

Non-HDL Cholesterol Versus Apolipoprotein B in Diabetic Dyslipoproteinemia

Alternatives and surrogates versus the real thing

Dyslipidemia in patients with diabetes has suddenly emerged as a vital clinical issue. Whereas better glucose control has not been shown to significantly reduce vascular mortality and morbidity (1), lowering LDL cholesterol has regularly been associated with substantial benefit. This may be just the beginning; fibrate therapy also holds promise (2).

The Adult Treatment Panel III (ATPIII) reaffirmed that LDL cholesterol should be the cornerstone of lipid diagnosis and therapy (3). At the same time, ATPIII also proposed that non-HDL cholesterol may be used for clinical decision making in hypertriglyceridemic patients. The argument is that non-HDL cholesterol includes the cholesterol in all the atherogenic lipoproteins and is therefore a better atherogenic index than LDL cholesterol, particularly in hypertriglyceridemic subjects. Non-HDL cholesterol has also been suggested to be an acceptable surrogate for apolipoprotein B (apoB), which measures total atherogenic particle number. Therefore non-HDL cholesterol has become an alternative for LDL cholesterol and a surrogate for apoB.

The article by Wagner et al. (4), which appears in this issue of *Diabetes Care*, presents a serious challenge to that decision. They show convincingly that non-HDL cholesterol is not an acceptable clinical surrogate for apoB in patients with diabetes. In the 26 patients with plasma triglycerides >2.25 mmol/l, non-HDL cholesterol and apoB were concordant. However, in the other 96 with levels less than this, they were not. Of these 96, 44 (46%) had increased non-HDL cholesterol whereas 68 (71%) had increased apoB. Moreover, of the 52 with a normal non-HDL cholesterol, 25 (48%) had an increased apoB. These are substantial differences that have practical consequences

for the initiation and adjustment of pharmacological therapy.

To be sure, their study is not large, but the results accord in general with our analysis of the much larger Quebec Cardiovascular Study cohort (5). We found high correlation but low concordance between apoB and non-HDL cholesterol. This was the case in both the 1,484 men with triglycerides <2.0 mmol/l and the 619 with triglycerides above this level. Our findings, therefore, indicate that irrespective of the triglyceride level, non-HDL cholesterol is not equivalent to apoB.

If non-HDL cholesterol is not an accurate alternative to apoB, then which matters more? There is no evidence I am aware of that shows non-HDL cholesterol to be superior to apoB. By contrast, the results of a number of epidemiologic studies and clinical trials have shown the converse, namely that apoB is superior to non-HDL cholesterol as an index of the risk of vascular disease and a guide to the adequacy of statin therapy (rev. in 6).

No doubt the debate will continue, but why? The case for apoB is straightforward. There is one molecule of apoB per atherogenic particle. Therefore, plasma apoB represents total atherogenic particle number, of which $>90\%$ are intermediate-density lipoprotein or LDL particles (7). The measurement of apoB is standardized (8) and automated, and fasting samples are not required, a major advantage for patients with diabetes. The risk of vascular disease relates more closely to the level of apoB than to the cholesterol indices, and the adequacy of statin therapy can be better judged by apoB level than by cholesterol indices (6).

The case for non-HDL cholesterol is not straightforward, even from a conceptual standpoint. Non-HDL cholesterol assumes that VLDL and LDL cholesterol pose equal risk. But they do not. Studies

of transgenic mice by Veniant et al. (9) clearly demonstrate that the cholesterol in the larger but much less numerous VLDL particles is not as atherogenic as the cholesterol in the smaller but much more numerous LDL particles. Moreover, VLDL size and composition can vary markedly. Therefore, there is no certain relation between VLDL cholesterol and VLDL particle number (10), and it is lipoprotein particles, not free lipids, that contact and penetrate the arterial wall.

Plasma apoB cannot be predicted from plasma triglyceride. Although the issue has not been examined in patients with diabetes, other studies have shown that the atherogenic risk of hypertriglyceridemic-hyperapoB is much greater than hypertriglyceridemic-normoapoB (rev. in 7). Similarly, a number of clinical trials have shown that apoB is a better index of the adequacy of statin therapy than any of the cholesterol indices (rev. in 6). That is yet another argument for apoB.

However, there are other issues. Measuring apoB in patients with diabetes makes it obvious that they are not all alike. Not all patients with type 2 diabetes are dyslipidemic, and not all hypertriglyceridemic patients with type 2 diabetes have an elevated apoB (11). Why? Does this have anything to do with the pathogenesis of the diabetes? For example, impaired fatty acid trapping by adipose tissue can be linked to both hypertriglyceridemic-hyperapoB and to dysglycemia, and so both malignant features in this subgroup may share a common pathophysiologic origin (7). Obesity is unquestionably a common precursor of insulin-resistant type 2 diabetes. But not all those who are obese and dysglycemic are dyslipidemic. For example, Pima Indians are obese and dysglycemic but, on average, are not dyslipidemic (12). Likewise, most individuals with morbid obesity are not dyslipidemic (13). Could these sub-

groups have hypereffective fatty acid trapping by adipose tissue, which results in dysglycemia but not in dyslipidemia (12)?

In summary, we do not fully assess the lipoprotein status of patients with type 2 diabetes if apoB is not measured. That means we will assess risk less well and will likely treat patients less effectively (6). Those who produced the recommendations of ATPIII have used their best efforts given the data before them. But the evidence base has moved, and our understanding of the determinants of fatty acid metabolism has advanced. All this progress should prompt a timely and in-depth review of how we classify and treat the atherogenic dyslipoproteinemias in patients with insulin resistance and type 2 diabetes. In my view, among the other changes that should be made, we should replace alternatives and surrogates with the real thing.

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