Supplement A: Critical Transfemoral Socket Design Features and Variations

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Introduction

According to the 2015 *Practice Analysis of Certified Practitioners in the Disciplines of Orthotics and Prosthetics* within the practice of transfemoral (TF) and knee disarticulation (KD) prosthetic care, ischial containment (IC) sockets have been predominant, followed by modest use of quadrilateral (Quad), sub-ischial, distal end bearing and ramal containment socket types.[1] Suspension techniques have been more diverse with the use of roll-on liners with a lock or lanyard system being most common, followed by skin-fit suction and suction achieved over a cushioning roll-on liner.[1] Recent years have seen the development of several nontraditional, modular sockets including the Lim Innovations Infinite TF[2], Martin Bionics Socket-less Socket[3], Otto Bock Varos Socket[4], and Ossur Connect TF.[5]

TF socket design and construction have a lengthy history with the first patents awarded in England in 1790,[6-9] and the first US patents awarded in 1846.[6,10] However, common standards of practice for socket design and construction as well as socket suspension and alignment have not been memorialized. The purpose of this narrative is to begin to establish the critical design elements of transfemoral socket design and construction that may comprise these standards.

History

Prior to 1949, instruction on TF socket design in the United States was confined to interactions between protégé's and their training mentors. Formal instruction began in 1949 with the University of California at Berkeley's introduction of short-term lessons on suction socket design. This was followed closely by the formal prosthetic education programs of the University of California Los Angeles, New York University and Northwestern University in the 1950s.[11] The original socket design in these early educational settings was the German based quadrilateral socket with skin-fit suction suspension,[12-13] with each school developing their own approach and associated laboratory manuals for the system. In the 1980s the first IC socket manuals were adapted across prosthetic training institutions with individual variations observed. As of this writing, according to the National Commission for Orthotic and Prosthetic Education (NCOPE) there are 13 accredited masters' level educational institutions for prosthetic and orthotic practitioner training in the United States, each presenting unique variations on the theories and practical applications of TF socket design and construction.[14]

While the range of clinical styles and techniques presented in these institutions and across clinical practice settings have facilitated the ability of individual practitioners to adapt socket solutions unique to their patients' specific needs and individual presentation, a common set of

critical design elements should be clearly established as a baseline upon which to apply these adaptations.

Basic Design Elements of the TF socket

The goal for any prosthetic socket is to be the interface with the residual limb and the distal prosthetic components. The desire is to achieve stability, maximize control and facilitate mobility while using the prosthetic device. For socket interface to be able to convert the energy generated by the residual limb of the prosthetic user into functional prosthetic movement, two basic functions must be met. The prosthetic socket interface must support the user's body weight during stance while stabilizing the residual limb throughout its movements in the gait cycle

While these functions seem simple, they can be difficult to achieve, with individual solutions varying between prosthetic users. To maximize support and control, the socket must be properly contoured and relieved for functional muscles, utilize stabilization forces where no functional muscles exist and properly distribute forces within the socket at pressures that are tolerable to the user.

These fundamental principles have been addressed in every current teaching manual utilized within the NCOPE Core Curriculum for all US based learning institutions and have been noted as far back as AA Mark in 1907 and the *Report to the Advisory committee on Artificial Limbs' Summary of European Observation* in 1949.[15]

A. Critical Design Elements of the TF socket

To satisfy the basic design elements of stabilization and control, a few critical factors must be addressed. These factors are common for any type of socket design within TF prosthetics and for any residual limb shape, size or length.[12-13,16-17] No matter what socket design is ultimately considered the socket must maintain a total contact fit and balance force couples within the socket.

1. Total Contact Socket Fit

In contrast to the early assumptions that sockets should feature an "abundance of room" to allow "a wholesome circulation of air,"[18] the importance of a Total Contact (TC) socket fit has since been recognized. Ultimately, the volume of the socket should match or be slightly less than the volume of the residual limb. The presence of any localized areas lacking contact within the socket may result in areas of negative pressure leading to localized edema, socket migration and compromised control of the prosthesis. A range of techniques have been developed to assess limb volume within the TF socket and include visual verification through a clear diagnostic interface, the use of tactile probes, electronic sensors, visual inspection through the distal air valve channel and evaluation of the limb immediately following doffing of the prosthesis. For various means of socket suspension on the residual limb, such as skin fit suction and sub-atmospheric vacuum assisted suspension, a TC fit is critical. Lack of a TC fit when using these particular suspension systems will not only lead to lack of control but can quickly lead to skin breakdown and ulceration. More recently, modular TF socket designs have abandoned the ideal

of a TC socket fit. However, these framed sockets are generally coupled with a TC fit of an interface liner to mitigate localized areas of negative pressure or window edema.

In addition, the TC fit of the socket must anticipate and mitigate any impingement against those tissues proximal to the superior trimlines of the socket and ensure tolerable forces within the socket, both during gait and while seated. Tissue bulging over the proximal trim lines can lead to skin breakdown, edema, sub dermal cysts, blisters, irritation or discomfort.[19] Similarly, appropriate TC must accommodate those bony structures within the socket which may be prone to discomfort or impingement. This includes the ischial tuberosity, the ascending pubic ramus, the adductor longus tendon, the greater trochanter and the distal end of the transected femur as well as neurovascular bundles around the anterior-medial area (Femoral Triangle) and distal to the Ischial/Ramal complex on the proximal medial aspect of the socket.[8,12-13,20-22] Intolerable pressures, either negative or positive, at these locations can lead to socket rotation, loss of control, pain, gait deviations and even outright rejection of the prosthesis.[23]

2. Force Couples and Socket Stability

The stability of the transfemoral socket in the sagittal plane can be considered through the requirements encountered in the gait cycle. During loading response, the resultant knee flexion moment acting upon the prosthesis must be countered by active contraction of the ipsilateral hip extensors, stabilizing the mechanical knee.[24] The ability of this hip extension moment to stabilize the prosthesis will depend upon the strength of the hip extensors, the length of the residual femur and the stability of the residual limb within the socket. Recognizing that the extension of the femur must ultimately translate through the medium of the socket to affect the alignment of the prosthesis, the fidelity of the socket fit is more fully appreciated. In the absence of adequate sagittal stabilization within the socket, users may not be able to maintain sagittal control and the prosthetic knee may buckle underneath their weight. If the fit is poor, the user may choose to reduce their step length, slow their cadence or artificially shift their body weight anteriorly in an attempt to reduce the external knee flexion moment and maintain a safer ambulation at the cost of higher energy consumption and lack of confidence with the prosthesis.[25-26]

During late stance, the opposite force couple is engaged as the user must actively flex their hip joint to initiate the ballistic action of the prosthesis in swing phase. The ability of the socket to translate these forces to the prosthesis will be dependent upon the fidelity of the socket fit over the residual limb.[17,20,24]

The stability of the socket in the coronal plane is most evident during single limb support. For the user of a transfemoral prosthesis, the nearly universal propensity is to shift the upper torso laterally over the prosthesis for stability.[22,27] Affected by both hip abductor strength and residual limb length, this Trendelenburg gait deviation can also be reduced by attempts to position the residual femur in relative adduction to improve the efficiency of the residual hip abductor muscles.[22,26] This may be facilitated by thoughtful contouring of the lateral socket wall to maintain relative femoral adduction, countered by a sufficiently high medial socket wall to maintain adequate counterforce pressure on the soft tissue below the ischial tuberosity or on the ischial/ramal boney structures.[12,16,21-22,27]

The stability of the socket in the transverse plane is most readily observed in the form of medially or laterally directed rotational "whips" of the prosthetic knee and shank in swing phase. Stabilization of the socket over the femur in the transverse plane is confined to the proximal anatomy. Here, socket rotations may originate from either improper alignment with the pelvic ramus angle, a proximal socket fit that is loose or generic in shape, or from an excessively tight socket fit that fails to provide space for muscle activation through the gait cycle or does not allow for adequate room for skeletal structures.

B. Socket Construction

Construction of most modern transfemoral sockets can be dichotomously characterized as either a hard socket or a flexible inner socket with an external rigid frame. The hard socket is a rigid, monolithic construction. Associated advantages include its relative simplicity, thin walled construction, general durability and low maintenance. Recognizing that this socket construction offers no flexibility nor adaptability, its use is optimally confined to those limbs with stable volume with firm tissue quality and at least fair sensation. By contrast, individuals with adherent scar tissue, soft tissue invaginations, sensitive bony prominences and unstable limb volumes are ill-suited for this construction and better managed with more forgiving, dynamic flexible inner socket construction.

In contrast to the hard socket, the flexible inner socket with an external rigid frame includes a flexible inner socket capable of elastic movements, supported, where appropriate, with the stability of an outer rigid frame. Generally, the proximal trimelines of the external rigid frame are typically lowered to increase the compliance of the flexible inner socket and by association, the end user's physical comfort. This approach permits flexibility in containment of the proximal soft tissue and boney anatomy while maintaining total contact and enhanced force compliance without the painful impingement that can occur in a hard socket.

Through the body of the socket, fenestrations or windows within the body of the external rigid frame can enhance the user's proprioceptive feedback on sitting surfaces as well as permitting expansion and movement of underlying muscle bellies during ambulation while maintaining a total contact fit.[28] Notably, material selection of the flexible inner socket should be considered as creep or stretch of the thermoplastic material can occur overtime. If the inner flexible material expands over the use of the prosthesis, the user will not be able to maintain a total contact fit.

In a relative recent adaptation of the flexible inner socket construction, dynamic floating rigid panels are integrated within the external rigid frame. These panels can be loosened or tightened to increase or decrease the volumetric pressure on the underlying flexible inner socket. This approach has been used to accommodate changes in limb volume or to allow the user to customize the tightness of the socket for certain activities.

A related variant is seen in the flexible socket with an embedded rigid frame. Similar to prosthetic systems popular prior to World War II where a metal frame was housed within a flexible leather socket.[6] In this modern approach, rigid frames are laminated between layers of a total contact flexible socket. Initial advantages associated with this developing technique include its overall compliance and flexibility, user comfort and improved perceived control of the

prosthesis. However, these benefits are currently countered by the increased weight, complex fabrication processes and reduced durability of the approach.

Several recent modular socket designs, including the Lim Innovations Infinite TF[2], Martin Bionics Socket-less Socket[3], Otto Bock Varos Socket[4], and Ossur Connect TF[5] represent extreme examples of adjustable frame style sockets. While these designs propose a number of benefits, evidence to support their use is still evolving.

C. Common Socket Design Elements

While the number of different transfemoral socket designs have been described, these can generally be reduced to two basic categories, ischial ramal containment and sub-ischial. Ischial ramal containment designs, alternately referred to as narrow medio-lateral (or narrow M-L) designs include the more commonly encountered IC design and the less frequently utilized ramal containment (RC) design (also described as the Marlo Anatomical Socket or MAS). Sub-Ischial (SI) sockets include the legacy Quad designs, and the more recently developed designs that are incorporate lower proximal trimlines than an IC socket and are frequently coupled with sub-atmospheric vacuum assisted suspension.[29]

While the IC and SI socket design differ in a way they utilize the ischium, they have many common design attributes. They have similar design considerations in the anterior, medial, posterior and lateral walls. While user's anatomy, muscle strength, range of motion and voluntary control vary, these aspects of the socket design will be constant.

1. The Anterior Wall

The anterior wall creates a compression force at the medial aspect by compressing the soft tissue around the neurovascular bundle known as the Scarpa's triangle or femoral triangle. This modification compresses the soft tissue to create a force that will help to ensure the ischial tuberosity remains posterior in the socket. For Quad sockets this pressure is a critical design element to maintain the ischial tuberosity on the posterior aspect of the socket for weight bearing purposes. For other SI or IC designs, this pressure is still required but less critical. Accurately modified, the anterior medial wall will give relief for the adductor longus tendon so it can have adequate room to fire in early stance while reducing the tendency to create socket rotation. The lateral aspect of the anterior wall should be accurately modified to maintain pressure on the rectus femorus muscle and be compliant enough to allow for muscle fire during stance and not over compress during sitting. The proximal height of the Anterior Wall varies from Ischial Level to 2 ½" proximal depending on how much posteriorly direct force is needed for Ischial support and how much hip range of motion is needed.[20-21,30]

2. Lateral Wall

From the Ischial level distal, the lateral wall helps to maintain the limb in relative adduction. With the femur in an adducted position the gluteus medius can fire more easily and the user can have a narrower base of support. A properly contoured lateral wall will support the femur in adduction and relieve pressure felt on the distal cut end of the bone. Proximal to the ischial level

the lateral wall has no real biomechanical function except to contain the proximal soft tissue or attach a suspension mechanism.

3. Posterior Wall

The posterior wall plays an important role in containing the tissue to maintain a TC fit, aiding with gluteal or ischial weight bearing and stabilizing the femur in early stance. In Quad designs the width and length of the proximal posterior wall is critical to maintain ischial weight bearing and maintain alignment. In IC and SI designs, the posterior wall is typically flexible to allow for sitting comfort and proprioception. The proximal height of posterior wall will terminate at the ischial level for ischial weight bearing sockets. For IC sockets it may be up to 2" proximal to the ischial height if it is desired to contain the gluteus maximus tissue within the socket for more control with shorter or weaker residual limbs.

4. Medial Wall

The medial wall contains the adductor muscle tissue to help stabilize the femur in the coronal plane and defines the ischial/ramal containment or support. Its proximal brim must be beveled or flared enough for comfortable ambulation. For Quad sockets the angle of the medial wall is parallel to the user's line of progression. For SI or IC designs, the medial wall may begin on the angle of the line of progression but angles internally below the Ischium to follow more closely to the ischial/ramal angle. Compression of the tissue below the ischium helps to define the seat to support the ischium if ischial weight bearing is desired and to help stabilize the femur in SI designs.

D. Ischial Containment Designs

As articulated earlier, in modern practice, the IC socket is the most commonly encountered, with modest variations across both institutional instruction and clinical practice. However, certain critical design elements are common to these variants along with the four walls described already.

1. Ischial/Ramal Containment:

In contrast to SI designs, the IC socket provides a medial proximal wall that encompasses part of the distal pelvic structure around the ischial tuberosity. Accordingly, the medio-lateral dimension of an IC socket tends to be narrower than that observed with a Quad socket. The amount of ischial containment is variable and not standardized, but the critical design element is that there is a 'boney lock' on the distal pelvis to improve coronal plane control in single limb support. The area of ischial containment on the medial socket wall should match the user's measured ischial ramal angle. This proximal extension of the socket wall is oriented to contain the medial bony anatomy of the pelvis at the ischial tuberosity up to the ascending ischial ramus.[21-22] Recent analysis based on computed topography scans of 200 subjects observed an the average ischial/ramal angle of 32.7±5.6 degrees relative to the mid-sagittal plane. Notably, contrary to commonly held beliefs, there was no statistically significant difference in ischial/ramal angle between sexes.[31] The amount of ischial containment is variable across designs, but may contain as much as 1" to 1 ¾" of the vertical height of the ischium.[21,32-33] Pilot

data has suggested progressive decline in socket comfort with the absence of ischial containment, especially when tissue loading in the subischial area are reduced.[34]

A core concept in obtaining appropriate ischial containment is the accurate the ischial-ramal angle measurement and the capture of an accurate skeletal medial-lateral or "skeletal ML"." The skeletal ML (also described as Diagonal ML),[35] is defined as the coronal plane distance between the medial aspect of the ischium and the lateral shaft of the femur immediately inferior to the greater trochanter inclusive of the subcutaneous adipose tissue and skin.[16,36] Various measurement techniques have been proposed and described. In addition, a recent study based on measurements from the CT scans of 200 subjects has suggested a multivariate linear regression model capable of explaining 76% of the variance in skeletal ML. Significant contributors to this variance included body mass, sex, inter-greater trochanter distance, pelvic depth and age.[36] Study authors suggest that using the regression model, skeletal ML could be better predicted with relatively small errors that could be easily and reliably adjusted during socket fitting.[36]

A variant of the IC socket design is the related RC design, epitomized in the Marlo Anatomical Socket (MAS) which attempts to confine its coronal stabilization against the ascending ischial ramus while lowering the anterior and posterior proximal trimlines of the socket.[35] These modifications have been associated with improved range of motion at the hip[37] and decreased metabolic costs.[38] However, they require a meticulous fit with very a low tolerance for volume fluctuations due to the localized pressures on the medial aspect of the ramus.

2. Relief at the Ramal Exit:

Generally, patients can tolerate medially directed forces acting across the ischium and the posterior aspect of the ramus. By contrast, superiorly directed pressures on the distal aspect of the pubic ramus, and medially directed pressures on the anterior aspect of the pubic ramus as it exits the socket are poorly tolerated. IC socket designs should provide adequate relief from these two forces as the ramus exits the socket while maintaining adequate encapsulation of the ischium. The use of flexible inner socket design can aide in increasing user comfort at the transition of the firm Ischial containment to the area where the ramus needs to exit the socket.

3. Soft Tissue Compression in the Sub-ischial Triangle:

The forces required to stabilize the transfemoral socket in the coronal plane can be distributed more broadly when the socket wall is modified to provide compression in the soft tissues of the sub-ischial triangle. Properly applied, this modification can reduce the medially directed loads on the pelvic anatomy and assist with the rotational stability of the socket. Pilot data has suggested progressive declines in socket comfort with reduced soft tissue compression in the subischial triangle, especially in the absence of proximal ischial containment.[34]

4. Flaring at the Medial Brim:

The stabilization of the transfemoral limb in relative adduction requires a medial brim of sufficient height to provide a counter force to the stabilizing forces applied across the lateral aspect of the mid and distal femur. However, edge pressures in the proximal medial socket will

cause patients to abduct the femur to reduce the localized pressure. Modest flaring of the medial brim reduces proximal edge pressures and facilitates the adducted alignment of the socket.

5. Hydrostatic Weight Bearing:

In contrast to the ischial weight bearing of its predecessor, the Quad Socket, IC sockets generally utilize a more generalize hydrostatic weight bearing.

E. Sub-Ischial Designs

While the Quad socket design preceded the modern SI socket designs, in both approaches the medial brim terminates below the level of the ischium. Unlike more modern SI sockets which rely exclusively on hydrostatic load bearing, the Quad socket incorporated ischial weight bearing on its posterior brim, with ancillary hydrostatic load bearing. In contrast to the narrowed coronal dimensions of the IC designs, the Quad socket requires a narrowed sagittal dimension to maintain the position of the ischium on the poster shelf of the socket. This narrow sagittal profile must be complimented by a wider coronal profile which can compromise the coronal stability of the socket and required additional alignment considerations such as positioning the knee to be beneath mid socket.

The first SI design to rely on hydrostatic weight bearing was described by Redhead in the 1960's.[39] Modern SI socket designs are based on these original hydrostatic weight bearing concepts, but incorporate roll-on elastomeric liner interfacing as vacuum assisted suspension. These sockets may be preferred by some users by virtue of their lowered proximal trimlines.[40] Other suggested benefits include increased limb health, volume stabilization, reduced perspiration, and increased comfort.[41]

F. Comparative Efficacy

Objective comparisons between IC socket and Quad socket designs are largely confined to dated publications produced near the emergence of IC socket designs. Hachisuka et al. reported improvements with respect to comfort in walking, sitting and stair negation.[42] Flandry has similarly observed improved patient satisfaction with the use of IC sockets, citing improved comfort, balance and control of the prosthesis.[43] Several authors have joined Flandry et al. in their observation of improved oxygen consumption with IC sockets while walking quickly.[25,43-46]

With regard to restrictions in hip mobility, Klotz et al. observed coronal hip motion to be more limited by transfemoral sockets than sagittal hip motion, adding that very similar levels of restriction were observed with IC and Quad socket designs, while IR socket design permitted some additional hip motion.[45] With respect to the related construct of femoral alignment, Hachisuka et al. observed a more adducted femoral alignment with IC socket designs.[42]

Most recent comparisons of IC and SI designs have shown increased patient compliance and range of motion with SI sockets, with most studies also showing decreased coronal plane control with the SI as compared to IC sockets.[26,34,40] As with Quad sockets in the past, there appear to be viable candidates with adequate soft tissue stabilization below the ischium to achieve coronal stability ischial containment.

