Lipoproteins, Apolipoproteins, and Low-Density Lipoprotein Size Among Diabetics in the Framingham Offspring Study

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Diabetes mellitus has been shown to be associated with lipid abnormalities. Prior studies have indicated that women with diabetes have a risk of coronary heart disease similar to that of men. We compared lipid parameters in diabetic and nondiabetic participants in cycle 3 of the Framingham Offspring Study. Values for plasma total cholesterol (TC), triglyceride, lipoprotein, cholesterol, apolipoprotein (apo) A1, B, apo and lipoprotein(a) [Lp(a)] and low-density lipoprotein (LDL) particle size were analyzed in 174 diabetic and 3,757 nondiabetic subjects. Data from a total of 2,025 men and 2,042 women participating in the third examination (1983 to 1987) of the Framingham Offspring Study were subjected to statistical analysis. Male and female diabetics showed lower high-density lipoprotein (HDL) cholesterol, higher triglycerides, higher very–low-density lipoprotein (VLDL) cholesterol, lower apo A1, and higher LDL particle scores, indicating smaller size, than nondiabetics. Female diabetics also showed significantly higher TC and apo B values than nondiabetics. The results remained statistically significant after controlling for obesity and menopausal status. The presence of small dense LDL particles (pattern B) was highly associated with diabetes and hypertriglyceridemia in both sexes, and the relative odds for pattern B remained significant in women but not in men after adjustment for age and hypertriglyceridemia. No differences in apo E isoform distribution were found for diabetics and nondiabetics. Diabetes was not associated with elevated LDL cholesterol levels. In conclusion, diabetics have lower HDL cholesterol and higher triglyceride levels and are more likely to have small dense LDL particles. Diabetes is not a secondary cause of elevated LDL cholesterol. Lipid screening of diabetics should include full quantification of lipids for proper assessment of potential atherosclerotic risk.

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IT HAS BEEN WELL established that diabetic patients are at increased risk for morbidity and mortality from cardiovascular disease.[1] The addition of diabetes to the other major cardiovascular risk factors, which include hypertension, cigarette-smoking, elevated low-density lipoprotein (LDL) cholesterol, and decreased high-density lipoprotein (HDL) cholesterol, elevates the overall risk for cardiovascular events.[1,2] Although many hypotheses exist, it is unclear exactly what specific abnormality or metabolic defects associated with diabetes augment cardiovascular risk.

Mechanisms proposed to increase the risk include glycosylation or oxidation of lipoproteins and arterial wall proteins, nephropathy and albuminuria, microvascular disease of the vaso-vasorum, hypertension, obesity, abnormalities in hemostasis and platelet function, and the various dyslipidemias associated with diabetes.[3] The dyslipidemias include altered concentration, composition, and metabolism of the lipoproteins. With improved laboratory techniques, these abnormalities have been defined with better detail than in the past.

The Framingham Offspring Study includes a cohort of more than 5,000 adults who are being evaluated to study risk factors for heart disease and other major diseases. This report presents cross-sectional data from the Offspring Study and compares serum lipids and characteristics of lipoproteins and apolipoproteins of the diabetic and nondiabetic participants.

SUBJECTS AND METHODS

Study Population

The design and methodology of the Framingham Offspring Study have been described elsewhere.[4] A total of 2,025 men and 2,042 women participating in the third examination (1983 to 1987) were studied. Participants were defined as diabetic if they were undergoing treatment for diabetes with insulin or oral hypoglycemic agents, or if their fasting glucose level at examinations 1, 2, or 3 was greater than 140 mg/dL. Persons with a diagnosis of diabetes before the age of 30 years or who were found to be ketosis-prone were classified as insulin-dependent (IDDM). All others were classified as non–insulin-dependent (NIDDM). Lipid data from the diabetics are compared with those from nondiabetics in the cohort referred to as controls. Women were classified as postmenopausal if they had not had a menstrual period within the previous 12 months.

