Similarity of the Impact of Type 1 and Type 2 Diabetes on Cardiovascular Mortality in Middle-Aged Subjects

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OBJECTIVE — To compare the risk of cardiovascular disease (CVD) death and the impact of hyperglycemia on the risk of CVD mortality associated with type 1 diabetes to that associated with type 2 diabetes.

RESEARCH DESIGN AND METHODS — The study comprised 173 participants with type 1 diabetes, 834 participants with type 2 diabetes, and 1,294 nondiabetic participants, aged 45–64 years at baseline and free of CVD. The age of onset of diabetes was >30 years in both diabetic groups.

RESULTS — During an 18-year follow-up, 86 participants with type 1 diabetes, 567 participants with type 2 diabetes, and 252 nondiabetic participants died. CVD mortality rates per 1,000 person-years were 23.1 (95% CI 16.9–31.9) in type 1 diabetic, 35.3 (30.8–40.4) in type 2 diabetic, and 4.6 (3.8–5.7) in nondiabetic participants. Adjusted hazard ratios for CVD mortality in participants with type 1 diabetes versus no diabetes was 3.6 (95% CI 2.2–5.7) in men and 13.3 (6.9–22.5) in women and in participants with type 2 diabetes versus no diabetes 3.3 (2.5–4.5) in men and 10.1 (6.7–17.4) in women. An increment of 1 unit (%) of GHb increased CVD mortality by 52.5% (95% CI 28.4–81.3) in type 1 diabetic subjects and by 7.5% (4.3–10.8) in type 2 diabetic participants.

CONCLUSIONS — The impact of type 1 and type 2 diabetes on CVD mortality was similar. The effect of increasing hyperglycemia on the risk of CVD mortality was more profound in type 1 than in type 2 diabetic subjects.

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Diabetes is a heterogeneous group of disorders characterized by high blood glucose levels (1). Type 1 diabetes is primarily due to destruction of pancreatic β-cells, resulting in absolute insulin deficiency. Type 2 diabetes, accounting for >80% of all diabetes cases globally, is characterized by insulin resistance and impaired insulin secretion (1). Type 1 and type 2 diabetes may share common predisposing genetic and environmental factors, including obesity (2–3).

It is unclear to what extent the pathobiology of vascular complications, the major burden of diabetes, is shared between type 1 and type 2 diabetes. Insulin resistance is of major importance for the development of complications in subjects with type 2 diabetes (4), but it also increases both micro- and macrovascular complications in subjects with type 1 diabetes (5). Hyperglycemia is the primary risk factor for microvascular complications in type 1 and type 2 diabetes (6–7). It is also considered to be a major risk factor of macrovascular complications in type 1 diabetes (8), but its role as a risk factor for cardiovascular disease (CVD) in type 2 diabetes has not been uniformly accepted (9).

It is not well established whether the risk of CVD associated with type 1 diabetes equals that associated with type 2 diabetes. Nor do we know whether the impact of hyperglycemia on mortality is comparable in these two main types of diabetes. Therefore, the aim of this study was to investigate the impact of type 1 and type 2 diabetes on the risk of CVD and the impact of glycemia on mortality in type 1 and type 2 diabetes in people with a diabetes diagnosis after the age of 30 years.

RESEARCH DESIGN AND METHODS

The original study population included 211 type 1 diabetic subjects, 1,059 type 2 diabetic subjects, and 1,373 corresponding nondiabetic subjects. A detailed description of study participants has been published previously (10). The selection of the diabetic study cohort was based on a drug reimbursement registry maintained by the Social Insurance Institution. All participants were aged 45–64 years. Diabetic participants fulfilled the World Health Organization diagnostic criteria for diabetes (11). Their age at onset of diabetes was >30 years. Type 1 diabetes was verified by the performance of glucagon-stimulated C-peptide measurement, with the 6-min stimulated level <0.20 nmol/l. A random control population sample of nondiabetic subjects matched for age was invited to participate in the study. The ethics committees of the Kuopio University Hospital and the Turku University Central Hospital approved the study. All study participants gave informed consent.

