Lipoprotein Compositional Abnormalities and Insulin Resistance in Type II Diabetic Patients With Mild Hyperlipidemia


Lipoprotein composition was determined using ultracentrifugation in 20 non-insulin-dependent (NIDDM) diabetic patients on diet only (D), 20 NIDDM patients on diet and sulfonylurea therapy (T), and 20 nondiabetic control subjects (C), all of whom had total plasma cholesterol concentrations <6.5 mmol/L and total plasma triglyceride concentrations <3.0 mmol/L. Although the groups were well matched for age, body mass index, total triglyceride levels, and total cholesterol concentrations, there were significant compositional abnormalities in the low-density lipoprotein (LDL) fractions of diabetic subjects. The LDL total lipid to apolipoprotein B weight ratio (representing the density distributions of LDL particles) was reduced in both diabetic groups: 3.75±0.3, 3.50±0.28, and 3.54±0.22 in C, D, and T groups, respectively (mean±SD; P<.05). This was associated with a significant shift in the hydrated density distributions of LDL in the diabetic groups, with the average peak densities being 1.0320 g/mL (in C), 1.0365 g/mL (in D), and 1.0380 g/mL (in T) (P<.05). The LDL particles were also smaller in the NIDDM patients: 21.1±0.7, 20.4±0.5, and 20.6±0.5 nm in C, D, and T groups, respectively (P<.05).

When the NIDDM groups were analyzed together, the LDL peak density was found to correlate with both insulin resistance (measured by a modified Harano technique; r=0.37, P<.015) and total triglyceride concentrations (r=0.40, P<.01). The results show that diabetic patients have small, dense LDL particles, which may be related to insulin resistance, and that these occur with minimal elevations of total triglyceride concentrations. These potentially atherogenic changes may contribute to the increased coronary heart disease in diabetic patients with mild hyperlipidemia. (Arteriosclerosis and Thrombosis 1993;13:1046-1052)

KEY WORDS • lipoprotein composition • apo B • dense LDL • cholesterol • triglycerides • NIDDM

Death from cardiovascular disease is three times more common in diabetic patients than in the nondiabetic population. Many factors have been implicated in the development of atherosclerosis in diabetes, including dyslipidemia, obesity, hypertension, hyperglycemia, and hyperinsulinemia. Patients with non-insulin-dependent diabetes mellitus (NIDDM) are twice as likely to be hyperlipidemic as nondiabetic subjects, with the most common lipid abnormality of NIDDM being hypertriglyceridemia. The 11-year follow-up of patients with NIDDM in the Paris Prospective Study found hypertriglyceridemia to be an independent risk factor for coronary heart disease. However, diabetic patients are still at risk of atherosclerosis, even when they are not obviously hyperlipidemic.

It has been suggested that the composition of the lipoprotein fractions, as well as the total lipid concentrations, may be important in the development of cardiovascular disease in diabetics. Some recent studies have described potentially atherogenic abnormalities in the composition of lipoproteins from diabetic patients who have levels of total plasma cholesterol and triglycerides that are considered acceptable. However, the results are conflicting, and there are a number of possible explanations. A wide range of methods have been used, which are not always clearly defined. Many groups have combined both ultracentrifugation and precipitation techniques to characterize the lipoprotein fractions. In addition, most studies have included patients and control subjects who were well matched for total cholesterol concentrations, although there were differences in other important variables, including triglyceride concentrations and body mass index (BMI). Drug therapy also causes confusion in the interpretation of results, as many patients with NIDDM are receiving cardioprotective drugs such as β-blockers, which are known to alter lipid concentrations. The treatment of diabetes with sulfonylurea therapy and insulin can also affect the lipoprotein profile. The racial background and cultural diversity of several groups further confound the problem.

The present study was designed to determine whether potentially atherogenic compositional abnormalities of lipoproteins occur in Caucasian patients with NIDDM.
who were only moderately hyperlipidemic, not on any cardioprotective drugs, and, to avoid other confounding variables, were well matched with control subjects.

Methods

Forty male Caucasian patients with NIDDM were recruited consecutively from two diabetic outpatient clinics in Newcastle upon Tyne. Patients were treated either with diet only, as recommended by the British Diabetic Association13 (20 patients), or with diet and sulfonylurea therapy (20 patients). No patients were taking lipid-lowering medication or any other drugs known to alter lipoprotein metabolism, such as thiazides, β-blockers, or metformin. All subjects had a BMI <32 kg/m² and an HbA1c <9.5% or HbA1c <13%. Twenty control subjects (recruited from university and hospital personnel) all had normal oral glucose tolerance tests by World Health Organization criteria. Patients and control subjects had total fasting plasma cholesterol concentrations <6.5 mmol/L and triglyceride concentrations <4.0 mmol/L. Local ethics committee approval was obtained for the study, and written consent was given by all patients and control subjects.