Lipid and Apolipoprotein Analyses

After an overnight 12- to 14-hour fast, blood was drawn from the subjects into tubes containing EDTA (final concentration, 1 mg/mL). Plasma total cholesterol (TC), triglyceride, HDL cholesterol, and 1.006-g/mL infranate cholesterol levels were determined enzymatically on an Abbott Diagnostics ABA-2000 bichromatic analyzer as previously described.[5] The laboratory participates in the Lipid Laboratory Research Clinics standardization program of the Centers for Disease Control (Atlanta, GA). Within- and between-assay coefficients of variation were less than 3%. The HDL supernate was obtained after precipitation of apolipoprotein

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(apo)B–containing lipoproteins with dextran-Mg^{2+}.[6] Ultracentrifugation of the plasma at density 1.006 according to the methods of the Lipid Research Clinics Program was performed to obtain the 1.006-g/mL infranatant pattern.[7] Plasma apo A1 and apo B were determined by noncompetitive enzyme-linked immunosorbent assays as previously described.[8,9] Between-assay and within coefficients of variation were less than 10%. LDL content cholesterol was calculated by difference.

Lipoprotein(a) Assay

Lipoprotein(a) [Lp(a)] content was measured in plasma using a commercially available enzyme-linked immunosorbent assay (Macra Lp(a); Strategic Diagnostics, Newark, NJ).[10-12] Plasma samples were incubated for 1 hour at room temperature in microtiter strip wells coated with a specific monoclonal anti-Lp(a) antibody that recognizes all apo(a) isoforms and does not cross-react with plasminogen. Unbound antigen was then removed by extensive washing. After a 20-minute incubation at room temperature with a polyclonal anti-Lp(a) antibody conjugated with the enzyme, horseradish peroxidase, plates were washed and incubated with hydrogen peroxide and *O*-phenylenediamine for an additional 20 minutes. The enzymatic reaction was then stopped by addition of sulfuric acid. The absorbance was read at 492 nm using an MR 600 microtiter plate reader (Dynatech, Vienna, VA). Coefficients of variation within and between assays were 2.8% and 4.3%, respectively.

Apo E Isoforms

Apo E phenotype was determined from very–low-density lipoprotein (VLDL) after ultracentrifugation in a 50 Ti rotor (Beckman Instruments, Fullerton, CA) at 39,000 rpm for 18 hours at 4°C at plasma density 1.006 g/mL. The detailed procedure for characterization of apo E isoforms from isoelectric-focusing gels has been previously described by Ordovas et al.[13]

LDL Particle Size

LDL subfractions were separated by 2% to 16% gradient gel electrophoresis (PAA 2-16%; Pharmacia, Piscataway, NJ) as previously described.[14] Scanning was performed on an Ultrascan XL laser densitometer (LKB Instruments, Paramus, NJ) interfaced with an AT&T personal computer (Murray Hill, NJ) and a Canon PJ-108A printer (Tokyo, Japan) using the LKB GSXL software for peak integration. Each specimen was assigned an LDL size, with the largest, LDL-1, being found in the density range of 1.025 to 1.033 g/mL, LDL-2 and LDL-3 at 1.033 to 1.038 g/mL, LDL-4 and LDL-5 at 1.038 to 1.050 g/mL, and the smallest, LDL-6 and LDL-7, at 1.050 to 1.063 g/mL. An LDL particle score was calculated as the sum of the relative areas under all LDL bands present. A higher particle score corresponds to a smaller denser LDL particle and a weighted LDL particle score of 3.5 or greater corresponds to pattern B, according to the methods of Krauss and Burke.[15]

Statistical Analyses

The SAS statistical program (SAS Institute, Cary, NC) was used for statistical analysis. Differences between means for continuous variables were tested after adjustment by other covariates using a general linear model (SAS PROC GLM). Differences in the proportions for dichotomous variables were tested using logistic regression models.

RESULTS

Age-adjusted means for various lipid factors including apos A1 and B, Lp(a), and a weighted LDL particle score are shown for male and female diabetics and controls in Tables 1 and 2. Data from 1,998 men including 120 diabetics and 1,933 women including 54 diabetics were analyzed. After chart review, it was estimated that nine of 174 diabetics could be classified as IDDM. Due to this small number, there were insufficient data to compare lipid values between NIDDM and IDDM subjects.