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Supplement B: Transfemoral Socket Interface Design and Suspension Considerations. A Systematic Literature Review

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Introduction

For an individual with limb loss, the most important component of the prosthesis is the socket interface which creates the connection between the prosthesis and residual limb. A truly effective connection allows for increased stability and user control of the device through gait, optimal component performance, increased user comfort and satisfaction and an overall improvement in all user functions. However, recent literature has identified the socket interface as the cause of most reported prosthetic issues. Key complaints include: discomfort, pain, and dermatological problems that lead to user dissatisfaction, decreased mobility and prosthetic use.[1-5]

Traditional socket interface designs for the transfemoral amputee (TFA) include the quadrilateral socket (Quad) and the ischial-ramus containment (IRC) socket. The Quad socket positions the ischial tuberosity on a posterior seat for weight bearing via an anterior/posterior counter pressure and a narrow anterior posterior (AP) dimension.[6] Clinical complaints included increased sciatic pressure, decreased coronal femur control, and sitting discomfort leading to de-emphasis of the anterior counter pressure and eventual development of the IRC.[7-9] The IRC utilizes high medial and lateral trim lines to contain the ischial tuberosity and create a coronal boney lock of the pelvis. Hypothetically, the aforementioned features and the narrow mediolateral dimension increases stance phase stability leading to improved gait quality and efficiency.[10,11] The IRC's counterforce between the femoral shaft and ischium, creating the boney pelvic lock, also reportedly decreases lateral socket shift and femoral abduction during stance. This is in contrast to that observed with Quad socket use, indicating improved stability with the IRC.[9,12] However, both socket interface designs depend on encompassing a large surface area of the residual limb as compared to newer alternative designs, which has been proposed to increase temperature, friction, and moisture causing increased skin problem incidence and overall discomfort . Recent literature has also demonstrated the potentially negligible biomechanical impact of higher trim lines and maintenance of coronal stability during gait with lowered trim lines and vacuum assisted suspension (VAS).[13]

User stability and control is also influenced by the method of prosthetic suspension, particularly during the swing phase of gait. Prothetic users report perception of greater control over their device during gait and improved proprioception with enhanced suspension.[14] Optimal suspension eliminates or minimizes any separation between the liner and socket and decreases prosthetic motion during swing.[5,14-16] In terms of minimizing axial prosthetic motion during swing, osseointegration may represent the ultimate form of prosthetic suspension by creating a direct connection between the prosthesis and skeleton, essentially eliminating socket-related challenges and creating direct prosthesis control.[17,18] However, this direct method of suspension is currently not widely approved or available and more evidence is needed to support widespread use.[19,20] Advances in liners, variable rigid frame designs, flexible interfaces, lower trim lines and VAS systems have allowed for alternatives to traditional TFA socket interface designs, such as the Dynamic Socket (DS) and sub-ischial (SI) to become clinically available and widely used. Reported improvements include increase stability and balance, improved proprioception, gait, and comfort, reduced prosthetic weight and reduction of dermatological complications leading to overall improved user function and satisfaction.[5,12,13,21-23] Currently, there is insufficient data to substantiate the proposed benefits of the Quad and IRC socket interfaces or the optimal mechanism of suspension, thus the optimal socket interface design for the TFA remains unknown.[12,24-26] Therefore the purpose of this systematic review is to assess current evidence regarding TFA interface design and suspension to identify the perceived and measured benefits of the various designs.

Materials and Methods

A literature search was performed July 12, 2019. The following databases were searched: Cumulative Index to Nursing and Allied Health (CINAHL), Ovid, and PubMed (Medline). The search terms used were: Transfemoral [title] AND prosthe* AND interface OR socket. Bibliographic citation software (EndNote X8, Thomas Reuters, Carlsbad, CA, USA) was used to gather the references and remove duplicates. The authors also searched the references of articles identified in the search. Further, articles personally known to the authors were included.

The title and abstract of the references were reviewed by the two authors as to the inclusion/exclusion criteria. Articles that could be immediately classified as pertinent or not pertinent based on this review were classified. Articles whose titles and abstracts did not permit immediate classification were read fully prior to making a determination. Disagreements regarding specific references were resolved pursuant to reading the full text article and further discussion. (Figure 1. Prisma Flow Diagram)

Articles had to meet the following criteria to be included:

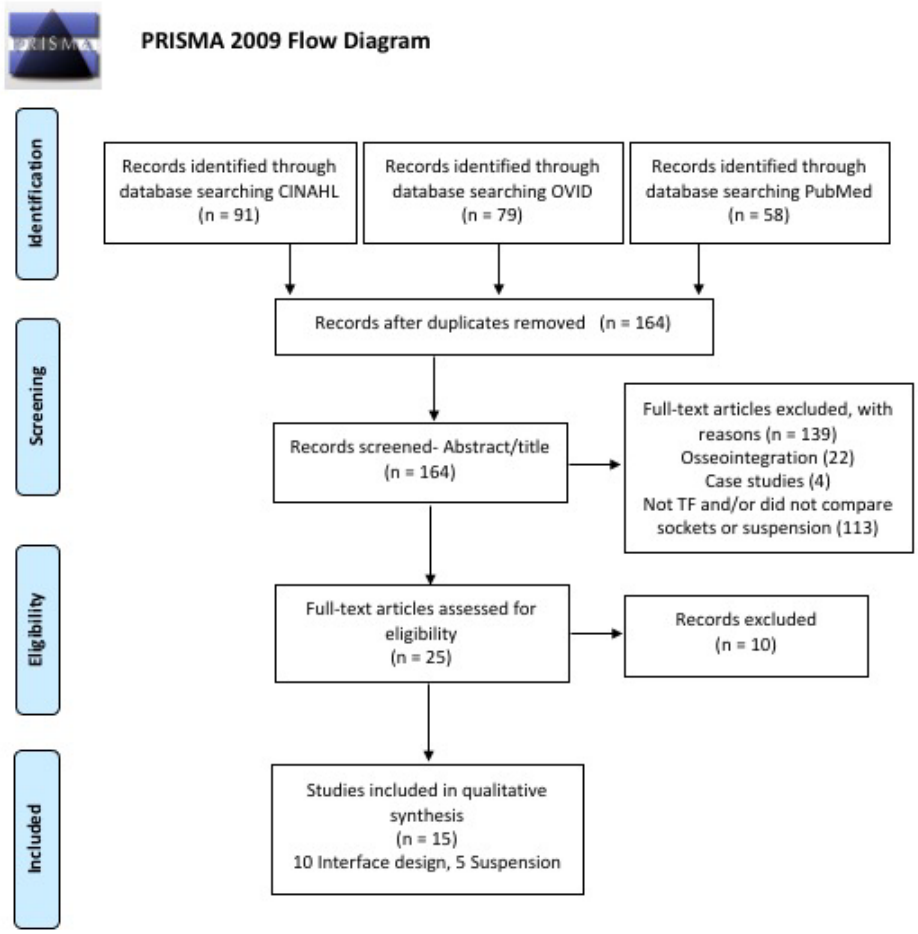
1. Published in English
2. Peer-reviewed
3. Published between 1999 – present

4. Study design must include a comparison of sockets or suspension designs

Articles were excluded if they met any of the following criteria:

1. Case studies or case series
2. Editorials
3. Technical notes
4. Articles regarding osseointegration
5. Non-English language
6. Published prior to 1999
7. Did not include a comparison of sockets or suspension designs
8. Articles regarding osseointegration

Figure 1.



Studies that included both transfemorals and transtibials were retained only if results regarding transfemoral were isolated from transtibials.

Results

Fifteen articles were identified. Articles were classified according to whether the study investigated socket (10) or suspension designs (5). Socket design studies included three prospective randomized clinical trials, five prospective non-randomized clinical trials, and two retrospective studies. Suspension design studies included one prospective randomized clinical trial, two prospective non-randomized clinical trials, and two retrospective studies; 546 transfemoral amputees were enrolled and 476 completed their respective data collections and were included in this analysis. Socket designs included in the studies were: no socket, test socket, ischial containment (IC), ischial ramus containment (IRC), sub-ischial (SI), thermoplastic, Infinite, High Fidelity (HiFi), quadrilateral (Quad), Icelandic-Swedish-New York (ISNY), Marlo Anatomical Socket (MAS).

Interface Design

Two publications by Kahle and Highsmith compared the IRC to sub-ischial socket with regard to hip angle, lateral shift, pistoning, pressure, preference, gait, balance, and mobility. [5,13] In Kahle and Highsmith, the sub-ischial socket reduced medial proximal pressure ($p=0.02$). Participants also subjectively preferred the brimless socket.[5] In Kahle and Highsmith, while IRC improved step length ($p=0.04$), sub-ischial allowed for a narrower base of support ($p=0.03$).[14] Similarly, Fatone et al. compared sockets with and without IC and various tissue loading (high, medium, low) specifically regarding comfort, step with, walking speed, lateral trunk lean, and coronal plane hip moment.[27] Tissue loading significantly affected walking speed ($p=0.03$) with the greatest distance being covered when wearing IC with high tissue loading. The effect of IC and tissue loading was significant for step width ($p=0.04$), with narrower step width occurring without IC. Socket Comfort score increased with no IC and decreased tissue loading. [27]

Traballesi et al. compared the IC to the Marlo Anatomical Socket (MAS), also known as the ischial-ramus containment (IRC) socket.[28] Use of the IRC socket significantly lowered the energy cost of walking in TFAs compared to the IC.[28] Isaacson et al. found that the Infinite socket was more comfortable ($p < 0.0001$), allowed users to walk further during the 2-minute walk test ($p = 0.007$), and demonstrated increased confidence in stepping activities during the Four Square Step Test ($p = 0.005$). [29]

Kahle et al. compared performance with IRC to High Fidelity (HiFi) socket using the Activities-Specific Balance Confidence (ABC) scale and 2 minute walk test (2MWT).[23] Amputees reported greater balance confidence on the ABC ($p=0.02$) and were able to walk farther ($p=0.0001$) with the HiFi socket.[23]

Hachisuka et al. found that, compared to the Quad socket, the IC provided greater comfort for users when seated in a chair ($p<0.05$).[8] However, cosmetic appearance was subjectively rated

lower than the Quad ($p<0.05$).[8] In objective measures, the IC was more effective than the Quad in maintaining the femur in proper adduction during gait ($p<0.05$).[8]

Aydin and Okur investigated whether using a test socket increased user satisfaction, decreased pain, and improved function.[30] Twelve TFAs were included in the test socket group and 13 TFAs were included in the no test socket group. Use of a test socket resulted in greater distance of painless daily walking ($p = 0.032$), and decreased time to climb10 steps ($p = 0.043$) and walk 10 meters at an 8% incline ($p=0.022$). Additionally, the Trinity Amputation and Prosthesis Experience Scales (TAPES) psychosocial adjustment ($p = 0.023$), activity restriction ($p= 0.048$) and prosthesis satisfaction ($p = 0.029$) subscales were significantly improved for the test socket group.[30]

Klotz et al. compared no socket, Quad, IC and IRC in a variety of outcome measures. All sockets restricted hip range of motion as compared to without a socket.[31] Global amplitude, defined as the sum of the angular values of flexion, extension, abduction, and adduction, were higher for IRC when compared to Quad and IC.[31] Finally, Macchi et al. compared microcirculation in a group who tolerated the ISNY IRC socket versus those who did not. The group that reported socket intolerance had statistically larger capillary loops ($p<0.001$), microaneurysms ($p<0.001$), and microhemorrages ($p<0.001$).[32] The authors hypothesized that pathophysiological changes at the microvascular level may help to explain prosthetic intolerance. This may be the case in diabetics who suffer from these conditions.[32]

Suspension

Suspension options investigated included vacuum, suction, seal-in liner, vacuum pumps, Icelandic Roll-on Silicone Socket (ICEROSS) silicone liner, and no liner. Vacuum suspension was frequently studied in the identified articles. The Gerschutz et al. study found a positive correlation between vacuum pressure fluctuations and distal displacement.[33] Rosenblatt and Ehrhardt compared vacuum assisted socket suspension (VAS) and non-VAS on fall risk.[34] While the study found a significant reduction of falls in transtibial amputees, no differences were found specific to TFA.[34] Major et al. compared the Otto Bock Harmony e-pulse electric vacuum pump to the Willow Wood LimbLogic, measuring time and rate of evacuation to reach 17-in Hg below atmospheric pressure during standing, and the number of times the pumps re-activated to reach the same pressure during treadmill walking.[35] The LimbLogic performed better in time to achieve 17-in Hg ($p<0.001$) and evacuation rate ($p<0.001$).[35]

When comparing seal-in liner versus common suction system (CSS), Gholizadeh et al. found satisfaction with Seal-in liner (ICEROSS Dermo Seal-In Liner - Ossur Inc, Grjothals 5, 110 Reykjavik, Iceland) over CSS in fit, sitting, and donning and doffing ($p<0.05$).[36] However, CSS was preferred over Seal-in ($p<0.05$) with regards to sweating, wounds, pain, irritation, pistoning, swelling smell, and sound. Additionally, CSS was found to be more durable than Seal-in liner ($p=0.000$).[36] A retrospective study by Trieb et al. investigated rehabilitation of geriatric patients

with TFA when wearing the ICEROSS silicone liner versus no liner.[37] Patients who wore the ICEROSS (Ossur HF, Grjoethals S, 110 Reykjavik, Iceland) increased the ambulatory capacity between discharge and follow-up compared to those who used no liner ($p<0.001$). Additionally, inpatient stay was significantly reduced by five days for the ICEROSS group ($p<0.05$).[37]

Interface design evidence based statements

- Sub-Ischial trim lines compared to IRC are preferred by subjects.[5,13]
- Sub-Ischial trim lines compared to IRC intensify tissue loading over smaller surface area.[5,13,27]
- Emerging data suggests that SI trim lines may contribute to less dynamic balance stability.[42]
- Alternative socket designs, including the HiFi™, Infinite™, MAS® sockets, compared to IRC may improve balance confidence, gait speed and walking distance and lower energy consumption.[23,28,29]
- IRC compared to Quad was more comfortable during sitting and reduced femoral abduction.[8]
- The use of at least 1 test socket can improve walking performance and patient satisfaction due to potentially improved definitive socket fit based on patient comfort and fit.[30]
- Compared to no socket, use of a transfemoral socket limits hip range of motion patient function and possibly quality of life.[31]
- A patient's pathophysiology at the microvascular level may help explain skin discomfort that leads to transfemoral prosthetic socket intolerance.[32]

Suspension evidence based statements

- VAS can reduce volume fluctuation and pistoning more so than suction.[33]
- VAS does not improve fall risk compared to non-VAS suspension.[34]
- Electronic vacuum pumps are an acceptable means of suspension in transfemoral interface use.[35]
- The use of gel liners could potentially improve walking distance, reduce hospital stay, and satisfaction for transfemoral interface users.[36,37]
- The use of gel liners can reduce common overall problems associated with transfemoral interfaces, such as pain and skin irritation, swelling and daily volume changes.[37]

Discussion

The included studies presented mixed methodology, outcome measures and study design, compromising the generalizability and clinical practice translation and usefulness. Similar patient numbers in other areas of healthcare have garnered significantly more healthcare research funding compared to prosthetic care for lower extremity amputees. This may explain a paucity of rigorous published comparative effectiveness research.[38] While the included studies maintained a theme of addressing socket interface issues through design or suspension, a

consistent comparison of a recognized standard of care versus an intervention was less consistent. Similar to past systematic reviews of lower extremity prosthetics, the uncertainty of effectiveness issue creates disagreement about which type of socket interface design and suspensions to compare in clinical trial research, at the study and policy level.[38] While the Department of Defense has invested a substantial amount of dollars to investigate these issues[39,40] and manufacturers have continued to develop and evolve socket technologies to support alternative interface designs, the lack of a sustained funding strategy from the National Institutes of Health (NIH) for rehabilitation research in the area of TF interface and suspension has contributed to a void in the evidence base for amputation rehabilitation and prosthetics care.[38,41]

Eight studies compared different TF interface designs.[5,8,13,23,27-29,31] Three studies reported the effects of sub-ischial design compared to IRC and reported the effect on pressure, tissue loading, skeletal kinematics, pistoning, gait, balance, mobility, comfort and preference. These three studies were in agreement in that the reported benefits of IRC design were not compromised by lowering the medial trim-line to the sub-ischial level. Further, subjects preferred the sub-ischial designs.[5,13,27] Three other studies compared alternative interface designs (HiFi™, Infinite™, MAS®) to IRC regarding gait speed, comfort, balance confidence, walking distance and energy consumption.[23,28,29] In all three studies, the alternative designs reportedly improved the respective performance compared to the IRC.

One study compared IRC to Quad sockets and found skeletal kinematics were more[8] anatomical and sitting was more comfortable with the IRC but equivalent in ambulatory metabolic efficiency. Aydin and Okur reported improved ambulation and psychosocial adjustment, activity restriction and prosthesis satisfaction among transfemorals receiving check sockets prior to finalizing the prosthesis, compared to those who did not receive a check socket.[30] Outcome measures included daily walking distance with prosthesis, 10-step climbing up, 10-meter walking up an 8% slope, walking VAS, and all TAPES subscales (including psychosocial adjustment, activity restriction, and prosthesis satisfaction. This suggests that fitting check sockets, while requiring more of the patient's time initially, could improve overall prosthesis function, patient function and satisfaction, and decrease technical difficulties with the socket in the long run.

Two studies did not compare interface designs, but rather reported on the limitations of wearing a transfemoral interface.[31,32] Macchi et al. compared users intolerant of prosthetic sockets compared to those tolerant of them.[32] Authors reported the pathophysiology of microcirculation in the residual limb may explain why one could be intolerant of wearing a prosthesis. The intolerance was not linked to a specific design, but rather the patients' physiology.[32] Finally, Klotz et al. compared 3 different socket designs including IRC and Quad to wearing no socket and found that all prosthetic socket designs restricted hip mobility and could compromise quality of life.[31] This suggests that alternative trimlines need to continue to be developed and studied to

allow prothetic users to retain hip mobility for optimal function leading to improved quality of life.

Regarding suspension systems, Vacuum assisted suspension (VAS) can control volume fluctuation and pistoning superior to suction.[33] However, the benefits of VAS did not translate to improving fall risk in the transfemoral population.[34] Major et al. reported on the equivalence of two different electronic vacuum pumps used in VAS fittings at the transfemoral level and found them both comparable in achieving adequate vacuum.[35] Further, both pumps provided effective VAS.[35] Finally, two studies agreed upon the benefits of gel liners for the transfemoral prosthetic user.[36,37] Specifically, Trieb et al. found that geriatric patients could walk further using a gel liner with a pin system attachment compared to using no liner.[37] Gholizadeh et al. reported gel liners with a sealing gasket suspension were preferred regarding fitting, sitting, donning and doffing, perspiration, wounds, pain, irritation, pistoning, swelling, smell, and sound. However, a non gel socket was found to be significantly more durable.[36]

Conclusion

This systematic review was unable to determine a consensus among the reported literature regarding optimal socket interface design and suspension. However, this study yielded eight evidence based statements in the area of TF interfaces and six evidence-based statements in the areas of TF suspension. SI and alternative design TF sockets were the most studied and the most common comparator was the IC or a variant thereof, suggesting the IC may be the standard of care. In terms of transfemoral suspension, VAS and liner systems were studied with high prevalence but were not without clinical considerations.

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Supplement C: The Role of Transfemoral Socket Design and Alignment to Prosthetic Mobility and Posture: A Narrative Review

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Introduction

Inherent to amputation at the transfemoral level is a significant loss of anatomy that can alter balance, force production, and neuromuscular control. The goal for prosthetic device prescription is to mitigate these consequences in a system that provides the biomechanical functions demanded for human movement without sacrificing comfort or cosmetic appearance.[1] The transfemoral socket is especially critical, serving as the interface between the device and the residual limb. While all socket designs seek to create an intimate fit to the natural contours of the residual limb, they vary in material composition and surface coverage. The four primary types of transfemoral sockets are the: 1) ischial containment, 2) ramal containment, 3) quadrilateral, and 4) subischial, vacuum-assisted suspension designs. To create a stable system, the transfemoral socket and distal prosthetic componentry are aligned in an orientation to support the residual limb and provide stability in sagittal and frontal planes. The numerous options of socket design and alignment allow clinicians the opportunity to customize the device to the needs of the user.

