Plasma and Lipoprotein Cholesterol and Triglyceride in the Pima Indian Population

Comparison of Diabetics and Nondiabetics

Barbara V. Howard, William C. Knowler, Barbara Vasquez, Annette L. Kennedy, David J. Pettitt, and Peter H. Bennett

Lipoprotein cholesterol and triglyceride concentrations were compared in diabetic and nondiabetic Pima Indians, a homogeneous population with a high occurrence of noninsulin-dependent diabetes mellitus. Data were available on 690 subjects with diabetes or impaired glucose tolerance. Total and very low density lipoprotein (VLDL) triglycerides were approximately 150% of the nondiabetic values, but very few diabetics had pronounced hypertriglyceridemia. Significant elevations in low density lipoprotein (LDL) triglyceride were also observed in diabetic men and women of all ages. Decreases in high density lipoprotein (HDL) cholesterol were similar in diabetic men and women, and the differences in HDL cholesterol were much greater in less obese individuals. Changes in HDL in the diabetics were reflected in all three subfractions, HDL₁, HDL₂, and HDL₃. Both total and LDL cholesterol were elevated in diabetic women, but not in diabetic men. Thus, there were greater changes in lipoprotein distribution in diabetic women. When multiple regression analysis was performed to examine the relationships in diabetics between lipoproteins and other variables, plasma glucose appeared to be the variable most closely associated with plasma lipoproteins in diabetics (positive with VLDL and LDL, negative with HDL). In diabetics, obesity was correlated with HDL but not VLDL, whereas alcohol consumption appeared to be associated with VLDL but not HDL.

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ing the effect of diabetes on plasma lipids. Moreover, the Pimas are subjects of a continuing epidemiological study. Thus, extensive data are available to allow the characterization of the diabetic state, the assessment of relationships among lipoproteins in diabetics, and assessment of variables such as age, sex, alcohol consumption, smoking, plasma glucose, and serum insulin concentrations that reportedly influence lipoproteins in nondiabetics.

**Methods**

**Study Subjects**

The study subjects were Pima Indians participating in a longitudinal population study in the Gila River Indian Community of Arizona. The protocols for this study have been approved by the human studies committee of the National Institutes of Health and by the Gila River Indian Community. Blood samples were collected for lipoprotein quantification between April 1979 and May 1982 from fasting subjects who were at least 15 years of age and of at least one-half Pima ancestry. The Pima study population over 15 years of age at that time consisted of approximately 1500 males and 1550 females. Fasting blood samples were obtained from 506 males (approximately 34%) and 885 females (approximately 57%). Fifty women who were pregnant or taking oral contraceptives were excluded.

Samples for lipoprotein determinations were obtained at the time of a routine biennial examination for the longitudinal study of diabetes. Written informed consent was obtained from each study subject. The examination included measurements of height, weight, and triceps skinfold thickness. A detailed medical history was obtained, and diabetes therapy was ascertained. Approximately 25 diabetics were on insulin therapy, and 160 were taking oral hypoglycemics. No significant differences in lipoprotein cholesterol and triglyceride were found in those receiving either oral hypoglycemic or insulin therapy; thus, diabetic subjects were not separated by treatment modes. Elimination of data from subjects receiving therapy did not alter the conclusions. Data on smoking habits were collected by using a designation of 0–3 (0 = never smoked; 1 = previously but not currently smoking; 2 = smoking up to one pack a day; and 3 = smoking more than one pack a day). For alcohol consumption, subjects were categorized according to the numbers of drinks a day (0 = none; 1 = less than one a day; 2 = one or two a day; 3 = three or more a day; and 4 = occasionally heavy drinker) without distinction of type of beverage consumed. Body mass index [BMI; wt(kg)/ht2(m2)] was used as the measure of obesity.

All subjects had an oral glucose tolerance test (75 g carbohydrate), and diabetes was diagnosed if the 2-hour postload plasma glucose level was at least 200 mg/dl at any survey examination or if the Indian Health Service hospital serving the community found a fasting, postprandial, or 2-hour postload plasma glucose concentration of at least 200 mg/dl. Impaired glucose tolerance (IGT) was diagnosed if the 2-hour postload glucose concentration was at least 140 but less than 200 mg/dl. It was previously established that diabetics in this population have Type II or noninsulin-dependent diabetes. Glucose was measured by the ferricyanide method and insulin by the Herbert modification of the radioimmunoassay of Berson and Yalow.

