfemoral Amputation showed significant improvements in quality of life up to five years after implantation.	1.482
Muderis et al[25]	2016	The Osseointegration Group of Australia Accelerated Protocol (OGAAP-1) for two-stage osseointegrated reconstruction of amputated limbs	Level III, clinical outcomes of 50 unilateral transfemoral amputees. One year minimum follow-up, 27 patients with adverse effects, significant improvements in all outcome measures (Q-TFA, SF-36, 6-MWT, TUG), 21 patient infections with 13 responding to oral antibiotic (AB) treatment, five to intravenous (IV) AB, three needed surgical soft-tissue treatment, four had peri-prosthtetic fractures. Revision of the implant in two patients.	2.948
Al Muderis et al[37]	2016	Safety of osseointegrated implants for transfemoral amputees: a two-center prospective cohort study	Level IV, therapeutic study with 86 patients with transfemoral amputation who were managed with an osseointegrated implant system prospectively recorded adverse events in patients at two centres. A customized porous-coated implant was placed in the first stage, and a stoma was created in the second. Of 86, 34 patients with no complications, 29 patients with infection (all grade 1 or 2), 26 no infection but 17 with stoma hypergranulation, 14 patients soft-tissue redundancy, three proximal femoral fractures, one inadequate osseointegration leading to implant replacement, two implant breakages and 25 patients with breakage of the pin used as a fail-safe mechanism.	4.840

(continued)

Table 1 (continued)

Author	Year	Title	Findings	IF
Stenlund et al[42]	2017	Effect of load on the bone around bone-anchored amputation prostheses	Level IV, experimental study. Load measurements of five patients with unilateral transfemoral amputation and OPRA implant at least two years post-operative site-specific loading measurements were made on amputees and used as input data in finite element analyses to predict the stress and strain distribution in the bone tissue. Within the limit of the evaluated bone properties the loads applied to the implant system may compromise the sealing function between the bone and the abutment, contributing to resorption of the bone in direct contact with the abutment at the most distal end.	3.414
Tillander et al[33]	2017	Osteomyelitis risk in patients with transfemoral amputations treated with osseointegration prostheses	Level IV, therapeutic study retrospectively analysing 96 patients receiving OPRA implants for osteomyelitis. Six patients LOF, follow-up. Implant-associated osteomyelitis in 16 patients corresponding to a 10-year cumulative risk of 20% (95% CI 0.12–0.33). Ten implants were extracted owing to osteomyelitis, with a 10-year cumulative risk of 9% (95% CI 0.04–0.20).	4.091
Zaborowska et al[39]	2017	Biofilm formation and antimicrobial susceptibility of staphylococci and enterococci from osteomyelitis associated with percutaneous orthopaedic implants	Level IV, experimental study to test novel biofilm devices and to determine the biofilm formation and antimicrobial resistance in clinical isolates causing implant-associated osteomyelitis. Biofilm susceptibility to 10 antimicrobials and its relationship to treatment outcomes were determined. The majority of the strains produced biofilm in vitro showing inter- and intra-species differences. Biofilms showed a significantly increased antimicrobial resistance compared with their planktonic counterparts. Slime-producing strains tolerated significantly higher antimicrobial concentrations compared with non-producers. All seven staphylococcal strains carried ica genes, but two did not produce slime. The degree of biofilm formation and upregulated antibiotic resistance may translate into a variable risk of treatment failure.	3.189
Targeted muscle re-innervation (TMR), regenerative peripheral nerve interface (RPNI)				
Alexander et al[49]	2019	Targeted muscle reinnervation in oncologic amputees: early experience of a novel institutional protocol	Level II, prospective comparative study, 31) patients underwent amputation with concurrent TMR during the study, comparison with a cross-sectional sample of 58 unselected oncologic amputees. NRS and PROMIS were used to assess post-amputation pain. Twenty-seven patients completed pain surveys; 15 had mean follow-up 14.7 months. Neuroma symptoms occurred significantly less frequently and with less intensity among the TMR cohort. Mean differences for PROMIS pain intensity, behaviour, and interference for phantom limb pain (PLP) were 5.855 (95% CI 1.159–10.550; P = .015), 5.896 (95% CI 0.492–11.300; P = .033), and 7.435 (95% CI 1.797–13.070; P = .011) respectively, with lower scores for TMR cohort. For residual limb pain, PROMIS pain intensity, behaviour, and interference mean differences were 5.477 (95% CI 0.528–10.420; P = .031), 6.195 (95% CI 0.705–11.690; P = .028), and 6.816 (95% CI 1.438–12.200; P = .014). 56% with opioids before amputation compared to 22% at one year post op.	3.114
Bowen et al[48]	2019	Targeted muscle reinnervation technique in below-knee amputation	Level III, retrospective comparative study, this article seeks to share the authors' clinical indications and surgical technique for targeted muscle reinnervation in below-knee amputation; a surgical description currently absent from our literature. TMR for the below-knee amputee has been performed on 22 patients, each patient has been followed on an outpatient basis for one year to evaluate symptoms of neuroma or phantom limb pain, patient satisfaction, and functionality. All subjects have denied neuroma pain following amputation. The majority of subjects reported phantom pain at one month. However, at three months, all patients reported resolution of this pain.	3.946
Kubiak et al[51]	2018	Prophylactic regenerative peripheral nerve interfaces to prevent postamputation pain	Level III, retrospective comparison study, reviewing post-operative outcomes of 90 patients. Forty-five patients underwent interface implantation at the time of primary amputation, and 45 control patients underwent amputation without interfaces. Six (13%) control patients developed symptomatic neuromas in the post-operative period compared with 0% in the prophylactic interface group (p = 0.026). Twenty-three (51%) interface patients reported PLP, compared with 41 (91%) control patients (p < 0.0001).	3.946
Valerio et al[45]	2019	Preemptive treatment of phantom and residual limb pain with targeted muscle reinnervation at the time of major limb amputation	Level II, prospective comparative study with 51 patients with major limb amputation with immediate TMR compared with 438 unselected major-limb amputees without TMR. Median PROMIS t-scores were lower in TMR patients for both PLP (pain intensity 36.3 vs. 48.3, pain behaviour 50.1 vs. 56.6, pain interference 40.7 vs. 55.8) and residual limb pain (pain intensity 40.7 vs. 57.3), TMR was associated with 3.03 (PLP) and 3.92 (residual) times higher odds of decreasing pain severity.	4.450

Note. IF, impact factor; Q-TFA, Questionnaire of transfemoral amputees; PF, Physical function; PCS, Physical component score ; SF-6D, Short form -6 dimensions; BMD, ; OPRA, osseointegrated prostheses for the rehabilitation of amputees; QALY, quality-adjusted life years; HRQoL, health-related quality of life; TUG, time up-and-go test; MMP-8, Matrixmetalloproteinase-8; SF-36, Short form health survey 36; 6-MWT, six-minute walk-test; NRS, Numeric rating scale; PROMIS, Patient Reported Outcome Measurement Information System.

