Do Interventions to Reduce Coronary Heart Disease Reduce the Incidence of Type 2 Diabetes?
A Possible Role for Inflammatory Factors

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Type 2 diabetes is as a major cause of coronary heart disease (CHD). In some studies, the rate of CHD in type 2 diabetic subjects approaches that observed in some subjects with prevalent CHD. Additionally, the case fatality rate of CHD is increased in type 2 diabetics. In one Finnish study, 50% of diabetic men who had a first coronary heart event died within a year of their initial presentation; 50% of these fatal cases died before they reached the hospital (“sudden death”). These subjects, by definition, could not benefit from a secondary prevention program. Clearly, preventing type 2 diabetes would be important in the reduction of CHD. The Diabetes Prevention Program is a large National Institutes of Health–funded trial to prevent diabetes in subjects with impaired glucose tolerance. The interventions being tested are metformin and intensive lifestyle changes. Recently, the Finnish Diabetes Prevention Program reported a 58% reduction in the incidence of type 2 diabetes in 523 subjects with impaired glucose tolerance (American Diabetes Association, personal communication, June 2000).

Approaches to reduce CHD have focused on the benefits of lowering LDL cholesterol with HMG CoA reductase inhibitors (statins) and angiotensin-converting enzyme (ACE) inhibitors. Recently, it was suggested that ACE inhibitors may prevent diabetes. In this issue, Freeman et al suggest that, in the West of Scotland Coronary Prevention Study (WOSCOPS), pravastatin reduced the incidence of diabetes by 30%. What might explain this effect? One possibility, as the investigators suggest, is that by reducing the risk of incident CHD, the need for β-blocker use (and perhaps thiazides) was reduced; some previous observational studies have suggested that β-blocker and thiazide use may be associated with an increase in the incidence of diabetes. The analyses in WOSCOPS and the Heart Outcomes Prevention Study (HOPE) studies should be repeated after stratification by individuals who did and did not have incident CHD; presumably, the protective effect of statins or ACE inhibitors would be stronger in the group that developed CHD if this hypothesis is correct. Because the rate of incident CHD is low, this intriguing possibility is not likely to explain the lower incidence of diabetes in WOSCOPS, which is a primary prevention trial.

A direct effect of pravastatin on glucose levels was not present in small studies. However, these studies lack statistical power. These authors further propose that pravastatin might reduce the incidence of diabetes by a reduction of triglyceride levels. This is unlikely because the effect of pravastatin on triglyceride levels is modest. Furthermore, therapy with gemfibrozil, a potent triglyceride-lowering agent, does not improve insulin sensitivity or glucose tolerance in some studies. Of course, triglyceride-lowering interventions that act by lowering free fatty acids, as some diabetic agents do, might have different effects on insulin sensitivity and glucose levels.

An attractive mechanism to explain the possible effect of pravastatin on the incidence of type 2 diabetes is a reduction of inflammation. Inflammatory factors may be a risk factor for CHD. Freeman et al show that white blood cell count predicted the incidence of type 2 diabetes in some, but not all, statistical models. Both pravastatin and simvastatin lower markers of inflammation such as C-reactive protein, so it is likely that there is a “class” effect of statins on inflammatory factors.

One link between inflammation and the incidence of type 2 diabetes may be insulin resistance. Festa et al recently showed that insulin resistance (measured by a frequently sampled intravenous glucose tolerance test) was related to C-reactive protein levels in nondiabetic subjects in the Insulin Resistance Atherosclerosis Study. Inflammatory factors were related to the incidence of diabetes in the Atherosclerosis Risk in Communities Study, although the relation was no longer significant after adjustment for plasma insulin levels. Several mechanisms may explain the relation between insulin resistance and inflammatory factors, such as the hypersecretion of proinflammatory cytokines (ie, interleukin-6 and tumor necrosis factor-α) from adipose tissue; these cytokines exert major stimulatory effects on the synthesis of acute phase proteins. The enhanced expression of inflammatory proteins through the counteraction of the physiological effect of insulin on hepatic acute-phase protein synthesis as a result of decreased insulin sensitivity may also play a role. The temporal relation between insulin resistance and inflam-
mation is not completely understood; it would be of interest to perform studies examining the effect of insulin-sensitizing agents on markers of inflammation (ie, C-reactive protein). Conversely, one could test the effect of anti-inflammatory agents on insulin resistance.

Clearly, a multifactorial approach to the prevention of diabetes is necessary. These interventions are likely to include lipid\(^5\) and blood pressure interventions, ACE inhibitors,\(^6\) and intensive glycemic control in subjects with clinical diabetes. Because the case fatality rate in diabetic subjects with initial presentation of CHD is high and many subjects die before hospitalization,\(^2\) primary prevention of type 2 diabetes will also be an important component of a program to reduce CHD in diabetic subjects. If further studies confirm the observations that ACE inhibitors and statins reduce the risk of developing type 2 diabetes, the perceived benefit of cardiovascular interventions in short-term clinical trials such as WOSCOPS,\(^4\) the Simvastatin Scandinavian Survival Study,\(^3\) and HOPE\(^7\) is likely to be markedly underestimated. The long-term cost-benefit analysis of these interventions may be more positive than previous studies have estimated. This effect is likely to be much more important for primary prevention studies such as WOSCOPS.\(^4\)

References

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