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Amputation in diabetic foot ulcer: A treatment dilemma

Amputation dilemma

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Abstract

Diabetic foot is one of the clinical manifestations of diabetes with a wide range of symptoms, including ulceration, osteomyelitis, osteoarticular destruction, or even gangrene, as a consequence of advanced disease. Some diabetic foot cases present general indications for amputation, including dead limb, threat to the patient's life, pain, loss of function, or nuisance.

Various tools had been introduced to help decision making in amputation for diabetic foot. However, it is still a conundrum as diabetic foot involves multiple pathomechanisms and factors hindering its outcomes. Moreover, sociocultural issues are often impede the treatment from the patient's side. We reviewed different perspectives in diabetic foot management, particularly when it is related to amputation. Not only deciding to amputate or not, the physicians should also deal with amputation level, timing, and how to avoid patients' deconditioning.

Surgeons should not be autocratic in these circumstances and should be aware of both beneficence and maleficence when considering the decision of whether to amputate. The main goal should be improving the patients' quality of life, rather than preserving the limb as much as possible.

Key Words: diabetic foot; amputation; decision making

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Core Tip: Making a decision in amputation for diabetic foot patients is not as simple as following a guideline such as scoring systems. There are many influential factors that not only come from different perspectives but sometimes also contradictory. The decision making should consider other clinical even sociocultural factors, with the improvement of patient's quality of life as the main goal.

INTRODUCTION

INTRODUCTION

The rising prevalence of diabetes represents a major public health and socioeconomic burden on society. Diabetes presents relatively mild symptoms that usually go unnoticed at early stages. Commonly, patients seek medical treatment in later stages when complications occur. Diabetic complications are known to be associated with poor glycemic control[1].

Diabetic foot is one of the clinical manifestations of diabetes with a wide range of symptoms, including ulceration, osteomyelitis, osteoarticular destruction, or even gangrene, as a consequence of advanced disease (Figure 1). Some diabetic foot cases present general indications for amputation, including dead limb, threat to the patient's life, pain, loss of function, or nuisance[2]. There are various scoring systems that are applicable for clinicians to determine whether the indication for amputation is presented, such as the mangled extremity severity score (MESS) or diabetic ulcer severity score (DUSS)[3, 4]. However, in many cases, clinicians have to address various factors that are not resolvable by those scoring systems; thus, decision-making is complicated. This article aimed to review the contributing factors that are often encountered during decision-making in diabetic foot management, especially when it is related to amputation.

CLINICAL CONSIDERATIONS

The etiology of diabetic foot ulcer is multifactorial. Poor glycemic control is the major underlying cause of advanced glycation end product (AGE) accumulation circulating in the body, affecting various organs. AGE formation is one of the main mechanisms responsible for vascular damage in diabetes patients and has also been shown to alter the angiogenic reaction[5]. Angiopathy indicates a vascular defect that is associated with angiogenic abnormalities. Angiogenesis itself results from the balanced functions of pro- and antiangiogenic molecules. Defects in this angiogenic balance may result in either excessive or antiangiogenesis[6]. This angiogenesis switch is determined by the activity of various regulators. Vascular endothelial growth factor (VEGF) is a signal protein responsible for blood vessel formation. Hypoxia-inducible factors (HIFs) are transcription factors that respond to decreases in cellular environment hypoxia. In normal cells, exposure to high glucose inhibits HIF and VEGF expression[6].

Peripheral artery disease (PAD) can be described as atherosclerotic occlusive disease of the lower extremities. Chronic hyperglycemia, dyslipidemia, and insulin resistance in diabetes mellitus patients are responsible for vascular wall derangements through promotion of vascular inflammation, endothelial cell dysfunction, abnormalities in blood cells, and factors affecting hemostasis[7]. AGEs are known to contribute to impaired angiogenesis via a reduction in collateral vessel development. In addition, AGEs also participate in the modification of extracellular matrix molecules, which in turn promote atherosclerotic lesion development[8, 9].

