



CME Digest

FUTURE DIRECTIONS IN DIABETES TREATMENT

In all types of diabetes, approximately 40% of patients eventually experience renal failure, but the rest do not. At present there is no way to predict which patients are at risk, although there must be a genetic predisposition. Diabetic renal failure occurs in family clusters, and is more common in blacks.

Currently, the best strategy to prevent renal failure is to control the blood sugar concentration as tightly as possible, and, in patients in the early stages of diabetic nephropathy, to use captopril to reduce glomerular hyperfiltration. Other angiotensin-converting enzyme inhibitors may also be effective, although their safety profile has not been confirmed to be equal to captopril's in this patient population.

The Diabetes Control and Complications Trial demonstrated that an intensive insulin regimen can decrease the risk of nephropathy by half over a 5-year-period, compared with conventional therapy. However, this benefit carried the price of a threefold increased risk of severe insulin reactions.

In the Collaborative Study Group's trial of angiotensin-converting enzyme inhibition on diabetic nephropathy, captopril therapy approximately halved the risk of progressing to end-stage renal disease or dying in patients with type I diabetes.

EXPERIMENTAL DRUGS

Experimental drugs that block some of the metabolic consequences of hyperglycemia may someday help patients with diabetes avoid renal failure and other complications of diabetes. Current research focuses on two processes: reduction of glucose to sorbitol and nonenzymatic glycosylation of proteins.

Aldose reductase inhibitors

Hyperglycemia leads to an increase in intracellular glucose, some of which undergoes reduction in the presence of the enzyme aldose reductase to sorbitol. The increased sorbitol concentration increases the osmotic pressure within the cell and is associated with depletion of the alcohols that become part of the phospholipid component of the cell membrane. With the resulting alteration in the cell membrane, there is less protein kinase C activity and less sodium-potassium adenosine triphosphatase activity, leading to depletion of *myo*-inositol. The clinical consequences may include neuropathy, cataracts, and nephropathy.

Studies in diabetic rats show that agents that inhibit aldose reductase can inhibit accumulation of sorbitol and prevent these complications. Trials of *myo*-inositol supplementation have not been as encouraging. Whether aldose reductase inhibitors will have clinical utility remains to be proved, but a number of companies are developing them.

Aminoguanidine

As the glucose concentration increases, glucose tends to interact with the free nitrogen arm of amino acids such as lysine in a reaction known as glycosylation. All proteins can be glycosylated, and the reaction does not require an enzyme. (The browning of toast and the outer layer of baked ham are examples of glycosylation.)

Glycosylated hemoglobin, which serves as a measure of ambient glucose concentrations, has a relatively short half-life and therefore does not undergo further biochemical reactions. However, structural proteins such as collagen, which can also undergo glycosylation, last long enough to undergo a number of subsequent complex nonenzymatic reactions that produce advanced glycosylation end-products.

These subsequent reactions, unlike the early glycosylation reactions, are irreversible. In addition, advanced glycosylation end-products can permanently bond with other proteins, both circulating (lipoproteins, albumin, immunoglobulins) and structural (collagen, fibronectin). This cross-linking of structural and circulating glycosylated proteins may be how hyperglycemia leads to the histologic vascular abnormalities of diabetes. Indeed, the thickening seen in the microvasculature and in the mesangium consists of glycoproteins. The amount of advanced glycosylation end-products (as determined by immunofluorescence assay) correlates with the severity of diabetic complications in diabetic patients.

Aminoguanidine has been shown to react with early glycosylation products and form a substituted glycosylated product. This aminoguanidine-glycosylated protein compound cannot undergo further reactions to form advanced glycosylated end-products, and it therefore blocks their formation and prevents protein cross-linking. Aminoguanidine has been shown to prevent basement-membrane and mesangial thickening in diabetic animal models. Human trials with aminoguanidine are being planned.

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SUGGESTED READING

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THE CLEVELAND CLINIC FOUNDATION

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