EDITORIAL (SEE LU ET AL., P. 16)

Non–HDL Cholesterol: Into the Spotlight

The elevated coronary heart disease (CHD) risk affecting patients with type 2 diabetes may be attributed to a combined dyslipidemia characterized by elevated triglycerides, reduced HDL cholesterol, small dense LDL particles (independent of the LDL cholesterol level), elevated triglyceride-rich remnant lipoproteins (TGRLs), and/or elevated apolipoprotein B (apoB) levels (1). All of these features have individually been implicated as contributors to CHD. Some reports suggest that the combined dyslipidemia may confer a higher magnitude of risk than elevated LDL cholesterol alone (2).

The role of triglycerides as a risk factor has been controversial. Much of its risk may be attributed to the associated low HDL cholesterol level, along with contributions from all of the other related variables. Although triglycerides do appear to be an independent risk factor (3), they likely act only as a marker for these associated features. The measurement of apoB has been advocated as an alternative index (4). Since each LDL particle contains a single apoB molecule, the apoB level reflects particle number, thus not only accounting for both remnant and LDL particles but also the density of particles when expressed in relation to particle cholesterol content. Despite these advantages, even the global standardization of apoB assays (5) has not made it routinely available to the clinician. This may be in part due to a general unfamiliarity with its interpretation outside of the research setting and because existing guidelines do not take advantage of the information it imparts. Its cost relative to its potential advantages for clinical decision-making also has not been adequately explored.

Existing guidelines, however, do take advantage of non–HDL cholesterol as an index of risk associated with this combined dyslipidemia. The recognition of this index is not new; this "beta" lipoprotein cholesterol fraction has been associated with increased CHD mortality in population-based studies that began in the 1950s (6). Non–HDL cholesterol is simply defined as the difference between total and HDL cholesterol and, thus, represents cholesterol carried on all of the potentially proatherogenic apoB-containing particles [primarily VLDL, IDL, and LDL as well as chylomicron remnants and lipoprotein(a)]. Many reports confirm a strong correlation between non–HDL cholesterol and apoB (7). In assessing the value of non–HDL cholesterol, it should be remembered that our routine determination of LDL cholesterol is not a measurement, but rather a calculation based on a measurement of triglycerides, total cholesterol, and HDL cholesterol, using the formula of Friedewald (8). The calculated LDL cholesterol level has been shown to be significantly different than a direct LDL cholesterol measurement by ultracentrifugation in type 2 diabetic patients (9). In fact, its very nature is to exclude the cholesterol of TGRLs, which are proatherogenic. Thus, for diabetic patients with the combined dyslipidemia, calculated LDL cholesterol fails to be an adequate index of overall lipid-associated risk.

The Third Adult Treatment Panel (ATP III) of the National Cholesterol Education Program (NCEP) has recommended the use of non–HDL cholesterol as a secondary target of lipid lowering, after achieving adequate control of LDL cholesterol and if triglycerides are elevated (≥200 mg/dl) (10). Because of its simple calculation, the non–HDL cholesterol level is easily available to the clinician with every lipid profile ordered, thus eliminating any additional costs. Because it circumvents the measurement of triglycerides, it avoids the potential limitation of triglycerides as a mere marker of CHD risk and instead directly reflects the cholesterol content of all particles that may be proatherogenic. Also, its derivation does not require a lipid profile to be done in the fasting state, and it avoids the potential inaccuracy caused by the inherent intraindividual variability of the triglyceride measurements. A routine calculated LDL cholesterol level cannot circumvent most of these limitations. The Friedewald equation requires a fasting triglyceride level <400 mg/dl in order to accurately calculate LDL cholesterol. Thus, in many cases of fasting hypertriglyceridemia common in diabetes, the clinician has no reliable estimate of LDL cholesterol, and therefore no objective index of lipid-associated CHD risk, unless ultracentrifugation is performed. Recently, an immunoseparation technique for a direct LDL cholesterol determination has been proposed as an alternative to the labor-intensive ultracentrifugation reference method. However, comparison studies demonstrate that in some hypertriglyceridemic samples, a significant bias (usually an overestimate) still exists with this method (11,12). Whiting et al. (13) have reported that the error of this method as a function of hypertriglyceridemia in diabetic patients is greater than that of the Friedewald calculation. In contrast, the non–HDL cholesterol level of a hypertriglyceridemic patient would still be available to the clinician, and could potentially be more accurate than either the directly measured or the calculated LDL cholesterol level (14). Non–HDL cholesterol thus represents a readily obtainable, inexpensive, and convenient measure of CHD risk that may be superior to LDL cholesterol in many respects. All that remains is for its reliability as a predictor of CHD risk to be established. The article by Lu et al. (15) in this issue of *Diabetes Care* highlights the predictive value of non–HDL cholesterol for CHD and the role that it may play in the management of diabetic dyslipidemia.