Among men, there was no significant difference between diabetics and controls for total and LDL cholesterol. Diabetics showed significantly lower HDL cholesterol ($P < .001$), higher triglycerides ($P < .001$), and higher VLDL cholesterol ($P < .05$) compared with controls. In women, diabetics had significantly higher TC ($P < .001$), although LDL cholesterol again showed no significant difference. Findings similar to those in men were observed for HDL cholesterol, triglycerides, and VLDL cholesterol ($P < .001$ for all).

Apo A1 was significantly lower in diabetics versus controls in both sexes ($P < .05$ in men and $P < .001$ in women). The inverse trend was seen with apo B, with higher levels in diabetics, although this was only statistically significant in women ($P < .001$). Neither sex showed a significant difference in levels of Lp(a). Despite a lack of statistical significance between groups for overall LDL cholesterol levels, diabetics had significantly higher weighted LDL particle scores compared with controls of both sexes ($P < .001$ in men and women). This suggests that diabetics have smaller denser LDL particles than controls.

Menopausal status is compared between the two groups, in addition to age and body mass index (BMI), in Table 2. A greater number of diabetic women were postmenopausal compared with controls ($P < .05$). BMI was also significantly greater in diabetics ($P < .001$). After adjustment for these factors in addition to age, there was still a statistically significant difference in the lipid factors described earlier.

Tables 3 and 4 display the age-adjusted rates for selected lipid parameters, both single and in combination, of diabetics and controls in each sex. Tests for a statistical association between diabetes and the various lipid parameters were performed using a logistic regression model that included age and diabetes as variables. The parameters

Table 1. Age-Adjusted Means (±SD) for Various Lipid Factors Among Men in the Framingham Offspring (1984 to 1987) for Diabetics and Nondiabetics

Parameter	Controls (n = 1,878)	Diabetics (n = 120)
TC (mg/dL)	213.2 ± 39.6	210.6 ± 50.8
HDL cholesterol (mg/dL)	44.5 ± 12.0	38.8 ± 12.4*
Triglycerides (mg/dL)	142.3 ± 112.2	180.2 ± 119.9*
VLDL (mg/dL)	31.4 ± 23.7	38.8 ± 23.6†
Direct LDL cholesterol (mg/dL)	137.3 ± 35.1	132.2 ± 43.8†
Apo A1 (mg/dL)	135.3 ± 32.4	125.2 ± 34.9
Apo B (mg/dL)	96.0 ± 29.3	101.2 ± 35.2
Lp(a) (mg/dL)	14.6 ± 17.0	13.6 ± 18.1
LDL particle score (weighted)	3.41 ± 1.17	3.98 ± 1.20*
Age (yr)	49.0 ± 10.4	56.4 ± 9.2*
BMI (kg/m^2)	27.2 ± 3.8	27.4 ± 4.8

*$P < .001$.
†$P < .05$.

Table 2. Age-Adjusted Means (±SD) for Various Lipid Factors Among Women in the Framingham Offspring (1984 to 1987) for Diabetics and Nondiabetics

Parameter	Controls (n = 1,879)	Diabetics (n = 54)
TC (mg/dL)	211.7 ± 42.8	229.5 ± 62.3*‡
HDL cholesterol (mg/dL)	57.1 ± 14.8	42.1 ± 11.8*†
Triglycerides (mg/dL)	102.2 ± 77.2	295.1 ± 538.1*†
VLDL (mg/dL)	22.6 ± 17.5	51.7 ± 68.3*†
Direct LDL cholesterol (mg/dL)	132.3 ± 38.2	133.9 ± 38.7
Apo A1 (mg/dL)	158.0 ± 35.8	134.1 ± 33.0*†
Apo B (mg/dL)	82.8 ± 27.3	106.0 ± 33.5*†
Lp(a) (mg/dL)	15.6 ± 17.8	16.7 ± 22.3
LDL particle score (weighted)	2.47 ± 1.03	3.69 ± 1.47*†
Age (yr)	48.2 ± 10.0	53.3 ± 8.3 ($P < .001$)
BMI (kg/m^2)	25.4 ± 5.1	30.3 ± 7.5 ($P < .001$)
Menopause (%)	49.8	62.4 ($P < .05$)

*$P < .001$: significance of diabetes effect after adjustment for age.

