Abnormalities of VLDL, IDL, and LDL Characterize Insulin-Dependent Diabetes Mellitus

Peter H. Winocour, Paul N. Durrington, Deepak Bhatnagar, Monica Ishola, Sharon Arrol, and Michael Mackness

To identify abnormalities of serum lipoprotein composition and concentration that were specific to insulin-dependent diabetes mellitus (IDDM), the procedure of discontinuous gradient ultracentrifugation was employed to isolate lipoprotein fractions in 44 patients with IDDM, 24 nondiabetic subjects with similar lipid and lipoprotein concentrations, and 19 healthy normocholesterolemic (<5.2 mmol/1 [<200 mg/dl]) subjects. The mass concentration of low density lipoprotein (LDL) was greater in IDDM than in both control groups. The free cholesterol to phospholipid ratio in large very low density lipoprotein (VLDL) was greatest in IDDM in comparison with both of the other groups. The contribution of triglyceride to total large VLDL mass was greater, whereas that of phospholipids was lower, in IDDM than in the dyslipidemic nondiabetic group. Protein concentration was reduced and phospholipid increased in small VLDL in IDDM in comparison with both control groups, and the contribution from protein to lipoprotein mass was least in IDDM. Similarly in intermediate density lipoprotein (IDL), the protein concentration and its contribution to overall mass was also lower in IDDM than in either control group, but by contrast, the phospholipid content was increased. The cholesteryl ester to protein ratio was highest in both small VLDL and IDL in IDDM in comparison with both control groups, whereas the free cholesterol to phospholipid ratio in IDL was least in IDDM. In LDL, total cholesterol and triglyceride concentrations were greatest and the contribution from protein to lipoprotein mass was least in IDDM in comparison with both control groups. The LDL free cholesterol to phospholipid ratio was greater in IDDM than in dyslipidemic control subjects. The average LDL particle size (as assessed by the total lipid to protein mass ratio) in IDDM was larger than in both control groups. This study demonstrates that both quantitative and qualitative abnormalities of VLDL, IDL, and LDL may be a characteristic feature of IDDM. These changes may increase the atherogenicity of these lipoproteins, even when the serum lipoprotein concentrations are similar to those of the nondiabetic population. (Arteriosclerosis and Thrombosis 1992;12:920–928)

KEY WORDS • lipoprotein composition • very low density lipoproteins • intermediate density lipoproteins • insulin-dependent diabetes mellitus • cholesterol • triglycerides • phospholipids • proteins

Disordered lipoprotein metabolism is characteristic of insulin-dependent diabetes mellitus (IDDM). Quantitative abnormalities of lipoproteins are more apparent in older patients and/or those with diabetic nephropathy or poor glycemic control. Increased production of both very low density lipoprotein (VLDL) and low density lipoprotein (LDL) has been described in insulin-replete IDDM with moderate blood glucose control, although reduced production of apolipoprotein B-containing lipoproteins accompanies impeccable blood glucose control and attainment of normocholesterolemia. Hypercholesterolemia and normocholesterolemia are, however, arbitrary concepts based on epidemiological data that attribute varying cardiovascular risk to different serum cholesterol concentrations. Current guidelines suggest that ideal total serum cholesterol levels (conferring low attributable risk) should be <5.2 mmol/l (200 mg/dl). In practice, the prevalence of higher serum cholesterol levels in adult IDDM may be as high as 60%, which is similar to the prevalence in a nondiabetic adult population, although the prevalence of elevated fasting serum triglycerides (>1.7 mmol/l [>150 mg/dl percent]) appears greater in IDDM.

We have previously suggested that compositional abnormalities of lipoproteins may also be a feature of IDDM, but we did not isolate and fully characterize all lipoprotein fractions in that report. More recent studies of small numbers of subjects with IDDM whose fasting serum cholesterol concentrations spanned 5.2 mmol/l have used various ultracentrifugation methods and have reported conflicting patterns of qualitative differences in the composition of lipoproteins. Cholesterol enrichment of VLDL was reported in small studies of men, although this was not confirmed by a larger study or by a study of women.
Increased concentrations of cholesterol and/or triglycerides in intermediate density lipoprotein (IDL) have been reported, although it is unclear whether lipoprotein mass is altered. In LDL, lipid concentrations have been reported to be increased or unaltered, and LDL composition was not apparently different.