Blood was withdrawn after a 14-hour fast and immediately centrifuged at low speed (800g); then 2 mL of serum was mixed with a preservative cocktail (5 µL of 8% Na₂EDTA and 5 µL of 30 mg/mL phenylmethylsulfonyl fluoride in dimethysulfoxide) and 7 µL of 22 mg/mL butylated hydroxytoluene in absolute ethanol per milliliter of serum. Samples were stored at −20°C for less than 7 days pending lipoprotein fractionation and analysis. This approach to the storage of samples for lipoprotein analysis was validated in a pilot study by demonstrating that samples stored at −20°C from NIDDM patients4 and control subjects2 gave identical results to fresh unfrozen samples. Serum was separated into lipoprotein fractions by sequential flotation ultracentrifugation14: 8 mL (0.189 mmol/L) NaCl was added to 2 mL serum to adjust the density to 1.006 g/mL. Samples were centrifuged at 20°C at 100 000g for 24 hours in a Beckman 70.1 Ti fixed-angle rotor. After centrifugation the top 2 mL, which contained very-low-density lipoprotein fractions were determined with a lipase-glycerol kinase end-point reaction method (Roche, Welwyn Garden City, UK). The between-batch CV was 8.2%, and the mean triglyceride recovery from lipoprotein fractions was 89% (range, 84% to 95%).

Free cholesterol and phospholipid were measured in the total serum and lipoprotein fractions by enzymatic colorimetric commercial kits from Boehringer Mannheim using an automated Cobas Bio centrifugal analyzer (Roche). The kits were modified by adjusting the volume of reagents to improve sensitivity. The interassay CV for phospholipid ranged from 0.22% for serum and LDL to 2.9% for IDL, with a mean recovery of 91% (range, 85% to 100%). The interassay CV for free cholesterol ranged from 0.7% for serum and LDL to 7.2% for VLDL, with a mean recovery of 99% (range, 85% to 105%). Protein concentration in the fractions was measured in a Cobas Bio centrifugal analyzer by the Lowry technique as modified by Markwell et al.19 Isopropanol was added to the lipoprotein fractions to precipitate apolipoprotein (apo) B. ApoB is insoluble in isopropanol (unlike apoE and apoC), and thus apoB concentrations could be determined in the lipid fractions as the difference between total protein and supernatant protein (containing albumin, apoE, and apoC) after precipitation.20 The selective precipitation of apoB by isopropanol was confirmed by sodium dodecyl sulfate (SDS)–polyacrylamide gel electrophoresis (PAGE). The interassay CV for the protein measurements ranged from 2.2% for LDL to 5.7% for VLDL.

An aliquot of the isolated LDL was separated further by density gradient ultracentrifugation using the Beckman 70.1 Ti rotor. The method was based on the procedure described by Shen et al.21 The gradient was prepared by layering sodium bromide solutions of different densities (d) in the following order from the bottom of the tube to the top: 2 mL of d=1.0504 g/mL, 0.5-mL sample; 0.5 mL of d=1.0400 g/mL; 2 mL of d=1.0298 g/mL; 2 mL of d=1.0218 g/mL; and 2 mL of d=1.0170 g/mL. After centrifugation at 40 000 rpm for 40 hours, 18 0.5-mL aliquots (fractions) were removed and analyzed for cholesterol and protein content. The density of the fraction containing the greatest LDL mass was designated the peak density. A blank tube with only sodium bromide solutions was run in each centrifugation spin so that the final salt densities in each fraction could be measured by refractometry.

