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Osseointegrated upper limb prostheses with and without neuromuscular control: benefits and risks

Sassu P, Granberg H, Bernhardsson S, Lindström AC, Magnusson K, Nachemson A, Stadig I, Wartenberg C

Osseointegrated upper limb prostheses with and without neuromuscular control: benefits and risks

[Osseointegrerade armproteser med och utan neuromuskulär kontroll: nytta och risker]

Sassu P[1], Granberg H[1*], Bernhardsson S[2], Lindström AC[3], Magnusson K[4], Nachemson A[1], Stadig I[4], Wartenberg C[2]

[1] Region Västra Götaland, Sahlgrenska University Hospital, Dept of Hand Surgery, Gothenburg, Sweden

[2] Region Västra Götaland, HTA-centrum, Gothenburg, Sweden

[3] Närhälsan Sörhaga Rehabilitation Clinic, Alingsås, Sweden

[4] Region Västra Götaland, Medical Library, Sahlgrenska University Hospital, Gothenburg, Sweden

[*]Corresponding author

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1. Abstract

Background

Acquired or congenital upper limb loss results in significant disability, especially with more proximal limb deficiency. Currently, most patients are provided with a socket prosthesis controlled by myoelectric signals captured by skin-surface electrodes. For some patients, problems in fitting and using these prostheses arise. Fixation of the prosthesis by an osseointegrated abutment is an alternative. Osseointegrated prostheses can be controlled by skin surface electrodes (non-neuromuscular, osseointegrated prostheses) or via neuromuscular control by implanted electrodes capturing efferent signals and providing feedback by cuff electrodes on nerves.

Question at issue

For adult individuals with congenital deficiency or amputation of an upper limb, what are the benefits and risks with neuromuscular osseointegrated prostheses controlled by implanted electrodes (I1) compared with non-neuromuscular osseointegrated prostheses (C1) in terms of function, activities of daily living, health-related quality of life, reoperation, and complications? How does each of these types of osseointegrated prostheses (I1 and I2) compare with standard, myoelectric, socket prostheses controlled by surface electrodes (C2)?

Methods

Database searches were performed in October 2021. Titles and abstracts, and later full text articles, were screened and selected independently by at least two authors. Final inclusion was decided upon in consensus amongst all authors. Included studies were critically appraised, and data were extracted. For outcomes where comparative data were available, certainty of evidence was assessed according to GRADE.

Results

Ten studies were included; one non-randomised controlled study, two within-patient comparisons, six case series, and one qualitative study. In total, the studies involved 37 patients; four patients with a neuromuscular osseointegrated prosthesis (I1), 26 patients with non-neuromuscular osseointegrated prostheses (I2/C1), and seven patients with myoelectric socket prostheses (C2).

Function: The ability to perform small movements and grasp fragile objects was significantly improved with neuromuscular (I1) compared with non-neuromuscular, osseointegrated prostheses (C1). However, due to study limitations and serious imprecision, it is uncertain whether function is improved with neuromuscular compared with non-neuromuscular, osseointegrated prostheses (GRADE ⊕◯◯◯).

The detection threshold for vibration was significantly lower with non-neuromuscular, osseointegrated (I2) than with myoelectric socket prosthesis (C2), whereas there was no difference in detection of pressure. However, due to study limitations and serious indirectness and imprecision, it is uncertain whether function is improved with non-neuromuscular, osseointegrated compared with myoelectric socket prostheses (GRADE ⊕◯◯◯).

Patients' experience: All three patients included in the qualitative study described that they experienced improved prosthetic control and function in daily tasks, as well as positive psychosocial effects, when using their neuromuscular, osseointegrated prosthesis (I1) compared to their previous experience of using non-neuromuscular, osseointegrated prostheses (C1).

Complications: For neuromuscular, osseointegrated prostheses (I1), two serious adverse events occurred in one of four patients who underwent implantation of electrodes, after previous provision of an osseointegrated abutment. The patient had to be hospitalised due to sepsis, and at a later point, the implanted electrodes were removed due to another infection. For non-neuromuscular, osseointegrated prostheses (I2), three of 18 patients with amputation at transhumeral level had their implants removed due to early loosening. Superficial infections and skin reactions at the penetration site, partial fracture during surgery to insert the fixation screw (eight of 18 patients), limited defects of the bony canal while drilling for the abutment (three of 18 patients), avascular skin flap necrosis (three of 18 patients), and one deep implant-associated infection were reported. In three of 11 patients with non-neuromuscular, osseointegrated prostheses at transradial level, fixture fractures were reported with prostheses of an older design used prior to 2003.

No comparative studies reporting activities of daily living, health-related quality of life, complications, re-operation, or extent of use were identified.

Economic aspects

Data on cost per patient are uncertain as data from only a few patients were available, but results indicate that the cost is substantially higher for neuromuscular and non-neuromuscular, osseintegrated prostheses compared with myoelectric socket prostheses. Among osseointegrated prostheses, the cost data point to neuromuscular implants being more expensive. The cost per patient varies substantially due to varying needs for revision surgery.

Concluding remarks

This HTA report is based on few studies, mostly case series. Worldwide, very few patients have been provided with osseointegrated upper limb prostheses and publications all stem from one hospital. The outcomes we sought to assess were scarcely reported, and comparative data were mostly lacking.

Comparing neuromuscular (I1) with non-neuromuscular, osseointegrated prostheses (C1), the certainty of evidence for any difference in function is very low. Yet patients with neuromuscular, osseointegrated prostheses expressed that they experienced benefits in terms of function. Two serious adverse events were reported in one patient who was hospitalised due to sepsis; later another infection led to removal of the implanted electrodes.

No studies compared neuromuscular, osseointegrated (I1) with myoelectric socket prostheses (C2).

Comparing non-neuromuscular, osseointegrated (I2) with myoelectric socket prostheses (C2), the certainty of evidence for improved function of osseointegrated prostheses is very low. Various complications, including serious adverse events, in relation to osseointegrated fixation were reported.

Additional substantial costs for prostheses with osseointegration and neuromuscular control must be considered.

2. Populärvetenskaplig sammanfattning – Plain language summary in Swedish

Bakgrund
Medfödd eller förvärvad avsaknad av en arm medför signifikant funktionsnedsättning för patienter, speciellt när det gäller avsaknad av både under- och överarm. De flesta patienter får en hylsprotes som styrs av muskelsignaler som fångas upp av elektroder på armens hud. Några patienter har dock problem att sätta fast och att använda dessa proteser. Protesen kan då i stället fästas på en skruv direkt i skelettet, så kallad benförankring (osseointegrering). Utöver benförankringen har man även utvecklat en metod för att operera in elektroder i armen i syfte att registrera muskelsignaler och ge återkoppling via nerverna i den kvarvarande armstumpen (neuromuskulär styrning).

Fokuserad fråga
För vuxna patienter med medfödd eller förvärvad avsaknad av en arm, innebär användningen av en neuromuskulärt styrd benförankrad armprotes (som styrs med hjälp av inopererade elektroder) några fördelar eller risker jämfört med icke-neuromuskulärt styrda benförankrade proteser som styrs med elektroder på armens hud, vad gäller utfallen funktion, dagliga aktiviteter, livskvalitet, omoperation eller komplikationer? Har dessa proteser fördelar eller risker jämfört med hylsproteser som styrs med elektroder på armens hud?

Metod
Med hjälp av etablerade metoder identifierade vi vetenskapliga artiklar som kunde bidra till att ge svar på den aktuella frågeställningen. Databassökningar gjordes i oktober 2021. Urval gjordes av minst två författare och projektgruppen beslöt gemensamt vilka artiklar som skulle inkluderas i rapporten. De ingående studiernas kvalitet granskades kritiskt och för de utfall där så var möjligt gjordes en sammanvägd bedömning av resultatens tillförlitlighet enligt GRADE.

Resultat
Tio studier inkluderades, varav en icke-randomiserad kontrollerad studie, två studier med jämförelse av olika styrmetoder av samma patienter, sex fallserier och en kvalitativ studie. Sammanlagt involverade studierna 37 patienter; fyra patienter med neuromuskulärt styrda benförankrade proteser, 26 patienter med icke-neuromuskulärt styrda, benförankrade proteser, och sju patienter med hylsproteser.