In the present study we have isolated and fully characterized the VLDL, IDL, and LDL lipoprotein fractions in adult IDDM and made comparison with a nondiabetic control group whose total serum cholesterol was greater than 5.2 mmol/l and in whom a similar proportion of subjects also had elevated fasting serum triglyceride levels. Our objective was to identify compositional abnormalities of these lipoproteins that were specific to and representative of IDDM.

Methods

The study was approved by the local area ethics committee, and written consent was obtained from all participants. Diabetic subjects were recruited from the clinic if their serum cholesterol levels were >5.2 mmol/l and if other criteria (see next paragraph) were fulfilled. Forty-four control subjects in the same age range were also studied consecutively and classified according to the diagnosis of diabetes. Those with IDDM had stable blood glucose control with insulin treatment from the time of diagnosis, previously documented ketoacidosis, or age <30 years at the time of diagnosis.

All protein concentrations, and phospholipid content was measured enzymatically: for cholesterol and triglycerides by a glucose oxidase method (Yellow Springs Analysers, Clandon Scientific, UK) and HbA1 by ion-exchange chromatography (Boehringer, Mannheim, FRG; normal range, 5.0–8.0%, with a between-assay variability of 3.0–6.0%).

All lipid and lipoprotein estimations were carried out in duplicate. Fasting serum cholesterol and triglyceride concentrations were measured enzymatically: for cholesterol by using a reagent supplied by Diamed (Murten, Switzerland) and for triglycerides by the glycerol phosphate oxidase-peroxidase-antiperoxidase method (Boehringer). Our laboratory currently participates in the UK national quality control scheme for cholesterol and triglyceride assays; the coefficients of variation were 1.5% and 2.1%, respectively.

Total protein content of the various lipoprotein fractions was measured by the BCA method (Pierce [Euro] and Bioger, The Netherlands; within-batch coefficient of variation, 5.4%, 16), which has greater stability and sensitivity than the Lowry method for low protein concentrations, and phospholipid content was quantified by using a commercial kit (Boehringer; within-batch coefficient of variation, 5.0%).

The procedure of discontinuous gradient ultracentrifugation (DGU) was used to sequentially isolate four lipoprotein fractions according to their density: large VLDL (60–400 Svedberg flotation units [Sf]), small VLDL (Sf 20–60), IDL (Sf 12–20), and LDL (Sf 0–12). Chylomicrons (Sf >400) were removed from samples for DGU after preliminary ultracentrifugation at 40,000g for 30 minutes. Then, 2 ml of the plasma sample was mixed with sodium chloride to attain a density of 1.118 g/l and carefully layered onto a sodium bromide solution with a density of 1.182 g/l. Thereafter, sodium bromide solutions of six different densities (1.099, 1.086, 1.079, 1.064, 1.059, and 1.072 g/l) were carefully layered in turn onto the plasma sample. After four sequential spins in a swing-out rotor (Beckman 40 Ti; Beckman Instruments, Palo Alto, Calif.) on an L8-55M preparative ultracentrifuge (Beckman), the supernatants were carefully removed by pipetting. The sequence was large VLDL (39,000g spin for 1 hour, 38 minutes); small VLDL (18,500g spin for 15 hours, 41 minutes); IDL (39,000g spin for 2 hours, 35 minutes); and LDL (30,000g spin for 2 hours, 10 minutes). The average recovery of cholesterol and triglyceride by this procedure was 88% (range, 84–91%) and 91% (range, 86–96%), respectively. Absolute concentrations of the lipo-
proteins were determined by addition of the serum concentrations (in milligrams per deciliter) of the four constituent parts.

HDL was isolated by ultracentrifugation. The background density of plasma was adjusted to 1.063 g/l by adding a sodium chloride-potassium bromide solution. The infranatants were obtained by tube slicing after ultracentrifugation at 100,000g for 48 hours (L8-55M ultracentrifuge with a 50.3 Ti rotor, Beckman). The within-batch coefficient of variation for the HDL cholesterol assay was 4.7%. Total serum apolipoprotein B concentrations were determined by immunoelectro-phoresis using goat antiserum (Immuno, Dunton Green, Kent, UK) and had a within-batch coefficient of variation of 5.4%.

