MAL PERFORANS: CLASSIFICATION AND PATHOGENESIS

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Introduction

Pedal ulcerations are a very significant cause of morbidity and mortality among the diabetic population. The statistics concerning diabetes and the diabetic are staggering.

Diabetes is the third leading cause of death in the United States (1).

Nearly 50% of all nontraumatic lower extremity amputations occur in diabetics (2).

Lower extremity disease is the most common disorder necessitating operation in diabetics (3).

Lesions of the feet are responsible for more than one fifth of the hospitalizations of diabetics (4).

Three percent of diabetics are amputees (5).

Gangrene is a principle or contributing cause of death in two thirds of diabetics (6).

The medical expenses involved and the time lost from work certainly place the cost of diabetic health care and its complications well into the billions of dollars annually.

The podiatric physician can readily attest to such grim facts. He has long been involved in the evaluation and treatment of lower extremity complications of diabetes. One major medical study at Mt. Sinai School of Medicine determined that over a three day clinic period only 12% of diabetic patients obtained a foot examination. Only 49% of the diabetic patients had undergone a foot examination in the prior year. The amazing fact is that the article dates from 1985 (7). The podiatric community involvement in diabetic foot health and foot health awareness is a long and proud tradition. Many diabetic feet have and will continue to be saved due in large part to podiatric commitment to the care of such patients.

Management of the diabetic patient with ulceration requires an appreciation and understanding of the multiple factors involved in pathogenesis and pathophysiology of such ulcers. Many factors playing major and minor roles act in concert to produce mal perforans. It is impossible to assess these factors individually. Many interrelationships exist that are only now being identified and understood.

Many facts are known but many controversies exist as well. This paper will highlight some of the dilemmas faced in treatment of the condition. Practical points relating to patient management will be emphasized. Important testing procedures and clinical signs and symptoms helpful in diagnosis and treatment planning will be reviewed.

Classification

Diabetic ulcerations can be classified into two major categories:

1. ischemic, and
2. neurotrophic (Fig. 1).

Diabetic pedal ulcerations can demonstrate a combination type presentation as well. Determination of the presence or absence of infection is critical. Treatment of infection in ischemic or neurotrophic ulcerations will be covered elsewhere. A constantly high index of suspicion should be maintained at all times by the clinician. There should be constant monitoring for infection throughout the course of treatment and at any stage of lesion development. Prompt and thorough treatment by surgical and medical approaches should be instituted as indicated.

These two broad classifications, neurotrophic and ischemic, help categorize and identify two major pathogenic mechanisms of diabetic ulcerations and herald treatment approaches.

Within each category further distinctions can be drawn based on size of lesion, depth of lesion, presence of infection, or combinations. As each of these two major categories is reviewed, contributing factors related to nutrition, blood glucose management, and more should be remembered.

Neurotrophic Ulcers (Mal Perforans)

Neurotrophic ulcerations in the diabetic are the classical painless ulcerative lesions or mal perforans. These lesions generally occur on the plantar aspect of the foot. Most commonly they present over bony prominences or areas of abnormal or increased stress to the skin and soft tissues. They may occur dorsally on the foot, on the digits or interdigital surfaces, and on the distal plantar aspect of the digits as well.