Table 2. Included studies in categories 'Prosthetic technology' and 'Bionics'

Author	year	Title	Findings	IF
Prosthetic technology (Socket)				
Ali et al[57]	2015	The effect of Dermo and Seal-In X5 prosthetic liners on pressure distributions and reported satisfaction during ramp ambulation in persons with transtibial limb loss	Level II, 10 transtibial amputees. Interface pressure between socket and residual limb was measured during walking on ramp and Prosthetic Evaluation Questionnaire (PEQ) was filled for each liner. Mean peak pressure was significantly ($P < 0.05$) lower with the Dermo liner in ramp walking, participants more satisfied with the Dermo liner (83.50 vs. 71.50) and mentioned fewer problems (87.00 vs. 69.00).	2.063
Bell et al[70]	2016	Performance of conventional and X2® prosthetic knees during slope descent	Level II, prospective comparative study including 21 service members with unilateral transfemoral amputation using the X2®, compared to a conventional knee, either mechanical (MECH) or microprocessor (MP), descending an instrumented 10° slope at a self-selected walking velocity. Use of the X2® in the MECH group resulted in greater hill assessment scores (8.5 to 11.0, $P = 0.026$), due primarily to decreased reliance on handrail use. The use of the X2® in the MP group increased prosthetic knee flexion to a median of 6.4° at initial contact ($P = 0.002$) and 73.7° in swing ($P = 0.005$), contributing to longer prosthetic limb steps ($P = 0.024$) and increased self-selected velocity ($P = 0.041$). Additionally, the use of the X2® in the MP group increased prosthetic limb impact peaks (11.6 N/kg, $P = 0.004$), improving impact peak symmetry to −1.3% ($P = 0.004$).	1.874
Cagle et al[59]	2018	A finite element model to assess transtibial prosthetic sockets with elastomeric liners	Level III. MRI scans from three people with characteristic transtibial limb shapes used to create a transtibial finite element model. Models identified five locations on the participants' residual limbs where peak stresses matched locations of mechanically induced skin issues they experienced in the nine months prior to being scanned.	2.039
Ernst et al[80]	2017	Standing on slopes: how current microprocessor-controlled prosthetic feet support transtibial and transfemoral amputees in an everyday task	Level II, study of four unilateral transtibial and four unilateral transfemoral amputees. Each of the subjects wore five different microprocessor-controlled prosthetic feet in addition to their everyday feet. Differences in the biomechanical parameters were observed between the different prosthetic feet and compared to the reference group for the investigated situations. Differences were most prominent while standing on a downward slope.	3.865
Eshraghi et al[56]	2015	Interface stress in socket/residual limb with transtibial prosthetic suspension systems during locomotion on slopes and stairs	Level II. Three transtibial prostheses, with a pin/lock system, a seal-in system, and a magnetic suspension system, were created for 12 transtibial amputees. Greatest peak pressure was observed with the seal-in system. The magnetic prosthetic suspension system caused significantly different peak pressure at the anterior proximal region compared with the pin/lock ($P = 0.022$) and seal-in ($P = 0.001$) during the stair ascent.	2.064
Fuenzalida Squella et al	2018	Enhancement of a prosthetic knee with a microprocessor-controlled gait phase switch reduces falls and improves balance confidence and gait speed in community ambulators with unilateral transfemoral amputation	Level II. Thirteen transfemoral amputees; assessment before and after eight weeks of accommodation to a microprocessor-enhanced knee. Self-reported falls significantly declined 77% ($p = .04$); Activities-Specific Balance Confidence scores improved by 12 points ($p = .005$), two-min walk test walking distance increased 20 m on level ($p = .01$) and uneven ($p = .045$) terrain, and patient satisfaction significantly improved ($p < .01$) with MPK.	1.482
Gholizadeh et al[54]	2018	Transtibial amputee gait during slope walking with the unity suspension system	Level I. Twelve people with unilateral transtibial amputation. Randomized and blinded walking trials were completed with the vacuum active or inactive. Statistically significant differences ($p < 0.05$) between vacuum conditions when walking uphill or downhill for temporal spatial, kinematic, and kinetic gait parameters. Prosthetic step length decreased for both vacuum conditions on downhill compared to uphill walking. Symmetry index was < 10% for step length, step time, and stance time for both vacuum condition during downhill walking. During incline walking, step length was only symmetrical with active vacuum. Knee range of motion was not restricted, for both conditions.	2.414
Hashimoto et al[64]	2018	The effect of transverse prosthetic alignment changes on socket reaction moments during gait in individuals with transtibial amputation	Level III. Effects of transverse prosthetic alignment changes on the sagittal and coronal socket reaction moments and temporal-spatial parameters (gait speed, cadence and step width) while walking in nine individuals with transtibial amputation using an instrumented prosthetic pyramid adaptor and a three-dimensional (3D) motion capture system; transverse alignment changes demonstrated significant effects on the socket reaction moments in the coronal plane at 5% ($P = 0.04$), 20% ($P = 0.04$) and 75% ($P = 0.0001$) of stance phase.	2.414
Highsmith et al[76]	2016	Functional performance differences between the Genium and C-Leg prosthetic knees and intact knees	Level I. Twenty community-ambulating persons with TFA and five non-amputee controls; Genium use improved upper-body flexibility, balance, and endurance domain scores (7.0–8.4%, $p \leq 0.05$) compared with the C-Leg.	1.277
Jayaraman et al[85]	2018	Impact of powered knee-ankle prosthesis on low back muscle mechanics in transfemoral amputees: a case series	Level IV. Impact of using a powered knee-ankle prostheses (PKA) on two transfemoral amputees who currently use advanced microprocessor-controlled knee prostheses (MPK); PKA allows the participants to walk with gait kinematics similar to normal gait patterns observed in a healthy limb.	3.648
Kaib et al[84]	2019	Prosthetic restoration of the forefoot lever after Chopart amputation and its consequences onto the limb during gait	Level II. An instrumented 3D gait analysis was performed in 13 subjects with Chopart amputation using a clamshell and/or a Bellmann prosthesis. The largest range of motion ($p < 0.05$) in the ankle joint was seen for the Bellmann prosthesis (32 ± 3°). The highest ankle joint moment ($p < 0.05$) was seen for the clamshell prosthesis (1.04 ± 0.24 Nm/kg).	2.414

