**LDL Subclass Phenotypes and Triglyceride Metabolism in Non-Insulin-Dependent Diabetes**

Kenneth R. Feingold, Carl Grunfeld, Miyin Pang, William Doerrler, and Ronald M. Krauss

Plasma low density lipoprotein (LDL) comprises multiple discrete subclasses differing in size, density, and chemical composition. A common, heritable phenotype characterized by the predominance of small, dense LDL particles (LDL subclass phenotype B) is associated with relatively increased concentrations of plasma triglycerides, reduced levels of high density lipoprotein, and increased risk of coronary artery disease in comparison with subjects with larger LDL (LDL subclass phenotype A). Population studies have indicated that approximately 20–30% of adult men have phenotype B, and another 15–20% have LDL of intermediate size. The lipid changes in phenotype B are similar to those that have been observed in patients with non-insulin-dependent diabetes mellitus (NIDDM). In the present study, we have assessed LDL subclass phenotypes in normolipidemic men with NIDDM and in age-matched control subjects who had similar lipid levels. There was a greater than twofold increase in the percentage of individuals with the LDL B phenotype in the NIDDM subjects. The LDL B phenotype was associated with higher plasma triglyceride levels and a trend toward lower high density lipoprotein cholesterol levels compared with the LDL A phenotype in the NIDDM subjects, as has been previously observed in control groups. Indices of diabetic control, such as fasting and hemoglobin A1c levels, were similar regardless of LDL phenotype pattern, suggesting that glycemic control was not likely to account for the increase in the LDL B phenotype. In both control and NIDDM subjects, the clearance of triglyceride-rich lipoproteins was slowed in the subjects with the LDL phenotype B compared with those with the A phenotype. Multiple regression analysis demonstrated that the diagnosis of NIDDM is an independent predictor of the LDL B phenotype. In summary, the present study demonstrates that NIDDM is associated with an increased prevalence of the LDL subclass phenotype B, even in the absence of frank hyperlipidemia. Thus, genetic and metabolic factors leading to the predominance of small, dense LDL may contribute to the increased risk of vascular disease in patients with NIDDM. (Arteriosclerosis and Thrombosis 1992;12:1496–1502)

**KEY WORDS** • non-insulin-dependent diabetes mellitus • low density lipoprotein subclasses • triglyceride metabolism

Plasma low density lipoprotein (LDL) comprises multiple discrete subclasses differing in size, density, and chemical composition. Initial studies demonstrated that approximately 65–75% of the general population has a predominance of large LDL particles, designated subclass pattern A; 20–30% of the population has a predominance of small, dense LDL particles, designated subclass pattern B; and a variable portion (15–20%) of the population has an intermediate pattern. Complex segregation analysis has indicated heritability of these phenotypic patterns, with evidence for a single major gene and an autosomal dominant pattern of inheritance of the LDL B phenotype. However, the penetrance of the LDL B phenotype is reduced in young males (<20 years of age) and premenopausal females. Recently, the LDL subclass B phenotypes have been genetically linked to a locus on chromosome 19, near that of the LDL receptor gene locus.

Increased plasma levels of triglycerides, very low density lipoprotein (VLDL), and intermediate density lipoprotein are associated with the LDL subclass B phenotype. High density lipoprotein (HDL) cholesterol levels are reduced because of a decrease in HDL2 with no change in HDL1 levels. In parallel with these changes, apoprotein B levels are increased and apoprotein A-I levels are decreased in individuals with the LDL B phenotype. The lipid and lipoprotein variations found in the LDL subclass B phenotype are associated with an approximately threefold increased risk of myocardial infarction.

Individuals with non-insulin-dependent diabetes mellitus (NIDDM) have an increased incidence of atherosclerotic vascular disease that is not entirely accounted for by the usual risk factors, such as elevated serum cholesterol concentrations, decreased HDL cholesterol levels, hyper-
tension, cigarette smoking, etc.12,13 Furthermore, patients with NIDDM commonly have a type of dyslipidemia characterized by elevations of plasma triglycerides and reductions in HDL cholesterol similar to those seen in conjunction with the LDL subclass phenotype B.14,15 Therefore, in the present study, we determined LDL subclass phenotypes in subjects with NIDDM but without severe dyslipoproteinemia.

