HDL Composition Predicts New-Onset Cardiovascular Disease in Patients With Type 1 Diabetes

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Dyslipidemia is independently associated with cardiovascular disease (CVD) in type 1 diabetes (1,2). In this article, we report the specific lipid abnormalities associated with new-onset CVD in an enriched cohort of patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS

— The study design and selection criteria have been previously described (3,4). Briefly, 153 patients with type 1 diabetes were recruited in the U.K. from the Diabetes outpatient clinics at Guy's and King's College Hospitals ($n = 75$) and in Finland from the Helsinki University Central Hospital ($n = 78$). Patients were recruited to represent differing degrees of urinary albumin excretion and matched for duration of diabetes and glycemic control. Participants were then followed for a median of 8.8 years, during which time they received standard medical care, including lipid-lowering agents where indicated.

Full methods of baseline examination have been published elsewhere (3–6). Briefly, clinical data were obtained from patient records including age, sex, diabetes onset, duration of diabetes, medication history, and the presence of microvascular complications. Lipids and lipid fractions were estimated in fasting samples and processed as previously described (3–6). The study outcome was defined post hoc by the occurrence of a fatal or nonfatal cardiovascular event, including coronary heart disease (myocardial infarction, coronary revascularization, or angioplasty), cerebrovascular disease (stroke), or peripheral vascular disease (amputation associated with large vessel disease) based on clinical records.

RESULTS

— A total of 148 patients with type 1 diabetes were studied for a median of 8.8 years, during which time 10 patients were lost to follow-up. Further, one patient died from malignancy, and one committed suicide before the primary outcome had been determined. This left 136 patients in whom the presence of CVD over the follow-up period could be ascertained. The baseline clinical characteristics and lipid levels of patients from this cohort study have been previously described and are provided in online appendix tables (available at http://dx.doi.org/10.2337/dc07-0030).

During the study follow-up, 26 patients experienced a fatal or nonfatal cardiovascular event (19%) including 8 cardiovascular deaths, 7 patients experiencing myocardial infarction, 5 patients undergoing coronary revascularization, 4 patients experiencing strokes, and 8 patients undergoing amputation.

The majority of patients experiencing new-onset CVD were male (77%, $n = 20/26$) compared with 49% of those who remained free of CVD ($n = 54/110$, $P < 0.01$). One-half of those experiencing new-onset CVD during the follow-up period were aged over 50 years ($n = 13/26$), compared with 12% of those who remained free of CVD ($n = 14/110$, $P < 0.01$). There was also a strong association between diabetic kidney disease and the incidence of CVD (Fig. 1*A*). However, after adjusting for age, sex, and kidney disease, new-onset CVD was also independently associated with the composition of HDL particles, such that diabetic individuals with a low ratio of HDL particles containing apolipoprotein (apo) A-I but not apo A-II (lipoprotein [Lp] A-I) to those containing both apo A-I and A-II (Lp A-I:A-II) had a fourfold increased risk of new-onset CVD (odds ratio 4.2 [95% CI 1.4–13.4]). Moreover, this effect appeared to be additive to that of kidney disease (Fig. 1*A*). In addition, for the same level of HDL cholesterol, individuals with lower Lp A-I compared with Lp A-I:A-II had the worst outcome (Fig. 1*B*).

CONCLUSIONS

— CVD is the major threat to longevity in patients with type 1 diabetes. In our cohort, one in five patients with chronic diabetes but no previous history of CVD died or had a cardiovascular event in 8.8 years of follow-up. Whereas some of this excess was attributable to kidney disease (7), dyslipidemia also had a significant and independent impact. Although HDL cholesterol levels are normal or even slightly elevated in type 1 diabetes (8), our study demonstrates that changes in composition of HDL particles are independently associated with cardiovascular risk.