Funktion: Studierna visade att patienterna i signifikant större utsträckning kunde utföra exakta rörelser med sin neuromuskulärt styrda, benförankrade protes och klarade oftare att greppa ömtåliga objekt än när de använde sin icke-neuromuskulärt styrda benförankrade protes. På grund av brister i studiekvalitet och låg precision är bedömningen dock att det är osäkert huruvida neuromuskulär styrning förbättrar funktionen av benförankrade armproteser jämfört med icke-neuromuskulär styrning (GRADE ⊕◯◯◯).
Tröskeln för att känna av skillnader i vibrationer var lägre för benförankrade proteser än för hylsproteser. Ingen skillnad sågs avseende tröskeln för att känna av skillnader i tryck. På grund av brister i studiekvalitet och överförbarhet samt låg precision är det osäkert huruvida benförankrade armproteser förbättrar funktionen av armprotesen jämfört med hylsproteser (GRADE ⊕◯◯◯).

Patienternas upplevelse: Alla tre patienter i den kvalitativa studien beskrev att de med neuromuskulärt styrda benförankrade proteser upplevde förbättrad kontroll av protesen, förbättrad

funktion i dagliga aktiviteter och positiva psykosociala effekter, jämfört med tidigare använd icke-neuromuskulärt styrd benförankrad protes.

Komplikationer: Två allvarliga komplikationer rapporterades hos en av fyra patienter som följdes upp efter att ha fått en neuromuskulär benförankrad protes med inopererade elektroder. Dessa patienter hade sedan tidigare en benförankrad protes. Den aktuella patienten behövde sjukhusvård pga blodförgiftning och vid en senare tidpunkt avlägsnades de implanterade elektroderna pga ytterligare en infektion.

Hos tre av 18 patienter med icke-neuromuskulärt styrda benförankrade armproteser med hudelektroder på överarmsnivå lossnade implantaten och behövde avlägsnas. Dessutom observerades att det förekom sprickor i benet hos åtta av 18 patienter samt skador på benkanalen hos tre av 18 patienter i samband med implantat av benförankringen, avaskulär nekros av hud (tre av 18 patienter) samt en djup implantatrelaterad infektion. Andra rapporterade komplikationer var ytliga infektioner samt hudreaktioner där benförankringen passerar huden. Hos tre av 11 patienter med benförankrad underarmsprotes av tidigare modell före 2003 rapporterades fraktur vid förankringen.

Inga publikationer identifierades som jämförde de olika protesmetoderna avseende utfallen hälsorelaterad livskvalitet, komplikationer, reoperationer, användningsgrad eller patientupplevelser.

Kostnader

Kostnaden per patient med de olika metoderna är osäker då underlaget bygger på ett fåtal patienter. Kostnaderna kan variera avsevärt mellan patienter beroende på om och vilken typ av komplikationer som kan inträffa. Underlaget tyder dock på att benförankrade proteser är betydligt dyrare än hylsproteser. Kostnadsskillnaden förklaras framför allt av kostnaderna för den operation som krävs för en benförankrad protes. Bland de benförankrade proteserna är kostnaden högre med neuromuskulärt styrda proteser jämfört med icke-neuromuskulärt styrda benförankrade proteser.

Sammanfattande slutsatser

Denna HTA-rapport är baserad på ett fåtal studier, huvudsakligen fallserier. Globalt har mycket få patienter erhållit en neuromuskulärt eller icke-neuromuskulärt styrd benförankrad armprotes. Det finns mycket begränsad information om de kliniska utfall som analysen gällde och speciellt jämförelser av olika protesmetoder saknas nästan helt.

Patienter med neuromuskulärt styrda benförankrade proteser har upplevt fördelar avseende protesens funktion jämfört med icke neuromuskulärt styrda benförankrade proteser, men tillförlitligheten i det vetenskapliga underlaget är mycket låg.

Två allvarliga komplikationer rapporterades hos en av fyra patienter med neuromuskulärt styrda benförankrade proteser.

Även tillförlitligheten i det vetenskapliga underlaget avseende funktionen av icke-neuromuskulärt styrda benförankrade proteser jämfört med hylsproteser är mycket låg. Olika komplikationer – även allvarliga – relaterade till benförankringen har rapporterats.

Inga studier som jämförde neuromuskulärt styrda benförankrade proteser med hylsproteser identifierades.

De högre sjukvårdskostnaderna för neuromuskulär styrning och benförankrade proteser behöver beaktas.

The above summaries were written by representatives from the HTA-centrum. The HTA report was approved by the Regional board for quality assurance of activity-based HTA. The abstract is a concise summary of the results of the systematic review. The plain language summary in Swedish is intended for decision makers.

Christina Bergh, Professor, MD

Head of HTA-centrum of Region Västra Götaland, Sweden, 7 December 2022

Regional board for quality assurance	
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Svensson, Mikael	Health economist, Professor
Wallerstedt, Susanna	MD, Professor
Wartenberg, Constanze	Psychologist, PhD

DDS Doctor of dental surgery

MD Medical doctor

PhD Doctor of Philosophy

OD Odontology doctor

PT Physiotherapist

RN Registered Nurse

3. Summary of findings

Outcomes	Study design Number of studies (number of patients)	Absolute effect	Certainty of evidence GRADE*
Neuromuscular OI (I1) vs non-neuromuscular OI (C1) upper limb prostheses			
Function	2 studies of the same patients (n=3); within-patient comparison	Study 1: Task to grasp and move fragile objects[1] Fewer blocks broken at 6 N with I1 than with C1 (p=0.003), no difference for objects breaking at 18 N. Slower task performance with I1 than with C1 (p=0.003) Study 2: precision of movements (mean (SD)) Smallest movement to open hand: I1: 1.4 (1.1) mm vs C1: 3.0 (1.9) mm p<0.01 Smallest movement to close hand: I1: 1.6 (1.2) mm vs C1: 4.5 (2.3) mm p<0.01 Smallest change in grip force: I1: 0.5 (0.5) N vs C1: 4.3 (2.7) N p<0.01	⊕◯◯◯[2]
No studies on ADL, HRQoL, reoperation, complications, extent of use or patient experience.			
Neuromuscular OI (I1) vs myoelectric socket (C2) upper limb prostheses			
No comparative studies available			
Neuromuscular OI (I1) upper limb prostheses			
Function	2 case series (n=3)	Large interindividual variability in perception and use of different modes of sensory feedback.	NA
Patient experience	1 qualitative study (n=3)	All three patients included in this study experienced increased function and use of prosthesis in daily tasks; positive effects on self-esteem, self-image, and social relations linked to improved trust in the prosthesis; improved relation between prosthesis and phantom limb.	NA
Reoperations	1 case series (n=4)	3 reoperations in 1/4 patients: 1) replacement of implanted electrodes, 2) replacement of abutment that had loosened, 3) removal of implanted electrodes	NA
Compli-cations	1 case series (n=4)	2 serious adverse events in 1/4 patients:1) sepsis after reoperation, requiring hospitalisation and antibiotic treatment; 2) local infection requiring removal of implanted electrodes and antibiotic treatment	NA
Non-neuromuscular OI (I2) vs myoelectric socket (C2) upper limb prostheses			
Function	1 non-RCT (n=16)	Detection threshold for vibration significantly lower for I2 than C2 Detection thresholds for pressure I2 vs C2, ns.	⊕◯◯◯[3]
No studies on function, ADL, HRQoL, reoperation, extent of use or patient experience.			
Non-neuromuscular OI (I2) upper limb prostheses			
Function ADL	1 case series (n=11)	Mean shoulder range of motion: Flexion 150° (SD 12.5), extension 65° (SD 9.1), abduction 154° (SD 9.7), adduction 25° (SD 5.3) 9/11 patients load their prostheses regardless of activity.	NA
Extent of use	1 case series (n=26)	At follow up: 16/26 myoelectric prostheses, 9/26 body-powered or cosmetic prostheses, 1/26 non-user	
Reoperation	1 case series (n=29)	6/29 patients had reoperations (one of these reoperated twice)	NA

Compli-cations	4 case series in overlapping study population (n=29)	OI prostheses at transhumeral level (18 patients): 3 implants removed due to early loosening, partial fracture at insertion of fixation screw (8/18), limited defects of the bony canal while drilling for the abutment (3 cases), avascular skin flap necrosis (3 cases), one deep implant-associated infection, superficial infections and skin reactions at penetration site. OI prostheses at transradial level (11 patients): 3 fixture fractures	NA

Footnotes: ADL: Activities of daily living; HRQoL: Health related quality of life; N: Newton; NA: not applicable; ns: not significant; non-RCT: non-randomized controlled trial; OI: Osseointegrated;

[1] Absolute effects not reported in the publication.

