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DIABETIC PERIPHERAL NEUROPATHIES

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Introduction

Limb amputations are among the most dramatic of medicial events from an individual and social perspective. Annually in the United States, there are approximately 85,000 limb amputations caused by a non-traumatic condition. Diabetes and diabetic foot ulcers are responsible for about 87% of these amputations, and the cost of care for this one complication alone exceeds $10 billion per year. Diabetic neuropathy, which is the most common form of neuropathies in the world, is the major cause and contributing factor to the development of foot ulcers and joint deformities (Figure 1), as well as limb threatening ischemia.

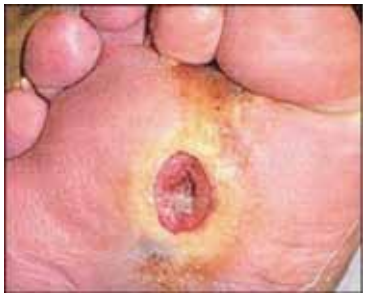

Figure 1. Diabetic foot ulcer.

With the alarming and increasing rate of obesity and diabetes across all ages, ethnic groups, genders, and educational levels, the global health care cost associated with this disease and its chronic complications is very high and rising. It is estimated that a 15- to 20-pound weight gain increases an individual's risk of developing diabetes by approximately 120%.

This view is enforced by the increasing recognition that individuals with even mild diabetes or impaired glucose tolerance, impaired fasting glucose, and metabolic syndrome may be at a greater risk for developing diabetic complications. The current diagnostic threshold for diabetes, however, may have limited sensitivity for early identification of individuals with the disease and its complications, and future revision in these criteria may be necessary. Accordingly, the prevention, early recognition, and treatment of diabetes and its complications, of which neuropathies are the most frequent, assumes a major role in the management of patients with diabetes.

Defining Diabetic Neuropathy

Diabetic neuropathy is not a single entity; it assumes several forms with varied clinical presentations and manifestations. It is therefore best to refer to these conditions as "diabetic peripheral neuropathies" rather than "diabetic peripheral neuropathy." As was agreed by The San Antonio Consensus Conference on Diabetic Neuropathy in 1988, diabetic neuropathy is defined as "the presence of symptoms or signs of peripheral nerve dysfunction in people with diabetes *after exclusion of other causes*." It cannot be overemphasized that diabetes is a very common disorder that may coincide with other conditions causing peripheral neuropathies, and the mere association of neuropathic symptoms with diabetes is not sufficient to diagnose the neuropathy as diabetic neuropathy. Other etiologies should always be sought and excluded.

The two major categories of diabetic peripheral neuropathies can be grouped into focal/multifocal and diffuse. The clinical manifestations, pathology, and mechanism of the pathogenesis of these neuropathies

are entirely different. In focal/multifocal neuropathies, a single or multiple nerve(s) are involved, including cranial nerves (especially the 3rd and 7th cranial nerves), intercostal nerves (thoracoabdominal nerves, Figure 2), the median nerve at the wrist/ulnar and the radial nerve, lateral femoral cutaneous nerves of the thigh, femoral nerves, the peroneal nerve, and the medial and plantar nerves of the feet. The lumbosacral nerve plexus can also be involved in a focal and asymmetric pattern.

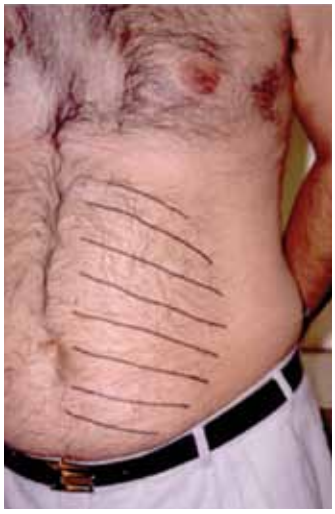

Figure 2. Diabetic thoracoabdominal neuropathy. The shaded area is painful with reduced sensation to pin prick.

