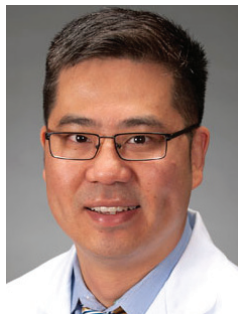


The at-risk diabetic limb: a shift in paradigm



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“As a discipline, diabetic wound care and limb salvage is in its infancy but is rapidly evolving.”



Despite advances in wound care, peripheral vascular interventions and development of specialized tertiary referral centers, complications related the diabetic lower extremity remains a major healthcare problem. Beyond the mental and physical toll on the patient, the burden on the healthcare system is unsustainable. The average length of hospital stay for an infected diabetic foot ulcer is 7 days with estimated hospital charges per patient continuing to increase, exceeding US\$30,000 in 2010 [1]. The adjusted hospital charges in 2010 for a minor amputation are US\$37,598 and for a major amputation are US\$53,779 [1]. Despite this steady rise in costs, the outcomes have not proportionally improved.

The major paradigm shifts in limb salvage discussed below acknowledge these economic realities and the changing demographic profiles, behaviors and expectations of patients. The purpose of this commentary is to advance dialogue and perhaps challenge inaccurate preconceived notions and biases. The shifts in thought are controversial and do not necessarily have broad consensus and thus the following qualifications apply: the arguments below specifically apply to the lower extremity of patients who are confronted with an acute infectious process with large tissue defects and/or have significant peripheral vascular disease, which is

the population most at risk for minor and major amputation; it is important to acknowledge that the at-risk diabetic limb is a progressive disease process that requires intensive management; the patient with a less complex lower extremity wound without significant comorbidities can be managed under the current paradigm of local wound care, increasing limb perfusion and biomechanical surgery. Although the paradigm shifts discussed below are separated for the purpose of organization they are in actuality closely interrelated and should be thought of collectively.

Paradigm shift #1: limb function preservation

The first paradigm shift is replacing the term ‘Diabetic Limb Salvage’ with ‘Diabetic Limb Function Preservation’. This change in nomenclature prioritizes function as the primary goal which may mean sacrificing more of the limb and sooner. The term Diabetic Limb Salvage implies the desire to preserve tissue length at all costs. Indeed, it is logical to equate tissue length with function preservation [2]. The more tissue that can be salvaged the more structures are preserved that contribute to ambulation. However, where this approach to the diabetic limb goes awry is when this concept is taken to the extreme. A common pattern emerges

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best described as ‘whittling’ when a partial toe amputation is followed by serial subsequent ascending amputations terminating in a major amputation or death. In other words, the thought that a distal amputation is a definitive procedure is shortsighted. Nehler *et al.* report only a 39% healed rate at 13 weeks after digital amputation [3]. Chu *et al.* report after an initial digital amputation, a reamputation rate of 12.5% (at year 1), 22.3% (at year 3) and 47.1% (at year 5) [4]. Izumi *et al.* reported similar findings in a 10 year observational study with reamputation rates of 26.7% (at year 1), 48.3% (at year 3) and 60.7% (at year 5) [5]. Kono *et al.* report an ipsilateral amputation rate of 49.1% within 3 years [6]. Each amputation frequently requires an extended hospital stay with readmission rates as high as 49% [7]. These and other reports have clearly demonstrated a high amputation recidivism rate.

The following hypothetical clinical scenario provides an example of the protracted course of a typical diabetic patient with an at-risk lower extremity. Mr Smith presents with a nonhealing toe ulcer that gets infected and requires hospital admission and surgical intervention. This surgical intervention is a partial toe amputation. After a week in the hospital, Mr Smith is discharged to home with regular visiting nursing visits. The amputation initially heals but ultimately due to biomechanical instability, in part caused by the amputation itself, a new wound develops. This wound is managed over several weeks in an outpatient clinic setting. This new wound does not heal and becomes infected. Mr Smith is readmitted to the hospital for 1 week for further surgical intervention culminating in a distal foot amputation and discharged to a rehabilitation facility with regular outpatient clinic visits. In the background, the patient’s overall health deteriorates from the frequent, prolonged and multiple hospitalizations. Further, progressive peripheral vascular disease and renal insufficiency/compromise deleteriously affects the healing process at the amputation site. Mr Smith then develops a new wound or dehisces the prior surgical incision, thus requiring readmission with further surgical intervention. This downward spiral of infection, admission, surgery, rehabilitation and regular clinic visits ultimately ends with Mr Smith undergoing a below knee amputation. Unfortunately, Mr Smith is unable to ambulate in a prosthetic device and is relegated to a wheelchair and ultimately dies from complications of