**Lipid and Lipoprotein Measurements**

Venous blood samples were collected in ethylenediaminetetraacetic acid (EDTA) after an overnight fast. Plasma was separated after centrifugation at approximately 700 g for 15 minutes at 10°C. A sample was removed for measurement of total cholesterol and triglyceride. Lipoproteins were then isolated by using ultracentrifugation procedures as described previously. Recovery of cholesterol in the lipoprotein fractions isolated by ultracentrifugation averaged 94%.

HDL fractions (HDL2b, HDL3a, and HDL3c) were isolated from HDL in a portion of the samples according to the method of Anderson et al. as described previously. Samples for HDL subfractions were not selected by clinical status and numbers, but were determined largely by laboratory workload. The recovery of cholesterol in the HDL subfractions averaged 96%.

Triglyceride and cholesterol in plasma and isolated lipoproteins were quantified on an autoanalyzer II (Technicon Instruments, Tarrytown, New York) by using the cholesterol extraction method of Rush et al. and the triglyceride enzymatic method of Bucolo and Davis. The triglyceride and cholesterol assays and HDL isolation procedure were standardized by using control plasma calibration pools supplied by the Lipid Standardization Laboratory, Centers for Disease Control (CDC), Atlanta, Georgia. Use of these controls resulted in stabilization of the population measurements over time and enabled direct comparison of the Pima data with values published for other U.S. populations. The coefficient of variation for the measurement of serum pools provided by the CDC was 2.8% for high cholesterol, 3.6% for low cholesterol, and 4.8% for triglyceride.

**Data Analysis**

Statistical analyses were performed by using the Statistical Analysis System, Cary, North Carolina. The significance of differences between means was assessed with Student’s t test. The relationships between two variables were assessed by Pearson correlation coefficients; for more than two variables, multiple linear regression analysis was used. Log transformations were used for triglyceride and insulin concentrations to make their distributions approximately normal. The differences between groups were assessed by analysis of covariance, with adjustment for age.
Results

Because noninsulin-dependent diabetes occurs over a wide age range in the Pima population, the subjects were divided into three age groups (Table 1). The prevalence of diabetes increased with age, so that in the younger age group a smaller proportion had diabetes or IGT, whereas in the older age group the majority had diabetes or IGT. The data demonstrate the frequent occurrence of obesity in all age groups in both nondiabetics and diabetics of this population. Diabetics were significantly heavier in the younger age groups; in the two older age groups, however, diabetics and nondiabetics did not differ significantly in BMI.

Lipoprotein Cholesterol in Diabetics Compared to Nondiabetics

In women, the total and LDL cholesterol levels, when adjusted for age by analysis of covariance, were significantly higher in diabetics than in nondiabetics (Table 2). In men, on the other hand, the total and LDL cholesterol levels were no different or even somewhat lower in diabetics than in nondiabetics. VLDL cholesterol, when adjusted for age, was higher in both diabetic men and women. HDL cholesterol was lower in both diabetic men and women than in nondiabetics. The difference, which ranged from 3 to 9 mg/dl in the various age groups, was significant in both men and women when adjusted for age by analysis of covariance.

In examining total and lipoprotein cholesterols in individuals with impaired glucose tolerance (Table 2), the values for total and VLDL cholesterol in women with impaired glucose tolerance were significantly elevated, when adjusted for age, compared to those of the nondiabetics, but were lower than those of the diabetics. HDL cholesterol levels in men and women with impaired glucose tolerance were significantly lower than in nondiabetics, but not significantly different from the diabetic group.

Lipoprotein Triglyceride in Diabetics Compared to Nondiabetics

Since total and VLDL triglycerides were not normally distributed, the significance of differences was evaluated by using the log of the concentrations. Values for total and VLDL triglycerides, when adjusted for age, were significantly higher in diabetic men and women (Table 3). The majority of the diabetics did not have elevations that could be considered as categorical hypertriglyceridemia (only 53 diabetic men and 66 diabetic women had plasma triglycerides above 200 mg/dl, and only nine diabetic men and six diabetic women had triglycerides above 500 mg/dl). LDL triglycerides were also significantly higher in both diabetic men and women when adjusted for age. Values for total, VLDL, and LDL triglycerides in those with impaired glucose tolerance were significantly different from both diabetics and nondiabetics, when adjusted for age, except for VLDL and LDL triglyceride in men.

