Poor Glycemic Control Is an Independent Risk Factor for Low HDL Cholesterol in Patients With Type 2 Diabetes

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OBJECTIVE — To determine whether the association observed between poor glycemic control and low HDL cholesterol in type 2 diabetes is dependent on obesity and/or hypertriglyceridemia.

RESEARCH DESIGN AND METHODS — We performed a cross-sectional study of 1,819 patients with type 2 diabetes and triglycerides <400 mg/dl enrolled at three diabetes centers in Italy. The risk for low HDL cholesterol was analyzed as a function of A1C levels. Odds ratios (ORs) were calculated after adjustment for confounding factors.

RESULTS — A 1% increase in A1C significantly increased the risk for low HDL cholesterol (OR 1.17 [95% CI 1.1–1.2], P = 0.00072); no changes were observed when age, sex, smoking, and lipid-lowering therapy were included in the model (1.17 [1.1–1.2], P = 0.00044). The association remained strong after adjustments for obesity and hypertriglyceridemia in multivariate analysis (1.12 [1.05–1.18], P = 0.00017).

CONCLUSIONS — Poor glycemic control appears to be an independent risk factor for low HDL cholesterol in type 2 diabetes.

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Cardiovascular disease (CVD) is a major cause of morbidity and mortality in patients with type 2 diabetes (1,2). Several studies have shown that aggressive comprehensive management of the mixed dyslipidemia associated with the metabolic syndrome and type 2 diabetes is needed to reduce the increased cardiovascular risk (3,4). Despite this evidence, treatments do not completely address all the components of diabetic dyslipidemia and therapeutic targets are still not achieved (5). Nearly half of type 2 diabetic patients have low levels of HDL cholesterol (5), a key component of diabetes-related dyslipidemia and a strong independent risk factor for CVD. HDL cholesterol is inversely correlated with cardiovascular risk, even when LDL cholesterol has been reduced with statin therapy (6–7).

An inverse relationship between HDL cholesterol and A1C levels has been described in type 2 diabetic patients (8,9). It is unclear, however, whether this relationship is partly dependent on obesity and/or hypertriglyceridemia, which are known determinants of low HDL cholesterol and frequently found in patients with poorly controlled diabetes. This study was designed to test the hypothesis that glycemic control is independently associated with HDL cholesterol in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — A cross-sectional study of 1,819 consecutive patients with type 2 diabetes and serum triglycerides <400 mg/dl was conducted at diabetes centers in three Italian cities (San Giovanni Rotondo [SGR], Catanzaro [CZ], and Rome) with institutional review board approval. Age, sex, height and weight, medical history, smoking status (current smokers vs. nonsmokers), and current medications—lipid-lowering agents in particular—were recorded for all patients. Venous blood samples were collected after a fast of 8–12 h and analyzed to determine serum levels of A1C (high-performance liquid chromatography, normal range 3–6%), glucose (glucose-oxidase method), cholesterol (total and HDL), and triglycerides (standard enzymatic assays). LDL cholesterol was calculated with the Friedewald formula: LDL cholesterol = total cholesterol – (HDL cholesterol + [triglycerides/5]). Low HDL cholesterol was defined as levels of <40 mg/dl (men) or <50 mg/dl (women) (10).

Statistical analysis
Data are reported as means ± SD. Mean differences were compared by unpaired Students’ t tests. Variables displaying skewed distribution (i.e., triglycerides) were logarithmically transformed. Multivariate logistic regression analysis was used to assess the effect of metabolic control on the presence/absence of low HDL cholesterol. Results were expressed as odds ratio (OR) and 95% CI. After exclusion of intersample heterogeneity, the three data sets were pooled and analyzed together following adjustments for sample. Analyses were performed with SPSS software, version 15 (SPSS, Chicago, IL), and a P value of <0.05 was considered significant.

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Table 1—Clinical characteristics of the study populations