(continued)

Table 2 (continued)

Author	year	Title	Findings	IF
Karakoç[58]	2017	Sockets manufactured by CAD/CAM method have positive effects on the quality of life of patients with transtibial amputation	Level III. Thirty-six patients who had CAD/CAM prosthetic sockets and 36 patients with traditional prosthetic sockets; sockets manufactured by CAD/CAM methods yield better outcomes in quality of life of patients with transtibial amputation than the sockets manufactured by the traditional method.	1.843
Kaufman et al	2018	Functional assessment and satisfaction of transfemoral amputees with low mobility (FASTK2): a clinical trial of microprocessor-controlled vs. non-microprocessor-controlled knees	Level II. Fifty unilateral transfemoral amputees tested using their current non-microprocessor-controlled knee, fit with a microprocessor-controlled knee and allowed 10 weeks of acclimation before being tested, and then re-tested with their original mechanical knee after four weeks of re-acclimation. Subjects had a significant reduction in falls, spent less time sitting, increased their activity level. Subjects also reported significantly better ambulation, improved appearance, and greater utility.	1.977
Kobayashi et al[65]	2015	Dynamic alignment of transtibial prostheses through visualization of socket reaction moments	Level IV. Smart Pyramid™ (currently Europa™) was used to measure the socket reaction moments under alignment conditions from an amputee with transtibial prosthesis. Socket reaction moments could complement information available to prosthetists to optimize prosthetic alignment.	0.930
Koehler-McNicholas et al[77]	2017	The influence of a hydraulic prosthetic ankle on residual limb loading during sloped walking	Level II. Comparison of a passive, hydraulic ankle–foot prosthesis to two related, non-hydraulic ankles in seven subjects on an instrumented treadmill set at various slopes. No significant differences in the torque at the distal end of the prosthetic socket.	2.776
Lamers et al[82]	2019	Subject-specific responses to an adaptive ankle prosthesis during incline walking	Level II. Gait analysis on seven individuals with unilateral transtibial amputation with a microprocessor-controlled ankle that adjusts ankle set-point angle to the slope. Patients walked with vs. without this set-point adjustment. The microprocessor-controlled ankle increased minimum toe clearance for all subjects.	2.576
Lansade et al[74]	2018	Mobility and satisfaction with a microprocessor-controlled knee in moderately active amputees: a multi-centric randomized crossover trial	Level II. Thirty-five individuals with transfemoral amputation or knee disarticulation; reduced median TUG time ($P = 0.001$), higher mean global LCI-5 ($P = 0.02$). Median global satisfaction score increased ($P = 0.001$), SF-36v2 improved ($P = 0.03$) after microprocessor-controlled knee use in comparison to non-MPK.	4.196
Lenz et al[60]	2018	A new method to quantify liner deformation within a prosthetic socket for below knee amputees	Level IV? Using a reflective marker system and a custom clear socket, evaluations were conducted with a clear transparent test socket mounted over a plaster limb model and a deformable limb model. Static and dynamic inter-marker distances within day and across days confirmed the ability to accurately capture displacements.	2.576
Lura et al[71]	2015	Differences in knee flexion between the Genium and C-Leg microprocessor knees while walking on level ground and ramps	Level II, randomized experimental crossover of persons with transfemoral amputation using the Genium and C-Leg microprocessor knees ($n = 25$), with an observational sample of non-amputee controls ($n = 5$). Gait analysis by 3D motion tracking of subjects ambulating at different speeds on level ground and on 5° and 10° ramps. Use of the Genium resulted in a significant increase in peak knee flexion for swing (5°, $p < 0.01$, $d = 0.34$) and stance (2°, $p < 0.01$, $d = 0.19$) phases relative to C-Leg use. There was a high degree of variability between subjects, and significant differences still remain between the Genium group and the control group's knee flexion angles for most speeds and slopes.	1.636
McLean et al[63]	2019	Socket size adjustments in people with transtibial amputation: effects on residual limb fluid volume and limb-socket distance	Level III. Recording of socket size, limb fluid volume, and distance from the limb to the socket, termed 'sensed distance', while 10 transtibial amputees walked on a treadmill wearing a motor-driven, cabled-panel, adjustable socket. Participants accepted socket sizes between –5% and +5% of their neutral socket volume. Rapid increase in limb fluid volume and sensed distance upon socket enlargement, rapid decrease upon reduction. Gradual changes in fluid volume and sensed distance.	1.977
Möller et al[69]	2019	Reduced cortical brain activity with the use of microprocessor-controlled prosthetic knees during walking	Level II. Individuals with a transfemoral or knee-disarticulation amputation, using non-microprocessor-controlled prosthetic knee ($n=14$) or microprocessor-controlled prosthetic knee ($n=15$) joints and healthy controls ($n=16$). Significant increase in cortical brain activity of individuals walking with a non-microprocessor-controlled prosthetic knee when compared to healthy controls ($p < 0.05$) and individuals walking with an microprocessor-controlled prosthetic knee joint ($p < 0.05$).	1.482
Pickle et al[83]	2017	The functional roles of muscles, passive prostheses, and powered prostheses during sloped walking in people with a transtibial amputation	Level II. Walking simulations from experimental kinematic and kinetic data in eight people with a TTA using powered and passive prostheses and eight non-amputees. Amputated leg hamstrings generated more power to both legs on uphill slopes in comparison with non-amputees. Using the powered prosthesis on uphill slopes reduced the contributions from the amputated leg hamstrings in all segments.	1.916
Prinsen et al[66]	2017	The influence of a user-adaptive prosthetic knee across varying walking speeds: a randomized crossover trial	Level II. A randomized crossover trial with nine persons with a transfemoral amputation or knee disarticulation were included and measured with their own N-MPK and with the Rheo Knee II. Measurements were performed at preferred walking speed, 70% preferred walking speed and 115% preferred walking speed. No differences on peak prosthetic knee flexion during swing between prosthetic knee conditions, prosthetic knee flexion increased with walking speed for both prosthetic knee conditions. At 70% preferred walking speed, vaulting of the intact ankle was decreased while walking with the Rheo Knee II compared to the N-MPK condition ($P = 0.028$). No differences in peak vertical acceleration of the pelvis during initial and mid-swing of the prosthetic leg.	2.273