The baseline examination, conducted between 1982 and 1984 in Kuopio, East Finland, and in Turku, West Finland, and the biochemical methods have been described in detail previously (10). Creatinine clearance was estimated by the

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Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease.

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Cockroft-Gault formula (12). Type 1 diabetic, type 2 diabetic, and nondiabetic participants with serum creatinine ≥200 μmol/l or with clinically significant atherosclerotic CVD (verified possible or definite previous myocardial infarction, stroke, or nontraumatic lower-extremity amputation) at baseline were excluded from the study. Finally, altogether, 173 type 1 diabetic (83 men and 90 women), 834 type 2 diabetic (429 men and 405 women), and 1,294 nondiabetic (581 men and 713 women) participants were included in the statistical analyses.

Table 1—*Cox model hazard ratio (95% CI) of total, CVD, CHD, and non-CVD mortality according to the presence and type of diabetes*

	Men	Women	All
Type 1 vs. no diabetes			
Total mortality	2.2 (1.5–3.2)	4.5 (3.0–6.8)	2.9 (2.2–3.8)
CVD mortality	3.6 (2.2–5.7)	13.3 (6.9–25.5)	5.2 (3.6–7.5)
CHD mortality	4.9 (2.9–8.4)	16.9 (7.6–37.2)	6.6 (4.3–10.1)
Non-CVD mortality	1.0 (0.5–2.0)	2.5 (1.4–4.3)	1.7 (1.1–2.5)
Type 2 vs. no diabetes			
Total mortality	2.6 (2.1–3.2)	4.5 (3.4–5.9)	3.2 (2.7–3.7)
CVD mortality	3.3 (2.5–4.5)	10.1 (6.7–17.4)	4.9 (3.8–6.3)
CHD mortality	3.7 (2.6–5.3)	10.8 (5.9–19.7)	5.1 (3.8–6.9)
Non-CVD mortality	1.9 (1.4–2.6)	2.1 (1.4–3.1)	2.0 (1.6–2.5)
Type 1 vs. type 2 diabetes			
Total mortality	0.8 (0.6–1.2)	0.9 (0.6–1.3)	0.9 (0.6–1.1)
CVD mortality	1.1 (0.7–1.7)	0.7 (0.4–1.1)	0.8 (0.6–1.2)
CHD mortality	1.1 (0.7–1.9)	0.7 (0.3–1.3)	0.9 (0.6–1.3)
Non-CVD mortality	0.5 (0.2–1.0)	1.2 (0.7–2.3)	0.8 (0.5–1.3)

Adjusted for age, sex (in the analyses of all participants), area of residence, BMI, current smoking, use of alcohol, systolic blood pressure, total cholesterol, HDL cholesterol, duration of diabetes (in comparison of type 1 diabetes versus type 2 diabetes), Cockroft-Gault estimate of creatinine clearance, and urinary protein (log).

Follow-up study

The follow-up period lasted until 1 January 2001. Copies of death certificates of those participants who had died before 1 January 2001 were obtained from the Cause-of-Death Register (Statistics Finland) to define the vital status and cause of death of all study participants at the end of the 18-year follow-up period. All death certificates of participants were reviewed by two of the authors (A.J. and S.L.). Hospital records, and autopsy records when available, were used in the final classification of the causes of death. According to the ICD-9, codes 390–459 were used to record CVD death and codes 410–414 to record coronary heart disease (CHD) death.

Definition of end points

The end points used in this study were total mortality, CVD mortality (ICD-9 codes 390–459), CHD mortality (ICD-9 codes 410–414), and non-CVD mortality.

