EDITORIAL (SEE JUUTILAINEN ET AL., P. 714)

Why Do People With Diabetes Die Too Soon?

More questions than answers

The excess mortality among people with diabetes and the role of cardiovascular disease (CVD) in shortening their lives have been recognized for decades (1–3). Recent studies suggest that all-cause mortality (4) and CVD incidence among people with diabetes (5) are declining; however, the proportion of CVD attributable to diabetes has increased over the past 50 years, largely due to the increase in diabetes prevalence (6). Furthermore, mortality follow-up of the National Health and Nutrition Examination Survey (NHANES) I, II, and III participants may suggest that despite some progress in reducing mortality in men with diabetes, women are still at a greatly increased risk (7). The vital question for an estimated 200 million people with diabetes worldwide today (8) is what to do to improve life expectancy and quality.

A study from Finland in this issue of *Diabetes Care* by Juutilainen et al. (9) attempts to shed some light on modifiable determinants of survival among patients diagnosed with diabetes after age 30 years. In a cohort of 173 type 1 and 834 type 2 diabetic patients followed for 18 years, the total mortality risk was increased threefold and CVD mortality was increased fivefold compared with the general population, confirming previous studies. The comparisons were adjusted for age, sex, duration of diabetes, area of residence, BMI, blood pressure, total and HDL cholesterol, proteinuria, creatinine clearance, smoking, and alcohol intake measured at baseline. Consistent with many previous reports, the increase in CVD mortality risk was much more dramatic in diabetic women (11- to 13-fold) than in diabetic men (3- to 4-fold) compared with the general population. The increase in total mortality risk was less pronounced: ~4.5-fold in women and 2-fold in men, respectively.

The novel finding appears to be that total and CVD mortality similarly affects patients with type 1 and type 2 diabetes diagnosed after age 30 years; however, the harmful effect of hyperglycemia on mortality is more profound in type 1 than in type 2 diabetes. Because interpretation of these results hinges heavily on the definition of type 1 versus type 2 diabetes, it is important to look more closely at the design of this study. In the early 1980s, the investigators set out to identify all diabetic patients aged 45–64 years and diagnosed after age 30 years in Kuopio (East Finland, with a population at high risk for CVD) and Turku (West Finland, lower CVD risk). Drug reimbursement data from the Social Insurance Institution identified 1,797 diabetic patients meeting the age and residence criteria. Of those receiving diabetes medication, 1,187 of 1,797 (66%) metthe eligibility criteria and participated in study examination from 1982 to 1984, 7% could not be located, 16% refused participation, 3% did not have diabetes, 4% were diagnosed before age 30 years, 1% were born outside the study area, and nearly 3% died before examination. Of the 1,187 participants, 1,059 were classified as having type 2 diabetes (10). The other 128 patients were believed to have type 1 diabetes because they were on insulin and their C-peptide levels were <0.20 nmol/l at 6 min after intravenous injection of 1 mg glucagon. Of all 278 patients treated with insulin, 128 (46%) were classified as having type 1 diabetes. Apparently additional patients were added to form a cohort of 211 type 1 diabetic subjects, of whom 173 of those were followed for mortality. Unfortunately, this group does not match any previous reports from this project (10–12).

Several biases are obvious. The study cohort overrepresented the more severe forms of type 2 diabetes; only 147 of 1,187 (12%) of the patients were treated with diet only at the time of examination and, because of the source of ascertainment, it is likely that patients with milder diabetes who were never prescribed insulin or oral agents were not included.

Also, type 1 diabetes was classified based on low C-peptide and insulin treatment; islet autoantibodies (to GAD65, IA-2, or insulin) were not measured, HLA Class II genotypes were not available, and it is unknown how long the patients were treated with diet and/or oral agents before they were put on insulin (oral treatment failure within 1 year of diagnosis is often used as a diagnostic criterion for type 1 diabetes). Early mortality was not captured, and a large number of patients with clinically significant CVD or serum creatinine ≥ 200 μmol/l were excluded from mortality analyses: 225 (21%) of type 2 and 38 (18%) of type 1 diabetic patients compared with only 79 (6%) of nondiabetic control subjects. If the analyses were not restricted to individuals who were healthy at the baseline, the excess mortality risk associated with diabetes would be even stronger. Finally, it is unclear whether the vital status was ascertained for all participants or whether some were lost to follow-up, e.g., due to migration.

