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An Overview of Diabetic Foot Complications

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ABSTRACT

The complications of Diabetic foot are the outcome of the association between impaired wound healing, peripheral vascular disease, and neuropathy. Diabetic peripheral neuropathy affects sensory, motor, and autonomic neurons and results in increased susceptibility to a foot ulcer. The most common trouble is the presence of wounds that are difficult to heal. Thus, the prevention of the formation of these wounds is of vital importance in patients who are recognized as being at risk for forming these wounds. Management involves a multidisciplinary approach and requires sufficient perfusion, proper wound care, and proper protection of the wound from pressure offloading. Neuro-osteoarthropathy or Charcot's disease of the foot is also frequent in diabetic neuropathic patients. The chief underlying cause is neuropathy which often results in the musculoskeletal disruption of the architecture of the foot and leads to severe deformity. Management of this condition is a big challenge and failure may result in limb loss.

INTRODUCTION

Complications related to the foot are common in patients with diabetes mellitus. Manifestations of these complications range from the simple to more complex entities, which can be limb or even life-threatening. The management of these foot complications ranges from medical interventions to prolonged hospitalizations. Foot pathology remains the chief diabetic complication requiring hospitalization[1]. The incidence and prevalence of diabetes mellitus and diabetic foot complications in the overall population are expected to increase. The costs of these complications are not only due to the medical costs but also because of the costs of lost productivity. For example, in 2002, the medical costs for treating patients with diabetes mellitus were 92 billion. An extra 40 billion could be attributable to lost productivity. It is approximate that the total expenditure of treatment will surge to around 200 billion by 2020. Diabetic foot complications, therefore, represent a major public health problem of growing proportions. Recently, risk factors and causal pathways leading to diabetic foot problems have been recognized. The importance of the key risk factors for the development of diabetic foot ulcers, which include peripheral neuropathy, peripheral vascular disease, and high foot pressures, is illustrious. These, along with other factors result in the development of diabetic foot complications, it is prayed that better approval of the pathogenesis of diabetic foot complications will afford us effective and preventative measures aimed at limb salvage[2].

MATERIALS AND METHODS

Exploration of published articles associated with diabetic foot ulceration was conducted and abstracts and full articles were incorporated for the preparation of this review from an online basis. We have measured for our review in the progression obtained from scientific publications with validation based methods and informed scrutiny. The databases utilized for obtaining information are scientific research publications from journals indexed/available through PubMed, Scopus, and Google Scholar, Science Direct, etc. Relevant facts were also obtained from general databases such as Google from a library source (Regional Research Institute of Unani Medicine, Hazratbal, Srinagar).

OBSERVATION:

Epidemiology

Foot ulcers are the outcome of several etiological factors and are wounds that are related to delayed or impaired healing. These causative factors take place from pathophysiological changes in the diabetic condition, anatomical deformities in the diabetic foot, and environmental influences. Annually, 2% of all patients with diabetesmellitus will develop a foot ulcer [3], whereas 15% will ulcerate during lifetime [3,4]. The prevalence of diabetic foot ulcers has been reported to range from5.3% to 10.5% [3,5,6,7]. This variation in the range maybe because of the lack of knowledge, awareness, and proper preventative care on the part of both patient and provider. Furthermore, this huge variation maybe because most studies choose only patients with diabetes who are at risk for diabetic foot complications for inclusion in the evaluation of ulcer formation. Foot ulcerations precede 85% of amputations and so the association between ulcers and lower extremity amputations is clear [8,9]. Alarmingly, 15% of all foot ulcers will ultimately require amputation, indeed the major risk factor for amputation is ulceration representing the major risk factor for amputation. Eventually, 15% of all ulcerations may develop an amputation at some level [3]. Other risk factors for amputation include longer duration of diabetes, peripheral vascular disease, peripheral neuropathy, poor glycaemic control, previous history of foot ulcers, previous foot surgery and amputation, retinopathy and nephropathy[10–15]. In the United States, approximately 50% of all amputations are performed on patients with diabetes[16], which is about 60% of total amputation[17]. Amputation rates have also been revealed to vary with both gender and ethnicity. Being male, African American or Hispanic has been related to a higher risk for amputation[18,19]. Lack of access to proper education and routine preventative care may be the underlying reason for this increase. When programs planned to prevent and promote awareness of diabetic foot complications were instituted in high-risk populations, the rate of amputations was decreased by nearly 50%[20].