[2] Starting from ⊕⊕◯◯for observational studies, downgraded for some study limitations (including e.g, incomplete information on statistical analyses, differing preconditions for within-patient comparisons), some indirectness and serious imprecision

[3] Starting from ⊕⊕◯◯for observational studies, downgraded for some study limitations (including e.g. missing information on baseline characteristics), serious indirectness and serious imprecision

***Certainty of evidence**

High certainty ⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty ⊕⊕⊕◯	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty ⊕⊕◯◯	Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty ⊕◯◯◯	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

4. Abbreviations/Acronyms

ADL: Activities of daily living

EMG: Electromyography

HrQoL: Health-related quality of life

N: Newton

OI: Osseointegration/osseointegrated

ROM: Range of motion

SD: Standard deviation

SU: Sahlgrenska University Hospital

VGR: Region Västra Götaland

5. Background

Disease/disorder of interest and its degree of severity

Acquired limb loss can result in significant disability to patients with a large proportion not returning to work (Livingston et al., 1994). Amputations above the elbow result in greater disability than forearm or partial hand amputations. Upper limb amputations may require specialised prostheses. A significant proportion of patients with an upper limb amputation do not use their prosthesis due to a variety of factors, such as poor fitting prosthesis, poor function, weight, or socket problems (Biddiss and Chau, 2007, Hanley et al., 2009, Middleton and Ortiz-Catalan, 2020). This can be a cause of frustration, reduced quality of life and self-esteem. A securely fitted prosthesis that is easy to use, may allow return to work and hobbies.

Prevalence and incidence

Each year, approximately 60 children are born with a limb deficiency in Sweden, of which approximately 10 have an upper limb deficiency not counting partial hand deficiencies (1177 Vårdguiden, 2022). Children with congenital upper limb deficiency are usually fitted with a myoelectric prosthesis at the age of 3 (Widehammar et al., 2018).

In adults, the most common cause of upper limb amputation is trauma, accounting for approximately 70%-80% of proximal upper limb loss (Datta et al., 2004, Maduri and Akhondi, 2022). The second and third most prevalent causes are cancer/tumors and vascular complications of diseases. Men aged 15 to 45 years are the most exposed group. The predominant level is transhumeral amputation (79%). There is no separate register for upper limb amputees, but available data from the Swedish National Board of Health and Welfare show that around 30 patients annually have had either primary or revision surgery of an upper limb amputation excluding hands (National Board of Health and Welfare, 2022). Men account for 78% of the patients with a traumatic amputation of the upper limb (excluding hand). Incidence is reported as 0.2/100 000 for traumatic amputations.

Present treatment

The mainstay of current treatment consists of socket prostheses that can be purely cosmetic, or functional. Functional prostheses can be body-powered (i.e. powered by bending the elbow or other joints) or myoelectrically controlled through skin-surface electrodes registering electrical activity in muscles (Carey et al., 2015) (see Figure 1).

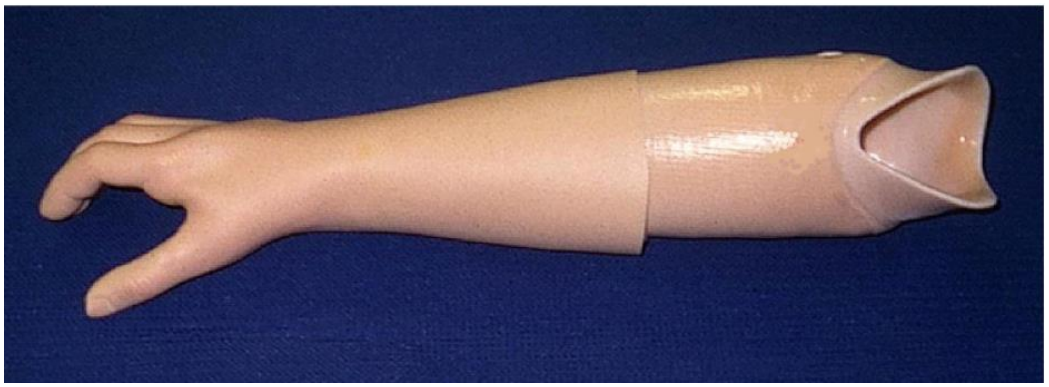

Figure 1: Myoelectric socket prosthesis. Surface electrodes to register EMG are placed inside the socket and come in contact with the skin when the patient puts on the prosthesis. Foto courtesy of Ann Nachemson.

The standard myoelectric socket prosthesis (Figure 1) is the most common type of prosthesis for patients with amputation at the mid/distal-forearm level. Since patients with amputation at this level have a relatively long stump, stability through the socket is acceptable and so is the overall function. However, myoelectric socket prostheses can be difficult to anchor to the body when the stump is very short. Furthermore, the skin-surface electrodes are susceptible to environmental factors, such as excessive sweating or dry skin during cold weather. They also may pick up electrical activity from other muscles which limits the amount of inputs available for reliable control of the prosthesis. This is often the case for patients with a short stump above the elbow where large muscles, such as the deltoid, interfere with signals coming from the biceps or triceps which should provide primary control for the prosthetic device. Because of this interference, when the patient raises the arm above 70-80 degrees, the motor control becomes unreliable and opening and closing the prosthetic hand in these positions is nearly impossible.

Today's modern prostheses allow for different grip patterns instead of just offering an open/close motion. To choose between different types of grips there are several strategies: pressing a button on the prosthesis with the healthy hand; co-contracting muscle groups; or using a distant device placed on the shoe. These prostheses can for many patients offer a function that is good enough, without extensive training or further surgical procedures. During control of these prostheses, patients rely entirely on visual feedback; that is the patient must watch the prosthetic hand to avoid crushing or dropping objects. These prostheses can have built-in sensors that automatically grasp objects more tightly when they are slipping out of the grip (Wijk et al., 2020).

In addition to the myoelectric socket prostheses described above, there are osseointegrated (OI), i.e. bone anchored, prostheses that provide stable attachment to the bone for those patients where a socket may not fit due to the remaining stump being too short. These can be combined with myoelectric control by surface electrodes (see Figure 2). Osseointegrated prostheses have so far remained an option only for a subgroup of patients with special requirements (Diaz Balzani et al., 2020).

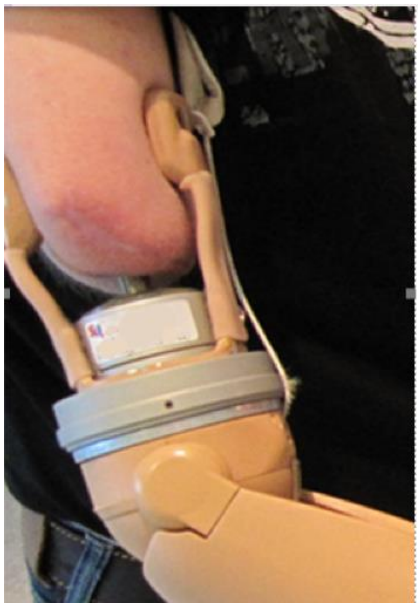

Figure 2: Osseointegrated prosthesis at transhumeral level with electrode holders. Foto courtesy of Carina Reinholdt.

In research contexts, a further development - neuromuscular OI prostheses - have been provided. These are described as the method at issue in Section 6 below.

Normal pathway through the healthcare system and current wait time for medical assessment/treatment

Patients who have an amputation are assessed in specialised limb amputation clinics within a multi-disciplinary team including hand and orthopedic surgeons, physiotherapists, occupational therapists, orthopedic engineers, technicians, and support staff. The majority of patients are fitted with a socket prosthesis but for selected patients an OI prosthesis might be considered. There is no wait time for assessment for prosthesis but there is currently a long wait time for OI surgery.