Methods

Patients

All subjects in the study were male. The subjects with diabetes (n=29) had a history of two fasting serum glucose values greater than 140 mg/dl and were being treated with either oral hypoglycemic agents or insulin. None of the diabetic subjects had a history of ketoacidosis, and they were classified as NIDDM on the basis of clinical criteria. NIDDM subjects with fasting plasma triglyceride levels greater than 325 mg/dl were excluded from this study. Control subjects (n=87) did not have diabetes, kidney failure, nephrotic syndrome, active liver disease, or other disorders that would affect lipid metabolism. None of the control subjects or diabetics were receiving hypolipidemic therapy or were taking drugs that might affect lipid metabolism. The control subjects were age matched to those with NIDDM.

Analytical Methods

Plasma triglyceride, cholesterol, HDL cholesterol, glucose, and hemoglobin A1c levels were determined by standard laboratory procedures. LDL cholesterol content was calculated by the method of Friedewald et al.16

Nondenaturing gradient gel electrophoresis of whole plasma was performed on 2-16% polyacrylamide gradient gels and analyzed by using a lipid stain (oil red O) followed by scanning with a Transdyne RFT scanning densitometer.7,10 Particle diameters were calculated from calibration curves by using protein standards of known size. Each subject’s scan was classified into one of three patterns (type A, type B, or intermediate) by one author (R.K.) using criteria previously described8-11 without knowledge of the clinical history or classification of the patient.

Triglyceride Clearance

All of the NIDDM subjects and an equal number of control subjects had the clearance of triglyceride-rich particles determined by the intravenous fat-tolerance test as described previously.17 In brief, after fasting plasma samples were drawn, the subjects were given 20% Liposyn II intravenous fat emulsion (Abbott Laboratories, North Chicago, Ill.) at a dose of 0.1 g/kg body wt. Plasma samples were then taken every 5 minutes for 30 minutes and then every 10 minutes for the next 20 minutes. Clearance was measured by nephelometry. Regression of a semilog plot of clearance was linear for each patient, and the half-time (t1/2) was determined by using SIGMA-PILOT software. The t1/2 for clearance by this method is not influenced by triglyceride levels in disorders with VLDL overproduction (reviewed in Reference 17).

Statistics

Differences between groups were analyzed by Student’s t test. Prevalence was compared by the χ² test. Multiple regression analysis and analysis of variance were performed with the STATVIEW II statistical package.

Results

Demographic Data and Plasma Lipid Levels

Table 1 presents the demographic data and plasma lipid levels in control and NIDDM subjects. As expected, body mass index is increased in the subjects with NIDDM. In these NIDDM subjects, plasma triglyceride and HDL cholesterol levels are similar to those of the control group, whereas small but statistically significant decreases in total plasma cholesterol and LDL cholesterol levels were seen. The absence of increases in plasma lipid levels in the NIDDM compared with control subjects is most probably due to the fact that we specifically excluded from this study NIDDM subjects with elevated triglyceride levels (plasma triglyceride levels >325 mg/dl) and those who were being treated with hypolipidemic drugs.

| Table 1. Demographic Data and Plasma Lipid Levels in Control and NIDDM Subjects |
|-----------------|-----------------|-----------------|-----------------|
|                  | Age (years)     | BMI (kg/m²)     | Triglyceride    | Cholesterol     | HDL cholesterol | LDL cholesterol |
| Control (n=87)  | 60±0.86         | 25±0.33         | 123±6.4         | 207±3.0         | 46±1.3          | 136±2.7         |
| Diabetic (n=29) | 62±2.3          | 28±0.82*        | 123±12.1        | 190±5.5*        | 42±2.0          | 124±4.6†        |

NIDDM, non-insulin-dependent diabetes mellitus; BMI, body mass index; HDL, high density lipoprotein; LDL, low density lipoprotein. All triglyceride and cholesterol measurements are in milligrams per deciliter.

* p<0.01 vs. control; † p<0.05 vs. control.

LDL Phenotype in Control and Diabetic Subjects

As shown in Table 2, in these NIDDM subjects there is an increase (116%) in the percentage of individuals with the LDL B phenotype and a decrease (41%) in the LDL A phenotype compared with control subjects. The percentage of individuals with the intermediate phenotype is similar in NIDDM and control subjects. Thus, diabetes, a disorder that can cause alterations in triglyceride metabolism, is associated with an increased prevalence of the LDL subclass phenotype B even when hypertriglyceridemic subjects are excluded.

| Table 2. LDL Phenotypes in Control and NIDDM Subjects |
|-----------------|-----------------|-----------------|
|                  | A (%)           | Intermediate (%) | B (%)           |
| Control (n=87)  | 47              | 29              | 24              |
| Diabetic (n=29) | 28              | 21              | 52              |

p<0.025 NS p<0.025

LDL, low density lipoprotein; NIDDM, non-insulin-dependent diabetes mellitus.
**Table 3. Demographic Data and Plasma Lipid Levels in Controls Subjects According to LDL Phenotype**