Many cross-sectional and prospective studies have demonstrated the value of non–HDL cholesterol as an index of CHD risk across different populations, including Europeans (6,16,17), Hawaiians (18), and cohorts in the U.S. (19–21). Non–HDL cholesterol appears to track with multiple CHD risk factors in U.S. ethnic minorities that are disproportionately affected by diabetes (22–24). Previous studies in diabetic subjects also used surrogate indexes such as intima-media thickness (25,26). In these respects, the article of Lu et al. (15) adds to the literature by establishing, in a prospective study, the predictive value of non–HDL cholesterol for clinical end points in a high-risk, ethnic diabetic population.

Few other reports have simultaneously examined the predictive value of non–HDL cholesterol and LDL cholesterol for CHD. The Honolulu Heart Program found the multivariate relative risk of non–HDL cholesterol to be no different than that of total or LDL cholesterol among elderly men of Japanese ancestry (18). In the SHEP Study cohort, LDL cholesterol was an independent predictor of CHD if triglycerides were <400 mg/dl, while non–HDL cholesterol was an independent predictor regardless of the triglyceride level (20). The Lipid Research Clinics (LRC) Program Follow-up Study found that the highest quartile of non–HDL cholesterol predicted CHD events while that of LDL cholesterol failed to do so in women. Also, the highest quartile of non–HDL cholesterol predicted all-cause mortality while that of LDL cholesterol failed to do so in either sex (21). The report of Lu et al. (15) demonstrated higher hazard ratios for the highest tertile of non–HDL cholesterol than that of LDL cholesterol, although the respective confidence intervals overlapped significantly. The difference between the findings of these latter two studies may be due to the larger number of participants, longer follow-up, and the higher baseline LDL and non–HDL cholesterol levels in the LRC study. Even if non–HDL cholesterol and LDL cholesterol are equivalent in their predictive power, the relative convenience and greater reliability of non–HDL cholesterol should make it the preferred index for use in clinical practice.

The incidence of type 2 diabetes is growing globally (27), and CHD accounts for the majority of type 2 diabetes–related morbidity and mortality. Given that non–HDL cholesterol is a simple, reliable, and reproducible index of overall CHD risk that may be equivalent, if not superior, to LDL cholesterol, should it be our *primary* lipid treatment target for patients with type 2 diabetes?

Such use of non–HDL cholesterol has been proposed for diabetic patients (1) as well as the general population (14,21,28). However, Grundy (29) points out that for non–HDL cholesterol to replace LDL cholesterol as the primary lipid target for the general population, strong evidence of its superiority will be needed. At present, such evidence is not yet available. Nevertheless, the NCEP has clearly acknowledged the importance of non–HDL cholesterol for patients with hypertriglyceridemia, which may include those with type 2 diabetes. The findings of Lu et al. (15) now shift the weight of evidence further in favor of the primacy of non–HDL cholesterol specifically for patients with type 2 diabetes.

For non–HDL cholesterol to be more applicable to clinical practice, additional studies are needed in other populations to verify its consistency as an independent predictor of CHD. Also, effective prediction of risk is often less meaningful if effective treatments are not available, and in this respect, intervention studies that report a lowering of non–HDL cholesterol (30–36) need to be supported by additional studies examining clinical end points. The Helsinki Heart Study (37), as one example, reported significant lowering of non–HDL cholesterol along with reduced CHD events, although the benefits of gemfibrozil in this landmark trial clearly extend beyond non–HDL cholesterol alone. It has also been suggested that the use of non–HDL cholesterol will not completely eliminate the need for a fasting triglyceride level. When an elevated non–HDL cholesterol level warrants drug treatment, the clinician must determine whether to use as first-line therapy an agent that targets LDL cholesterol (HMG-CoA reductase inhibitor or bile acid sequestrant) or one that targets VLDL cholesterol (fibric acid derivative or niacin). In such cases, a measure of fasting triglycerides and calculation of LDL cholesterol will still be needed.

Lu et al. (15) also report that the ratio of total to HDL cholesterol (TC/HDL) was a strong predictor of CHD, although the confidence intervals again overlapped significantly. A reanalysis of data from the LRC cohorts (38) also reported similar findings for TC/HDL. Thus, in the search for the optimum index of risk, TC/HDL should also be compared.

Despite these obstacles, further studies of non–HDL cholesterol must be undertaken. If future studies in diabetic patients can confirm its superiority over LDL cholesterol, perhaps the NCEP or their international counterparts will recommend in future consensus statements the use of non–HDL cholesterol as the primary lipid target for patients with type 2 diabetes. For now, however, sufficient evidence exists for non–HDL cholesterol to at least move squarely into the spotlight and be scrutinized for its potential utility in the management of diabetic dyslipidemia.

STANLEY H. HSIA, MD

From the Charles R. Drew University of Medicine and Science, Los Angeles, California.

Address correspondence to Stanley H. Hsia, MD, Charles R. Drew University of Medicine and Science, 1731 East 120th St., Los Angeles, CA 90059. E-mail: sthsia@cdrewu.edu.

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