(continued)

Table 2 (continued)

Author	year	Title	Findings	IF
Prinsen et al[68]	2015	Influence of a user-adaptive prosthetic knee on quality of life, balance confidence, and measures of mobility: a randomised cross-over trial	Level II, randomized crossover trial with nine patients. Higher scores were found for the Rheo Knee® II on the Residual Limb Health subscale of the Prosthesis Evaluation Questionnaire when compared to the non-microprocessor-controlled prosthetic knee (median [interquartile range] resp. 86.67 [62.21–93.08] and 68.71 [46.15–94.83]; P = 0.047). In addition, participants needed significantly more steps to complete an obstacle course when walking with the Rheo Knee® II compared to the non-microprocessor-controlled prosthetic knee (median [interquartile range] resp. 23.50 [19.92–26.25] and 22.17 [19.50–25.75]; P = 0.041). On other outcome measures, no significant differences were found.	2.403
Rink et al[55]	2016	Elevated vacuum suspension preserves residual-limb skin health in people with lower-limb amputation: randomized clinical trial	Level I, comparison of EVS with non-elevated vacuum suspension in 10 people with lower-limb amputation. EVS improved residual-limb oxygenation during treadmill walking, reactive hyperaemia was attenuated, skin barrier function was preserved with EVS but disrupted after control socket use.	1.277
Sanders et al[61]	2017	Effects of socket size on metrics of socket fit in trans-tibial prosthesis users	Level II. Nine participants were each provided with two sockets, a duplicate of their as-prescribed socket and a modified socket that was enlarged or reduced by 1.8 mm. Visual analysis of plots and estimated effect sizes (measure as mean difference divided by standard deviation) showed largest effects for step time asymmetry, step width asymmetry, anterior and anterior-distal morning-to-afternoon fluid volume change, socket comfort scores, and self-reported measures of utility, satisfaction, and residual limb health.	1.785
Sanders et al[62]	2018	Residual limb fluid volume change and volume accommodation: relationships to activity and self-report outcomes in people with trans-tibial amputation	Level II. Twenty-nine participants – 'accommodators' (*n* = 14) or 'non-accommodators' (n = 15) based on self-report prosthetic sock use. Morning-to-afternoon percentage limb fluid volume change per hour was not strongly correlated to percentage time weight-bearing or to self-report outcomes. As a group, non-accommodators spent more time with their prosthesis doffed and reported better outcomes than accommodators.	1.482
Schmalz et al[79]	2019	Lower limb amputee gait characteristics on a specifically designed test ramp: preliminary results of a biomechanical comparison of two prosthetic foot concepts	Level II, biomechanical analysis of 'Daily Life Feet' (DLF) vs. 'microprocessor-controlled feet' (MPF) on a specifically designed ramp – four transtibial amputees vs. 10 non-amputees (NA). Compared to DLF the MPF considerably improved the ankle adaptation to the abruptly changing inclination which was reflected by a significantly increased stance phase dorsiflexion which was comparable to the NA group.	2.414
Struchkov et al[81]	2016	Biomechanics of ramp descent in unilateral trans-tibial amputees: comparison of a microprocessor controlled foot with conventional ankle–foot mechanisms	Level II, prospective comparative study including nine active unilateral transtibial amputees repeatedly walking down a 5° ramp, using a hydraulic ankle–foot with microprocessor active or inactive or using a comparable foot with elastic ankle device. Foot-flat was attained fastest with the elastic foot and second fastest with the active hydraulic foot (P = 0.001). Prosthetic shank single-support mean rotation velocity (p = 0.006), and the flexion (P = 0.001) and negative work done at the residual knee (P = 0.08) were reduced, and negative work done by the ankle–foot increased (P = 0.001) when using the active hydraulic compared to the other two ankle types.	1.874
Bionics				
Clites et al[52]	2018	Proprioception from a neurally controlled lower-extremity prosthesis	Level III, surgical reconstruction of agonist–antagonist myoneural interfaces (AMI) in one patient after transtibial amputation. Improved control over prosthesis compared to a group of four subjects with traditional amputation.	17.161
De Pauw et al[87]	2019	Cognitive performance and brain dynamics during walking with a novel bionic foot: a pilot study	Level II. Six able-bodied, six unilateral transtibial and six unilateral transfemoral amputees performed trials. In contrast to transtibial amputees, transfemoral amputees required more attentional demands during walking with a novel powered prosthesis compared to the current passive prosthetic device and able-bodied individuals (reaction time and accuracy: $p \leq 0.028$).	2.776
Hargrove et al[88]	2015	Intuitive control of a powered prosthetic leg during ambulation: a randomized clinical trial	Level II. Electrodes were placed over nine residual limb muscles and EMG signals were recorded as patients ambulated and completed 20 circuit trials. Including EMG signals and historical information in the real-time control system resulted in significantly lower classification error compared with using mechanical sensor data only.	37.684
Malcolm et al[86]	2015	The influence of push-off timing in a robotic ankle–foot prosthesis on the energetics and mechanics of walking	Level IV. Ten able-bodied participants wore a tethered ankle–foot prosthesis emulator on one leg using a rigid boot adapter. When push-off began at or after leading leg contact, metabolic rate was about 10% lower than in a condition with Spring-like prosthesis behaviour. Early push-off led to increased prosthesis-side vastus medialis and biceps femoris activity during push-off and increased variability in step length and prosthesis loading during push-off.	2.419
Young et al[89]	2014	Analysis of using EMG and mechanical sensors to enhance intent recognition in powered lower limb prostheses	Level IV. EMG and mechanical sensor data from eight transfemoral amputees using a powered knee/ankle prosthesis. EMG information was not as accurate alone as mechanical sensor information ($p < 0.05$); EMG in combination with mechanical sensor data did significantly reduce intent recognition errors ($p < 0.05$).	3.295

Note. IF, impact factor; MPK, microprocessor-controlled knee; TFA, transfemoral amputation; CAD/CAM, computer-aided design/manufacturing; TUG, time up-and-go test; Locomotor capabilities index-5, LCI-5; Short form health survey, SF-36; TTA, transtibial amputation; EVS, elevated vacuum suspension; EMG, electromyography.

of the study (GMH, KD), including the study selection over the three steps as mentioned above. Those studies finally eligible for the review were evaluated by the first author (GMH). No additional analyses were performed.