| Characteristic                        | SGR, % | CZ, % | SGR, % | CZ, % |
|--------------------------------------|--------|-------|--------|-------|
| Age (years)                          | 62.1 ± 9.5 | 69.2 ± 7.5 | 62.1 ± 9.5 | 69.2 ± 7.5 |
| Diabetes duration (years)            | 11.6 ± 9.2 | 11.3 ± 9.0 | 11.6 ± 9.2 | 11.3 ± 9.0 |
| Sex (M/F)                            | 1,031/788 | 1,031/788 | 1,031/788 | 1,031/788 |
| BMI (kg/m²)                          | 30.5 ± 5.4 | 30.5 ± 5.4 | 30.5 ± 5.4 | 30.5 ± 5.4 |
| Current smoking (%)                  | 14.3    | 14.3   | 14.3    | 14.3   |
| A1C (%)                              | 8.1 ± 1.9 | 8.1 ± 1.9 | 8.1 ± 1.9 | 8.1 ± 1.9 |
| A1C ≥7% (% of patients)              | 68.5    | 68.5   | 68.5    | 68.5   |
| Total cholesterol (mg/dl)            | 190.1 ± 45.7 | 190.1 ± 45.7 | 190.1 ± 45.7 | 190.1 ± 45.7 |
| HDL cholesterol (mg/dl)              | 46.5 ± 13.7 | 46.5 ± 13.7 | 46.5 ± 13.7 | 46.5 ± 13.7 |
| Triglycerides (mg/dl)                | 141.4 ± 69.2 | 141.4 ± 69.2 | 141.4 ± 69.2 | 141.4 ± 69.2 |
| LDL cholesterol (mg/dl)              | 115.2 ± 37.8 | 115.2 ± 37.8 | 115.2 ± 37.8 | 115.2 ± 37.8 |
| HDL cholesterol <40/50 mg/dl         | 7%      | 7%     | 7%      | 7%     |
| LDL cholesterol ≥100 mg/dl (% of patients) | 64.9 | 64.9 | 64.9 | 64.9 |
| Triglycerides ≥150 mg/dl (% of patients) | 35.5 | 35.5 | 35.5 | 35.5 |
| Diabetes therapy (%)                 | 36.8    | 36.8   | 36.8    | 36.8   |
| Insulin ± OHA                        | 49.4    | 49.4   | 49.4    | 49.4   |
| OHA                                  | 13.8    | 13.8   | 13.8    | 13.8   |
| Diet                                 | 36.7    | 36.7   | 36.7    | 36.7   |
| LLA (%)                              | 36.7    | 36.7   | 36.7    | 36.7   |
| Statins (%)                          | 1.6     | 1.6    | 1.6     | 1.6    |
| Fibrate (%)                          | 2.5     | 2.5    | 2.5     | 2.5    |
| Other hypolipemic drugs (%)          | 59.2    | 59.2   | 59.2    | 59.2   |
| No hypolipemic drugs (%)             |        |        |        |        |

Data are expressed as mean ± SD or percentage. LLA, lipid-lowering agents; OHA, oral hypoglycemic agents.

RESULTS — Table 1 summarizes the clinical and biochemical characteristics of the three populations studied. Higher A1C levels were recorded in SGR and CZ (P < 0.001 vs. Rome). The prevalence of low HDL cholesterol ranged from 28% in Rome to 34% in CZ and 55% in SGR. In SGR, patients were more frequently treated with insulin than with oral hypoglycemic agents compared with the patients in Rome and CZ; moreover, a smaller percentage of patients in SGR and CZ were treated with hypolipemic therapy than in Rome. At all three centers, A1C levels tended to be higher in patients with low HDL cholesterol than in those with HDL cholesterol levels ≥40/50 mg/dl. This difference was statistically significant in SGR (8.7 vs. 8.3%, P = 0.0001) and Rome (7.0 vs. 6.7%, P = 0.04) but not in CZ (7.8 vs. 7.5%, P = 0.2). There was no significant interaction between the variables A1C level and sample in modulation of the risk of low HDL cholesterol (P = 0.86).

Analysis of pooled data revealed that a 1% increase in A1C values significantly increased the risk for low HDL cholesterol (OR 1.17 [95% CI 1.1–1.2], P = 0.00044). The strength of this association was also maintained when additional adjustments for obesity (BMI ≥30 kg/m²) and hypertriglyceridemia (≥150 mg/dl) were included in the multivariate analysis 1.12 [1.05–1.18], P = 0.00017).

The linear regression from individual data between A1C and HDL cholesterol is shown in the online appendix available at http://care.diabetesjournals.org/cgi/content/full/dc09-0256/DC1.

CONCLUSIONS — LDL cholesterol lowering therapy with statins reduces CVD in patients with type 2 diabetes and is recommended by current guidelines as the first-line approach for the treatment of diabetic dyslipidemia (11). However, patients who achieve LDL cholesterol targets with statins may have a “residual” elevation of cardiovascular risk related to low HDL cholesterol, which is an independent predictor of major cardiovascular events (12). Consequently, increasing HDL cholesterol levels is now being proposed as an additional worthwhile therapeutic goal in diabetes (11). Because nearly half of all type 2 diabetic patients have low HDL cholesterol levels (3), the variables associated with this phenomenon need to be clearly defined.

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In the large Italian diabetic population we studied, low HDL cholesterol was strongly associated with higher A1C levels. This observation is consistent with previous reports (5,8,9,13). Lopes-Virella et al. (13) demonstrated a negative correlation between HDL cholesterol and serum glucose levels in diabetic subjects.

More interesting, our study found the association between poor glycemic control and low HDL cholesterol remained significant even after adjustments for obesity and hypertriglyceridemia. Both are highly prevalent in patients with type 2 diabetes, especially in those with poor glycemic control, and are known to independently lower HDL cholesterol. Experimental findings demonstrated that glycation of HDL cholesterol impairs its functional ability to bind to the receptor and to promote intracellular cholesterol efflux (14).

It has also been observed that poor glycemic control promotes glycation of the protein component of HDL cholesterol (apolipoprotein A1), altering HDL cholesterol metabolism and its ability to activate lecithin-cholesterol acyltransferase and the reverse cholesterol transport pathway (15). This is a mechanism by which glycated HDL cholesterol could worsen diabetic atherosclerosis.

To our knowledge, these findings are the first evidence that impaired glycemic control is an important independent risk factor for low HDL cholesterol in patients with type 2 diabetes. If confirmed in future studies, this observation may provide an additional means for establishing optimal glycemic targets tailored to individual patient characteristics.

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