In all lipid and lipoprotein analyses, high- and low-density lipoprotein was derived from the overall lipoprotein mass (i.e., resaturation) were assessed by a x2 test. The size (i.e., diameter) of the lipoprotein was derived from the overall lipoprotein mass from the following equation:

\[
\text{Diameter}^2 (r^2) = \frac{\text{lipoprotein mass}}{\pi}
\]

Results

General Characteristics of Study Groups

The three groups were comparable with respect to gender ratio, smoking habits, and alcohol intake. Both the diabetic and the dyslipidemic control groups were significantly older; of greater body mass; and had higher levels of blood pressure, total serum lipids, and lipoproteins in comparison with the healthy normolipidemic control group (Table 1).

Correlations Between Lipoprotein Classes, Serum Lipids, and Diabetic Control

In IDDM, total serum triglycerides were significantly correlated with the cholesterol and triglyceride concent-
The cholesteryl ester to protein and cholesteryl ester to triglyceride ratios were also noted in IDDM. Similar extents of triglyceride ratios were comparable in all groups. Phospholipid concentrations were significantly lower in the normolipidemic control group in comparison with the other two groups. The protein concentration was lower and phospholipid concentration significantly lower in the normolipidemic control group in comparison with the dyslipidemic control populations, with a trend for higher values in IDDM (p<0.1). The cholesterol and triglyceride concentrations were significantly lower in the normolipidemic control group in comparison with the other two groups, whereas phospholipid concentrations were higher in IDDM in comparison with both control groups. In contrast to large VLDL, protein concentration was comparable in the IDDM and normolipidemic group but reduced in comparison with the dyslipidemic control group. The cholesteryl ester to protein ratio was markedly increased in IDDM in comparison with the control groups, but the cholesteryl ester to triglyceride and free cholesterol to phospholipid ratios were similar in all groups.

IDL (SF 12–20) (Table 4). Serum IDL mass concentration was increased in both IDDM and dyslipidemic control groups, with suggestive higher concentrations in IDDM (p<0.1). The total cholesterol (predominantly cholesteryl ester) and triglyceride concentrations were significantly lower in the normolipidemic control group in comparison with the other two groups. The protein concentration was lower and phospholipid concentration higher in IDDM in comparison with both control groups.

Table 3. Serum Concentrations of Small VLDL (SF 20–60) Components and Lipoprotein Mass in Insulin-Dependent Diabetes Mellitus, Dyslipidemic, and Normolipidemic Control Groups

<table>
<thead>
<tr>
<th>Component</th>
<th>IDDM (group 1)</th>
<th>Dyslipidemic controls (group 2)</th>
<th>Normolipidemic controls (group 3)</th>
<th>Scheffé's test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>0.42 (0.05–1.69)</td>
<td>0.37 (0.04–1.06)</td>
<td>0.14 (0.06–0.50)</td>
<td>1 vs. 3, 2 vs. 3†</td>
</tr>
<tr>
<td>Cholesteryl ester (mmol/l)</td>
<td>0.24 (0.03–1.04)</td>
<td>0.21 (0.03–0.73)</td>
<td>0.07 (0.02–0.28)</td>
<td>1 vs. 3, 2 vs. 3†</td>
</tr>
<tr>
<td>Free cholesterol (mmol/l)</td>
<td>0.17 (0.01–0.79)</td>
<td>0.16 (0.01–0.63)</td>
<td>0.06 (0.03–0.22)</td>
<td>1 vs. 3, 2 vs. 3†</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>0.38 (0.11–4.97)</td>
<td>0.31 (0.02–2.44)</td>
<td>0.13 (0.06–0.36)</td>
<td>1 vs. 3, 2 vs. 3†</td>
</tr>
<tr>
<td>Protein (mg/ml)</td>
<td>0.07 (0.01–0.39)</td>
<td>0.14 (0.04–0.39)</td>
<td>0.09 (0.04–0.26)</td>
<td>1 vs. 2, 2 vs. 3†</td>
</tr>
<tr>
<td>Phospholipid (mmol/l)</td>
<td>0.29 (0.08–0.68)</td>
<td>0.18 (0.08–0.44)</td>
<td>0.12 (0.05–0.25)</td>
<td>1 vs. 2, 1 vs. 3†</td>
</tr>
<tr>
<td>Total lipoprotein mass (mg/dl)</td>
<td>98.2 (29.8–525.8)</td>
<td>75.4 (22.0–318.9)</td>
<td>40.3 (25.5–66.1)</td>
<td>1 vs. 3, 2 vs. 3†</td>
</tr>
<tr>
<td>Cholesteryl ester to protein ratio</td>
<td>1.56 (0.35–12.5)</td>
<td>0.57 (0.21–2.58)</td>
<td>0.32 (0.03–0.83)</td>
<td>1 vs. 2, 1 vs. 3†</td>
</tr>
<tr>
<td>Cholesteryl ester to triglyceride ratio</td>
<td>0.63 (0.13–4.15)</td>
<td>0.67 (0.08–5.53)</td>
<td>0.56 (0.21–2.59)</td>
<td>1 vs. 3, 2 vs. 3†</td>
</tr>
<tr>
<td>Free cholesterol to phospholipid ratio</td>
<td>0.69 (0.21–2.53)</td>
<td>0.90 (0.05–1.74)</td>
<td>0.62 (0.24–1.71)</td>
<td>1 vs. 2, 2 vs. 3†</td>
</tr>
</tbody>
</table>