After the amputation, when the wound is healed and stable, all patients are followed-up by the specialised multi-disciplinary team clinics that provide the patients with upper limb prostheses, including fitting, training and follow-up of possible complications such as stump problems. The patient meets the multi-disciplinary team to discuss indication for treatment and available treatment alternatives depending on the level of amputation and quality of remaining tissues. When a decision is made, the orthopedic technicians and engineers manufacture the socket and the myoelectric prostheses, which are tested multiple times until they sit comfortably at the patient's arm. Later, an occupational therapist starts the training programme and the patient returns to meet the whole team if and when an overall assessment is necessary. Orthopedic technicians and engineers are available for technical adjustments throughout the years.

Number of patients per year who undergo current treatment regimen

The prosthetic clinic in VGR supplies around 75 prostheses every year and repairs about 2.5 times that amount (VGR, 2022).

Present recommendations from medical societies or health authorities

No current recommendations regarding the treatment at issue have been identified at the time of publication of this report.

6. Health technology at issue: Osseointegration and neuromuscular control of upper limb prostheses

Osseointegrated prostheses with neuromuscular control from surgically implanted electrodes directly on to nerves or muscles (see Figure 3), were developed in the last decade in Gothenburg with the aim to provide better motor control and sensory feedback for a selected group of patients (Middleton and Ortiz-Catalan, 2020), especially patients with short stump who have major difficulties in wearing a socket prosthesis. These patients often experience problems regarding the fitting of a standard socket prosthesis. In addition, the motor control by surface electrodes is often unpredictable due to cross-talk, i.e. interference of activity from the large muscles, (i.e. the deltoid) with electromyography (EMG) signals from the biceps and triceps that are used to control the prosthesis. Furthermore, changes in body temperature as well as slight displacement of the surface electrodes can contribute to poor signal transmission and therefore poor function of the myoelectric socket prosthesis in some patients.

The aim of the OI prosthesis with implanted electrodes is to use EMG signals from a larger number of muscle units for control of the prosthesis than socket prostheses with skin-surface electrodes. Also, the quality of signals directly from the muscles' surface is expected to be better than that from skin-surface electrodes where the signal needs to travel through the skin. The aim with neuromuscular control is that control of the prosthesis is more natural and intuitive and avoids

using switching strategies between different grip functions. It is expected that cross-talk is avoided, thus allowing patients to grasp objects above shoulder level without interference of signals from other muscles. In addition, the aim is to provide sensory feedback to the patient.

For provision of an OI prosthesis, a titanium screw, called fixture, is inserted into the bone and is the main component that promotes OI and an abutment protrudes distally through the skin, providing the mechanical connection between the prosthesis and the bone. Similar to standard socket prostheses, OI prostheses can be controlled by surface electrodes (see Figure 2 above).

If neuromuscular control is provided, an electrical central screw, attaches proximally to the fixture. Several wires from the e-CS travel into the medullary bone canal and then through a cortical window to muscles and nerves in the arm (Figure 3A-B). Two surgical incisions in the arm allow for implantation of muscular and neural electrodes. Often, techniques such as targeted muscle re-innervation and regenerative peripheral nerve interface are used to increase the number of functional motor units available. Targeted muscle re-innervation implies re-innervating non-functional muscles by re-routing major amputated nerves. While the intact muscles keep their original innervation and are used for hand open and close, the re-innervated muscles provide signals for other functions such as independent thumb or finger activation. Regenerative peripheral nerve interface implies transfer of small muscle grafts from the lower limb to the amputated stump, placing them around nerve fascicles of major nerves and coupling them with an intramuscular electrode. A few months later, after re-vascularisation and re-innervation, each of these muscles can generate EMG signals that are registered by the implanted electrodes and sent to the connector in the abutment (Figure 3). When the prosthesis is attached to the arm, muscles' signals will be used to activate all motor functions. For sensory feedback, a cuff electrode is wrapped around a major nerve; when the prosthetic fingertip touches an object the information reaches the electrode and stimulates the nerve. This will provoke a vibratory sensation that changes in intensity depending on the force applied on the fingertips.

Following surgery, rehabilitation is offered in several stages. The first three to six months are dedicated to progressive loading without prosthesis, with the aim to promote OI and allow bone healing. Bioengineers conduct tests to verify the function of the implanted electrodes and patients can start training the control of their prosthesis.

Provision of OI neuromuscular prostheses is currently only available in very few hospitals around the world who conduct these interventions within research programmes. In Sweden, the method has only been used at Sahlgrenska University Hospital (SU); a total of around 45 patients have received a non-neuromuscular OI upper limb prosthesis, and a total of seven patients have received a neuromuscular OI upper limb prosthesis (internal hospital records).

Fig. 3A and 3B: Osseointegrated neuromuscular implant at the transhumeral level.

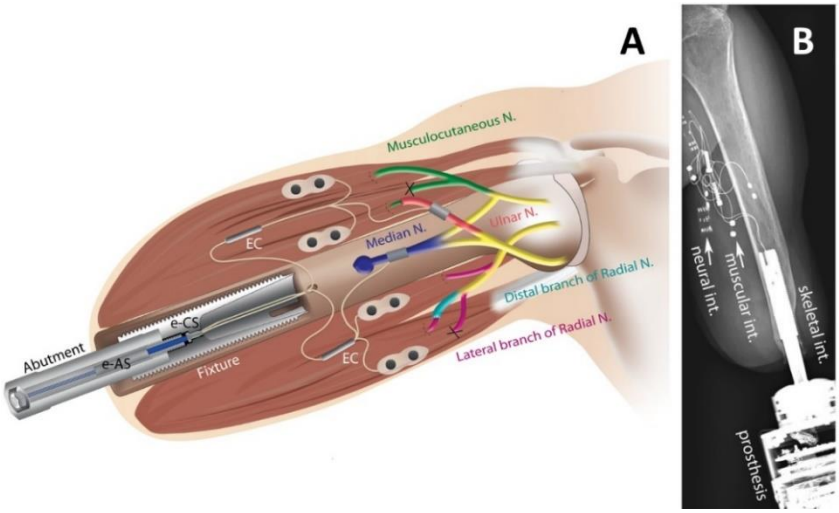

Illustration courtesy of
Max Ortiz-Catalan, 2022

Figure 3A: Osseointegrated neuromuscular implant at the trans-humeral level. The abutment, which contains an electrical central screw (e-CS), penetrates the skin and, proximally, is coupled to the fixture. The latter is screwed tightly into the bone and is responsible for the osseointegration. Wires travel from the central screw (e-CS) into the medullary bone canal. A cortical window in the bone gives all wires access to the muscles' compartments in the arm. At this level, two connectors (EC) put in contact the electrodes placed on muscles and nerves to the e-CS. In the figure, original and transferred nerves are marked in different colours as in TMR procedures. RPNI are not presented in this drawing.
Figure 3B: A radiographic image of the osseointegrated implant and the wires in the arm.

7. Focused question

For adult individuals with congenital deficiency or amputation of an upper limb, what are the benefits and risks with neuromuscular osseointegrated prostheses controlled by implanted electrodes (I1) compared with non-neuromuscular osseointegrated prostheses (C1) in terms of function, activities of daily living, health-related quality of life, reoperation, and complications? How does each of these types of osseointegrated prostheses (I1 and I2, respectively) compare with standard, myoelectric, socket prostheses controlled by surface electrodes (C2)?

PICO: P= Patients, I= Intervention, C= Comparison, O=Outcome

P	Adult individuals with congenital upper limb deficiency or upper limb amputation, unilateral or bilateral
I	I1: Neuromuscular osseointegrated protheses (implanted muscle electrodes) I2: Non-neuromuscular osseointegrated protheses (skin surface electrodes) (same as C1)
C	C1: Non-neuromuscular osseointegrated protheses (skin surface electrodes) (same as I2) C2: Myoelectric socket protheses (skin surface electrodes)
O	<u>Critical for decision making</u> Function (hand-, grip- and arm function), including gripping ability, force (incl. grip force and grip load force), sensibility, motor control, range of motion) Activities of daily living (ADL) Health-related quality of life (HRQoL) Reoperation Complications, including infections, complications in conjunction with first stage operation, complications during use (including skin problems under the socket and at the screw, electromagnetic disturbance) <u>Important for decision making</u> Extent of use Patient experience

Eligible study designs were randomised controlled trials, non-randomised controlled studies, and case series (for I2 with ≥ 10 patients (for complications only), and for I1 case reports), and qualitative studies. Publication year was limited to 1990 or later. Systematic reviews were searched for only for commenting on in the discussion. Publications in English, Swedish, Norwegian, and Danish were eligible.