Table 1. Characteristics of the Study Groups

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Diabetic status</th>
<th>No.</th>
<th>BMI*</th>
<th>Fasting glucose‡ (mg/dl)</th>
<th>2-hr glucose‡ (mg/dl)</th>
<th>No.</th>
<th>BMI*</th>
<th>Fasting glucose‡ (mg/dl)</th>
<th>2-hr glucose‡ (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15–34</td>
<td>Nondiabetic</td>
<td>190</td>
<td>31</td>
<td>94 ± 1</td>
<td>101 ± 2</td>
<td>278</td>
<td>31</td>
<td>91 ± 1</td>
<td>103 ± 1</td>
</tr>
<tr>
<td></td>
<td>Impaired glucose tolerance</td>
<td>26</td>
<td>36</td>
<td>107 ± 3</td>
<td>160 ± 3</td>
<td>55</td>
<td>34</td>
<td>101 ± 2</td>
<td>161 ± 2</td>
</tr>
<tr>
<td></td>
<td>Diabetic</td>
<td>34</td>
<td>35</td>
<td>195 ± 14</td>
<td>317 ± 20</td>
<td>61</td>
<td>36</td>
<td>210 ± 11</td>
<td>347 ± 15</td>
</tr>
<tr>
<td>35–54</td>
<td>Nondiabetic</td>
<td>57</td>
<td>31</td>
<td>98 ± 1</td>
<td>108 ± 3</td>
<td>83</td>
<td>33</td>
<td>99 ± 1</td>
<td>111 ± 2</td>
</tr>
<tr>
<td></td>
<td>Impaired glucose tolerance</td>
<td>22</td>
<td>31</td>
<td>108 ± 2</td>
<td>171 ± 3</td>
<td>53</td>
<td>35</td>
<td>107 ± 2</td>
<td>165 ± 2</td>
</tr>
<tr>
<td></td>
<td>Diabetic</td>
<td>95</td>
<td>30</td>
<td>202 ± 7</td>
<td>336 ± 11</td>
<td>161</td>
<td>34</td>
<td>212 ± 7</td>
<td>362 ± 10</td>
</tr>
<tr>
<td>≥55</td>
<td>Nondiabetic</td>
<td>23</td>
<td>27</td>
<td>95 ± 2</td>
<td>109 ± 5</td>
<td>20</td>
<td>31</td>
<td>95 ± 2</td>
<td>116 ± 4</td>
</tr>
<tr>
<td></td>
<td>Impaired glucose tolerance</td>
<td>9</td>
<td>27</td>
<td>97 ± 3</td>
<td>163 ± 6</td>
<td>18</td>
<td>34</td>
<td>106 ± 2</td>
<td>167 ± 4</td>
</tr>
<tr>
<td></td>
<td>Diabetic</td>
<td>50</td>
<td>27</td>
<td>180 ± 10</td>
<td>327 ± 16</td>
<td>106</td>
<td>28</td>
<td>217 ± 8</td>
<td>390 ± 14</td>
</tr>
</tbody>
</table>

BMI = body mass index as determined by the equation wt (kg)/ht^2(m)^2.
*Values are means with range in parentheses.
†Values are means ± SEM.
### Table 2. Plasma and Lipoprotein Cholesterol Values in Men and Women according to Diabetic Status