Risk Factors

The risk factors for diabetic foot ulceration can be divided into three different groups: pathophysiological, anatomic deformities and environmental influences. The pathophysiological changes, which occur at the biomolecular level lead to changes that result in the progression of peripheral sensory neuropathy, peripheral vascular disease, and a compromised immune system with alteration in wound healing capabilities. The second

group with anatomic deformities is largely the effect of motor neuropathy and in some cases Charcot neuro-arthropathy. Finally, external or environmental influences in the form of acute or chronic trauma frequently precipitate the beginning of ulceration with initial soft tissue injury. It is essential to note that most of these risk factors do not act independently to develop foot ulceration. Instead, it is usually a combination of these risk factors that activates a pathway leading to ulceration. Such risk factors can consist of several elemental causes, such as peripheral neuropathy, foot injury, foot deformity, lower limb ischemia, foot edema, and callus formation. Though, some risk factors appear to be more important in causing foot ulcerations. An important triad of neuropathy, minor foot trauma, and foot deformity was found in more than 63% of foot ulcers in one study[21]. In the huge majority of diabetic foot ulceration, the first major constituent is the development of sensory neuropathy that causes pain insensitivity. The next component is the development of trauma, frequently related to the high foot pressures that develop under the foot during walking. The trauma caused by the elevated foot pressures seen during normal walking is often the result of the changes in foot structure that occur as a result of the motor component of peripheral neuropathy. The third major component is the impaired wound healing, related to altered immune response, and decreased blood supply at the wound area, and abnormal expression of growth factors and other cytokines that are concerned in the healing process. It is usually the combination of these three major components that lead to the development of chronic ulceration and amputation in cases where these progress to a limb or life-threatening condition[11]**.** Other risk factors for the development of diabetic foot ulcers include long duration of diabetes, previous foot ulcer, and earlier amputation. Duration of diabetes for more than 20 years has been found to increase the risk of ulceration six-fold when compared with patients with a history of diabetes of fewer than 9 years. Several studies have demonstrated that a previous history of ulceration or amputation considerably increases the possibility of a subsequent ulcer [22,23].

Clinical Examination and Screening Techniques

It is a well-established fact that prevention remains the best means of preventing the potentially devastating results of diabetic foot complications. It has been estimated that up to 80% of diabetic foot ulcers are preventable [24]. Therefore, regular clinical examination to categorize those diabetic patients at risk for ulceration has been advocated. This requires a thorough history and clinical examination of the foot to include vascular, neurological, dermatological, and musculoskeletal examination[25].

Clinical assessment of a patient with diabetes should start with a detailed clinical history to establish if a patient has a previous history of ulceration or amputation. A past medical history of foot ulceration or amputation increases the risk for future ulceration, infection, and amputation. Up to 60% of patients with diabetes with a history of a foot ulcer will develop another ulcer within a year following wound healing [26]. Other dimensions of history should include a detailed history of symptoms of neuropathy. For instance, pain, weakness, numbness, burning or tingling sensation, pins and pricks, hyperesthesia/ dysesthesia, or any other abnormal sensations in the feet or legs should be noted. Painful symptoms, such as sharp shooting or aching pains should also be recognized. It should be emphasized that the absence of neuropathic symptoms is not to be equated with the absence of neuropathy and that a large number of patients develop neuropathic ulceration without ever having or experiencing any symptoms. The clinical examination begins with the vascular assessment. Peripheral vascular disease is the cause of approximately 25% of foot ulcers and might contribute to the failure of an ulcer to heal [27].

The vascular evaluation includes a brief history of the existence of intermittent claudication. Clinical examination for the palpation of all lower extremity pulses and the presence or absence of hair should be done. The skin should be examined for texture, turgor, color, and temperature. The lack of hair growth, absence of palpable foot pulses (dorsalis pedis, posterior tibial), or the existence of non-healing ulceration should prompt non-invasive vascular examination along with consultation with a vascular surgeon. The next move in the clinical examination involves neurological testing to evaluate for the presence of neuropathy. The perception of pain, touch, and vibration can be simply tested using simple standard equipment, such as a pinprick, cotton or wool, and a tuning fork. The main characteristic feature the clinician should look for is a sensory level below which all the earlier mentioned modalities are reduced. Early loss of protective function can be detected in the foot of diabetic patients by using the 10 g monofilament. Ten sites viz, at the pulp of toes 1,3and 5 as well as the corresponding metatarsophalangeal joints. Other sites include two sites on the plantar aspect of the midfoot, one site on the plantar aspect of the heel, and one on the dorsum of the midfoot are chosen, and the monofilament is applied with sufficient pressure to bend the filament for the duration of not less than 2 seconds. It is tested three times at each site and it is enough if the patient answers correctly in 2 out of 3 applications. Failure to sense the monofilament in more than 4 sites indicates loss of protective sensation. The risk of ulcer formation is greater. This test is 95% sensitive and 80% specific.

