Cardiovascular Complications of Non–Insulin-Dependent Diabetes
The Difficult Search for Causality
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Diabetes of the non–insulin-dependent type (NIDDM) is a continuing mystery, still defying clinicians and researchers with unsolved questions. It took decades to reach an agreement over its definition— and it may be that we should revise it, if we follow recent results indicating that the oral glucose tolerance test may better diagnose chronic alcoholism than “pure” diabetes. Its origin is still unknown, although considerable progress has been made in opening the question of the insulin resistance/insulin deficiency balance and which comes first. The first attempts for treatment led to one of the major controversies in the history of medicine. There also is the problem of cardiovascular complications. They are indeed more frequent in diabetic subjects—most strikingly, women—compared with the rest of the population, and this cannot be explained either by the (commonly found) perturbations of major risk factors, ie, blood pressure and plasma cholesterol, or even by hyperglycemia. This suggests that there must be a “specific” diabetes-related cardiovascular risk factor, which would not be hyperglycemia, or hyperglycemia alone.

One recently emerging candidate for such a risk factor is the level of plasma triglycerides. It has been found predictive of major cardiovascular events in diabetic subjects by three studies to date: the Schwabing Study, a follow-up of a cohort of outpatients with insulin-treated NIDDM, the Paris Prospective Study, which analyzed coronary heart disease mortality in subjects with either impaired glucose tolerance or diabetes, and the Diabetes Intervention Study, a 5-year clinical trial involving patients with newly diagnosed NIDDM (J. Schulze, personal communication). None of these studies had collected at baseline the concentration of high-density lipoprotein (HDL) cholesterol, which is known to be highly inversely correlated to plasma triglycerides and hence could have replaced triglycerides as a stronger predictor in multivariate risk models. However, since both high triglycerides and low HDL cholesterol are present in most cases of NIDDM, the important implication of these results was that one marker of this abnormal lipid profile had been recognized as a predictor of cardiovascular complications.

This suggested that “diabetic dyslipidemia” could be the specific diabetes-related risk factor that was searched for.

In this issue of Circulation, Laakso and colleagues add one study to the three mentioned above, which once again identifies diabetic dyslipidemia as a predictor of coronary events in a diabetic population. Moreover, they have been able to test for prediction a series of lipoproteins, not only HDL cholesterol, but also total HDL and its HDL2 and HDL3 fractions; total, HDL, and very low-density lipoprotein (VLDL) triglycerides; total, low-density lipoprotein (LDL), and VLDL cholesterol. While supporting the hypothesis that perturbations of lipid metabolism may play a role in the cardiovascular complications of NIDDM, their findings give more insight into the complex interrelations of lipoproteins that may exist in association with an insulin-resistant state.

The central result of the study is that, after following for a mean 7 years a cohort of 313 NIDDM patients, Laakso established that there were two statistically significant independent predictors of coronary heart disease (CHD) mortality or morbidity: age and HDL cholesterol. Neither hypertension nor smoking were associated with CHD events in this population. Although duration of diabetes and glycated hemoglobin were significantly related to CHD death in univariate analysis, multiple adjustment removed this statistical significance.

HDL cholesterol appears to be, as was envisaged, a stronger predictor than triglycerides of CHD in subjects with NIDDM. Can this be interpreted as meaning that the causal factor, if there is one, within diabetic dyslipidemia would be HDL cholesterol and not triglycerides? The answer is not as straightforward as it was thought to be in times when multivariate models were the cornerstone for selecting variables deemed worthy to enter into the search for causality. In particular, it has now been recognized that in such models, one or the other of two closely linked variables may indifferently bear the whole predictive power of the couple, leaving its partner in the dark. This is why, in the case of HDL cholesterol and triglycerides, which are not only statistically correlated but also metabolically dependent, finding the stronger predictor is not sufficient to conclusively show the other as innocent.

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Laakso and colleagues are well aware of the problem, and they have therefore conducted a thorough analysis of the pattern of prediction entailed by the various lipoprotein fractions that were measured. Of all them, they found that HDL cholesterol, HDL₂ cholesterol, VLDL cholesterol, total triglycerides, and VLDL triglycerides were related to CHD complications in the population they studied. Between some of these variables, high correlation coefficients existed, indicating that they could be completely interchanged and that measuring one or the other would give the same information. This was the case between HDL and HDL₂ cholesterol (r = .941), total and VLDL triglycerides (r = .988), and VLDL triglycerides and VLDL cholesterol (r = .814). On the other hand, the correlation coefficient between VLDL triglycerides and HDL cholesterol (or their respective fellow creatures) was only −.530. Hence, despite the large array of lipid variables that were measured, the problem could still be summarized as “which of high triglycerides or low HDL cholesterol is the potential culprit?”

The question, as was said earlier, is not to be resolved entirely by statistical adjustment. This is further illustrated by an astute analysis performed by Laakso and colleagues, a stratified prediction model. The idea was to somehow verify that at a given level of HDL cholesterol triglycerides would not be linked to CHD, which was the logical assumption to be derived from the results of the multivariate analysis. Hence, Laakso selected from the population a group of subjects with “low” HDL cholesterol, namely with concentrations below the median value, and there he found “... that VLDL triglycerides were the only variable significantly associated with all CHD events.” Incidentally, VLDL triglycerides were a better predictor of CHD events than HDL cholesterol in the subgroup who had LDL cholesterol levels below the median.

This probably means that if there is a culprit, there may be two. Indeed, these two, low HDL cholesterol and high triglycerides, often go as a couple: Are they partners in crime? While epidemiology has not yet decided which one should be cross-examined first, pathophysiology has started the investigation on both and has found convincing arguments of possible malice on both sides, all of which are thoroughly reviewed in Laakso’s article. So far, however, they constitute mere presumptions. For instance, let us consider the couple in its usual context, NIDDM; or even in a broader context, that of the insulin resistance syndrome, where accumulating evidence places them. Many other disturbances accompany them: hyperinsulinemia, which has already been found as a predictor of heart disease; frank or mild hyperglicemia, which, despite the fact that it does not appear as a strong correlate to macroangiopathy, is nevertheless the main factor enhancing microangiopathy in diabetes; elevated blood pressure, which needs no comment regarding cardiovascular risk; and maybe others, such as defective fibrinolysis. It cannot be excluded that the dyslipidemic couple is only an informer about this gang of villains.

Nevertheless, the current facts are that (1) diabetic dyslipidemia has been shown repeatedly as the strongest predictor of cardiovascular complications in subjects with NIDDM, and (2) there are pathophysiological arguments in favor of a causal role. As there appear to be no means at present of lowering triglycerides without elevating HDL cholesterol or vice versa, the question of whether we should treat one or the other or both is purely academic. The real question is: Should we treat dyslipidemia in subjects with NIDDM? The answer can only come from the definitive proof of causality: a clinical trial.

References

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