Due to these limitations, caution should be taken when interpreting the finding that total and CVD mortality were similar in patients with type 1 and type 2 diabetes, especially given that adjustments were made for duration of diabetes, blood pressure, total and HDL cholesterol, proteinuria, and creatinine clearance. Although it is useful for evaluation of the effects of hyperglycemia, this overadjustment may lead to an incorrect impression that CVD and total mortality are indeed similar in type 1 and type 2 diabetic patients of similar age. To the contrary, a typical middle-aged type 1 diabetic patient has a longer duration of diabetes and more advanced renal disease than a type 2 diabetic patient of the same age. HDL cholesterol levels, though higher in type 1 than type 2 diabetic patients, do not have the expected protective effect on CVD risk due to functional HDL deficiencies related to core lipid enrichment in triglycerides, cholesteryl ester depletion, altered apolipoprotein A-I conformation, replacement of apolipoprotein A-I by serum amyloid A, and covalent modification of HDL protein components by oxidation and glycation (13). The excess CVD risk in type 1 compared with type 2 diabetic patients is even more visible if the comparison is not restricted to patients older than 30 years at diabetes diagnosis and initially free of CVD or renal disease.

The other major finding in the Finn-

ish study appears to confirm current views that when all other factors held equal, the deleterious effects of hyperglycemia on mortality are more profound in type 1 than in type 2 diabetes. The authors report that an increment of 1 unit (%) of glycohemoglobin increased CVD mortality by 53% (95% CI 28–81) in type 1 and by 8% (4–11) in type 2 diabetic participants. Unfortunately, inspection of Fig. 2 of the Finnish paper strongly suggests that the reported differences in the effect of glycemic control on mortality between type 1 and type 2 diabetic patients (slope) are solely driven by extremely high CVD mortality in men with type 1 diabetes at the highest tertile of HbA1. It is unfortunate that this apparent interaction between sex and HbA1 was not fully explored. The reported difference between the effect of hyperglycemia in type 1 versus type 2 diabetes is limited to a small subgroup of patients, and this conclusion is based on a single measurement of glycated hemoglobin (HbA1) at the very beginning of the 18-year follow up for mortality. Previous studies of CVD in type 1 diabetes have shown a strong effect of hyperglycemia if the HbA1 or A1C were measured on multiple occasions and either averaged (14) or expressed as changed from baseline (15). There appears to be a systematic bias in the literature; studies of CVD outcomes in patients with type 1 diabetes tend to have much more robust repeated measurements of hyperglycemia than studies in type 2 diabetic patients that use a single baseline A1C measurement and see less of an association between hyperglycemia and CVD. Of note, A1C remains stable or improves over time in most type 1 diabetic patients but nearly invariably worsens over time in patients with type 2 diabetes (16). Despite solid data from the baseline visit, this study fails to address the issue of how other modifiable risk factors (smoking, alcohol, lipids and lipoproteins, BMI, hypertension, and renal disease) have influenced survival in this cohort.

Patients and laypeople often ask me whether we are winning the "war" on diabetes, whether our patients are living longer compared with 20 years ago, and how much diabetes shortens lives today. Unfortunately, we do not have reliable data to support the general belief that diabetes shortens life expectancy much less today than a couple of decades ago. The Diabetes Natural History Study, conducted at the Joslin Clinic, followed for up to 25 years patients diagnosed between 1939 and1959 (17). Among men diagnosed between ages 30 and49 years, there was no excess mortality until after age 50 years, in contrast with women, who experienced significant excess mortality from age 30 years and on. The median survival age was 66 years for men and 65 years for women, respectively, 5 and 12 years shorter than in the general population. Patients diagnosed between ages 50 and 69 years could expect median survival of 71 and 72 years, respectively—2 and 5 years shorter than the general population.

A 29-year follow-up study included 166 diabetic patients newly diagnosed at average age of 63 years (range 15–81) in rural East Germany during 1962–1963 (18). Initially, 27% of the patients were treated with insulin. Only 19% of the patients had either reached or exceeded the life expectancy of the general population. The life expectancy was shorter by 5.3 years in men and 6.4 years in women. In this population, the shortening of life expectancy decreased with increasing age at onset. Both underweight (BMI <20) and extreme obesity (BMI >40) were associated with a higher loss in life expectancy (14.7 vs. 10.8 years), but the survival time was not significantly different by treatment regiment.

A number of excellent, long follow-up, population-based mortality studies in patients with type 1 diabetes diagnosed in childhood have been published over the past 10 years. Alas, solid mortality follow-up data for patients diagnosed as adults are few and far apart. The East-West Finland study is a good step toward answering the burning question: why do adults with diabetes die too soon?

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