Symposium
Third of three articles on diabetes

Lipid metabolism in type II diabetes

Preview
Hypertension, dyslipidemia, insulin resistance, and hyperinsulinemia--acknowledged risk factors for coronary artery disease--are all more common in persons with non-insulin-dependent diabetes than in nondiabetic persons. The interrelationships of these risk factors are becoming increasingly recognized. This article discusses the dyslipidemias commonly seen in type II diabetes and describes their relationship to glucose metabolism.

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Diabetes is a well-known risk factor for coronary artery disease. In diabetic persons over 20 years of age, coronary artery disease is the chief cause of death. Also, risk of atherosclerosis is three to four times higher in diabetic than in nondiabetic persons. . Insulin resistance is well recognized as an important factor in the pathogenesis of non-insulin-dependent (type II) diabetes. However, the effects of insulin resistance on fat metabolism arid its subsequent contributions to worsening hyperglycemia, dyslipidemia, and resultant coronary artery disease, although investigated by specialists, are not as well known among primary care physicians. An understanding of these relationships may help physicians to make more rational therapeutic choices for patients with type II diabetes.

Effects of lipid metabolism on blood glucose levels

In nondiabetic persons of normal weight, administration of insulin leads to an increase in glucose up- take by insulin-sensitive tissues, inhibition of lipolysis, and a de- crease in serum levels of free fatty acids. Normally, far less insulin is needed to inhibit lipolysis {and thereby decrease free fatty acid levels) than is needed to stimulate glucose uptake. However, in insulin-resistant states accompanied by hyperinsulinemia, such as occur in obesity and type II diabetes, there is resistance to the antilipolytic effect of insulin; this resistance results in increased fat breakdown and in- creased serum levels of free fatty acids and glycerol. That there is competition between free fatty acids and glucose for entry into oxidative pathways is well known. Recently, it has been shown in humans that free fatty acids impair insulin-mediated glucose uptake. The increased glycerol resulting from lipolysis tends to drive gluconeogenesis by mass effect, thereby leading to increased glucose production by the liver, further contributing to hyperglycemia. All of these effects tend to worsen hyperglycemia. Effects of lipid metabolism on lipid levels When increasing amounts of free fatty acids are made available to the liver, they are taken up, esterified into triglycerides and phospholipids, and secreted as very low-density lipoproteins (VLDLs) or ketone bodies. VLDL is the endogenously synthesized primary carrier of triglyceride. Greatly in- creased VLDL apoprotein B-l 00 is associated with obesity, which occurs in many patients with type II diabetes.(1)

Significant correlations exist between resistance to insulin-stimulated glucose uptake, plasma insulin concentration, VLDL-triglyceride secretion rate, and plasma triglyceride concentration.(2) In the circulation, lipoprotein lipase acts upon VLDL in the endothelium of capillaries, removing triglycerides from the VLDL particle and allowing the triglycerides to be taken up by cells for energy or storage. However, lipoprotein lipase has two obligate cofactors that are required to lyse triglyceride from the VLDL; these are apo C-II (an apoprotein that is normally present on the VLDL particle) and insulin. In the presence of marked insulin resistance or insulin deficiency, the removal of triglyceride from VLDL may be impaired; this can contribute to the hypertriglyceridemia so commonly associated with type II diabetes. In diabetics, triglyceride levels correlate with electrocardiographic evidence of coronary artery disease and are considered an independent risk factor for it.

Effect of hyperglycemia on atherogenesis

Glucose is among the agents (free radicals, autoantibodies, glycosaminoglycans, malondialdehyde, urea) that are known to modify low-density lipoprotein (LDL) particles to enhance their uptake by the scavenger receptors on

monocyte macrophages to promote atherogenesis. Hyperglycemia leads to glycation of LDL particles. Glycation makes LDL particles more susceptible to oxidation (ie, glycoxidation). Not only LDL particles are glycated, making them more atherogenic, but high-density lipoprotein (HDL) particles are also glycated. Glycation of HDL particles decreases their binding to receptors, decreases activity of apo C (a cofactor necessary for LDL to remove triglycerides), and decreases cellular cholesterol efflux by 30% to 56%, thereby interfering with reverse cholesterol transport (ie, removal of free cholesterol from tissues). Even lipoprotein receptors can be glycated, further impairing reverse cholesterol transport and removal of atherogenic particles from the bloodstream.

