Ratio of Total Cholesterol to HDL-C Is a More Relevant CV Risk Marker in T1DM

Written by Kate Mann

Christel Hero, MD, Sahlgrenska University Hospital, Gothenburg, Sweden, presented results from a large observational study in patients with type 1 diabetes mellitus (T1DM) that assessed cardiovascular disease (CVD) risk predictors and showed that low-density lipoprotein cholesterol (LDL-C) was not a good marker of CV risk [Hero C et al. ADA 2014 (oral session 381-OR)].

In the general population and in patients with type 2 diabetes mellitus (T2DM), elevated LDL-C is a well-known marker of CVD. Patients with T1DM are at high risk for CVD, but less is known about the association of CVD and LDL-C in these patients. The Standards of Medical Care in Diabetes—2014 [American Diabetes Association. *Diabetes Care* 2014] recommends statin therapy in addition to lifestyle therapy if LDL-C remains > 100 mg/dL in patients at low risk (no overt CVD and < 40 years old) or in those with multiple CVD risk factors without prior CVD.

The objective of this study was to evaluate LDL-C and the ratio of total cholesterol (TC) to HDL-C (TC:HDL-C) as predictors of CVD in patients with T1DM and to evaluate CVD risk at different levels of LDL-C. This analysis from the National Diabetes Register in Sweden included 30,778 patients, who were aged 18 to 79 years, identified between 2003 and 2006, and followed for a mean of 7 years. Mean patient age was 46 years, and mean duration of T1DM was 20 years. The outcomes evaluated were fatal and nonfatal CVD (acute myocardial infarction, unstable angina, percutaneous coronary intervention and coronary artery bypass graft, stroke, and peripheral vascular disease). Patients were divided into 2 groups by use of lipid-lowering medication (n = 22,608) or not (n = 1973), and they were further subdivided. Two subgroups of patients were also analyzed: those not taking lipid medication and ≥ 40 years with one CVD risk factor (n = 9324) and those taking lipid medication with a history of CVD (n = 1973). At baseline, the patients on lipid-lowering therapy were older, had a longer duration of diabetes, more frequently took an antihypertensive medication, and had a lower mean estimated glomerular filtration rate (eGFR; 75 mL/minute/m^2), and more (24%) had a history of CVD.

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Cox regression analyses were performed with LDL-C and TC:HDL-C as predictors of fatal and nonfatal CVD outcomes, adjusted for traditional CVD risk factors and treatment.

CVD events during follow-up are shown in Table 1. Two-thirds of patients with a history of CVD had a new event within 7 years. In the subgroup of patients > 40 years with one CVD risk factor, the risk was substantially higher for a new CV event (21%) in 7 years.

Table 1. Proportion of Cardiovascular Disease Events During Follow-Up

Patient Groups	Events (n)	Events (%)	Events per 1000 Patient-Years
All; no lipid medication	2196	9.7	13.8
≥40 years + 1 CVD risk factor	1978	21.2	32.4
All with lipid medication	2537	31.0	51.7
History of CVD	1339	67.9	169.1

CVD = cardiovascular disease

In patients not on lipid-lowering therapy, the risk of a CVD event was increased for each 1 mmol/L increase in LDL-C (HR, 1.08; 95% CI, 1.01 to 1.11; p = .02) in the overall group and in the patients ≥ 40 years with one additional CVD risk factor (HR, 1.08; 95% CI, 1.01 to1.15; p = .03).

When these patients were divided into octiles, there was no significant difference. For patients on lipid-lowering therapy, no significant difference was found for LDL-C as a continuous variable or by octiles.

There was, however, a strong correlation between CVD and the TC:HDL-C ratio per 1 unit increase in patients not on lipid-lowering therapy (HR, 1.08;95% CI, 1.03 to 1.14; p< .001) in the overall group and in the patients ≥ 40 years with one additional risk factor (HR, 1.15; 95% CI, 1.09 to 1.21; p< .001). There was a linear relationship between increasing TC:HDL-C ratio and CVD risk.

In patients taking lipid-lowering medication, there was a weaker, but still statistically significant, correlation between the TC:HDL-C ratio and the risk of CVD overall (HR, 1.06; 95% CI, 1.01 to 1.11; p = .02).