Surgical techniques including bone-bridging, distal weight-bearing femoral implants, adductor myodesis

Tibiofibular bone synostosis is an option to modify the transtibial residuum into an intentionally full weight-bearing stump by creating an osseous bridge between the cut ends of the fibula and tibia. A recent retrospective comparative study in young military servants could not show any differences between the bone-bridging technique (Ertl procedure) and Burgess procedures in either speed for the temporal-spatial parameters during gait analysis or mechanical work metrics.[15] In a small case-control study, 11 participants after Ertl-procedure performed a five-time sit-to-stand task quicker (9 sec) than the seven participants with Non-Ertl TTA (13 sec). Although the intact knees of both groups produced more knee peak power, the ground reaction forces of the affected side in the Ertl group was significantly higher.[16] A little advantage of a greater roll-off vertical ground reaction force during the fast walking in the bone-bridge group was overwhelmed by the influence of the residual limb length when the two groups were combined to test in a linear regression model, showing that patients with longer residual limbs had generally improved in force values during self-selected walking.[15] Another huge case series of 512 transtibial amputees after combat-related amputation between 2001 and 2011 showed equal results in military-specific outcome data after Physical Evaluation Board Liaison Office (PEBLO) rating (0–100). However, the Ertl group returned to active duty at a higher rate ($p = 0.021$).[17] Thus, there is only a small amount of prospective data about the advantages of the Ertl technique, and further prospective data on this topic is urgently needed. Young, mobile patients might profit from the procedure. We are looking forward to the results of the transtibial amputation outcomes study (TAOS).[18]

Guirao et al described an attempt to allow distal support of the residuum after transfemoral amputation by means of a titanium distal femoral implant. In this experimental before and after case series including 10 TFA patients, participants showed improvements in their walking distance as well as their gait speed after 14 months follow-up.[19] Finite element analysis of a similar implant shows that contact forces and shear forces are clearly shifted to the weight-bearing area, holding off friction from the lateral stump area.[20] However, these two level IV studies deal with an important topic not ready to be used in an everyday clinical setting.

Patients with adductor myodesis might be easier to fit with a prosthesis and might be more likely to remain able to ambulate.[21,22] After transfemoral amputation, stump length or residual limb ratio are important parameters, with increasing flexion-abduction thigh deformity being created in a higher level of transection due to loss of adductor muscle and muscular imbalance. Short residual limb length and flexion-abduction both lead to more pelvic tilt, lateral flexion, obliquity excursion and slower gait velocity.[23] Older literature shows the advantage of adductor myodesis in TFA and many amputees might benefit from the procedure. New prospective literature would be preferable.

In lower-extremity amputation due to trauma, critical length can sometimes be achieved using 'spare parts' surgery. This technique describes the scavenging of skin, free muscle flaps and/or bone tissue from the non-salvageable extremity to improve the function of the remaining limb/stump, requiring expertise and experience from the surgeon.[24] The literature reports case studies and small case series on this topic concerning the lower extremity. To prevent above-knee amputation, Peng and Lahiri showed a form of reconstruction using an innervated medial plantar flap being harvested from the amputated leg with success in a lower leg amputation.[24]

Bone-anchored prostheses (BAP)

The direct anchoring of a prosthesis in the bone by an implant has proven to be an excellent alternative for transfemoral amputees who suffer from complications of a conventional socket prosthesis especially when heat sensation, bacterial infections and perspiration lead to frequent discomfort. Studies including bone-anchored prostheses were categorized as evidence level III and IV and were mostly cohort studies. Topics were sorted into three categories: clinical outcome, complication/infection and bone-remodelling/loading.

Clinical outcomes

In terms of surgical procedure, available literature recommends a standardized two-stage operation. First, the fixation screw/stem is implanted in the medullary canal, followed by a non-weight-bearing healing phase. In a second step, the soft-tissue technique and formation of a direct skin–bone interface, again followed by a further increasing weight-bearing rehabilitation period with 3–6, 1.5–2 or 3–4 months between Stage 1 and 2, and a total recovery time of 3–18 or 2.5–4.5 months is done. All studies showed significant improvements in overall mobility scores. Muderis et al described the Osseointegration Group of Australia accelerated protocol (OGAAP-1) for a two-stage osseointegrated reconstruction in 50 TFAs with improvements in all measured tests: Questionnaire of transfemoral amputees (Q-TFA), Short Form 36 (SF36), amputation Mobility Predictor scores, six-minute walk-test (6-MWT) and time up-and-go test (TUG) in both a one and a two-year follow-up study.[25,26] Hagberg et al showed improvements in prosthetic function and quality of life in TFAs with osseointegrated prostheses for the rehabilitation of amputees (OPRA) implants compared to socket-users in a prospective case-control study, but pointed out that the use of walking aids and the presence of phantom pain were unchanged.[27] Leijendekkers et al reported a case series of 40 consecutive patients with improvements in strength, walking distance and quality of life measures but without improvements in the 6-MWT under repeated measures before, 6 and 12 months post-operatively after integral leg prosthesis (ILP), osseointegrated prosthetic limb (OPL) and custom-made implants.[28]

Both osseo-perception, the ability to directly perceive pressure, position and balance of the leg, and muscle activity patterns comparable to healthy subjects during gait after 12–24 months may be reasons for the overwhelming clinical improvements.[29,30] Furthermore, amputees show reduced energy costs of walking and less discomfort of sitting in socket-prostheses.[31,32]