When determining what transfemoral prosthetic system is going to be most appropriate for a transfemoral amputee, it is important to consider the complexity of the human movement system. While both the socket design and alignment can strongly influence the success of the user, the human body is dynamic and cannot easily be categorized.[2] This chapter will describe gait deviations and postures commonly seen after transfemoral amputation and review the existing literature to discuss how socket design and alignment contribute to these compensatory movements.

Transfemoral Prosthetic Mobility

Postural asymmetries and altered gait mechanics are commonly seen in people with unilateral transfemoral amputation. Frequently observed is a slower and less efficient gait pattern[3,4] that is hallmarked by a wider base of support and step length asymmetry.[5] Kinetic changes are also common during transfemoral gait, for example during early stance phases the intact limb has an almost 300% increase in hip extensor work[4], and the prosthetic limb exhibits earlier and longer hip extensor activity.[6] People with transfemoral amputation also commonly walk with kinetic asymmetry, as the loss of knee flexion to absorb shock of prosthetic limb during weight acceptance results in greater vertical displacement of the center of mass and increasing oxygen

consumption.[7] The long term adoption of asymmetric movement patterns and resultant forces are commonly blamed for the high rates of low back pain,[8] and pathologic changes to the joints[9] and plantar surfaces[10,11]of the intact limb.[12,13] Understanding how these adverse effects can be managed by socket design and alignment could have significant impact on clinical practice.

Adjustments in socket design and alignment have been shown to influence the severity of these presentations, but there are numerous additional contributing factors. Compensatory patterns can present as a result of a muscular weakness or imbalance, range of motion (ROM) deficits, presence of pain, lack of proper training, or even a prior habitual pattern. The transfemoral socket may directly impose mechanical constraints to the hip of the residual limb, due to variations in trim lines between the designs.[14-16] While normal gait demands approximately 40 degrees of sagittal plane hip motion, ideally 10 degrees of hip extension and 30 degrees of hip flexion[15], functional tasks such as sitting, bending over, and getting off the floor, have greater demands for hip movement. The proximal brim of some transfemoral socket designs may be a cause of discomfort during these activities.[15]

Socket alignment can also be a source of movement constraint to the hip of the residual limb.[18-20] For example, to accommodate for a hip flexion contracture the transfemoral socket is aligned in increased flexion. When this alignment change is significant, the amputee will be unable to achieve the hip extension required for normal gait. Therefore, requiring the user to adopt a compensatory motion of excessive lordosis and/or anterior pelvic tilt during prosthetic stance phases. Compensatory patterns of posterior pelvic rotation and lumbar flexion will be used if hip flexion ROM is limited by a mobility deficit or socket restriction.

Considerations for Postural Asymmetry

The increased demand on the intact limb is not isolated to mobility tasks, but is also seen in quiet standing.[21] During static postures, transfemoral amputees asymmetrically increase the weight distribution onto the intact limb.[21] The center of mass is shifted toward the sound limb[21] through multi-planar pelvic movements resulting in excessive anterior pelvic tilt[22] and pelvic obliquity.[8] The asymmetric standing posture of transfemoral amputees is potentially problematic for clinicians. In the asymmetric posture, a prosthesis that appears vertically aligned (with respect to the sagittal and frontal planes) would in fact be short; as the intact limb is relatively adducted, externally rotated, and flexed due to changes in the acetabular orientation. While the pelvis, hip, and lumbar spine can compensate for the leg length discrepancy in bipedal standing, the discrepancy will be magnified in single limb support phases of gait. Therefore, it is suggested that clinicians reposition patients into a more symmetric standing position before static alignment of a transfemoral prosthesis.

A study by Gaunard et al., 2011 found a high prevalence of leg length discrepancies (LLD) in people with transfemoral amputation.[22] A shorter prosthetic leg length was discovered in almost half of the subjects, with leg length differences ranging from 0.7-2.5 centimeters. While it is not known how LLD could impact movement of a transfemoral amputee, we can draw conclusions

by examining research on non-amputee populations. A systematic review concluded that imposed leg length discrepancies as small as 1 cm can lead to pelvic obliquity, gait deviations, and greater energy demands.[23] The study identified several compensatory strategies adopted by both the shorter and longer limb. According to the systematic review, a transfemoral amputee would compensate for a shorter prosthetic limb with increased force and vertical CoM displacement during weight acceptance. While the intact limb would compensate for the longer length with a global increase in mechanical work during stance. The projected gait deviations based on LLD are surprisingly similar to common gait deviations seen in people with transfemoral amputation[8], suggesting that assessment of LLD might be an important clinical consideration for prosthetic alignment.

Any accommodation of the socket will by nature cause an asymmetry compared to the sound side. The abnormal forces of these asymmetries will be translated through the pelvis and spine which can increase the risk for low back pain. If a socket is accommodated for a 10 degree hip flexion contracture (socket flexed at approximately 20 degrees from neutral), then the user will stand, ambulate, and sit with this 20 degree hip angle discrepancy. This will cause hip flexion angles in sitting to be greater than 90 degrees, increasing posterior pelvic rotation and lumbar flexion. Asymmetrical hip flexion angles in sitting can also cause a pelvic innominate rotation, and can present as sacroiliac dysfunction or low back pain.[22] A more sedentary transfemoral amputee will have a greater exposure to these forces. The long term consequences of these asymmetries needs to be considered. The clinician will need to determine the functional abilities and goals of the user to help determine socket style and accommodations.

Socket Stability during Single Limb Support

Mediolateral stability is a critical element in gait to allow the contralateral limb to advance in preparation for the subsequent step. In a transfemoral prosthesis the socket design and alignment play a critical role for how the amputee can 1) control the lateral and vertical displacement of the center of mass with a residual limb that has a short level arm and altered muscle insertion and 2) maintain erect trunk posture. Socket design and alignment play a critical role in keeping the trunk vertical during single limb support. During midstance, the femur of the residual limb creates a closed kinetic chain by stabilizing against the lateral wall of the socket, provided by the socket shape, adducted alignment, and mediolateral dimension. The amount of support required varies with the residual limb length and hip abductor strength of the individual, with weakness and shorter residual limbs requiring designs that are more aggressive with support. Failure of the socket to provide adequate stability will result in either a lateral deviation of the trunk, proximal-lateral gapping, or an abducted (medial leaning) prosthesis during this gait phase. Pain at the pubic ramus or distal lateral femur can also contribute to lack of normal lateral displacement during this phase.

During single limb support, the transfemoral socket must also provide adequate anterioposterior stability to prevent compensatory movements. During this phase of peak hip extension, the

socket must be aligned in sufficient flexion to match the hip mobility of the individual. Inadequate socket flexion can lead to compensation by excessive lordosis. Providing adequate sagittal stability can be difficult when the length of the residual limb or hip extensor strength are not sufficient to maintain pressure on the posterior wall.

Movement constraints in the transfemoral socket design may also contribute to observed compensatory changes in late stance. Rabuffetti et al., attributed decreased sound side step length to ischial containment socket constraints on hip extension.[24] The authors postulate that the socket design limits the ability of the hip to achieve full extension, and thus forces the pelvis into an anterior pelvic tilt. This was supported by Klotz et al., who concluded that a transfemoral socket, regardless of ischial containment design, quadrilateral design, or ischial-ramal design, will limit the hips motion relative to normal physiologic conditions.[16] The study also reported that between designs, the ischial-ramal containment socket was the least restrictive to hip movement. Conversely, Kahle and Highsmith reported decreased base of support width when subjects used brimless sockets suggesting less restriction than in IRC designs.[25] Ultimately, there is little evidence available to determine whether a socket restriction or limited hip extension ROM has a larger contribution to these compensatory strategies. Likely, we will see more of the hip extension limitations due to the socket from those users that have greater hip extension ROM.

Outcomes to Assess Prosthetic Satisfaction and Socket Fit

To ensure good clinical outcomes, we must evaluate how well the intervention, specifically the socket design and alignment, provides function, comfort, and an acceptable cosmetic appearance. Prosthetic satisfaction is a complex concept that is influenced by the cosmesis, function, and comfort of the device. However, the importance of each of these aspects will vary by the individual. Analysis of gait biomechanics can be very helpful to a clinician to evaluate how well the transfemoral prosthetic system is meeting the functional needs of the user. However, it does not provide information relating to the comfort or appearance, and may not be as important to the user. This idea is supported by a study by Kark and Simmons that found that domains of prosthetic utility, frustration, and social burden were highly correlated to prosthetic satisfaction, while domains of functional mobility and quality of gait were not significant.[26]

Regardless of prosthetic socket design, the fit and alignment are critical to proving the biomechanical basis to respond to the external demands of walking, standing, and performing transfers. There are numerous challenges to fit and comfort of a transfemoral socket including: residual limb shape, length, volume fluctuations, and skin breakdown. For this reason, outcome measures have been developed and validated to assess socket comfort and fit.[27] The Socket Fit Comfort Scale (SFCS) was developed as a single item assessment, that has the prosthetic user rate the comfort and fit of their socket on a 0-10 rating scale.[28] The validated measure has been shown to be sensitive to prosthetic interventions for socket adjustments and replacements.[27,28] The SFCS is also a part of the Revised Trinity Amputation Prosthesis Experience Scale (TAPES-R), which is a 64 question survey.[29] The patient reported outcome measure includes subscales

related to prosthetic satisfaction and residual limb pain that can be administered separately. To assess the satisfaction with the prosthetic socket, Gailey et al. developed the Comprehensive Lower limb Amputee Socket Survey (CLASS).[30] The CLASS is a 15 item questionnaire that assesses the prosthetic users perception of the stability, suspension, comfort, and appearance of the socket using a 4 level rating system from strongly agree to strongly disagree. The measures assess prosthetic socket satisfaction during specific functional activities including sitting, standing, walking, stairs, and wearing tight pants.

As healthcare providers we place high value on the functional performance of our interventions and the ability to normalize gait mechanics, but if these are not shared values with our patients it cannot be our only clinical outcome. Utilization of clinical outcomes measures that assess socket comfort, appearance, and prosthetic satisfaction should be utilized in combination with gait analysis to ensure that the transfemoral prosthetic device meets the needs of the user.

Conclusion

The prosthesis is the tangible object that tends to be focused on when a movement constraint or compensation is occurring. In order to find a balance between function, comfort, and minimizing postural and gait deviation, the clinician must take a more holistic approach to the socket design, fit, and alignment. The transfemoral socket design should be chosen to achieve necessary anatomical mobility while also giving the individual the structural support needed. An accurate and thorough assessment of the user's anatomic mobility is paramount in determining sagittal and frontal plane alignment. Knowing the typical compensatory patterns, and possible prosthetic contributor to these patterns will help the clinician during the fitting process.

Many times, an adjustment to the prosthesis can make an immediate impact on the desired outcome, positive or negative. However, an adjustment to the prosthesis does not account for the remainder of the variables based on the individual user. The clinician should strive for a methodology that accounts for the individual's goals, physiology, medical history, and prior level of function. Due to complexity of the human movement system, and poorly defined socket fitting criteria, more research needs to be done in order to further help the clinician determine the parameters around the transfemoral socket to maximize the user's outcome.

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Supplement D: Dermatoses in Patients who use Transfemoral Prostheses

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Skin Related Epidemiology

Prosthesis users experience more skin problems and at higher rates than non-amputees. Dermatologic issues occur in 7% of ambulatory visits in the U.S.[5,6] whereas amputees experience a dermatologic issue in 15 to 41% of ambulatory visits, representing a 2-6 fold increase compared with non-amputees. Therefore, rehabilitation clinicians must become comfortable in managing common skin concerns and recognize when to refer if the cutaneous problem worsens, fails to improve, or is beyond the scope of routine prosthetic care.

Prosthetic use challenges integumentary integrity in many ways. For instance, heat transfer is impaired and perspiration mechanisms are altered. Additionally, the skin is exposed to contact with new materials and novel forces in associate with prosthetic suspension and weight bearing. Other associations with skin disease include younger age exposures, traumatic amputations, level of amputation, ambulation without an assistive walking device, smoking, antibacterial soap, frequency of residual limb cleansing and increased activity level.[7,8] Time out of the prosthesis may be required to allow healing in some circumstances.[9]

Transfemorally amputated residual limbs (RLs) experience these same concerns but are unique in that they have a singular lower limb bone compared with two at the transtibial level. This challenges transverse rotational stability and makes pelvic weight bearing attractive prosthetically. Further, transfemoral RLs have a considerably greater soft tissue volume compared to other amputation levels which impacts the artificial limb interface. Interestingly, transfemoral patients have less skin problems when compared to any other level of amputation.[7,10] Approximately 22% of patients with transfemoral amputations (TFAs) self-reported skin concerns compared to 38-45% of transtibial amputee patients..[7,10-12] TFAs also self-report less concerns with odor, perspiration and soreness as well as an observed decreased incidence of heat rash and folliculitis when compared to transtibial amputees.[13]

Cutaneous Problems

A. Dermatitis

Dermatitis is among the most commonly reported issues in prosthetic users and translates to skin inflammation. Dermatitis is a broad term describing redness and erythema but more information is required to elucidate the etiology and best management strategy. Inflamed skin typically presents with erythematous patches. Acutely, the rash may also be pruritic, weeping, have fluid filled vesicles, or larger bullae. More chronic dermatitis will again show erythema but will more often have secondary skin findings such as excoriations, crusting, or lichenification. This inflammatory response compromises integrity and may lead to secondary issues such as infection. Fissures, psoriasis, lichen planus, pigment alteration, ulceration, lichenification, or infection can result within the affected areas but may also occur independently. Although there are multiple causes of dermatitis, selected conditions more common in patients with amputations will be discussed further below.

1. Contact dermatitis

Contact dermatitis is an inflammatory response occurring when a substance comes into direct opposition with the skin. The two main forms of contact dermatitis are Irritant Contact Dermatitis (ICD) or Allergic Contact Dermatitis (ACD). ICD may occur on first exposure from direct tissue damage and is the most common type of contact dermatitis. ICD should cause a reaction in all human skin equally, for example, friction or battery acid.

Dermatitis resulting from an immunologic hypersensitivity cascade in select persons following repeated allergen exposure is called allergic contact dermatitis. ACD is a delayed hypersensitivity reaction upon repeat exposure in select individuals. An offending agent may cause ACD in one person but not in others. Materials used in the production, repair, or maintenance of prosthetic devices are possible agents in contact dermatitis reactions.[14] The practitioner must elicit a precise medical history to determine the possible causes of dermatitis although this may not always be possible to elucidate. Patch testing is the gold standard for determining or excluding an immunologic allergen that must be avoided to ensure resolution.[15,16]

Management is centered on avoidance of the offending agent(s). Other therapeutic modalities include separating the skin from the irritant by a physical barrier (i.e. liner.) or topical barrier, emollients, or possibly corticosteroids.

2. Intertrigo

Intertrigo is another common dermal inflammatory response partially due to friction between two constantly opposing skin surfaces. Other contributing factors include elevated heat, perspiration, shearing forces, and maceration. Intertrigo occurs in skin folds. Transfemoral patients have an increase in soft tissue volume compared to other levels of amputation. A poorly fitting prostheses or invaginated scar could compress skin surfaces together resulting in intertrigo.[17] Intertrigo

should improve in a well-fit prosthetic device in a patient with good hygiene practices. The application of a topical barrier, emollient, or corticosteroid may be necessary in some cases.

3. Heat Rash

Miliaria rubra, or prickly heat, is characterized by occluded sweat that leaks into the lower epidermis or superficial dermis and elicits an inflammatory response with erythematous macules, patches, and papules. Prickly heat rash is commonly seen under the prosthetic device due to the artificial interface with sustained exposure to friction, lack of cooling mechanisms and elevated temperatures. Typically, significant improvement occurs abruptly when the prosthesis is not worn for a single day, typically requiring no further treatment.

4. Urticaria

Urticaria, or hives, is a transient pruritic eruption with central pale dermal edema and surrounded by redness that blanches with pressure. These wheals can resolve rapidly, often within an hour but may persist for nearly an entire day. Subtypes of urticaria include physical, cholinergic, cold, heat, vibration, and pressure among others.[18] As in most cases of dermatitis, a careful and complete history is critical to determine if the patient is indeed having hives. Testing for a physical urticaria is not advised in the prosthetic evaluation unless the practitioner is trained and equipped to treat a possible anaphylactic reaction. Treatment generally includes avoiding the underlying eliciting factor, oral antihistamines, and possibly topical corticosteroids.[18]

B. Infection

Skin is naturally equipped to minimize the risk of infection. Defense mechanisms include intact skin, normal flora of microbes, the complement system, and both the innate and adaptive immune systems. The skin of the RL has an increased microbial flora compared to sound limbs in the same person. Further, the prosthetic interface creates an unnatural environment that could compromise many of these defenses. Infections may present as a localized issue on the RL or may become systemic recognized by constitutional symptoms such as elevated core temperature, chills or other flu-like symptom, which may represent a life threatening complication necessitating immediate care.[17] Improving hygiene practices may assist to prevent all of the infections presented in this section.[19]

1. Folliculitis

Inflammation of the hair follicle is an extremely common problem in patients using prosthetic devices that is often related to microbial infection. Small folliculocentric pustules are typically scattered in an affected area and are more prevalent in those with hyperhidrosis, increased hair, oily skin, obesity, shaving, elevated temperatures, and friction.[20,21] Staphylococcus or Streptococcus are commonly associated but other bacteria or even fungi, such as Malassezia, are common. Shaving should be discouraged and counselling should be emphasized to ensure the area is kept cool and as free from friction as possible. In some cases, topical antimicrobials such

as benzoyl peroxide have been used. Alternatively, Clindamycin solution may be used in bacterial folliculitis whereas Ketoconazole shampoo may treat folliculitis resulting from Malassezia. Occasionally, systemic antibiotics are prescribed depending on the severity and microbes involved. Permanent laser epilation can also be considered in some patients.

2. Furuncle

Some infections are due to deeper dermal infection than is seen in folliculitis. Many patients refer to these infections as a boil, but they are more precisely termed furuncle.[22] Pustules are not visualized in these lesions. Instead, furuncles present as an indurated erythematous nodule often with tenderness or irritation. Furuncles are generally found on areas of mechanical friction and increased sweating.[23] Commonly affected areas include the axilla and groin so it is not surprising to see them on the RL of a patient with a TFA. Furuncles may also require topical or systemic antibiotics, antimicrobial soaps or cleansers (i.e. chlorhexidine), or could require surgical drainage. In cases of suspected furuncle, a discussion with a dermatologist is advisable depending upon the previous rate of skin problems, hygiene, symptoms, and presentation.

3. Abscess

Infection that involves more surrounding and yet deeper tissues than previously discussed may result in a fluctuant and very painful abscess. An abscess could result in systemic symptoms and a wound culture should be taken to determine the microbial etiology and susceptibility to antibiotics. Treatment must include incision and drainage of these purulent lesions. Although systemic antibiotics are commonly used they are generally not necessary as long as the lesion is drained appropriately.

4. Superficial fungal infections

Jock itch and athlete's foot are common skin problems seen in the general population in areas of friction and maceration. At the artificial interface of the RL, dermatophytes invade the disrupted skin barrier to produce an erythematous annular patch which is a ring of redness (i.e. ring worm) along with central clearing.[24] Yeast could also affect the skin and forms distinct beefy red patches with satellite lesions just beyond the primary dermatitis. Topical antifungals are the mainstay of treatment but must be correctly matched to the underlying microbe.