†$P < .001$, ‡$P < .05$: significance of diabetes effect after adjustment for age, BMI, and menopause.

were chosen based on recent guidelines on cholesterol (National Cholesterol Education Program) and a consensus conference on hypertriglyceridemia. Data for 2,025 men were analyzed. The most significant differences were found in extremes involving HDL cholesterol less than 35 mg/dL, triglycerides greater than 250 mg/dL, and a combination of the two ($P < .001$ for all). Of note, LDL cholesterol less than 100 mg/dL was seen in significantly more diabetics than controls ($P < .05$). Extremes in LDL particle size and lipid ratios were also compared. Significant increases in the prevalence of LDL particle size of 3.5 or greater (pattern B), TC/HDL ratio of 5 or greater, and TC/HDL ratio of 6 or greater were noted for the diabetics ($P < .05$, $P < .05$, and $P < .001$, respectively). In an age-adjusted model, diabetes was associated with pattern B LDL particle size in both sexes (men: odds ratio [OR] = 1.79, $P = .002$; women: OR = 5.27, $P < .0001$). In a subsequent analysis that included age, diabetes, and triglycerides and greater than

Table 3. Age-Adjusted Rates of Lipid Parameters for Male Diabetics and Nondiabetics in the Framingham Offspring (1984 to 1987)

Parameter	Controls	Diabetics
HDL cholesterol <35 mg/dL	20.3%	43.9%*
Triglycerides >500 mg/dL	1.5%	1.1%
Triglycerides >250 mg/dL	9.3%	22.6%*
TC <200 mg/dL	39.6%	31.3%
TC ≥240 mg/dL	22.8%	18.3%
LDL cholesterol <100 mg/dL	15.1%	20.4%†
LDL cholesterol ≥160 mg/dL	27.0%	22.4%
HDL cholesterol <35 mg/dL and triglycerides ≥250 mg/dL	4.9%	11.7%*
TC ≥240 mg/dL and triglycerides ≥250 mg/dL	4.8%	6.7%
LDL size ≥3.5 (pattern B)	32.5%	49.2%†
TC/HDL ≥4	71.5%	76.6%
TC/HDL ≥5	47.2%	64.7%†
TC/HDL ≥6	26.2%	39.2%*

NOTE. N = 2,025.

*$P < .001$.

†$P < .05$.

Table 4. Age-Adjusted Rates of Lipid Parameters for Female Diabetics and Nondiabetics in the Framingham Offspring (1984 to 1987)

Parameter	Controls	Diabetics
HDL cholesterol <35 mg/dL	9.3%	37.7%*‡
Triglycerides >500 mg/dL	0.2%	10.9%*‡
Triglycerides >250 mg/dL	3.0%	29.3%*‡
TC <200 mg/dL	45.2%	37.4%§
TC ≥240 mg/dL	22.7%	41.1%*§
LDL cholesterol <100 mg/dL	24.1%	26.4%
LDL cholesterol ≥160 mg/dL	22.2%	35.0%
HDL cholesterol <35 mg/dL and triglyerides ≥250 mg/dL	1.0%	23.4%*‡
TC ≥240 mg/dL and triglycerides ≥250 mg/dL	2.3%	12.6%*‡
LDL particle size ≥3.5 (pattern B)	10.7%	40.3%*
TC/HDL ≥4	38.2%	79.7%*
TC/HDL ≥5	18.7%	59.1%*
TC/HDL ≥6	7.5%	35.3%†

NOTE. N = 2,042.

*$P < .001$, †$P < .05$: significance of diabetes effect after adjustment for age.

‡$P < .001$, §$P < .05$: significance of diabetes effect after adjustment for age, BMI, and menopause.