Relevance of the outcomes from a patient perspective was confirmed by a patient representative.

8. Methods

Systematic literature search (Appendix 1)

During October 2021 two authors (IS, KM) performed systematic searches in Medline, Embase, the Cochrane Library and Cinahl. The websites of Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) and Norwegian Institute of Public Health (Folkehelseinstituttet) were visited. Reference lists of relevant articles were also scrutinised for additional references. Search strategies, eligibility criteria and a graphic presentation of the selection process are presented in Appendix 1. These authors conducted the literature searches, selected studies, and independently assessed the obtained abstracts and made a first selection of full-text articles for inclusion or exclusion. Any disagreements were resolved in consensus. The remaining articles were sent to all participants of the project group. All authors read these articles independently and decided in a consensus meeting which articles should be included in the assessment.

The HTA was registered on PROSPERO on 20th January 2022 (registration code CRD42022297120), prior to data extraction.

Critical appraisal and certainty of evidence

The included studies and their design as well as patient characteristics are presented in Appendix 2. Data were extracted and controlled by at least two authors. Excluded studies are listed in Appendix 3. Included studies were critically appraised using appropriate checklists from the SBU modified by HTA-centrum. Depending on study design, the checklist for non-randomised controlled trials, case series or qualitative studies was used. In Appendices 4.1 through 4.6 the results and the quality of each study are presented per outcome. Results per outcome and the associated certainty of evidence are summarised in a Summary-of-findings table (page 9). The certainty of evidence was assessed according to GRADE (Atkins et al., 2004), with reasons for downgrading described in text. Certainty of evidence was only assessed for those outcomes in which a comparison was available.

Ongoing research

A search in Clinicaltrials.gov (2022 Feb 17) using the search terms *(e-OPRA OR eOPRA OR OPRA OR prosthes* OR prosthetic* OR neuroprosthes* OR neuroprosthetic* OR neuralprosthes* OR neuralprosthetic* OR endoexoprosthe* OR exoendoprosthe* OR exoprosthe* OR robot* OR artificial hand* OR artificial arm* OR artificial limb* OR artificial extremit* OR bionic) AND AREA[ConditionSearch] (limb* OR upperlimb* OR extremit* OR upperextremit* OR arm OR arms OR brachium* OR shoulder* OR forequarter OR fore-quarter OR glenohumer* OR transhumer* OR humer* OR forearm* OR antebrachium* OR elbow* OR transradi* OR radial OR radius OR ulna* OR wrist* OR hand OR hands OR amput* OR congenital)* identified 227 trials. A search in WHO ICTRP (2022 Feb 17) using the search terms *condition: (limb* OR upperlimb* OR extremit* OR upperextremit* OR arm* OR brach* OR should* OR forequarter OR glenohumer* OR transhumer* OR humer* OR forearm* OR antebrach* OR elbow* OR transradi* OR radi* OR ulna* OR wrist* OR hand* OR amput* OR congenital) AND intervention: (e-OPRA OR eOPRA OR OPRA OR prosthes* OR prosthetic* OR neuroprosthes* OR neuroprosthetic* OR neuralprosthes* OR neuralprosthetic* OR endoexoprosthe* OR exoendoprosthe* OR exoprosthe* OR robot* OR artificial OR bionic)* identified 239 trials. In total 466 ongoing trials were identified.

9. Results

Search results and study selection (Appendix 1)

The literature search identified 2,037 articles after removal of duplicates. After reading the abstracts 1,925 articles were excluded. Another 80 articles were excluded by two authors after reading the articles in full text. The remaining 32 articles were sent to all participants of the project group, and ten articles were finally included in the assessment (Appendix 2).

Included studies

A total of ten studies were included, of which one non-randomised controlled study, two within-patient comparisons, six case series, and one qualitative study. All studies were performed at SU in Sweden, with several studies including the same patients. The studies involved a total of four patients with a neuromuscular OI prosthesis (I1), seven patients with myoelectric socket prostheses (C2), and twenty-nine patients provided with non-neuromuscular OI prostheses (I2/C1) (18 with transhumeral and 11 with transradial amputation). In 2011, at a follow-up of twenty-six patients who had received non-neuromuscular OI prostheses, seven of 16 patients with transhumeral level amputation used myoelectric prostheses, and nine patients used body-powered or cosmetic prostheses. Of 10 patients who received OI prostheses at transradial level, nine patients used myoelectric prostheses and one used a cosmetic prosthesis (personal communication 2022 March 07 with the first author of the article by Jönsson et al., 2011).

Given the small number of patients worldwide who have received the treatment in question, the study populations in the included studies were very small resulting in severe imprecision. Directness of the studies was assessed as limited due to the small number of patients with transradial amputation level, the small proportion of women, and all studies being performed at the same hospital. Studies on neuromuscular OI prostheses included four male patients aged 44 to 47 years with amputation at transhumeral level. In addition, the studies suffered from some study limitations; e.g. in the comparative studies information regarding the statistical analyses was sparse, in the cohort study (Jacobs et al., 2000) information on baseline characteristics was missing and in the within-patient comparisons (Mastinu et al., 2019, Mastinu et al., 2020) the preconditions for task performance differed between the two sessions to be compared. The qualitative study (Middleton and Ortiz-Catalan, 2020) on patients' experiences of living with a neuromuscular OI prosthesis was found to be of high quality in all assessed domains but was also conducted in the same limited sample.

Neuromuscular osseointegrated (I1) vs non-neuromuscular osseointegrated (C1) upper limb prostheses

Function (Appendix 4.1)

For this comparison, function was reported in two within-patient comparison studies of OI prostheses controlled by neuromuscular electrodes vs by surface electrodes. Three patients with transhumeral amputation participated in both studies, and one additional patient with amputation at the same level in one of the studies. Both studies had some study limitations, uncertainty regarding directness, and serious imprecision.

Grip force control and motor coordination were evaluated in one study (Mastinu et al., 2019). Three patients performed the Virtual Eggs test and the Pick and Lift test, under two conditions of controlling their OI prostheses: a) by implanted electrodes (corresponding to I1) and b) by surface electrodes (corresponding to C1). In the Virtual Eggs test the task is to grasp and move a fragile

object which breaks at a certain threshold of grip force. In each condition the patient performed repeated tasks with objects breaking at 6N and another set of tasks with objects breaking at 18N. In tasks with 6N, patients broke fewer blocks when controlling the prosthesis by implanted electrodes as compared to use with surface electrodes (p=0.003). This difference was not observed with objects breaking at 18N. Both when handling objects with 6N and 18N threshold, performance with the implanted electrodes was slower than with surface electrodes (p=0.003 and p=0.042, respectively). Absolute differences in task performance between the two conditions were not reported.

The Pick and Lift test implies grasping, lifting and subsequently putting down an object. In this task, exertion of a stable grip force during movement of the object is preferable. The change in grip force during movement of the object was significantly smaller when patients controlled their prosthesis with implanted electrodes (median (IQR) change of grip force: 0 (0.2) N) than when performing the same tasks with surface electrodes (median (IQR) change of grip force: 9 (27) N).

Precision in prosthetic control was assessed in one study (Ortiz-Catalan et al., 2020, corrected 2022), which had the same within-patient comparison design. The ability for precise movements was measured in terms of smallest increment in force and smallest movement for opening and closing the hand. Significantly more precise control was observed with implanted than with surface electrodes regarding minimal increase in grip force (mean (SD) 0.5 (0.5) N with implanted vs 4.3 (2.7) N with surface electrodes (p=0.01). The smallest movement when opening the prosthetic hand (measured as distance between prosthetic thumb and index finger) was mean (SD) (1.4 (1.1) mm with implanted vs 3.0 (1.9) mm with surface electrodes, and the smallest movement when closing the prosthetic hand (measured as distance between prosthetic thumb and index finger) was mean (SD) (1.6 (1.2) mm with implanted vs 4.5 (2.3) mm with surface electrodes.

Conclusion: It is uncertain whether there is any improvement in function with neuromuscular compared with non-neuromuscular OI prostheses (controlled with surface electrodes) (very low certainty of evidence, GRADE ⊕◯◯◯).