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Age (years)</th>
<th>BMI (kg/m²)</th>
<th>Triglyceride</th>
<th>Cholesterol</th>
<th>HDL cholesterol</th>
<th>LDL cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (n=41)</td>
<td>60±1.3</td>
<td>24±0.45</td>
<td>87±4.6</td>
<td>202±4.1</td>
<td>52±1.8</td>
<td>132±3.9</td>
</tr>
<tr>
<td>Intermediate</td>
<td>58±1.6</td>
<td>26±0.70</td>
<td>127±5.3</td>
<td>211±6.4</td>
<td>43±2.3</td>
<td>139±5.2</td>
</tr>
<tr>
<td>B (n=21)</td>
<td>61±1.6</td>
<td>26±0.48</td>
<td>187±16.3</td>
<td>214±4.9</td>
<td>37±1.6</td>
<td>139±5.5</td>
</tr>
<tr>
<td>A vs. intermediate</td>
<td>NS</td>
<td>p&lt;0.05</td>
<td>p&lt;0.001</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>A vs. B</td>
<td>NS</td>
<td>p&lt;0.01</td>
<td>p&lt;0.001</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Intermediate vs. B</td>
<td>NS</td>
<td>p&lt;0.01</td>
<td>p&lt;0.001</td>
<td>NS</td>
<td>p&lt;0.05</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Diabetic Data and Plasma Lipid Levels According to LDL Phenotype**

Table 3 presents the demographic data and plasma lipid levels in control subjects divided by LDL phenotypes. As was seen in previous studies, there is an increase in plasma triglyceride levels and a decrease in HDL cholesterol levels in control subjects with the LDL B phenotype compared with subjects with the LDL A phenotype. Control subjects with the intermediate LDL phenotype have plasma triglyceride and HDL cholesterol levels that are between those for the A and B phenotypes. Thus, the presence of the LDL B phenotype is associated with an atherogenic lipid profile.

Table 4 presents the demographic data and plasma lipid levels in NIDDM subjects within each LDL phenotype. As observed in control subjects, the LDL B phenotype is associated with higher plasma triglyceride levels in NIDDM subjects within each LDL phenotype. As was seen in previous studies, there is an increase in plasma triglyceride levels and a decrease in HDL cholesterol levels in NIDDM subjects within each LDL phenotype. Most importantly, the diagnosis of NIDDM is also an independent predictor of the LDL B phenotype. Similar regression coefficients for the lipid variables were found for the control subjects when considered separately, whereas none of the coefficients was significant for the NIDDM subjects considered separately (data not shown).

**Triglyceride Clearance and LDL Phenotype**

In the NIDDM subjects and in a subset of the control subjects, the clearance of triglyceride-rich particles was determined by the intravenous fat-tolerance test. In these control subjects, as shown in Figure 1A, mean plasma triglyceride levels are elevated in subjects with the LDL B phenotype compared with the LDL A phenotype. Importantly, indices of diabetic control, such as fasting glucose and hemoglobin A₁, levels, are similar regardless of LDL phenotypic pattern, and thus glycemic control is not likely to account for the increase in the LDL B phenotype.

**Multiple Regression Analysis of Factors Contributing to the LDL B Phenotype**

A multiple regression model for the effect of key variables on the LDL B phenotype for the entire group is shown in Table 5. Plasma triglyceride levels are the strongest independent predictor of the LDL B phenotype. Reduced plasma HDL levels also predict LDL B phenotype. Most importantly, the diagnosis of NIDDM is also an independent predictor of the LDL B phenotype. Similar regression coefficients for the lipid variables were found for the control subjects when considered separately, whereas none of the coefficients was significant for the NIDDM subjects considered separately (data not shown).