In summary, LDL-C was not the best predictor of CVD risk in patients with T1DM. The results of this study do not provide support for an LDL-C treatment goal of 100 mg/dL in patients with T1DM. The ratio of TC:HDL-C was, however, a significant predictor for CVD in patients not taking lipid-lowering medications. Furthermore, the ratio of TC:HDL-C was a more relevant risk marker for primary prevention in T1DM.

Human Islet Cell Transplantation Successful in Patients With Type 1 Diabetes Who Have SH

Written by Kate Mann

Preliminary data from the Islet Transplantation in Type 1 Diabetes study [NCT00434811] were presented by Bernhard J. Hering, MD, University of Minnesota, Minneapolis, Minnesota, USA. The Phase 3, open-label, single-group study was conducted by the Clinical Islet Transplantation (CIT) Consortium. The CIT was created by the National Institutes of Health to advance islet transplantation for patients with type 1 diabetes mellitus (T1DM) and severe hypoglycemia (SH) and patients who have had a kidney transplant.

A total of 8 centers enrolled 48 patients (aged 18 to 65 years) with a diabetes duration of 5 years or longer, an absence of stimulated C-peptide (< .3 ng/mL), 1 or more episodes of SH in the previous year, and either documented hypoglycemia unawareness or marked glycemic lability. Patients received up to 3 intraportal infusions of purified human pancreatic islets (PHPI) within an 8-month period. Induction immunotherapy included rabbit anti-thymocyte globulin and etanercept, and maintenance immunosuppression consisted of sirolimus and tacrolimus.

Dr. Hering reported secondary efficacy and safety outcomes. The primary outcome—the proportion of patients with an HbA1C less than 7.0% at Day 365 and free of hypoglycemic events from Day 28 to Day 365 inclusive following the first islet transplant—has been submitted for publication. All 48 patients have reached the 1-year follow-up after the initial islet transplant for the primary endpoint evaluation. Of these, 26 received a second transplant and 1 patient received 3 transplants.

The mean dose was 806,587 islet equivalents (IEQs), and the mean number of IEQs per kilogram of body weight was 11,476 in the 48 patients overall. In the patients who received only 1 islet treatment, the mean dose was 589,101 IEQs, and the mean number of IEQs per kilogram of body weight was 8372.

Evidence of islet graft function was found in approximately 95% of patients at Day 75 and approximately 90% at Day 365, as measured by C-peptide. At Day 365, 50% of patients were insulin-independent (insulin could only be given between Days 75 and 240).

Insulin requirements fell from a median at baseline of approximately 0.49 U/kg/day to a median of 0.00 U/kg/day (range, 0.00 to –0.43 U/kg/day) at Day 365 and were sustained to Day 730. C-peptide secretion increased in response to a mixed-meal tolerance test to a median 4 ng/mL at 90 minutes on Day 365, while glucose concentrations decreased to a median of approximately 150 ng/mL at Day 365. Awareness of hypoglycemia was significantly improved as measured by the Clarke Score (median 6 at baseline reduced to 0 at Day 365; p< .001) and the Ryan Hypoglycemia Score (p< .001). The Glycemic Lability Index decreased from approximately 800 at baseline to approximately 100 at Day 365 (p< .001) and the Mean Amplitude of Glycemic Excursions Score improved (p< .0002). The median percentage of time in glucose range (50 to 180 mg/dL) was approximately 95% at Day 365.

There were no deaths or permanent morbidities related to the study treatment. There were 19 serious adverse events, of which 5 were related to the procedure, 13 to immunosuppression, and 1 to insulin-related hypoglycemia. Other adverse events involved 6 patients with non-zero calculated panel reactive antibodies (only 1 was donor specific) and 1 patient with an acute kidney injury of unknown origin. The initiation of islet therapy transplantation was associated with a small but significant decrease in glomerular filtration rate (–8.1 mL/minute; p< .0001), with no further significant change at Days 75 and 365.

In summary, transplanted PHPI safely restored and then sustained glycemic control to near normal levels and provided protection against SH in patients with T1DM.