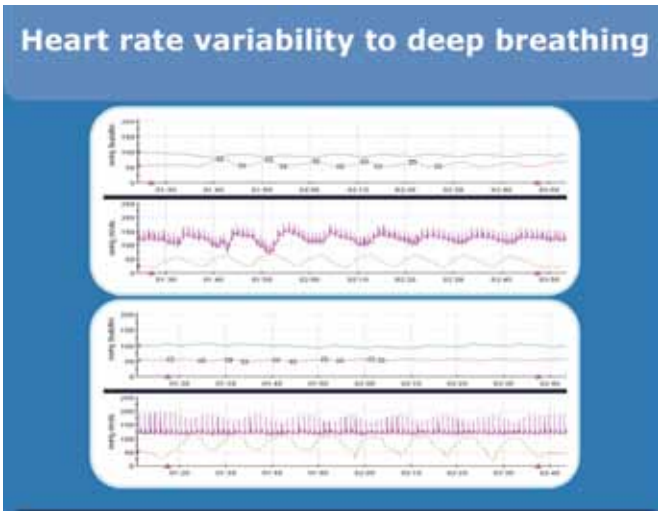

Figure 3. Impaired heart rate variability to deep breathing in diabetic autonomic neuropathy (lower panel); upper panel is normal.

The nerves of the diabetic patients are, in general, more susceptible to compression and entrapment than those without diabetes leading to mononeuropathies. For example, carpal tunnel syndrome is three times more frequent in diabetics than in the normal population. Of the diffuse or generalized neuropathies, diabetic polyneuropathy (distal symmetrical polyneuropathy) is the most common form, comprising 90% of all diabetic neuropathies. It produces generalized but distally predominant and relatively symmetric dysfunction of peripheral nerves with sensory functions being affected more than motor function. It is in this form of neuropathy that complications such as foot ulcers and joint abnormalities are often observed. The autonomic nerves may also be diffusely and symmetrically involved and affect any body system or organ; in particular, sudomotor and vasomotor, cardiovascular, gastrointestinal, and genitourinary systems can be affected. Both sympathetic and parasympathetic nerves are involved to varying degrees and combinations. Cardiac autonomic neuropathy is the earliest manifestation of generalized autonomic dysfunction (Figure 3).

Contrary to common belief, most patients with diabetic polyneuropathy remain asymptomatic, with the examination and tests of nerve function often revealing the neuropathy. Those with symptoms often complain of sensory symptoms including a burning and/or tingling sensation, pain, and hypersensitivity of the feet. The sensory disturbances typically assume a stocking-glove distribution and follow a length-dependant pattern, with the toes and the feet, innervated by the longest nerves in the body, being affected early and more severely. This gradually spreads proximally; when it reaches the above-knee level, the fingers and hands innervated by the body's second-longest nerves become affected. In more advanced cases, sensation becomes impaired over the anterior chest and abdomen area involving the intercostal nerves (the third-longest nerves), producing a truncal wedge-shaped area of sensory loss (Figure 4).

The knowledge of the length dependency of diabetic neuropathy is important in differentiating this condition from other disorders that cause sensorymotor symptoms. For example, if a patient complains of sensory and/or motor symptoms involving the legs but not the arms, the diagnosis of diabetic neuropa-

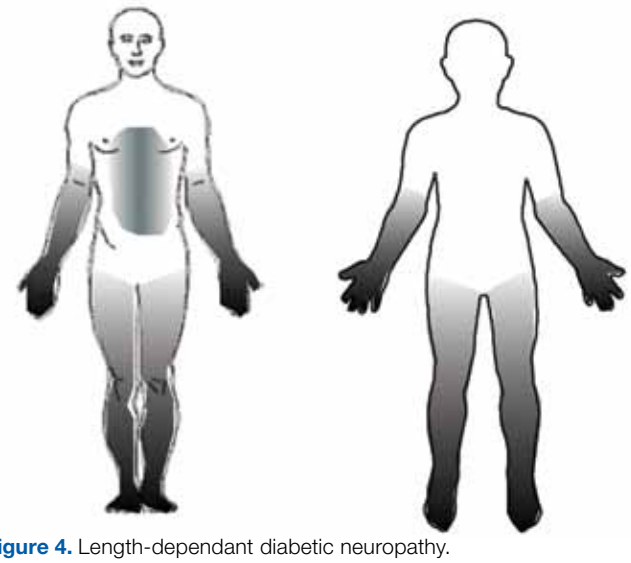

Figure 4. Length-dependant diabetic neuropathy.

thy will be unlikely and other etiologies such as the spinal cord and nerve roots pathology should be investigated. In diabetic polyneuropathy, the smaller nerve fibers that convey pain sensation and autonomic function are often involved, but the dysfunction of the larger nerve fibers that subserve motor function, vibratory, and position sensation may also be present. In general, and depending on the stage of the disease, diabetic neuropathy frequently forms a continuous spectrum ranging between small fiber and large fiber neuropathy. When a significant and predominant large nerve fiber is involved, distal and painless paresthesia will predominate and muscle stretch reflexes are diminished. In advanced cases, significant ataxia may develop due to sensory deafferentation.