C. Volume Change

Volume changes occur commonly in patients with an amputation. Volume mismatching between stump and prosthetic interface is among the most common and considerable source of dermatologic maladies and impaired function for the prosthesis user. Prosthetic use results in abnormal tissue stress of the RL. During weight bearing for example, axial loads are applied through the stump resulting in forces acting upon and through tissues that are not anatomically suited to manage them. For example, a distal cut end of the femur requires translocating muscle bellies beneath this boney prominence to be used for bearing axial load instead of the foot. It is

highly conceivable how this can contribute to abnormal forces, edema, and ulceration at the RL. Steps to minimize volume change must be pursued and optimizing prosthetic fit 0is paramount.

1. Friction (lichenification, blister, callus)

Abnormal forces are applied to the RL during prosthetic use. This friction will result in changes within the skin. Initially, redness and irritation will form but blisters are not uncommon. This friction is actually a form of ICD discussed earlier. As such with time, the skin may harden which is termed “lichenification”. Clinically, lichenification can be identified easily with exaggerated skin lines secondary to thickening of cutaneous tissue in the affected area. Improving prosthetic fit and teaching pressure relief strategies (i.e. release the pin lock during prolonged sitting, doff the prosthesis) is recommended as first line treatment. Secondary lichenification can be treated with corticosteroids if indicated.

2. Ulceration (Volume Change; Pressure Sores and Ulceration)

With continued friction and pressure between the skin and bone the skin may become ischemic and begin to break down at the RL. Initially, redness may develop at the affected area followed by a superficial erosion. With continued friction and irritation decubitus ulcers, or “bed sores” will likely result. A decubitus ulcer is among the most common concerns in prosthetic skin care. Most pressure sores seen in medical treatment facilities are seen on the heels and sacrum of supine positioned, bed-bound patients. Decubiti can develop in any skin wherever mechanical pressure is applied over a bony prominence. A poorly fit or aligned prosthesis creates focal pressure and shear forces over bony prominences referred to as “hot spots.” Ulcers can result and may be complicated by bacterial infections, vascular disease or focused mechanical prosthetic pressure.[10,17,25,26] Concerted efforts to resolve ulcers should be made as long-standing chronic ulcers can become scarred, complicate healing, increase risk of cancer, and affect future prosthetic use.

3. Negative Pressure Hyperemia

Negative pressure systems use vacuum or suction forces to ensure the prosthesis is held onto the stump during unweighting periods (i.e. swing phase of gait).[27] Any loss of contact between stump and interface with negative pressure suspension will result in a void with lowered resistance to circulation in that area. This increased circulation at an area of negative pressure pulls in vascular and lymphatic fluid creating congestion termed Negative Pressure Hyperemia (NPH).[18]

If the loss of contact persists, the site will become sharply demarcated, red, swollen, and exquisitely painful. Volume change is the most common cause of NPH with weight gain a common contributor preventing full and total distal contact. A period of prosthetic disuse may be recommended due to the pain the suction will cause during unweighting. Temporary padding may be used to facilitate temporary distal prosthetic contact in active patients. Fabrication of a

new better-fitting socket will likely be needed as total and complete distal contact of the interface with the RL is required.

4. Verrucous Hyperplasia

Verrucous hyperplasia (VH), or lymphostasis papillomatosis is a warty appearance at the distal end of the stump.[21,28] VH was possibly more prevalent in previous decades as prosthetic socket designs present at that time minimized distal contact and preferentially loaded proximal tissues. This constricted fluid exchange and created a space of low resistance at the distal end of the stump. The condition is almost exclusively a problem in the distal skin of the amputated RL which seems to result from proximal constriction and lack of distal contact or appropriate distal circumferential contact pressures and no viral particles have been described.[21,28,29] The mechanism above and treatment of VH are generally agreed upon by using compression, restoring distal contact and optimizing prosthetic fit. A biopsy is indicated if the condition fails to improve or worsens.

D. Tumors

A Tumor is a neoplastic growth that may be solid or fluid filled as well as benign or malignant. The term is often used interchangeably with neoplasia but should not be used synonymously with cancer. Cancer implies a malignant growth into other tissues (local invasion or metastasis) that can alter the function of those structures. Tumors in contrast, could also be benign, may not invade surrounding structures nor alter function. Benign tumors typically do not infiltrate into surrounding organs or alter function as opposed to malignant cancer.

1. Cyst

A cyst is defined as an intradermal or subcutaneous tumor with an epithelial lining and typically filled with keratin or sebum. Epidermoid cysts are the most common type of cutaneous cysts in the RL at the termination of trimlines. The proximal adductor thigh, inguinal crease, and ischial region are typical associated sites. Patients often present for treatment when the lesions are irritated or infected. Their size may vary from a few millimeters to several centimeters. Epidermal cysts are usually asymptomatic but irritation and pain may occur. Surgical excision is the preferred treatment intervention of the symptomatic formed cyst although improving interface fit to reduce friction and restore appropriate pressures are vital to prevent repetitive recurrences.[21,22]

2. Squamous cell carcinoma

Squamous cell carcinoma (SCC) is very rare but is the second most common cancer affecting the skin and is the most common malignant tumor to affect the RL of amputees[30] Risk factors for SCC include sun damage, immunosuppression, smoking, Human Papilloma Virus (HPV) infection, prior skin cancers, radiation, arsenic, lymphedema, chronic sores, chronic inflammation, chronic ulceration, or scarring.[31-33] A subset of SCC forms a verrucoid

appearance, termed verrucous carcinoma, and has been documented in the RL of amputee patients. These lesions are clinically similar to verrucous hyperplasia. Excision of the affected tissue is the treatment of choice but a RL revision leading to a more proximal amputation could be required.

E. Common Symptoms and Concerns

1. Pruritus

Pruritus is the is the most common symptom affecting the skin of patients with amputations.[34] The neurological pathways that transmit itch also transmit pain and could be one's interpretation of mild pain. Pruritus, or itching, may present without any visible rash or other skin lesions. It is reasonable to recommend a trial of common anti-pruritic therapies such as a cold compress for fifteen minutes several times per day, emollients, camphor-menthol, pramoxine hydrochloride or systemic antihistamines as directed by the package insert, over the counter. It is imperative to search for and treat the underlying cause of pruritus as first line management. If the patient fails to improve within two weeks of conservative treatment, the severity of symptoms awakes the patient during sleep, or if systemic symptoms are present, then a referral for systemic evaluation to a physician is indicated.

2. Xerosis

Dry skin, or xerosis, is extremely common and is typically associated with pruritus. In the general population, xerosis affects approximately 3 out of 4 people over the age of 64.[34,35] Xerosis was also the most common skin condition observed in one report of 261 outpatient lower limb prosthetic visits but was rarely the primary reason for scheduling a visit with the prosthetist or other provider.[17] Xerosis is identified by dry, scaly, rough, and possibly itchy skin. Xerosis affects the limbs more than the trunk and is more prevalent in the winter. Xerosis is routinely managed with good hygiene practices and skin moisturizers. In prosthetic management, applying a moisturizer on the stump immediately prior to donning a gel liner is not recommended. In such cases, liners with integrated emollients or moisturizers would be preferable but could become a potential chemical irritant. Introduction of new components or chemicals require skin monitoring for reaction. Patients should be reminded to seek medical advice if symptoms fail to improve or become worse.

3. Scar

Scars can be a common source of symptoms affecting the RL and are an inherent complication of surgery. Traumatic amputations often result in larger scar formation and has been described as an underlying source of increased cutaneous symptoms.[7,10] After one year, the scar is fully mature with a peak strength that is about 75% of the pre-wounding strength and will never attain the strength of normal skin.[36]

Following primary healing, scar desensitization and myofascial manipulation by a physical therapist may be of benefit to optimize scar strength and healing.[37] Itching, irritation, and pain are common complaints related to scar tissue even when the scar is ideal in appearance. Underlying comorbidities, smoking, nutritional status, suture selection, undermining, as well as other technical aspects of closure may ultimately affect the final outcome of healing and scar formation. Ideally, the site will heal with a normal flat asymptomatic scar. However, an atrophic scar, hypertrophic scar, or keloid may form at the surgical site. Over the counter silicone has shown benefit in several studies but intralesional corticosteroids have proven to be most effective in the authors' experience. Laser treatments and scar revisions may be necessary in some cases.

4. Hyperhidrosis

Hyperhidrosis is a condition characterized by an abnormal increase in perspiration beyond the typical quantity required for thermoregulation. It can be associated with burden to quality of life affecting emotional and social domains.[38] Contact with a prosthesis impairs radiation heat loss. Similarly, convection requires moving air to remove heat and thus prosthesis to skin contact prohibits air movement and convection. The process of conduction exchanges heat between two contacting surfaces.[21] This is clearly functioning in prosthesis users as interface materials warm-up to body temperature, likely maintain it along with any additional temperature elevations resulting from added forces associated with movement. Evaporation of perspiration is another heat transfer pathway that is impaired or eliminated during prosthetic use. Nutrition, food supplements, sensory stimuli, and stimulants may contribute to the increase in perspiration.[21,39]

Reflex sweating is total body sweating that occurs when any single body part is exposed to a threshold temperature and may be associated with spinal cord injury but has been discussed in association with amputation.[21,40] Reflex sweating induces perspiration in other places of the body even if all other body parts are below the threshold for sweat production. For instance the RL skin temperatures may be elevated signaling perspiration even though the amputee's core temperature, sound limb, hands and head are at a comfortable sub-sweat production temperature.[21] Amputees who use prostheses are likely to feel warmer and experience total-body, reflex sweating at rates higher than non-amputees.

First line treatment involves using over-the counter topical anti-perspirants containing aluminum ions to provide relief in many patients by temporarily occluding sweat gland pores. Prescription strength aluminum chloride may be necessary or switching to other topical preparations such as anticholinergics, boric acid, 2-5% tannic acid solutions, resorcinol, or potassium permanganate but each substance has its own drawbacks. In some patients, systemic anti-cholinergics (i.e. glycopyrrolate) are effective but could be associated with adverse events such as dry mouth, difficulty with micturition, and constipation. Some patients have been treated with neuromodulating toxins, such as Botox®[41-44] Laser epilation has been recently used as a successful treatment option in axillary hyperhidrosis and has been used by the author with

improvement at the RL. Interestingly, there was also a reduction of cyst formation at the treatment site(s).

5. Odor

Sweat is secreted as an odorless and sterile substance but bacteria can alter the secretion into a noxious smell, termed Bromhidrosis.[16] Eccrine bromhidrosis has also been described secondary to ingestion of medications (i.e. Bromides), foods (i.e. Garlic), or other metabolic abnormalities. When assisting the amputee patient in assessing and managing complaints of odor, the most important aspect is to ensure high quality hygiene as described previously. A thorough diet and medication history is also encouraged to minimize ingestion of known provocative substances. Topical antimicrobial cleansers (i.e. chlorhexidine), and prescription antibiotics (i.e. Clindamycin solution) may be necessary for improvement in some cases.[45] Finally, odor could emanate from the prosthesis necessitating investigation in areas such as the flexible interface and rigid frame and between foot shell and foot structure. These components should be inspected and cleaned thoroughly to optimize management.

Current and Emerging Prosthetic Literature Related to Skin Health in the Transfemoral Amputee

Prosthetic Fit

A 2014 systematic review covered multiple topics including *Prosthetic Fit* and *The Residuum*. A total of 1832 amputees and eight liner materials were investigated in the *Prosthetic Fit* theme.[8] Authors reported that stump integrity, the amputee care regiment and pain impact the ability to become or remain mobile. Importantly and more relevant here is that skin problems were considerable factors identified in 40-63% of participants as the primary reason preventing effective prosthetic use. Skin problems reportedly occurred throughout the prosthetic life cycle with higher activity levels and lower age being more likely predictors of issues. The most prevalent skin problems were pressure ulcers, infection hyperhidrosis and persistent heat rashes. Other skin issues included irritation, inclusion cyst, callus, verrucous hyperplasia, blister, fungal infection, cellulitis, delayed postsurgical wound healing. These findings[8] reaffirm the importance of a quality skin management program, patient education and the need for further study of skin issues relative to care for the transfemoral amputee.

The Residuum

In the aforementioned review[8], three studies were identified that impact or were related to the residual limb. Topics included pressure measurement and the effect of socket alignment on resultant stump/socket interface pressures. Studies impacting the residuum consistently reported complex daily and long-term fluctuations in interface pressures and shear stresses that may lead

to RL tissue changes. Available studies report that interface pressure monitoring provides additional valuable information to the clinical assessment, however there was no consistent approach for its measurement. Techniques included peak pressure and resultant shear stress measured by numerous transducers placed within the socket, vertical force measured by force plate and force sensing resistor insoles placed between the prosthetic foot and shoe and peak pressures, time of peak pressures and time-pressure integral measured by force sensing resistor strips placed within the socket.[8]

Pressure Recording

As previously mentioned, another promising area receiving increased attention in recent publications is interface pressure recording. Because pressure ulcers are among the most prevalent dermatologic malady in lower extremity prosthetic use, the recording of pressure related to prosthetic function is attractive.

A recent transtibial prosthesis user case study yielded shear and normal forces that were highest with the addition of a three ply sock. Longitudinal shear stresses ranged from 0.4–7.66 kPa, transverse shear stresses ranged from 0.01–7.79 kPa and normal stresses ranged from 2.7–61.9 kPa. Increased shear and normal forces can cause a significant decrease in blood perfusion, linked to an increased risk of ulcer formation.[46] Stresses were calculated based on the contact area of the load cell within the socket. For the gel liner condition, peak normal stresses were on average 61.7 ±1.7 kPa. This compared well with others who measured normal stresses for a sleeve suspension in the mid-fibular region to be on average 61.3 kPa. Case results average normal stresses for the gel liner were 27.5 kPa throughout the entire gait cycle. Still others found mean pressure throughout gait to be 36.1 ±11.4 kPa in the mid to distal fibular region.[46] The translatability of these transtibial findings to the transfemoral limb is not yet clear. Using a coefficient of friction of 0.5 during stance, an older study using finite element analysis obtained a maximum pressure of 65 kPa at the distal end of the RL in a full distal-end loading model which was comparable to a more recent study where maximum peak pressures of 80.6, 52.4 and 73.4 kPa were observed at the bottom of the RL surface in three walking load cases.[47,48] However, a more recent study used the Mflex Sensor Distribution System[49] and measured maximal interface contact pressure on above-knee RL at mid stance during walking of 258.90 kPa, which is considerably higher than others. The differences in the pressure magnitude may be associated with pressure sensors manufacturing differences or placement. Nonetheless, interface pressure measurement continues to be a promising measurement given the prevalence of pressure related ulceration in the TFA prosthetic user however the lack of standardization and varied measurement outcomes also makes this outcome an area in need of further study and technological development.

Tribology of Prosthetic Socks

Li et al.[50] studied the tribologic and clinical effects of prosthetic socks. According to the different frictional behavior, skin surface microscopic trauma, skin irritations and sensations obtained from their results, the following suggestions were made in terms of selecting appropriate prosthetic socks. Against the skin, use of wool and nylon socks resulted in obvious microscopic skin trauma along with irritation and discomfort due to their coarse knitting weave surfaces and hard protruding textile fibers. Conversely, cotton and silk socks with their corresponding soft and smooth surface textile features create less microscopic trauma, irritations and discomfort sensations to skin. Therefore, authors concluded it would be advisable for amputees to wear 100% cotton or silk knitted socks if socks must contact skin directly to avoid skin trauma as much as possible.

Skin Health Measures

Rink et al.[51] presented a standardized approach to quantitatively assess RL skin health in individuals with lower limb loss at both the transtibial and transfemoral levels. Probe-based measurements were used to measure skin barrier function via transcutaneous epidermal water loss (TEWL) and skin hydration via surface electrical capacitance (SEC). Briefly, RL transcutaneous oxygen tension was significantly lower in participants with lower limb loss as compared to able-limb controls. Individuals with lower limb loss had significantly higher TEWL and SEC in RL skin as compared to able limb controls, indicative of skin barrier disruption.

Osseointegration

Osseointegration (OI) is an emerging form of prosthetic management. The skin is breached to implant a bone anchored suspension system to support prosthesis coupling and suspension. The surgically implanted components reside in the bone canal passing through the soft tissue envelope including the skin. While this is a relatively novel idea in prosthetic management of patients with extremity amputation, it is similar to a dental implant that is anchored into the jaw bone. Stoma related maladies can be seen in both conditions and are emerging now in the limb prosthetic community as a result. Erythema and a granulation ring were observed in nearly half of OI patients in one study. Bacteria were detected in 90% of patients found commonly in the bone canal among other locations. Common pathogens included Staphylococcus aureus, coagulase-negative staphylococci, streptococci, and Enterococcus faecalis. Problematically, these were present independent from traditional clinical signs of infection.[52,53]

Osseointegrated stomal microbiota may be distinct from those of thigh skin, heterogeneous and temporally unstable. They may become stable community types with dominant taxa by approximately seven months following stoma establishment. There may also be numerous permutations and combinations of microbiota that have potentially beneficial (i.e. protective)

effects that prevent serious infection and stimulate local innate immune responses against pathogenic invasion.[52]

Consequently, a daily hygiene routine must be taught to patients. However, research suggests the routine may either require reanalysis and possible revision or that patient compliance with the regiment must be reinforced or better understood.[53]

Following TFA, the risk of implant osteomyelitis with OI increases with time. This is a considerable problem, as OI is intended to be a lifetime prosthetic solution. Some believe that infections which do not lead to OI explanation, only moderately reduce prosthetic function and thus, the improved daily living outweighs the risks and inconvenience of treatment for most patients.[54] Nonetheless, it is clear that soft tissue and skin management, hygiene and infection are key concerns with OI making them relevant to this overview of dermatologic considerations in the TFA prosthetic user.

Conclusions

Common dermatoses in persons with TFA who use prostheses were presented. It is clear that prosthetic use increases the likelihood of skin issues of the RL. Therefore, the prosthetist must have a basic understanding of routine skin issues the prosthetic user may experience. The prosthetist must then focus on prevention, management of common skin maladies in prosthetic users and educate the patient with regard to hygiene, self-care and clinical management of common issues. Finally, when skin problems are refractory to routine rehabilitative and prosthetic management or are clearly beyond the scope of the rehabilitation team, a referral to the primary care physician, emergency room physician, or dermatologist must be made. Interdisciplinary communication and collaboration will ultimately optimize care in such cases. As long as artificial limbs interface with skin, there will be problems with the skin. Those providing care for persons with TFA who use prostheses, require fundamental knowledge of how to care for all facets of these unique patients' lives including their skin.

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Supplement E: Prosthetic treatment considerations for females with transfemoral limb loss or limb difference

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Introduction

It has been established that physical, physiological, and psychosocial differences exist between men and women.[1-3] The fields of educational psychology, human physiology, and pathology have investigated these differences and how they influence the care provided to men and women with various medical conditions. Despite women comprising approximately 35% of the amputee population, differences between male and female amputees are not well researched.[4, 5] Additionally, women with limb loss have demonstrated a decreased overall satisfaction with the prosthesis relative to their male peers.[6]

Existing literature supporting clinical decision-making practices for persons with limb loss are often not completely representative of the entire limb loss community. Unique considerations for these populations, specifically females with limb loss, must be highlighted to ensure patient-focused care can be provided by the medical team when treating these individuals. The purpose of this review is to assess the differences between prosthetic considerations for male and female unilateral transfemoral amputees.

Methods

A review of the literature was performed by searching Pubmed, MEDLINE, Cochrane and Google Scholar. Key words searched were transfemoral amputation, residual limb volume, female amputee, amputee pregnancy, transfemoral, lumbar lordosis, sex difference in, gait kinematics, motor learning, learning strategies, and amputation. Articles were excluded if they were not deemed relevant or were of poor quality. The authors reviewed the data for validity and quality.

Results

The literature search yielded limited results regarding female transfemoral amputees. Presented with this limitation, the authors evaluated non-amputee literature in certain cases and drew generalizations for concepts with regards to a female amputee patient population. The sections that follow incorporate relevant results from this literature review where possible and clinically-relevant guidance.