No studies were identified that compared neuromuscular with non-neuromuscular OI upper limb prostheses regarding the outcomes ADL, QoL, complications, re-operation, extent of use, or patient experience.

Neuromuscular osseointegrated (I1) vs myoelectric socket (C2) upper limb prostheses

No studies were identified that compared neuromuscular OI prostheses with myoelectric socket upper limb prostheses.

Neuromuscular osseointegrated (I1) upper limb prostheses without comparator

Function (Appendix 4.1)

Function was also reported in two case series and one qualitative study. One case series (Mastinu et al., 2020) explored how different types of feedback affect motor coordination when grasping and lifting objects. The study included three participants with transhumeral amputation and neuromuscular OI upper limb prostheses. Function was measured as motor coordination when receiving somatosensory tactile feedback during routine grasping and grasping with uncertainty regarding the weight of the grasped object. Four different feedback conditions were provided in random order: continuous pulse modulation, discrete stimulation, a hybrid of the aforementioned modes, or no feedback. Both objective metrics and subjective experiences were assessed. The

study showed considerable interindividual differences in the patients' perception and use of different types of sensory feedback. The results indicate that feedback is more relevant under uncertainty and that feedback does not need to be perceived as "natural" to be useful.

One case series (Ortiz-Catalan, 2020, corrected 2022) reported increased ability to discriminate differences in the frequency of vibration stimuli after daily training with implanted electrodes.

One qualitative study (Middleton and Ortiz-Catalan, 2020) reported that all three included patients experienced enhanced prosthetic function with the neuromuscular OI prosthesis.

Activities of daily living (Appendix 4.2)

Activities of daily living were reported in the qualitative study by Middleton and Ortiz-Catalan (2020). The patients described increased and more diverse prothesis use in tasks of daily living when using the neuromusculoskeletal OI prosthesis compared to prior experiences with socket prostheses and/or OI prosthesis with surface electrodes.

Reoperation (Appendix 4.3)

One case series (Ortiz-Catalan et al., 2020; Correction, 2022) reported three reoperations in one of four patients. One reoperation was performed to replace the electrodes three years after implantation. A second operation 1.5 years later was performed to replace the abutment component of the implant due to loosening. In a third reoperation (two surgeries four weeks apart), the implanted electrodes were removed due to infection 33 months after their implantation.

Complications (Appendix 4.4)

One case series (Ortiz-Catalan et al., 2020; Correction, 2022) followed four patients after the implant of electrodes for neuromuscular OI prostheses. These patients had previously received an OI abutment. For three of the four patients, no serious adverse events were reported during one month's follow-up after electrode implantation. For the fourth patient, no follow-up data were reported in the original publication (Ortiz-Catalan et al., 2020). However, a correction of the article published in November 2022 (Correction, 2022) describes that the fourth patient had two serious adverse events: first sepsis leading to hospitalisation, and later another infection that led to removal of the implanted electrodes. This patient had received implanted electrodes that were replaced after three years. One and a half years later, he had surgery for replacement of the abutment component of the implant that had loosened and 11 days after this surgery he was hospitalised due to sepsis and received 8 weeks of antibiotic treatment. In addition, 33 months after implantation, the electrodes and leads had to be removed due to infection requiring additional 12 weeks of antibiotic treatment.

Patient experiences (Appendix 4.6)

Patients' experiences of living and working with a neuromuscular OI prosthesis were reported in a qualitative interview study (Middleton and Ortiz-Catalan, 2020) and, to a limited extent, in the case series by Ortiz-Catalan et al. (2020; Correction 2022). The qualitative study was assessed as being of high methodological quality in all assessed domains, but was conducted in the same limited sample of patients as other included studies. Three Swedish men, with transhumeral level amputation who had lived with their neuromuscular OI prostheses between two and six years, participated. All three patients had implanted electrodes for both control of their prosthesis and sensory feedback. The study showed that the patients adapted and integrated the prosthesis technology into functional and social arenas of daily living, with positive psychosocial effects on self esteem, self image, and social relations linked to improved trust in the prosthesis. Patients also experienced enhanced function with the prosthesis and increased and more diverse prothesis use in tasks of daily living. Phantom limb pain, experienced by two of the three participants before, ceased after provision of neuromuscular OI prostheses. On the downside, the patients experienced challenges related to durability of the prosthesis, occasional breakdowns or malfunction of the prosthetic devices, and limitations related to battery life of the prosthesis.

Another publication by Ortiz-Catalan et al. (2020; Correction 2022), also describes the experience reported by the three patients who were interviewed in the study by Middleton and Ortiz-Catalan (2020). The three patients described that the prosthesis felt as if it was a part of themselves and reported improvement in self-esteem, self-image, and social relations with the new prosthesis compared to prior experiences (two of the patients had initially used socket prostheses, all three patients had used non-neuromuscular OI prostheses before receiving implanted electrodes). Note that the original publication by Ortiz-Catalan et al 2020 mentioned that one patient was lost to follow-up, but had use of his neuromuscular prosthesis for two years and six months. The correction of the article published 2022 describes serious complications in this patient (see under Complications above).

Non-neuromuscular osseointegrated (I2) vs myoelectric socket (C2) upper limb prostheses

Function (Appendix 4.1)

One non-randomised controlled study (Jacobs et al., 2000) investigated the osseoperception phenomenon and somatosensory feedback with prosthetic limbs comparing OI (9 upper limbs) to socket (7 upper limbs) prostheses.

The study had some study limitations, serious indirectness and serious imprecision. Thresholds for detection of vibration and pressure stimuli were studied in relation to thresholds in the contralateral healthy arm. The thresholds for pressure detection were not significantly different between the OI and socket prostheses. Thresholds for detection of vibratory stimulation were significantly lower for OI compared to socket prostheses. Compared to the healthy arm, a 10% smaller frequency difference between vibration stimuli could be detected with the OI prostheses. With a socket prosthesis, a 10% - 20% larger frequency difference was necessary for detection compared to the healthy arm.

Conclusion: It is uncertain whether there is any improvement in function with non-neuromuscular osseointegrated prostheses compared with myoelectric socket prostheses (very low certainty of evidence: GRADE ⊕◯◯◯).

Apart from this study, no publications comparing non-neuromuscular OI vs myoelectric socket upper limb prostheses were identified.

Non-neuromuscular osseointegrated (I2) upper limb prostheses without comparator

Function (Appendix 4.1)
One case series on 11 patients with OI upper limb prostheses (Stenlund et al., 2019) reported function in terms of range of motion. Mean range of motion was reported as 150° (SD 12.5) for arm flexion, 65° (SD 9.1) for extension, 154° (SD 9.7) abduction and 25° (SD 5.3), adduction. This can be compared with normal range of motion in healthy individuals, which is: flexion 180°, extension 60°, abduction 180°, and adduction 45° (SWESEMs utbildningsutskott, Svensk förening för akutsjukvård).

Activities of daily living (Appendix 4.2)
One case series on 11 patients with OI upper limb prostheses (Stenlund et al., 2019) investigated use of the prosthesis in ADL. Nine of the 11 patients reported that they used their prosthesis regardless of activity, whereas two patients avoided use while shovelling gravel and during weight-lifting respectively.

Health-related quality of life
No studies reported this outcome.

Reoperation (Appendix 4.3)
One study (Li et al., 2017) reported seven reoperations among 29 patients who had received either a transradial or a transhumeral level OI prosthesis without neuromuscular control. Reoperation at transradial level was performed in three patients due to fixture fracture and replacement. All three patients had an old version of the implant, and it was replaced with the new version that was introduced in 2003. In the transhumeral group, three patients were reoperated: Two patients were reoperated due to primary implant failures - the fixture failed as a result of loosening within two years from first surgery. There was no clinical sign of infection, the only symptom was pain at loading. Intraoperative cultures were positive for Staphylococcus aureus. After implant removal the patients received antibiotics and a negative culture was secured before reimplantation. One of the two patients had a second fixture loosening, underwent fixture removal and is not using any kind of prosthesis. The other patient had no more problems with the revised fixture.

A third patient had a reoperation due to osteoarthritis of the shoulder implying that he could not wear any prosthesis because of pain. Therefore, the abutment was removed. This was not related to failure of the implant.