Risk Factors of Diabetic Neuropathy

Although the duration of diabetes and degree of metabolic control remain the two major predictors of the development and severity of diabetic polyneuropathy, other risk factors are involved. Older patients, males, those who are taller, hypertensive, or hyperlipidemic, and those who consume excessive alcohol or use tobacco products are at greater risk for developing neuropathies. Intuitively, reduced alcohol consumption, cessation of tobacco use, and treatment of hypertension and hyperlipidemia should delay the development of neuropathy and/or moderate its severity. Genetic factors also may play a role in an individual's susceptibility. Aldose reductase gene (AKR1B1) polymorphisms have been implicated in the early development of neuropathy and the rate of decline of nerve function. This enzyme plays an important role in the pathogenesis of diabetic neuropathy (see below). The severity, but not the development, of diabetic neuropathy may also be related to the presence of E3/4 and 4/4 APOE genotype. Having this genotype is the equivalent of having 15 extra years of age or diabetes duration in terms of neuropathic risk. APOE genotype may influence the severity of neuropathy by accelerating atherosclerosis of blood vessels supplying the peripheral nerves. The presence of the D allele of the angiotensin I-converting enzyme (ACE) is also reported to be associated with increased risk of peripheral neuropathy in type II diabetes. Curiously, this effect is observed only in diabetic women. The role of angiotensin II, which has a pro-oxidant and pro-inflammatory property, has been implicated in the development of vascular complications of diabetes in several studies. ACE, by catalyzing the conversion of angiotensin I to angiotensin II, facilitates this process. The benefits of ACE inhibitors in delaying the progression of complications of diabetes, including nephropathy, retinopathy, and possibly neuropathy, is now well-established. Women who have the

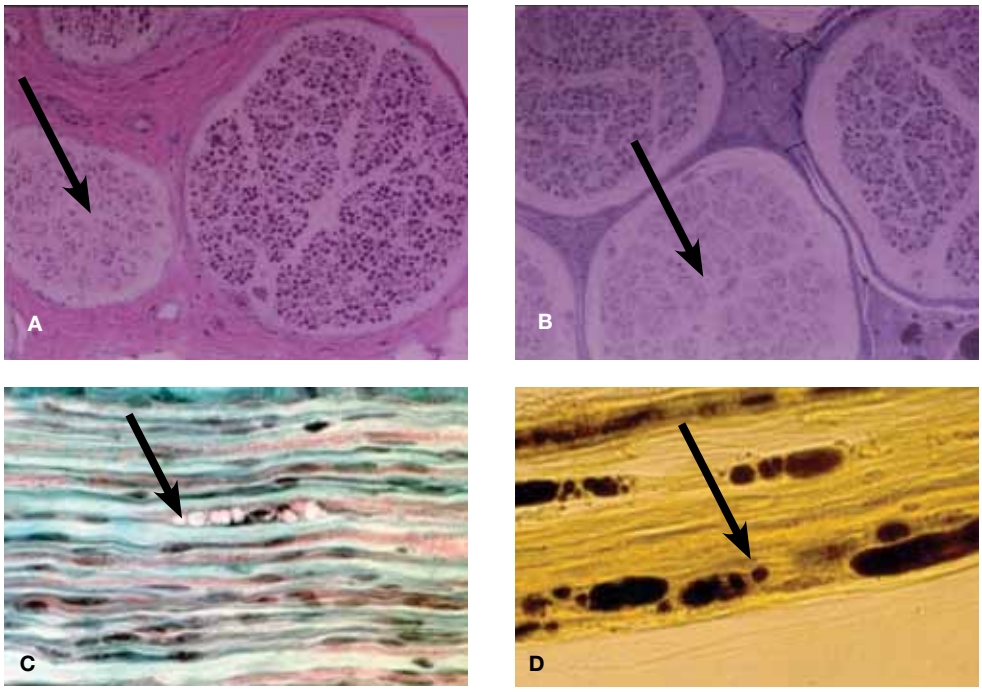

Figure 5. Pathology of diabetic neuropathy. A (hematoxylin- and eosin-stained section) and B (semi-thin section) show selective nerve fascicle degeneration (arrow) caused by vascular abnormality and ischemia. C (longitudinal section of nerve stained with modified Gomori's Trichrome) and D (teased nerve fibers) show myelin breakdown due to axonal degeneration (arrows).