VLDL, very low density lipoprotein; IDDM, insulin-dependent diabetes mellitus. Values are geometric mean and (range).

Significant differences between two groups (p<0.05) by Scheffé's test.

Differences by one-way analysis of variance between groups: p<0.001, p<0.0001.
The saturation of the fractions reflects the cholesteryl ester to triglyceride ratio. Total lipoprotein mass (mg/dl) was lower in the non-necardemic control group in comparison with both control groups, with the free cholesterol to phospholipid ratio also different between control groups, although the cholesteryl ester to triglyceride ratios were similar in all groups.

LDL (Sf 0–12) (Table 5). Serum LDL mass concentration was increased in IDDM and dyslipidemic control groups, with significantly greater increases in diabetic patients. The Sf 0–12 cholesterol and triglyceride concentrations and the cholesteryl ester to protein ratios were significantly lower in the normolipidemic control group in comparison with the other two groups. Phospholipid concentrations differed between the control groups. Consequently, the cholesteryl ester to protein and the free cholesterol to phospholipid ratios were increased and reduced, respectively, in IDDM in comparison with both control groups, with the free cholesterol to phospholipid ratio also different between control groups, although the cholesteryl ester to triglyceride ratios were comparable in all groups.

Saturation of lipoprotein subclasses with various components. The saturation of the fractions reflects the percent contribution from the mass of cholesterol, triglyceride, phospholipid, and protein to the overall mass of the lipoprotein subclasses (Figure 1). Differences in molecular mass are also demonstrated in Figure 1 and Tables 2–5.

The composition of large VLDL (Sf 60–400). The composition of large VLDL in IDDM was altered. The contribution to lipoprotein mass from triglycerides was higher and from phospholipid lower in comparison with both groups of control subjects (both p<0.05), whereas the proportion of cholesterol was greater only in IDDM in comparison with normolipidemic control subjects (p<0.05). Total lipoprotein mass was least in the normolipidemic control group (Figure 1).

Small VLDL (Sf 20–60). Small VLDL in IDDM was relatively saturated with triglycerides in comparison with the normolipidemic control group, and depletion of protein characterized IDDM to a greater extent than the dyslipidemic control group. Protein concentrations and the cholesteryl ester to triglyceride ratios were comparable in all three groups.

Phospholipid concentrations differed between the control groups. Consequently, the cholesteryl ester to protein and the free cholesterol to phospholipid ratios were increased and reduced, respectively, in IDDM in comparison with both control groups, with the free cholesterol to phospholipid ratio also different between control groups, although the cholesteryl ester to triglyceride ratios were similar in all groups.
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in comparison with both control groups ($p<0.05$) (Figure 1). Lipoprotein mass was greater only in IDDM in comparison with the normolipidemic control group.

LDL ($S_r$ 0–12). LDL in IDDM was characterized by relative cholesterol and triglyceride saturation and protein depletion in comparison with normolipidemic control subjects ($p<0.05$). Furthermore, LDL was relatively depleted in protein in IDDM in comparison with the dyslipidemic control group ($p<0.05$). Relative protein depletion was also recorded in the dyslipidemic control group in comparison with the normolipidemic control group ($p<0.05$) (Figure 1). Total lipoprotein mass was greatest in IDDM in comparison with both control groups and less in normolipidemic in comparison with dyslipidemic control subjects.