Broadly, the literature supports that females with transfemoral level limb loss have unique needs that should be considered when providing prosthetic care. Special consideration should be given to prosthetic socket design, component selection, alignment considerations, and approaches to motor learning. Additionally, the health care team must consider how hormonal fluctuations, menses, pregnancy, and menopause affect women uniquely with regard to prosthetic fit and care. Lastly, the unique psychosocial needs of females living with limb loss and limb difference must

be taken into consideration when assessing women's prosthetic rehabilitation needs, in order to provide the most effective, patient-centered healthcare by the multidisciplinary team.

Discussion

A. Socket Design and Alignment Considerations

There is a general perception that men and women walk differently. For example, when walking at the same velocity, women tend to take shorter steps, and walk with a faster cadence than men.[7] Observationally, pelvis and torso motions also differ between men and women. For example, data shows that women walk with greater pelvic obliquity and rotation, hip ab/adduction, and hip rotation during loading than men[8]. Women also tend to walk with less torso sway, but more torso rotation and more arm swing.[8] Therefore, despite potentially less stability, indicated by more movement at the pelvis, women walk with less movement at the torso than men.[7] The increased coronal motion at the pelvis may lead to an observed decrease in vertical center of mass displacement in women, compared to men.[8] These differences may warrant considerations for gait training and prosthetic programming for women with transfemoral limb loss and may indicate a need for socket designs that maximize rotational control and containment of the pelvis, as transverse forces would be increased in this population.

1. Socket stability

For women living with transfemoral limb loss or limb difference, the socket stability in coronal and transverse planes are of special note. As women age, there is a decrease in muscle density and increase in fatty deposits throughout the body.[9] Socket designs with little or no ischial containment rely on thigh tissue for stability. Therefore, the healthcare team might consider an ischial containment socket design for women to increase coronal stability, due to differences in tissue density in women. Additional rotational forces during ambulation in women would support consideration of foot selection in regards to heel stiffness as a factor in providing transverse plane stability. A softer heel would absorb some of those rotational forces at initial contact and provide increased stability.

2. Ramal Angle

Contrary to previously held beliefs, ramus angle does not vary significantly by sex.[10] However, men and women differ physiologically in skeletal bone structure, muscle mass, and visceral fat deposits.[1-3,11] Generally, hip and lumbo-pelvic strength, motion, and alignment may impact how a transfemoral prosthetic device is fit and functions. For example, women tend to display increased lumbar lordosis, decreased lumbar flexion range of motion, and increased lumbar axial rotation range of motion relative to their male counterparts.[12] These differences are fairly consistent across all stages of life. Care should be taken to ensure excess lumbar lordosis in the female population is prevented, as it is a more common compensatory strategy in this population. The prosthetist should be aware of this propensity for women and discourage lumbar lordosis to increase knee stability as a gait strategy. Being cognizant of that propensity might prevent undue lower back strain. The tendency for lumbar lordosis and spinal flexibility in women might warrant increased socket flexion to accommodate hip flexion contractures and prevent any additional strain in the lumbar spine.

Postural asymmetries in 52 unilateral transfemoral amputees were studied during standing and ambulation, and noted increased pelvic tilt in the majority of the subjects.[13] This study included

men and women, but did not list how many subjects of each sex were in the subject group, and did not discuss result differing by sex. Literature discussing socket constraints and compensation strategies discuss the mechanical constraints of socket shape, trim lines and resulting compensatory actions in single speed locomotion. Amputees adopt strategies to obtain a functional step length and symmetrical thigh inclinations.[14] However, no literature was found that studied the pelvic constraints of a socket in activities other than normal human locomotion.

3. Seating

Another consideration during prosthetic fit and design is time spent seated. Adults spend an average of 9.4 hours per weekday sitting[15] and an appropriately fitting socket is vital to achieve sitting comfort. Asymmetries and compensations in sitting have been reported by transfemoral users as a bothersome aspect of using a prosthesis. Both asymmetries and compensations in sitting vary depending on the seated surface and position. Since women tend to have shorter stature resulting in shorter lower limb length, the prosthetic foot may not touch the ground in sitting in a standard chair. In this case, it is necessary to assess pressure of the socket on the distal anterior femur, comfort at the proximal socket brim, and appropriate ASIS relief. Materials and trim lines that allow female amputees to sit on a rigid seat, such as a toilet, are recommended to comfortably achieve toileting ADLs. Identifying the common underlying causes of the sitting discomfort and common strategies to achieve most comfort would be of benefit to study in order to provide a socket design that provides greater sitting comfort and spine health in this population.

B. Component Selection

Prosthetic manufacturers design components for use by the largest population and the most frequent tasks of that population. For example, all microprocessor knees currently available are built to accommodate individuals with a weight limit of 275 pounds or higher, but no minimum weight recommendation is provided. Currently prosthetists are limited in the selection of components available for smaller body mass and stature, leaving females and small statured individuals with components that are disproportionate to their body mass. It could be hypothesized that this minority population is utilizing increased energy to perform the same tasks as their larger statured counterparts due to the mismatch in size of the patient and the components. There is currently a need for innovation and product development to address this gap in technology for small stature amputees. This would include adolescents that are nearing skeletal maturity and have not matured into adult body weight and stature, bilateral transfemoral amputees who are of lighter mass, or unilateral, lighter weight individuals.

C. Bone health

Osteoporosis is a common and costly disease that is associated with high morbidity and mortality.[16] Lower bone mineral density values put amputees, particularly the above-knee amputees, at increased risk for osteoporosis and fragility fractures in the hip.[17] In the US, 6 million women over the age of 50 have osteoporosis and another 15 million have osteopenia. Women are 3 times more likely to suffer from osteopenia or osteoporosis than men. Osteoporosis causes 1.5 million fractures in the US annually, including 300,000 hip and 700,000 vertebral fractures.[17] Individuals with amputation tend to favor their intact limb during ADLs, spending more time on the intact limb than the prosthetic side. Because of the higher risk of osteoporosis or osteopenia in women and in the amputee population, the healthcare team may need to consider

the individual fall risk of each patient, and try to minimize the risk of falls and subsequent fractures through alignment and appropriate componentry.[18] Prosthetic fit, alignment, and componentry can influence posture and comfort, which may promote equal force distribution across the intact and prosthetic sides during gait and decrease the susceptibility to osteoporosis.[19]

D. Motor Learning Styles

Often the physical rehabilitation of individuals with transfemoral limb loss has focused on the design and function of the prosthesis, rather than the learning strategy of the patient.[20] Research specific to learning strategies of how to use a prosthesis would be of great benefit, and determining if strategies vary by sex would be of interest to the healthcare team. Generalized from literature in sports science, motor learning strategies have been shown to vary with respect to gender. One study found males prefer experimentation or "doing" where females were found to use reflective observation, and more verbal discussion when learning.[21] In regards to motor skills acquisition, males prefer more initial physical investment where females held more verbal exchange in motor skills development. This might lead a clinician to be more verbal when educating a patient who is learning to ambulate with a prosthesis.

Another study demonstrated that women perform best when instructions for motor learning are directed with an internal focus rather than external focus. Women showed a greater learning advantage when provided external focus, such as the outcome of the action rather than the action itself.[22] This study is inconsistent with the reflective observation study listed previously. Research on sex differences in motor learning is conflicting, but of interest for further study. More information on motor learning styles might lead to improved acquisition of new motor skills for women and higher acceptance of the prosthesis in daily activities, decreasing the disparity in prosthetic satisfaction between men and women. It was of note that there was no difference in men and women in learning in groups. Both populations show improved learning in dyads, or social groups.[23] This supports the roles of amputee peer mentor relationships for novice prosthetic users equally for men and women. If transfemoral amputees learn best in social groups, perhaps a support group or activity-based program would be an ideal means to provide physical therapy, gait training, or learning new motor skills with improved results.

E. Reproductive Physiological Changes Over Female Lifespan

1. Hormonal Cycles

Changes in residual limb volume and shape lead to problems in reduced comfort and diminished function of the prosthetic socket. Anecdotally, some women TF prosthetic users seem to battle this issue more frequently than men, as their limb volume fluctuation tends to correlate with their menstrual cycle. Sanders and Fatone discuss the limited evidence in volume management of the residual limb in amputees, and the lack of adequate resolution for measuring daily fluctuations of limb volume.[24] Adequate ways to track, measure and accommodate volume fluctuation for women might be considered to provide them with the tools to use their prosthesis consistently and successfully. Additionally, sockets that allow some degree of adjustability, to compensate for cyclical volume fluctuation, may be indicated.

2. Pregnancy

Female prosthetic users of childbearing years have many questions about what to expect as they consider having families. Pregnancy brings about many unique changes for women, and those changes have the potential to impact fit and function when using a prosthesis. Understanding body changes is necessary for the allied healthcare team in supporting women through and post pregnancy. During the first trimester, there are minimal changes in overall body mass, likely resulting in minimal biomechanical changes, but waist circumference has been noted to increase.[25] After the first trimester, noted changes in body mass and pelvic width have been measured.[26] With these changes, there was also a noted increase in the step width, sagittal plane pelvic motion, center of mass motion as the pregnancy progressed. An increased anterior pelvic tilt was observed during the second and third trimesters.[25-27] Finally, pregnancy can increase a woman's risk of falling.[28]

Change in overall body mass will impact the fit of the prosthesis, and indicates a potential need for multiple sockets during this time to maintain mobility and healthy activity. Alignment of the prosthesis and prosthetic component settings may need to change to compensate for the center of mass shifting anteriorly and overall changes in body position, segment inertia, and gait mechanics.[29]

While many female prosthetic users ambulate throughout the entire pregnancy, currently no guidelines exist regarding safety or expectations during this body change. Further, at this time the National Commission on Orthotic & Prosthetic Education (NCOPE) does not have documented competencies to guide the team on caring for prosthetic users during pregnancy. This is one disparity that should be addressed for women's safety and health. Items to be discussed might include: when it is appropriate to provide a socket change, the number of sockets to be considered appropriate during pregnancy, frequency of follow up for assessments and adjustments, risks and benefits of ambulating during the third trimester, and alignment considerations throughout pregnancy. Additionally, consultation with physical therapy for falls risk assessments, training, and education should be included.

3. Menopause

As women approach menopause, hormonal changes lead to reduction in ability to maintain body temperature. Menopause can present significant problems with thermo-regulation, since all patients with transfemoral amputations are already challenged with the ability to dissipate heat.[30] Women not affected by limb loss report that hot flashes are physically and socially challenging. While there has been recent interest in studying sweat and thermo-regulation in the general amputee population, we found no research discussing thermo-regulation for women in the perimenopausal period of life, or how it might impact socket fit or comfort.

F. Psychosocial/Emotional Adjustments to Amputation

Mental Health Depressive symptoms are prevalent among persons with limb loss. The prevalence of significant depressive symptoms (CES-D score, ≥10) was 28.7%.[31] Females are reported to have higher incidence of and higher significant impairment from PTSD from trauma-related amputations in both civilian and non-civilian populations.[32] By properly managing pain and other medical comorbidities, some of these depressive symptoms may be mitigated. Education about depressive symptoms and treatment options may improve receipt of mental health services among persons with limb loss reporting significant levels of depressive symptoms. There was no research showing a difference in depression rates by sex.

1. Self-Reported Quality of Life

A comfortable, effective, and easy-to-use prosthesis makes a positive contribution to an amputee's ability to accomplish ADLs.[33] Existing data suggests that dissatisfaction may be higher among female users of TF prostheses. This demographic of patient has a higher rate of artificial limb rejection, thus challenging providers to address needs for cosmesis and function that varies from those of male counterparts.[4]

2. Positive Body Image / Feminine Identity/ Confidence

Societal constructs exist where women are expected to wear clothing that is often form fitting, uses thin and soft materials, and shows underlying body shape. Women's clothing is often form fitting and sheer in design. Marketing strategies are built on the idea that women need to look a certain way to feel good and to be attractive. Additionally, women tend to wear a wider variety of shoes with different heel height to maintain social engagement at work, in sports and recreation, and for social occasions. The clothing and fashion industry invests millions of dollars sending messages to women that clothing and shoes offer femininity, social status, and attractiveness. Most prosthetic foot options require the use of a single heel height of shoe. TF amputees are even more limited in footwear options because heel height and the stiffness of shoe materials can greatly affect the function and safety at transfemoral and higher amputation levels.

Limitations

There are several limitations in the information that is presented in this paper. Many of the subjects discussed have very limited or no evidence specific to the female amputee population. Non-amputee research that considers gender/sex differences was used when no appropriate evidence was available for the female TF amputee population. The authors can generalize that the same trends would hold true in an amputee population, but further research is needed. In studies that did include female transfemoral amputees, the sample sizes are very small. Funding for research on gender differences in the amputee population could improve the quality and type of evidence on this subject.

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Supplement F: Transfemoral Amputation Surgery and Prescription Considerations

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Introduction

Amputation at the transfemoral level can be very challenging for the amputee as well for the surgeon, the prosthetist, the physical therapist, and every member of the health care team. Even terminology continues to be a challenge for some. The correct International Organization for Standardization (ISO) term for amputation done between the knee joint and the hip joint is a transfemoral amputation. In the United States, this amputation level is still commonly referred to as an above-knee amputation (AKA). The term transfemoral amputation is more accurate because the amputation occurs in the thigh, through the femur, and the term transfemoral amputation more accurately distinguished this level from the knee disarticulation, or hip disarticulation amputation levels.

The transfemoral amputation results in anatomic loss and change that creates dramatic change in the pelvis and hip area. Major issues that may exist include: muscle imbalance, skeletal loss of lever arms, hip joint contracture or the risk of hip joint contracture, transection of large diameter major nerves divided during this amputation, and a bone transection through diaphyseal bone that typically has low tolerance for end bearing.[1,2] The thoughtful surgeon must be aware of these issues and attempt to address or manage these issues.

Pre-prosthetic rehabilitation following transfemoral amputation must address the realities of the loss of the thigh for bed mobility, sitting balance and the impact of transfemoral amputation on bowel and bladder management, and ability to get on and off a toilet. The loss of the leg affects the ability to transfer independently, to go from sit to stand, and single leg stance on the remaining leg. Another reality following transfemoral amputation is the increased demands on the individual's arms, with increased use and loading of the arms in weight bearing mode for transfers, sit to stand, walking in parallel bars with a one-leg gait, and the use of a walker or crutches. Moreover, implications for other body regions must be considered such as load on the remaining limb, the spine and others.

Finally, when the physician and the prosthetist contemplate prosthetic prescription, prosthetic alignment and fabrication, they must re-assess and consider the post-surgical issues of femoral length, femoral alignment, muscle imbalance, hip joint contractures, pelvis alignment and lumbar

spine lordosis. All of these anatomic changes should be considered along with the understanding of the difficulty in weight transfer from the prosthesis to the residual limb and pelvis. Unlike a knee disarticulation, a transfemoral amputation results in a residual limb that cannot bear the body's weight directly on the transected end. In my experience, every transfemoral amputee has differences in anatomy, tissue tolerance, transected nerve location and where they have pain. These anatomic and amputation related differences mean that every transfemoral amputee is slightly different in how they will tolerate the weight bearing forces, and in how weight will be successfully transferred through the socket to their residual femur and pelvis.

Skin

When performing a transfemoral amputation, the goal is a painless, pliable and non-adherent scar. The amputation site functions as the patient's foot, and as such, requires reconstructive design to provide a durable interface for walking and the transfer of body weight. The prosthetic interface and socket design can make the location of the scar of increased importance. When uncomplicated primary healing results in scars that are nontender, pliable, mobile, and durable, then location does not really matter. However, when healing is less than ideal, and scars become adherent, tender, thin and non-durable, or thick and prominent, location matters a great deal. The thoughtful surgeon, when possible, plans scar placement appropriately to minimize future issues just in case less than perfect healing results.

When closing, fasciocutaneous flaps should be made as broad-based as possible to maximize profusion and avoid compromise of blood supply. The skin closure must be without tension but it cannot be redundant. Particularly in the dysvascular limb, care must be taken to avoid separating the skin from the underlying subcutaneous tissue and fascia. Pressure sensitive areas exist in residual limbs and care should be taken not to place scars over a bony prominence or the subcutaneous bone. The more skin surface available for contact with the prosthetic socket, the less pressure will be applied to each unit area of skin surface. A cylindrical shaped residual limb with muscular padding presents fewer skin problems than the bony, atrophic tapered residual limb.[1,2]

Along with fasciocutaneous flaps and free flap techniques, skin grafts are a viable option in modern amputation surgeries and prosthetic fittings. It is possible for split-thickness skin grafts to hold under the forces applied by a prosthesis, but grafts will be most successful when not adherent to bone. Application of the graft over a cushioned, mobile muscle bed is ideal. However, without the fine layer of subcutaneous fat to absorb shear forces, grafts are not as durable as normal skin. Fortunately, liners made of elastomeric materials have improved prosthetic success for individuals with scar and skin grafting. This is of particular help for burn victims, as amputations in burned limbs often require skin grafts. The grafted skin and burn tissue will become more pressure tolerant over time if the shear and skin stretch are moderated by careful prosthetic fit and the introduction to the prosthesis is gradual. The amount of time

wearing the prosthesis, the amount of force applied, and the activity level of the patient must be carefully controlled and slowly calibrated forward. Over a period of many months, the badly burned limb with amputation and free graft coverage may develop a tolerance that can provide optimum function. Such patients can often use prosthetic devices successfully and thereby avoid amputation at a higher level.

Skin problems remain a major concern for amputees throughout their lives. The amputation surgeon needs to be familiar with the many different types of short and long-term skin and wound healing problems. Post-operative infections, wound dehiscence, and partial skin flap failure occur with unfortunate frequency in the short-term healing process. Contact dermatitis, skin irritation, reactive hyperemia, callus formation, verrucuous hyperplasia, folliculitis, epidermoid cysts, hidradenitis, fungal infections, and chronic breakdown are potential long-term skin ailments. Complicated skin problems often require multidisciplinary approaches requiring prosthetists, wound care specialists, dermatologists and the original surgical team.

Transfemoral Amputation Flaps and Flap Design

The flap design for transfemoral amputation is traditionally a classic symmetric fish-mouth shaped incision, an asymmetric fish-mouth shaped incision, or the medially based flap design as advocated by Dr. Frank Gottschalk.

In cases due to trauma, often the surgeon has little choice on flap design, and must use and incorporate the remaining, least traumatized tissue to create potential flaps for closure or partial closure of the amputation. As discussed above, the goal is a closure with healthy full thickness skin. Some cases, especially in trauma, require the use of free tissue transfer and skin grafting techniques in order to maintain some functional length of the residual limb. There is very little data on comparison of different transfemoral flaps surgeries.

Another situation arises in cases due to vascular disease. There are often pre-existing incisions on the thigh from previous vascular reconstructions or harvesting of the saphenous vein. The thoughtful surgeon must understand that the apex of the new incisions for amputation flaps should blend into the previous incision, and not transect the previous incision whenever possible. The illustration highlights that a poorly perfused area of skin can result from not placing the apex of the new incisions on the previous scar, and not blending the amputation flaps optimally.

Common location of pre-existing vascular surgery incision.	Placement of the apex of the new amputation incisions to blend into previous incision.	Suboptimal placement of apex that does not blend into previous incision and creates area of poorly perfused skin

Figure 1: Resulting poorly perfused area of skin from suboptimal placement of amputation incision.

Length of the Femur and Residual Limb

In general, longer femoral residual limbs serve better than short residual limbs. The femur is a structural lever arm, and the longer the femur the greater the force transmission of muscles reattached through myodesis to the distal end of the amputated femur. The circumstances leading up to amputation vary dramatically, and there are times when the surgeon has very little discretion on the length of femur. There are other times when the surgeon has a great deal of discretion and decision-making. Whenever possible, the greatest amount of femoral length with suitable soft tissue coverage should be considered. If the entire femur can be saved and a knee disarticulation performed with reasonably healthy soft tissue coverage most, but not all, surgeons agree this is preferable to a transfemoral amputation.

