Targeting High-Density Lipoprotein Cholesterol in Diabetic Patients to Reduce Cardiovascular Risk

Grant RW, Meigs JB. Prevalence and treatment of low HDL cholesterol among primary care patients with type 2 diabetes: an unmet challenge for cardiovascular risk reduction. Diabetes Care 2007;30:479–84.

Study Overview

Objective. To evaluate the prevalence and predictors of low high-density lipoprotein (HDL) cholesterol, characterize use of lipid therapy, and estimate the theoretical benefit of more effective HDL cholesterol–raising methods among patients with type 2 diabetes.

Design. Multicenter, retrospective analysis.

Data sources. Patients aged ≥ 18 years with type 2 diabetes who received care at least once between 1 July 2004 and 30 June 2005 at 1 of 12 primary care practices in eastern Massachusetts were identified (n = 7692). Currently prescribed medications were grouped into statins and nonstatins (fibrates, niacins, n-3 fatty acids). Published studies were used to estimate possible benefits of raising HDL cholesterol levels.

Main measures. Low-density lipoprotein (LDL) cholesterol level (goal, < 100 mg/dL), HDL cholesterol level (goal, ≥ 40 mg/dL for men, ≥ 50 mg/dL for women), statin prescription status, prescription of nonstatin HDL cholesterol–raising therapy, and presence of diagnosed cardiovascular disease (CVD).

Main results. 68.7% of patients had an LDL level < 100 mg/dL. 49.5% of patients had low HDL cholesterol (< 40 mg/dL for men, < 50 mg/dL for women). Low HDL cholesterol, younger age, and worse glycemic control were independently associated with CVD prevalence. 63% of patients were taking statins, whereas 8% of patients were taking nonstatin medications. Based on published studies, CVD mortality would be reduced by 42% in women and 23% in men if low HDL were normalized in this study population.

Conclusion. Almost half of patients in this primary care cohort had low HDL cholesterol levels. Although many patients were appropriately taking statin medications, few were taking nonstatin medications known to have HDL-raising effects. Low HDL cholesterol is a potential target for cardiovascular risk reduction in high-risk diabetic patients.

Commentary

While the observation of low HDL in this diabetic population is not unexpected, focusing on HDL-raising therapy as defined in this study by Grant et al (niacin, fibrates, and n-3 fatty acids) can be argued. The authors state "Many patients with diabetes have an atherogenic pattern of dyslipidemia characterized by relatively normal levels of dense LDL cholesterol particles." In fact, for the majority of diabetic patients who have normal or low LDL cholesterol levels, most also have elevated levels of small, dense LDL (apolipoprotein B [apoB]-containing atherogenic lipoprotein) particles [1–3]. Although this can be easily measured by calculating non-HDL cholesterol levels, in many cases measuring apoB levels or LDL particle number is needed to identify these unmeasured atherogenic lipoprotein particles. This focuses attention on what continues to be a major gap in education for many practitioners in the evaluation of lipoproteins in patients with diabetes.

Aggressive education is needed regarding the paradigm of lipoprotein particle evaluation when evaluating cardiovascular risk and aggressive lowering of these atherogenic lipoproteins when identified. Grant et al point to the American Diabetes Association guidelines regarding raising HDL [4]; however, the National Cholesterol Education Program guidelines clearly state that in high-risk patients who have met their LDL goal, the secondary target should be lowering of non-HDL cholesterol in patients with low HDL [5]. The "HDL-raising drugs" mentioned in this study (fibrates, niacin, and high-dose n-3 fatty acids) all have effects on apoB-containing lipoproteins. In fact, n-3 fatty acids have minimal effects on HDL; their effect on lipoprotein particles is mostly a shift from smaller to larger particles with minimal change in particle size [6].

Despite accumulating evidence demonstrating conflicting results when attempting to raise HDL levels with medications and the emerging evidence on the importance of HDL function on risk [7] rather than levels, physicians continue to be instructed to measure traditional lipids only and try to raise lipid fractions that may simply be a marker of the atherogenic process of diabetes. The focus of our efforts should be to teach and train practitioners about the importance of lipoproteins along with lipids in cardiovascular

risk evaluation and treatment. It is through understanding of this new paradigm that cardiovascular risk can best be identified, managed, and reduced.

Applications for Clinical Practice

In high-risk populations (eg, diabetic patients), there is a significant degree of residual cardiovascular risk even after aggressive LDL cholesterol–lowering with statin medications. This risk can be evaluated by calculating non-HDL cholesterol levels (total cholesterol – HDL cholesterol) or measuring apoB levels or LDL particle levels. Further reduction can indeed be obtained by combining statins with drugs such as niacin, fibrates, and n-3 fatty acids. While these drugs may affect HDL cholesterol levels, it is unclear if this effect is related to the cardiovascular risk reduction associated with their use. This study highlights the underutilization of these medications in clinical practice. Recognizing that they have very important effects in addition to raising HDL is key to understanding their proper use in cardiovascular risk reduction.

—Review by James A. Underberg, MD, MS (New York University Medical School, New York, NY) and Nirav R. Shah, MD, MPH

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