Macroangiopathy or microangiopathy presents a tendency to inhibit nutrient/oxygen supply. Successively, they put the foot at risk for ulceration and subsequently hinder the wound healing process[6]. These vascular problems in combination with increased plantar pressure due to fibrosis-related Achilles tendon contracture and loss of protective sensory function will result in recalcitrant complicated foot ulceration[10]. The involvement of infrapopliteal vessels is commonly found in diabetes patients with PAD. When ischemia is established, restoration of

pulsatile blood flow by revascularization is paramount for limb salvage. The treatment options are angioplasty, surgical bypass, or subintimal recanalization with varied results[11, 12].

Infection is a common complication in diabetes particularly attributable to hyperglycemia-related immunosuppression in which polymorphonuclear lymphocyte activity is hindered. Infection results in prolonged inflammation that in turn will prevent wound healing and keep the microorganism portal of entry open, eventually causing further infections[13]. Diabetic foot infection is considered difficult to manage. Timely diagnosis and appropriate intervention are principal in management strategies. Diabetic foot osteomyelitis (DFO) is the consequence of a soft tissue infection that spreads into the bone, involving the cortex first and then the marrow. DFO showed an increased multidrugs resistant organisms mainly methicillin-resistant Staphylococcus aureus (MRSA) or extended-spectrum of beta-lactamase-producing[14, 15]. The presence of osteomyelitis impedes infection control and raises the further need for medical treatment and surgeries[16]. In general, osteomyelitis require surgery to remove portions of bone that are infected or dead. However, although an aggressive surgical approach could be mandatory, retrospective studies have shown that conservative treatment is effective to promote wound healing and reduce the risk of major amputations[14, 17]. Recurrent ulcers have been a significant cause of hospitalization and amputation[18].

Although in general diabetic foot ulcer is considered painless as viewed as the main reason for ulcer formation due to loss of protective sensory function, as many as 27% of patients experience painful diabetic peripheral neuropathy (PDPN) to various degrees[19]. However, severe neuropathy is not the only cause of pain, as there are other causes precipitating pain, including ischemia, infection, and oxidative stress-related mechanisms. Other than clinical findings, diabetic peripheral neuropathy (DPN) can be diagnosed using several adjunct examination tools, such as nerve conduction studies. One of the newest tools is the assessment of transcutaneous oxygen pressure ($TcPO_2$), in which the sitting-supine position difference in $TcPO_2$ is higher in DPN patients than control subjects[20]. Various drugs have been introduced to address this problem,

including selective serotonin and norepinephrine reuptake inhibitors, anticonvulsant agents, and opioid receptor agonists, but pain relief remains poor for most patients[21].

Longstanding diabetic foot, particularly when treated insufficiently, may pose some disabling deformities. In that condition, the wound may be healed, but functional gait or ambulation is hindered. When physical activity is decreased, static positioning with fibrotic changes within the muscle will lead to contracture formation. Considering the muscle imbalance between the anterior and posterior groups, equinus contracture will likely develop[10]. Combined with muscle atrophy resulting from disuse and neuropathy, deformity and function loss may occur, resulting in a condition called damned nuisance, in which the limb is functionless, and amputation followed by prosthesis application would be a better solution. The deformity can also occur from osteoarticular destruction or from prior autoamputation.

AMPUTATION CONUNDRUMS

In general, amputation is the last choice for the treatment of nonsalvageable limbs[22]. The main indications of amputation consist of various conditions, including posing threats to the body, such as spreading of infection or tumors, the presence of necrotic tissue that constitutes not only a medium for pathological microorganism growth but also a functionless limb, and some situations in which although there are no dead or dangerous limbs, the patient and clinician believe that amputation will yield better results in terms of overall function and quality of life. In practice, decision-making concerning whether to amputate or to determine the amputation level frequently deviates from the factors that the patient and surgeon first considered when the patient first presented with diabetes.