There is some discussion on whether a transfemoral amputation can be too long. When adequate length of the femur and soft tissues is present, but a knee disarticulation cannot be done, there is some debate on the value of amputations where the femur is cut in the metaphysis or at metaphyseal/diaphyseal junction. Some argue that some transfemoral amputations might possibly be too long, and that additional space for the socket, connector, and components such as a rotator would be valuable. Others argue the additional length, if coverage by suitable soft tissue padding, is valuable, and outweighs the downside of having the knee joint lower on the amputated limb be located lower than the knee joint level on the non-amputated leg, as occurs in individuals with knee disarticulation. There is inadequate literature to provide empirical

guidance on this issue. Therefore, clinicians should discuss with the patient and treating prosthetist when possible and use their best clinical judgement until such time that evidence is available to better inform this decision.

Conventional teaching was that the amputation is made at the junction of the middle and distal thirds of the thigh. Proximally, it is often discussed that a minimum of 10cm of femur below the lesser trochanter is needed. Shorter residual limbs are very difficult to fit with a transfemoral prosthesis and often develop severe flexion/abduction contracture from muscle imbalance. Many of these individuals with excessively short femoral length must be fit with a hip disarticulation style prosthesis and may be less stable and efficient ambulators.

Bone Management

The forces traveling between prosthesis, residual limb and the remaining body are in large part transmitted through the retained bone in the amputated limb. As discussed above, the diaphyseal femur should be sectioned at the length consistent with reconstructive soft tissue closure. Managing the edges of severed bone is essential to pain-free healing, and the sharp cortical bone edges and irregularities should be carefully contoured and rounded. In general, the femur is divided perpendicular to its long axis, the edges are surgically smoothed, but no bevel is intended or performed. The protocol for the successful management of the periosteum is less well defined or agreed upon.

Diaphyseal bone does not exist without an outer cover of cortex in its natural state. Thus, it is intuitively physiologic to seal the end of the bone following amputation, and techniques have been refined for performing an osteo-periosteal bone cap over the end of diaphyseal bone, also known as the ‘Ertl’ procedure. However, even without a surgical osteo-periosteal flap, the end of the bone naturally heals by formation of bone callous and fibrous tissue. When a periosteum cuff is available it may be sutured over the end of the bone, but excessive use of periosteal strips can cause problems. As occasionally seen in traumatic amputations or when the periosteum is circumferentially peeled off the bone before sectioning, the residual periosteal strips can slowly form irregular bone spikes. These spikes or bone spurs can cause painful pressure points for the amputee that may require unique prosthetic accommodations or surgical revision. The surgeon should be aware of this potential problem in order to minimize its occurrence. Most of the published literature on the Ertl procedure discusses the transtibial technique and outcomes in transtibial amputees. To date, the transtibial literature is not conclusive. The author is unaware of any conclusive literature in transfemoral amputees and any literature comparing surgical osteo-periosteal flap (Ertl Procedure) to circumferential division of the periosteum and clean transection of the femoral diaphysis.

Pediatric transfemoral amputation may well be different. In the growing child, proportional change occurs in residual limb length from childhood to adulthood—an important concept to keep in mind when determining the surgical approach. A diaphyseal amputation in an infant or

young child removes one of the epiphyseal growth centers, and the involved bone therefore does not keep proportional growth with the rest of the body. What initially appears to be a long transfemoral amputation in a small child can turn out to be a short and troublesome residual limb when the child reaches skeletal maturity. All attempts should be made to save the distal-most epiphysis by disarticulation. If this is not technically possible, the greatest amount of bone length should be saved. In instances of diaphyseal amputation, children tend to form new bone with periosteal and endosteal bone overgrowth at the end of the amputation. Capping the end of a diaphyseal amputation with a piece of osteochondral bone, often obtained from part of the amputation specimen itself, has been shown to minimize bony overgrowth.

Patellar or osteochondral bone capping has a long history in the adult population as well. Historically, surgically placing the patella over the distal end of the transected femur is called the Gritti-Stokes amputation.[3-6] The initial goal was to provide an improved end-bearing bone surface to the simple transected femoral diaphysis. Literature has been very limited on definitely discussing benefits and complications of this technique.[3-6]

Muscle Management and Hip/Pelvis Muscle Balance

The role of the normal skeletal and muscle anatomy in stabilization of the core of the body over the legs is demanding and very unique. The anatomic balance depends on length of femur (the longest bone in the body) and its function as a mechanical lever arm. The hip joint has a natural anatomic adduction alignment of the femur and the unique muscle requirements for stabilization of the body over the leg in single leg stance.

This anatomy is dramatically altered during transfemoral amputation surgery, and even the best attempts at surgical reconstruction do not restore the function and balance of the original anatomy. In transfemoral amputation, when the femur is shortened, the full lever arm is no longer present, and distal muscle attachments are lost or altered.

Hip flexor muscles still attach to the lesser trochanter, but may become contracted and hip flexor joint contractures are common pre-operative and especially post-operatively. Hip abductor muscles still attach to the greater trochanter, but the natural skeletal adduction of the femur is lost, and these muscles function at a disadvantage. Hip external rotators are still attached anatomically around the greater trochanter, but they often overpower the loss of internal rotation muscles that are divided during the surgery. The adductor and extensor muscles are, however, attached at the lower end of the femur and will be divided in a transfemoral amputation surgery. This results in weakness and a limited ability to adduct and extend the hip. (Table 1.) Without the normal attachment of the adductor and extensor muscles, imbalance exists. The remaining portion of the femur will be pulled into simultaneous flexion, abduction and external rotation after transfemoral amputation.

Table 1. Hip Muscle Groups and Their Impact Related to Transfemoral Amputation Surgery.

Because the external rotators, flexors and abductors are divided during TFA surgery, imbalance and contractures toward the unimpaired or unimpacted muscle groups can commonly occur.

Anatomic Plane	**Hip Muscle Groups Adversely Impacted During Transfemoral Amputation Surgery**	**Hip Muscle Groups Spared During Transfemoral Amputation Surgery**
Transverse	Internal Rotators	External Rotators
Sagittal	Extensors	Flexors
Coronal	Adductors	Abductors

The surgeon can attempt to counterbalance flexion and abduction forces by reattaching distal attachment muscles to the femur or its periosteum. The most important muscles to reattach are the adductor muscles and the hamstring muscles. The term for the surgical technique by which muscles are reattached to bone following amputation is myodesis (Figure 2). A surgical myodesis can help make the residual limb stronger and more balanced and can help keep the femur centered in the muscle mass. There are two main methods for performing a myodesis. One is to drill holes through the bone and suture the muscle directly to the bone. In the other method, the surgeon secures the muscle over the bone and sutures to the periosteum, the thick tissue covering the bone. For the transfemoral amputation, in which a more secure attachment is required, the first method is usually indicated. The goal of surgery is to try to regain muscle balance and to properly position the femur for weight bearing and ambulation. However, it should be noted that while muscle insertions can be re-attached with myodesis, the involved muscles are always weaker post-operatively, and never regain full strength. Given current techniques and technology the goal of regaining muscle balance is not met. A need exists to improve the strength in muscles that are transected and re-attached.

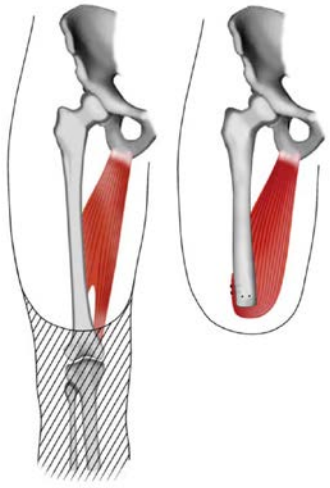

Figure 2: Myodesis. Reprinted with permission from Berke, G. M., et al. "Transfemoral Amputation: The Basic and Beyond." *Prosthetics Research Study* (2008).

Performing a secure myodesis does have a major technical problem, in that muscle tissue does not hold sutures very well. Think of the tissues of the muscles as being like a string mop that is encased in a plastic wrapper. The plastic wrapper is like the fascia, which is the tissue that covers the muscle. Suturing muscle is like sewing through the plastic bag and the strings of the mop. The fascia provides some reinforcement, but the individual strands of muscle do not hold suture well. A suture inserted at midthigh will drift downward in the muscle tissue because there is nothing to which it can be securely attached. If the surgeon tries to suture across the strands and loop them together, blood flow is cut off to the end of the muscle. Tendon and skin hold sutures well; muscle does not; and the fascia at midthigh is quite thin and tears easily. So while myodesis is important, it may not always be successful at this level. Occasionally the myodesis will stretch out or even pull free in the postoperative period. Patients will usually say they "felt something give." Some surgeons do not use myodesis as part of transfemoral amputation surgery, and sometimes, even with good surgical technique, the myodesis fails or the distal attachment stretches out gradually over time.

Prosthetic Considerations for Inadequate Myodesis

In situations where muscle myodesis was not performed, or where myodesis failed, the end of the femur may be very prominent and located subcutaneously in an anterior/lateral location of the residual limb. The patient may have pain at the distal lateral aspect of the residual limb, the prosthetic socket may not fit well, and the patient may walk poorly. When severe, skin breakdown may begin to occur where the distal femur contacts the anterior/lateral socket. One approach to managing distal femoral contact pain or pressure is to modify the prosthetic socket. Creating a 'relief in the distal socket is usually not adequate by itself, as proximal pressure on the femur must be changed. One simple modification is to pad the inside of the socket on the anterior/lateral aspect of the socket at the midthigh, above the painful end of the femur. This pad

helps to push the femur into adduction and extension. By applying pressure over a broad area over the middle of the femur, it avoids increasing contact and pressure on the painful distal end of the femur. A second option is to revise the socket with the intent to apply more medially oriented force, thus adducting the femur using the rigid frame while simultaneously relieving the painful distal end.

For patients with excessive hip abductor weakness due to inadequate myodesis, one possible prosthetic solution is to aggressively align the socket into adduction. This may even require changing the point where the socket attaches to the knee unit. This alignment change will pre-position the entire thigh, including the femur, into adduction to both improve loading on the lateral side of the femur and maximize the abductors.

If the pain and femoral position cannot be managed by socket modification or by aggressive adduction of the socket to preposition the femur in adduction, then surgical revision can be considered. Myodesis is harder to perform during a revision procedure than during the initial amputation, but it can be done.

The Adductor Roll

Myodesis also may help to reduce "the adductor roll," a collection of tissue that sometimes forms high on the inner thigh above the socket line (Figure 3) and which can be quite bothersome. While this roll is commonly caused by issues such as weight gain, mismatched socket geometry and volume, or improper donning of the residual limb, some also believe that this adductor roll is caused in part by the retraction of muscles that have been transected and are no longer held in place. This tissue, while still contained in the skin envelope, then spills out over the top of the socket, and before long a significant roll of soft tissue has accumulated in that area. The prosthetic socket may dig painfully into this extra tissue. Myodesis helps secure the adductor muscles and the soft tissue over these muscles. This secure attachment of the adductor muscles appears to assist in minimizing risk of development of an adductor roll.

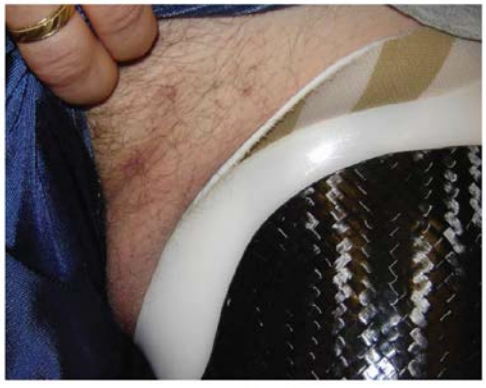

Figure 2 – Adductor roll

Figure 3: Adductor Roll. Reprinted with permission from Berke, G. M., et al. "Transfemoral

Amputation: The Basic and Beyond." *Prosthetics Research Study* (2008).

New Concepts in Muscle Management

Mathew Carty, Hugh Herr and Shriya Srinivasan have developed, implemented, and have early publications on a novel surgical technique to pair portions of agonist and antagonist muscles to improve proprioception of the amputee.[7-9] The surgical technique was first used in a transtibial amputee, and was termed the Ewing procedure, named after the first patient. The group of researchers at the Center for Extreme Bionics at the MIT Media Lab invented the agonist-antagonist myoneural interface (AMI). They discuss that AMI is a method to restore proprioception to persons with amputation.

Nerve Management

The management of sectioned nerves remains a controversial aspect of amputation surgery. The free end of a divided nerve heals by forming a neuroma. This intertwined mass of scar and nerve tissue can be painful to pressure, stretching and other types of physical manipulation. Even when completely undisturbed, electrical potentials may arise within the mass, causing negative local and distant sensory and motor phenomena. These sensations can be bothersome and painful to the amputee. While numerous techniques have been devised in order to minimize neuroma formation, none have proven uniformly successful. Some methods have included cauterizing the nerve ends using chemicals or heat, burying the nerve in bone, encasing the nerve in impervious material, ligating the nerve or injecting the nerve with a variety of chemicals. Other methods include sewing the sectioned nerves to other nerves or sewing them back onto themselves, thereby creating a nerve loop. Others' methods entail simply dividing the nerve and allowing it to retract.

Since neuroma formation is to some degree inevitable, the generally accepted management procedure is drawing the nerve distally, sectioning it and allowing it to retract away from areas of pressure, scarring and pulsating vessels. Ligation of a nerve is indicated if the nerve is likely to bleed, as is the case with the sciatic nerve. When a nerve is severed in the amputation process, the surgeon's goal is to position the nerve ending in a well-cushioned soft tissue site away from the incision and any scar tissue. There it will not be irritated by traction, pressure from the prosthetic socket or any other potential sources of contact.

Neuromas in very scarred and adherent areas are the most symptomatic. When working in these areas the surgeon should apply moderate tension to the nerve and section it cleanly, allowing it to retract away from the site of amputation and into the proximal soft tissues. This circumvents the distal end of the nerve scarring to the surgical site where traction and pressure are more likely. Traction on the nerve at the time of sectioning should not be excessive, as too much tension can

lead to proximal pain and neuropathy. As with the conservation of muscle tissue in the residual limb, the surgeon's goal is to retain and employ as much of the useful remaining nerve function. Care should be taken to avoid disturbing the nerve fibers innervating the remaining limb structures, particularly those innervating the muscles and skin.

The theory that proximity between nerves and blood vessels causes symptoms is undergoing renewed interest. When a nerve is unintentionally ligated together with a pulsing vessel a situation may result in which the nerve endings sense the vessel's cadence and become a source of throbbing and pain. In the transtibial amputation, the two most common nerves ligated with a vessel are the deep peroneal nerve and the tibial nerve. This happens if the deep peroneal nerve is not separated off the anterior tibial vessels, or the tibial nerve is not separated off the posterior tibial vessels. At revision surgery, the separation and division of the nerve away from the re-ligated vessels can relieve the throbbing. Extra caution concerning the nerves should always be exercised in the high-level upper extremity amputations. Unfortunately, particularly in surgeries involving the brachial plexus, nerves are often accidentally included in the ligatures with the axillary vessels.

New Techniques of Nerve Management

A. Targeted Muscle Reinnervation (TMR)

Targeted muscle reinnervation (TMR) is a procedure developed primarily by Dr. Todd Kuiken, MD, PhD at Northwestern University and the Rehabilitation Institute of Chicago. In traditional nerve management, the nerve is transected, and remains 'dead-ended' with no physiologic control. The goal of targeted muscle reinnervation is to surgically transfer a transected nerve onto the motor point of a denervated target muscle. The axons grow into the targeted muscle and arborize out along the neural pathways in a treelike pattern. Both motor and sensory axonal regrowth occurs. The transected nerve becomes physiologic again. The original goal of this surgical procedure as discussed by Todd A Kuiken, MD, PhD and Gregory A Dumanian, MD was to improve control of advanced myo-electric prosthetic limbs. Thoughts from the brain, that had no connection to distal muscles, had no output or physiologic pathway out of the body. By TMR surgery, these dead-ended nerves now connect to muscle that contracts in response to the brain's thoughts. The muscle contraction can be interpreted by myo-electric sensors to add control to prosthetic limbs. These techniques have been used in a knee disarticulation amputee to improve prosthetic control.[10]

In addition to improved prosthetic control, there is a growing belief that improved nerve management through TMR can reduce or improve amputation related pain. Early evidence suggests that TMR surgical techniques may reduce neuroma formation, and possibly improve phantom pain.[11-13]

B. Regenerative Peripheral Nerve Interface (RPNI)

Researchers working primarily at the University of Michigan have developed the concept of wrapping the transected end of an amputated nerve in free muscle tissue graft. They use the term, regenerative peripheral nerve interface (RPNI) and propose this nerve management strategy both for improved control of myo-electric prosthetic devices, and as a surgical strategy for management of neuromas. The group discusses that the RPNI construct consists of a residual peripheral nerve implanted into a free autologous skeletal muscle graft after excision of a terminal neuroma bulb. The muscle tissue is both denervated, and de-vascularized as a free muscle graft. The RPNI was originally conceived as a biological interface designed to harness residual peripheral nerve signals to control a neuroprosthetic device. They discuss that they have found the RPNI can also be used to treat a symptomatic neuroma or can be performed prophylactically at the time of limb amputation to potentially prevent neuroma formation.[14-17]

Blood Vessels

Adequate hemostasis and the management of blood vessels and bleeding sites is of utmost importance in amputation surgery. Major arteries and veins should be isolated and ligated securely. Double ligation of large arteries should be standard, especially when the amputation is carried out in the presence of normal blood supply. Cauterization should be reserved for smaller bleeding points only. The central artery of a large nerve such as the sciatic nerve can be a troublesome source of bleeding. Excessive bleeding in this instance can be avoided by ligation with absorbable suture. Bleeding from the sectioned bone end is best controlled by pressure. Occasionally critical intra-osseous vessels will require cauterization or a small amount of bone wax. However, bone wax is in actuality only very rarely required. Bone wax should be used as infrequently as possible because it remains as a foreign body within the surgical site and can lead to potential complications.

Adequate blood supply to the distal tissues and to the wound margins facilitates proper healing. For appropriate blood supply, the surgeon should avoid dissection of the subcutaneous tissue and keep the muscular investing fascia with the skin whenever possible. Dissection should not damage the proximal blood vessels. Skin or preferably fasciocutaneous flaps, even when broad based, should be developed with careful attention to blood supply. This is especially important for patients suffering from vascular disease and diabetes. Careful attention to hemostasis and managing the vascular supply to the flaps can make the difference between healing and failure, particularly when blood supply is marginal.

Amputation sites are usually drained surgically with suction drainage, as sectioned muscle and bone can often result in a surgical site that is not and cannot be perfectly dry. A post-operative hematoma can be a major complication that predisposes the patient to infection. In worst-case scenarios, hematomas result in delayed wound healing or complete failure. If a large post-operative hematoma is identified the patient should be returned to the operating room for evacuation, irrigation and debridement. Complete hemostasis should be attained before leaving

the operating room the second time. Revision surgery and higher-level amputation have been necessitated due to hematoma formation. The surgeon should do his utmost to avoid this, but if a hematoma does form, it must be identified early and treated quickly.

Skin Closure

The standard protocols for skin closure in any other surgery also apply to closing the wound following an amputation. Dead space should be eliminated and drain systems used when necessary. When closing the wound, opposing tissue layers are sewn under physiologic tension, and care must be taken so that the final closure is neither too light nor too loose. As with all surgery, careful judgment is necessary in the selection of suture and closure technique, and the amputation surgeon must be aware of the options and differences between various techniques. Many patients have only marginal blood supply and the utmost surgical care and technique is required to maximize their wound healing potential.

Osseointegration and the Direct Skeletal Attachment of Prosthetic Limbs

Surgery designed to directly attach prosthetic limbs to the skeleton has a long history, with literature dating back to the 1940s. Other authors in this Multi-Sector State of the Science Conference will address the history, recent advances, advantages and potential complications of osseointegration surgery and prosthetic care.

Pre-Prosthetic Training and Mastering Basic Skills

Because the prosthesis does not provide lifting power, the transfemoral amputee must have sufficient strength in the contralateral limb, the torso, the pelvis, and the arms to get the body up and over the prosthetic device, and added strength in the thigh and pelvis to use a transfemoral prosthesis properly and safely. Some physicians require their patients to meet certain criteria before they will prescribe a transfemoral prosthesis. If the ultimate goal is ambulation with a transfemoral prosthesis, the amputee should first master three skills: transfers, sit-to-stand, and ambulation without the prosthesis before being fit for a prosthesis or beginning prosthetic gait training.