The neurotrophic foot without a significant ischemic

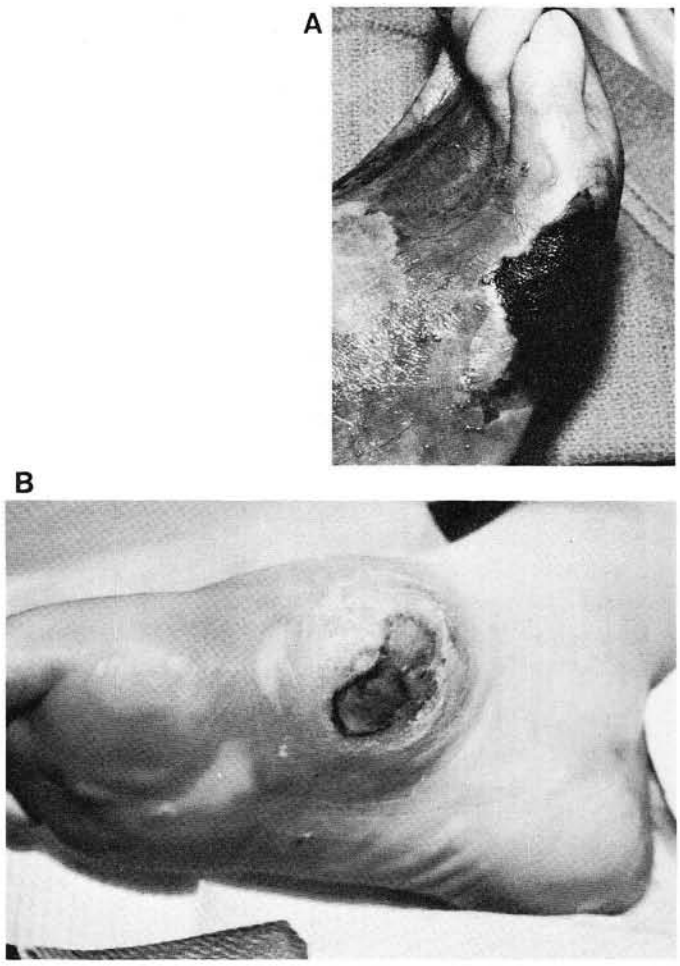

Fig. 1. Diabetic ischemic ulceration and neuropathic ulceration are represented in above photographs. **A.** Ischemic ulceration. **B.** Neuropathic ulceration.

component is rather characteristic. Good pulses are generally present and the foot may not appear to be at risk.

Hair growth, texture of skin, and overall general appearance can be quite satisfactory. The foot type is often high arched or cavus. Hammertoe deformities are common. It is felt they are a sequel to the loss of innervation and stabilizing power of the intrinsic foot muscles. Hammertoe deformities are felt to contribute to the cavus foot attitude. The presence of Charcot joint changes promotes pes valgus deformity. The neurotrophic foot may or may not present with Charcot joint changes.

Callosities may be present over bony prominences designating areas at risk. Callus tissue containing hemorrhage or masceration upon debridement is indicative of possible early neurotrophic ulcer development. Calluses may represent only the tip of the iceberg and must be recognized as part of a continually deteriorating process of soft tissue breakdown.

Sensory evaluation will demonstrate the absence of vibratory and proprioceptive sensations early. Distal to proximal loss of pain and temperature sensation follows and is less marked in the hands than the feet. The patient commonly has a history of painful neuropathy that seems to herald the future painless neuropathy. Both painful and painless neuropathy may be present simultaneously. The diabetic history is generally of long duration, possibly of childhood onset with a long history of insulin requirements.

Mal perforans lesions may appear initially as areas of callus, callus with hemorrhage, or callus with masceration. The external callus tissue can act as a seal to tissue breakdown as a hidden crater of dead space develops. Accumulations of blood, serum, and tissue fluids are an open invitation to infectious invasion. The crater can ulcerate to the surface or extend inward to deep tissue planes, joints, and osseous structures. It can burst outward providing drainage or escape of its contents. Eventual progression of the size and depth of the ulcer will involve deeper subcutaneous structures. Progression of infection along paths of minimal resistance can be life threatening.

Throughout its entire development the process is painless and possibly unknown to the patient. The patient may present at any point along the evolutionary path of the lesion. There may be multiple lesions in various stages of development on the same foot. Each lesion should be assessed carefully and individually and treated as such. Occasionally the less serious appearing ulcer on first inspection may prove to be the portal of entry for deeper infection. Unresponsiveness to appropriate treatment should alert the clinician to further evaluation of the circulatory status of the limb. Peripheral vascular compromise, like infection, can worsen or occur at any time. Its status should be constantly monitored.