**Table 4. Demographic Data and Plasma Lipid Levels in NIDDM Subjects According to LDL Phenotype**

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Age (years)</th>
<th>BMI (kg/m²)</th>
<th>Triglyceride</th>
<th>Cholesterol</th>
<th>HDL cholesterol</th>
<th>LDL cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (n=8)</td>
<td>60±4.1</td>
<td>26±1.6</td>
<td>92±15.9</td>
<td>190±7.0</td>
<td>48±6.00</td>
<td>124±6.0</td>
</tr>
<tr>
<td>Intermediate</td>
<td>58±5.9</td>
<td>28±1.3</td>
<td>73±9.1</td>
<td>166±12.8</td>
<td>47±5.2</td>
<td>105±10.4</td>
</tr>
<tr>
<td>B (n=15)</td>
<td>61±3.2</td>
<td>29±1.2</td>
<td>160±16.8</td>
<td>200±7.6</td>
<td>36±2.05</td>
<td>132±6.48</td>
</tr>
<tr>
<td>A vs. intermediate</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>A vs. B</td>
<td>NS</td>
<td>NS</td>
<td>p&lt;0.01</td>
<td>NS</td>
<td>p&lt;0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Intermediate vs. B</td>
<td>NS</td>
<td>NS</td>
<td>p&lt;0.001</td>
<td>p&lt;0.05</td>
<td>NS</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>

**Fasting glucose (mg/dl) and HbA₁* (%)**

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Fasting glucose</th>
<th>HbA₁* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (n=8)</td>
<td>217±24.1</td>
<td>13.5±1.52</td>
</tr>
<tr>
<td>Intermediate</td>
<td>204±26.0</td>
<td>13.9±1.39</td>
</tr>
<tr>
<td>B (n=15)</td>
<td>201±21.0</td>
<td>12.5±0.98</td>
</tr>
<tr>
<td>A vs. intermediate</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>A vs. B</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Intermediate vs. B</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

LDL, low density lipoprotein; BMI, body mass index; HDL, high density lipoprotein. All triglyceride and cholesterol measurements are in milligrams per deciliter.

*Normal range, 4.3–7.7.
TABLE 5. Multivariate Predictors of LDL Subclass Phenotype B

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Regression coefficient</th>
<th>SEM</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>0.014</td>
<td>0.018</td>
<td>NS</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>0.007</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.004</td>
<td>0.002</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>-0.018</td>
<td>0.006</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diagnosis*</td>
<td>-0.399</td>
<td>0.148</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

LDL, low density lipoprotein; BMI, body mass index; HDL, high density lipoprotein.
*Presence (0) or absence (1) of non-insulin-dependent diabetes mellitus.

...phenotype, but there is considerable overlap between the two groups. As shown in Figure 1B, the t_{1/2} of triglyceride clearance is delayed in subjects with the LDL B phenotype compared with subjects with the LDL A phenotype (LDL B, 24.5±2.4 minutes versus LDL A, 12.3±0.6 minutes; p<0.001). Subjects with the intermediate LDL phenotype have a clearance midway between these values (LDL intermediate, 17.4±1.6 minutes; p<0.05 versus LDL B, p<0.01 versus LDL A). Of note is that except for a single individual with LDL B, there is no overlap in clearance rates between the LDL B and LDL A groups, suggesting that the clearance rate of triglyceride-rich particles may be a strong marker for the LDL B phenotype. After adjustment for fasting plasma triglyceride by analysis of covariance the relation of fat clearance and LDL phenotype remained significant at p<0.05.

Figure 2A shows the plasma triglyceride distribution in the NIDDM subjects divided according to LDL subclass phenotype. As expected, plasma triglyceride levels are increased in subjects with the LDL B phenotype, but again, there is considerable overlap between groups. Similar to our observations in control subjects, the clearance of triglyceride-rich particles (Figure 1B) is delayed in NIDDM subjects with the LDL B phenotype compared with those with the LDL A phenotype (LDL B, 25.3±2.7 minutes versus LDL A, 13.8±1.8 minutes;
The LDL B phenotype is associated with increased plasma triglyceride levels. Whether hypertriglyceridemia itself leads to the formation of small, dense LDL or whether those who inherit the LDL B phenotype are more susceptible to the development of hypertriglyceridemia is unresolved. The transfer of triglyceride from triglyceride-rich lipoproteins to LDL in exchange for cholesterol has been postulated to alter the metabolism of LDL and thereby ultimately lead to the formation of small, dense LDL. However, small, dense LDL may arise from distinct precursors whose levels are influenced by variations in triglyceride metabolism.

Diabetes is associated with alterations in triglyceride metabolism. In studies including more subjects with diabetes, plasma triglyceride levels correlate directly with indices of glycemic control, and improvements in glycemic control by oral hypoglycemic agents or insulin therapy lead to decreases in plasma triglyceride concentrations. Studies have shown that the clearance of triglyceride-rich lipoproteins is decreased and the production of triglyceride-rich lipoproteins is increased in diabetes. The decrease in the clearance of triglyceride-rich lipoproteins may be due to decreased activity of lipoprotein lipase, an enzyme whose synthesis is dependent on insulin. The increase in hepatic triglyceride production is thought to be secondary in part to the increased delivery of free fatty acids to the liver in individuals who are in poor metabolic control.

