The Effects of Diabetes on the Development of Atherosclerosis

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Introduction

Patients with diabetes mellitus have a much greater incidence of vascular disease than the normal population. Diabetics not only die at an earlier age than non-diabetics from vascular disease affecting the coronary and cerebrovascular systems, but also suffer significant morbidity from disease affecting the retinal arteries, renal arteries and peripheral arteries. These pathologic changes in the vascular beds account for 75% of deaths in diabetic patients.1

Despite considerable research, the exact mechanisms responsible for acceleration of atherosclerosis in diabetes mellitus remain unclear. Insulin deficiency in laboratory animals induces many metabolic and pathologic changes identical to those in man. Biochemical and rheological factors also play a role in the progression. Genetic factors certainly modulate the development and progression of vascular disease in diabetics. Relatives of diabetics develop the disease 4–10 times more frequently than relatives of non-diabetics.2 The incidence in monozygote twins is 70% compared to 10% in dizygotic twins.3

It is also unclear that careful control of blood glucose levels will diminish vascular complications. Studies of oral hypoglycemic agents indicate that the combination of diet and these agents is no more effective than diet alone in prolonging life. In fact, the cardiovascular mortality may be higher with these agents.4 Similar clinical studies of insulin failed to produce any decrease in vascular complications, even when prolonged normoglycemia was achieved.5 Contrary to this are animal studies that demonstrate a reduction of diabetic-like lesions in eye, kidney and nerve with reduction of hyperglycemia by insulin.6 This review will attempt to elucidate the clinical patterns of peripheral vascular occlusive disease seen in the diabetic and elaborate on the theories of the etiology of the microangiopathy at the cellular level.

Clinical Patterns of Peripheral Vascular Occlusive Disease in the Diabetic

Arterial occlusive disease can be divided into macro-

angiopathy and microangiopathy. Macroangiopathy results in plaque formation and subsequent obstruction of large and medium-sized vessels and is morphologically indistinguishable from atherosclerosis in the non-diabetic.7 The aortoiliac and femoro-popliteal-tibial arterial systems are the vessels involved in this process. Although their clinical presentation can be similar to nondiabetics, the lesions tend to be more widespread and generally more severe in the diabetic. These patients present with claudication, rest pain or ischemic ulcerations of their feet as do nondiabetics, but the fact that the severity of the disease is greater in the diabetic is evident in a study by Haimovici et al.8 This study revealed that 81% of diabetics had occlusions of the tibio-peroneal vessels as opposed to 57% of non-diabetics. Lower extremity amputation was fifty times more frequent in the diabetic than in the nondiabetic in another autopsy study.9

Microangiopathy is a process which involves the vessel wall of the capillary and precapillary arteriole and venule. This process is unique to diabetics and is most commonly seen in juvenile-onset and insulin-dependent diabetics. There are a number of theories regarding the pathophysiologic basis of this small vessel disease unique to the diabetic. This process affects the vascular beds of the retina, peripheral nerves, kidneys and the distal peripheral arteries. It is the microangiopathy that is felt to play a major role in the development of skin ulcerations and gangrenous changes of the feet.

The diabetic with peripheral vascular occlusive disease is indistinguishable from the nondiabetic if the process is limited to the large and medium sized vessels. The most interesting and frequent clinical presentation of the diabetic is the "diabetic foot." The cellulitis, ulcerations and gangrenous changes in the foot of the diabetic are related to:

1. proximal occlusive disease (macroangiopathy)
2. distal occlusive disease with involvement of the small vessels in the foot (microangiopathy)
3. peripheral neuropathy

The clinical picture involves claudication and rest pain of the foot which is often severe and unrelenting. Distal tibio-peroneal occlusions despite a patent popliteal artery is a common angiographic finding (Figure 1). Skin fragility and atrophy occurs secondary to the microvascular obstruction in conjunction with tibio-peroneal disease and leads to ulceration. Both pathophysiologic processes result in cool feet, delayed venous filling, dependent rubor and ischemic ulcers.
Peripheral neuropathy in the diabetic is a common coexisting problem that can lead to skin trauma and subsequent ulceration. Segmental demyelination of the Schwann cell involving the most distal portion of the nerve results in loss of perception of light touch and pain. This leads to unintentional foot trauma that cannot be healed due to the concomitant vascular disease.