Complications (Appendix 4.4)
Four publications reported complications after provision of OI upper limb prostheses (Tillander et al., 2010, Jönsson et al., 2011, Tsikandylakis et al., 2014, Li et al., 2017). There is considerable overlap of the study population in the four publications. Li et al. (2017) included all patients who had received OI upper limb prostheses at SU up to 2010.

The previous publication by Tillander et al. (2010) focused on the risk of infections, and publications by Jönsson et al. (2011), and Tsikandylakis et al. (2014) provide detailed subgroup information.

For the 18 patients who had received OI implants at transhumeral level between 1995 and 2010, a total of 43 adverse events were reported; 21 mild, 16 moderate, six severe (Tsikandylakis et al., 2014, Li et al., 2017). Three implants were removed due to early loosening (Tsikandylakis et al., 2014) (see also section 4.3 Reoperations). The most frequent complications in patients with prosthesis at transhumeral level were superficial infections of the skin at the penetration site (5/18

patients). In addition, skin reactions at the skin penetration site, partial fracture at insertion of fixation screw (8/18), limited defects of the bony canal while drilling for the abutment (three cases), avascular skin flap necrosis (three cases), and one deep implant-associated infection that resolved after 3 months oral antibiotics were described (Tillander et al., 2010, Tsikandylakis et al., 2014). Implant survival rate was reported as 83% at two years (three failures) and 80% at five years (Tsikandylakis et al. 2014).

For the 11 patients who had received OI implants at transradial level, three fixture fractures were reported in patients provided with OI prostheses of an older design that was used prior to 2003. No mechanical problems were registered for the three patients treated since 2003 (Li et al., 2017).

Usage (Appendix 4.5)

Prosthetic usage for patients with upper limb OI abutment was reported in one study (Jönsson et al., 2011). Of 16 patients with prostheses at transhumeral level, seven patients were reported using a myoelectric OI prosthesis, and nine patients used body-powered or cosmetic prosthesis (personal communication 2022 March 07 with the first author of the article by Jönsson et al., 2011).

Of 10 patients with prostheses at transradial level, nine patients had used a myoelectric prosthesis for a mean of 13.9 years (range 5 – 17.6 years); one patient became a non-user after the fixture fractured as a consequence of an overload accident.

10. Organisational aspects

Time frame for the putative introduction of the new health technology

Neuromuscular OI prosthesis is a technology that is already used in a research setting at SU and competence in performing the operation and post-surgery training of the patient is available from hand surgeons, orthopaedic surgeons, and specialised occupational therapists. All surgeries as well as pre- and post-operative assessments of patients are planned in cooperation with bioengineers from the Chalmers University and the Center for Bionic and Pain Research, who have developed the mechatronic system based on osseointegration and electrode implantation. All surgeries performed in Gothenburg involving implantation of neuromuscular electrodes have been performed in the context of research and were funded by regional and national grants.

Present use of the technology in other hospitals in Region Västra Götaland

SU is currently the only hospital in Sweden that uses the technology of neuromuscular OI prosthesis and we did not identify any publications on use of this technology abroad.

Consequences of the new health technology for personnel

The provision of neuromuscular OI prostheses requires highly experienced teams of surgeons and bioengineers. As the surgical procedure has previously been performed at SU, the involved staff is already familiar with it. Should the procedure be implemented in routine practice, additional staff will need specific training to become acquainted with all steps including bone fixation, microsurgical nerve transfer, muscle graft harvest, and electrode testing. Surgical indications are limited to amputees who have a short stump at the arm/forearm level that makes wearing a socket prosthesis unpractical, as well as those who have insufficient motor control of their prosthesis with surface electrodes. We therefore estimate about five patients per year with the osseointegration and implanted electrodes, which seems manageable with only a slight increase of resources, particularly from the rehabilitation side. Bioengineers have already been part of these surgeries and are well instructed about the basic requirements of sterility in the operating theatre. Since much information on muscles' activity and signal transfer is recorded by bioengineers, it is essential that the rehabilitation personnel work closely together with the bioengineers in order to understand timing for training, load progression, and sensory stimulation. Many of these aspects are new and under investigation, being part of research projects that aim to refine the methods previously used in patients provided with skin-surface electrodes.

Physiotherapists and occupational therapists may require further training and routines if the new health technology is implemented in routine practice.

Consequences for other clinics or supporting functions at the hospital or in the Region Västra Götaland

Implementing OI prostheses in routine practice would entail an increased need for availability of operating theatres due to longer operating time. The need for neuromuscular OI prosthesis is estimated to be about five patients per year at SU; the technology is not expected to be implemented at other hospitals in VGR and referrals from other hospitals may have to be considered.

11. Economic aspects

Treatment cost of the technologies

The cost data are surrounded with substantial uncertainty for a number of reasons. Treatment with neuromuscular OI prostheses has currently been undertaken as part of a research study with only a few patients (cost data available from two patients). The cost data for treatment with non-neuromuscular OI prostheses are also based on a very small number of patients (n=4). The cost varies substantially between patients primarily due to differences in the need for revision surgery. Considering these uncertainties, the approximate costs per patient and technology are:

Cost per patient (Swedish kronor)	Neuromuscular OI (I1) (n=2)	Non-neuromuscular OI (I2/C1) (n=4)	Myoelectric socket protheses (C2)
Operation cost + protheses	1,025,000 to 1,395,000	405,000 to 1,150,000	115,000 to 150,000
Physician visits	47,000	47,000	6,000
Orthopaedic engineer visits	15,000	15,000	21,000
Occupational therapist	19,000	19,000	14,000
Total cost	1,106,000 to 1,476,000*	486,000 to 1,231,000	156,000 to 191,000

*Not including cost for electrodes or costs for contribution of bioengineers

The cost data demonstrate that the OI technologies are substantially more costly per patient compared with myoelectric socket protheses. Regarding the costs for neuromuscular OI prostheses, it should also be noted that the cost per patient does not include the cost for the electrodes, which we have not been able to properly identify. For implantation of neuromuscular interface and electrodes and follow-up, bioengineers from Chalmers and the Center for Bionic and Pain Research are present during part of the surgery and at several outpatient visits together with the rehabilitation staff. The cost for their participation is not included. The difference between the neuromuscular OI prostheses and other protheses would thus be slightly larger if these costs were to be included.

Possibility to adopt and use the new technology within the present budget

Myoelectric socket prostheses (C2) represent the standard of care for patients who have undergone an upper limb amputation. Offering an OI implant to patients, with motor control of the prosthesis through skin surface electrodes (I2/C1) or with neuromuscular electrodes (I1), will not currently be possible within the present budget. It will require an increase in budget funds or a displacement of other health services.

Available economic evaluations or cost advantages/disadvantages

No economic evaluations or cost-consequence studies were identified in the literature search.

12. Ethical aspects

Amputation or deficiency of an upper limb is a health condition of high severity with significant disability, and patients encounter major obstacles in their daily life. A small group of patients cannot use standard prostheses and the aim of providing neuromuscular OI prostheses to these patients is to improve function and capability in activities of daily living, which would result in increased autonomy and work ability.

The present analysis shows that there is very low certainty of evidence for the benefit outweighing the risk with neuromuscular compared with non-neuromuscular OI upper limb prostheses, and with OI upper limb prostheses compared with standard, myoelectric, socket prostheses. The number of patients who have been fitted with neuromuscular OI prostheses is very limited, with three patients reporting intended benefits and one patient suffering from serious adverse events.

The provision of neuromuscular OI prostheses requires highly experienced teams of surgeons and bioengineers who work closely together. All studies included in this HTA were conducted at the same site in Sweden. Given the early stage of development there is a close connection between the clinical experts providing the new treatment to patients and involved in research, and the developer of the devices for OI and neuromuscular OI prostheses. This potential conflict of interest must be considered when evaluating the existing evidence base for the technology.

Further evaluation of this new technology is needed, yet difficult, given the small number of patients eligible for this type of prosthesis.