In the present study, we demonstrate that the frequency of the LDL B phenotype is increased approximately twofold in normolipidemic subjects with NIDDM, whereas the frequency of the LDL A phenotype is decreased by 41%. The percentage of diabetic subjects with the intermediate phenotype is similar to that of control subjects. Studies by other investigators using different techniques to examine LDL size and composition have demonstrated that diabetic LDLs have increased heterogeneity, with a tendency to greater quantities of small, dense LDL.

To the best of our knowledge the present study is the first to classify a group of NIDDM subjects according to LDL subclass phenotype. There were no differences in fasting plasma glucose and hemoglobin A levels (indices of glycemic control) in the diabetic subjects with either the LDL A, B, or intermediate phenotype. This suggests that poor glycemic control is not a major factor in determining LDL phenotypic pattern. As expected, plasma triglyceride levels are increased and HDL cholesterol levels decreased in NIDDM subjects with the LDL B phenotype compared with NIDDM subjects with the LDL A phenotype. Of note is that despite the exclusion of diabetics with increased plasma triglyceride levels (triacylglyceride values >325 mg/dl) and those on hypolipidemic therapy, the present study still demonstrated an increased prevalence of the LDL B phenotype. It is likely that a study of diabetic subjects with hyperlipidemia, especially hypertriglyceridemia, would demonstrate an even higher prevalence of the LDL B phenotype.

Although the LDL B phenotype was related to plasma triglyceride values within both the control and NIDDM groups, plasma triglyceride levels in these NIDDM subjects and the control subjects were identical. Yet the NIDDM subjects had a higher prevalence of the LDL B phenotype, suggesting that rather than being simply related to increased plasma triglyceride levels per se, the development of the LDL B phenotype may be dependent on underlying changes in triglyceride metabolism. As shown in Figures 1A and 2A, there is considerable overlap in plasma triglyceride levels between individuals with the LDL A and B phenotypes. In contrast, in control subjects the clearance of triglyceride-rich particles is delayed approximately twofold in subjects with the LDL B phenotype, and there is little overlap between the individuals with the LDL A and B phenotypes. Only a single individual with the LDL B phenotype has a clearance rate within two standard deviations of the mean rate of clearance of the LDL A group (Figure 1B). These results suggest that the slowed clearance rate of triglyceride-rich particles may be a better marker for the LDL B phenotype in controls than are plasma triglyceride levels. In NIDDM, there is greater variability in the clearance of triglyceride-rich lipoproteins, which may reflect the underlying metabolic disorders. As a consequence there is a greater overlap in clearance rates between the LDL A and LDL B groups, although the degree of overlap of the clearance rates is still somewhat less than that observed with plasma triglyceride levels.

Interestingly, the diagnosis of diabetes is also an independent determinant for the presence of the LDL B phenotype. Whether this indicates a direct relation between NIDDM and the LDL B phenotype or whether this is merely due to NIDDM causing disturbances in lipid metabolism that are not taken into account in our multivariate analysis is unclear. Both NIDDM and the LDL B phenotype are genetically determined, and it is possible that they are linked. Insulin resistance is a characteristic abnormality in NIDDM, and preliminary studies have suggested that the prevalence of the LDL B phenotype is increased in non diabetic subjects who have insulin resistance. Thus, in NIDDM the
situation is potentially very complex, with the increased prevalence of the LDL B phenotype being secondary to a variety of factors, including hypertriglyceridemia, alterations in lipid metabolism not reflected in plasma lipid levels, and perhaps to a linkage between two common genetic disorders.

Regardless of the cause of the increased prevalence of the LDL B phenotype in NIDDM, these changes have important clinical implications. The LDL B phenotype is associated with an approximately threefold increased risk of myocardial infarction in nondiabetic subjects. This risk may be due to associated lipid abnormalities, such as increased serum triglyceride levels and decreased HDL cholesterol concentrations. Additionally, for any level of cholesterol there are more apoprotein B-containing particles, which may increase the risk of vascular disease. Lastly, small, dense LDL have been shown to have increased susceptibility to oxidation.

In summary, the present study demonstrates that NIDDM is associated with an increased prevalence of the LDL B phenotype, even in the absence of frank hyperlipidemia. This may account for some of the increased independent risk of vascular disease in patients with NIDDM.

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