Ischemic Ulcers

Ischemic ulcerations are generally seen in older diabetic patients. The diabetic disease history will denote a later onset of the disease. There is occasionally a history of intermittent, or worse, nocturnal claudication. The distinction between neuropathic pain and ischemic pain can be difficult. Neuropathic pain is more characteristically a night pain with no relief by dependency. The ischemic foot demonstrates changes in the soft tissues as a consequence of diminished nutrician. The soft tissues and skin are thinned and atrophic in appearance. The normal bony prominences appear enlarged. The skin has poor turgor and elasticity, is hairless and dry. The nails are thickened and demonstrate trapped skin scaling as periungual and subungual debris.

Nonhealing fissures can be found about the periphery of the plantar-dorsal skin junctional area. The typical ulcerations are flat, atrophic, and demonstrate no particular pat-

tern of distribution. Involvement of the distal end arteries will demonstrate patchy patterns of distribution with a predilection for the distal aspect of the digits. The skin surrounding the ulcer is erythematous and a central black eschar may be present.

The ischemic foot hurts. The lesions described above are exquisitely painful, out of proportion to their clinical presentation. Advanced cases demonstrate pain to gentle palpation. Even the pressure of stance and gait can be painful. This pain can vary from easy fatigue to unbearable discomfort depending on the degree of vascular compromise and possible coincidental neurotrophic involvement.

Infection is possible, as in the neurotrophic lesions, at any point in the pathogenesis. A high index of suspicion and constant monitoring are mandatory. Distal necrosis about a digit with blackened, mummified, atrophic changes is termed *dry* gangrene. It occurs as a result of occlusion or thrombus of end arteries. *Wet* gangrene occurs as a result of more proximal large vessel occlusion. Larger area are involved such as entire limbs. The circulation is diminished below that required for tissue survival and necrosis occurs.

Clinically the ischemic foot has diminished pulses. There is rubor and edema on dependency that becomes pallor on elevation. The venous filling time is greater than 20 seconds (1). The ischemic index is reduced and the pulse demonstrates a less pulsatile waveform.

Pathophysiology

Sensory Nerve

The insensitive foot has lost the ability to inform the patient of impending problems through the medium of pain. The warning system is gone for both internal and external environmental changes (8). The internal environment includes structural alterations, functional changes, connective tissue alterations, and vascular compromise. The external environment includes shoe gear, foreign bodies, socks and stockings, and the home or workplace. The compromised warning system of sensory nerves is but one effect of the neurological deficit.

Sympathetic Nerves

Edema is worse in denervated limbs and is prone to result from denervation (9). Wounds created in denervated limbs and inoculated with known amounts of bacteria, allowed greater soft tissue bacterial growth than identical wounds in normally innervated limbs (10). This may be more a factor of the sympathetic than sensory denervation. The role of the sympathetic nervous system in diabetic foot ulcers is being appreciated more and more. The interrelationship of vascular and autonomic function is vital to skin and soft tissue response to traumatic stress. The trauma, no matter how subtle or overt, is occurring unknown to the patient. Yet, the inadequacy of the autonomic system does not permit an appropriate response for healing.

Systemic complications of autonomic neuropathy include painless myocardial infarction and postural hypotention. The necessity of a thorough medical evaluation and preoperative appraisal of cardiac status in the diabetic are apparent.

The foot presenting with autonomic neuropathy is warm, reddish or erythematous appearing, and with the fullness of dermal edema. Sweat gland function may be hyperactive or absent (11). This can lead to presentations of moist skin problems such as tinea and interdigital masceration, or to drying of the skin with peripheral heel fissures and cracking.

This autosympathectomy has been implicated in arterial smooth muscle calcification. Such calcification can be seen radiographically and is termed Monckeberg's calcific sclerosis. Alteration of blood flow through sympathetic malfunction has also been implicated in Charcot joint development.

Only the surface is being scratched with the recent attention in the literature to the autonomic nervous system and its relationship to the pathogenesis of diabetic complications. Many similarities to the findings in reflex sympathetic dystrophy are intriguing.