LDL size was determined by gradient gel electrophoresis22 with Phast gels from Pharmacia (Pharmacia LKB Biotechnology, Uppsala, Sweden). Forty-five microliters of the isolated LDL and 100 µL of standard protein were each mixed with 5 µL of 0.05% bromophenol blue. A standard was added, which contained proteins of known molecular weight and diameter and included the following: thyroglobulin (diameter, 17 nm), ferritin (diameter, 12.2 nm), catalase (diameter, 10.4 nm), and lactate dehydrogenase (diameter, 8.1 nm). Two microfilters of sample was applied to the gels and run on the Phast system according to a set program: Step 1, 400 V, 10.00 mA, 2.5 W, 15°C for 30 volt-hours; step 2, 400 V, 1.0 mA, 2.5 W, 15°C for 2 volt-hours; and step 3, 400 V, 10.00 mA, 2.5 W, 15°C for 268 volt-hours. After electrophoresis, the gels were stained with 0.05% Coomassie blue R-250, 50% methanol, and 10% acetic acid for 24 hours. The gels were destained with 10% methanol and 9% acetic acid until the background of
the gels was clear. The diameter of the LDL particles was determined by scanning the gels with a laser densitometer (LKB 2202 Ultrascan), and the migration distance for each LDL sample was measured relative to the migration distance of the standard proteins of known particle diameter.

Glycemic control was determined by both HbA1c and HbA1 assays because of a change in laboratory methods during the study. HbA1c levels were measured by immunoassay (Novo Nordisk, Dako) with a reference range of 2.8% to 4.4%, and HbA1 concentrations were determined by electroendosmosis (Corning) with a reference range of 4.5% to 7.1%. All results were converted to HbA1c concentrations (for statistical analysis) using the linear regression equation $y = 0.82x - 0.91$, where $y$ is HbA1c and $x$ is HbA1. This equation was determined on data from 173 patient samples (diabetic and nondiabetic) over a range of HbA1c from 4% to 16%. Agreement between these two methods across this range was confirmed by using a bias plot. The correlation coefficient ($r$) was used to evaluate the degree of linear association between variables.

**Results**

**General Characteristics and Total Lipid and Apolipoprotein Concentrations**

Age, BMI, HbA1c, fasting glucose, insulin, and insulin resistance are shown in Table 1. The diabetic patients tended to be older and heavier, but there were no significant differences between the groups. As expected, the NIDDM patients had higher fasting glucose, insulin, and HbA1c concentrations than the control subjects. The NIDDM patients were insulin resistant as assessed by the modified Harano technique, with a mean steady-state plasma glucose of 9.1 mmol/L in the NIDDM patients on diet only and 9.4 mmol/L in the NIDDM patients on diet and sulfonylurea therapy. Insulin sensitivity was not measured in the normal control subjects, but it is unlikely that they were insulin resistant because of their normal oral glucose tolerance tests and normal fasting insulin concentrations.

The groups were well matched for total cholesterol concentrations (5.7±0.5, 5.6±0.4, and 5.6±0.5 mmol/L in control subjects, NIDDM patients on diet only, and NIDDM patients on diet and sulfonylurea therapy, respectively) and for total triglyceride concentrations (1.4±0.6, 1.7±0.8, and 1.5±0.6 mmol/L in the same groups). There was no significant difference in the apoB concentrations between the groups (Table 1).

**Lipid Concentrations**

In the lipid fractions VLDL, IDL, and LDL, there were no significant differences in the lipid concentrations among the three groups, although in both diabetic groups VLDL triglyceride concentrations were higher and HDL cholesterol concentrations lower than in the normal control subjects (Tables 2, 3, and 4). There was, however, a significant reduction in the protein content of the HDL fraction in the diabetic patients (Table 5).

**Composition of Lipoproteins**

Although there were no changes in the concentrations of the lipoproteins in the LDL fraction, there were...
marked differences in the lipoprotein composition of the LDL particles (Table 6). The relative composition of each lipid component in the LDL particle was calculated from the mass of the lipid component–apoB weight ratio (the mass of apoB remains constant in each lipoprotein particle). The total lipid mass–apoB mass ratio, which determines the mean density of LDL particles, showed a reduction in both diabetic groups. The reduction was due to a decreased cholesterol-apoB ratio, with loss of both cholesterol esters and free cholesterol from the LDL particles. The loss of cholesterol esters resulted in a reduction of core lipids in LDL particles (Table 6).

The difference in density of the LDL particles was confirmed when isolated LDL was separated further by density gradient ultracentrifugation. The results showed a shift in the average peak density (ie, the fraction with the greatest lipid mass) from fraction 10 in the normal control subjects, to fraction 13 in the NIDDM patients on diet only, and to fraction 14 in the NIDDM patients on diet and sulfonylurea therapy. This represented a significant shift in peak density from a range of 1.0320 g/mL to 1.0365 g/mL to 1.0380 g/mL and is shown diagrammatically in the Figure. The sizes of the LDL particles were smaller in both diabetic groups compared to fraction 10 in the normal control subjects, to fraction 13 in the NIDDM patients on diet only, and to fraction 14 in the NIDDM patients on diet and sulfonylurea therapy, respectively (P<.05).