Effect of insulin on atherogenesis

Insulin is known to stimulate proliferation and migration of smooth-muscle cells in arterial walls but has no effect on large-vessel endothelial cells in culture. Insulin also stimulates cholesterol synthesis and LDL binding in both arterial smooth-muscle cells and monocyte macrophages.(3)

Long-term infusion of insulin into one limb of an animal leads to development of atherosclerosis limited to that limb.(3) Experimental atherogenic diets almost always induce insulin resistance and hyperinsulinemia in susceptible animals. The atherosclerosis caused by the atherogenic diets can regress with subsequent feeding of a low-fat, low-cholesterol diet. Furthermore, such regression with low-fat, low-cholesterol diets is prevented with concurrent long-term administration of systemic insulin(3); such treatment also reverses the relative resistance to development of atherosclerosis that is usually conferred by estrogens.

Postprandial insulin values in insulin-resistant subjects reach levels that routinely produce significant increases in circulating norepinephrine, which itself can impair insulin action and enhance lipolysis (as well as elevate blood pressure and increase myocardial oxygen demand).(4)

Effect of type II diabetes on HDL

HD L levels are often reduced in direct proportion to the increase in triglycerides in insulin- resistant states and are decreased in patients with type II diabetes.(5) HDL; are important for reverse cholesterol transport. This is accomplished by apoprotein A acting as both an acceptor of free cholesterol and a cofactor for lecithin cholesterol acyltransferase, which is the enzyme that catalyzes the esterification of free cholesterol. After esterification, the cholesterol ester is transferred to the interior of the HDL particle. The mature HDL can then be removed from the circulation by the liver (by means of LDL receptor-like protein receptors). The HDL, by means of cholesterol ester transfer protein (CETP), can also transfer its cholesterol to other lipoprotein particles, such as LDL;, intermediate-density lipoproteins (IDLs), and VLDL;. In insulin-resistant states such as type II diabetes or obesity, or in the presence of hyperinsulinemia, activity of CETP is increased, leading to cholesterol enrichment of VLDLs, IDLs, and LDLs. Although the amount of CETP in the plasma of diabetics is increased by only about 10%, its activity may be increased eightfold in poorly controlled diabetics; this increased activity leads to enhanced cholesterol transport by the atherogenic particles and decreased clearance of cholesterol (by means of HDL) by the liver.

The mean fractional catabolic rate of HDL in type II diabetes is directly related to the fasting blood glucose level and the free insulin concentration, indicating that the decrease in HDL cholesterol and apo A-I levels that is often seen in type II diabetes is due to the increased catabolic rate of apo A-I/HDL.(6) This occurs despite apo A-I/HDL synthesis rates that are greater in patients with type II diabetes than in normal controls.

VLDL, on the other hand, has a decreased fractional catabolic rate in type II diabetes, as does VLDL apoprotein B to a similar degree; the decrease in fractional catabolic rate is directly related to the impairment of diabetes control.(1)

Rationale of therapy for hyperlipidemia in type II diabetes

The goals of treatment of dyslipidemia in type II diabetes are to reduce VLDL formation, normalize CETP activity, decrease triglyceride levels, increase HDL levels, and improve glycemic control.

Dietary therapy is the corner- stone of lipid and diabetes management. In addition to adopting modifications intended to improve glycemic control

(eg, daily exercise), patients with type II diabetes should have a diet low in fat (<30% of total calories), saturated fat (<10% of calories), cholesterol (<300 mg/day), and calories (if weight loss is indicated). Dietary cholesterol reduces the number of LDL receptors in the liver by suppressing their synthesis (down-regulation); this leads to a decrease in hepatic removal of atherogenic lipoprotein particles and an increase in circulating levels of lipoprotein. Serum cholesterol levels increase an average of 8 to 10 mg/dL for every 100 mg of cholesterol in the diet, although this varies greatly among individuals. Dietary intake of saturated fat reduces the activity of LDL receptors in the liver, leading to an average increase in serum cholesterol of 2.7 mg/dL for every 1% of calories in the diet as saturated fat. Excess caloric intake (resulting in obesity) leads to overproduction of VLDLs. Polyunsaturated fat reduces VLDL synthesis in the liver by an unknown mechanism; however, no more than 8% of total calories should be polyunsaturated fat, since some studies suggest a link to cancer with larger amounts. A prudent diet, along with blood glucose control, decreases VLDL production in the liver.