- Transfers: The transfemoral amputee should be able to transfer independently, either using a slide board or a stand-pivot technique.
- Sit-to-Stand: The amputee should be able to independently come to a stand either out of the wheelchair or off a mat table. This may involve coming to a stand without the use of an assistive device, coming to a stand into a walker or parallel bars, or coming to a stand using crutches.
- Ambulation without the prosthesis: The transfemoral amputee who wishes to ambulate with a prosthesis also should be able to ambulate without a prosthesis. At a minimum, the amputee should be able to ambulate the length of a set of parallel bars and back without

needing a rest and with minimal assistance.

It should be emphasized that mastery of the basic skills should take place prior to prosthetic prescription and prosthetic fitting. The chance of successful prosthetic fitting for an individual who cannot independently perform the basic skills is considered by nearly all providers to be very low.

Web Based Just-in-Time Surgical Education

The team at Prosthetics Research Study embarked on creating just in time surgical education material, and housed this at a web site originally call “AmpSurg.Org”. The limb loss education site is now housed at the University of Washington with the web link: http://www.orthop.washington.edu/patient-care/limb-loss-education.html

This educational web site has the complete text of Chapter Two, "General Principles of Amputation Surgery", by Douglas G. Smith, MD, from the Atlas of Amputation and Limb Deficiencies, and is available with permission from the American Academy of Orthopaedic Surgeons. This educational site also has two fully narrated surgical videos of how to perform a basic transfemoral amputation.

Conclusion

The thoughtful surgeon must understand the entire course of the amputation process, from the initial emergency department visit to the selection of the final prosthesis. Transfemoral amputation surgery, and the surgical decisions needed are complex, requiring advanced surgical skills and understanding how the residual limb interacts with a prosthesis, as well as understanding of the post-operative and rehabilitation processes. Amputation can be both devastating for the patient and challenging for the surgeon. The surgeon capable of performing a successful amputation surgery can indeed help improve healing, rehabilitation, and quality of life for the amputee.

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Supplement G: Clinical, Regulatory, Ethical and Other Considerations with Osseointegration

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Introduction

Percutaneous osseointegration (OI) allows for direct skeletal attachment of a prosthesis to the residual limb of an individual with amputation, eliminating the need for a socket and suspension systems. Over the past two decades, OI has become an established treatment option in several areas of the world including Europe and Australia. Within the United States, OI is gradually becoming more widely accepted with access to the technology available either under Institutional Review Board (IRB) approved research protocols, through U.S. Food and Drug Administration (FDA) Premarket approval (PMA), FDA Humanitarian Device Exemptions (HDE) or as custom implants. While many amputees and clinicians acclaim improvement in quality of life following OI, complications associated with osseointegrated implants for patients with limb loss, as well as a lack of evidence supporting candidate selection and optimal rehabilitation strategies advise a more cautious approach. In addition, questions surrounding possible clinician and prosthetic manufacturer liability as well as the unanswered future of reimbursement remain reasons for concern.

Clinical Significance

In the United States, an estimated 1.3 million (86%) of the estimated 1.6 million Americans with limb loss have lower limb amputation.[1,2] For the individual with acquired limb loss, it is a life-changing event affecting quality of life, mobility, employment, and participation in recreational activities. This is particularly challenging for younger individuals with traumatic and

malignancy-related amputations as well as when amputations occur at more proximal levels such as above-the-knee. Considerable technological advancements in prosthetic componentry over the past two decades have improved both safety and function of the lower limb prosthetic user.[3,4]

Despite these advances, limitations remain to successful prosthetic use with the quality interface of the residual limb and the socket being one of the most critical factors. Due to the fluctuating volume of the residual limb and the fact that underlying soft tissues of the residual limb are not designed to bear external pressures, shear stress and other irritants at the limb socket interface, it is very common for amputees to develop multiple skin problems, pain, and discomfort with prosthetic wear which can negatively impact mobility and quality of life.[5-7] In one study of 78 trauma-related amputations, only 43% expressed satisfaction with comfort of their prosthesis and one-quarter reported problems with wounds, skin irritation or pain.[5] Dillingham, et al, found one-third of 935 study participants expressed dissatisfaction with their prostheses' comfort.[6] In a study of 97 non-vascular related transfemoral amputations, one-fourth considered themselves to have a poor or extremely poor overall situation. The most commonly reported issues that negatively impacted their quality of life included heat/sweating in the prosthetic socket (72%), skin breakdown/irritation from the socket (62%), inability to walk in woods/field (61%) and inability to walk quickly (59%).[7]

Improved understanding of the prosthetic limb interface and the development of new materials such as elastomeric liners and flexible sockets have not led to significant changes in clinical practice or amputee satisfaction. This has led to the pursuit of techniques to attach the prosthetic components directly to the residual limb, eliminating the need for a socket interface. The concept of direct skeletal attachment dates to the 1940s.[8,9] However, it was not until the 1950s when Dr. Per-Ingvar Brånemark's work in this field led to the discovery that titanium components could integrate with bone and his coining of the term osseointegration.[10] Progressive use and advances have occurred since that time.

Direct skeletal attachment is currently used successfully for joint replacement, dental implants, bone-anchored hearing aids, and maxillofacial reconstruction. Since the 1990s, the use of osseointegration to attach an artificial limb directly to the skeleton has slowly evolved and is currently offered in several countries and, most recently, in the United States using different Food and Drug Administration (FDA) approval pathways. Surgical techniques vary with use of both one and two-stage surgeries as do the rehabilitation strategies. While the potential benefits of elimination of the need for a socket, i.e. improved comfort, fit, performance, osseoperception, and quality of life are touted, significant reported risks, i.e. infection, bone and implant breakage, and unknowns, i.e. candidate selection, rehabilitation strategies, necessitate a review of the findings to date as well as any identified moral, ethical, and legal considerations moving forward.[13-32]

FDA Considerations

The Food and Drug Administration (FDA) classifies percutaneous osseointegration implants used for the direct skeletal attachment of prosthetic limbs as Class III devices requiring the highest degree of control to assure that the device is safe and effective. Osseointegration implants are being placed in individuals with amputations in the United States under different FDA approval pathways. These pathways include Institutional Review Board (IRB) and FDA approved research protocols, full FDA Premarket approval, FDA approved Humanitarian Device Exemptions and Custom Device Exemption designations.[11,12]

A Humanitarian Use Device (HUD) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 8,000 individuals in the United States per year.[8] While a Humanitarian Device Exemption (HDE) application is exempt from the effectiveness requirements of a Pre-Market application (PMA), the application must contain sufficient information for FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury. An HUD may only be used in facilities that have established a local institutional review board (IRB) to supervise clinical testing of devices and after an IRB has approved the use of the device to treat or diagnose the specific disease. The FDA Custom Device Exemption pathway allows for unique devices to be used to meet the specific needs of individual patients.[11] Custom devices represent a narrow category of devices used to treat sufficiently rare conditions or rare physician needs for which clinical investigations cannot be practicably conducted. A device that is currently being studied or capable of study under an Investigational Device Exemption (IDE) does not meet the definition of a custom device. The custom device exemption allows for up 5 units of a particular device type to be placed or used each year at a particular institution.

The Integrum Osseointegrated Prosthesis for the Rehabilitation of Amputees (OPRA) implant system initially received FDA Humanitarian Device Exemption clearance for use in select adults with transfemoral level amputation in 2015. The OPRA implant received full FDA Premarket Approval for use in those with transfemoral amputation in December 2020, and this implant system is also currently being investigated in an FDA Early Feasibility Study for individuals with transhumeral level amputations. An FDA Early Feasibility Study has been completed using the Percutaneous Osseointegrated Prosthesis (POP) in subjects with transfemoral level amputations and further investigations are being planned including an FDA Early Feasibility Study in individuals with transhumeral level amputations. The Compress implant system developed by Zimmer-Biomet has been used in the United States under a Custom Device Exemption designation and a multi-center research investigation with this implant system is anticipated. Other implants systems have not been approved by the FDA for implantation within the United States, but these devices are currently in use in other countries.

State of Science Related to Outcomes and Complications

Overall Summary

The pertinent research literature identified for this review spans a time period of approximately 19 years from 2000 to present. Excluding case series reports, study sample sizes have generally been in the 11-100 range, with the majority of subjects having unilateral transfemoral amputations. The majority of studies evaluating the safety and efficacy of osseointegrated implants have been classified as Level III and IV observational studies because they used observational cohort designs which are either retrospective or prospective. Only a few studies have been classified as Level II evidence. Most investigations have utilized a pre-post design with subjects serving as their own controls while a few have utilized a separate control group using socket-based prosthetic limbs. Due to the inability to blind either subjects or investigators from the intervention, no formal randomized controlled trials have been performed. Studies have generally focused on outcomes within 1-3 years following the intervention while a few investigations have examined longer-term outcomes.

The literature in this field has been summarized in 6 systematic reviews published between 2015 and 2018.[13-18]All of these reviews involved qualitative synthesis of the available literature. An initial review published in 2015 included an analysis of 13 studies with a total of 540 subjects and all studies were evaluated for methodological quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) checklist.[13] A second review of clinical outcomes with osseointegration for lower limb amputation was published in 2017 and reviewed 14 articles published between 2003 and 2017. Five studies were rated as Level II therapeutic evidence, 5 as Level III evidence and 4 as Level IV evidence.[14] Another review of the safety and efficacy of osseointegration prostheses after limb amputation was published in 2018. This review included 22 articles comprising 13 unique studies published between 2003 and 2017.[16] In addition, a best evidence synthesis was performed by a group of researchers from the Netherlands and this review found 7 studies eligible for inclusion. This article was published in 2017 and concluded that while the available evidence supported improvements in quality of life and function following osseointegration, a standard set of outcome measures was needed.[15] Another subsequent review by this same group published in 2018 included 12 studies more specifically examining complications associated with bone-anchored prostheses in individuals with extremity amputation.[17] This review excluded 12 publications secondary to overlapping data and patient populations. The methodological quality of the included articles was independently assessed by two reviewers and scored using the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies. Using this strategy, all 12 articles received a global rating as weak evidence.[17] A sixth review published in 2018 included 21 observational studies published between 2000 and 2016.[18] This review utilized Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methods and the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria to more objectively synthesize the findings of the included studies. Based on this methodology, the review rated the available literature as Level III or IV evidence

and concluded that of the outcomes reported in the literature, only one, the Questionnaire for Persons with Transfemoral Amputation (Q-TFA), was supported by moderate quality evidence while all others were supported by low to very low quality evidence.[18] One additional study, not included in these 6 systematic reviews, examining osseointegration outcomes in the United Kingdom between 1995 and 2018 was also included in this state-of-the-science review.[19]

A number of challenges exist with this body of research and associated publications.[13-19] Most of these research studies have been conducted outside of the United States. Many are retrospective in nature such that subjects were not enrolled and tracked through a formal research protocol with some subjects being lost to follow-up or not included in data analyses for other reasons. As mentioned, overlapping subjects have been utilized in different publications and the available literature includes studies using different types of implants and varied subject enrollment criteria. These factors in combination with the variety of outcomes examined, makes it difficult to synthesize the available studies in a quantitative fashion. These studies have also commonly been performed by the implant developer which may create bias in favor of the intervention. Because different outcome measures have been used to evaluate the efficacy of the implant systems, there is limited consensus on the most appropriate definition of success. One recently published systematic review summarized these challenges by stating that the conclusions reported from this body of research should be interpreted with caution given the limitations in the study designs including the low methodological quality of many studies, the lack of appropriate controls in some studies, outcomes self-reported by study participants, and selective reporting of outcomes.[16]

Participant Selection Considerations

Although there is variability in the specific subject inclusion criteria used in different studies, these studies have generally included skeletally mature adults with transfemoral level amputations not related to vascular disease or diabetes. [13-19] Most of the included subjects have a single unilateral amputation, although the procedure has been performed on those with bilateral amputations. A few studies have included subjects with transtibial level or upper extremity amputations.[17] The procedure is performed on those with an existing amputation and has not typically been performed at the time of primary amputation. The inclusion criteria in most studies states that subjects must have experienced some difficulty with the use of a socket-based prosthesis, however, this criterion has been variable and poorly defined across studies. Studies have included participants with variable levels of functional mobility from those who primarily utilize a wheelchair for mobility to those are able to participate in high level physical activity while wearing a prosthesis. Studies have included female subjects although to a lesser degree than male subjects.[13-19] Most include some type of exclusion criteria related to body weight with several limiting the intervention to subjects weighing less than 100 kilograms and most studies have included only non-smokers. Most studies also exclude subjects with significant medical co-morbidities, complex musculoskeletal conditions or immunosuppression.

Outcome-Related Findings

While some outcomes following osseointegration relate to changes that occur at the tissue level (residual limb bone changes at the implant interface), the most widely reported and significant outcomes relate to either functional performance or quality of life.[13-19] Functional performance has been assessed through both self-report and physical performance measures. Despite the limitations noted previously, the majority of studies have reported favorable outcomes in relation to both functional performance and quality of life.[13-19] Less frequently reported outcomes include vibratory stimulation, biomechanics and energy consumption, pain, and economic implications.[18] Most of the studies have analyzed the entire population together. One study included a subgroup analysis evaluating the effect of intervention based on gender, body mass index, and smoking.[20]

Functional performance in these studies has included assessments of walking ability, prosthesis use, and functional mobility. Functional performance has been the most consistently reported outcome and these functional domains have been assessed using a variety of validated physical performance measures such as the six-minute walk test and the timed up and go test. The most commonly used self-report measure used to assess functional performance is the Questionnaire for Persons with Transfemoral Amputation (Q-TFA). The Q-TFA is a validated, condition-specific outcome measure that includes 4 subscales; prosthetic use, prosthetic mobility, prosthetic problems, and global health. Some studies have also reported functional outcomes in relation to the Medicare Functional Index Levels (K-Levels). Independent of the specific outcome measure utilized, the literature reports consistently favorable and statistically significant positive outcomes in prosthesis use and wearing time, general physical health, and walking ability in persons using osseointegrated implants.[13-19]

Quality of Life is the other outcome domain that has been most consistently reported across the available literature. The measures used to assess quality of life have been the Short-Form 36 (SF-36) and the global subscale of the Q-TFA. Despite subject concerns related to the ongoing risk of infection or fracture, studies have consistently reported statistically significant improvements in both general and condition-specific quality of life following osseointegration in those with transfemoral amputations.[13-19] Although less widely reported, studies that have assessed physical quality of life subscales and subject satisfaction have reported general satisfaction with both functional outcomes and quality of life.[14,15,18]

Radiographic and bone-related outcomes are important because these findings correspond to both the short and long-term stability of the implant. The primary concern with osseointegrated implants is stress-shielding of the distal residual limb bone which can result in bone resorption distally leading to potential loosening and migration of the implant.[21,22] The design of the implant including the location and extent of porous coating as well as the implant style (threaded implant vs. press-fit) can greatly influence the risk and extent of stress shielding. Unfortunately, many studies have not reported radiographic outcomes and in those studies reporting results, no standardized or previously validated measure has been consistently applied across the literature.

Because of the identified need for a standardized assessment methodology, the Osseointegration Group of Australia (OGA) has proposed a zonal analysis methodology using reverse Gruen zones to serve as a common reference standard.[22]

Several additional outcomes have been reported to a lesser extent in the research literature. Two studies have reported vibratory stimulation results.[22,23] These studies concluded a heightened ability for subjects with osseointegration to detect vibratory stimulation as compared with a socket prosthesis and these findings have theoretical implications for improving agility and functional abilities while wearing a prosthesis. A limited number of biomechanical performance studies have been performed and these studies have failed to show a strong effect when comparing osseointegration to socket prostheses. Studies examining the impact of osseointegration on joint range-of-motion have identified improvements in hip extension and a more normal anterior pelvic tilt in subjects following osseointegration.[25,26] Two studies examining metabolic outcomes following osseointegration have demonstrated that subjects were able to perform the timed up and go faster with 18% less energy[27] and a significantly reduced energy cost using the Physiologic Cost Index at 2 years compared with baseline.[28] Pain outcomes have not been reported consistently across studies using a standardized or validated pain measure. One study using the SF-36 bodily pain sub-score reported significant score improvements at the 2 year time point compared to baseline.[29] In order to assess the economic impact of osseointegration, two studies have reported on the number of visits associated with care following implant placement. These studies showed small magnitude effects, but provide insights into potential lines of research for the future.[30,33]

Complication-Related Findings

Complications associated with osseointegration implants used for the direct skeletal attachment of prosthetic limbs include infection (superficial and deep), other soft tissue complications, implant bending and breakage, implant loosening, peri-implant fracture, and implant failure. These complications may require additional complication-related procedures to be performed including long-term antibiotic use, surgical soft tissue debridement or revision, implant revision surgery, and implant removal. The types of complications reported and the rate of these complications has varied across the literature to a significant degree. This variability is likely the result of low quality studies, the risk of bias, different complication definitions and the fact that studies used different types of OI prostheses and different protocols. Additionally, it has been noted that complication rates have decreased over time as there have been improvements in implant design and surgical technique as well as more standardized rehabilitation protocols.

According to the systematic review by Al Muderis et al., seven studies reported on complications associated with osseointegration.[18] Studies reporting complications were rated as low quality and used different types of OI prostheses and protocols which resulted in inconsistent findings across the studies. The review by Hebert et al. identified that infection or other complications were reported in 13 of the 14 articles reviewed.[14] This descriptive review noted that superficial

infection was the most commonly reported complication across studies. Other complications such as fractures, implant loosening, implant breakage and need for surgical revision surgery were reported less frequently. The systematic review conducted by Kunutsor et al. identified 14 studies that specifically reported infection rates.[16] The majority of infections were reported as low-grade soft tissue or superficial infections, which were treated effectively with oral antibiotics. Across these studies, the infection rate ranged from 1 (95% c.i. 0 to 5) to 77 (95% c.i. 59 to 88%) over a mean follow-up of 5months to 5 years.

The review conducted by Atallah et al. which included 12 studies provided a more detailed review of both complications and complication-related interventions.[17] Explanation of the implant was the only complication that was reported in all articles included in the systematic review. This review is also unique in that subgroup analyses were performed by implant type (screw, press-fit and other types of implants) and level of amputation (transfemoral, transtibial and upper extremity amputation). Soft tissue infections and complications were commonly noted in the reviewed studies. Implant infection rates in transfemoral implants were (screw: 2±11%, press-fit: 0±3%, Compress: 0%) and implant loosening rates were (screw: 6%, press-fit: 0±3%, Compress: 0%). Rates of implant infection and loosening were much higher with transtibial implants (29%) and upper extremity implants (13±23%). Intramedullary device breakage was rare in transfemoral implants (screw: 0%, press-fit: 1%, Compress: unknown).

Subgroup analysis of complication rates has been reported in a group of 86 subjects with transfemoral amputation who were treated with the Integrated Leg Prosthesis.[20] In this study, only 36% of subjects sustained no complications. Superficial infection (Grade 1 or 2) developed in 34% of subjects but there were no deep complications reported. The subgroup analysis found that female gender was associated with a 6-fold increase risk of severe infection, BMI>25 was associated with increased risk of mild infection, and smokers had a 7-fold higher risk of recurrent infection.

Two relatively recently published articles report longer-term outcomes and complications specifically related to the OPRA implant. The article by Matthews et al. reported outcomes from 18 subjects treated with the OPRA implant in the United Kingdom between 1995 and 2018.[19] This study is significant in that it reports results from a group outside of the implant developer. The mean follow-up period was 11.4 and 12.3 years for those pre and post implementation of the formal rehabilitation protocol. 28% of the implants failed and had to be removed during the follow-up period with most failures related to deep infection. Two additional subjects (11%) developed deep infections that were able to be suppressed with antibiotics. The study also highlights that infection and implant failure can occur even 10 years or later after implant placement. The other important finding from this study is that even though radiographic outcomes were not highly standardized, 83% of subjects showed a trend towards distal bone resorption. The article by Tillander et al. is a retrospective review of 96 individuals treated at the investigators center in Sweden between 1990 and 2010.[31,32] Implant associated osteomyelitis

was diagnosed in 16 subjects (10 year cumulative risk of 20%). Ten implants were removed for infection resulting in a 10 year cumulative risk of 9%.