250, diabetes was no longer associated with pattern B in men (men: OR = 1.39, $P = .13$; women: OR = 2.61, $P = .0091$). A significant association was found with the elevated triglycerides in both sexes (men: OR = 18.59, $P < .0001$; women: OR = 34.12, $P < .0001$).

Among 2,042 women, results were similar with respect to low HDL cholesterol and high triglycerides. Diabetics showed significantly higher triglycerides at levels greater than 250 mg/dL and greater than 500 mg/dL ($P < .001$ for each). Two differences were seen for comparisons with men. TC greater than 240 mg/dL was more prevalent among diabetics than controls ($P < .001$). Unlike the men, there was no significant difference in the rate of LDL cholesterol levels less than 100 mg/dL. Among the extremes of LDL particle size and lipid ratios, significant increases were found in the diabetic group for all of the categories ($P < .001$ for all except TC/HDL ratio ≥ 6, which was $P < .05$). When these results were adjusted for BMI and menopausal status in addition to age, statistical significance remained for most categories. Among the extremes of LDL particle size and lipid ratios, the results became insignificant. New significance was noted for TC less than 200 mg/dL where this result was more prevalent among controls ($P < .05$).

The prevalence of apo E isoform phenotypes is shown for men and women for both groups in Table 5. Among 1,372 men there were 100 diabetics, and among 1,262 women there were 40. In comparison to the most common allele, E3, neither of the less common alleles, E2 ($P = .83$ for men and .76 for women) or E4 ($P = .43$ for men and .11 for women), were associated with diabetes in this population sample.

DISCUSSION

The lipid abnormalities of diabetes mellitus have been reviewed extensively elsewhere.[16-19] These dyslipidemias

Table 5. Apo E Isoforms in Men and Women in the Framingham Offspring (1984 to 1987) for Diabetics and Nondiabetics

Group	E3/E3	E2/E3	E3/E4	E2/E2	E2/E4	E4/E4
Men						
Controls (n = 1,272)	62.2	12.9	19.0	0.8	2.1	3.0
Diabetics (n = 100)	63	16	19	0	2	0
Women						
Controls (n = 1,242)	63.0	13.7	18.6	0.5	1.2	3.1
Diabetics (n = 40)	55.0	12.5	30.0	0	0	2.5

NOTE. Values are the percentage of the total number of subjects.

have been the subject of much research because of the excess of cardiovascular morbidity and mortality seen in the diabetic population. The Framingham Offspring results resemble data from other populations that have been studied.

Results of an analysis such as this are affected by the definition of diabetes used in the methods. Our definition is based on the presence of specific therapy for the disease or a fasting glucose level greater than 140 mg/dL at examinations 1, 2, or 3. As a result, the control group may include a subset of participants who would actually be classified as having impaired glucose tolerance by National Diabetes Data Group criteria.[20] Ideally, a better classification would involve glucose tolerance testing or glycosylated hemoglobin levels. An area that has not been extensively studied is the profile of lipid abnormalities in patients with impaired glucose tolerance by American Diabetes Association criteria. The number of patients in this category in the Framingham Offspring Study was too small for analysis. Additionally, as mentioned earlier, due to the small number of IDDM subjects, the group of diabetics was not subdivided and the results thus reflect primarily lipid abnormalities of NIDDM.

Our results reflect a diabetic dyslipidemia characterized by low HDL cholesterol and apo A1 and high VLDL cholesterol and triglycerides. Previous data suggest that poorly controlled diabetics demonstrate abnormalities with these characteristics.[21,22] A deficiency of insulin increases hepatic production of VLDL and reduces VLDL clearance because of decreased activity of lipoprotein lipase. These VLDL particles are rich in triglyceride and help to promote hypertriglyceridemia. Levels of HDL cholesterol have been shown to be inversely correlated with triglycerides.[22] This appears to be related to the metabolism of VLDL particles. The elevation in triglycerides was more marked in women than in men. A similar pattern was noted by Walden et al,[23] but the cause is not clear.