Blood Vessels

The calcifications of the arterial tree has already been mentioned. This is not the only effect the diabetic state has on the blood vessels and blood supply. Wagner (12) proposed a classification system of diabetic ulcerations that is applicable to any insensitive or dysvascular foot:

Grade 0: Skin intact (may have bony deformities)
Grade 1: Localized superficial ulcer
Grade 2: Deep ulcer to tendon, bone ligament, joint
Grade 3: Deep abscess, osteomyelitis
Grade 4: Gangrene of toes or forefoot
Grade 5: Gangrene of the whole foot

The important first step in Wagner's schematic approach to ulceration management is the Doppler evaluation and the ischemic index. Satisfactory healing can be predicted if the blood flow is pulsatile and the ischemic index is over 0.45. The wound healing success rate for 134 procedures utilizing this criteria was 93% (13). The ischemic index is a measure of large vessel blood flow. The values can be distorted by the noncompressibility of arterial calcification. The ischemic index is determined by dividing the lower extremity systolic blood pressure by the brachial systolic blood pressure. The blood pressure determination should be obtained with a blood pressure cuff 120% the diameter of the extremity or digit (14). The evaluation is performed with the patient in a supine resting position. This determination is

a noninvasive procedure that can easily be performed in the office or hospital setting with frequent repetition for monitoring progress or regression possible.

Large vessel disease presents as atherosclerosis in the diabetic. It is extremely widespread affecting 1/3 of all diabetics who present with ulcers. The diabetic large artery system seems especially prone to develop atheroma. Not only lower extremity vascular problems but cardiovascular and cerebrovascular problems may be present as well. The entire vascular tree may be affected to varying degrees.

Small vessel disease has become an area of extreme controversy. Recent research has cast doubt on what was once considered a main complication of diabetes (15). Thickening of the basement membrane of the capillaries was observed along with proliferation of the endothelial lining (16, 17). Recent research has shown these changes visible microscopically but may not actually affect the vessels functionally. The affected capillaries are still permeable to test materials (18). Percutaneous oxygen measurements are similar in affected, unaffected, and normal nondiabetic controls all with adequate large vessels (19). These lesions have not been demonstrated to produce capillary occlusion. The small vessel changes are variable findings and may depend on sampling and slide preparation and fixation techniques (20).

Large vessel disease is a known complication of diabetes. It is a serious and yet potentially correctable problem with advanced vascular reconstructive and bypass techniques. Smaller vessels are becoming more amenable to bypass as surgical techniques improve. For this reason, large vessel disease mandates early identification to effect possible surgical reconstruction.

Small vessel disease involvement is currently controversial and its role in diabetic foot problems is under question (21). Arteriorlar disease, disease of the medium to small vessels involved in precapillary blood flow and inflammation regulation and response, is likewise being questioned. Pathological microscopic evaluation of amputated parts and biopsy specimens from diabetics with ischemic necrosis has not demonstrated significant histological change of these vessels (22, 23). There is evidence that the functional response of these vessels is likewise unaffected.

Mechanical Forces

In the nonischemic condition, it appears some force or pressure is needed to produce the plantar ulcerations of mal perforans in the diabetic foot. Ischemic necrosis or gangrene results from vascular occlusion not generally mechanical pressure influences. The role of the various types of mechanical pressures that result in neurotrophic ulcerations will be reviewed.

Three types of force have been identified that affect the soft tissues and skin to produce ulcerations. These include:

1. continuous pressure,
2. concentrated high pressure,
3. repetitive mechanical stress (24), and
4. excessive heat and cold.

These pressures may occur in nondiabetic feet but do not necessarily result in mal perforans. The actual occurrence of mal perforans probably results from a multiplicity of local biochemical, structural, and nutritional problems. These will be reviewed in later sections of this text. The character and types of forces involved, however, are an important consideration in evaluating the diabetic foot.