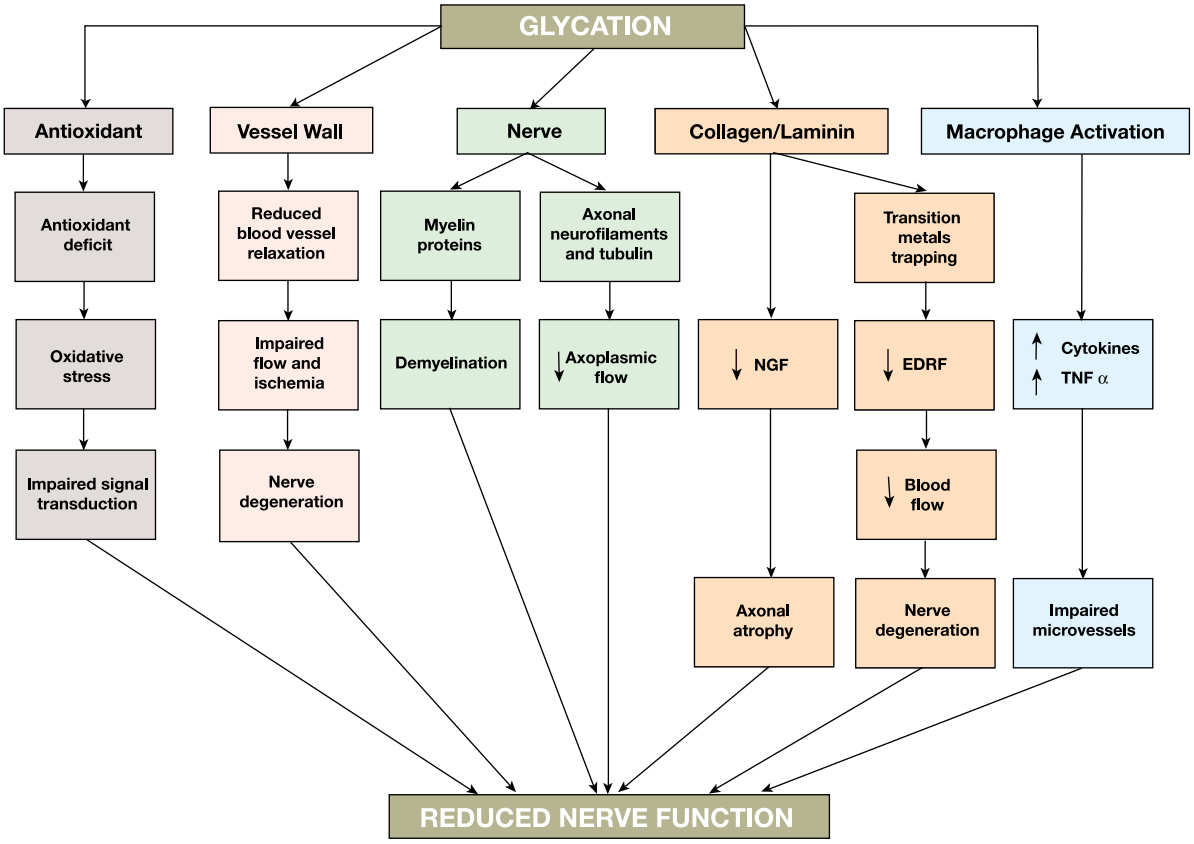

Figure 6. Glycation as the pathogenesis of diabetic neuropathy.

D allele of the ACE gene have the higher ACE activity; hence, the more angiotensin II effect, the more progression of micro- and macrovascular complications. Why gender is a risk in the ACE genotype is not clear, but modulation of ACE activity by estrogens — resulting in a relatively higher ACE level — remains a plausible explanation. The suggested role of genetic factors in the development and severity of diabetic neuropathy, and the knowledge that less than half of diabetic patients do not develop any of the complications even after 25 years of diabetes, necessitate further longitudinal studies in large numbers of patients to identify predictor or protective factor that influence diabetic complications.

Pathogenesis

The pathogenesis of diabetic neuropathies cannot be explained by a single mechanism. Most of the current knowledge has been derived from studies of several animal models of diabetic neuropathy. However, no ideal animal model that could address both the acute and chronic aspects of the disease exists. Within these limitations, several mechanisms for the pathogenesis of diabetic neuropathies have been proposed, but none have achieved general acceptance. For focal and multifocal neuropathies, an ischemic/vascular and/or a compressive process may explain the nature of these neuropathies. The vascular changes that lead to impaired nerve circulation may result from the metabolic derangement of hyperglycemia and/or advanced atherosclerosis. For generalized polyneuropathies with gradual progression, a number of metabolic derangements have been implicated in their pathogenesis (metabolic hypothesis). Some of these hypotheses include accumulation of sorbitol through activity of aldose reductase, increased oxidative stress and glucose auto-oxidation, reduced nerve sodium-potassium-ATPase, and non-enzymatic glycation of proteins. Involvement of the nerve microvasculature (vasa nervorum) has also been implicated as the primary pathogenic factor in diabetic polyneuropathy (vascular hypothesis) (Figure 5).