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Diabetic status</th>
<th>Men (mg/dl)</th>
<th></th>
<th></th>
<th>Women (mg/dl)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>VLDL‡</td>
<td>LDL‡</td>
<td>HDL§</td>
<td>Total‡</td>
<td>VLDL‡</td>
</tr>
<tr>
<td>15–34</td>
<td>Nondiabetic</td>
<td>171 ± 2</td>
<td>15 ± 1</td>
<td>115 ± 2</td>
<td>44 ± 1</td>
<td>160 ± 2</td>
<td>12 ± 1</td>
</tr>
<tr>
<td></td>
<td>Impaired glucose tolerance</td>
<td>186 ± 6</td>
<td>20 ± 3</td>
<td>127 ± 5</td>
<td>38 ± 1</td>
<td>162 ± 3</td>
<td>15 ± 2</td>
</tr>
<tr>
<td></td>
<td>Diabetic</td>
<td>186 ± 7</td>
<td>28 ± 4</td>
<td>122 ± 5</td>
<td>36 ± 1</td>
<td>172 ± 5</td>
<td>18 ± 1</td>
</tr>
<tr>
<td>35–54</td>
<td>Nondiabetic</td>
<td>187 ± 4</td>
<td>22 ± 2</td>
<td>124 ± 3</td>
<td>42 ± 2</td>
<td>175 ± 4</td>
<td>15 ± 1</td>
</tr>
<tr>
<td></td>
<td>Impaired glucose tolerance</td>
<td>187 ± 7</td>
<td>21 ± 2</td>
<td>126 ± 6</td>
<td>40 ± 1</td>
<td>172 ± 4</td>
<td>15 ± 1</td>
</tr>
<tr>
<td></td>
<td>Diabetic</td>
<td>186 ± 4</td>
<td>28 ± 4</td>
<td>116 ± 3</td>
<td>41 ± 1</td>
<td>183 ± 3</td>
<td>22 ± 1</td>
</tr>
<tr>
<td>≥55</td>
<td>Nondiabetic</td>
<td>185 ± 7</td>
<td>15 ± 2</td>
<td>124 ± 7</td>
<td>48 ± 2</td>
<td>189 ± 8</td>
<td>15 ± 2</td>
</tr>
<tr>
<td></td>
<td>Impaired glucose tolerance</td>
<td>178 ± 14</td>
<td>13 ± 3</td>
<td>116 ± 12</td>
<td>48 ± 5</td>
<td>204 ± 11</td>
<td>19 ± 3</td>
</tr>
<tr>
<td></td>
<td>Diabetic</td>
<td>180 ± 5</td>
<td>23 ± 2</td>
<td>117 ± 5</td>
<td>41 ± 1</td>
<td>190 ± 4</td>
<td>24 ± 1</td>
</tr>
</tbody>
</table>

Values are means ± SEM. Densities for LDL are d = 1.006–1.063.

*Significantly different in diabetics compared to nondiabetics and to individuals with impaired glucose tolerance (IGT) by Duncan’s multiple range test after adjusting for age.

†Significantly different in diabetics and IGTs compared to nondiabetics by Duncan’s multiple range test after adjusting for age.

‡Significantly different in diabetics, IGTs, and nondiabetics by Duncan’s multiple range test after adjusting for age.

§p < 0.05.

### Table 3. Plasma and Lipoprotein Triglycerides in Men and Women according to Diabetic Status

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Diabetic status</th>
<th>Men (mg/dl)</th>
<th></th>
<th></th>
<th></th>
<th>Women (mg/dl)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total‡</td>
<td>VLDL†</td>
<td>LDL§</td>
<td></td>
<td>Total‡</td>
<td>VLDL†</td>
<td>LDL§</td>
</tr>
<tr>
<td>15–34</td>
<td>Nondiabetic</td>
<td>121 ± 5</td>
<td>80 ± 4</td>
<td>36 ± 1</td>
<td></td>
<td>99 ± 3</td>
<td>60 ± 2</td>
<td>32 ± 1</td>
</tr>
<tr>
<td></td>
<td>Impaired glucose tolerance</td>
<td>148 ± 13</td>
<td>107 ± 13</td>
<td>47 ± 4</td>
<td></td>
<td>130 ± 17</td>
<td>79 ± 13</td>
<td>37 ± 2</td>
</tr>
<tr>
<td></td>
<td>Diabetic</td>
<td>220 ± 29</td>
<td>154 ± 25</td>
<td>60 ± 6</td>
<td></td>
<td>155 ± 11</td>
<td>97 ± 9</td>
<td>48 ± 3</td>
</tr>
<tr>
<td>35–54</td>
<td>Nondiabetic</td>
<td>154 ± 12</td>
<td>103 ± 9</td>
<td>45 ± 3</td>
<td></td>
<td>123 ± 6</td>
<td>72 ± 5</td>
<td>39 ± 2</td>
</tr>
<tr>
<td></td>
<td>Impaired glucose tolerance</td>
<td>157 ± 14</td>
<td>104 ± 12</td>
<td>45 ± 3</td>
<td></td>
<td>126 ± 8</td>
<td>72 ± 6</td>
<td>41 ± 2</td>
</tr>
<tr>
<td></td>
<td>Diabetic</td>
<td>204 ± 17</td>
<td>140 ± 17</td>
<td>50 ± 3</td>
<td></td>
<td>168 ± 9</td>
<td>108 ± 8</td>
<td>50 ± 3</td>
</tr>
<tr>
<td>≥55</td>
<td>Nondiabetic</td>
<td>119 ± 12</td>
<td>68 ± 9</td>
<td>40 ± 3</td>
<td></td>
<td>114 ± 11</td>
<td>65 ± 10</td>
<td>40 ± 3</td>
</tr>
<tr>
<td></td>
<td>Impaired glucose tolerance</td>
<td>108 ± 19</td>
<td>61 ± 16</td>
<td>36 ± 3</td>
<td></td>
<td>145 ± 17</td>
<td>88 ± 13</td>
<td>47 ± 3</td>
</tr>
<tr>
<td></td>
<td>Diabetic</td>
<td>167 ± 13</td>
<td>109 ± 11</td>
<td>48 ± 3</td>
<td></td>
<td>168 ± 8</td>
<td>106 ± 6</td>
<td>51 ± 2</td>
</tr>
</tbody>
</table>