Amputation can be divided into major or minor, according to its level. Major amputation was defined by any ankle disarticulation, transfemoral amputation, or transtibial amputation, whereas minor amputation was defined as a toe or transmetatarsal amputation[23]. Determining the amputation level is critical to the efficacy of management. In general, amputation should be performed at a level with

sufficient blood supply for wound healing. Arterial angiography, Doppler ultrasonography, and perfusion pressure are among the acceptable methods to be utilized. The latest advanced examination tools, such as transcutaneous oxygen pressure measurement, have been proven reliable in predicting wound healing in diabetic foot[24]. Soft tissue coverage should also be considered in deciding the amputation level. For great toe gangrenes, for example, ray amputation is preferred over metatarsophalangeal joint disarticulation despite good blood supply and biomechanical advantages of the latter. Less soft tissue bulk and higher pressure at the distal part will result in eventual wound breakdown. Exposed cartilage following disarticulation may be a source of infection through necrotic tissue formation[22]. In addition to local vascular status, systemic condition will also determine the result. Lower albumin and higher glycated hemoglobin (HbA1c), C-reactive protein (CRP), white blood count (WBC), and creatinine levels have been shown to be determinants of failed amputations needing subsequent reamputation[25]. In such situations, amputation is contraindicated and delayed until systemic improvement is achieved, except in emergency situations.

Despite the clear clinical findings prompting amputation, the negative perception of amputation remains, resulting in hesitation to undergo amputation[22]. The ability to cope with an amputation will be affected not only by clinical measurements but also by cosmesis, cultural issues, social support, and the patients' preamputation coping style[26]. Whereas many patients refuse amputation and are discharged against medical advice, in many cases, they request that the surgeon perform amputation as distally as possible without understanding the indications. The fact that amputation can still be perceived as a taboo will make discussion with patients and their relatives difficult[27].

Leg amputation is related to increased dependence. In addition to the medical benefit obtained from well-indicated amputation, function can be restored by using proper prosthetics aiming to regain the patient's independence. However, the recovery of function is not solely based on prosthetics. Older age, poor balance, previously low

function level, and higher amputation level are among the determinants of disability status[26]. Considering the physical demands, amputee patients spend more energy during walking than able-bodied persons. In the matter of comparison between transtibial and transfemoral amputation, the energy expenditure of transfemoral amputees will be higher[28]. Therefore, choosing the amputation level should also be in concordance with further postoperative rehabilitation plans.

DECISION MAKING

In regard to decision-making regarding amputation, various factors may be determinants. Choosing the level of amputation is surely the mainstay of treatment, but aside from that, the timing of surgery is also important.

While establishing the indication is paramount, its contraindication is also critical. Mainly, the general contraindication for amputation is the patient's inability to tolerate anesthesia or the surgery itself, such as the accompanying systemic problems. Amputation at a particular level is contraindicated when inadequate blood supply for wound healing is encountered, when the infarcted area is still undetermined, or when malnutrition occurs that hinders wound healing. In sum, amputation is contraindicated if the quality of life is reduced afterward.

PAD and infections are the main causes of lower-leg amputations. Limb salvage in diabetic patients with PAD requires comprehensive management, including medical therapies. Other than glucose-lowering and lipid-lowering drugs, such patients need medications that aim to improve vascular functions, including antiplatelet therapy, protease-activated receptor-1 antagonists, anticoagulants, or vasodilators[29]. Due to ischemic and neuropathic pain, many diabetic foot patients continually consume analgesics, including several anticonvulsants[21]. Antihypertensive and antithrombotics are among the major medications related to polypharmacy management for the elderly population, increasing the risk of adverse drug reactions (ADRs)[30]. Moreover, chronic kidney disease has been known to occur as a diabetic complication through renal fibrosis. Hence, longstanding drug administration in limb preservation should be

monitored carefully. Correspondingly, deprescription should be considered to avoid ADRs. In diabetes patients, PAD is difficult to treat due to various comorbidities. Atherosclerotic lesions are multilevel with a high prevalence of long occlusions. Recently, new techniques and technologies have been introduced for addressing PAD with various results that were probably related to the individual patient conditions[31, 32].