Statistical methods

Data analyses were conducted with the SPSS 14.0.1 program (SPSS, Chicago, IL). The group differences of continuous variables were analyzed by Student's *t* test, if appropriate, or Mann-Whitney *U* test and of dichotomous variables by the χ^2 test. Logarithmic transformations were used for triglycerides and urinary protein to correct their skewed distribution. Group-specific incidence rates (95% CI) per 1,000 person-years were calculated. Cox proportional hazards models were used to compare the study groups adjusted for age, area of residence, sex (in the analyses of all subjects), current smoking, use of alcohol (user versus nonuser), systolic blood pressure, BMI, total cholesterol, HDL cholesterol, duration of diabetes (in comparisons of type 1 versus type 2 diabetes), Cockroft-Gault estimate of creatinine clearance, and urinary protein (log). The association of GHb with event rates per 1,000 person-years was evaluated with a linear trend test by group-specific tertiles. The interaction of GHb tertile × diabetes type was evaluated for CVD and total mortality. Risk increase per a unit increase of GHb was calculated as 100% × (hazard ratio −1) (95% CI) for the study groups. The rates of CVD deaths per 1,000 person-years were calculated in the groups defined by the combinations of high/low GHb/urinary protein, with the group-specific medians for GHb and urinary protein as cutoffs (9.85% and 143 mg in type 1 diabetic men, 10.07% and 138 mg in type 1 diabetic women, 9.51% and 147 mg in type 2 diabetic men, 10.14% and 134 mg in type 2 diabetic women). A P value <0.05 was considered statistically significant, with the exception of <0.10 when testing interactions.

RESULTS — During the 18-year follow-up, 88 type 1 diabetic (43 men and 45 women), 567 type 2 diabetic (291 men and 276 women), and 252 nondiabetic (164 men and 88 women) participants died. Respectively, 54 type 1 diabetic (31 men and 23 women), 366 type 2 diabetic (179 men and 187 women), and 100 nondiabetic (77 men and 23 women) participants died of CVD, and 43 type 1 diabetic (25 men and 18 women), 258 type 2 diabetic (134 men and 124 women), and 66 nondiabetic (52 men and 14 women) participants died of CHD.

At baseline type 1 diabetic participants, when compared with nondiabetic participants, were leaner and had higher HDL cholesterol and lower diastolic blood pressure, but they had a slightly higher prevalence of hypertension, higher systolic blood pressure, and higher content of urinary protein than nondiabetic participants. Type 2 diabetic participants, when compared with nondiabetic participants were older, heavier, and more often nonusers of alcohol and had a higher frequency of hypertension, higher systolic and diastolic blood pressure, lower HDL cholesterol, higher triglycerides, higher content of urinary protein, and higher estimated creatinine clearance. Type 1 diabetic participants, when compared with type 2 diabetic participants were younger, leaner, and less frequently nonusers of alcohol and had lower prevalence of hypertension, lower diastolic and systolic blood pressure, higher HDL cholesterol, lower triglycerides, longer duration of diabetes, and lower estimated creatinine clearance.

Mortality rates for all-cause, CVD, and CHD were 50.9, 31.2, and 24.9%, respectively, in type 1 diabetic participants; 19.5, 7.7, and 5.1%, respectively, in nondiabetic participants; and 68.0, 43.9, and 30.9%, respectively, in type 2 diabetic participants during the 18-year follow-up. In type 1 diabetic, type 2 diabetic, and nondiabetic participants the incidence rates (deaths [95% CI]) per 1,000 person-years were 37.7 (28.0–50.8), 54.6 (47.2–63.2), and 11.7 (10.2–13.4),

respectively, for total mortality; 23.1 (16.8–31.9), 35.3 (30.8–40.4), and 4.6 (3.8–5.7), respectively, for CVD mortality; and 18.4 (13.0–26.0), 24.9 (21.5–28.8), and 3.1 (2.4–3.9), respectively, for CHD mortality, in the combined analysis of both sexes.

