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Plasma Lipid Abnormalities in Diabetes Mellitus:
Observations on HDL Cholesterol and
Recommendations for the Management of Lipid Abnormalities

Dorothy Kahkonen, MD*

The manifestations of lipid abnormalities in diabetes are variable, as might be expected considering the heterogeneous nature of diabetes as well as the complexity of lipid disorders. The association of hyperlipidemia with diabetic ketoacidosis was first reported by Bloor in 1916 (1). Subsequently, the association of impaired glucose tolerance with several of the primary lipid disorders has been well recognized. Interest in the combination of lipid abnormalities and diabetes has greatly increased in the past 25 years, along with an increasing awareness that the propensity to atherosclerosis is a major threat for the diabetic patient.

All the now well-known lipoproteins and their components may participate in the lipid abnormalities associated with diabetes. The least dense lipoprotein particle is the chylomicron from exogenous sources; it is composed of as much as 95% triglyceride and serves to transport dietary fat. The very low density lipoprotein (VLDL) particles are primarily endogenous triglycerides synthesized by the liver and small intestine. The enzyme lipoprotein lipase is responsible for the progressive breakdown of chylomicrons and VLDL to intermediate density lipoproteins (IDL), the remnant triglycerides. The low density lipoprotein (LDL) particles, which transport primarily cholesterol, are derived from the metabolism of VLDL and are bound and degraded by most extrahepatic cells (2). High density lipoprotein (HDL) particles are synthesized in the liver and intestine and seem to facilitate the transport and excretion of cholesterol (3).

In insulin-dependent (Type I) diabetes mellitus, the characteristic associated or secondary lipid disorder is a combination of endogenous and exogenous hypertriglyceridemia. Elevated plasma lipids result from deficiency in the insulin-dependent activity of lipoprotein lipase (LPL). The insulin deficiency which characterizes Type I diabetes accounts for decreased LPL activity and the consequent inability to metabolize chylomicrons as well as VLDL particles. The frequent result is very high plasma triglyceride levels, 2,000 to 10,000 mg/dl.

The most common lipid abnormality in non-insulin-dependent diabetes (Type II) is endogenous hypertriglyceridemia, which is related to overproduction of VLDL particles. Hypertriglyceridemia is usually mild, plasma levels reaching only 250 to 500 mg/dl. Type II diabetes is characterized by excess caloric intake, hyperglycemia, and elevated plasma-free fatty acid concentrations. These conditions stimulate overproduction of VLDL. Obesity, increased carbohydrate intake, and ingestion of alcohol are all known to contribute to triglyceride formation.

Elevated serum cholesterol concentration also occurs in diabetic patients, but the increases are usually mild to moderate. The significance of elevated cholesterol appears to depend on the degree of elevation as well as the lipoprotein component responsible for the increase—VLDL, LDL, or HDL. One possible mechanism for increased LDL cholesterol in diabetic persons is disturbed cholesterol metabolism secondary to glycosylation of LDL. Many body proteins are excessively glycosylated in diabetics, and the apolipoproteins may be similarly altered. Glycosylation interferes with normal lipoprotein metabolism via LDL receptors. In addition, insulin may increase cholesterol synthesis by stimulation of the rate-limiting enzyme hydroxy-methyl glutaryl Co A reductase (4). This mechanism could operate to produce hypercholesterolemia when either endogenous or exogenous hyperinsulinemia is present.

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Just as lipid abnormalities occur in many patients with diabetes mellitus, disturbed carbohydrate metabolism accompanies several of the primary hyperlipidemias. This association is characteristic of Type III hyperlipidemia of the Lees and Frederickson classification, also termed "broad beta" disease because of its electrophoretic characteristics (5). In this disorder, impaired glucose tolerance coexists with elevated plasma cholesterol concentration and the accumulation of remnant triglycerides. Secondary hyperlipidemia as endogenous hypertriglyceridemia or the combination of endogenous and exogenous hypertriglyceridemia, which characterizes many diabetic patients, is much more common than primary hyperlipidemia. In the latter syndrome, treatment is directed primarily to the lipid abnormality because the impaired glucose tolerance, while of great interest, is seldom severe.

The observed inverse correlation between HDL cholesterol concentration and the incidence of coronary artery disease has stimulated interest in the significance of this lipid fraction in patients with increased susceptibility to atherosclerosis. Deficient HDL cholesterol concentrations, if found in diabetic patients, could contribute to macrovascular changes.

