Myopathies Related to Diabetes Mellitus and Other Metabolic Diseases

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ABSTRACT

Although it has long been known that both large and small blood vessels are abnormal in the tissues of diabetic patients, recent work has emphasized the widening of capillary basement membranes in diabetic tissues. Current views of the nature of this lesion and its relationship to diabetes are discussed and diabetic muscle and nerve lesions are emphasized. Other metabolic diseases with significant muscle pathology are types II, III and VII glycogen storage diseases. Myopathy with abnormal mitochondria is reviewed.

In recent years, the concept of diabetes mellitus as a disease consisting solely of the consequences of insulin deficiency have been challenged by new data. Although hyperglycemia can be controlled successfully, many of the so-called “complications” of this disease are not significantly reduced. No attempt will be made to survey the entire diabetic syndrome involving all the complexities of islet cell function or the responses of all the target organs. Instead, this paper is limited to some aspects of microangiopathy particularly as they affect striated muscle, some data concerning pathologic changes in diabetic nerves and neuromuscular junctions and limited material on some other kinds of metabolic myopathy.

Microangiopathy

It has long been known that small vessels are abnormal in the tissues of diabetic patients. The characteristic vascular lesion consisting of endothelial proliferation is confined primarily to precapillary arterioles and capillaries. In more recent years, attention has been directed to the capillary basement lamina, a layer of amorphous material chemically resembling collagen that coats the exterior of the endothelial cells. This layer is located between the blood carrying oxygen and nutrients and the tissues. Widening of the capillary basement lamina in skeletal muscle biopsies from diabetic patients was reported by Zacks et al and extensively confirmed and quantitized subsequently by several investigators. Characteristically, the endothelial cells appear unremarkable but the basement lamina is greatly widened and often redundant and laminated with various materials interspersed between the lamina. Not all the capillaries in a given muscle are uniformly involved. There is apparent increase in severity of capillary basement membrane widening in muscles distal to the inguinal region. There is also evidence that basement membrane widening is segmental in a given capillary. Most investigators agree that though not entirely specific, this change is strongly associated with the diabetic syn-
drome. Siperstein et al\textsuperscript{16} claimed a 98 percent incidence of capillary changes whereas in a more recent review by Williamson et al\textsuperscript{21} a 62 percent incidence in all diabetics and 63 percent in insulin dependent diabetics was found. These investigators reported that there is a highly significant correlation between the incidence of capillary basement membrane widening and duration of carbohydrate intolerance in insulin dependent diabetics.

There is quite considerable controversy as to whether or not the capillary changes can be identified in so-called pre-diabetics. Additional data has recently been provided by Pardo et al\textsuperscript{14} who reported on the incidence of capillary basement lamina changes in juvenile diabetics. These investigators found that the mean minimal basement lamina thickness was significantly increased in skeletal muscle capillaries although there was considerable overlap of individual values with the control data. The data obtained in this study support the idea that involvement of the capillaries is a late, rather than early, phenomenon in diabetic patients which occurs after prolonged, clinically manifest diabetes. It should be stressed that the entire capillary bed appears to be affected and that lesions in skeletal muscle, fat, pancreas and peripheral nerve capillaries are similar to the changes that occur in the more clinically important ocular and renal lesions.

In recent years, a pathogenetic mechanism to explain the layering of the basement lamina in the capillaries has been offered by Vracko and Benditt.\textsuperscript{20} These investigators have suggested that layering results from repeated episodes of endothelial and pericyte regeneration following repeated episodes of cell death and replacement. Thus, as this cycle is repeated, layers of basement lamina are added. These authors\textsuperscript{20} reject the alternative possibilities of sequential or periodic excessive synthesis and secretion of basement lamina or possibly defective resorption of basement lamina. Although the suggested mechanism that the basement lamina serves as a scaffolding for regenerating cells is well known in the case of peripheral nerve (Schwann cell tube) and skeletal muscle, its applicability to capillary endothelium is not established. The apparent absence of degenerating endothelial cells with or without microhemorrhages in myofiber capillaries appears not to support the hypothesis. In any event, the abnormal production of basement lamina appears to be widespread in the capillary bed of patients suffering from diabetes mellitus and these capillary abnormalities have important consequences with respect to many of the lesions that occur in this disease.

**Diabetic Amyotrophy**

Pain and weakness of the lower extremities and muscular atrophy are characteristic symptoms and signs of muscle disease in diabetic patients.\textsuperscript{8,11} As described by Garland,\textsuperscript{8} diabetic "amyotrophy" consists of bilateral asymmetric atrophy and weakness of proximal muscles of the lower limbs accompanied by pain. It is found in older male diabetic patients and often does not correlate very well with treatment. Deep tendon reflexes and sensation may be normal or reduced. According to this author,\textsuperscript{8} diabetic amyotrophy may be distinguished from the common form of diabetic neuropathy since amyotrophy is usually asymmetrical and the ataxia, trophic changes and sensory abnormalities that accompany diabetic neuropathy are absent. This has been challenged by Gregersen\textsuperscript{10} who has suggested that amyotrophy is a manifestation of diabetic neuropathy.

