Identifying Causes for Excess Mortality in Patients With Diabetes: Closer but Not There Yet

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Diabetes Care 2016;39:1851–1853 | DOI: 10.2337/dci16-0026

Diabetes is a chronic disease associated with increased morbidity and mortality (1), mainly from cardiovascular disease (2–6). Treatment of diabetes includes normalizing hyperglycemia to attain glycemic targets and treatment of cardiovascular risk factors such as hypertension and dyslipidemia. This multifactorial intervention strategy has been shown to decrease cardiovascular and all-cause mortality among patients with type 2 diabetes (7). Nevertheless, mortality in diabetes remains elevated (2,5).

A number of epidemiological studies have quantified the risk of death among patients with diabetes and assessed the causes of death (2–6), with highly varying results (Table 1). The South Tees Diabetes Mortality Study (2) found an over threefold increase in all-cause mortality, mainly attributed to increased cardiovascular deaths, but found no increased risk of cancer mortality. The Australian Diabetes, Obesity and Lifestyle Study (AusDiab) (3) of over 10,000 individuals reported a little over twofold increase in the risk of all-cause mortality, with the majority due to cardiovascular causes. The Emerging Risk Factors Collaboration (ERFC) study (6), involving over 800,000 individuals, reported a little under twofold increase in the risk of all-cause mortality associated with diabetes. It also found that diabetes was associated with an increased risk of death from cancer (hazard ratio [HR] 1.25 [95% CI 1.19–1.31]), from vascular disease (HR 2.32 [95% CI 2.11–2.56]), and from nonvascular and noncancer etiologies (HR 1.73 [95% CI 1.62–1.85]). More recently, a study using the Swedish National Diabetes Register (5) on over 400,000 patients with type 2 diabetes matched to more than 2 million subjects with no diabetes found a smaller excess risk of all-cause mortality associated with type 2 diabetes (HR 1.15 [95% CI 1.14–1.16]). The main contributors of mortality in this study were cardiovascular- and diabetes-related disorders, whereas cancer was found to have a lesser effect.

Overall, the studies to date have confirmed that diabetes is associated with an increased risk of all-cause mortality, but the magnitude of this excess risk is highly variable, with the relative risk ranging from 1.15 to 3.15. Nevertheless, all studies agree that mortality is mainly attributable to cardiovascular causes (2–6). On the other hand, studies of cancer-related death have generally been lacking despite the diabetes–cancer association and a number of plausible biological mechanisms identified to explain this link (8,9). In fact, studies assessing the specific causes of noncardiovascular death in diabetes have been sparse.

In this issue of *Diabetes Care*, Baena-Díez et al. (10) report on an observational study of the association between diabetes and cause-specific death. This study involved 55,292 individuals from 12 Spanish population cohorts with no prior history of cardiovascular disease, aged 35 to 79 years, with a 10-year follow-up. Diabetes was defined by self-report or a fasting glycemia over 6.94 mmol/L (125 mg/dL) at baseline examination. Cause of death was identified using electronic medical records, death certificates, and/or autopsy reports. The main outcomes were all-cause mortality, cardiovascular mortality, cancer mortality, and noncardiovascular noncancer mortality, for which the risk was analyzed using two statistical approaches: proportional subdistribution hazard, which accounts for competing risks, and cause-specific hazard, which does not account for competing risks. This study found that individuals with diabetes compared with those without diabetes had a higher risk of cardiovascular death, cancer death, and noncardiovascular noncancer death with similar estimates obtained using the two statistical approaches.

The study by Baena-Díez et al. (10) has a number of strengths. First, this study was the first to use statistical techniques of data analysis that can provide a more accurate understanding of the cause of increased mortality associated with diabetes, which is particularly important when assessing cancer outcomes given

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See accompanying article, p. 1987.

Table 1—Summary of observational studies assessing the risk of mortality among individuals with diabetes

Reference	Study	Year	Population	Sample size	Follow-up	Risk of all-cause mortality, HR (95% CI)
Roper et al. (2)	South Tees Diabetes Mortality Study	2002	South Tees, U.K.	4,842	6 years	Male*: 2.56 (1.73–3.80) Female*: 3.15 (2.51–3.95)
Barr et al. (3)	Australian Diabetes, Obesity and Lifestyle Study	2007	Australia	10,428	5.2 years	2.3 (1.6–3.2)
Seshasai et al. (6)	Emerging Risk Factors Collaboration	2011	Worldwide**	820,900	13.6 years	1.80 (1.71–1.90)
Tancredi et al. (5)	National Diabetes Register	2015	Sweden	435,369 with type 2 diabetes and 2,117,483 control subjects	4.6 years	1.15 (1.14–1.16)

*Aged 40–59 years. **The majority of participants were from Europe and North America.

that cardiovascular death is a significant competing risk in diabetes. Second, this study involved participants who had no known cardiovascular disease at baseline, which allowed the assessment of a risk of cardiovascular death more likely attributable to diabetes and not to a preexisting cardiovascular condition.

This study also has limitations, many acknowledged by the authors. First, the comparison could not account for differences in duration of diabetes, presence of microvascular complications, and glycemic control, all measures of diabetes severity known to affect mortality risk (5). Second, there was no adjustment for confounding by pharmacological therapies. The use of anticoagulants and statins has been shown to have beneficial effects on cardiovascular mortality (11,12), and recent studies have suggested potential benefits of statins on cancer mortality (13–15). Third, a history of cancer was not adjusted for in the analyses, an important factor since such patients may be more likely to be screened and diagnosed with diabetes. Finally, the risk factors that were measured and adjusted for in the analyses produced rather unexpected results. For instance, BMI and total cholesterol were not associated with cardiovascular death, and systolic blood pressure in women was inversely related to cardiovascular death. Such inconsistent results for known risk factors imply a possible bias in the reported findings regarding the diabetes–mortality association.

It remains that all studies of excess mortality associated with diabetes, including the current one, have produced highly variable results. The reasons may be methodological. For instance, it may be that because of the wide range of age in these studies, comparing the rates of death between the patients with diabetes and those without diabetes using a measure based on the ratio of the rates may be misleading because the ratio can vary by age. Instead, a measure based on the difference in rates may be more appropriate (16). Another issue relates to the fact that the studies include patients with longstanding diabetes of variable duration, resulting in so-called prevalent cohorts that can result in muddled mortality estimates since these are necessarily based on a mix of patients at different stages of disease (17). Thus, a paradigm change may be in order for future observational studies of diabetes and mortality, in the way they are both designed and analyzed. With respect to cancer, such studies will also need to tease out the independent contribution of antidiabetes treatments on cancer incidence and mortality (18–20). It is thus clear that the quantification of the excess mortality associated with diabetes per se will need more accurate tools.

Thus, despite advances in the treatment of diabetes, there still appears to be a persistent excess risk of mortality among this population (21). Baena-Díez et al. (10) showed that individuals with diabetes have an approximately threefold increased risk of cardiovascular mortality, which is much higher than what has been reported by recent studies (5,6). While this may be due to the lack of adjustment for important confounders in this study, there remains uncertainty regarding the magnitude of this increase. As such, the reported association and the extent of the effects between diabetes and the noncardiovascular-related deaths observed in this study will need to be confirmed in other studies. Nonetheless, the results from this study support the ongoing need for routine cancer screening, provision of vaccinations, healthy lifestyle intervention, and smoking cessation for patients with diabetes. Moreover, the findings from this study highlight the need for further research to determine the missing elements in the management of diabetes to reduce the excess mortality observed in this population.

Funding. S.S. is the recipient of the James McGill Professor award.
Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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