Complications and infection

Several level IV case series reported the surgical outcomes of bone-anchored prostheses, in which the risk of infection in reported long-term outcomes is, at least while earlier surgical techniques were used, a weak spot. The cumulative 10-year risk of explanted implants due to osteomyelitis from a very early Swedish cohort was 9%.[33] The UK trial with OPRA implants showed improvements in implant survival from 40–80% after a minimum follow-up time of nine years after the introduction of the OPRA implant protocol with removal of implant due to infection in 3/18 patients.[34] In line with these results a German group also reported very early results (mean follow-up two years) with a reduction of infection rate from 55% to 0% after an implant design change of the ILP prosthesis.[35] In a prospective cohort study, the OPRA implant shows an implant survival of 92% after five years post-operatively with a deep infection risk of 25% and partially recurring superficial soft-tissue infections in 34 out of 51 (66%) of the patients, which was controlled conservatively and by antibiotic treatment.[36] The Australian group reported an infection rate of 43% at two-year minimum follow-up in traumatic unilateral transfemoral amputees without any implant removal. A joint study from Australia and the Netherlands summarizing results of 86 patients with press-fit implants and a minimal follow-up of two years and a mean follow-up of 34 months showed a total infection rate of 34%, with no osteomyelitis being noted in this shorter observation period. On the other hand, 26% of patients needed further intervention; 17% due to stoma hypergranulation, 7% due to femur or pin fracture and 2% of different causes.[37]

The potential risk of infection has provoked attempts for a deeper understanding of microbiological aspects. There is, for example, a positive correlation of TNF-alpha expression and presence of *Staphylococcus aureus* in bone-anchored prostheses, and for fixture loosening being correlated with reduced interleukin 10. However, the authors conclude that further long-term studies are needed in order to precisely understand host–bacteria interactions.[38] Furthermore, there is evidence that there are different degrees of biofilm production by bacteria causing implant-associated infection, which may influence future decision making by orthopaedic surgeons.[39] Porous titanium alloy flanges that are coated with fibronectin-functionalized hydroxyapatite may reduce the susceptibility to infection by increasing soft-tissue integration.[40]

Load and cortical bone remodelling

Recent radiographic and X-ray absorptiometry data according to Haket et al contradicts earlier observations of a decrease of cortical bone around press-fit prostheses (ILP). Twenty-four-month follow-up radiographs showed a mean increase of 0.54 mm of cortical thickness in all periprosthetic zones compared with immediate post-operative radiographs;[41] however, distally from the bone-integrated parts next to the abutment in OPRA, loads applied to the implant may compromise the bone.[42]

Targeted muscle re-innervation (TMR), regenerative peripheral nerve interface (RPNI)

There is increasing evidence for significant pain relief by new neuromuscular surgical techniques ready to be implemented into the daily routines of amputation surgery. The incidental observation of fewer limb pain sensations in patients after TMR for bionic reconstruction in the upper extremity have led to an increasing use of this technique in the lower extremity.[43,44] There is a high prevalence of residual limb pain and phantom pain of the limb in lower-extremity amputees. Although different in their origins, they have commonly been considered to be difficult to treat using a number of low efficient surgical and non-surgical treatment options until now. Residual limb pain is mostly caused by cut nerve endings sprouting and interacting with scar tissue leading to painful neuromata, whereas phantom limb pain is seen in a complex interaction with multiple levels of the central nervous system and cortical reorganization. A randomized controlled trial by Dumanian et al resulted in improved phantom limb pain and trend towards improved residual limb pain in major limb amputees by removing neuromata and redirecting the newly cut nerve, originally controlling muscles of the amputated limb, to a newly divided nearby motor nerve above the amputation.[43] (See Fig. 4) In a recent multicentre cohort study with 51 patients undergoing major limb amputation

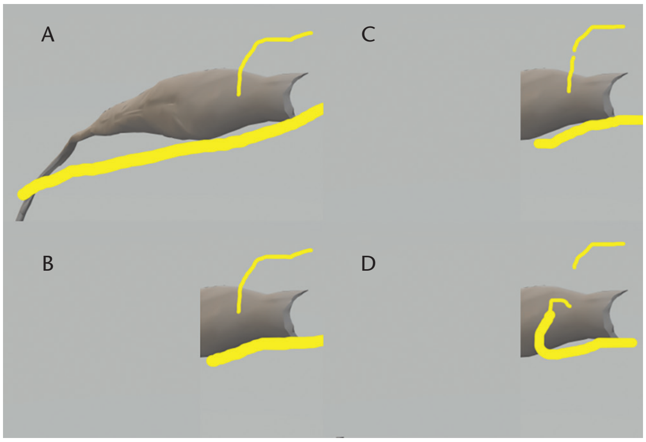

Fig. 4. Illustration of the principle of targeted muscle reinnervation (TMR). (A) Muscle before amputation with motor nerve and by-passing mixed nerve. (B) Muscle and by-passing nerve are cut during amputation. (C) Muscle is denervated. (D) Mixed nerve re-innervates the muscle. (based on BodyParts3D, [http://lifesciencedb.jp/bp3d/] © The DatabaseCenter for Life Science licensed under CC Attribution-ShareAlike 2.1 Japan)

with immediate TMR compared with unselected major limb amputees without TMR, TMR was associated with 3.03 lower odds for PLP.[45] Meanwhile there has been a feasibility study to provide roadmaps for incision placement and identification of motor nerve targets to guide surgeons in the performance in both lower-leg and transfemoral amputations.[46–48] In the lower leg, for example, handling the peroneal nerve is done through an anterolateral approach targeting the tibialis anterior and extensor digitorum muscle by finding motor entry points in both of these muscles.[46] In transfemoral amputees, coaptation of the tibial part of the sciatic nerve to motor entry points in the semimembranosus muscle and a coaptation of the peroneal part to motor entry points of the biceps femoris muscle have been described.[47] Very recently, 22 lower-extremity amputees due to bone and soft-tissue sarcoma and further malignancies underwent TMR primarily. In comparison to a cross-sectional sample of unselected oncological amputees, their phantom limb pain and residual limb pain respectively were lower after one year.[49]

Another technique derived from animal experiments for the purpose of prosthetic control has now been introduced as a reproducible method for neuroma therapy. Regenerative peripheral nerve interface (RPNI) describes a method of providing free muscle grafts as physiological targets for peripheral nerve ingrowth. Woo et al describe surgical methods of how to harvest a small free muscle graft and wrap it around newly cut nerve endings of peroneal and sciatic nerves and bury it into surrounding tissue in a case series of 14 lower-extremity neuroma pain patients.[50] (see Fig. 5) Patients reported a 71% reduction in neuroma pain score from 8.7 ± 1.4 pre-operatively to 2.5 ± 2.1 post-operatively. In a further retrospective controlled study RPNI in major limb amputees resulted in a lower incidence of both symptomatic neuromata and phantom limb pain in 51% compared to 91% in control patients.[51] Prophylactic RPNI might potentially become a standard method in prohibiting stump pain in a simple, easy to implement, time and cost-efficient manner.