Decreased apo A1 and increased apo B levels have been associated with premature coronary artery disease. The former is the major protein of HDL, and the latter is the major protein of LDL. Lower apo A1 levels in diabetics with poor metabolic control have been noted previously, suggesting worse glycemic control among diabetics relative to nondiabetics.[21,24] There was a notable trend toward increased apo B levels that was significant in female diabetics despite no significant difference in LDL cholesterol levels. This also has been noted previously. Lp(a) has been the subject of some controversy in the recent literature. Haffner[25] has recently reviewed the role of this lipoprotein as a cardiovascular risk factor in diabetes. As with other factors already mentioned, Lp(a) levels in IDDM patients have been shown to correlate directly with glycosylated hemoglobin.[26] However, Jenkins et al[27] reported that Lp(a) was similar in IDDM patients without microalbuminuria compared with nondiabetic controls. Lp(a) concentrations have been reported to be lower in NIDDM patients than in nondiabetics and do not reflect poor glycemic control.[28-30] In our study, Lp(a) levels were similar in diabetics and controls.

LDL particle size has also recently been studied with respect to cardiovascular risk. Decreased plasma LDL particle size has been associated with premature coronary artery disease, but Campos et al[31] have reported that this is not an independent predictor for coronary artery disease after conventional risk factors and lipoprotein parameters have been taken into account. Studies have suggested that in patients with NIDDM, smaller denser particles are associated with obesity and hypertriglyceridemia.[16,32] The clearance of triglyceride-rich lipoproteins has also been noted to be slower in this LDL phenotype.[33] Insulin resistance has been shown to be positively correlated with these types of LDL particles, although the mechanism is not clear.[34] The age-adjusted BMI of our diabetic men was not significantly different from that of the controls (27.2 *v* 27.4 kg/m^2). This difference between groups correlates with the difference in triglyceride levels, which appears to be a better predictor for LDL size difference.

Apo E polymorphism may modulate serum TC and LDL cholesterol levels and apo B. E4 has been associated with elevations in these levels, whereas E2 is associated with decreased level.[35] Studies have shown that the allele frequencies of apo E in IDDM have not significantly differed from those in healthy controls.[24] We did not find any difference in allele frequencies between groups, although the total number of diabetics was relatively small.

We have noted that the majority of our results remained unchanged when adjusted for BMI and menopausal status in addition to age in the women. Additionally, significant differences were noted between the groups in more categories among the women than among the men. The Framingham Study has shown previously that menopausal status is a significant risk factor for elevations in plasma LDL cholesterol, apo B, and Lp(a) after controlling for age and BMI in the first two parameters.[9,11,36] Postmenopausal women were also found to have decreased LDL particle size when compared with premenopausal women.[37] This difference was reduced when the data were controlled for age and BMI.

In data uncontrolled for other variables, Walden et al[23] showed that diabetes had a greater effect on increasing triglycerides and decreasing HDL cholesterol in women versus men when compared with controls.[23] Haffner et al[38] studied LDL particle size in male and female diabetics compared with controls. A smaller denser LDL particle was seen in diabetic subjects of both sexes. However, when the results were adjusted for triglycerides and HDL cholesterol, the association remained significant only in women. We found the same initial results in both sexes for LDL particle size of 3.5 or greater (pattern B). In female

diabetics, the results were insignificant after adjustment for BMI and menopausal status. When these initial data were adjusted for hypertriglyceridemia, the differences remained significant in women and approached significance in men. Thus, similar to the report by Haffner et al, it may be concluded that diabetes and hypertriglyceridemia are associated with small dense LDL particles.

In conclusion, our data on the interaction of diabetes and lipoprotein abnormalities are consistent with the following concepts: (1) diabetes is associated with elevated triglyceride and VLDL cholesterol levels and decreased LDL particle size in both men and women; (2) diabetes is not associated with either elevated LDL cholesterol or Lp(a) levels in men or women; and (3) diabetes in women leads to more profound lipoprotein abnormalities than in men, with significant hypertriglyceridemia and elevated apo B and decreased HDL cholesterol and apo A1 being noted. These abnormalities are still present after controlling for the effects of age, menopausal status, and BMI.

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