Treatment of patients with macroangiopathy consists of aorto-femoral, femoral-popliteal or femorotibial bypasses. However, if distal disease is present, an adequate outflow bed, including a pedal arch, is often not present. These patients are often not reconstructible and if severe pain or infection cannot be alleviated, amputation is the only option.

Preventative foot care is extremely vital in the diabetic as mild trauma or infections can rapidly lead to limb loss in these patients. Daily foot washings, avoidance of ingrown toenails, wearing properly fitted shoes, treating any fungal infection promptly and obtaining immediate medical attention for even minor foot lesions can result in much less morbidity.

Pathologic Processes

The clinical presentation and treatment of the diabetic is well known. Of interest, however, is the underlying pathologic processes that produce the syndrome of diffuse atherosclerosis and microvasculature involvement. Thickening of the basement membrane is widely accepted as the ultrastructural factor of diabetic microangiopathy, however, its significance remains obscure.

The first reports of diabetic retinopathy led to a great deal of research culminating in the concept of an angiopathy specific to diabetes by Lundbaek in 1953. The electron microscopic evaluation of capillary basement membranes by a number of researchers led to the conclusion that the capillary basement membrane in diabetes is both thickened and altered in chemical composition.

However, there are other changes in the diabetic patient which may contribute to the development of microangiopathy apart from basement membrane thickening. These include endothelial and platelet malfunction, lipoprotein disturbances, altered blood flow properties and disturbed oxygen transport.

1. Basement Membrane Thickening

Many studies have demonstrated that basement membrane thickening occurs as a manifestation of the diabetic state. The exact mechanism behind this thickening is unclear, as is its role in the development of the microangiopathy. Some of the theories include impairment of basement membrane removal resulting in its thickening, and abnormal regeneration of the basement membrane after premature death of pericytes. The thickening of the vascular basement membrane is similar to that seen in the basement membrane of the kidney (Figure 2). Controversy also exists as to whether the thickening of basement membrane is a product of the diabetes, or occurs in
the natural aging process as seen in the elderly nondiabetic.21

3. Platelet Malfunction

Many studies have shown that platelet adhesiveness is greater in the diabetic patient. In vivo studies of platelet and fibrinogen turnover in diabetics have shown that they both disappear more quickly than in nondiabetics. The hypercoagulable state is due to the elevated levels of platelet-produced prostaglandins (PGE2) and thromboxane. In the healthy patient, prostacyclin, a potent vasodilator and antiplatelet aggregating, would counteract the effects of thromboxane. Data now reveal that there is impaired release of prostacyclin from the endothelium of the diabetic.27 Thus, diabetes is characterized by endothelial damage, excessive platelet adhesiveness due to excess thromboxane and decreased prostacyclin.

There is controversy regarding whether platelet changes precede the vascular injury or are a result of the injury. Most studies now indicate the former. Animal models have shown promising results of improved platelet function with good control of diabetes by insulin or pancreatic islet transplantation.28,29

4. Lipoprotein Disturbances

Just as in nondiabetic vascular occlusive disease, abnormalities in lipid metabolism play a major role in the pathogenesis of plaque formation. Elevated plasma triglyceride levels are more commonly found in the diabetic than elevated cholesterol levels. The patient with hypertriglyceridemia has a predictable low HDL-cholesterol level. However, even diabetics with normal triglyceride and cholesterol levels will have low HDL levels.30 This resultant high total cholesterol to HDL-cholesterol ratio favors the deposition of cholesterol in tissues and may play an important role in accelerated atherosclerosis in the diabetic.

Good control of the hyperglycemia will normalize elevated plasma cholesterol levels as well as the HDL-cholesterol ratio. If a coexistent lipoprotein disorder is present, this may require both dietary control and lipid-lowering agents.

5. Altered Blood Flow Properties

Altered rheologic properties can contribute to changes in the microcirculation of the diabetic. As mentioned above, platelet function abnormalities lead to platelet aggregation and enhanced viscosity. Increased erythrocyte aggregation has been documented in vitro and also contributes to altered blood flow properties.

