Diabetes and Hypertension and Atherosclerotic Cardiovascular Disease
Related or Separate Entities Often Found Together

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See related article, pp 891–897

The Finnish diabetologist, Yki-Järvinen, stated it most provocatively in a 1999 lecture: “Diabetes is a cardiovascular disease which you diagnose by measuring blood glucose.” The relation between diabetes mellitus and ischemic heart disease is tight, and patients with diabetes mellitus carry the same risk of cardiovascular death as patients with a previous myocardial infarction and no diabetes mellitus.1,2

Hypertension is also so common in diabetes mellitus that a metabolic syndrome that groups diabetes mellitus and hypertension has been postulated and driven much research. Although the prevalence of hypertension in the general population is usually estimated to be in the order of 25%, the prevalence of hypertension in patients with diabetes mellitus ranges from 40% to 80% in various studies depending on hypertension definition.3 Does this imply a tight relation or are hypertension and diabetes mellitus merely separate risk factors that add to a risk of cardiovascular complications in the future? For a good many years, hypertension in diabetes mellitus has been assumed to be a particular entity that at least required more attention and lower treatment targets than hypertension in general. Such concepts stem first of all from the Hypertension Optimal Treatment Study.4 This elegantly conceived study was designed to test the clinical impact of randomizing hypertensive patients to target diastolic blood pressures of ≤90, ≤85, and ≤80 mm Hg. The study was not highly successful, and the achieved reductions in blood pressure by groups were lower than planned with great overlap, and there were no significant differences among the 3 target blood pressure groups. Nevertheless, in the subgroup of patients with diabetes mellitus, a substantial and significant reduction of 51% in major cardiovascular events was observed in those randomized to the lowest diastolic blood pressure. This observation was coupled to a series of studies, primarily in type 1 diabetes mellitus, where a substantial lowering of blood pressure was associated with a delay in deterioration of renal function. Although unsatisfactory from a rigorous scientific point of view, this information was coupled to assume diabetic hypertension to be tightly connected to atherosclerotic cardiovascular disease and diabetic hypertension to require lower blood pressures than hypertension in general.

In the current issue of Hypertension, Chen et al5 provide further intriguing data to the story of the relation among hypertension, diabetes mellitus, and atherosclerotic cardiovascular disease. Of 1145 Framingham participants with diabetes mellitus, but without a history of cardiovascular events, 663 had hypertension, defined as a blood pressure exceeding 130/80 mm Hg or current use of antihypertensive therapy, and 642 had hypertension, using the conventional epidemiological definition of hypertension as a blood pressure exceeding 140/90 mm Hg or receiving treatment with antihypertensive medication. Many of the diabetic hypertensive patients in the Framingham population had a poorly controlled blood pressure averaging 147 mm Hg for systolic blood pressure and 84 mm Hg for diastolic blood pressure. The corresponding figures in their normotensive diabetic counterparts were 118 mm Hg and 71 mm Hg, respectively. It is worth noting that only ≈5% of the Framingham patients with diabetes mellitus in this study were on cholesterol-lowering drugs. Using the conventional definition of hypertension enabling direct comparison, 23% had hypertension in the nondiabetic group and 56% had hypertension in the diabetic group. The relative risk increase of hypertension was very similar in patients with and without diabetes mellitus for various aspects of cardiovascular disease and not changed by including multiple covariates. As a new way of looking at the cardiovascular risk of hypertension in diabetes mellitus, Chen et al5 went on to calculate population-attributable risks that implied hypertension to account for 30% of deaths in diabetes patients and for 25% of cardiovascular events in diabetes patients, which increased even further to 44% when 110 normotensive diabetic subjects developing hypertension during the study were excluded. In contrast, when hypertension and diabetes mellitus were regarded as independent, the population-attributable risk from diabetes mellitus was only 7% for all-cause mortality and 9% for any major atherosclerotic cardiovascular event.