Correlation coefficients were calculated with LDL size and LDL peak density as dependent variables and with BMI, total triglyceride concentration, HbA1c, insulin, and insulin resistance as independent variables. This analysis was first carried out for all subjects (control and NIDDM subjects) and showed that LDL peak density correlated independently with total triglyceride concentrations and insulin and that LDL size correlated independently with total triglyceride concentrations, HbA1c, and insulin levels (Table 7). When both diabetic groups were analyzed together (excluding the normal control subjects), total triglyceride concentrations and insulin resistance correlated with LDL peak density, but only total triglyceride concentrations correlated significantly with LDL particle size (Table 8).

### Discussion

This study has demonstrated that compositional abnormalities thought to be atherogenic exist in NIDDM patients who are only mildly hyperlipidemic. The modest degree of hyperlipidemia is shown by the fact that in northern England, 50% of the male population has a cholesterol concentration >5.9 mmol/L and triglyceride concentration >1.9 mmol/L, values which are greater than the mean values for NIDDM patients (cholesterol concentration, 5.6 mmol/L; triglyceride concentration, 1.6 mmol/L) and control subjects (cholesterol concentration, 5.7 mmol/L; triglyceride concentration, 1.4 mmol/L) included in the present study.

### Table 3. Lipid Concentrations in the IDL Fraction in NIDDM and Normal Subjects

<table>
<thead>
<tr>
<th>Lipid Concentration</th>
<th>NIDDM</th>
<th>Control subjects</th>
<th>Diet only</th>
<th>Diet and drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>0.15 ±0.1</td>
<td>0.17 ±0.07</td>
<td>0.15 ±0.08</td>
<td></td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>0.28 ±0.1</td>
<td>0.32 ±0.1</td>
<td>0.28 ±0.1</td>
<td></td>
</tr>
<tr>
<td>Free cholesterol (mmol/L)</td>
<td>0.14 ±0.03</td>
<td>0.14 ±0.03</td>
<td>0.12 ±0.04</td>
<td></td>
</tr>
<tr>
<td>Cholesteryl ester (mmol/L)</td>
<td>0.22 ±0.06</td>
<td>0.18 ±0.06</td>
<td>0.16 ±0.07</td>
<td></td>
</tr>
<tr>
<td>Phospholipid (mmol/L)</td>
<td>0.14 ±0.06</td>
<td>0.13 ±0.03</td>
<td>0.11 ±0.04</td>
<td></td>
</tr>
<tr>
<td>ApoB (g/L)</td>
<td>0.07 ±0.07</td>
<td>0.08 ±0.02</td>
<td>0.06 ±0.03</td>
<td></td>
</tr>
</tbody>
</table>

IDL, intermediate-density lipoprotein; NIDDM, non-insulin-dependent diabetes mellitus; apo, apolipoprotein. Results are expressed as the mean±SD.

### Table 4. Lipid Concentrations in the LDL Fraction in NIDDM and Control Subjects

<table>
<thead>
<tr>
<th>Lipid Concentration</th>
<th>NIDDM</th>
<th>Control subjects</th>
<th>Diet only</th>
<th>Diet and drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>0.20 ±0.05</td>
<td>0.19 ±0.06</td>
<td>0.18 ±0.04</td>
<td></td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>2.68 ±0.4</td>
<td>2.63 ±0.4</td>
<td>2.72 ±0.4</td>
<td></td>
</tr>
<tr>
<td>Free cholesterol (mmol/L)</td>
<td>0.85 ±0.1</td>
<td>0.82 ±0.1</td>
<td>0.83 ±0.1</td>
<td></td>
</tr>
<tr>
<td>Cholesteryl ester (mmol/L)</td>
<td>1.85 ±0.32</td>
<td>1.81 ±0.3</td>
<td>1.88 ±0.3</td>
<td></td>
</tr>
<tr>
<td>Phospholipid (mmol/L)</td>
<td>0.72 ±0.14</td>
<td>0.76 ±0.18</td>
<td>0.76 ±0.17</td>
<td></td>
</tr>
<tr>
<td>ApoB (g/L)</td>
<td>0.64 ±0.11</td>
<td>0.71 ±0.09</td>
<td>0.71 ±0.11</td>
<td></td>
</tr>
</tbody>
</table>

LDL, low-density lipoprotein; NIDDM, non-insulin-dependent diabetes mellitus; apo, apolipoprotein. Results are expressed as the mean±SD.