pneumonia. This is a common scenario that occurs all too frequently.

Our interventions tax the healthcare system and more importantly negatively impact the quality of life of the patient. This is not necessarily the fault of the surgeon or the patient. This is always a difficult discussion between the patient and the surgeon regarding treatment options. If given the option for limb salvage or major amputation, the patient will almost always elect limb salvage unless there is unremitting pain involved or imminent death. Despite the surgeon recognizing the course that the patient is on toward major amputation it is difficult to convince the patient that a more proximal amputation earlier may be more beneficial to the patient in the long run.

The concept of diabetic limb salvage is based on the thought that higher-level amputations result in an increase in morbidity and mortality. Thus, every attempt should be made to save limb length. There is an increasing load on the cardiovascular system with higher amputation levels due to the increased effort needed to ambulate with a longer prosthetic device [8]. With this population already cardiovascularly compromised, the amputation may be the pivotal event that leads to death. Lee *et al.* reported a 67%, 8-year mortality rate, for an above-knee amputation as compared with a 39% for toe and forefoot amputations [9]. On the surface these results support the contention that there is a benefit to salvaging distal tissue. However, the study often referenced above reflects a specific highly vulnerable population of Native American Indians, thus its external validity is questionable. A recently presented robust observational University of Michigan study (TRIAD) seems to indicate minimal difference in 10-year mortality rates for minor versus major amputations [10]. This study is yet to be published but would be the most robust of its kind and may challenge current dogma.

The concept of diabetic limb function preservation is a change in paradigm in the approach to this challenging problem. This concept places the patient at the core of the treatment plan with their functional expectations as the key driver. One of the founding fathers of diabetic limb salvage, Christopher Attinger at Georgetown University Hospital, writes ‘Our task as physicians is to determine the best solution for each patient such that they have the highest likelihood of achieving their desired level of activity as quickly as possible’ [11]. For example, a 50-year old diabetic patient

confronted with full limb salvage effort versus a major proximal amputation should be immediately considered for the major amputation. On the other hand, an 85-year-old diabetic patient should be considered for full limb salvage effort. This appears to be paradoxical. Why would a younger, presumably healthier patient be immediately considered for a major amputation whereas an older, less healthy patient is considered for limb salvage? Simply stated the younger patient is more likely to be able to ambulate in a prosthetic device. The expectation by the younger patient is to return to work and perhaps other more vigorous activities due to their longer life expectancy. Ambulation in a prosthetic device requires the physical capacity to complete rehabilitation and gait training. A younger presumably healthier patient is more likely to obtain this goal. The elderly and presumably sicker patient's expectations most likely include ambulating within their homes, transferring from bed to wheelchair and other less strenuous activities. A major amputation in this case will most likely relegate that patient to a wheelchair or bed for the remainder of their lives due to their inability to ambulate in a prosthetic device due to balance or strength issues. A residual longer limb in this case would be enough to provide the functional needs of the patient. Thus, a salvage attempt for more distal tissue may be a better option. In both cases, a patient-centric approach based on their individual functional capacity and expectations should dictate the treatment plan.

