Hypertriglyceridemia and Low HDL Cholesterol in Japanese Patients With NIDDM

Minoru Okubo and Toshio Murase

Diabetes is frequently associated with the combination of hypertriglyceridemia and low HDL cholesterol level, a known risk factor for cardiovascular disease. We evaluated the frequency of elevated serum triglyceride and reduced HDL cholesterol levels in Japanese male NIDDM patients. Hypertriglyceridemia (>1.69 mmol/l) and low HDL cholesterol level (<0.91 mmol/l) were frequently found in Japanese male NIDDM patients (30.4 and 14.2%, respectively). The combined abnormality, i.e., hypertriglyceridemia with concomitant low HDL cholesterol level, was more common in patients with poor glycemic control. We observed that inpatient diet therapy markedly reduced serum triglyceride but serum HDL cholesterol did not change significantly. This is in marked contrast to primary hypertriglyceridemia, in which HDL cholesterol level generally increases in parallel with a reduction in serum triglyceride level. We discuss the defective removal of triglyceride-rich lipoproteins and ineffective HDL production caused by lipoprotein lipase (LPL) deficiency. We also discuss possible correction of this combined abnormality by certain maneuvers that increase LPL activity.
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Diabetes is associated with a two- to fourfold increased risk of cardiovascular disease (CVD) (1). The results of a number of studies have indicated that the abnormalities in serum lipids and lipoprotein composition commonly observed in diabetic patients are possible risk factors for CVD. One of the most frequent lipid abnormalities associated with diabetes is hypertriglyceridemia (2). There is increasing evidence of an association between triglycerides and increased risk of CVD (3–5). The potential atherogenic changes associated with hypertriglyceridemia include: *1*) increases in small, dense LDL; *2*) exaggerated postprandial lipemia; *3*) changes in the clotting system; *4*) manifestation of the insulin resistance syndrome, which includes a series of events leading to atherosclerosis; and *5*) frequent association with low HDL cholesterol (6). Recently, the results of two large clinical trials (Helsinki Heart Study and PROCAM Experience) have indicated that hypertriglyceridemia–low HDL cholesterol syndrome constitutes a powerful risk factor for CVD (7,8).

In the present study, we investigated the frequency of association between hypertriglyceridemia and low HDL cholesterol levels in Japanese men with NIDDM and changes in their serum triglyceride and HDL cholesterol concentrations after diet therapy.

From the Department of Endocrinology and Metabolism, Toranomon Hospital and Okinaka Memorial Institute for Medical Research, Tokyo, Japan.

Address correspondence and reprints requests to Dr. Toshio Murase, Department of Endocrinology and Metabolism, Toranomon Hospital, 2-2-2 Toranomon, Minato-ku, Tokyo 105, Japan.

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CVD, cardiovascular disease; FBG, fasting blood glucose; LPL, lipoprotein lipase; STZ, streptozotocin.

RESEARCH DESIGN AND METHODS

Subjects

Studies on outpatients. The subjects of this study were 303 male NIDDM patients (35–89 years of age). The diagnosis of diabetes was made using World Health Organization criteria (9). Our patients were characterized by impaired insulin secretion, i.e., low insulin with impaired insulin response after glucose loading (10), and they visited our diabetes outpatient clinic regularly. Diet alone was used to treat 150 patients, 106 were treated with oral hypoglycemic agents, and 47 were treated with insulin. Patients who had obvious diabetic nephropathy were excluded.

Studies on inpatients. In an attempt to understand how diet therapy reverses lipid abnormalities in NIDDM patients, we examined a consecutive series of 17 male patients (31–61 years of age) admitted to our hospital for education purposes who had selective hypertriglyceridemia >2.26 mmol/l and normal cholesterol levels. They were given a regular diet, with a daily caloric intake of 30 kcal/kg standard body weight for Japanese. Blood glucose and serum lipids were measured twice, on the day after admission and 1 week later.

Blood glucose and serum lipids. Blood was collected after an overnight fast. Fasting blood glucose (FBG), serum triglyceride, and serum HDL cholesterol levels were measured by standard methods.

Statistical analysis. Data are expressed as means ± SD. Comparisons between groups were performed using the unpaired Student's t test. χ^2 analysis was used to evaluate the prevalence of lipid abnormality between groups.

RESULTS

Studies on outpatients

Serum triglyceride levels in NIDDM patients. The distribution of the serum triglyceride concentrations of patients in the outpatient study is shown in Fig. 1*A*. The prevalence of hypertriglyceridemia (>1.69 mmol/l) was 30.4% (92 of 303). Patients with poor glycemic control (FBG >7.7 mmol/l) tended to have a higher prevalence of hypertriglyceridemia than those with good glycemic control (FBG <6.6 mmol/l) (37 of 97 vs. 36 of 130, $P < 0.1$).