Vibration pressure threshold (VPT) is one more useful technique to identify patients at risk of ulceration**.** VPT or biothesiometer is essentially a glorified tuning fork and can be used for assessment of vibration in a graded manner using the dial up to a maximum of 50mV. When the neuropathy is mild, the reading is more than 15mV, more than 25mV when it is moderate, and more than 40mV when the neuropathy is severe. Measurements were recorded at the plantar aspect of both rights and left foot at 6 points i.e. Great toe, 1st metatarsal, 3rd metatarsal, 5th metatarsal, Instep, and heel[28,29].

The clinical examination concludes with a comprehensive musculoskeletal examination to understand the overall structure and dynamics of the foot being evaluated. An examination for the presence of foot deformities and limitation of joint mobility is carried out. Both these entities raise foot pressures that lead to ulceration. Osseous prominences can be seen secondary to Charcot neuro-arthropathy, motor neuropathy, and common foot deformities, such as hallux abductovalgus, hallux limitus/rigidus, and hammertoe or contracted toe. Also, the physician should look for callus formation. In the past, the occurrence of calluses was speculated to be a protective mechanism with debridement of these lesions not recommended. Though, it is now well-known that most calluses are focal areas of increased pressure and can serve as sites of potential ulceration. Any areas of erythema secondary to shoe wear irritation should be protected with padding or appropriate accommodative shoe wear dispensed to alleviate the pressure[30, 31].

Classification of Diabetic Foot Ulcer

There are various classifications given for describing diabetic foot ulcers. The most commonly used and most often referred to is the Wagner system classifies diabetic foot ulcers into five different grades, based on anatomical location and depth. Wagner grade 0 describes a pre- or post-ulcerative lesion. Grade 0 ulcerations are healed sites of ulcerations however risk factors for ulcer development, such as calluses and foot deformities are present. Wagner grade 1 ulcerations are superficial, full-thickness ulcers with infiltration past the epidermis. Grade 1 lesions are often suggestive of the presence of peripheral sensory neuropathy, and usually another risk factor for ulceration. Constant weight-bearing on grade1 ulcerations will affect progression past the dermis with the involvement of deeper structures, such as tendons, ligaments, joint capsules, and neurovascular structures. These are grade 2 ulcerations. Grade 2 lesions do not explore bone and osteomyelitis is not present. Wagner grade3 ulcerations are characterized by the presence of deep tissue infection with or without

bone involvement and are frequently the result of grade2 ulcerations, which have worsened because of insufficient or lack of successful treatment. Other factors are lesions with rapidly forming tissue necrosis or puncture wounds. Wagner grade4 ulcers are characterized with partial gangrene of the foot. Grade4 ulcers typically are associated with peripheral vascular disease. Infection is also present and necessitates hard-line management by a limb salvage team to limit tissue loss. Partial amputation in patients with these ulcerations is not unusual. Grade 5 ulcers are characterized by extensive necrosis and gangrene of the foot, which is usually managed with aggressive treatment and amputation [32].

Principles and Treatment of Foot Ulceration

Treatment of diabetic foot ulcers varies deeply depending on the severity of the ulceration as well as the presence of ischemia. However, essential key points of treatment for full-thickness ulcers are effective debridement, offloading of pressure, treatment of infection, and local wound care. However, a greater understanding of the pathophysiology of wound healing has led to advanced wound care products representing promise in accelerating wound healing.

Debridement

The objective of wound debridement is the complete removal of all necrotic debris, dysvascular, and nonviable tissue to achieve a red, granular wound bed. Sharp surgical debridement using sharp instruments, such as a scalpel blade is best. Using this procedure all necrotic tissues are removed until a healthy bleeding ulcer bed is produced with cauterisation of the wound edges. Ulcerations with unnecessary hyperkeratotic rim should be aggressively debrided to remove this hyperkeratotic tissue. This will help to decrease pressure on the wound when the patient ambulates. It will also help better visualization of the wound for a more thorough evaluation. The bacterial load at the ulcer site can also be reduced by debriding ulceration aggressively. This procedure can be done in the OPD setting except in the rare cases when extensive debridement is required or sensation to the foot is not intact and the use of the operating room might be required. Also, if ischemia is suspected, aggressive debridement should be delayed until vascular examination and revascularization are achieved[33]. Other debridement methods are also available, but none has gained universal acceptance. Autolytic debridement means the body's mechanism of removing devitalized tissue. This process is mainly undertaken by macrophages, which release proteolytic enzymes to degrade nonviable tissue[34].

