COMMENTARY

Diabetic Kidney Disease: A Determinant of Cardiovascular Risk in Type 1 Diabetes

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Diabetes, regardless of type, has well-accepted vascular consequences. In fact, atherosclerotic cardiovascular disease (CVD) is the most important cause of death attributable to diabetes (1). Acute complications of diabetes such as hypoglycemia, hyperglycemia, and diabetic ketoacidosis are important causes of morbidity and mortality beginning early in its course. However, microvascular and macrovascular complications drive excess mortality over the long term (2–4).

Diabetic kidney disease (DKD) is strongly associated with CVD (5). DKD may be a marker of cumulative vascular damage due to diabetes or may causally promote CVD through several mechanisms, such as blood pressure dysregulation, retention of uremic toxins, anemia, and altered mineral metabolism. Provocative studies suggest that the preponderance of excess CVD risk in both types 1 and 2 diabetes is restricted to people with DKD (6–8).

The question posed by Groop et al. (9) in this issue of *Diabetes Care* was whether patients with type 1 diabetes have heightened CVD mortality risk in the absence of DKD compared with people without diabetes. To examine this question, they looked at two different databases. The first was a registry of 10,737 Finnish children followed for 10 years after the initial diagnosis of type 1 diabetes, a period considered generally too early for DKD development. The mortality rate of children in the Finnish registry was compared with that of the general population as a standardized mortality ratio (SMR) that adjusts for demographic characteristics. Children with diabetes had a mortality rate of 8 per 10,000 person-years, yielding an SMR of 2.6. (An SMR of 1 would represent no difference.) The main cause of death was acute complications of diabetes.

A second cohort studied included 2,544 participants with type 1 diabetes from the Finnish Diabetic Nephropathy Study (FinnDiane) who were observed to have persistently normal urine albumin excretion (10). For each FinnDiane patient, mortality outcomes were compared with *1*) the age- and sex-matched general population (as the SMR) or *2*) three control individuals without diabetes selected from the Population Register Centre, matched for sex, age, and place of residence in the year of diabetes diagnosis in the FinnDiane patient.

In the FinnDiane cohort without albuminuria, the median age at baseline was 36 years, the median duration of diabetes was 16 years, and the mortality rate was 34 per 10,000 person-years. This mortality rate was not significantly different from the general Finnish population (SMR 1.02, 95% CI 0.84–1.22) but was modestly higher than in matched control subjects without diabetes (hazard ratio 1.33, 95% CI 1.06–1.66). The most frequent cause of death in the FinnDiane cohort was ischemic heart disease.

The authors reasonably concluded that compared with people without diabetes of similar age and sex, mortality rates are higher among people with type 1 diabetes even when DKD is not present. They further concluded that acute complications of type 1 diabetes drive excess mortality during the first 10 years while CVD is the main cause of mortality in later years.

This study is consistent with prior observations that DKD is a major driver of mortality in type 1 diabetes. Indeed, the mortality rate among FinnDiane participants without albuminuria (34 per 10,000 person-years) is substantially less than that previously reported for the overall FinnDiane cohort (7). In the Pittsburgh Epidemiology of Diabetes Complications Study of type 1 diabetes, mortality rates (per 10,000 person-years) were 30 for participants without albuminuria (similar to the current results from the comparable FinnDiane subset), 160 for those with microalbuminuria, 300 for those with macroalbuminuria, and 860 for those with end-stage renal disease (6).

Nonetheless, the observations published in the current study offer relevant guidance for clinical care of patients without DKD, suggesting continued vigilance to reduce CVD risk in addition to prevention of acute complications of diabetes. Within FinnDiane, smoking was more

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common among those who died during follow-up (30.4% vs. 22.8%, high proportions that could be reduced to improve outcomes). Also, while there was almost a threefold higher number of people taking statins in the deceased group compared with those still alive at the end of follow-up, only 19% in the deceased group and 6.7% in the alive group were receiving statins at baseline. These proportions are far below the more than 65–70% of people receiving statins in contemporary trials among patients with type 2 diabetes (11,12). Moreover, the LDL cholesterol concentrations seen in both groups were far above the current guideline recommendations independent of statin use (11). In addition, although mean study blood pressures were reasonably well controlled, the deceased group had a higher diastolic blood pressure and a wider standard deviation, suggesting more participants were above or at a diastolic pressure of 90 mmHg. Finally, differences in mortality rates when comparing FinnDiane participants to matched controls appeared to be larger for women than men, at least on the relative scale. This is consistent with prior observations that the reduced rates of CVD and death in women versus men that are observed in the general population are blunted in the setting of type 1 diabetes (13).

Groop et al. (9) did not find a significant association of baseline hemoglobin A_{1c} with mortality within the FinnDiane subpopulation without DKD. This should not be interpreted to mean that hyperglycemia plays no role in CVD and premature death in type 1 diabetes. First, use of a single baseline value of hemoglobin A_{1c} does not adequately capture cumulative exposure to hyperglycemia. Second, and more importantly, hyperglycemia appears to contribute to CVD and premature death at least in part through the development of microvascular complications, particularly DKD (14). By intentionally excluding FinnDiane participants who developed DKD, the adverse impact of hyperglycemia may be largely outside the scope of the studied subpopulation.

The Diabetes Control and Complications Trial (DCCT) clearly demonstrated that early intensive diabetes therapy substantially reduces the risks of DKD, CVD, and mortality in type 1 diabetes (15–17). In mediation analyses, the effects of intensive diabetes therapy on CVD were completely explained by effects on hemoglobin A_{1c} or partially explained by effects on urine albumin excretion. These results make it clear that hyperglycemia is a primary driver of long-term CVD in type 1 diabetes and suggest that kidney disease is either a mechanism or a marker of this process.

In short, it is known that poor early glycemic control promotes development of DKD, which is associated with increased risk of CVD. Groop et al. demonstrate that acute diabetes complications drive excess mortality early in type 1 diabetes and CVD drives excess mortality later in the disease course. Taken together, these observations reinforce the need to control glycemia and other CV risk factors early in type 1 diabetes to help prevent DKD and ultimately reduce CVD risk.

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