Undoubtedly a close interrelationship among these various hypotheses exists, but the precise detail of these interactions remains unknown. The formation of advanced glycation end products (AGEs) through the slow process of non-enzymatic glycation of various proteins may serve as a unifying bridge between the vascular and metabolic hypotheses explaining many of the diabetic complications, including neuropathy (Figure 6).

The AGEs are formed when irreversible binding of high levels of glucose to various extracellular and intracellular proteins occurs. These products eventually alter the structure and function of a vast array of proteins and enzymes, leading to their dysfunction. The accumulation of glycated proteins in areas such as endothelial cells, basement membrane, or elastic lamina leads to vascular dysfunction. This causes impaired blood vessel relaxation, reduced nerve blood flow, nerve hypoxia or other nutritional deficiencies, and ultimately nerve degeneration. Binding of glucose to proteins also occurs with DNA and various crucial enzymes including antioxidants — leading to their deficiency, dysfunction, or ineffectiveness and further tissue damage. When AGEs are formed in the peripheral nerves and intra-axonal structures, both axonal transport and nerve function become impaired. The degree of the accumulation of these products in the different structures of the peripheral nerve correlates with the degree of nerve fiber loss. The accumulation of AGEs in the vessel wall also results in increased macrophage recognition and uptake and stimulation of macrophage-derived and other growth factors, leading to smooth muscle proliferation, atherogenesis, and further nerve hypoxia.

If the accumulation of AGE is responsible for initiating cascades of metabolic, physiologic, and structural abnormalities in various tissues, including peripheral nerve, would the inhibition of AGE formation prevent or ameliorate these complications? Unfortunately, there are no compounds that effectively, specifically, and in a non-toxic fashion inhibit the glycation reaction, and the experience with compounds such as aminiguanidine or pyridoxamine have been generally disappointing.

Regardless of how vascular abnormalities begin in diabetes, they exert a profound effect in the nerve function. Patients who have diabetes and lower limb vascular insufficiency tend to have a more severe neuropathy than patients without ischemia. However, the structural microvascular and electrophysiological abnormalities seen in diabetic neuropathy are late occurrences, and the earliest derangements are generally metabolic resulting from direct exposure of nerve to glucose, where, unlike other tissues, its uptake and transfer does not require insulin. It is in the metabolic phase that early therapeutic interventions may prove effective; however, when the structural abnormalities are established, such interventions are often ineffective.

There is considerable evidence supporting the association between good diabetic control and less-severe peripheral nerve complications. Management of hypertriglyceridemia, an increasingly recognized risk factor for neuropathy, is also essential. Experience with a variety of aldose reductase inhibitors, growth factors, vasodilators, and antioxidants or protein kinase C inhibitors are either disappointing or have yielded minimum benefit in the treatment of neuropathy.

Although pain in diabetic neuropathy occurs in only 10% of patients, treatment remains a challenging problem. Many drugs are used to treat painful diabetic neuropathy, but none have achieved a therapeutic benefit beyond 30% above placebo. In general, the current strategies used for treating neuropathic pain are aimed at one or several of the following: reducing afferent input, sympathetic activity, and inflammation; reducing release of excitatory amino acids and blockage of their receptors; blocking nerve sodium channels; decreasing protein kinases; and increasing central inhibition of pain. To achieve these goals, several classes of drugs — alone or in combination — are usually employed, including antidepressants, anticonvulsants, NMDA antagonists, anti-arrhythmics, neurokinin receptor antagonists, anti-inflammatory drugs, and sometimes narcotic analgesics. Since marked variations in the serum glucose level and the episodes of hyperglycemia may enhance the pain perception in diabetic neuropathy, maintaining a steady level of glycemic control is essential in pain management.

Despite significant progress in understanding the clinical aspects of diabetic neuropathies, many questions remain unanswered in terms of causation, risk factors and genetic susceptibility, efficacy of treatment, restoration of nerve function, and pain management. We strive to find answers to these questions and, ultimately, eradicate diabetes and its complications.

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