Table 1 presents Cox model hazard ratios of men, women, and all participants for all-cause, CVD, CHD, and non-CVD mortality in three comparisons: type 1 versus no diabetes, type 1 versus type 2 diabetes, and type 2 versus no diabetes. Type 1 diabetes–related mortality risk was similar to the risk related to type 2 diabetes. Diabetes-related risk of CVD, irrespective the type of diabetes, was 3- to 4-fold increased in men and 10- to 13-fold increased in women. Diabetes-related risk of CHD was 4- to 5-fold increased in men and 11- to 17-fold increased in women. Total and CVD mortality rates are illustrated in Fig. 1. The curves of diabetic subgroups for all-cause mortality merge, but CVD mortality seems to be slightly higher in type 1 diabetic men than in type 1 diabetic women. However, this difference is statistically nonsignificant (hazard ratio 1.8 [95% CI 0.9–3.4]).

The effect of glycemia on mortality in type 1 diabetic men and women compared with that in type 2 diabetic men and women is illustrated in Fig. 2, which shows CHD, CVD, non-CVD, and all-cause mortality per 1,000 person-years by group-specific tertiles of GHb. *P* values for CVD mortality by tertiles of GHb were <0.001 in type 1 diabetic and <0.001 in type 2 diabetic participants, <0.001 in type 1 diabetic men and 0.146 in type 1 diabetic women, and <0.001 in type 2 diabetic men and <0.001 in type 2 diabetic women. The tertiles of GHb were associated with total mortality in all groups, defined by type of diabetes and sex. The effect of GHb on total mortality was stronger in type 1 diabetic participants than in type 2 diabetic participants, with a *P* value of 0.024 for the interaction of diabetes type × tertile of GHb after adjustment for age, sex, and area of residence. CVD and total mortality rates were lower in type 1 diabetic participants than in type 2 diabetic participants in the lowest tertile of GHb, but in the highest tertile of GHb CVD and total mortality rates were similar.

Table 2 demonstrates how much an increment of 1 unit (%) of GHb increases CVD mortality in Cox models. In model 3, an increment of 1 unit (%) of GHb increased the risk of cardiovascular mortality by 52.5% (95% CI 28.4–81.3) in type 1 diabetic participants and 7.5% (4.3–10.8) in type 2 diabetic participants. In sex-specific analyses, the corresponding increment of cardiovascular risk was 80.1% (37.5–135.8) in type 1 diabetic men, 48.4% (7.8–104.3) in type 1 diabetic women, 6.0% (1.0–11.1) in type 2 diabetic men, and 10.2% (5.4–15.2) in type 2 diabetic women. When separately tested, in women with type 1 diabetes, the risk associated to increment of GHb noticeably increased after also introducing the renal variables into the model.