In our early description of capillary changes in diabetic muscle,\textsuperscript{24} the authors described subsarcolemmal vacuolar degeneration and focal myofilament loss. Locke et al\textsuperscript{12} described atrophy of individual myofibers and occasional amorphous of granular myofibers lacking striation scattered throughout the muscle bundles. Bloodworth and Epstein\textsuperscript{3} preferred the term degeneration to describe the changes in diabetic myofibers. In this ultrastructure study, the authors\textsuperscript{3} found fragmentation and loss of
myofilaments, disorganization of striations and abnormal sarcoplasmic reticulum and mitochondria. Occasionally smudging and smearing of Z bands, a non-specific change also found in denervation atrophy, myositis and forms of myopathy, were found in the diabetic muscle. Thus, the muscle lesion in diabetes may be part of a general, genetically transmitted disorder in diabetic cells that make them abnormally vulnerable to injury. The pathologic pattern does not suggest denervation atrophy. There is insufficient physiologic data to evaluate the role of ischemia or possible alteration in diffusion of macromolecules across the abnormal capillary basement lamina to explain the pathogenesis of the muscular lesion.

Tomonaga et al\textsuperscript{18} found that myofiber atrophy in diabetic amyotrophy primarily involved type II myofibers, and these investigators also described changes in the Z band. Furthermore, there were changes in mitochondria, accumulation of glycogen and also abnormalities in the intramuscular nerve branches. They concluded that diabetic amyotrophy is a non-specific manifestation of diabetic neuropathy. It is of interest that Tomonaga et al found that type II myofibers were particularly affected because type II myofiber atrophy occurs under conditions of denervation, disuse or malnutrition. It has been suggested that a neural trophic factor may be involved in type II myofiber atrophy.

The symptoms and signs of diabetic neuropathy have been extensively described in the clinical literature. However, it was not until the work of Woltman and Wilder\textsuperscript{22} that the degeneration of peripheral nerves was described in a detailed pathologic study. Fagerberg\textsuperscript{7} studied several sural nerve biopsies from diabetics with particular reference to staining of the blood vessels with the PAS method and Dolman\textsuperscript{5} studied neural tissue from 36 diabetic patients and suitable controls. In this study of autopsy material, dorsal column degeneration was found in 15 of 34 spinal cords, with maximal changes in the lower segment and marked atrophy of posterior roots with demyelination was found.

The peripheral nerves were the site of patchy demyelination with persistence of axon cylinders in many specimens. Electron microscopic studies of peripheral nerve biopsies from 15 diabetic subjects, including 3 juveniles, by Bischoff\textsuperscript{2} revealed thickening of Schwann cell basement membrane and accumulation of phospholipid material within the cytoplasm of Schwann cells. It was concluded that diabetic neuropathy is primarily due to a defect of Schwann cells. Similarly, Thomas and Lascelles\textsuperscript{17} and Ballin and Thomas\textsuperscript{1} concluded that the segmental demyelination in the peripheral nerves of diabetic subjects, some with hypertrophic changes similar to those observed in hypertrophic neuropathy, is probably due to abnormal Schwann cells. The segmental nature of the demyelination supports this concept.

**Metabolic Myopathies**

Other important diseases of abnormal carbohydrate metabolism involving skeletal muscle include the various forms of glycogen storage disease. These are characterized by abnormal accumulations of glycogen resulting from a defect in certain specific enzymes. Four of these syndromes affect skeletal muscle. They include acid maltase deficiency in type II glycogenesis (Pompe's disease), deficient debrancher system in type III glycogenesis (Cori's disease) and phosphofructokinase deficiency in type VII disease.\textsuperscript{15} Light microscopic study of affected muscles reveals increased accumulation of glycogen in type II disease where there is massive accumulation of glycogen throughout the myofibers visible as PAS stained granules that are sensitive to diastase and in type III disease, subsarcolemmal glycogen aggregates without massive increase in glycogen deposits between the myofibrils. Similar collections of glycogen occur in skeletal muscles of patients with types V and VII glycogen storage diseases.
In type V disease, there is deficiency of phosphofructokinase. This may be specifically diagnosed by suitable histochemical methods for the demonstration of phosphofructokinase activity. In type VII disease, phosphofructokinase deficiency is manifest in the form of subsarcolemmal glycogen aggregates. Deficiency in this enzyme may be detected by means of a histochemical staining method. Electron microscopy is required for the more specific localization of the glycogen granules.

Also to be considered among myopathies of metabolic origin are those with abnormal mitochondria. Mitochondrial abnormalities occur in many diseases of skeletal muscle and appear to be non-specific with the exception perhaps, of the patient described by Luft et al\textsuperscript{13} where loosely coupled oxidative phosphorylation was demonstrated biochemically.

References