The Pathogenesis of Diabetic Foot Problems

An Overview

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Foot ulceration and lower limb amputation are still common complications of diabetes. Diabetic peripheral neuropathy and peripheral vascular disease are the most important etiologic factors, but there is a complex interplay between these abnormalities and a number of other contributory factors, such as altered foot pressures, limited joint mobility, glycemic control, ethnic background, and cardiovascular parameters. Identification of patients at high risk of ulceration is nevertheless simple, and education of such patients can achieve a major reduction in amputation and ulceration rates. ***Diabetes*** **46 (Suppl. 2):S58–S61, 1997**

The diabetic foot can present with many different problems, but the most important clinically are ulceration, amputation, and Charcot neuroarthropathy. These problems will be the focus of this review. Many diabetic complications have a great impact on the foot, and it is therefore not surprising that diabetic foot problems account for more hospital inpatient days than do any other diabetic problems (1). Diabetic neuropathy and peripheral vascular disease are the main etiologic factors in foot ulceration and may act alone, together, or in combination with other factors, such as microvascular disease, biomechanical abnormalities, limited joint mobility, and increased susceptibility to infection. A thorough understanding of the contributory factors that lead to foot ulceration and amputation is essential for successful treatment of established pathology. Perhaps more importantly, as the role of education and appropriate footwear in preventing ulceration and amputation is now established, accurate identification of high-risk patients on whom these services can be focused is vital.

PERIPHERAL VASCULAR DISEASE

Atherosclerotic vascular disease is probably present (at least in a subclinical form) in all patients with diabetes of long duration. The basic pathophysiology of atherosclerosis is no different in diabetic than in nondiabetic patients and is characterized by endothelial damage followed by platelet aggregation, lipid deposition, and smooth muscle proliferation with plaque formation. The same risk factors also operate and include smoking, hypertension, dyslipidemia, abnormal fibrinolysis, and altered platelet function (2). These risk factors, however, do not fully explain the huge excess of vascular disease in diabetes, and attention has recently focused on endothelial dysfunction and particularly adhesion molecules. Binding of monocytes, leukocytes, and platelets to the endothelium is one of the earliest steps in the pathogenesis of atherosclerosis and is promoted by adhesion molecules. Such molecules have now been found to be elevated in diabetes (3) and especially so in patients with microalbuminuria (4).

Like other forms of macrovascular disease, peripheral vascular disease (PVD) is more common in diabetes. The Framingham study found a 50% excess of absent foot pulses in diabetic women and a nonsignificant 23% excess in diabetic men (5). In another study using Doppler pressures, PVD was found to be 2.5 to 3 times more common in diabetic than in nondiabetic subjects (6). Only women with type 1 diabetes did not have more PVD than control subjects.

The distribution of vascular disease in the lower limb is thought to be different in diabetes, with more frequent involvement of vessels below the knee. Surprisingly, there are few good studies available to support this widely held belief; but in diabetic patients with vascular disease, Strandness et al. (7) reported that two-thirds of the patients had infrapopliteal diseases, and King et al.(8) found that involvement of the profunda femoris was increased in diabetes. A recent detailed study of angiograms (9) demonstrated that among patients requiring angiography, proximal disease was equally common in diabetic and nondiabetic subjects, but calf vessel stenoses were about twice as frequent in diabetic subjects. Although PVD is more prevalent among the diabetic population, once established it does not progress any more rapidly than does PVD in the nondiabetic population (10). The difficulties posed by the distribution may be further complicated by a reduced ability to develop a collateral supply; despite these problems, revascularization procedures are frequently successful, although they may require a more distal anastomosis.

In the pathogenesis of ulcers, ischemia is a major factor in 38–52% of cases (11,12), and Pecoraro et al. (13) attributed 46% of amputations to ischemia. Spontaneous ischemic ulceration is rare, and the usual trigger is minor trauma. Injury leads to increased demands on the circulation that cannot be met, and ischemic ulceration and risk of amputation follow.

