THE COMPLICATIONS OF DIABETES MELLITUS

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The present concept of the pathogenesis of diabetic complications is discussed with particular emphasis on abnormalities in sorbitol and myoinositol metabolism and the effects of glycosylation of proteins.

The modern approach to selected chronic complications of diabetes, particularly those that have serious and troubling implications, are reviewed.

The complications of diabetes fall into two major categories: acute and chronic.

The acute complications of diabetes mellitus are ketoacidosis, nonketotic hyperglycemic coma, and hypoglycemic reactions. These complications can be readily attributed to alterations in the metabolism and in the level of blood glucose.

The chronic complications are retinopathy, nephropathy, neuropathy, and arteriosclerosis. These complications are serious and account for the fact that the diabetic has 25 times the incidence of blindness as the nondiabetic, 17 times the incidence of renal disease, four times the incidence of peripheral vascular disease, twice the incidence of coronary artery disease and stroke, and an almost universal incidence of neuropathy.

The cause of these chronic complications has been disputed for years, but gradually the consensus is that they are a consequence of metabolic alterations subsequent to insulin lack. As a result, the emphasis on tight control as a method of preventing these complications is evident in most clinics in this country.

It is usual to regard retinopathy and nephropathy as due to microangiopathy and coronary artery disease and stroke as due to macroangiopathy (arteriosclerosis).

In trying to explain these complications, three biochemical alterations have moved to the forefront: abnormal accumulation of sorbitol, depletion of myoinositol, and glycosylation of proteins. A relation between sorbitol accumulation, myoinositol depletion, and the activity of the Na^+–K^+ ATPase pump has become evident. The glycosylation of proteins has been clarified so that we now know that some proteins are reversibly glycosylated, but that many of the long-lived proteins, such as myelin protein, are irreversibly glycosylated. Irreversible glycosylation of long-lived proteins makes the process of complete alleviation of symptoms by any treatment rather unlikely. Hence, the emphasis is on prevention.

The atherosclerotic complications of diabetes can likewise be attributed to the metabolic consequence of poor diabetic control. Some of the factors in question are high cholesterol levels, increased platelet aggregation, increased fibrinogen levels, decreased fibrinolytic activity, and decreased levels of antithrombin III (one of the long-lived proteins that is irreversibly glycosylated).

PATHOGENESIS OF COMPLICATIONS

When insulin was introduced into the therapy of diabetes in 1921, it was

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hoped and expected that complete control of diabetes was at hand. Even after further understanding of insulin action and further purification of insulin, however, it became evident that most diabetics developed diseases of the eye, kidney, and nerves despite treatment with insulin.

A puzzling fact was that the above-described target organs were found not to be insulin sensitive. In other words, these tissues did not require insulin for the entry of sugar. Recently, the focus of scientific inquiry has centered around the role of hyperglycemia rather than insulin lack per se. Studies of diabetic cataracts in animals revealed an accumulation of sorbitol in the lens.[1] Sorbitol is a sugar alcohol formed by the reduction of glucose under the influence of aldose reductase. Normally, when glucose enters a tissue it is oxidized to glucose 6 phosphate under the influence of hexokinase. In the lens, in the presence of high blood glucose levels, a significant amount of the glucose is reduced by aldose reductase to sorbitol. It was found that if aldose reductase is inhibited, cataracts did not form.[2] Sorbitol accumulation causes osmotic damage and depletes reduced glutathione and adenosine triphosphate.

Further study revealed that the target organs in question shared two biochemical abnormalities: A hexokinase, which is saturated at glucose levels of 300 mg/dL or greater, and high levels of aldose reductase.

Hyperglycemia causes depletion of myoinositol, a ubiquitous hexitol (C–6 H–12 0–6) that is an integral part of the Na–K ATPase pump. This pump is responsible for a significant part of the energy expenditure of the cell. Myoinositol depletion of the peripheral nerve is associated with prolongation of nerve conduction; repletion of myoinositol has been shown to improve nerve conduction.[3] Myoinositol depletion is linked to sorbitol accumulation and it has been shown that the use of sorbinil, an aldose reductase inhibitor, restores myoinositol levels to normal as well as reducing the accumulation of sorbitol.

Hyperglycemia causes glycosylation of many proteins. Glycosylation of hemoglobin is the best known of these reactions, but other proteins such as albumin, antithrombin III, and collagen are also glycosylated. Glycosylation of short-lived proteins is reversible, but long-lived proteins may undergo additional reactions and form irreversible glycosylation products. Irreversible glycosylated proteins may form crosslinks and trap immunoglobulins and other proteins, may promote blood clotting (eg, glycosylated antithrombin III), and increase the permeability of basement membranes (eg, glycosylated collagen).[4]

Hemodynamic changes also contribute to the production of diabetic complications. It is well known that at the onset of diabetes some diabetics have supernormal glomerular filtration rates. At least one study indicates that poor prognosis for renal disease occurs in the group of patients who have increased glomerular filtration rates.[5] Hyperglycemia is responsible, in part, for the hemodynamic changes, but even after the hyperglycemia is corrected, some degree of increased glomerular filtration may remain. This residual abnormality has been attributed to growth hormone and other factors.