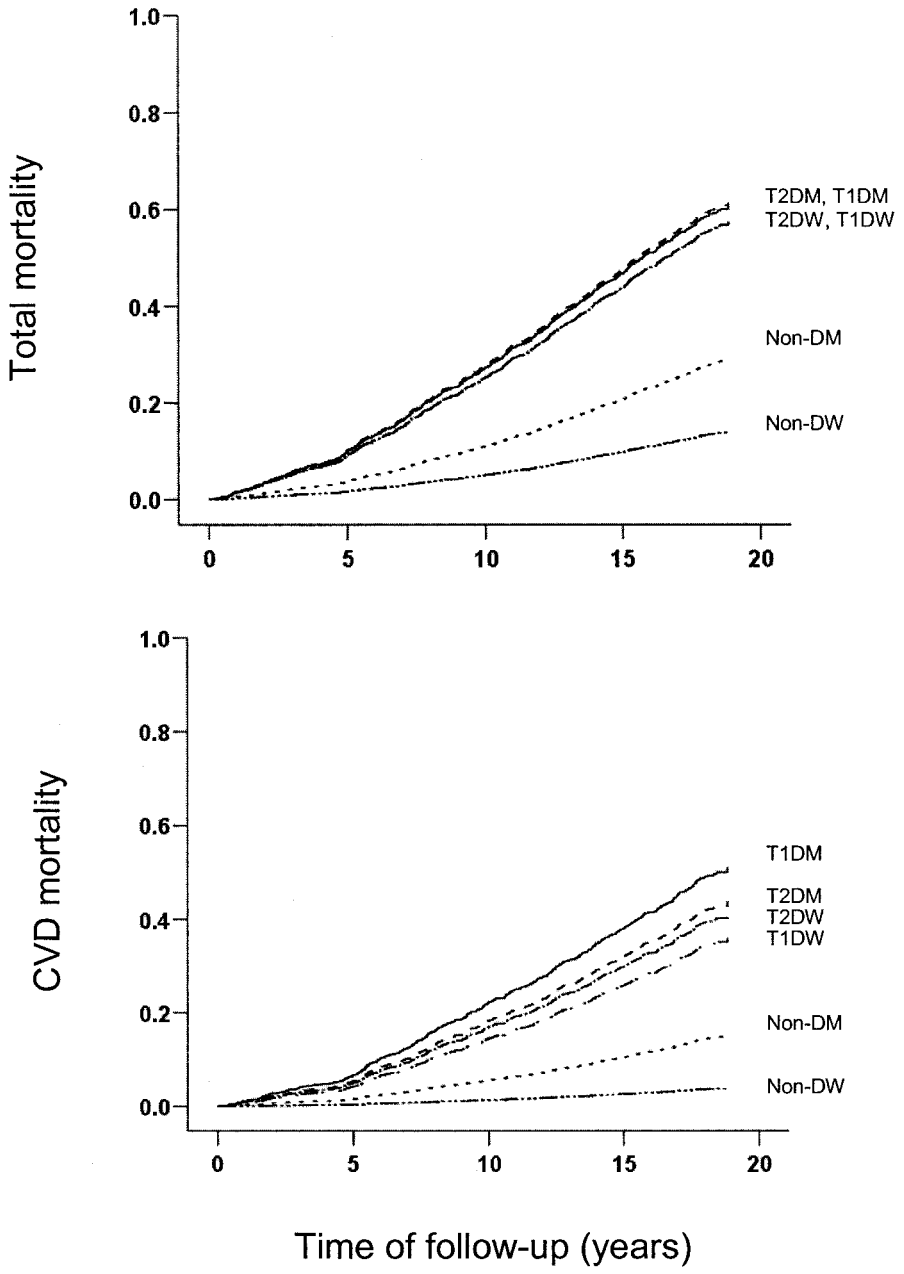

Figure 1— *Total and CVD mortality during 18 years of follow-up in type 1 (T1D) diabetic, type 2 diabetic (T2D), and nondiabetic (Non-D) men (M) and women (W). The Cox model plot for total and CVD mortality, adjusted for age, area of residence, current smoking, use of alcohol, systolic blood pressure, BMI, total and HDL cholesterol, Cockroft-Gault estimate of creatinine clearance, and urinary protein (log).*

To evaluate the effect of high GHb on CVD mortality in participants with high or low urinary protein, the groups were dichotomized using the group-specific medians for GHb and urinary protein. The rates of CVD deaths for the groups of high GHb and high urinary protein/low GHb and high urinary protein/high GHb