Revascularization is a procedure to restore blood supply to the tissue by addressing the blocked blood vessels. The aim is to salvage the limb by healing the trophic disorder. The indications included critical ischemia with some suggestive vascular examination findings (arterial pressure <50 mmHg or $TcPO_2$ < 30 mmHg). However, prerequisite conditions must be met, including a satisfactory support bed, a distal artery of a good caliber, and the presence of a plantar arch[11]. Vascular surgeons generally choose between endovascular prodecures (transluminal or subintimal), bypasses, or hybrid techniques that include both. The choice of revascularization technique depends on the type of lesion, the presence or absence of stenosis, and thrombosis as well as their length[11]. Iatrogenic injuries were reported but were mostly self-limited and of minimal clinical significance. Some life-threatening complications may occur, including ruptures, perforations, and pseudoaneurysms. Patient subpopulation selection is important to avoid unpredicted complications[33]. The main objective of revascularization is wound healing and limb salvage. Taking the results into consideration, at the one-year follow-up, 60% or more ulcers had healed with either endovascular procedures or open bypass surgery. Notwithstanding, the overall results demonstrate improved rates of revascularization compared with conservative treatment[31].

Revascularization is mandatory in ischemic limbs, not only for wound healing but also as a prerequisite for further surgical procedures, including debridement and amputation; otherwise, reamputation will likely be needed[22]. Many patients presented contraindications for minor or major amputation, either systemic or local, including unfeasible revascularization. In this setting, autolytic debridement could be an option,

or else, major amputation at the safe level. Autolytic debridement itself is considered safe, as it utilizes the natural ability of the body's own enzymes to remove dead tissues. To achieve autolytic debridement, the maintenance of a moist local wound environment is paramount[34].

Regarding limb salvage options, wound bed preparation through serial debridement is important, initially to limit the spread of infection. There are various advanced treatment options for recalcitrant diabetic foot wounds, such as hyperbaric oxygen therapy and platelet-rich gel treatment. The hyperbaric oxygen therapy involves the patient entering a pressurized room and breathing almost pure oxygen, thus increases the amount of oxygen in bloodstream, and eventually boosting oxygen flow to the wound. Hyperbaric oxygen therapy offers great benefit in the diabetic foot ulcers treatment and the reduction of amputation[35, 36]. Autologous platelet-rich gel therapy is other option that can effectively improving the healing of diabetic foot ulcers, through increasing concentrated platelets and growth factors in the wound, and improves the surrounding microenvironment[37]. When the infection can be controlled and granulation has seen healing, limb reconstruction can proceed. Thus, vascular flow is predominant. Thorough evaluation and approaches are needed to ensure this reconstructive procedure. Small, vascularized areas with no bone exposed can be grafted for nonbearing areas or local flaps in weight-bearing areas. Complex wounds are considerable for limb reconstructive procedures. Either way, the decision has to be made by the team and family[38].

Other than clinical measurements, patients' quality of life is an important thing to evaluate. Diabetic foot patients are known to have a negative impact on their quality of life. Pain from ischemia, dependent status, daily ulcer dressing, and unemployment stress were among the major causes of decreased quality of life[39]. Considering the frustrating circumstances along with physical deconditioning caused by prolonged immobilization, early major amputation might be a viable option. With early major amputation followed by appropriate prosthesis use, particularly in those who had less possibility of successful limb salvage, deconditioning can be avoided, and quality of life

is preserved or even improved. Cost analysis must also be considered. Earlier amputation might decrease the costs from length of hospital stay, repeated surgery, medications, and daily expense. On the other hand, patients undergoing major amputation will need proper rehabilitation exercise and prostheses that would possibly be costly as well[40]. For this reason, decisions should be made carefully and promptly.

CONCLUSION

Amputation is an option for patients with diabetic foot ulcers. While there are absolute or relative indications for amputation, there is also a clinical decision algorithm to determine whether a limb can be salvaged. However, various influencing factors should also be considered (Figure 2). The objective is to reach an immediate optimum state for the patient and to increase their quality of life. In contrast to clinical discussion, cultural values also played a role in patients' willingness to undergo amputation, as suggested. Surgeons should not be autocratic in these circumstances and should be aware of both beneficence and maleficence when considering the decision of whether to amputate.

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