### Table 5. Lipid Concentrations in the HDL Fraction in NIDDM and Normal Subjects

<table>
<thead>
<tr>
<th>Lipid Concentration</th>
<th>NIDDM</th>
<th>Control subjects</th>
<th>Diet only</th>
<th>Diet and drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>0.16 ±0.03</td>
<td>0.16 ±0.03</td>
<td>0.15 ±0.02</td>
<td></td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>1.47 ±0.31</td>
<td>1.30 ±0.31</td>
<td>1.31 ±0.27</td>
<td></td>
</tr>
<tr>
<td>Free cholesterol (mmol/L)</td>
<td>0.33 ±0.08</td>
<td>0.30 ±0.07</td>
<td>0.30 ±0.06</td>
<td></td>
</tr>
<tr>
<td>Cholesteryl ester (mmol/L)</td>
<td>1.14 ±0.24</td>
<td>1.0 ±0.25</td>
<td>1.0 ±0.21</td>
<td></td>
</tr>
<tr>
<td>Phospholipid (mmol/L)</td>
<td>0.91 ±0.2</td>
<td>0.78 ±0.2</td>
<td>0.80 ±0.2</td>
<td></td>
</tr>
<tr>
<td>Protein (g/L)</td>
<td>1.69 ±0.2</td>
<td>1.55 ±0.2*</td>
<td>1.35 ±0.5*</td>
<td></td>
</tr>
</tbody>
</table>

HDL, high-density lipoprotein; NIDDM, non-insulin-dependent diabetes mellitus. Results are expressed as the mean±SD.

*Significant difference between the NIDDM groups and the control subjects by the Student-Newman-Keuls test at P<0.05.
TABLE 6. Lipoprotein Composition of LDL Particles in NIDDM and Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>Control subjects</th>
<th>Diet only</th>
<th>Diet and drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG/apoB</td>
<td>0.28±0.09</td>
<td>0.24±0.07</td>
<td>0.23±0.06</td>
</tr>
<tr>
<td>Chol/apoB</td>
<td>1.61±0.17</td>
<td>1.43±0.15</td>
<td>1.48±0.12</td>
</tr>
<tr>
<td>CE/apoB</td>
<td>1.11±0.1</td>
<td>0.99±0.12</td>
<td>1.02±0.11</td>
</tr>
<tr>
<td>FC/apoB</td>
<td>0.50±0.07</td>
<td>0.44±0.07</td>
<td>0.45±0.05</td>
</tr>
<tr>
<td>Phos/apoB</td>
<td>0.86±0.13</td>
<td>0.82±0.13</td>
<td>0.82±0.12</td>
</tr>
<tr>
<td>Lipid/apoB</td>
<td>3.75±0.31</td>
<td>3.50±0.28</td>
<td>3.54±0.22</td>
</tr>
<tr>
<td>Core/apoB</td>
<td>2.80±0.73</td>
<td>2.24±0.37</td>
<td>2.35±0.56</td>
</tr>
<tr>
<td>Surface/apoB</td>
<td>1.36±0.19</td>
<td>1.27±0.19</td>
<td>1.27±0.15</td>
</tr>
</tbody>
</table>

LDL, low-density lipoprotein; NIDDM, non-insulin-dependent diabetes mellitus; TG, triglycerides; apo, apolipoprotein; chol, cholesterol; CE, cholesteryl ester; FC, free cholesterol; phos, phospholipid; lipid, TG+cholesterol+phos+apoB; core, CE+TG; surface, FC+phos. Lipid components per particle are expressed as lipid mass to apoB mass ratio. Results are expressed as the mean±SD.

*Significant difference between the NIDDM groups and the control subjects by the Student-Newman-Keuls test at P<.05.

The main lipoprotein abnormalities that occur in NIDDM are increased VLDL concentrations and associated decreased HDL concentrations. In the present study there was a trend toward higher VLDL triglyceride concentrations and lower HDL cholesterol concentrations in both diabetic groups compared with the control subjects. Although these differences are not as marked as in previous findings, this probably reflects the modest degree of hyperlipidemia in the present study together with the close matching of the groups for total cholesterol and triglyceride concentrations.

