The apoB/apoA-I ratio and insulin resistance: sorting out the metabolic syndrome

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Online publish-ahead-of-print 28 September 2007

This editorial refers to ‘ApoB/apoA-I ratio: an independent predictor of insulin resistance in US non-diabetic subjects’ by J. Sierra-Johnson et al., on page 2637

Sierra-Johnson et al.,1 demonstrate that the apoB/apoA-I ratio is an independent predictor of insulin resistance in non-diabetic Americans. This was the case in men and women and was independent of the traditional risk factors, components of the metabolic syndrome, and inflammatory risk markers such as C-reactive protein (CRP). The strengths of this study are the meticulous construction of the NHANES database on which it is based and the meticulous analysis of it that was undertaken. Previously, these authors and others have shown that the apoB/apoA-I ratio becomes progressively more abnormal as the number of components of the metabolic syndrome increases2 and that apoB is more closely tied to dysglycaemia and inflammation than low-density lipoprotein (LDL) cholesterol or non-high-density lipoprotein (HD) cholesterol.3–6 This is the first study, however, to examine systematically the relationship of the apoB/apoA-I ratio to insulin resistance in a large representative cohort.

If nothing else, the metabolic syndrome has expanded the net of those labelled at high risk of vascular disease. The problem is that not all those caught are equal: the gradient in risk amongst those who qualify for the diagnosis is probably not much different from the gradient in risk amongst those who do not. Diluting the value of the high-risk label multiplies the costs and diminishes the benefits of therapeutic intervention. Moreover, lumping alikes with not-alikes ensures we will never work out the pathogenesis of either the individual components or their interaction.

This diagnostic inflation is the consequence of diagnostic imprecision. Why are hypertriglyceridaemia and low HDL cholesterol the two diagnostic lipid abnormalities of the metabolic syndrome? To be sure, hypertriglyceridaemia is more common in patients with vascular disease, insulin resistance, abdominal obesity, and diabetes than hypercholesterolaemia. However, hypertriglyceridaemia has never stood up as an independent risk factor for vascular disease, and lowering triglycerides has not lowered clinical events. Amongst patients with hypertriglyceridaemia, it is apoB and apoA-I that determine risk, not the plasma triglycerides or HDL cholesterol.7 In these patients, small dense cholesterol-depleted LDLs are the rule. Accordingly, LDL cholesterol is an inaccurate guide to the number of LDL particles and therefore to risk. ApoB measures the total number of atherogenic particles, and LDLs make up the vast majority of these. Only about a third of patients with hypertriglyceridaemia have an elevated apoB, and it is this third that is at markedly increased risk.8,9 Moreover, benefit from fibrate therapy relates to their effects on LDL and HDL not to triglycerides as such.10

Not only are lipids inadequate for diagnosis, they are also inaccurate for determining if therapy has been maximally effective. Statins lower LDL cholesterol and non-HDL cholesterol more than they lower apoB. Therefore, LDL cholesterol and non-HDL cholesterol can be at ‘target’ and atherogenic particle number still not optimally reduced.11 Thus, using apoB means fewer patients will need to be treated with pharmacological therapy but better results will be achieved. On the other hand, HDL is unquestionably a major determinant of risk, but most recent studies indicate that apoA-I, the major apolipoprotein in HDL, is better for this purpose than HDL cholesterol.12 The basis for this functional superiority has not been worked out as clearly as for apoB. Hypertriglyceridaemia lowers HDL cholesterol more than apoA-I, and apoA-I may be the functional site of the HDL particle.13 Not its least advantage is that apoA-I can be measured more accurately and reproducibly than HDL cholesterol by the clinical laboratory.

It should not be surprising, therefore, except perhaps to the die-hard lipid afficianados, that the apoB/apoA-I ratio is superior to any of the cholesterol ratios as a summary index of the risk of vascular disease. This applies to those who are asymptomatic as well as those who are symptomatic, to those who are on therapy as well as those who are not, to females as well as males, and to older individuals as well as younger.9
The results of Sierra-Johnson therefore add further evidence that the diagnosis of the metabolic syndrome should be revised. The metabolic syndrome is just a list of common abnormalities. Surely, we want our diagnostic criteria to be as accurate and discriminating as possible. Why not switch to apoB and apoA-I from triglycerides and HDL cholesterol? Fewer patients at higher risk would be identified and therefore therapy would be more cost-effective. However, their data point to an even greater challenge: understanding the pathophysiological relationships of dysglycemia and dyslipidaemia. Considerable opinion supports the view that insulin resistance is the driving force for most of the abnormalities that characterize the metabolic syndrome. On the other side of the debate is the fatty acid hypothesis, which states that excessive fatty acid flux to the liver produces atherogenic dyslipoproteinaemia and excessive fatty acid flux to skeletal muscle produces insulin resistance and ultimately type 2 diabetes. Thus, one side believes that insulin resistance is what matters, whereas the other believes that fatty acid flux is all that really counts.

Biological extremes can be helpful in testing our hypotheses. In an elegant study of lean young subjects with insulin resistance, Shulman and his colleagues demonstrated reduced muscle and liver glycogen synthesis with increased hepatic lipogenesis following an oral glucose load. However, while plasma triglycerides were increased, LDL particle number was not. Insulin resistance, on its own, did not produce hyperTg hyperapoB. This is typically the case also in Pima Indians, so many of whom are obese, insulin resistant, and diabetic, but their plasma triglycerides, triglyceride clearance, and apoB are characteristically normal. Furthermore, patients with partial lipodystrophy are intensely insulin resistant and hypertriglyceridaemic but their plasma apoB is normal. Thus insulin resistance may be a contributory cause to atherogenic dyslipoproteinaemias, but it is not a sufficient cause.

That does not mean insulin resistance can be dismissed. That is why the results of Sierra-Johnson are so important. They have shown within the American population that these two strands of metabolic dysfunction are powerfully linked; but how? The combination of diabetes and dyslipidaemia multiplies the risk of vascular disease madly but again we do not know how. Hyperglycaemia does not seem to explain very much of macrovascular risk. Is insulin resistance the answer, as the results of the Quebec Cardiovascular Study suggest? Or is insulin resistance a marker for changes within the arterial wall such as glycation of the glycans that multiply the atherogenic potential of LDL particles that enter?

The metabolic syndrome, as currently defined, is a large loose aggregate of patients, who share some characteristics but not the same destiny. Naming something is not the same as understanding it. Also, the shadows things cast are not the things themselves. The apoB/apoA-I ratio and insulin resistance appear to be the two key elements of the metabolic syndrome. We already have the technology to measure apolipoproteins. We must develop more robust methods to quantitate insulin resistance reproducibly. We must learn how energy excess relates to both. Then we will be able to determine if there is such a thing as the metabolic syndrome.

Conflict of interest: none declared.

References