Values for total and VLDL triglycerides are the arithmetic means (± SEM) with geometric means shown in parentheses. Significance of differences was assessed by using the log transformed data, since total and VLDL triglycerides were not normally distributed. Densities for LDL are d = 1.006–1.063.

*Significantly different in diabetics compared to nondiabetics and those with impaired glucose tolerance (IGT) by Duncan’s multiple range test after adjusting for age.

†Significantly different in diabetics and IGTs compared to nondiabetics by Duncan’s multiple range test after adjusting for age.

‡Significantly different in diabetics, IGTs, and nondiabetics by Duncan’s multiple range test after adjusting for age.

§p < 0.05.

†p < 0.01.
Influence of Obesity on Plasma Lipoproteins in Diabetics

Since there is such a high prevalence of obesity in the Pima population, the influence of obesity on the diabetes-related differences was evaluated by comparing lipoprotein values when the population was stratified into tertiles by BMI. The differences in total and VLDL triglycerides between diabetics and nondiabetics were similar regardless of obesity (data not shown). However, obesity appeared to have a marked influence on the diabetes-associated differences in HDL cholesterol (Figure 1). The largest decreases in HDL cholesterol occurred in the lower BMI tertile in both sexes. Nondiabetics in the upper tertile of obesity had much lower values for HDL cholesterol than those in the lower tertile, and there were no significant differences in diabetics in this group. In the middle BMI tertile, the relationships were intermediate between the lower and upper tertiles (data not shown).

Lipoprotein Cholesterol Distribution and HDL Subfractions in Diabetics

Women with diabetes had lower ratios of both HDL/total cholesterol and HDL/LDL cholesterol in all three age groups (Figure 2). On the other hand, men with diabetes had significantly lower ratios of HDL/total cholesterol and HDL/LDL cholesterol than nondiabetics only in the youngest age group.

The association between diabetes and HDL was examined further by measuring the distribution of HDL subfractions in diabetes over 35 years of age (Table 4). Diabetes was shown to be associated with lower concentrations of all three subfractions in both sexes. Since the changes were small, the differences, after adjustment for age, reached statistical significance only in the case of HDL₃.

Multiple Regression Analyses

When considering VLDL triglyceride in a multiple regression analysis that included obesity, plasma

Figure 1. Influence of obesity on differences in HDL cholesterol between diabetics and nondiabetics. The population was stratified into tertiles by body mass index (BMI) and into three age groups, as indicated. (●—●) = diabetics; (○—○) = nondiabetics. The BMI ranges were 16.6 to 28.0 for the lowest tertile, 28.1 to 34.3 for the middle tertile, and 34.4 to 72.6 for the upper tertile.