The changes in viscosity and in erythrocyte aggregation can be attributed to altered plasma protein composition by acute phase reactants.31 These proteins are released in response to stress (such as hyperglycemia or infection in the diabetic) and result in a decreased serum albumin level and an increased level in proteins such as fibrinogen. The rheologic changes result in increased flow resistance and subsequent diminished perfusion of the microcirculation and worsening of the clinical picture of the diabetic.
6. Disturbed Oxygen Transport

Even in the presence of unaltered flow, the transportation of oxygen across the cell membranes is disturbed in the diabetic patient. This can lead to relative tissue ischemia with its resultant effects.

In the diabetic, a minor hemoglobin component, hemoglobin A1c (Hb A1c), is increased to levels twice those in normal patients. This molecule has a much greater affinity for oxygen than does hemoglobin without this molecule, and reduces the ability of releasing oxygen to the tissues. 35 Peterson et al. 34 showed that control of diabetes could correct the elevation of Hb A1c and subsequently correct measured functional abnormalities of erythrocytes, leukocytes and platelets.

Erythrocyte 2, 3 DPG content tends to oppose the increased affinity for oxygen by Hb A1c. Elevation of this intracellular phosphate would be expected in the diabetic. In fact, 2, 3 DPG has been measured at higher levels in diabetics with vascular complications 36 indicating that oxygen transportation may play a role in the angiopathy of the diabetic.

Discussion

The fact that diabetics have a higher incidence of vascular disease and its complications is well known. These patients often present in a similar clinical fashion to the nondiabetic when large vessels are obstructed by atherosclerotic plaque. However, diabetics present more frequently with distal disease resulting in a “diabetic foot.” Many theories abound regarding pathophysiologic processes associated with the microangiopathy of the diabetic. No single theory can explain the deterioration in the microcirculation. Thickening of the basement membrane, endothelial and platelet malfunction, lipoprotein disturbances, altered blood flow properties and disturbed oxygen transport may all play a role in the progression of disease. However, it is difficult to separate the pathophysiologic changes that produce the deterioration in the microcirculation from the effects of the microcirculatory dysfunction.

It is interesting to speculate that careful control of the plasma glucose levels may be an important factor in slowing or preventing the progression of atherosclerosis in the diabetic. A number of treatment methods are available, including dietary control, oral hypoglycemic agents, daily insulin injections, and continuous insulin infusion pump. The first study to look at these various therapeutic modalities was by the University Group Diabetes Project. 45 This group found that there was certainly no benefit from oral agents and, in fact, cardiovascular mortality may have been elevated. These studies have been criticized for patient selection but no other study has been able to disprove them. However, certain studies have attempted to show that enthusiastic control of diabetes can reduce the microangiopathy. Retinopathy was shown to be less prevalent in a prospective study of insulin controlled diabetics as compared with the control group. 36 In animal studies, 6 insulin therapy prevented or minimized formation of diabetic-like lesions in eye, kidney and nerve. In biological studies, sorbitol accumulation in nerve, eye and vascular tissue was decreased with insulin treatment. 47

These studies demonstrate that control of diabetes may play an important role in control of the microvascular disease. This is particularly applicable to the juvenile-onset diabetic who is at greatest risk of complications from diabetes.

The controversy in the benefits of good glucose control evokes two points. First, more careful randomized trials are necessary to resolve whether careful glucose monitoring will alter the morbidity from vascular disease in the diabetic. Secondly, assuming that there is some benefit from good control, the development of more physiologic insulin delivery systems or approaches to the correction of the underlying insulin-deficiency mechanism must be pursued with vigor in an attempt to minimize the risk of the diabetic patient with regard to progressive vascular disease.

Medical maneuvers other than glucose control may assist in neutralizing the metabolic abnormalities in the diabetic. Normalizing lipoprotein elevation, diminution of platelet adhesiveness with the use of aspirin, elevation of phosphate levels by its administration and reducing the amount of Hb A1c by careful glucose control may all play a part in the overall reduction of the progression of the microvascular damage.

Further research is required for a better understanding of the mechanisms behind the development of the small vessel disease in the diabetic before we can apply current or future treatment techniques to help control the long-term effects of the disease.

References