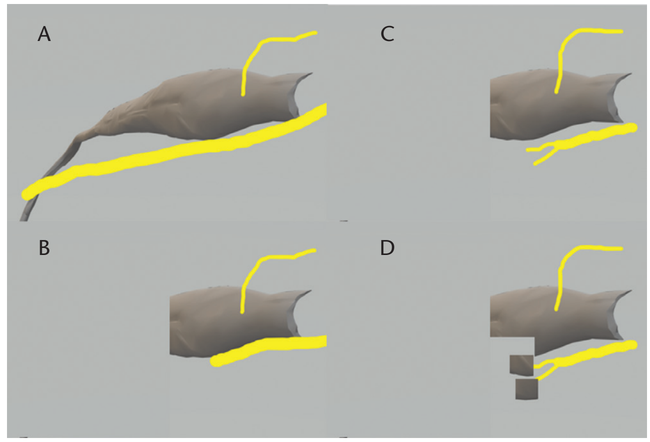

Fig. 5. Illustration of the principle of regenerative peripheral nerve interface (RPNI). (A) Muscle before amputation with motor nerve and by-passing mixed nerve. (B) Muscle and by-passing nerve are cut during amputation. (C) Two free muscle grafts are harvested from a nearby muscle. (D) Two RPNIs are designed by wrapping the nerve ends with the free muscle flaps. (based on BodyParts3D, [http://lifesciencedb.jp/bp3d/] © The DatabaseCenter for Life Science licensed under CC Attribution-ShareAlike 2.1 Japan)

Prosthetic technology

The clinical standard of care for limb amputation surgery has not changed significantly over the last two centuries[52] and although remarkable costs are associated with hospital and rehabilitation care as well as with prosthetic provision, there appears to be very little high-quality literature about prosthetic interventions suggesting only 1.4 evidence statements available per year.[53] Most studies are low-numbered pre–post case series with an evidence level of II–IV and only a few studies are randomized crossover trials. The following topics were addressed by 39 included studies: socket, interface, alignment, microprocessor knee, ankle/foot (see Fig. 6).

Socket, interface and alignment

A lot of different scientific approaches to improve skin health and prosthetic fitting are pushing onto the market. Vacuum-assisted suspension systems (VASS) show superiority over total surface bearing (TSB) interfaces in terms of decreased pistoning and improved post-operative mobility. Elevated vacuum suspension systems demonstrated improvements in uphill and downhill walking over non-vacuum,[54] and a

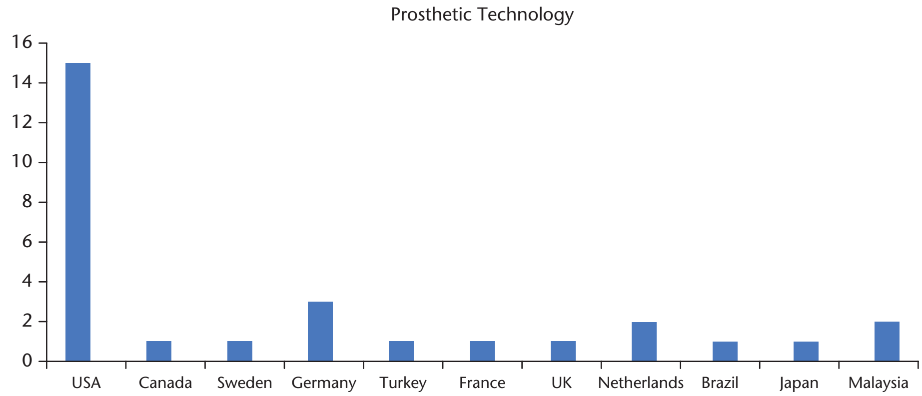

Fig. 6. Numbers of publications split by countries of origin in category 'prosthetic technology'.

randomized clinical trial in a crossover design comparing elevated vacuum suspension against non-vacuum showed an attenuating socket-induced reactive hyperaemia and preserved skin barrier function.[55]

Two included observational studies comparing different suspension systems including a pin/lock, a seal-in and a magnetic suspension during ramp walking identified that seal-in liners caused the highest peak pressures, leaving the participants more satisfied with magnetic and pin/lock systems.[56,57] Meanwhile, computer-aided design/manufacturing (CAD/CAM) renders many benefits at least in TTAs compared with manually manufactured sockets. Apart from shorter socket application and adaption, patients with TTAs feel more satisfied, pain free and do walk longer distances than those with conventional TTAs.[58] Furthermore, finite element modelling seems promising in simulating modern prosthesis design. According to Cagle et al, a transtibial finite element model (FEM) including the complete liner–socket geometry and interfaces between both limb and liner, and liner and socket, showed results in accordance with participants' tissue responses.[59] Further improvements to improve liner design and prosthetic fitting by a motion capture system-based method ought to detect deformation of gel liner.[60]

Besides skin problems, fluctuations in limb volume are very common. Patients with higher activity levels might have less fluid volume loss, but morning-to-afternoon fluid volume change might also depend on yet unknown factors. Nevertheless, volume changes may compromise patients' wellbeing as well as several objective parameters, such as step time and wide asymmetry.[61,62] McLean et al conducted an interventional study on TTAs, adjusting the socket to changes in limb fluid volume and socket size in order to be able to maintain consistent limb fluid volume within a certain range. Consequently, they found that an automatic adjustable socket could alleviate the problem of volume fluctuations.[63] A completely different approach for socket fit was taken in a rural setting in Indonesia. A main goal was that measurement, manufacturing and fitting could be performed in one. Therefore, a modular socket system, produced directly on the residual limb, was tested in a quantitative longitudinal study. Fifteen lower-limb amputees showed constant satisfaction and general health values over the period of 4–6 months. Not unimportantly, prosthetic alignment affects gait, while foot rotation influences coronal socket reaction moments.[64] Prosthetic alignment has depended on the manufacturing skills of the prosthetists; however, socket reaction moments could be used to complement knowledge to optimize loading on sensitive areas, as Kobayashi et al demonstrate in a technical note.[65]

Despite most advanced technology, the immediate benefit for amputees still has to be transposed into literature with a higher level of evidence rather than being presented in technical notes and low-numbered case series.