Pressure Offloading

Reduction of pressures is necessary for the healing of plantar foot ulcers. Ulcerations take place in high-pressure areas of the insensate foot. There are various methods used for the reduction of foot pressures, with varying success rates. The most acknowledged methods include total contact casting, half shoes, short leg walkers, and felted foam dressings. Total contact casting has been considered the most effective means of offloading diabetic foot ulcers as measured by wound healing rate [35]. Paul Brand enlightens the total contact casting involves the use of a well-molded minimally padded plaster cast to distribute pressures evenly to the entire limb. It allows for patient mobility during treatment and has been found to help control edema linked to impairment of healing while maintaining the forced patient compliance because of the inability to remove the apparatus [36]. Drawbacks include the substantial skill and time required for application, the possibility of secondary skin lesions because of cast irritation, and the incapability to assess the wound daily. Patients also complain of the total contact cast making sleeping and showering complicated. Because of the considerable disadvantages associated with the total contact cast, few physicians use it as the procedure of choice in regular clinical practice. Alternatively, commercially available off the shelf devices, such as the half shoe and prefabricated short leg walker is more commonly used. Both these devices are comparatively inexpensive, easy to use, and readily accepted by the patient. However, pressure reduction is significantly less compared with total contact casting and patient compliance cannot be assured because of the removable nature of the devices [37]. Felted foam dressings are accommodative offloading devices designed from a felt foam pad with an aperture corresponding to the ulceration for customized pressure relief. The pad is attached to the patient's skin with a pliable adhesive, preventing migration of the pad, and thereby ensuring a degree of patient compliance. Wound care and wound assessment can be performed through the aperture or window that is formed for access to the wound. The felted foam is often used in combination with a surgical shoe or half-shoe and must be changed every 10–14 days to make sure the integrity of the dressing. Felted foam dressings in combination with a surgical shoe or half-shoe were found to be more useful in pressure reduction when compared with a short leg walker or a half-shoe alone [38].

Treatment of Infection

Bacteria colonize ulcerations and these ulcerations may serve as a portal of entrance resulting in the development of an infection. The diagnosis of infection mainly depends on clinical

appearance, relying on clinical signs such as erythema, edema, pain, tenderness, and warmth. Care must be taken to diagnose and treat infections adequately as mild cellulitis can rapidly progress to a limb-threatening infection if left untreated. Indeed the spectrum of infections may range from the local cellulitis to severe, limb-threatening deep abscesses with osteomyelitis. Further clinical information may be obtained with cultures, radiographs, and more advanced imaging techniques. When clinical infection of an ulcer is suspected, cultures of the wound will aid in directing following antibiotic therapy. Empirical antibiotic therapy should be started for cases of infection, with a review of therapy pending culture results.

Radiographical imaging of the infected foot can demonstrate increased density and thickening of the subcutaneous fat along with blurring of the usually visible fat planes [39]. The existence of Periostitis, cortical bone damage and focal osteopenia might clinch a diagnosis of osteomyelitis. However, these changes only become clear after osteomyelitis has been present for 10–14 days and require up to 50% bone loss before becoming identifiable[40]. Sophisticated imaging techniques, such as magnetic resonance imaging and computed tomography may help in the accurate diagnosis of osteomyelitis as well as demonstrate abscess formations. Treatment of infection consists of debridement of all necrotic or non-viable tissue with aggressive, adequate drainage along with specific antibiotic therapy. Antibiotic selection should take into report the likely causative organisms, whereas bearing in mind the possible toxicity of the agents. In the diabetic foot, the bacteria most commonly responsible for minor, non-limb threatening infections such as cellulitis are *Staphylococcus* and *Streptococci*. However, more severe and limb-threatening infections are generally the outcome of a polymicrobial infection [41]. Antibiotic selection should be based on the suspected bacterial organisms along with modifications to address likely resistant micro-organisms that might have been present during earlier episodes of infection. Antibiotic selection should decrease toxicity and be cost-effective. Broad-spectrum antimicrobial therapy should be initiated empirically with reassessment following the results of culture data.[42] The time period of antimicrobial therapy for severe soft tissue infections of the foot is based on response to the antibiotics and wound care. Two weeks of therapy is the standard guideline, however, recalcitrant infections might require longer courses. Despite the ulcer has not been completely healed, antibiotics can be discontinued when evidence of infection has been resolved. Continuation of antibiotics beyond this duration has not been demonstrated any effect on wound healing [43, 44].

