The Relationship of Lipoprotein Lipase Activity and LDL size Is Dependent on Glucose Metabolism in an Elderly Population

The Hoorn Study

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Small LDL size is common in patients with type 2 diabetes and is associated with an increased risk of cardiovascular disease (1). LDL size is determined by various constituents of lipoprotein metabolism, such as lipoprotein lipase (LPL) and hepatic lipase (HL) activities, cholesteryl ester transfer protein (CETP), as well as triglyceride concentrations (2–4). Although abnormalities in LPL, HL, and CETP levels are associated with a diabetic lipoprotein profile, a relation to insulin resistance has been found only with lipase activities (5–7) but not with CETP (8,9). In this cross-sectional study, we investigated the relationship of LPL and HL activities and CETP mass with LDL size in 426 subjects with normal and impaired glucose metabolism or type 2 diabetes.

RESEARCH DESIGN AND METHODS — The Hoorn Study is a population-based cohort study of glucose metabolism and cardiovascular risk factors among 2,484 inhabitants of the municipality of Hoorn, which started in 1989. In 2000–2001, a follow-up was conducted in selected subjects then aged 60–87 years, as previously described (10). We invited all surviving subjects with type 2 diabetes ($n = 176$) and random samples of individuals with normal glucose metabolism ($n = 705$) or impaired glucose metabolism ($n = 193$) based on their glucose metabolism status (World Health Organization 1999 criteria) at the previous examination in 1996–1998 (11). Of the 1,074 individuals invited, 648 (60.3%) subjects participated. At the follow-up examination, a sample of 566 participated in the postheparin test. The Ethical Review Committee of the VU University Medical Center approved the study. Written informed consent was obtained from all participants. LDL size was measured by high-performance gel-filtration chromatography (12). CETP mass was determined using a two-antibody sandwich immunoassay (13). LPL and HL activities were measured in plasma collected 20 min after contralateral intravenous administration of heparin, using an immunochemical method (14). One hundred and seven samples were excluded from analyses because very low activities of LPL and HL in postheparin plasma indicated insufficient heparin delivery. Activities were considered as very low if LPL activity was <50 units/l and if HL activity was <72 units/l. The contribution of HDL cholesterol, triglycerides, insulin, LPL, HL, and CETP to LDL size was analyzed in univariate and multivariate linear regression models in categories of glucose metabolism, with LDL size as the dependent variable with adjustment for sex.

RESULTS — Mean LDL size (in nanometers) was 21.6 ± 0.4, 21.5 ± 0.4, and 21.2 ± 0.5 in subjects with normal, impaired glucose metabolism, and diabetes, respectively. Mean LPL activity (in units per liter) was 150 ± 51, 147 ± 51, and 135 ± 42, respectively. There were no differences in HL activity (mean 372 ± 135 units/l) and CETP mass (1.87 ± 0.56 mg/l) between the three glucose metabolism categories.

In this elderly population, we observed a stronger positive association between LPL activity and LDL size in subjects with impaired glucose metabolism and type 2 diabetes than in subjects with normal glucose metabolism, even after adjustment for triglyceride concentration, which was the most important independent determinant of LDL size in all glucose metabolism categories. A test for interaction between LPL activity and glucose metabolism was significant ($P = 0.03$), indicating that glucose metabolism is an effect modifier in the relationship between LPL activity and LDL size (Table). Thus, higher LPL activity might protect against the development of small LDL size, especially in subjects with type 2 diabetes, who have increased triglyceride concentrations.

Mechanisms responsible for the presence of smaller LDL size in diabetic subjects compared with nondiabetic subjects are not fully understood. Lower LPL activity contributes to an impaired removal

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Abbreviations: CETP, cholesteryl ester transfer protein; HL, hepatic lipase; LPL, lipoprotein lipase.

Table—*Associations with LDL size: linear regression analysis*

	NGM	IGM	Diabetes
Univariate models*			
Triglyceride	−0.54 (−0.63 to −0.44)	−0.58 (−0.72 to −0.43)	−0.72 (−0.86 to −0.59)
HDL cholesterol	0.42 (0.29–0.54)	0.57 (0.40–0.73)	0.59 (0.41–0.77)
Insulin	−0.18 (−0.30 to −0.06)	−0.25 (−0.42 to −0.08)	−0.10 (−0.30 to 0.11)
LPL activity	0.09 (−0.03 to 0.21)	0.24 (0.05–0.43)	0.23 (0.01–0.45)
HL activity	−0.21 (−0.33 to −0.09)	−0.18 (−0.37 to 0.01)	−0.10 (−0.34 to 0.14)
CETP mass	−0.02 (−0.15 to 0.11)	−0.13 (−0.3 to 0.05)	0.03 (−0.18 to 0.24)
Multivariate model†			
Triglyceride	−0.53 (−0.64 to −0.42)	−0.51 (−0.66 to −0.36)	−0.69 (−0.83 to −0.55)
Insulin	−0.02 (−0.13 to 0.09)	−0.11 (−0.26 to 0.04)	−0.02 (−0.16 to 0.12)
LPL activity	−0.02 (−0.13 to 0.09)	0.09 (−0.06 to 0.24)	0.17 (0.03–0.32)
HL activity	−0.02 (−0.13 to 0.10)	−0.09 (−0.25 to 0.06)	−0.02 (−0.17 to 0.12)
CETP mass	−0.01 (−0.11 to 0.10)	−0.09 (−0.23 to 0.06)	−0.05 (−0.20 to 0.10)

Data are β (95% CI). *Adjusted for sex; †model with sex, triglyceride, insulin, LPL, HL, and CETP. IGM, impaired glucose metabolism; NGM, normal glucose metabolism.

of triglyceride-rich lipoproteins, whereas an increased HL activity is associated with a greater lipolysis of triglyceride-enriched LDL. Several investigators have demonstrated that individuals with type 2 diabetes have increased triglyceride, reduced HDL, and increased small dense LDL concentrations, all of which are thought to have their origin in the insulin resistance syndrome (15–17). Fasting insulin, commonly used as a measure of insulin resistance, showed an inverse relation to LDL size in a large population with various degrees of glucose metabolism (18), which was confirmed in this study. Also, the negative association of triglyceride concentration with LDL size was previously reported in a population of 50 young healthy subjects (9). Normally, insulin reduces hepatic apolipoprotein (apo)B secretion by suppressing the delivery of nonesterified fatty acids from adipose tissue to the liver and by inhibiting new hepatic cholesterol synthesis. Insulin also enhances lipolysis and hepatic uptake of triglyceride-rich apoB-containing lipoproteins, including chylomicron remnants, by the upregulation of LPL activity and the stimulation of LDL receptor activity, respectively (19).

The amount of circulating triglycerides is the single most important and independent factor affecting LDL size in the present and other studies (5). Only in univariate analysis, HL activity contributed to LDL size in subjects with normal and impaired glucose metabolism. However, in the multivariate model containing plasma triglyceride, LPL, and CETP, HL activity did not contribute to LDL size in any of the glucose metabolism groups. This finding may indicate that in our population, HL activity is not rate limiting in the formation of small dense LDL.

CONCLUSIONS — In conclusion, we have demonstrated that high triglyceride concentration and low LPL activity are determinants of small LDL size, especially in individuals with abnormal glucose metabolism. These findings suggest that, beyond triglyceride concentration, activities of lipolytic proteins explain the differences in LDL size in diabetic and nondiabetic people.

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