Microprocessor-controlled knee prostheses

Prosthetics ought to support the body weight, allow mobility and balance. In a randomized crossover trial comparing active microprocessor-controlled knees (A-MPKs) and Non-MPKs while walking at different speeds on level ground, no differences in any gait parameters could be seen.[66] However, amputees still face difficulties with walking on uneven ground, negotiating slopes and stairs and have issues with increased metabolic costs, frequent falls and slower gait.[67] Despite contradictory results,[68] motorized actively powered prosthetic components such as A-MPKs, are able to overcome these obstacles partly by volitional control and autonomous adaption.[67] Compared to non-MPK users, A-MPK users can reduce their cortical brain activity by decreasing their cognitive demands during walking,[69] and there may also be functional differences between different A-MPKs as indicated by Bell et al and Lura et al.[70,71] Fuenzalida Squella et al could show a decline in self-reported falls by 77% and significant improvements in balance confidence in a comparative within-subject clinical study including 13 young active patients when using the MPK.[72] In line with these results, Kaufman et al could show similar improvements by the same methods in a study including 50 transfemoral amputees, with a mean age of 69 years.[73] Not only do highly active amputees benefit from a microprocessor-controlled knee, but also amputees with moderate activity levels, as seen in a recent multicentre crossover trial randomized to different MPK/Non-MPK sequences.[74] Even safety issues in terms of more natural walking patterns and the perception of safety when low-active TFA changed from a mechanical joint to an active MPK could be shown in a pilot study.[75] However, Highsmith et al emphasized in a randomized experimental crossover design study comparing two different generations of MPKs that although Genium users improved concerning upper-body flexibility and balance over C-Leg Genium users, they were still not as persistent as non-amputees.[76]

Microprocessor-controlled ankle prostheses (MPA)

The benefit of passive MPA over non-hydraulic ankles in TTAs is not overwhelming in either gait kinematics or in socket comfort. Koehler-McNicholas et al conducted a controlled study with seven Medicare functional classification level (K- level) 3 TTAs which showed that all feet were sufficient for slope walking; however, none of the feet could mimic able-bodied controls in terms of ankle function.[77] Montgomery et al pointed out that the use of active MPAs shows only a small benefit compared with passive-elastic ankles; however, gait symmetry was improved and metabolic costs were reduced when ascending and descending ramps with an active MPA compared with a passive MPA,[78] and Schmalz et al could show that a group of four TTAs with MPA had a nearly normal knee extension moment and a significantly increased stance-phase dorsiflexion when compared with non-amputees in a ramp-walk study with abruptly changing inclination ankles.[79] The same group found that an auto-adaptive dorsiflexion stop as well as a sufficient range of motion are crucial for standing on inclinations.[80] Another study emphasized the reduction of biomechanical compensation in the knee due to MPA.[81] Most studies present group levels of gait, however. Lamers et al pointed out in a study with seven subjects, that with active-ankle slope-walking some patients preferred forefoot landing, whereas others rearfoot landing. This indicates the importance of individual walking styles in acceptance of powered ankle walking.[82] Pickle et al used electroencephalogram (EEG) data on muscle groups to use musculoskeletal modelling and simulation in TTAs using active MPA and passive prostheses. This data indicated that the power added by A-MPA reduced the need for hamstrings to compensate for lost ankle function.[83]

After Chopart amputation there is an inverse relationship between range of ankle motion and forefoot lever, so that although very restricted to a sagittal joint movement of about 10°, the most suitable forefoot lever of about 1 Nm/kg was reached by a high-profile prosthesis with a ventral shell.[84]

Very limited data are available about kinematics and gait patterns in TFAs provided with powered knee-ankle prostheses (PKA). Jayaraman et al reported similar to normal gait patterns and a reduced level of asymmetry specifically in lower back muscles compared to MPK in a limited case series.[85]

Bionics

Actively powered prosthetic joints or limbs need different ambulation modes and control sequences to make a patient able to walk on level ground as well as in ramp or stair ascent and descent. An automatic identification of the actual walking mode by mechanical sensors is necessary to safely mimic a patient's gait. A lot of additional knowledge is needed to improve ambulation by powered devices in points of metabolic rate reduction or different amputation levels. Malcolm et al could show that the timing of push-off with a powered ankle prosthesis after leading leg contact saved energy by 10%, reducing vastus medialis and biceps femoris activity.[86] De Pauw et al found a higher attentional demand in TFAs when walking with a powered ankle joint than TTAs in an experimental study comparing the Go-No go-Go task in electroencephalogram data. The authors concluded that the propulsive forces of powered ankle joints ought to be better controlled in TFAs.[87] Furthermore, it is necessary to reduce sensor errors to enable safe gait. Hargrove et al combined mechanical sensor data with real-time electromyography (EMG) data and could reduce the classification error, which is defined as the percentage of false predicted steps of a control system, from 14.1% to 7.0% in a blinded randomized crossover trial of seven unilateral above the knee/knee-disarticulation patients.[88] Similarly, Young et al could reduce the intent recognition error when changing from one ambulation mode to another by combining EMG and mechano-sensory data.[89]

Proprioception is essential for spatial positioning. Muscle spindles are identified as mediators of joint proprioception[90] and agonist–antagonist muscle pairs are crucial in natural joint sensation.[91] The agonist–antagonist myoneural interface (AMI) uses a surgically created tendon-to-tendon construct made of antagonizing muscles in order to create stable and natural mechanoreceptor-proprioceptive signalling to the central nervous system.[52] Clites et al described an unilateral transtibial amputee with one AMI composed of tibial posterior and peroneus longus tendons to control a bionic ankle joint in eversion and inversion. A second AMI composed of the lateral gastrocnemius muscle and tibialis anterior tendon was designed to control a bionic ankle joint in dorsiflexion and plantarflexion.

Conclusion

In conclusion, patients ought to be supported to receive appropriate prosthetic components or available new surgical therapies to reach their everyday goals in a desirable way. Both bone-anchored implants and soft-tissue techniques in amputation surgery give patients hope for drastic improvements in function and quality of life and ought to be considered for lower-limb amputees. Bone-anchored prostheses enhance stability without serious problems with the surrounding skin and soft-tissue; TMR and RPNI provide surgical techniques that are considerably responsible for improved stump and phantom pain relief.

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ICMJE CONFLICT OF INTEREST STATEMENT

RB reports board membership of, consultancy to and stock options in Integrum AB, outside the submitted work.

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