What is truly interesting and important is whether this removal from diabetes mellitus of a large part of it is cardiovascular risk and passing it on to hypertension is biologically reasonable. The calculation of population-attributable risk requires that the risk factors to which risk is distributed are independent. In the study of Chen et al,5 the risk of hyper-
tension was indeed similar in patients with and without diabetes mellitus, but their study relied on office blood pressure. Because of impaired baroreflexes and stiffer arteries, patients with diabetes mellitus have higher blood pressure variability than nondiabetic people. Fortunately, a soon-to-be published study provides results of ambulatory blood pressures from population surveys. These data have been used to compare the risk of hypertension in patients with and without diabetes mellitus and the study confirms that the risk of blood pressure increase is similar in patients with and without diabetes mellitus. For hypertension and diabetes mellitus to be regarded as independent risk factors, it is also necessary for the treatment consequences to be similar. Although the Hypertension Optimal Treatment Study indicated that lower blood pressures should be achieved in diabetes mellitus, this contention has been challenged recently in a critically important study, The Action to Control Cardiovascular Risk in Diabetes Study randomized 4733 participants with type 2 diabetes mellitus with and without a diagnosis of hypertension to target systolic blood pressures of 140 versus 120 mm Hg. The study conduct was successful, with most patients achieving close to target blood pressures. There was no difference between the 2 treatment arms in the primary outcome of myocardial infarction, stroke, and cardiovascular death. Until ongoing studies of tapered blood pressure reduction are reported, it should be assumed that the blood pressure targets are similar in hypertensive patients with and without type 2 diabetes mellitus, and in the current context they add further to the concept of hypertension and diabetes mellitus being independent entities in terms of risk and consequences.

Yrki Järvinens’s provocative input raises the question of whether the removal of risk related to atherosclerosis from diabetes mellitus continues. Given the tight relation between diabetes mellitus and cardiovascular risk it was reasonable to assume that effective glucose-lowering therapy would ameliorate atherosclerotic cardiovascular disease. Although the United Kingdom Prospective Diabetes Study provided marginal hope, the major effect of additional glucose lowering in that study was on microvascular disease. Again, the Action to Control Cardiovascular Risk in Diabetes Study has provided critical new insight. Tight glucose control did not improve mortality or cardiovascular mortality, the effect on atherosclerotic cardiovascular events was marginal, and the risk of hypoglycemia was high. The removal of risk is also evident in studies of the importance of cholesterol-lowering therapy. Thus, based on randomized trials and a range of subgroup analyses, cholesterol lowering with statins has been shown to be highly beneficial for patients with diabetes mellitus if their cardiovascular risk is high.

At this point, it is relevant to briefly discuss the concept of risk identified in an epidemiological study, such as the study of Chen et al., versus risk in randomized trials where the expected risk reductions based on epidemiological studies are not achieved. It is important to remember here that the various treatment strategies with medicine may not be without serious adverse effects. Thus, it could be speculated that if blood glucose and blood pressure could be lowered by perfectly safe drugs in patients with diabetes mellitus, then the expected reductions in cardiovascular disease risk implied from epidemiology would be seen. So, there is certainly still room for epidemiological studies, such as the study of Chen et al. In this context, it is worth noting that, whereas “the lower the better” clearly does not hold true for blood pressure and blood glucose in patients with diabetes mellitus, it may well be true for cholesterol-lowering with statins. As mentioned previously, statins were rarely used in the study of Chen et al, so it would be interesting to replicate their study in a diabetes population with contemporary use of statins.

In conclusion, with current insight, the concept of a metabolic syndrome that tightly couples diabetes mellitus with hypertension and atherosclerotic cardiovascular disease appears to be weakened, at least in terms of the interventions available at this time. Although diabetes remains a risk factor for atherosclerotic cardiovascular disease, the main focus of intervention needs to be directed to hypertension and cholesterol control in terms of reducing this risk, and treatment should most likely be completely independent of the presence of diabetes mellitus.

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References
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