Regulatory Considerations and Access to Care for those seeking OI

Regulatory guidance contained in the World Medical Association's Declaration of Helskinki, [34] the Belmont Report, [35] and Federal Human Subjects Protections Regulations 45 CFR 46 and 21 CFR 50[36,37] emphasize the protection of autonomy, safety, privacy, and the welfare of human research subjects. The Belmont Report is the ethical cornerstone for human research regulations focused on three primary ethical principles: beneficence, justice, and autonomy. Beneficence is the requirement of the clinical investigator to maximize the benefits for an individual participant and/or society, while minimizing the risk of harm. Good experimental design, sound research procedures, and plans to minimize risks can increase a study's beneficence. Justice refers to the equitable selection of participants and the avoidance of groups that may be unfairly influence into participating (i.e. prisoners, institutionalized individuals, and the military). Justice requires that those who participate in research be able to benefit from the research. Autonomy is the right of an individual to determine what procedures they will or will not undergo. A criterion for autonomy is that the individual be fully informed of the risks and benefits associated with the activities they are being asked to perform and they make choices free from coercive influence. Certain populations are recognized to have reduced autonomy, by virtue of impaired cognition (i.e. children, cognitively-impaired elderly, or mentally ill subjects), circumstance (i.e. seriously ill or impoverished people), or influence (i.e. prisoners or the military).

Presently, OI is not a generally accepted standard of practice within the US and those providing OI have ethical obligations that must be considered to include access to care following OI surgery. With OI being a relatively novel procedure in the US, the ethical and regulatory challenges are just beginning to be made known and can be discussed in the context of the pathways to obtaining OI. Initially within the US, those wanting OI received a device as part of FDA Early Feasibility Studies (EFS).[38] Currently within the US, OI is available through an FDA Humanitarian Device Exemption (HDE, 21 CFR 814 Subpart H)[39] or Custom Device Exemption (CDE, FD&C Act Section 520b).[40] Additionally, many individuals sought OI surgery outside the US. Each of these pathways has its own unique requirements and challenges for the clinician, patient, and health care system.

EFS-IDE

The Percutaneous Osseointegrated Prosthesis (POP) System was developed by VA scientists in collaboration with DJO Global (Vista, California) and placed in 10 transfemoral amputees as part of an FDA EFS at the University of Utah. An EFS permits clinical evaluation of medical devices to generate initial clinical safety data and proof of concepts. Sponsors and clinicians can work to determine which patient characteristic may yield the best outcomes and/or start to generate new device modifications based on human factors testing. An EFS is a clinical trial and must be

justified with an appropriate benefit-risk ratio and approved by an IRB to assure adequate human subject protections. Prior to seeking approval for an EFS, investigators or sponsors must submit an investigational device exemption (IDE) to the FDA.[41] The POP was initially evaluated under an IDE to characterize its efficacy and safety with specific interests in the subdermal seal, bone integration, functional performance, and quality of life measures. As an EFS, this study was limited to a small population of 10 US Military veterans with transfemoral amputations. Utilizing the same IDE EFS mechanism, the VA Hospital in Salt Lake City, Utah with a VA Rehabilitation Research and Development grant (RX001208-01) launched a second POP study to determine the resident microbial ecology of the OI exit site and measure systemic and local stomal immune responses. Similarly, the investigators recruited a small population of 10 US Military veterans with transfemoral amputation to follow over a 52-week period post-surgery.

Beneficence

The beneficence of these initial EFS IDE studies can be debated. In general, EFS are useful when clinical experience is necessary and information is needed to advance device development. Thus, EFS are often performed using new devices with limited prior clinical experience. In this context, the risks to the subjects in the POP studies may have been greater than in traditional clinical trials. Thus, the rationale for EFS IDE studies to be conducted in only a limited number of subjects (i.e. n=10). One benefit for these subjects is the early, exclusive access to a novel, potentially positive life-changing technology before others in the US. In addition, the participation of these initial subjects was meant to benefit the larger of population of amputee that could potentially utilize an OI in the future. The nature of these studies was focused on the safety, efficacy, and functionality POP system to support follow-up device innovation. But, the information from these studies could potentially only assist one group or manufacturer as the existence of an IDE or any summary data related to the safety and effectiveness of the data.[42] At the time there is premarket approval (PMA) of the device by the FDA, study data will become publicly available to support the decision to approve the PMA. The exception is that the IDE holder must report adverse effects related to the device and the FDA will regularly make this information available and potentially revoke the IDE if adverse events become serious and/or consistent. While not the beneficence of these EFS may not be clear to the individual, society as a whole could benefit due to enhancements in safety and/or focus on the patient's characteristics who may benefit the most from the device. Thus, these initial volunteers deserve appreciation for being pioneers with limited tested products and techniques.

HUD-CDE

In contrast to the EFS IDE mechanism, devices could be designated as humanitarian use devices (HUD) by the FDA and used clinically with an HDE IRB approval, but without needing to be part of a clinical trial. The nature of the HUD is that benefits weighed against the risks are evaluated on a case-by-case basis potentially maximizing the "clinical" beneficence to the individual. The "research" beneficence may be uncertain or non-existent as research studies may

not accompany the use of these HUDs. On July 16, 2015, the OPRA System was approved by the FDA as a HUD (H080004) for use in patients with transfemoral amputations due to trauma or cancer and who cannot use a conventional socket prosthesis. Both the Military Health System (MHS) and VA have OI programs and provide Fact Sheets[43, 44] for beneficiaries interested in OI. In general, OI is not a covered TRICARE benefit and thus individuals cannot receive OI outside of research being conducted at a participating military treatment facility or VA. A CDE allows for unique devices to be used to meet the specific needs of individual patients. CDEs are used to treat rare conditions and up to 5 units of a particular device can be placed or used each year at a particular institution. Similar to the HDE, the CDE is used specific for the needs of the patient. Thus, the "clinical" beneficence for the individual patient may be higher than a traditional clinical trial. The Compress Transcutaneous (Zimmer Biomet) is an OI device currently available through a CDE designation.

Along with supporting these clinical pathways for obtaining OI devices, these groups have partnered to study questions surrounding the use of these devices. This includes documenting long-term functional outcomes like gait and mobility changes and physiologic responses like infection and bone health. These studies do not involve the implantation of the OI devices, but instead recruit patients who have or will be getting an OI device for clinical reasons.

Justice

With many of the initial OI surgeries and research in the United States being conducted in the Military and Veteran populations, questions surrounding the ethics principle of Justice arise. Do these populations have unique anatomic or physiologic qualities that made them better OI candidates than other amputee populations? Do these populations have unique mobility goals compared to other amputees? If part of Justice is the equitable selection of participants, why are the Military and the Veteran populations being targeted to receive OI over other amputee populations? In addition to the equitable selection of participants, Justice has the requirement that those who participate in research be able to benefit from the research. In order for those receiving OI to maximize their outcomes, they must have access to a multi-disciplinary team of physicians, therapists, and prosthetists prepared to deliver the coordinated care required by a novel procedure at no to little financial burden. Both the MHS and VA can provide follow-up care and services for eligible beneficiaries who received OI through and internal research protocol or through another means. This includes access to rehabilitation services who can provide guidance through the treatment regime recommended by the research team or treating surgeon. In addition, eligible beneficiaries have access to certified prosthetists to assist in fabricating and fitting prosthetic limbs to the OI device. As with any patient, prosthetic prescription is individualized and the prosthetist will likely discuss this prescription with the research team or treating surgeon. Besides the clinical care resources that are unique to the Military and the Veteran population, these initial procedures are also focusing primarily on patients whose amputations are traumatic in origin as opposed to dysvascular. In practice of justice and beneficence, investigators have excluded subjects with conditions that may slow or

hinder healing. Thus, only patients who have the best chances to benefit from OI while also minimizing risks of complications like infection are included in these initial studies.

Foreign Studies and Autonomy

Despite the increasing availability of OI devices in the US, patients may choose to seek OI outside of the US either through a foreign-based clinical trial or as a strictly clinical procedure. OI groups operate in Italy, Sweden, Netherlands, the United Kingdom, and Australia with devices like the Integral Leg Prosthesis (ILP), Osseointegrated Prosthetic Limb (OPL), and Osseointegrated Human-Machine Gateway (OHMG) available. None of these three OI devices are approved by the FDA, however, foreign researchers are recruiting for research on ClinicalTrials.gov. Rehabilitation clinicians should be aware of these trials and prepared to discuss the possibility of their patients seeking OI outside the US. To the greatest extent possible, rehabilitation clinicians should help their patients become informed before choosing OI whether foreign or domestic. In helping their patients understand the risks and benefits associated with OI, the clinician is supporting the autonomy of their patient to make an informed choice. More detailed informed consent must be provided by the investigation team or the clinical team actually performing the procedure.

There are a few things that an individual should know about foreign studies. First, the FDA has no jurisdiction over foreign clinical trials. Potential subjects must consult the foreign regulatory policies of the study country to understand their rights even if the study has a domestic partner. Obtaining and reviewing the informed consent form with the domestic healthcare team would be ideal and will allow the team to work with the patient to formulate a plan of care. The informed consent to address items such as travel costs, the cost of the procedure, how long will acute recovery last, who is responsible for rehabilitation and prosthetic care, what happened if there are complications, and what happens once the trial is concluded. The subject may find that financially they are on their own for travel and recovery following the OI procedure. The subject may need to rely on their insurance and local resources following foreign OI. As previously mentioned, Military and Veteran beneficiaries may be uniquely positioned to utilize resources provided by MHS and VA OI programs. However, the general public will need to reach out to their insurer and healthcare team to determine if they have the ability to provide follow-up care and services.

Costs for the follow-up care may not be biggest issue to address. Given the novel nature of OI, the lack of clinical experience with OI will likely limit the success of a patient seeking OI independent of an establish research protocol or OI group. This should not discourage the patient or their providers, but encourage networking and communication. Researchers and surgeons providing OI have an ethical obligation to ensure positive outcome form their patient and should make available rehabilitation protocols and prosthetic fitting schedules and recommendations to the providers that will follow these patients. This informed consent for research and/or for the

clinical procedure should address these concerns and creates an obligation to adhere to commitments made to the patient in the consent.

With recent successes with IDEs, HDEs, and CDEs, patients are gaining greater access to OI devices. Those who have already received an OI device might be asked to join a research study to help justify a medical device premarket approval and pave the way for future clinical trials. They may also have the opportunity to test upgraded technologies. For example, in one of the more recent domestic studies open to enrollment, a team from Massachusetts Institute of Technology, is trialing the e-OPRA Implant System.[45] This is a further development of the OPRA with a bidirectional interface into the human body that allows control of a prosthetic limb using implanted electrodes. As these studies become more prevalent and larger, researcher and clinicians must continue discussions to make sure that regulatory and ethical issues are addressed.

Ethical Considerations with Osseointegration

We have previously alluded to ethical issues related to osseointegrated prostheses (OI) in post-trial access and informed consent. However, to our knowledge there is little or no literature that addresses ethical issues for OI. This section examines ethical issues in OI in greater detail and provides recommendations for practice and research. We address the following key questions: Should implantation of osseointegrated prostheses be viewed through the ethical lens of research, clinical practice, or a different perspective? What are the specific ethical challenges and considerations for patients, practitioners, and researchers to date in OI? What are crucial recommendations for OI ethics in both research and practice?

Ethical Lens: Research, Clinical Practice, or Other?

Implantation of osseointegrated prostheses represents a novel development that is currently being performed as both experimental research with Institutional Review Board approval or through FDA Humanitarian Device Exemption, and also as clinical practice either via custom implant designations within the United States Patients may also receive an OI prosthesis via clinical care outside of the United States. The fact that osseointegration appears to straddle practice and research is significant from an ethical perspective. Traditional ethics literature has rigorously separated clinical ethics from research ethics.[46,47] The argument has been that researchers and clinical practitioners have different responsibilities and goals. While the long-term goal of the practitioner is the individual patient's care, the long-term goal of the researcher is to produce outcomes that can be generalizable to the larger population.[48] This distinction in research or practice role is relevant to the level of review and process for informed consent required in each context, with requirements for research review and informed consent typically being higher. Ethical guidelines for research mandate specific provisions; such as, balancing of risks and benefits, compensation for injuries, and access to the benefits of the research.[34, 49] While clinical

ethical oversight relies more on professional self-regulation, research ethics depends on formal oversight through institutional review board (IRB) review and other similar mechanism.[35]

Despite the traditional divide between research and practice, it is not uncommon for new procedures to fall into both categories. The Belmont Report[35] recognized these procedures as "experimental:" "The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called "experimental" when the terms "experimental" and "research" are not carefully defined." The Belmont Report recommends that innovations should undergo formal review early in the development process.

There has been significant debate about the most appropriate type of ethical oversight for surgical innovations.[47,50,51] The concern for protecting participants through a formal oversight process must be weighed against concerns about the time involved in a formal process that could inhibit advances in care.[47,52] In a systematic review of 59 articles focused on ethical issues in surgical innovation, Broekman et al.[52] found 4 major ethical themes: oversight, informed consent, learning curve, and vulnerable patient groups. The majority of authors recommended a formal oversight process, with some authors recommending that the oversight process also address conflicts of interest and costs. Based on the fact that OI prostheses are not FDA approved, serious potential complications may result and limited outcomes data is available, we recommend that OI be viewed from a research perspective requiring a formal oversight mechanism. Even though OI is being performed as clinical practice outside of the United States, formal oversight and stringent ethics monitoring are still recommended due to its experimental status within the United States. Of course, these recommendations are difficult to enforce internationally. Similarly, Veterans who seek care internationally may not be fully aware of risks and benefits.

What specific ethical challenges exist for patients, practitioners, and researchers in OI?

As a device that has not achieved FDA approval, within the United States OI is subject to FDA guidelines for experimental research. Key ethical concerns in OI include informed consent, weighing risks against benefits, post-trial access to care, issues of justice, benefit-sharing, therapeutic misconception, runaway diffusion, and stakeholder input. In the following section we refer to the Declaration of Helsinki (DoH), [34] a document produced by the World Medical Association that delineates basic ethical guidelines for research for medical research.

Informed consent requires the researcher to provide the information necessary for a competent person to make a voluntary decision about participation or treatment, whether in research or clinical practice. However, the expectation is that the process and content of informed consent in the research setting should be more stringent based on potential risks to the patient and the goals of research. Formal ethical oversight provides strict guidelines for informed consent. The participant should be fully informed of the goals and methods of the study, conflicts of interest,

and risks and benefits of the study.[34] Principles 16-18 of the DoH delineate considerations of risks, benefits and burdens, obligating the researcher to weight the risks with the potential benefits of the procedure: "When the risks are found to outweigh the potential benefits or when the conclusive proof of definitive outcomes, physicians must assess whether to continue or immediately stop the study."[34] Weighing the risks, benefits, and burdens is challenging in studies with a small number of participants, as is the case with OI and other innovative surgical procedures. A systematic review of ethical issues involved in surgical innovation by Broekman et al[52] provided the following specific recommendations for information that should be discussed during informed consent in cases of surgical innovation:

- innovative nature of the surgery
- surgeon's experience and "learning curve" with the procedure
- possible unforeseen our unknown outcomes or risks
- evidence or lack pf evidence about outcomes
- experimental nature of the procedure
- Process of informed consent
- consider a patient advocate or other advocate, especially if researcher is also a physician
- multimedia presentation to assist[52]

These recommendations expand the discussion of risks, benefits and burdens in surgical innovation beyond the merely foreseeable risks suggested in the DoH. In the case of OI, these recommendations suggest that informed consent should include a broad discussion of possible outcomes, risks, evidence, and unforeseen outcomes. Based on this broader burden of disclosure, informed consent in OI should not only include potential infection and complications (as delineated above) but also discussion of availability and continuity of care following the procedure. Likewise, this discussion should address the limited evidence for outcomes and impact of the procedure on cost and availability of future care.

Principle 34 of the 2013 DoH indicates that researchers and others "should" provide post-trial access to interventions found beneficial during the trial and disclose this information as part of informed consent. This latest formulation of the post-trial access represents significant change since the first appearance of post-trial access in the 2000 document.[53,54] DoH ethical guidelines require that researchers provide post-trial access to care and disclose before surgery how participants would access this care. This would include disclosure of increased costs, limited availability to materials, or limited healthcare practitioners educated in care for patients after OI. Post-trial access to care has a foundation in the ethical concept of justice and benefit-sharing.[55,56] The ethical principle of justice refers to ideas of fairness, equality, and equity with regard to rights, resources, and process.[57] Horner[57] provides this basic definition of justice: "Justice as a moral notion takes several overlapping forms: substantive (the actual rights), procedural (the decision-making process), and distributive (allocation of benefits and burdens)." From the

standpoint of distributive justice, benefits may be allocated based on their needs, merits, or contributions. Benefit-sharing suggests that participants in research should, as a matter fairness, benefit from the research to which they have contributed. Hutchison, Johnson and Carter[58] discuss issues of justice that expensive surgical innovations may create for individuals and the health system. Relevant to OI, Hutchison et al. note that difficult or technologically dense surgical innovations may create geographic barriers to care that are unfairly distributed. For example, patients with lower socioeconomic means may have less access. They recommend that projections and planning for innovative intervention include funding for travel to address such inequities.

Responding to Earl's[51] call for less formal oversight of innovation, Haines et al.[59] delineate the external factors that increase the risks of prematurely fostering innovations. These risks are driven in part by publicity and media coverage of new technology. Three significant problems resulting from the current environment are false hope, therapeutic misconception[17,18] and runaway diffusion.[59] In therapeutic misconception[60,61], a patient may be convinced that research will necessarily be beneficial, even when risks have been fully disclosed. Runaway diffusion represents the widespread confidence in interventions that have been shown not to be effective.[59] As Haines et al.[59] note, this may be exacerbated by for profit or predatory health care entities. The authors recommend rigorous formal oversight. Likewise, researchers should make every effort to present OI in a realistic and non-sensational manner when reporting about the process.

OI researchers and patients may learn from the experiences of others who have undergone highly-publicized innovative procedures, such as hand or face transplantation. As in OI, there are a limited number of patients who have undergone hand transplants. Ethical guidelines generally emphasize the need to inform patients of existing evidence and outcomes. However, the existing evidence may be limited. Because of the limited number of patients, those considering transplant or OI may not have access to the experiences of those who have undergone the same procedure. Herrington and Parker[62] performed narrative interviews with patients and their family members after hand transplant to augment objective data about the procedure with qualitative information. The authors recommend stakeholder involvement in the representation of innovative procedures, and suggest that qualitative patient accounts should augment clinical cases. Qualitative interviews and patient stories (both positive and negative) would increase the voice of patients in research and practice, and provide a more complete picture of the risks and benefits of OI for quality of life for those considering the procedure.

Conclusion

Direct skeletal attachment of prosthetic limbs through the use of osseointegrated percutaneous implants has the potential to reduce or eliminate many of the challenges associated with socket-based suspension systems. While this technology has been available outside of the United States for over 20 years, osseointegration is not a generally accepted standard of care currently within the United States. Despite this, the procedure has become more widely available in the United

States either through research protocols or FDA approved exemption pathways. This article summarizes the state-of-science related to osseointegration and highlights the need for specialized providers and researchers to address the host of clinical, regulatory and ethical considerations that remain unanswered regarding this technology. Due to the fact that osseointegration is a developing technological innovative, specific ethical guidelines are not always clear or available to patients, researchers and clinical practitioners. We recommend the development of clear guidelines for informed consent, post-trial access, and other ethical issues related to OI. In addition, we suggest that appropriate educational materials addressing the clinical and ethical aspects of OI should be readily available to patients, family members, practitioners, researchers and policymakers. Educational materials should include narrative and case materials describing patient experiences to support patient decision-making.

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