**Discussion**

We chose to study a diabetic population with, on average, relatively modest hypercholesterolemia, which is endemic in both the adult diabetic and nondiabetic populations of the United Kingdom and the United States.2-7-9

Our study demonstrated that modest hyperlipidemia in IDDM was characterized by both quantitative and compositional changes in large and small VLDL, IDL, and LDL. These alterations in the relative amounts and absolute concentrations of the components of lipoprotein subclasses in IDDM were most apparent in comparison with healthy normolipidemic control subjects, but there were also differences between lipoproteins in IDDM and those in dyslipidemic control subjects whose serum cholesterol was $>5.2$ mmol/l. This suggests that certain modifications of lipoproteins were specific to IDDM. In particular, the free cholesterol to phospholipid ratio of large VLDL was increased, with a reduction in the contribution from phospholipid to lipoprotein mass; small VLDL and IDL were enriched in cholesteryl ester and phospholipid, but depleted of protein; and LDL molecules were more saturated with cholesterol and triglyceride, with protein contributing less to overall lipoprotein mass. Increases in small VLDL and IDL lipid in IDDM were closely related to serum concentrations of triglycerides and cholesterol, respectively.

The present data obtained by DGU support our previous hypothesis that VLDL, IDL, and LDL compositions are altered in IDDM.10 Several smaller studies would also support this view.12-14,20,21

A definitive study the size and scope of the present one was important because smaller studies that used other techniques may have been misleading for several reasons. Recovery of lipid components of lipoprotein was, on average, 90–100% in our present report and in some other studies,11,14 although often it was not stated.12,13,15,21 Furthermore, the use of different density gradients has led to confusion in the classification of lipoprotein particles of the same density. Thus, in the

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**FIGURE 1.** Pie charts showing differences in lipoprotein particle size and composition between insulin-dependent diabetes mellitus (IDDM) and dyslipidemic and normolipidemic control groups. Percent contribution of each component to lipoprotein composition is indicated by the angle subtended by each slice. Components that are significantly different from other groups ($p<0.05$) are shown detached from the center of the circle: +, vs. normolipidemic control group; *, vs. normolipidemic and dyslipidemic control groups. Lipoprotein mass is indicated by the total area of all components of each circle. Significantly different from other groups ($p<0.05$): $, vs. normal control; $$, vs. normolipidemic and dyslipidemic control groups. VLDL, very low density lipoprotein; IDL, intermediate density lipoprotein; LDL, low density lipoprotein.
present study we isolated four non-HDL fractions of varying density, and as in the study of James and Pometta,
by contrast, Rivellese et al. claimed to have isolated IDL, although the density of their isolated fraction (Sf 12–60) would clearly have included VLDL components; Joven et al. did not comment on their composition, and they isolated VLDL of a wide density range (Sf 20–400), thereby missing subtle differences in surface components in the Sf 20–60 and Sf 60–400 fractions; and Georgopoulos and Rosengard also isolated a fraction of wide density range (Sf 20–100) without examining IDL composition.

Finally, unlike previous reports, we specifically examined lipoprotein composition in IDDM where hypertriglyceridemia was present in a representative proportion of cases. This may have a prevalence of at least 30% in IDDM and might have been expected to fundamentally alter lipoprotein composition. Notwithstanding such differences, some of the presently reported compositional abnormalities of lipoproteins are compatible with the findings of other groups. The altered proportions of the components of large and small VLDL are not dissimilar, although the impact of hypertriglyceridemia must be taken into account. Nonetheless, the abnormal saturation of small VLDL with cholesteryl ester in the core (implied by the cholesteryl ester to protein ratio) is in agreement with the findings of Georgopoulos and Rosengard, whereas the less marked alteration in the surface composition of large VLDL (implied from the free cholesterol to phospholipid ratio) has also been noted previously.