Serum HDL cholesterol levels in NIDDM patients. The mean prevalence of low HDL cholesterol (<0.91 mmol/l) among diabetic patients was 14.2% (43 of 303). The percentage of diabetic patients with hypertriglyceridemia who had low HDL cholesterol levels was 7.6-fold higher than those with normal serum triglyceride levels (33 of 92 vs. 10 of 211, $P < 0.01$). As shown in Fig. 1*B*, the frequency of low HDL cholesterol increased as the serum triglyceride level rose. When we selected patients with poor glycemic control and with good glycemic control and compared them, the former group had an increased prevalence of low HDL cholesterol, paralleling an increase in serum triglyceride levels (21 of 97 vs. 13 of 130, $P < 0.02$). The actual prevalence of combined

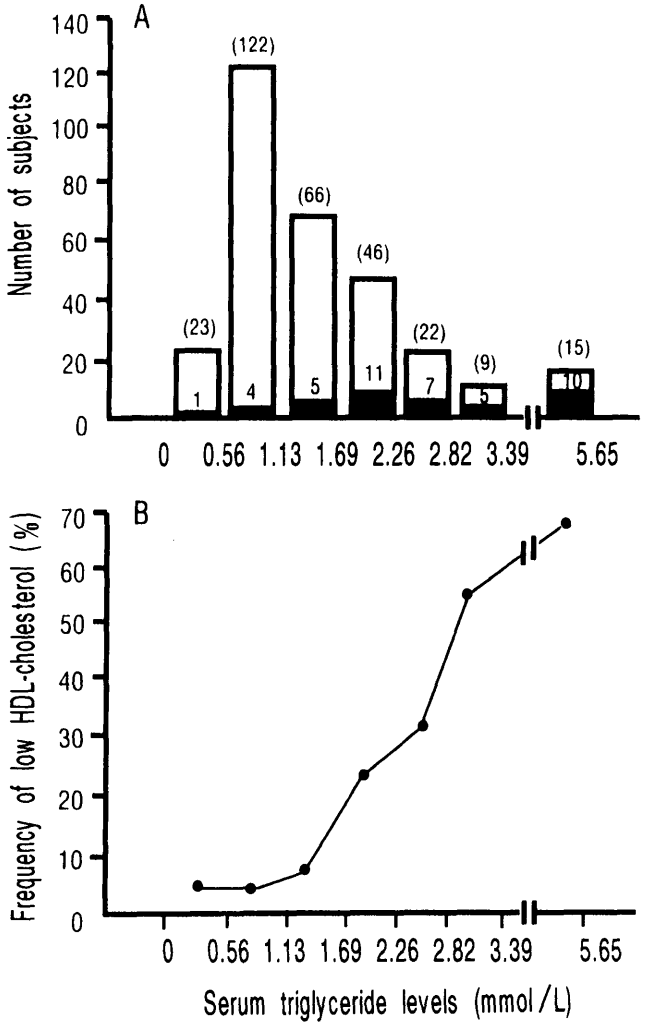

FIG. 1. *A:* **Distribution of serum triglyceride concentrations (white bars) and the number of male diabetic patients with low HDL cholesterol (black bars).** *B:* **Frequency of low serum HDL cholesterol levels in relation to serum triglyceride levels.**

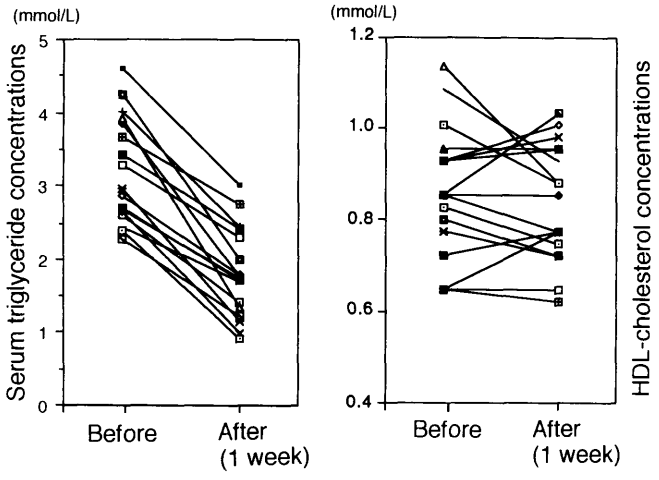

FIG. 2. Changes in serum triglyceride and HDL cholesterol concentrations after diet therapy in 17 male NIDDM patients (serum triglyceride level >2.26; total cholesterol level <5.69 mmol/l).

hypertriglyceridemia and low HDL cholesterol level in patients with poor glycemic control was 13.4% (13 of 97).

Effects of treatment on serum lipid levels. The FBG levels of the patients in the diet alone, oral hypoglycemic agents, and insulin groups were 6.89 ± 1.76, 7.22 ± 1.76, and 8.43 ± 3.53 mmol/l, respectively. There were no significant differences between serum triglyceride and HDL cholesterol levels based on type of treatment (triglycerides: 1.54 ± 0.98, 1.35 ± 0.88, and 1.43 ± 1.87 mmol/l, respectively; HDL cholesterol: 1.27 ± 0.41, 1.27 ± 0.41, and 1.24 ± 0.32 mmol/l, respectively).