A major amputation should not be considered a definitive procedure devoid of complications. Wong *et al.* report a mortality rate of 21.2% within 6 months after a below-knee amputation (BKA) with only 50.3% of patients returning to mobility [12]. The majority of reports of BKA outcomes are based on diabetes related amputations performed after a limb salvage attempt was already attempted and failed. The BKA is performed as a last option. It would be interesting to look at complication rates if the major amputation was performed at an earlier stage. Perhaps, the patient is not as sick at an earlier time point in their disease course. In other words, the patient's comorbid states are not as advanced including their peripheral vascular disease, insulin resistance, obesity and cardiovascular disease, among others. As discussed above, multiple hospitalizations, extended rehabilitation facility stays and regular outpatient clinic visits lead to deconditioning and a worsening of the patients' overall health if aggressive limb salvage attempts are made.

How should an earlier major amputation option be presented to the patient? This poses the biggest challenge to performing an earlier major amputation. When given a choice, the patient almost always will elect to keep as much of their lower extremity as possible. However, the patient lacks the experience and knowledge of the physician with a better understanding of the difficult road ahead for the patient and possible consequences of their choices. A thoughtful conversation with the patient regarding their functional capabilities and expectations should be conducted prior to implementing a treatment plan. A consultation between the patient with a prosthetist and a physical therapist is often helpful. Further, attending an amputee support group or a one-on-one conversation with an amputee can provide valuable insight to the patient. After receiving thorough counseling, the patient now has the information to make an educated decision. The physician has the obligation to provide information to the patient as to the expected course of the disease as well as acknowledge that major amputation may be inevitable.

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Paradigm shift #2: patient-reported outcome measures

An amputation (major or minor) is an intervention not a negative outcome or adverse event. However, the medical literature is replete with studies where amputation is considered an adverse event or perceived as a failure. As discussed above, an amputation can result in a more functional limb and preserve or enhance the quality of life. A patient may not necessarily care that they have an amputation, but they may care about how the amputation will impact their lives on a daily basis. In other words, can the patient continue to perform their daily tasks and continue to participate in the activities that they enjoy?

The most meaningful measure of success or failure of a treatment plan is the impact of the intervention(s) on the daily lives of the patient. The quality of life of patients can be subjectively quantified using patient-reported outcome measures (PROMs). There are a variety of meaningful and validated tools that allow the patient to inform the physician whether or not a treatment is effective. Quality of life measures such as the Short Form-36 (SF-36) include domains that assess a variety of psychological and physical dimensions as reported by the patient. Ultimately, how the patient feels

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about their disease or treatment and the impact on their lives is the only thing that matters. The physician does a disservice to the patient if we do not improve the quality of life of the patient we are treating.

Unfortunately, PROMs are not frequently utilized as an end point in the medical literature for diabetic limb care. The focus in the wound care world is on rate of wound healing and percent of wounds that heal. Physicians utilize these markers because it allows for tracking the progress of the wound in a quantitative fashion primarily for billing and medical-legal purposes. The US FDA also utilize these end points as indicators of efficacy/effectiveness of wound related devices, biologics and drugs in clinical trials. These markers may be important to the patient too but for different reasons. They view these markers as progressing toward their goal to be wound-free and to be able to return to their normal activities and thus improve their quality of life.

There is an emerging interest in utilizing PROMs as an outcome assessment tool for the diabetic limb. Pioneers such as Dane Wukich from the University of Pittsburgh have advocated for the use of quality of life measures in the diabetic foot and ankle [13,14]. Other examples exist in diabetic limb treatment specifically for assessing the outcomes of vascular interventions [15,16]. However, the use of PROMs remains largely ignored in assessing and comparing outcomes for the diabetic limb despite its wide adoption in other areas of medicine and surgery.

We began employing PROMs in January 2012 for all patients who present to our academic hospital based tertiary wound referral center. We utilize the SF-36 at the initial visit, regular intervals in the clinic, and before and after a surgical intervention. This document becomes a part of the patient's medical record. The SF-36 allows us to track our clinical outcomes as well as become a source of data for research studies. We have received positive feedback from both the hospital administration and the patients themselves. From the patient perspective, filling out the SF-36 seems to empower them and also demonstrates to the patient that the physicians care about how the patient perceives their own health state. It is the author's hope that the use PROMs becomes commonplace in research and in daily clinical practice.