In the LDL fraction there were no significant differences in lipid concentrations between diabetic and control subjects in contrast to previous investigations. In the study by Joven et al, the groups were well matched for total cholesterol concentrations, although there was a wide range of total triglyceride concentrations (mean±SD, 1.6±2.0 mmol/L), possibly accounting for the increased LDL cholesterol and IDL triglyceride concentrations seen in the diabetic patients. Kasama et al found increased cholesterol concentrations in the IDL-1 (Sf 20 to 60) subfraction in NIDDM patients but no significant difference in the IDL-2 (Sf 12 to 20) subfraction, which corresponds more closely to the LDL fraction defined in this study.
women. However, in NIDDM the relation between insulin resistance and plasma lipoproteins is complex. Peripheral insulin resistance is associated with increased nonesterified fatty acid concentrations and hepatic glucose production, both of which are important for triglyceride synthesis in the liver. Laakso et al have shown correlations between VLDL triglyceride concentrations and insulin resistance. Despite the fact that the NIDDM patients in the present study did not have marked hypertriglyceridemia, there was still a trend toward increased VLDL triglyceride concentrations in these patients.

Insulin resistance may be important in the catabolism of VLDL, IDL, and LDL. Lipoprotein lipase activity is dependent on insulin and has been shown to be reduced in NIDDM patients. As lipoprotein lipase acts preferentially on large particles, limiting amounts or a reduced activity of the enzyme may result in accumulation of smaller remnant particles. The additional catabolism of IDL to LDL, which may involve hepatic lipase, may also be affected by insulin resistance, as strong correlations between insulin resistance and increased hepatic lipase activity have been described.

Thus, formation of the small, dense LDL particles may well be due to insulin resistance and its effect on both lipoprotein and hepatic lipase activity.

The modification of the LDL particle is important in regard to its subsequent metabolism. Galeano et al reported that small, dense LDL particles showed decreased immunoreactivity with a monoclonal antibody that recognizes the apoB receptor-binding site. In NIDDM there may be additional alterations in LDL particles that contribute to changes in metabolism. Glycation of as few as 2% to 5% of the lysine residues in LDL decreases its catabolism by 5% to 25%. Insulin may also influence LDL catabolism, as in vivo studies have demonstrated that insulin may directly enhance LDL receptor activity and insulin therapy increases the LDL apoB catabolic rate in NIDDM patients by 19%. Thus, insulin resistance in NIDDM could decrease LDL clearance, possibly allowing more time for glycation and oxidation of LDL, both of which processes have been linked to increased uptake by macrophages, foam cell formation, and the development of atherosclerosis.

In the present study, the fact that no subjects were receiving cardioactive drugs allowed us to examine the effect of sulfonylurea therapy on lipoprotein composition. Previous investigations have shown that sulfonylureas improve lipid profiles mostly by improving glycemic control, an effect not seen in this study, as both diabetic groups were well matched in this respect. However, although there were no significant differences between diet-controlled NIDDM patients and NIDDM patients on treatment and diet, the latter group of patients were more insulin resistant and had a greater shift in peak density of the LDL particles.

In contrast to the small, dense LDL particles in NIDDM patients, type I diabetic patients (IDDM) have been shown to have large LDL particles. These differences could be explained by the role of insulin action in determining lipoprotein composition, with the relative lack of insulin (insulin resistance) being linked to smaller LDL particles as in NIDDM and appropriate insulin treatment in IDDM resulting in larger LDL particles. The presence of proinsulin molecules in NIDDM may also contribute to and explain the contrasting results.

In conclusion, the present study has demonstrated that small, dense LDL particles occur in NIDDM patients who are mildly hyperlipidemic. The size of the LDL particles in the NIDDM patients correlated with triglyceride concentrations, and the peak density of the LDL particles in these patients correlated with triglyceride concentrations, insulin, and insulin resistance. Although conclusions concerning a causal relationship cannot be drawn, these findings are important in improving our understanding of both the formation of LDL particles and their further metabolism. In view of these potentially atherogenic changes in NIDDM patients with mildly abnormal lipid concentrations, further management aimed at preventing coronary heart disease in diabetes should consider the effect of treatment, not just on the total lipid concentrations but also on the composition of the lipoprotein fractions.

References


Lipoprotein compositional abnormalities and insulin resistance in type II diabetic patients with mild hyperlipidemia.
M W Stewart, M F Laker, R G Dyer, F Game, J Mitcheson, P H Winocour and K G Alberti

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