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Association of Apolipoprotein B with Incident Type 2 Diabetes in an Aboriginal Canadian Population†

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Abstract

BACKGROUND—Expanding evidence indicates that apolipoprotein B (apo B) is superior to LDL cholesterol as a marker of vascular disease. Although traditional lipid measures are known to predict type 2 diabetes, limited data are available regarding apo B. We assessed the association of apo B with incident type 2 diabetes and compared it with traditional lipid variables as a risk predictor in aboriginal Canadians.

METHODS—Of an initial cohort of 606 individuals without diabetes in 1993–1995, 540 were contacted for the 10-year follow-up evaluation in 2003–2005. Fasting and 2-h postload glucose concentrations were obtained at baseline and follow-up to determine incident type 2 diabetes. Baseline fasting serum lipids were measured with standard laboratory procedures.

RESULTS—The cumulative 10-year incidence of type 2 diabetes was 17.5%. High concentrations of apo B, triglycerides, and LDL cholesterol, and low concentrations of HDL cholesterol were individually associated with incident type 2 diabetes in univariate analyses. Comparing C statistics of univariate models showed apo B to be a superior determinant of incident diabetes compared with LDL ($P=0.026$) or HDL ($P=0.004$) cholesterol. With multivariate adjustment including waist circumference, apo B (odds ratio, 1.50; 95% CI, 1.11–2.02) and triglycerides (odds ratio, 1.49; 95% CI, 1.12–1.98) remained associated with incident diabetes, whereas LDL and HDL cholesterol became nonsignificant.

CONCLUSIONS—The association of plasma apo B with incident type 2 diabetes and its better prediction of risk compared with LDL or HDL cholesterol suggest the potential for the use of apo B in type 2 diabetes risk communication and prevention.

The association between plasma apolipoprotein B (apo B)¹¹ concentration and the development of vascular disease is well established (1–4). Expanding evidence further indicates that apo B is a superior marker of vascular disease compared with conventional plasma lipid indices, including LDL cholesterol (1, 4).

Although conventional lipid measures are associated with incident type 2 diabetes (5, 6), limited data are available regarding apo B. One report demonstrated that apo B was associated with incident type 2 diabetes among Turkish women (7). We assessed whether apo B was associated with incident type 2 diabetes and was a better risk predictor than traditional lipid variables in an aboriginal community undergoing rapid cultural transition and with high prevalences of obesity and impaired glucose tolerance (IGT) (8).

The Sandy Lake Health and Diabetes Project is a cohort study designed to determine factors associated with incident diabetes among aboriginal Canadians. Baseline data were obtained from 728 residents of Sandy Lake First Nation (age range, 10–79 years) in 1993–1995 (8).

¹¹Nonstandard abbreviations: apo B, apolipoprotein B; IGT, impaired glucose tolerance; OR, odds ratio.

Among 606 residents free of diabetes at baseline, 540 (89.1%) participated in the 10-year follow-up evaluation in 2003–2005 (5). Those who did not return for follow-up ($n = 66$) were slightly younger than respondents but were not different with respect to sex ratio and body mass index (5). After we excluded participants who died during follow-up ($n = 27$), had missing baseline fasting and 2-h postload glucose data, or had diabetes at baseline as defined by the revised WHO diagnostic criteria (5), 492 men and women remained in the present study. The Sandy Lake First Nation Band Council and the University of Toronto Ethics Review Committee approved the study, and signed informed consent was obtained from all participants.

Baseline blood samples were collected into tubes containing EDTA after the participants had fasted overnight for 8–12 h, and the tubes were refrigerated immediately after collection (8). Samples were centrifuged, and the plasma was removed within 20 min of the blood draw and then frozen at $-70\text{ }^{\circ}\text{C}$ before shipment on dry ice to St. Michael's Hospital, Toronto, Canada, for analysis. A 75-g oral glucose tolerance test was administered, with a postload glucose sample drawn at 120 min. Glucose concentration was measured with the glucose oxidase method, and the lipid profile was evaluated with the standard methods described in the Lipid Research Clinics manual of operations, with LDL cholesterol calculated with the Friedewald formula (9). Anthropometric measures at baseline have been described previously (5). Height and weight were measured with an Accustat wall-mounted stadiometer (Genentech) and a hospital balance-beam scale (Health-o-Meter/Pelstar), respectively. Waist circumference was measured at the iliac crest with an inelastic tape.

Incident type 2 diabetes was defined as the presence of any one of the following at follow-up: (a) fasting plasma glucose ≥ 7.0 mmol/L or 2-h postload glucose ≥ 11.1 mmol/L on a 2-h oral glucose tolerance test; (b) current use of insulin or oral hypoglycemic agents; or (c) a positive response to the question, "Have you ever been diagnosed with diabetes by a nurse or doctor?" (5).