The additional effect of variable blood glucose control on lipoprotein composition in the current study and in previous reports may partially account for subtle differences in the diabetes-specific compositional changes. Alternatively but not necessarily exclusively, the changes in lipoprotein composition in IDDM could reflect varying degrees of absolute insulin deficiency, relative insulin deficiency (i.e., secondary to insulin insensitivity), or peripheral hyperinsulinemia with disturbed portal-peripheral insulin gradients. Absolute insulin deficiency was only likely to have exerted a minor effect in the present study, in which blood glucose control was broadly representative of IDDM in general. In addition, compositional abnormalities of lipoproteins in IDDM and insulin-treated non-insulin-dependent diabetes have persisted after improved blood glucose control in recent reports. The possibility remains that insulin insensitivity intrinsic to IDDM and peripheral hyperinsulinemia secondary to insulin treatment may have contributed to differences from the dyslipidemic control group.

Lipoprotein composition in IDDM could, of course, also be affected by a host of other factors, including body mass, diet, and gender. We attempted to minimize their impact by ensuring that our diabetic and dyslipidemic control groups were comparable in these respects. One further possible confounding variable could have been early diabetic nephropathy, which has previously been shown to affect HDL concentrations most consistently, but which can also be associated with disturbances of the mechanisms that control the metabolism of triglyceride-rich lipoproteins. However, we have previously shown that early diabetic nephropathy itself only exerts minor effects on IDL composition and that lipoprotein composition was otherwise comparable, irrespective of minor degrees of albuminuria in nonnephrotic normoalbuminuric IDDM subjects.

IDDM was characterized by abnormalities in both surface and core IDL and LDL compositions, which have not been previously highlighted. Part of the explanation for this pattern could be accelerated conversion of the triglyceride-rich IDL to LDL, particularly because a proportion of cases had hypertriglyceridemia. This process might be secondary to increased hepatic secretion of triglyceride-rich particles in IDDM coupled with the stimulatory effect of peripheral hyperinsulinemia on endothelial lipoprotein lipase activity. Glycation of apolipoprotein B and apolipoprotein E could have slowed the rate of receptor-mediated hepatic uptake of IDL and LDL.

Lecithin:cholesterol acyltransferase controls the formation of cholesteryl ester. Its activity is normal or increased in IDDM. Cholesteryl ester transfer protein activity has also been reported to be increased in nondiabetic dyslipidemia and in IDDM complicated by vasculopathy (a feature of a proportion of patients in the present report). Thus, increased transfer of cholesteryl ester from HDL into the VLDL/IDL/LDL pool could also have compounded the effect of the other factors and led to cholesteryl ester enrichment of IDL. The increase in triglycerides in LDL may also partially reflect a movement of cholesteryl ester back to VLDL in exchange for triglycerides, a process mediated by cholesteryl ester transfer protein. Such abnormalities of LDL may lead to smaller, denser molecules that are recognized to be associated with an increased risk of coronary disease. Abnormal surface lipoprotein composition may also have atherogenic potential. In the present study, the free cholesterol to phospholipid ratio was somewhat increased in large VLDL and LDL in comparison with that of matched control subjects. Bagdade and Subbaiah demonstrated a similar abnormality in IDDM (from a plasma fraction containing both VLDL and LDL), which has been shown to be a strong predictor of ischemic heart disease risk in nondiabetic males.

There is increasing evidence that serum concentrations of both cholesterol and triglycerides predict the risk of both coronary and peripheral arterial disease in diabetes. The results of the present study indicate that IDL concentrations are directly proportional to both total serum cholesterol and triglycerides; i.e., IDL in IDDM is present in greatest concentrations in combined hyperlipidemia. We previously suggested that IDL might be a major determinant of cardiovascular risk in IDDM. In type III hyperlipoproteinemia, lipoproteins in the intermediate density range are increased, and both coronary and peripheral arterial atherosclerosis are prevalent, in contradistinction, for example, to familial hypercholesterolemia, in which the primary abnormality is an increase in LDL and coronary heart disease is common while peripheral arterial disease is unusual. Further evidence that IDL is atherogenic in nondiabetic populations has since been reported, and in IDDM it has been shown that VLDL and IDL are readily taken up by macrophages without the need for oxidative modification, as is the case for the
&-VLDL in type III hyperlipoproteinemia. Although not a primary object of the present study, a somewhat greater prevalence of both coronary and peripheral arterial disease was noted in IDDM in contrast to the dyslipidemic control group. This suggests that longitudinal investigations of the atherogeneity of IDL in IDDM should prove particularly rewarding.

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