Constant pressure results in ischemia and necrosis. The pressure can occur as high pressure for short periods or low pressure for prolonged periods. The capillary blood pressure of only 13-33 mm Hg attests to the minimal pressure needed for obstruction of flow at this level (8). Foot-ankle orthoses can produce pressure, cast pressure, shoe pressure, or bed and resting posture over the course of time can result in ulcerations by this mechanism. Pain may not be present to warn of the insult resulting in ulceration in the face of neuropathy.

Concentrated high pressures are the result of trauma. The traumatic force exceeds the tearing tension of the skin, 600-700 lbs/inch (25). Trauma of this type can occur to any person. The problem for the diabetic patient is the lack of awareness of the insult. The diabetic may also lack an adequate response to invading microorganisms to ward off an infection. The circulatory status may not be adequate to promote timely wound healing.

Repetitive mechanical stress is primarily responsible for most typical plantar mal perforans noted in clinical practice. Areas subject to the repetitive trauma of gait exaggerated by deformity or abnormal function are prone to ulceration (24). Amputations of digits and rays can particularly potentiate such problems. Tissue glycosolation and structural biomechanical changes possibly alters tissue responsiveness to this type of pressure (26, 27). Absence of moisture in the form of sweat and other secretions alters external skin response. Sympathectomized skin with the resultant dermal edema and nutritional deficit is less able to respond to the micro-repair needs of the soft tissues.

Systemic Complications

Systemic factors, such as blood glucose control and glucose utilization, are related not only to tissue structural changes but also to tissue response to trauma and its repair. Derangements in collagen metabolism have been shown in animal models. Granulocyte dysfunction, extracellular hyperglycemia, and intracellular glucose deficiency alter the early stages of the inflammatory response in tissue healing. This results in impaired collagen synthesis (28). Insulin administration will often restore a normal metabolic environment and allow the production of sufficient collagen (29).

Keratin and collagen both have been identified as being

affected by nonenzymatic glycosolation and hyperglycemia (26,27). The resulting healed wound of collagen cross links lacks compliance resulting in rigid and firm yet flexible tissues (30). The collagen produced is resistant to collagenase producing a dense impermeable protein matrix (31). This matrix is a poor tissue structure that does not promote adequate nutrient diffusion. Such tissues are more susceptible to injury and mount a less than adequate repair process.

Dietary malnutrition is an important systemic factor for consideration. Poor use of ingested glucose and body energy and nutritional stores occurs in diabetics. Vitamin and zinc deficiency strongly effect the soft tissues' ability to respond to stress (32).

Conclusion

Many factors are involved in the development of mal perforans in the diabetic foot. The clinician needs to be well apprised of all such factors. The effective treatment dependant on thorough evaluation and assessment of the many related factors contributing to the ulceration.