Distributions of continuous variables were assessed for normality, and natural logarithm transformations of skewed variables were used in descriptive statistical analyses when appropriate. Baseline characteristics of participants with and without incident diabetes were compared with the Welch modified t -test or the χ^2 test, as appropriate. Multiple logistic regression analysis was conducted to evaluate associations of lipid measures with incident diabetes. The odds ratio (OR) per 1-SD increase in the corresponding lipid variable and the 95% CI were calculated. Sex interactions with lipid variables were assessed by adding an interaction term to a model adjusted for age, sex, and hypertension, in addition to the main effect. In addition, the interaction of LDL cholesterol with apo B was evaluated. To compare the ability of different logistic models to discriminate between participants with and without incident diabetes, we calculated C statistics, which are analogous to the area under the ROC curve, and used the DeLong algorithm to determine the statistical significance (10).

Of 492 participants, 86 (17.5%) had developed type 2 diabetes at follow-up: 72 of 383 participants (18.8%) were ascertained from the fasting and/or 2-h postload glucose data at follow-up, and 14 of 109 participants without follow-up blood samples (12.8%) were ascertained from the self-reported clinical diagnosis only. Participants without follow-up

blood samples were younger ($P=0.009$) but were not different at baseline with respect to sex or body mass index ($P=0.05$ for both). Individuals who developed diabetes had higher values for plasma apo B concentration, body mass index, waist circumference, fasting glucose concentration, and 2-h postload glucose concentration and were more likely to have had hypertension at baseline (all $P<0.001$; Table 1). At baseline, apo B concentration correlated with HDL cholesterol, LDL cholesterol, and triglyceride concentrations ($r=-0.29$, $r=0.93$, and $r=0.69$, respectively; all $P<0.001$, Spearman correlation analysis).

In univariate analyses, increased baseline apo B, LDL cholesterol, and triglyceride concentrations, and low baseline HDL cholesterol concentrations were individually associated with incident diabetes (Table 2). Comparing C statistics of univariate regression models (Table 2) revealed apo B to be a superior discriminator of participants with and without diabetes, compared with either LDL or HDL cholesterol ($P=0.026$ and 0.004 , respectively), whereas C statistics for triglycerides and apo B were not significantly different ($P>0.05$). Although there was no significant interaction between apo B and LDL cholesterol ($P=0.23$), apo B concentration was significantly associated with incident diabetes among those in the lowest tertile of LDL cholesterol (OR, 1.97; 95% CI, 1.09–3.56; $P=0.02$), whereas LDL cholesterol was not significantly associated with this outcome among those in the lowest apo B tertile (OR, 1.49; 95% CI, 0.70–3.18; $P=0.30$). Associations of apo B with diabetes in the second and third tertiles of LDL cholesterol were not statistically significant, nor were associations of LDL cholesterol with diabetes in the second and third tertiles of apo B (see Table 1 in the Data Supplement that accompanies the online version of this Brief Communication at <http://www.clinchem.org/content/vol56/issue4>). This observation suggests that apo B may be particularly useful when the LDL concentration is low, although this observation requires confirmation in future studies, given that our statistical power was limited for these tertile-based analyses.

With multivariate adjustment for age, sex, hypertension, waist circumference, and fasting plasma glucose, LDL and HDL cholesterol concentrations were not significantly associated with incident diabetes, whereas high apo B and triglyceride concentrations remained significantly associated (Table 2). With the same adjustment, the ratio of apo B to apo A-I and the ratio of apo B to HDL cholesterol were associated with incident diabetes, but to a slightly lower degree of risk than for apo B alone [ORs, 1.41 (95% CI, 1.07–1.84) and 1.42 (95% CI, 1.09–1.85), respectively]. There were no statistically significant sex interactions with individual lipid measures with respect to diabetes incidence (all interaction P values >0.05 ; data not shown).

In the Insulin Resistance Atherosclerosis Study, increased apo B and triglyceride concentrations were associated with men, who had a higher prevalence of central obesity than women in this study population, and with IGT (11). Central obesity has been associated with insulin resistance, which leads to a defect in the ability of insulin to suppress free fatty acids (12), and this defect in insulin action has been associated with increased apo B and triglyceride concentrations (11, 13). This evidence is relevant to the current study population, aboriginal Canadians, who have high prevalences of central obesity, insulin resistance, and IGT (5, 8). In addition, increased free fatty acids have been shown to decrease the uptake of glucose by peripheral tissues, to reduce hepatic insulin clearance, and

to promote hepatic gluconeogenesis (14–16). Hence, the compromised ability of insulin to suppress free fatty acids in the presence of central obesity may contribute to the development of type 2 diabetes, and this pathophysiological pathway may be marked by increased triglyceride and apo B concentrations.