**Materials and Methods**

HDL cholesterol concentrations were measured in 453 diabetic patients, both Type I and Type II, men and women, with and without vascular disease. We compared our patients to 48 normal men and 57 normal women, studied concurrently, who had no evidence of vascular disease.

Diabetic patients were classified according to the criteria published by the National Diabetes Data Group (6). In this classification, impaired glucose tolerance refers to a state of fasting euglycemia in which postprandial glucose levels are not normal but are not high enough to establish the diagnosis of diabetes mellitus. Type I diabetes is insulin dependent, generally characteristic of young people and slender adults, while Type II diabetes is non-insulin dependent, characteristic of overweight adults who may or may not require insulin for control of symptoms of hyperglycemia. Nevertheless, the heterogeneity of the diabetic population and the influence of many other known and unknown factors on HDL cholesterol concentrations may complicate interpretation of these studies.

Our study population consisted of diabetic patients attending the diabetes clinic at Henry Ford Hospital. Random or fasting blood samples for total and HDL cholesterol determinations were collected during a routine office visit. Diabetic patients were separated into groups with and without vascular disease. We defined vascular disease as a history of myocardial infarction, angina pectoris, cerebrovascular accident, or occlusive peripheral vascular disease.

Normal subjects were healthy colleagues and employees who volunteered to serve as normal control subjects. They were known not to be diabetic, but family histories of diabetes and vascular disease were not obtained.

HDL cholesterol was measured in serum after precipitation of LDL and VLDL by the addition of dextran sulfate and magnesium chloride. Normal values in our laboratory are similar to those reported elsewhere, 55 ± 14 mg/dl for women and 45 ± 12 mg/dl for men.

**Results**

In women, HDL cholesterol concentrations from normal subjects were significantly higher than from those with diabetes and vascular disease, but did not differ from those of women with diabetes but no vascular disease. A significant difference was demonstrated in HDL concentration between the two diabetic groups, higher levels characterizing those without vascular disease (Table I). Of 81 diabetic women with vascular disease, 79% had HDL cholesterol concentrations below the normal range.

| TABLE I |
| HDL Cholesterol Levels in Normal Women (N), Diabetic Women without Vascular Disease (DMo), and Diabetic Women with Vascular Disease (DM+) |
| Female Subjects | HDL Cholesterol mg/dl ± SD |
| Normal (57) | 53 ± 13 mg/dl |
| DMo (151) | 49 ± 13 mg/dl |
| DM+ (81) | 45 ± 12 mg/dl |

Although mean HDL concentrations were within the normal range for men of all three groups in the study, values for the normal subjects presented greater variability than did those of the diabetic patients but were not statistically different from either diabetic group. On the other hand, HDL concentration was higher in diabetic men without vascular complications than in those so afflicted. The difference was statistically significant (p< .005) (Table II).
Lipid Abnormalities in Diabetes

### TABLE II

<table>
<thead>
<tr>
<th>Male Subjects</th>
<th>HDL Cholesterol</th>
<th>mg/dl ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (48)</td>
<td>45 ± 15 mg/dl</td>
<td></td>
</tr>
<tr>
<td>DMo (146)</td>
<td>49 ± 13 mg/dl</td>
<td></td>
</tr>
<tr>
<td>DM+ (75)</td>
<td>43 ± 13 mg/dl</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Male Subjects</th>
<th>NS vs DMo</th>
<th>NS vs DM+</th>
<th>DMo vs DM+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p&lt;0.005</td>
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</table>

Kannel and Castelli (7) suggest that the ratio of total cholesterol to HDL cholesterol (TC/HDL) is more important than the HDL cholesterol alone in predicting the risk of coronary artery disease. These authors reported the significance of these ratios as follows:

**Women**

- One-half average risk: 3.27
- Average risk: 4.44
- Double average risk: 7.05

**Men**

- One-half average risk: 3.43
- Average risk: 4.97
- Double average risk: 9.55

Calculation of the TC/HDL ratio for our population confirms the significant difference between the normal women and diabetic women with vascular disease (p<0.01). In men, a highly significant difference is shown between the diabetic groups with and without vascular disease (p<0.001), although results in the normal subjects are inconsistent (Table III).