To increase VLDL, IDL, and LDL clearance by the liver, it is appropriate to increase the number of LDL receptors in the liver. These receptors are responsive to the amount of cholesterol in the liver, so that anything that leads to a decrease in hepatic intracellular cholesterol tends to up-regulate (increase) the number of LDL receptors. This increase is an attempt to take up more cholesterol from the circulation in order to supply the liver with the cholesterol necessary for the formation of bile acids, an important product of the liver. Since bile is normally secreted into the intestine to assist with the absorption of fat, and then reabsorbed distally, reabsorption of bile salts through the enterohepatic circulation is a major source of recycled cholesterol. If this recycling is interrupted by the binding of bile acids to non-absorbable material, such as the bile acid-binding resins cholestyramine (Cholebar, Questran) and colestipol (Colestid), thereby leading to bile acid excretion from the body, then the LDL receptors in the liver would be expected to up-regulate in order to take up more cholesterol from the bloodstream. This would lead to a decrease in circulating cholesterol levels. Unfortunately, in diabetics and other hypertriglyceridemic patients, this often leads to an increase in hepatic VLDL formation, so bile acid-binding resins may be relatively less indicated for treatment of hypercholesterolemia in patients with type II diabetes.

Niacin (nicotinic acid, vitamin B3) is very effective in decreasing VLDL and LDL levels and raising HDL levels. Unfortunately, it has the side effect of inducing insulin resistance in both diabetic and nondiabetic persons, so that insulin sensitivity decreases by about one third. This can lead to the development of glucose intolerance or frank diabetes in persons who were previously nondiabetic. In persons with preexisting diabetes, it usually leads to severe deterioration in carbohydrate metabolism, and the diabetes often cannot be well controlled despite greatly increased insulin doses. For this reason, niacin is relatively contraindicated in diabetic patients. (The worsening of glycemic levels often leads to an overall worsening of the lipid profile as well, since the effects of insulin resistance may drive lipolysis and triglyceride formation more than the niacin opposes it.)

Hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitors, by partially and reversibly inhibiting the rate-limiting step to cholesterol synthesis, decrease the formation of cholesterol in the liver. With decreased endogenous production of cholesterol, the liver up-regulates its LDL receptors in order to take up enough cholesterol from the bloodstream to meet its needs for synthesis of bile acids. This results in a reduction in circulating cholesterol, IDL, and LDL.

The hypertriglyceridemia seen in diabetics (and also in other hypertriglyceridemic persons at high risk for coronary artery disease) is associated with an increased number of smaller, denser (ie, containing less cholesterol) LDL particles thought to be relatively more atherogenic than the usual population of LDLs.

Hypertriglyceridemia can be significantly perturbed by the ingestion of alcohol or estrogens; individual sensitivity to the effects of these agents varies tremendously, but both agents tend to show a dose-response relationship in sensitive persons.

Gemfibrozil (Lopid) and clofibrate (Atromid-S), both fibric acid derivatives, increase the activity of lipoprotein lipase, apo A-I synthesis,

and fecal elimination of bile acids. Their entire mechanism of action is not known, but they are very effective in decreasing triglyceride levels and raising HDL levels; in some patients, however, especially, those with combined familial hyperlipidemia, these drugs may also raise LDL levels.

The use of fish oils for the treatment of hypertriglyceridemia in type II diabetes is debated but in general is not recommended unless other therapies have been unsuccessful or are not tolerated and the triglyceridemia is severe enough to increase the risk of pancreatitis. The amount of fish oil necessary to produce a positive effect on triglycerides is a significant source of fat calories; also, fish oil tends to worsen insulin resistance in diabetics and can lead to significant deterioration in glucose control.

Conclusion

Lipid metabolism in patients with non-insulin-dependent (type II) diabetes may differ significantly from that in the nondiabetic state. Hypertriglyceridemia is more common and is itself a risk factor for coronary artery disease in diabetics. Although dietary recommendations for control of diabetes and control of dyslipidemia are complementary, several standard drug therapies are relatively contraindicated because of their adverse effects on glucose metabolism.

References

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