DIABETIC NEUROPATHY

Somatic neuropathy. Chronic sensorimotor peripheral neuropathy is one of the most common long-term complications of diabetes affecting at least one-third of older diabetic patients in the U.K. according to a recent survey (14). Its onset is insidious, and data suggest that only 13–15% of patients with objective evidence of neuropathy have any symptoms (15). Thus, progression to the insensitive foot at high risk of ulceration can occur without the patient being

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PVD, peripheral vascular disease; TGF, transforming growth factor.

aware of any disorder. Identification of the neuropathic foot at risk of ulceration therefore relies on careful examination. The presence of neuropathic pain does not, of course, mean that sensation is intact; usually the opposite applies, and positive neuropathic symptoms are accompanied by reduced or absent sensation, rendering the foot at high risk of ulceration. The high-risk foot typically has reduced or absent sensation to painful, thermal, and vibration modalities. Moreover, the motor component leads to small-muscle wasting with a consequent imbalance of flexor and extensor muscles, leading to clawing of the toes and prominence of the metatarsal heads.

Peripheral somatic neuropathy has been associated with foot ulceration in several cross-sectional studies (16,17), and its central role in ulceration has been confirmed by a recent prospective study. Young et al. (18) showed that in a population free of significant PVD, peripheral neuropathy as measured by vibration perception using a biothesiometer was associated with a sevenfold increase in the risk of foot ulceration during a 4-year follow-up period.

Autonomic neuropathy. Sympathetic dysfunction affecting the lower limbs leads to reduced sweating and results in dry skin that is prone to crack and fissure. It also increases blood flow (in the absence of large vessel PVD), with arteriovenous shunting leading to the warm foot. It can also markedly reduce toe blood pressure (19). The insensitive foot is, therefore, often warm, which results in a false sense of security as the patient believes that because the circulation is intact, the risk is minimal.

It must be pointed out, however, that the neuropathic foot does not ulcerate spontaneously: it is the combination of neuropathy and trauma, whether extrinsic from, for example, ill-fitting footwear or intrinsic from repetitive pressure on the metatarsal heads during walking that results in tissue breakdown (20).

OTHER RISK FACTORS FOR FOOT ULCERS

Biomechanical aspects. The trauma required to ulcerate the neuropathic foot can take several different forms. Sometimes it is a single event, such as stepping on a nail, but more frequently it occurs as repeated minor trauma, such as unperceived shoe rubbing to the toes or increased pressure beneath the metatarsal heads during walking. A number of studies have clearly demonstrated that dynamic plantar foot pressures are elevated in diabetic neuropathy and especially in patients with a history of plantar ulceration (20,21). More importantly, a prospective study has shown that elevated plantar pressures are predictive of ulceration, with 17% of patients with high foot pressures developing plantar ulcers during a 30-month follow-up period, while no plantar ulcers developed in patients with normal pressures (22). The presence of callus (produced in response to pressure) may exacerbate the problem, both by acting as a foreign body and by increasing plantar pressures. The presence of callus has been shown to be the strongest single predictor of plantar ulceration (23), and its removal significantly reduces foot pressures (24).

The main cause of increased pressure is thought to be the alteration in foot shape that results in prominent metatarsal heads. Atrophy of the intrinsic muscles of the foot (predominantly plantar flexors of the toes) alters the flexor/extensor balance at the metatarso-phalangeal joints, causes clawing of the toes, and may be associated with subluxation at the metatarso-phalangeal joints. This leads to anterior displacement of the submetatarsal fat pads, and reduced subcutaneous tissue thickness at the metatarsal heads has indeed been confirmed in diabetic neuropathy (25).

A further contributing factor to elevated plantar pressure is limited joint mobility. Glycosylation of collagen results in thickening and cross-linking of collagen bundles. This is manifested clinically as thick, tight, waxy skin and restriction of joint movement. Limited joint mobility of the subtalar joint alters the mechanics of walking and is strongly associated with high plantar pressure (26). Further support for an alteration in the mechanics of walking in neuropathy comes from our own recent data (27), in which peak pressure (the only parameter measured in most previous studies) was found to be much less abnormal than were pressure time integrals, indicating an abnormality in the way that forces are applied to the foot during walking.

Other long-term complications. Patients with retinopathy and nephropathy have been shown to have an increased risk of foot ulceration and amputation (28–30). The pathogenic mechanisms by which other complications lead to ulceration and amputation are not entirely clear, but visual impairment makes it more difficult for patients to identify a lesion at an early stage, and tissue repair is slow in nephropathy because of edema, the frequent coexistence of macrovascular disease, and immunological abnormalities. Thus, such patients must always be regarded as being at high risk.

Previous foot ulceration. Several studies have confirmed that foot ulceration is more common in those patients with a past history of ulceration or amputation and in patients with a poor social background.