13. Discussion

Summary of main results

This HTA is based on data from four patients with neuromuscular OI prostheses, 29 patients with non-neuromuscular OI prostheses, and seven patients with myoelectric socket prostheses. The evidence base for this emerging method is limited due to study limitations/risk of bias and imprecision, as well as limited directness. Neuromuscular OI compared to OI prostheses controlled by surface electrodes improved the precision in control of the prosthetic hand in specific laboratory tasks, yet task performance was significantly slower. In a qualitative study, all three patients described enhanced function of their neuromuscular OI prosthesis in daily tasks as well as positive psychosocial effects. Explorative information on the perception and use of sensory feedback has been described. The threshold for detection of vibration was significantly lower in OI prostheses than in socket prostheses, whilst no difference in detection of pressure was observed. Range of motion and patients' courage to load their OI prosthesis in activities of daily living have been described in case series.

Two serious adverse events – sepsis and infection leading to removal of implanted electrodes – were reported in one of four patients provided with neuromuscular OI prostheses. Complications after provision of the abutment for OI upper limb prostheses included early loosening, fixture fractures, partial fracture at insertion of fixation screw, limited defects of the bony canal while drilling for the abutment, avascular skin flap necrosis, one deep implant-associated infection, and superficial infections and skin reactions at penetration site. Fixations were removed in three of 18 patients with amputation at transhumeral level, and three of 11 fixations at transradial level were replaced due to fixture fractures attributed to a design of the implant used prior to 2003.

Given the very limited available research and wide variation of clinical results there is very low certainty of evidence for the benefit outweighing the risk of neuromuscular compared with non-neuromuscular OI upper limb prosthesis and with OI upper limb prosthesis compared with standard, myolectric, socket prostheses.

Overall completeness and applicability of evidence

The procedure of neuromuscular OI has worldwide only been performed at one site – SU - in a total of seven patients. Of these, four male patients aged 44 to 47 years with amputation at transhumeral level have had their new prosthesis long enough to be able to contribute data to several of the published studies.

Assessing the function of upper limb prostheses is complex, with many different aspects to consider. The tasks studied in the clinical studies so far have focused on precise control of grip force eg in handling fragile objects and available data on functional aspects are fragmented. Further aspects of prostheses' function that are important in daily life may be relevant to study.

At SU, OI prostheses are currently considered for patients who cannot use a socket prostheses. For these patients, benefits and risks with using neuromuscular and non-neuromuscular OI prostheses may need to be considered in relation to the natural course in upper extremity amputated patients without prostheses. This comparison has not been evaluated in the present HTA report.

Agreements and disagreements with other studies and reviews

As the technology of neuromuscular OI is just emerging, research in the field is scarce. No reviews regarding this technology were identified. Our search identified a few reviews on OI prostheses without neuromuscular control. However, these reviews included both upper and lower limb amputees and typically did not separate outcome data nor complications data for upper and lower extremity. The reviews reported a wide range of infection rate. A review by Kunutsor et al., (2018) reported infection rates in upper and lower extremities between 1% and 77%, with most infections being low-grade soft tissue or superficial infections related to the skin–implant interface. A review by Balzani et al. (2020) reported an overall infection rate for both upper and lower extremity of 32%, and concluded that OI is associated with a high rate of postoperative complications, but with significant improvements in clinical outcomes and survivorship of the implants. Another review of both lower and upper extremity reported a rate of implant infection of 13±23% in upper limb implants, and that soft tissue infections and complications were common (Atallah et al., 2018). In a recent review by Gerzina et al. (2020), infection rate ranged between 18% and 63% (for both upper and lower extremity), with most infections being superficial and easily treated with antibiotics.

Implications for research

Even though the first patient with neuromuscular OI was implanted 9 years ago, the technology is still at an early stage. More research is imperative before neuromuscular OI prostheses could be considered a safe and viable treatment alternative.

14. Future perspectives

Scientific knowledge gaps

Research on neuromuscular OI upper limb prostheses is difficult given the small number of patients who are candidates for this specific treatment. Evidence so far stems from 4 male patients aged between 44 – 47 years, who all had amputation at transhumeral level, and who were willing to participate in several clinical studies. This HTA shows a lack of studies comparing neuromuscular OI upper limb prostheses with other treatment options such as non-neuromuscular OI prostheses, or the current standard of care - myoelectric socket prostheses. Also, the analysis shows the challenge of defining and investigating clinically relevant outcomes for upper limb prostheses, e.g. measures of different functional aspects of upper limb prostheses. Furthermore, a continuous systematic long-term evaluation of potential complications is mandatory to improve the understanding of the risks associated with this new technology.

Ongoing research

The search for ongoing research identified one case series in the Clinicaltrials.gov database and one case series in the WHO ICTRP portal.

- Study NCT03957226: *An osseoanchored percutaneous prosthesis study evaluating stable neural signal transmission in subjects with transhumeral amputations*, a case series of ten patients with upper limb osseointegrated prostheses. The primary endpoints are the quality of signals between implanted electrodes and prosthesis, and adverse events up to 2 years after surgery. Further endpoints are HrQoL, prosthetic functionality, and pain. The study is conducted in USA, was started in 2020 and is planned to be completed in 2024.

- Study NCT03836755: *Evaluation of the stability of osseointegrated implant in amputees (METACOS)*, a case series of two patients with upper or lower limb OI prostheses (relevance of the study for this report depends on inclusion of patient(s) with upper limb prosthesis). The primary endpoint of the study is the change in position of the prosthesis relative to the bone one year after implant. Further endpoints are HrQoL, function and mobility measures. The study is conducted in Italy, was started in 2019 and is planned to be completed in 2022.

In addition to this information from the databases, there is ongoing research at SU, including patients with amputation at transradial level.

Of note, search in the two databases resulted in many hits that did not address our focused question, but reflect considerable development and research activities to improve the functionality of myoelectric socket upper limb prostheses (e.g. by surgical treatment to improve myoelectric signals that can be captured by surface electrodes or different solutions for sensory feedback). These developments are out of scope for the present HTA report.

15. Participants in the project

The question was nominated by

Carina Reinholdt, MD, Head of operations, Dept of Hand Surgery, Sahlgrenska University Hospital, Region Västra Götaland, Gothenburg, Sweden.

Participating healthcare professionals

Hannes Granberg, MD, Junior consultant, Department of Hand Surgery, Sahlgrenska University Hospital, Region Västra Götaland, Gothenburg, Sweden.
Ann-Charlotte Lindström, OT, Närhälsan Sörhaga Rehabilitation Clinic, Region Västra Götaland
Ann Nachemson, MD, PhD, Senior consultant, Dept of Hand Surgery, Sahlgrenska University Hospital, Region Västra Götaland, Gothenburg, Sweden.
Paolo Sassu, MD, PhD, Senior consultant, Dept of Hand Surgery, Sahlgrenska University Hospital, Region Västra Götaland, Gothenburg, Sweden.

Participants from HTA-centrum

Susanne Bernhardsson, PT, associate professor
Constanze Wartenberg, psychologist, PhD
Mikael Svensson, health economist, professor
Pernilla Rönnholm, project coordinator
All from HTA-centrum, Region Västra Götaland, Gothenburg, Sweden.

Participants from the Medical Library

Ida Stadig, librarian
Kajsa Magnusson, librarian
Both from Region Västra Götaland, Medical Library, Sahlgrenska University Hospital, Gothenburg, Sweden.

Patient representative

A patient representative contributed to the PICO discussion and confirmed the relevance of the outcomes that were included.

External reviewers

Johan Kärrholm, MD, PhD, Professor, Department of Orthopaedics, Sahlgrenska University Hospital, Mölndal, Sweden
Eric Hamrin Senorski, PT, PhD, Assoc. Professor, Department of Health and Rehabilitation Sahlgrenska Academy, University of Gothenburg and SportRehab, Sports Medicine Clinic, Gothenburg, Sweden

Declaration of interests

P. Sassu was coauthor in two of the included studies and did not participate in the risk of bias assessment for those studies. Dr. Sassu is principal investigator for the study '*Osseointegrated Human Machine-Gateway - implanterbart styrsystem för armproteser' (Diarienummer 769-12)* and has performed the surgery of four of the seven patients who have received an eOPRA prosthesis, supplied by Integrum AB. Dr. Sassu declares having no direct connection to Integrum AB and has never received any remuneration from the company.

S. Bernhardsson, H. Granberg, A-C. Lindström, A. Nachemsson and C. Wartenberg declare no conflicts of interest.

Project time

The HTA was accomplished during the period of 21 September 2021 – 7 December 2022.

Literature searches were made on 1 October 2021.