### TABLE III

**Results of Total Cholesterol/HDL Cholesterol Ratios**

**Female Subjects**

<table>
<thead>
<tr>
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<tbody>
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<th>DMo vs DM+</th>
</tr>
</thead>
<tbody>
<tr>
<td>p&lt;0.01</td>
<td>p&lt;0.05</td>
<td></td>
</tr>
</tbody>
</table>

**Male Subjects**

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<th>N vs DMo</th>
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</tr>
</thead>
<tbody>
<tr>
<td>p&lt;0.01</td>
<td>NS</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

### Discussion

The population reported is a heterogeneous group with both Type I and II diabetes represented. It includes patients from 20 to 60 years of age and represents varying degrees of metabolic control. Normal subjects are similarly heterogeneous and are distinguished from the study patients by having neither impaired glucose tolerance nor overt vascular disease. Nevertheless, results confirm that in diabetic patients, as compared to the general population, HDL cholesterol concentrations are higher in groups without clinical macrovascular disease. The presence or absence of diabetes, however, seems less relevant to HDL concentration. In other reports, HDL cholesterol concentrations apparently correlated less well with the risk of vascular disease in individuals younger than 50 (8) and carried more significance for Type II than for Type I diabetic patients (9). In addition, improved metabolic control has been reported to result in higher HDL cholesterol levels (10).

Lipid disorders in diabetic patients should be managed very much as the same disorder in nondiabetic patients. Improvement in blood glucose levels will generally lower triglyceride concentrations in insulin-dependent diabetics, and several intensive therapeutic regimens have demonstrated a decrease in total serum cholesterol levels, primarily in LDL cholesterol (11,12). In non-insulin-dependent diabetic patients, the benefit of careful glycemic control for lowering elevated lipid levels is not as readily apparent (13). The most pressing reason for control of elevated triglycerides is the risk of acute pancreatitis, which is especially prevalent when triglyceride levels exceed 1,000 mg/dl. Although hypertriglyceridemia may be associated with the increased incidence of atherosclerotic vascular disease, data in this regard remain controversial. The Framingham study (14) demonstrated that the fasting level of plasma triglycerides did not correlate prospectively with the incidence of atherosclerosis. However, other retrospective studies in diabetic patients (15) report a more frequent association of atherosclerosis with hypertriglyceridemia than with elevated cholesterol concentrations.

To treat hyperlipidemia, in diabetic as well as nondiabetic patients, we recommend a diet with a caloric value designed to achieve and maintain ideal body weight. The recommended fat content of 30% of total calories must be further reduced if chylomicrons are demonstrated in fasting serum specimens. One half of dietary fat should be unsaturated, and cholesterol intake should be limited to 200-300 mg/day. Weight reduction for the obese patient cannot be overemphasized as a measure to correct lipid abnormalities. In fact, maintenance of body weight 10% below the calculated ideal may be necessary to achieve normal plasma triglyceride concentration in some individuals. Dietary carbohydrates should be about 50% of the calories, preferably of a complex type with increased amounts of fiber. The remaining 15-20% of calories comes from protein foods.
Regular kinetic exercise is widely recommended in the therapy of hyperlipidemia. Although this measure has a less direct, less specific effect on plasma lipids, overall conditioning produces considerable benefit, and risk factors of vascular disease are demonstrably reduced. Lowering of plasma lipid concentrations which may occur acutely is often not sustained. However, reduced triglyceride and cholesterol levels have been observed in non-insulin-dependent diabetics who follow a regular exercise program (16).

Drug therapy for hyperlipidemia may be recommended for diabetic individuals who do not respond to other measures. Bile sequestering agents are effective in lowering plasma cholesterol concentrations, along with less frequently used drugs like nicotinic acid, probucol, and d-thyroxin. Clofibrate and nicotinic acid are recommended to control elevated triglycerides in addition to a new drug, gemfibrozil. Side effects (primarily gastrointestinal), complications, and marginal effectiveness limit the application of currently available drug therapy. The occurrence of cholelithiasis and the observed increased incidence of gastrointestinal neoplasms associated with the use of clofibrate are causes for concern, although the relationship is equivocal (17).

Efforts to increase the level of HDL cholesterol have received much attention because of the potentially protective effect against coronary heart disease. Increased physical activity, weight loss, and stopping cigarette smoking are reasonable measures which seem effective. Increasing or initiating alcohol consumption is contraindicated, despite the experimental evidence that HDL cholesterol levels might be increased thereby.

References