Limitations of our study include the challenges of conducting investigations in the setting of a remote community. Specifically, we were unable to collect interim data to analyze the time to the onset of diabetes. We were also unable to obtain follow-up blood samples from all participants. Diabetes outcome assessments of 109 (22.2%) participants were by self-reported clinical diagnosis only. This percentage of the participants without blood samples might have caused underreporting of incident type 2 diabetes. In addition, the current findings from a study population with a young mean age and a high prevalence of central obesity might not be generalizable to all populations.

In summary, a high plasma apo B concentration was associated with incident type 2 diabetes and was superior to LDL and HDL cholesterol in predicting the disease in this aboriginal population with high prevalences of obesity and IGT (8). With additional confirmation from future studies, apo B could be incorporated into communicating increased risk for diabetes, in addition to the progression of atherosclerotic disease, especially among high-risk populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics of the Sandy Lake Health and Diabetes Project participants according to the presence or absence of incident diabetes at the 10-year follow-up.^a

Characteristic	No diabetes	Incident diabetes	P
Participants, n	406 (82.5%)	86 (17.5%)	
Age, years	25.4 (13.0)	31.5 (12.4)	<0.001
Male/female sex, n ^b	173/233 (42.6%/57.4%)	34/52 (39.5%/60.5%)	0.60
Body mass index, kg/m ²	25.4 (5.5)	29.4 (5.3)	<0.001
Waist circumference, cm	94.4 (14.1)	104.7 (12.1)	<0.001
Hypertension, yes, n ^{b,c}	54 (13.3%)	29 (33.7%)	<0.001
Apo B, g/L	0.99 (0.27)	1.15 (0.26)	<0.001
Apo A-1, g/L	1.48 (0.22)	1.49 (0.26)	0.67
Apo B/apo A-1 ratio	0.68 (0.21)	0.80 (0.25)	<0.001
Apo B/HDL cholesterol ratio	0.83 (0.32)	1.03 (0.40)	<0.001
HDL cholesterol, mmol/L	1.26 (0.28)	1.19 (0.25)	0.02
LDL cholesterol, mmol/L	2.42 (0.74)	2.74 (0.66)	<0.001
Triglycerides, mmol/L ^d	1.10 (0.81–1.53)	1.48 (1.16–1.82)	<0.001
Total cholesterol, mmol/L	4.25 (0.88)	4.68 (0.75)	<0.001
Fasting glucose, mmol/L	5.3 (0.46)	5.6 (0.58)	<0.001
2-h Postload glucose, mmol/L	5.4 (1.62)	6.5 (2.08)	<0.001

^aExcept where indicated, data are presented as the mean (SD) with the Welch *t*-test performed.

^b χ^2 Test.

^cHypertension is defined as a systolic blood pressure \geq 130 mmHg, a diastolic pressure of \geq 85 mmHg, or receiving antihypertensive medication therapy.

^dData are presented as the median (25th–75th percentiles); Welch *t*-tests were performed on ln-transformed data.

Table 2

Logistic regression analysis of the associations of lipids with incident type 2 diabetes.

	SD ^a	C statistic ^a	OR (95% CI) ^e			
			Model 1 ^a	Model 2 ^b	Model 3 ^c	Model 4 ^d
LDL cholesterol	0.739	0.652	1.50 (1.18–1.90)	1.30 (0.99–1.69)	1.24 (0.93–1.63)	1.25 (0.94–1.66)
HDL cholesterol	0.273	0.575	0.75 (0.58–0.97)	0.72 (0.55–0.93)	0.84 (0.64–1.11)	0.84 (0.64–1.11)
Triglycerides ^f	0.446	0.687	1.93 (1.52–2.46)	1.79 (1.37–2.32)	1.53 (1.16–2.03)	1.49 (1.12–1.98)
Apo B	0.272	0.689	1.79 (1.42–2.27)	1.67 (1.26–2.20)	1.50 (1.12–2.01)	1.50 (1.11–2.02)

^aUnadjusted.

^bAdjusted for sex, age, and hypertension, with hypertension defined as a systolic blood pressure \geq 130 mmHg, a diastolic pressure of \geq 85 mmHg, or receiving antihypertensive medication therapy.

^cAdjusted for model 2 variables and waist circumference.

^dAdjusted for model 3 variables and fasting plasma glucose.

^eOR (95% CI) per 1-SD change.

^fIn-Transformed triglyceride data used.