Wound Care

The successful use of dressings is mandatory to make sure that the best management of diabetic foot ulcers. In recent years, the perception of a clean, moist, wound-healing environment has been widely accepted. Benefits to this perspective include prevention of tissue dehydration and cell death, acceleration of angiogenesis, and facilitating the interaction of growth factors with the target cells. Moreover, patients have reported less discomfort with moist wound dressings. The idea that a moist wound environment increases the risk of developing an infection appears to be unsupported. There are multitudes of wound care products available in the market that endorse moist wound healing, however, wet-to-dry normal saline gauze remains the standard of care[45].

Advanced Wound Care Products

Advanced wound care products have been developed in response to an improved understanding of the impaired wound healing essential in diabetic foot ulcer. A greater understanding of wound pathophysiology with deficiencies, such as decreased growth factors production and altered cellular inactivity ehas led to the development of products that tackle these deficiencies. These consist of recombinant platelet-derived growth factor and biological skin substitutes. Recombinant human PDGF-BB (Becaplermin) is the only growth factor to date approved by the US Food and Drug Administration (FDA) for the management of diabetic foot ulcers. PDGF-B is a powerful mitotic and chemotactic agent for connective tissue and stromal cells and may perform to augment wound vascularisation by stimulating endothelial cell proliferation, movement, and tube development. Levels of PDGF have been shown to be lesser in chronic wounds [46]. Becaplermin as it is known is formulated as a gel to help uphold proper moisture balance. It was found to increase both the incidence of complete wound closure and decreased the time to achieve complete wound healing [47]. Biological skin substitutes, also known as living skin equivalents (LSE), are commercially obtainable. The LSEs are produced through tissue-engineering technology. Available for epidermal, dermal, and composite (epidermal and dermal) wounds, LSEs offer distinct advantages compared with traditional skin grafting as their use is non-invasive, does not require anaesthesia, can be performed in an outpatient setting, and avoids potential donor site complications, such as infection and scarring [48]. Two LSEs were approved for use in diabetic foot ulcers, Dermagraft and Apligraf. Dermagraft consists of neonatal skin fibroblasts cultured in vitro onto a bio absorbable polyglactin mesh, producing a living, metabolically active tissue containing the

normal dermal matrix proteins and cytokines. Dermagraft has been shown to slot in quickly into the wound with good vascularization and with no adverse effects [49, 50]. In a prospective randomized multicentric clinical trial, Dermagraft-treated ulcers were revealed to compare favourably with more complete and rapid healing. Along with the added benefit of a reduction in the ulcer recurrence rate compared with conventional therapy [51]. Dermagraft has since been discontinued. Apligraf is documented a mixed graft, containing both epidermal and dermal components. The outer layer consists of allogenic human keratinocytes made with an inner dermal layer consisting of human fibroblasts on type 1 collagen dispersed in a protein matrix. Apligraf histologically is akin to human skin, but it does not include structures, such as blood vessels, hair follicles, or sweat glands. Apligraf acts like human skin, producing all the cytokines and growth factors produced by normal skin during the wound healing process[52] In diabetic foot ulcers, Apligraf was revealed to greatly increase the wound healing rate as well as decreasing the median time to complete wound closure. Ulcer recurrence rate was alike in both Apligraf treated ulcers and standard treatment group. The exact mechanism of action of Dermagraft and Apligraf is not fully understood. It is implicit that improved wound healing is because of filling of the wound with extracellular matrix proteins and with the subsequent induction, and expression of growth factors and cytokines essential for wound healing[53, 54].

CONCLUSION

Diabetic foot is a global health pandemic with high morbidity, mortality and socioeconomic burden. Poor patient education, deprived preventive care, poor glycaemic control and lack of multi specialist diabetic foot care clinics are the major concerns in our community, thus the need of the hour is to improve our knowledge by conducting various community health education programs regarding diabetic foot,early intervention, diabetic foot care and strict glycemic control can decrease the number of patients to go through limb amputation as well as the number of amputees.

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