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Amputation in diabetic foot ulcer: A treatment dilemma

Raden Andri Primadhi, Rani Septrina, Putie Hapsari, Maya Kusumawati

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Abstract

Diabetic foot is a clinical manifestation of diabetes with a wide range of symptoms, including ulceration, osteomyelitis, osteoarticular destruction, and 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 have been introduced to help decision-making in amputation for diabetic foot. However, it remains a conundrum because diabetic foot involves multiple pathomechanisms and factors that hinder its outcomes. Sociocultural issues often impede treatment from the patient's side. We reviewed different perspectives in diabetic foot management, particularly related to amputation. In addition to deciding whether to amputate, physicians should address amputation level, timing, and ways to avoid patient deconditioning. Surgeons should not be autocratic in these circumstances and should be aware of beneficence and maleficence when considering 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; Ulcer; Amputation; Decision-making; Perspective

Core Tip: Making a decision regarding amputation for diabetic foot patients is not as simple as following guidelines, such as scoring systems. There are many influential factors that come from different perspectives and are sometimes contradictory. Decision-making should consider other clinical and sociocultural factors, with the improvement of patient quality of life as the main goal.

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INTRODUCTION

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

Diabetic foot is one clinical manifestation of diabetes with a wide range of symptoms, including ulceration, osteomyelitis, osteoarticular destruction, and 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]. Various scoring systems are applicable for clinicians to determine whether the indication for amputation is present, such as the mangled extremity severity score or diabetic ulcer severity score[3,4]. However, clinicians must address various factors that are not resolvable by these scoring systems in many cases. Therefore, decision-making is complicated. This article reviewed 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, which affects various organs. AGE formation is one of the main mechanisms responsible for vascular damage in diabetes patients, and it alters 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 excessive or antiangiogenesis[6]. The activity of various regulators determine this angiogenesis switch. 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 hypoxia. Exposure to high glucose inhibits HIF and VEGF expression in normal cells[6].

Peripheral artery disease (PAD) may 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 *via* promotion of vascular inflammation, endothelial cell dysfunction, abnormalities in blood cells, and factors affecting hemostasis[7]. AGEs contribute to impaired angiogenesis *via* a reduction in collateral vessel development. AGEs also participate in the modification of extracellular matrix molecules, which promote atherosclerotic lesion development[8,9].

Macroangiopathy or microangiopathy has a tendency to inhibit nutrient/oxygen supply. These conditions put the foot at risk for ulceration and 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 result in recalcitrant complicated foot ulceration[10]. The involvement of infrapopliteal vessels is commonly found in diabetes patients with PAD. When ischemia is established, the 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, and it is particularly attributable to hyperglycemia-related immunosuppression in which polymorphonuclear lymphocyte activity is hindered. Infection results in prolonged inflammation that prevents wound healing and keeps the microorganism portal of entry open, which eventually causes further infections[13]. Diabetic foot infection is difficult to manage. Timely diagnosis and appropriate intervention are essential in management strategies. Diabetic foot osteomyelitis (DFO) is the consequence of a soft tissue infection that spreads into the bone, and it involves the cortex first then the marrow. DFO showed an increase in multidrug-resistant organisms, primarily methicillin-resistant Staphylococcus aureus or extended-spectrum beta-lactamase-producing

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Figure 1 A complicated diabetic foot ulcer which required a careful decision-making.

bacteria[14,15]. The presence of osteomyelitis impedes infection control and raises the further need for medical treatment and surgeries[16]. Osteomyelitis requires surgery to remove portions of bone that are infected or dead. Although an aggressive surgical approach may be mandatory, retrospective studies showed that conservative treatment effectively promoted wound healing and reduced the risk of major amputations[14,17]. Recurrent ulcers are a significant cause of hospitalization and amputation[18].

Although diabetic foot ulcer is generally painless, it is viewed as the main reason for ulcer formation due to the loss of protective sensory function, and as many as 27% of patients experience painful diabetic peripheral neuropathy (DPN) to various degrees[19]. However, severe neuropathy is not the only cause of pain because there are other causes precipitating pain, including ischemia, infection, and oxidative stress-related mechanisms. Other than clinical findings, DPN may 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 produce some disabling deformities. The wound may be healed in this condition, 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 and result 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 prior autoamputation.

AMPUTATION AND COMMON CONUNDRUMS

Amputation is generally the last choice for the treatment of non-salvageable limbs[22]. The main indications for amputation include various conditions, such as posing a threat to the body, such as the spreading of infection or tumors, the presence of necrotic tissue that constitutes a medium for pathological microorganism growth and a functionless limb, and some situations in which the patient and clinician believe that amputation will yield better results in overall function and quality of life in the absence of dead or dangerous limbs. Clinical decision-making on whether to amputate or to determine the amputation level frequently deviates from the factors that the patient and surgeon initially considered when the patient first presented with diabetes.

Amputation is divided into major or minor, according to its level. Major amputation is defined by any ankle disarticulation, transfemoral amputation, or transtibial amputation, and minor amputation is defined as a toe or transmetatarsal amputation[23]. Determining the amputation level is critical to the

efficacy of management. Amputation should be performed at a level with sufficient blood supply for wound healing. Arterial angiography, Doppler ultrasonography, and perfusion pressure are acceptable methods. The latest advanced examination tools, such as transcutaneous oxygen pressure measurement, are 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, 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 result in eventual wound breakdown. Exposed cartilage following disarticulation may be a source of infection *via* necrotic tissue formation[22]. In addition to local vascular status, systemic condition will also determine the result. Lower albumin and higher glycated hemoglobin, C-reactive protein, white blood count, and creatinine levels are determinants of failed amputations that need subsequent reamputation[25]. Amputation is contraindicated in these situations and delayed until systemic improvement is achieved, except in emergency situations.