Diabetes duration and control. Several studies, including a recent large case-control study in the U.S. (30), have demonstrated that poor glycemic control as measured by HbA_{1c}, fasting blood glucose, and even a single random blood glucose is strongly predictive of subsequent amputation.

Race. Lower-extremity amputation rates have been shown to be high among several groups of American Indians (28,32,33), and although these studies have not measured the rate among white Americans, comparison with other data indicated an excess risk in most of these populations. This is most marked in the Oklahoma Indians (33), whose amputation rate is more than four times higher than that in the general U.S. diabetic population. Studies in the U.K. have shown lower incidences of amputation and foot ulceration in the Asian than in the white population (34,35). Data on the rates in black patients are rather scanty. Most and Sinnock (36) reported that amputation was performed more than twice as frequently in black compared with white diabetic patients, but Selby and Zhang (30) recently found no difference in a population with good access to health care. Unfortunately, none of the studies of ethnic groups directly addresses the reasons for the reported differences. Access to health care seems an unlikely explanation for all of these findings, and biological variation between races is probably important.

Cardiovascular factors. Several prospective studies have linked hypertension with amputation (30,33), and although this was not confirmed in Pima Indians or middle-aged Finnish subjects (28,29), a similar nonsignificant trend was apparent in both of these populations. Neither lipid abnormalities nor, surprisingly, smoking appeared to predict amputation.

Behavioral/psychological factors. Despite the fact that causal pathways to ulceration are well recognized and that many high-risk patients receive education, ulceration remains common. It has been suggested that denial of risk is the main reason for this, and indeed Walsh et al. (37) have previously published a series of cases demonstrating extreme denial in foot ulcer patients. However, in our own prospective study of psychological factors in foot ulceration (38), measures of denial have failed to predict ulceration. In contrast, neuropathic patients developing ulcers showed a more negative attitude toward the feet, and their belief in the efficacy of advice was lower compared with patients who did not develop ulcers.

Wound healing. Slow wound healing and increased susceptibility to infection increase the problems of foot ulceration and may predispose to amputation. A number of inherent immunological abnormalities have been documented in diabetes, and several studies have shown an increased infection rate in postoperative wounds (39). Neutrophil function is impaired, with abnormalities of adherence, chemotaxis, phagocytosis, and killing ability (40), and these may be partly due to ascorbic acid transport defects (41). We have recently looked at transforming growth factor (TGF)-β in diabetic foot ulcers, as TGF-β is known to be central to the process of wound healing (42). We observed that there was a failure of upregulation of TGF-β_1 in and around diabetic foot ulcers, despite the obvious requirements for tissue repair. There was also a suggestion that TGF-β_1 was present at lower levels in diabetic than nondiabetic skin.

Another factor that may be important in the development of ulceration is the tissue response to trauma. Recent interesting work from Exeter, U.K. (43), has shown increased capillary fragility in the feet of neuropathic patients with a history of ulceration compared with those of neuropathic control subjects. As hemorrhage into callus commonly precedes ulceration, this may be an important finding.

CHARCOT NEUROARTHROPATHY

A Charcot joint is characterized by the simultaneous presence of bone and joint destruction, fragmentation, and remodeling. Diabetes is the most common cause of the Charcot foot, and most patients have a dense neuropathy but good circulation (44). Early animal experiments suggested that walking on an insensitive limb could lead to joint destruction (45). Excessive and repetitive stress to bones leads to microfractures, which render the bone more brittle and could lead to joint destruction (46). However, the degree of bone destruction often seen in the absence of major injury has suggested an underlying bone abnormality. Diabetic neuropathy leads to an increase in bone blood flow (47), which may promote osteoclastic activity and bone resorption. Indeed, recently Selby et al. (48) have shown a 16% reduction of bone mineral density in the lower limbs of patients with a Charcot foot compared with neuropathic control subjects. A full understanding of the pathological process leading to the often dramatic and progressive destruction seen in this condition has not yet been reached, and as the condition is rare and usually presents late, the opportunities for further studies are limited.

CONCLUSION

Although the roles of peripheral neuropathy and PVD are now well established as the main etiologic factors in diabetic foot ulceration, there is much work to be done both in the way in which ulcers develop and in the interactions of the main risk factors with each other and with the other risk factors discussed in this article. However, this complexity should not deter the clinician, as it is now very clear that simple clinical tests will identify patients at risk of ulceration and amputation and that appropriate but simple education about foot care can greatly reduce the likelihood of developing diabetic foot problems.

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