References

1. Kosak GP, Hoar CS, Rowbotham JL: *Management of Diabetic Foot Problems,* Philadelphia, WB Saunders Co, 1984, p 1.
2. Ecker ML, Jacobs BS: Lower extremity amputation in diabetic patients. *Diabetes* 19:189, 1970.
3. Penn I: Management of the diabetic foot. *Continuing Education Family Physician* 13:37, 1980.
4. Pratt TC: Gangrene and infection in the diabetic. *Med Clin North Am* 49:987, 1965.
5. Boulton AJM: Detecting the patient at risk for diabetic foot ulcers. *Practicing Cardiology* 9:135, 1983.
6. Levin ME, O'Neal LW: *The Diabetic Foot,* ed 3. St Louis, CV Mosby, 1983, p 178.
7. Baily TS, Yu HM, Rayfield EJ: Patterns of foot examination in a diabetic clinic. *Am J Med* 78:371, 1985.
8. McGlamry ED (ed): *Fundamentals of Foot Surgery,* Baltimore, Williams & Wilkins, 1987, p 436.
9. Exton-Smith AN: Nature of edema in paralyzed limbs of hemiplegic patients. *Brit Med J* 2:1280, 1957.
10. Robson MC, Krizek TJ: The role of infection in chronic pressure ulcerations. In Fredericks S, Brody GS (eds): *Symposium on the Neurologic Aspects of Plastic Surgery.* St Louis, CV Mosby Co, 1978.
11. Ozeran RS, Wagner GR, Reimer TR, Hill RA: Neuropathy of sympathetic nervous system associated with diabetes mellitus. *Surgery* 68:953, 1970.
12. Mooney V, Wagner FW Jr: Neurocirculatory disorders of the Foot. *Clin Orthop* 122:53, 1977.
13. Mann RA (ed): *Surgery of the Foot,* ed 5. St Louis, CV Mosby Co, 1986, p 423.
14. Kirkendall WM, Burton AC, Epstein PH, Freis ED: Recommendations for human blood pressure determination by sphygmonanometers. *Circulation* 36:980, 1967.
15. Logerfo FW, Coffman JD: Current concepts. Vascular and microvascular disease of the foot in diabetes. Implications for foot care. *New Engl J Med* 311:1615, 1984.
16. Kilo C, Vogler N, Williamson JR: Muscle capillary basement membrane changes related to aging and to diabetes mellitus. *Diabetes* 21:881, 1972.
17. McMillan DE: Deterioration of the microcirculation in diabetes. *Diabetes* 24:944, 1975.
18. Trap-Jansen J: Increased capillary permeability to 131-iodine and (51-CR) edta in the exercising forearm of long term diabetics. *Clin Sci* 39:39, 1970.
19. Wyss CR, Matsen FA III, Simmons CW, Burgess EM: Transcutaneous oxygen tention measurement on limbs of diabetic and non-diabetic patients with peripheral vascular disease. *Surgery* 95:339, 1984.
20. Williamson JR, Ronald E, Hoffman P, Kilo C: Influence of fixation and morphometric technics on capillary basement-membrane thickening prevalence data in diabetes. *Diabetes* 25:604, 1976.
21. Kwasnik EM: Limb salvage in diabetics: challenges and solutions. *Surg Clin North Am* 66:305, 1986.
22. Nielsen PE: Dose diabetic microangiography cause the development of gangrene? *Scand J Clin Lab Invest* [Suppl 128], 31:229, 1973.
23. Strandness DE Jr, Priest RE, Gibbons GE: Combined clinical and pathologic study of diabetic and nondiabetic peripheral arterial disease. *Diabetes* 13:336, 1964.
24. Hall OC, Brand PW: The etiology of the neuropathic plantar ulcer. *J Am Podiatr Med Assoc* 69:173, 1979.
25. Brand PW: Management of the insensitive limb. *Phys Ther* 59:8, 1979.
26. Delbridge L, Ellis CS, LeQuesne LP: Nonenzymatic glycosylation of keration from the diabetic foot. *Br J Surg* 70:305, 1983.
27. Schnider SL, Kohn RR: Glycosylation of human collagen in aging and diabetes mellitus. *J Clin Invest* 66:1179, 1980.
28. Goodson WW III, Hunt TK: Wound healing and the diabetic patient. *Surg Gynecol Obstet* 149:600, 1979.
29. McMurray LF Jr: Wound healing and diabetes mellitus. Better glucose control for better wound healing in diabetes. *Surg Clin North Am* 64:769, 1984.
30. Hamlin LR, Kohn RR, Luschin JH: Apparent accelerated aging of human collagen in diabetes mellitus. *Diabetes* 24:902, 1975.
31. Yue DK, McLennan S, Delbridge L, Handelsman DJ, Reeve T, Turtle JR: The thermal stability of collagen in

diabetic rats: correlation with sensitivity of diabetes and nonenzymatic glycosylation. *Diabetologia* 24:282, 1983.

32. Engel ED, Krlick NE, Davis RH: Diabetes mellitus: impaired wound healing from zinc deficiency. *J Am Podiatr Med Assoc* 71:536, 1981.