Sorbinil is an aldose reductase inhibitor that has not yet been released for general use in the human diabetic. As previously noted, however, it has restored nerve conduction in the peripheral nerves of rat and man. Sorbinil has prevented cataracts in experimental diabetes and also reduced the leakage of retinal vessels.[5] Finally, it has abolished the proteinuria of streptozocin-induced diabetic rats.[6]

Physicians are being advised to control diabetes very tightly. The retrospective studies of Pirart[7] show clearly that poor control is associated with an increased incidence of complications. The picture, however, is not entirely clear, because several studies involving tight control have failed to support the idea that tight control will eliminate complications. Studies at the Steno Memorial Hospital compared a group of diabetics on conventional therapy with a group treated by insulin pump. The control of the blood sugar in the pump group was better than that in the conventionally treated groups, but at the end of one year there was greater deterioration of retinopathy in the pump group.[8] A similar study was done by the Kroc Multicenter Group comparing a pump group with conventionally treated diabetics. They evaluated retinopathy and microalbuminuria. After eight months the pump group showed more deterioration of retinopathy than the conventionally treated group, but the pump group showed improvement (lessening) of the microalbuminuria.[9]

As indicated in these studies, tight control has not produced unequivocal evidence of lessening of diabetic complications. Perhaps, earlier institution of tight control for longer periods will furnish additional evidence.

SELECTED DIABETIC COMPLICATIONS

Neuropathic Foot Ulcers

The neuropathic foot ulcer is responsible for the majority of ampu-

tations at Howard University Hospital. The ulcer begins on the plantar surface of the foot in an area of pressure, usually the base of the first or fifth metatarsal or the heel. The ulceration is surrounded by callus and initially has a clean base. Eventually, most of these ulcerations become infected and develop osteomyelitis, which frequently ends in amputation. The neuropathic foot is insensitive and has lost the innervation to the intrinsic muscles of the foot. Because of the loss of sensation, most neuropathic foot ulcers are presented to the physician late. Diabetic feet should be inspected regularly, preferably at each visit. The presence of a callus with or without ulceration should prompt referral to a podiatrist or orthopedic surgeon for prescription of an insert for the shoe or a special shoe to relieve pressure.

Once an infected ulcer is present, one should obtain deep cultures. Invariably at least two organisms will be found. Antibiotic therapy should be appropriate for the organisms found and the patient should be given antibiotics intravenously for a period of three to six weeks. An effort should be made to establish whether osteomyelitis is present. The bone scan is more sensitive than x-rays in making this diagnosis. Surgical help should be obtained early when an infected neuropathic ulcer is diagnosed.

Arteriosclerotic Foot Ulcers

The patient with an arteriosclerotic foot ulcer usually complains of intermittent claudication and unilateral nocturnal leg pain for months prior to development of an ulceration. It is during this early phase that the physician should examine the peripheral pulses carefully and obtain Doppler studies and angiograms to clarify what can be done. Endarterectomy or saphenous vein bypass may relieve the problem. Amputation is a last resort. The prognosis of patients with peripheral vascular disease is poor, in part related to the fact that they usually have associated coronary artery disease.

Diabetic Diarrhea

Diarrhea is an example of diabetic autonomic neuropathy, and may represent the loss of alpha-adrenergic neurons in the bowel. This complication is characterized by profuse watery diarrhea, 15 to 20 stools daily, frequent nocturnal stools, and fecal incontinence. The patients are usually middle-aged, obese women who do not lose weight. A more severe form is called diabetic steatorrhea. This form occurs primarily in type I male diabetics who have postural hypotension, retrograde ejaculation or impotence, fecal incontinence, and steatorrhea. Some of these patients have gastric stasis and overgrowth of bacteria in the upper gastrointestinal tract. They may be helped by metoclopramide (Reglan) and/or tetracycline. More recently, clonidine, an α_2-adrenergic agonist, has been used with good results.[10]

Diabetic Renal Disease

Selective hypoaldosteronism is the most common abnormality of renal function seen in the Diabetic Clinic. It is characterized by intermittent or constant modest elevation of serum potassium. Serum cortisol is normal in these patients; resting and stimulated renin and aldosterone levels are low. The etiology of this syndrome is unclear, but the following factors have been implicated: (1) disease of the juxtaglomerular apparatus, (2) loss of adrenergic stimulus for renin release, (3) chronic expansion of the plasma volume, and (4) abnormality of prostacyclin synthesis.[11] This last factor puts new emphasis on the necessity for care in using nonsteroidal, anti-inflammatory drugs like indomethacin (Indocin) and ibuprofen (Motrin) in diabetics. The treatment of selective aldosteronism may be simply careful observation if serum potassium levels are between 5 and 5.6 mEq, but 9 alpha fluorohydrocortisone (florinef, 9 alpha FF) may be required if the levels are higher. One must be cautious to not induce sodium and water retention when using 9 alpha fluorohydrocortisone.

The most dreaded complication involving the kidney is glomerulosclerosis. It has commonly been considered that this is an irreversible lesion. Recently, however, four cadaveric kidneys from diabetics have been transplanted into normal patients.[12] Subsequent biopsy revealed that the glomerulosclerotic changes had disappeared. Obviously, then, a normal biochemical environment can reverse some of the changes of glomerulosclerosis. The treatment of glomerulosclerosis should involve early recognition of increased glomerular filtration and/or microalbuminuria.[13] For the hemodynamic changes, enalapril is probably the best drug. For general improvement of prognosis, a diet low in protein ($\frac{1}{2}$ g/kg of ideal body weight) offers additional help.[14]

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