Studies on inpatients. None of the inpatients was obese (BMI 24.5 ± 3.0). The fasting serum insulin levels were <120 pmol/l, and the insulin response after 100-g oral glucose loading was also low (Δ immunoreactive insulin/Δ blood glucose <0.5) in all of the subjects (10). FBG decreased from 7.99 ± 2.53 to 5.79 ± 0.88 mmol/l after 1 week of diet therapy. As shown in Fig. 2, all patients showed a marked reduction in serum triglyceride after 1 week, whereas HDL cholesterol remained unchanged in most patients.

DISCUSSION

The present study demonstrated that the prevalence of hypertriglyceridemia and low HDL cholesterol levels among diabetic patients is very high and that hypertriglyceridemia with concomitant low HDL cholesterol is more common in patients with poorly controlled diabetes. Dietary restriction resulted in a marked fall in serum triglyceride levels, but no significant increases in HDL cholesterol were detected.

The high frequency of hypertriglyceridemia among diabetic patients may be a consequence of either overproduction of VLDLs by the liver or defective removal of triglyceride-rich lipoproteins from the circulation, or both. When we focused on the second possibility, it was important to be aware that lipoprotein lipase (LPL), a rate-limiting enzyme for triglyceride degradation, is an insulin-dependent enzyme (11). Nikkilä et al. (12) showed that LPL activity is decreased in IDDM. In NIDDM, however, it is difficult to demonstrate any decrease in LPL activity by standard methods. Pykälistö et al. (13) reported that no postprandial increase in adipose tissue LPL occurs in diabetic patients, but an increase does occur in nondiabetics. Brunzell et al. (14) showed that postheparin plasma LPL activity declined after prolonged insulin infusion in diabetic patients but not in nondiabetic patients. These observations suggest that LPL synthesis is defective in diabetic patients and that the decrease in the activity of this enzyme is one of the major causes of the elevation of serum triglyceride levels in diabetic patients. In contrast with many white and Pima Indian NIDDM patients, most Japanese patients with NIDDM are not obese and have impaired insulin secretion (low fasting insulin with impaired insulin response after glucose loading) (10). The decrease in LPL is probably one of the major causes of the hypertriglyceridemia in Japanese patients with NIDDM.

Low HDL cholesterol is frequently observed in association with hypertriglyceridemia in both diabetic and nondiabetic patients. These two abnormalities may be linked metabolically. Previous reports have demonstrated that enhanced lipolysis of triglyceride-rich lipoproteins results in an increase in HDL cholesterol, and a precursor-product relationship has been suggested between triglyceride-rich lipoproteins and HDL cholesterol (15). Recently, we showed that inhibition of LPL by protamine sulfate, an LPL inhibitor, resulted in a rise in serum triglyceride and a reduction in HDL cholesterol levels in normal rats (16). In addition, streptozotocin (STZ)-diabetic rats had low amounts

of mRNA encoding LPL, and insulin administration markedly increased the amounts of mRNA (17).

The important finding is that dietary restriction resulted in a marked reduction of serum triglyceride levels in almost all patients and that no significant increase in HDL cholesterol occurred in patients whose serum triglyceride levels fell markedly. This contrasts with primary hypertriglyceridemia, in which HDL cholesterol concentrations generally increase in parallel with a reduction in serum triglyceride level (6). This is the problem in NIDDM patients with hypertriglyceridemia and low HDL cholesterol. The decrease in LPL activity due to insulin deficiency could account for the low HDL cholesterol in diabetes.

Because diabetes per se is a risk factor for CVD, association of hypertriglyceridemia with a low HDL cholesterol level should increase the risk of CVD, and thus, this combined abnormality must be corrected. We expect that maneuvers that increase LPL activity will correct the hypertriglyceridemia with low HDL cholesterol levels in diabetic patients. Recent work by our group has shown that administration of NO-1886, which increases LPL activity in experimental animals, resulted in a significant reduction of serum triglycerides and concomitant elevation of serum HDL cholesterol (16). This compound exerted the same action in STZ-diabetic rats. NO-1886 raised the LPL activity of diabetic rats and corrected the combined abnormalities of hypertriglyceridemia–low HDL cholesterol without any changes in blood glucose or insulin levels (17). Such a compound is potentially beneficial for the treatment of hypertriglyceridemia–low HDL syndrome, which is an extremely common complication of diabetes. Clinical trials are now under way.

In summary, we have reported that Japanese male NIDDM patients frequently have hypertriglyceridemia with concomitant low HDL cholesterol and that this combined metabolic abnormality is common in those with poorly controlled diabetes. Possible correction of this combined abnormality has been discussed in connection with certain maneuvers that increase LPL activity.

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