While we performed a detailed analysis of lipid composition and the observational follow-up was long, interpretation of study findings is limited by our small cohort size and number of new CVD cases, which may lead to a type 1 error. However, by enriching the study cohort with patients with chronic kidney disease (and therefore the greatest risk of adverse outcomes), we were able to observe sufficient events to perform multivariate analysis. The factors leading to changes in HDL composition in patients with type 1 diabetes may also partly con-

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Abbreviations: apo, apolipoprotein; CVD, cardiovascular disease; Lp, lipoprotein;

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

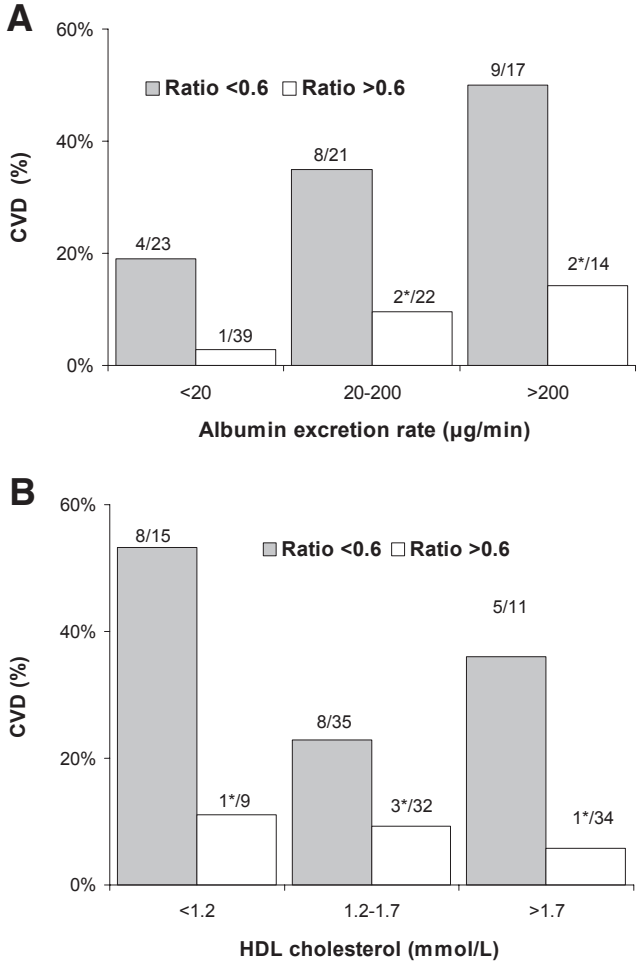

Figure 1— *The incidence of CVD or death in patients with type 1 diabetes, stratified for the ratio of Lp A-I to Lp A-I:A-II particles (above and below the median value) and the stage of nephropathy* (A) *and HDL cholesterol concentration* (B)*. The number above bars denotes the raw number of events divided by the number of patients in each group.* *P < *0.05 above vs. below the median ratio of Lp A-I to Lp A-I:A-II particles.*

found their association with adverse cardiovascular outcomes. Diabetic kidney disease contributes to changes in HDL composition (9). Whereas Lp A-I and the Lp A-I–to–Lp A-I:A-II ratio were the lowest in patients with macroalbuminuria, the impact of lipid changes on CVD was observed in all stages of diabetic kidney disease (Fig. 1*A*). Smoking, obesity, and lipid-lowering drugs may also modify HDL composition, but in our study, new-onset CVD was not associated with these parameters. However, physical exercise, dietary habits, alcohol intake, and menopausal status were not formally assessed, and we cannot exclude that they may impact on both HDL composition and CVD.

Cholesterol efflux significantly contributes to the development and progression of CVD in type 1 diabetes. A key mediator of cholesterol efflux is the HDL particle, of which there are two major populations in humans, Lp A-I and Lp A-I:A-II (10). The concentration of Lp A-I particles is known to be reduced in patients with coronary artery disease (11–13), paralleling reductions in cholesterol efflux capacity. In the present study, we show that a reduced concentration of Lp A-I particles is independently associated with the development of CVD in patients with type 1 diabetes.

Moreover, for the same level of HDL cholesterol, individuals with a lower Lp A-I concentration when compared with Lp A-I:A-II had the worst outcome (Fig. 1*B*). These data further suggest that broadly increasing HDL cholesterol may not be sufficient to confer cardioprotection.

In summary, CVD is common in patients with type 1 diabetes, even though HDL cholesterol levels are normal or elevated. However, changes in the composition of HDL particles are associated with new-onset CVD in type 1 diabetes, in a fashion independent of and additive to the stage of kidney disease, sex, and age.

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