Paradigm shift #3: surrogate outcomes

There are several customary comparative interventional outcome end point measures in diabetic

limb research. The rate of wound healing and the percent of wounds that heal are the most commonly utilized outcome measures as discussed in the previous section. These outcomes are most appropriate to clinic-based wound care center where wound healing progress/lack of progress is measured over an extended period of time. On the other hand, the general goal for the inpatient management of wounds is to reverse an acute process (e.g., infection, ischemia) or conduct a definitive procedure (graft, primary or secondary closure, free or local tissue flap). Thus, the rate of wound healing and percent of wounds that heal is not appropriate for the inpatient setting. Other current measures of outcome include the number and level of amputation. The data regarding the number and level of amputation should be collected but should not be considered a negative outcome or adverse event, but rather be viewed as simply an intervention.

Again, the principal clinical goals for the acute inpatient management of the diabetic limb are infection eradication, reperfusion and definitive closure or coverage. Although these are important clinical goals to the physician, we are often encumbered by external factors that dictate what is considered a success or failure. These include economically driven surrogate resource utilization outcomes namely length of hospital stay and readmissions. The physician is caught between two conflicting objectives: decrease the length of hospital stays, and prevent a readmission for the same problem postdischarge. Both are driven by economic factors related to reimbursement whereby the hospital receives a lump sum for the hospitalization and penalized for a readmission. In other words, the physician must resolve the acute issue during the admission in the shortest amount of time while not rushing too quickly resulting in a readmission after discharge. As this is the reality of the current healthcare environment, our research outcome end points should reflect this as well.

There are also clinical implications of these surrogate outcomes that are arguably more important than economic considerations. Hospital acquired disease states (e.g., pneumonia, urinary tract infections, bacterial resistance, etc.) becomes more commonplace with longer hospital stays. Deconditioning due to inactivity and emotional/mental distress from confinement can cause patients to become sicker with protracted courses for recovery. Thus, the urgency to resolve the acute problem and prevent readmission is of

utmost importance. The surrogate outcome end points of length of hospital stay and readmission may not directly reflect the character of the wound, but are meaningful nevertheless.

Other inpatient surrogate outcome end points including the number of operations and the proportion of closed/grafted wounds prior to discharge are important as well. The number of operations and the proportion of closed/grafted wounds reflect the efficiency of the treatment plan of converting the wound to a more definitive or stable state. The best outcome for a patient with an infected wound is to eradicate the infection with minimal number of operations. Each time the patient goes to the operating room there is a risk of anesthesia-related complications, mental stress and physical toll and increased healthcare costs. Further, patients should be closed or grafted prior to discharge. Despite its flaws, the hospital environment provides a stable, relatively controlled and predictable environment (nutritionally, blood glucose management, ambulatory status); whereas the same cannot be said of the home or rehabilitation facility. Thus, providing the more definitive procedure of wound closure/grafting, if possible, while the patient is in the hospital is ideal. The alternative of weekly or biweekly visits to an outpatient wound clinic with daily dressing changes and visiting nursing care for an open wound is not clinically or economically prudent and again detrimentally effects the patient's quality of life.

Research endeavors to objectively measure outcomes that reflect real-world practice in a meaningful way. In the world of the at-risk

limb, inpatient-based surrogate outcome end points are appropriate. The surrogate outcome end points of length of hospital stay, readmission rate, the number of operations and the proportion of wounds closed/grafted prior to discharge more globally takes into account treatment efficacy/effectiveness, efficiency and economics.

Conclusion

The practice of diabetic limb care continues to evolve dictated by emerging data and economic constraints. This includes the use of terms such as 'diabetic limb function preservation' which more accurately describe the goals for treatment. A patient centered approach including measuring outcomes based on PROMs should become convention. Further, recognizing the difference in outcome measures in determining success or failure for clinic-based wound care versus inpatient-based limb care. As a discipline, diabetic wound care and limb salvage is in its infancy but is rapidly evolving. Thus, it is important to continually challenge dogma and question our assumptions in order to improve the lives of the patients we serve.

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