Figure 2. Lipoprotein cholesterol distribution in diabetic men and women compared to nondiabetics. Ratios were computed from lipoprotein and total cholesterol concentrations. (●—●) = diabetics; (○—○) = nondiabetics.
Table 4. High Density Lipoprotein (HDL) Subfractions in Men and Women over 35 Years according to Diabetic Status

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Diabetic status</th>
<th>Men (mg/dl)</th>
<th>Women (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HDL(_{2b})</td>
<td>HDL(_{3a})</td>
</tr>
<tr>
<td>35-54</td>
<td>Nondiabetic</td>
<td>5.0 ± 1.0</td>
<td>7.9 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>Impaired glucose tolerance</td>
<td>3.5 ± 0.2</td>
<td>7.9 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>Diabetic</td>
<td>4.6 ± 0.4</td>
<td>6.6 ± 0.4</td>
</tr>
<tr>
<td>≥55</td>
<td>Nondiabetic</td>
<td>6.1 ± 1.0</td>
<td>9.3 ± 1.2</td>
</tr>
<tr>
<td></td>
<td>Impaired glucose tolerance</td>
<td>6.4 ± 2.5</td>
<td>10.0 ± 4.7</td>
</tr>
<tr>
<td></td>
<td>Diabetic</td>
<td>4.8 ± 0.5</td>
<td>7.1 ± 0.6</td>
</tr>
</tbody>
</table>

Values are means ± SEM. Numbers of male subjects with data available for HDL subfractions were 30 nondiabetic, 10 with impaired glucose tolerance (IGT), and 62 diabetics aged 35–54 years, and 14, 3, and 30 older than 55 years, respectively. Numbers of female subjects were 48, 32, and 101 aged 35–54 years, and 15, 15, and 83 older than 55 years.

*Significantly different in diabetics compared to nondiabetics and IGTs by Duncan’s multiple range test after adjusting for age.
†Significantly different in diabetics and IGTs compared to nondiabetics by Duncan’s multiple range test after adjusting for age.

Table 5. Multiple Regression Coefficients of Selected Variables Related to Very Low Density Lipoprotein (VLDL) Triglyceride in Nondiabetics and Diabetics

<table>
<thead>
<tr>
<th>Sex</th>
<th>Diabetic status</th>
<th>BMI (kg/m²)</th>
<th>Plasma glucose (mg/dl)</th>
<th>Log serum insulin (µU/ml)</th>
<th>Alcohol</th>
<th>Smoking</th>
<th>Age (yrs)</th>
<th>Multiple R-square</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Nondiabetic</td>
<td>0.25</td>
<td>0.41*</td>
<td>49.36†</td>
<td>7.45</td>
<td>2.31</td>
<td>0.21</td>
<td>0.109</td>
</tr>
<tr>
<td></td>
<td>Diabetic</td>
<td>1.88</td>
<td>-0.30†</td>
<td>-18.95</td>
<td>9.00</td>
<td>8.40</td>
<td>-0.87</td>
<td>0.096</td>
</tr>
<tr>
<td>Female</td>
<td>Nondiabetic</td>
<td>0.13</td>
<td>0.10</td>
<td>34.50†</td>
<td>7.30*</td>
<td>3.45</td>
<td>0.41*</td>
<td>0.120</td>
</tr>
<tr>
<td></td>
<td>Diabetic</td>
<td>-0.69</td>
<td>0.17†</td>
<td>15.30</td>
<td>24.81†</td>
<td>-2.21</td>
<td>0.012</td>
<td>0.108</td>
</tr>
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</table>

Regression coefficients are shown for VLDL triglyceride in mg/dl per unit change in each variable, for ease of interpretation. Multiple regression analysis with log VLDL triglyceride yielded qualitatively similar results. The diabetic group includes those with impaired glucose tolerance.

Multiple regression analysis for plasma glucose was performed by using 2-hour postload glucose concentrations; similar results were obtained by using fasting glucose values.

Multiple regression analysis for log serum insulin was performed by using fasting insulin values; similar results were obtained by using 2-hour postload insulin values. Analysis was performed on the log-transformed values, since serum insulin was not normally distributed.

Alcohol consumption and smoking were relative measures (see Methods).

*p < 0.05.
†p < 0.01.
‡p < 0.001.