Despite the clear clinical findings prompting amputation, the negative perception of amputation remains, which results in hesitation to undergo amputation[22]. The ability to cope with an amputation is affected by clinical measurements, cosmesis, cultural issues, social support, and the patients' pre-amputation coping style[26]. Although many patients refuse amputation and are discharged against medical advice, they often request that the surgeon perform amputation as distally as possible without understanding the indications. The fact that amputation may be perceived as a taboo makes 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 may be restored using proper prosthetics 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 some determinants of disability status[26]. Considering the physical demands, amputee patients spend more energy during walking than able-bodied persons. The energy expenditure of transfemoral amputees is higher than transtibial amputation[28]. Therefore, choosing the amputation level should also be in concordance with further postoperative rehabilitation plans.

DECISION-MAKING

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

While establishing the indication is paramount, its contraindication is also critical. 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 undetermined, or when malnutrition occurs that hinders wound healing. Therefore, amputation is contraindicated when 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, these 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 the major medications related to polypharmacy management for the elderly population, which increase the risk of adverse drug reactions (ADRs)[30]. Chronic kidney disease occurs as a diabetic complication *via* renal fibrosis. Therefore, longstanding drug administration in limb preservation should be monitored carefully. Deprescription should be considered to avoid ADRs. PAD is difficult to treat in diabetes patients due to various comorbidities. Atherosclerotic lesions are multilevel with a high prevalence of long occlusions. New techniques and technologies have been introduced for addressing PAD with various results that were likely 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 procedures (transluminal or subintimal), bypasses, or hybrid techniques that include both procedures. The choice of revascularization technique depends on the type of lesion, the presence or absence of stenosis, and thrombosis and 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. At the one-year follow-up, 60% or more ulcers had healed

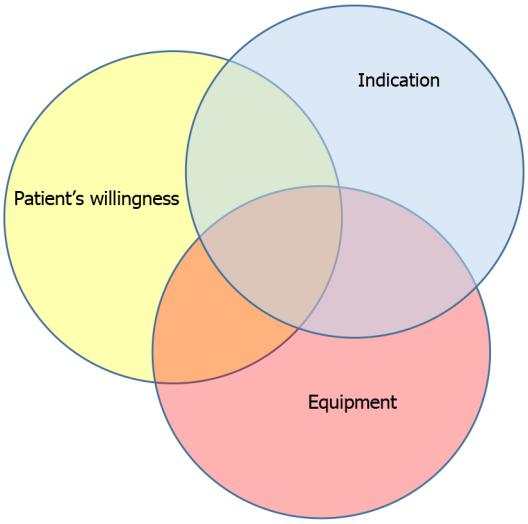

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Figure 2 Contributing factors in decision-making process for amputation.

with endovascular procedures or open bypass surgery. However, the overall results demonstrate improved rates of revascularization compared to conservative treatment[31].

Revascularization is mandatory in ischemic limbs for wound healing and as a prerequisite for further surgical procedures, including debridement and amputation. Otherwise, re-amputation will likely be needed[22]. Many patients presented contraindications for minor or major amputation, systemic or local, including unfeasible revascularization. Autolytic debridement may be an option in this setting, or major amputation at the safe level. Autolytic debridement itself is safe because it uses 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 *via* 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. Hyperbaric oxygen therapy involves the patient entering a pressurized room and breathing almost pure oxygen, which increases the amount of oxygen in the bloodstream and eventually boosting oxygen flow to the wound. Hyperbaric oxygen therapy offers great benefit in diabetic foot ulcer treatment and the reduction of amputation[35,36]. Autologous platelet-rich gel therapy is another option that effectively improves the healing of diabetic foot ulcers by increasing the concentration of platelets and growth factors in the wound and improving the surrounding microenvironment[37]. When the infection is controlled and granulation induces healing, limb reconstruction can proceed. Therefore, vascular flow is predominant. Thorough evaluation and approaches are needed to ensure this reconstructive procedure. Small, vascularized areas with no bone exposed may be grafted for nonbearing areas or local flaps in weight-bearing areas. Complex wounds are considerable for limb reconstructive procedures. Either decision must be made by the team and family[38].

Other than clinical measurements, patients' quality of life is an important factor to evaluate. Diabetic foot has a negative impact on patient quality of life. Pain from ischemia, dependent status, daily ulcer dressing, and unemployment stress were some the major causes of decreased quality of life[39]. Considering the frustrating circumstances and physical deconditioning caused by prolonged immobilization, early major amputation may be a viable option. With early major amputation followed by appropriate prosthesis use, particularly in patients who had lower possibility of successful limb salvage, deconditioning may be avoided, and quality of life is preserved or even improved. Cost analysis must also be considered. Earlier amputation may decrease the costs from the length of hospital stay, repeated surgery, medications, and daily expense. However, patients undergoing major amputation will need proper rehabilitation exercise and prostheses that may be costly as well[40]. Therefore, decisions should be made carefully and promptly.

CONCLUSION

Amputation is an option for patients with diabetic foot ulcers. Although 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 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 beneficence and maleficence when considering the decision of whether to amputate.

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