Discussion

The Pima population offered advantages for the evaluation of the influence of diabetes on plasma lipoproteins because a large number of diabetics...
Table 6. Multiple Regression Coefficients of Selected Variables Related to High Density Lipoprotein (HDL) Cholesterol in Nondiabetics and Diabetics

<table>
<thead>
<tr>
<th>Sex</th>
<th>Diabetic status</th>
<th>BMI (kg/m²)</th>
<th>Plasma glucose (mg/dl)</th>
<th>Log serum insulin (µU/ml)</th>
<th>Alcohol</th>
<th>Smoking</th>
<th>Age (yrs)</th>
<th>Multiple R-square</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Nondiabetic</td>
<td>-0.37†</td>
<td>-0.023</td>
<td>-2.49</td>
<td>2.12†</td>
<td>-0.20</td>
<td>0.50</td>
<td>0.121</td>
</tr>
<tr>
<td></td>
<td>Diabetic</td>
<td>-0.36‡</td>
<td>-0.015†</td>
<td>-6.22*</td>
<td>0.82</td>
<td>-0.26</td>
<td>0.0040</td>
<td>0.150</td>
</tr>
<tr>
<td>Female</td>
<td>Nondiabetic</td>
<td>-0.33‡</td>
<td>-0.068*</td>
<td>-8.38‡</td>
<td>2.73‡</td>
<td>-1.13</td>
<td>0.16‡</td>
<td>0.210</td>
</tr>
<tr>
<td></td>
<td>Diabetic</td>
<td>-0.13*</td>
<td>-0.007*</td>
<td>-3.75</td>
<td>-0.74</td>
<td>-0.70</td>
<td>0.090*</td>
<td>0.072</td>
</tr>
</tbody>
</table>

Regression coefficients are shown for HDL cholesterol in mg/dl per unit change in each variable. The diabetic group includes those with impaired glucose tolerance.

Multiple regression analysis for plasma glucose was performed by using 2-hour postload glucose concentrations; similar results were obtained by using fasting glucose.

Multiple regression analysis for log serum insulin was performed by using fasting insulin values; similar results were obtained by using 2-hour postload insulin values. Analysis was performed on the log-transformed values since serum insulin was not normally distributed.

Alcohol consumption and smoking were relative measures (see Methods).

*p < 0.05.
†p < 0.01.
‡p < 0.001.

Regression coefficients are shown for LDL cholesterol in mg/dl per unit change in each variable. The diabetic group includes those with impaired glucose tolerance.

Multiple regression analysis for plasma glucose was performed by using 2-hour postload glucose concentrations; similar results were obtained by using fasting glucose values.

Multiple regression analysis for log serum was performed by using fasting insulin values; similar results were obtained by using 2-hour postload insulin values. Analysis was performed on the log-transformed values since serum insulin was not normally distributed.

Alcohol consumption and smoking were relative measures (see Methods).

*p < 0.05.
†p < 0.01.
‡p < 0.001.
sults from the presence of genetic hyperlipemia; the
data also suggest that diabetes is most consistently
associated with mild hypertriglyceridemia. This is
supported by analyses of diabetics from a Lipid Re-
search Clinics population11 and from a hospital clinic
population, 32 in which the increased triglyceride lev-
els were about the same as those observed in this
study.

The elevations in triglycerides in the Pima diab-
etics were observed uniformly in men and women of all
ages. Furthermore, obesity did not seem to influence
the extent of the increase in triglyceride, which sug-
gests that overweight individuals with diabetes have
no greater probability of developing severe hyper-
triglyceridemia.

At least two mechanisms have been proposed for
the increases of plasma triglyceride in Type II diabe-
etics. A clearance defect has been postulated10, 32 as a
result of decreases in lipoprotein lipase observed in
Type II diabetics. A decreased fractional catabolic
rate for VLDL triglyceride has also been observed19
in metabolic studies of VLDL metabolism in a group
of young Pima male diabetics. However, in other
groups of Type II diabetics, overproduction of VLDL
triglyceride has also been observed9 in metabolic stud-
ies of VLDL metabolism in a group of young Pima male diabetics. However, in other
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HDL Changes In Diabetes

A second consistent finding in the Pima diabetics
was a lower HDL cholesterol, which occurred in both
sexes and at all ages. The difference in HDL chole-
sterol between diabetics and nondiabetics was rela-
tively small (3–9 mg/dl) but similar to that observed in
comparing individuals of low and high risk for cardio-
vascular disease.37 The changes in HDL in diabetics
occurred in all subfractions, so that in both men and
women HDL2a, HDL2b, and HDL3 were all lower in
diabetics compared to nondiabetics. Differences in
HDL cholesterol were much greater in the less obese
diabetics, because HDL concentrations were higher
in less obese nondiabetics.21 This confounding effect of obesity might explain some of the conflicting pre-
vious reports of changes in HDL levels in diabetics.
Differences in HDL between diabetics and nondia-
betics were similar in men and women. However,
women showed greater changes in lipoprotein chole-
sterol distribution, as measured by the ratios of
HDL/LDL or HDL/total cholesterol, presumably be-
cause LDL was higher in diabetic women.

There have been few studies that elucidate possi-
bile metabolic mechanisms for the diabetes-associ-
ated decrease in HDL. One possibility is that HDL is
decreased because of decreased lipoprotein lipase,
since HDL and lipoprotein lipase have been shown10
to be correlated in Type II diabetics. On the other
hand, postheparin hepatic lipase, which removes

HDL from the circulation, has been observed38 to be
high in obese diabetics.

**LDL in Diabetics**

In the Pima population, total and LDL cholesterol
were significantly elevated in diabetic women, but
not in diabetic men. The changes in LDL in women
were small, and were more consistent in the young-
est age group. The reason for this modulation of
hyperglycemia-related changes in LDL by age and
sex is not clear. Of great interest was the consistent,
significant increase in LDL triglyceride in both male
and female diabetics of all ages. This observation
implies that there may be changes in LDL composi-
tion in diabetics. This has been suggested previously
by Schonfeld et al.39 and Lopes-Virella et al.40 and
also by a previous study of Pima diabetics.7 This
composition difference might have an important
influence on LDL metabolism in diabetics.

**Variables Related to Plasma Lipids in Diabetics**

The variable most strongly correlated with VLDL
triglyceride in diabetics of both sexes was plasma
glucose. Neither serum insulin nor obesity correlated
significantly with VLDL triglyceride in diabetics after
all the other variables were considered. The most
significant correlates with HDL levels in diabetics
were obesity and plasma glucose. Among diabetics,
norther serum insulin nor alcohol were significantly
related to HDL. These data strongly suggest that in
diabetes the most important influence on plasma li-
roprotein levels is plasma glucose. In the case of
HDL, but not VLDL, this influence is modified by the
extent of obesity.

Although the extent of hyperglycemia is undoubt-
edly related to changing insulin levels in diabetes,
insulin was not significantly related to any of the lipoproteins in the multiple regression analyses and, in
addition, was negatively related to VLDL-triglyceride
in simple correlation analysis (data not shown). One
possible difficulty in assessing the relationship be-
tween insulin and plasma lipids is the nonlinear rela-
tionship between insulin and glucose; insulin in-
creases with plasma glucose (by 2 hours) until it
reaches approximately 200 mg/dl and is inversely
related to glucose in more hyperglycemic individ-
uals.41–42 However, when we conducted our present
analysis on diabetics without including those with
impaired glucose tolerance, thus separating the two
groups at the approximate point of inflection of the
relationship between insulin and glucose, we still did
not observe significant relationships between insulin
and VLDL triglyceride or HDL cholesterol among the
diabetics (data not shown).

The data for this study suggested that in diabetics,
alcohol was more closely associated with VLDL than
with HDL. It must be emphasized that the data col-
lection method for alcohol consumption did not di-
rectly quantify ounces of alcohol per day and, of
course, was subject to the limitations of patient cooperation and recall. Smoking in the present study showed little association with lipoproteins in diabetics. Since there is a very low occurrence of smoking in the Pima population (only 400 of 1341 patients reported current smoking in any amount), this issue must be examined in a population of diabetics with higher smoking prevalence.

**Lipoproteins and Cardiovascular Disease**

Previous studies have indicated that although arteriosclerotic cardiovascular disease in this population is relatively infrequent, it is more common among diabetics. The lipoprotein patterns observed in the Pima diabetics are consistent with those associated with cardiovascular disease. Although decreases in HDL were similar in diabetic men and women, the women had increased LDL and a greater change in lipoprotein distribution. This might be related to the greater influence of diabetes on cardiovascular risk in diabetic women. Finally, individuals with impaired glucose tolerance exhibited significant increases in VLDL and decreases in HDL, which suggests that individuals with only minimal impairment of glucose tolerance may incur increased risk for cardiovascular disease.

**Acknowledgments**

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