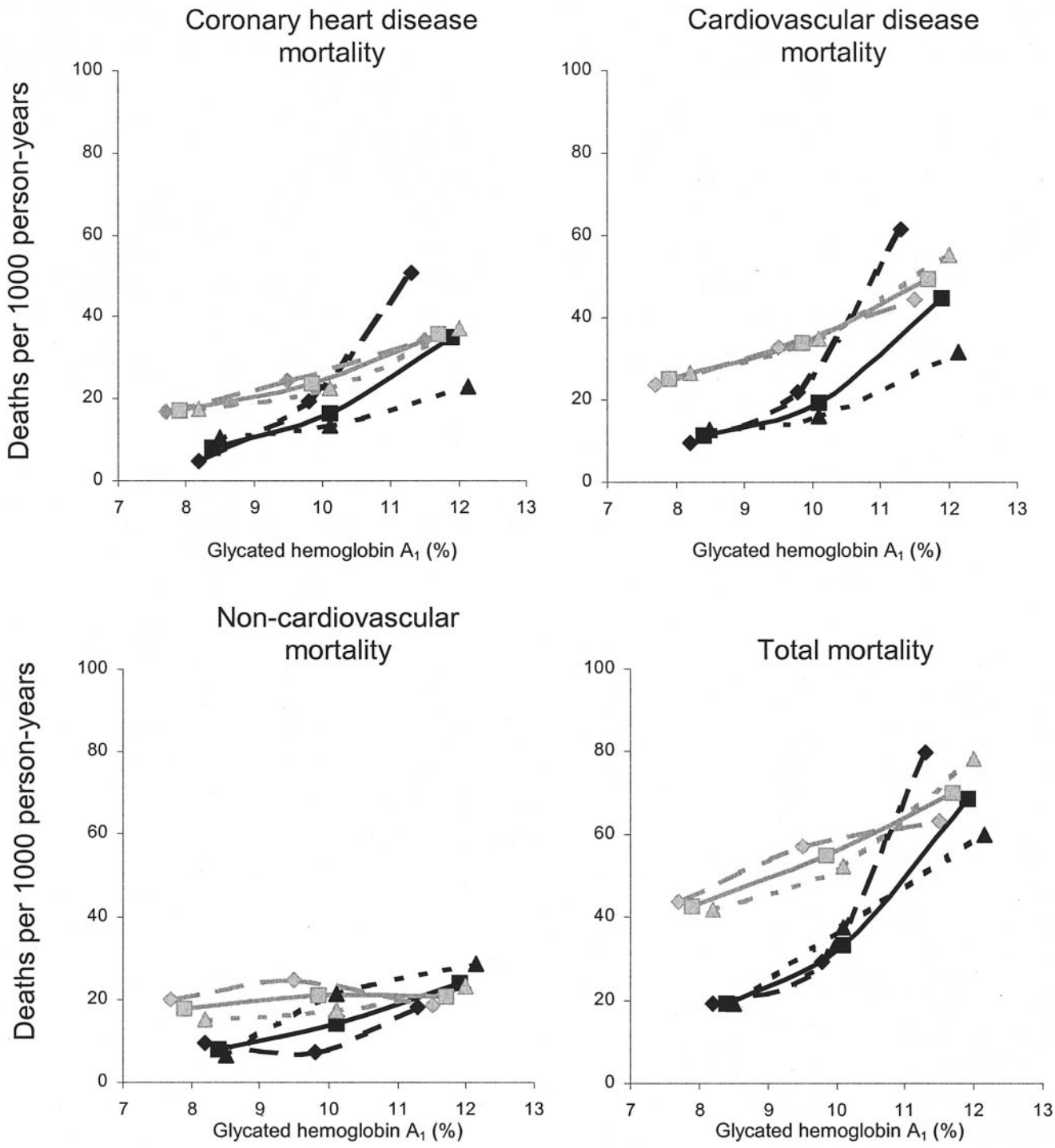

Figure 2—*CHD, CVD, noncardiovascular, and total mortality according to the status of diabetes and glycemia. Deaths per 1,000 person-years (y-axis) by GHb (x-axis) plotted by group-specific medians of tertile ranges. Black lines, type 1 diabetic participants; gray lines, type 2 diabetic participants; solid lines, men and women; long dashes, men; short dashes, women.*

and low urinary protein/low GHb and low urinary protein were 44.5/23.1/47.0/7.7 in type 1 diabetic men, 32.3/12.2/20.0/13.0 in type 1 diabetic women, 57.7/35.1/22.3/23.9 in type 2 diabetic men, and 54.1/34.2/40.0/27.1 in type 2 diabetic women.

CONCLUSIONS — Our study showed that in people with diabetes diagnosis after the age of 30 years, the impact of type 1 and type 2 diabetes on the risk of CVD and total mortality was similar. Furthermore, the harmful effect of hyperglycemia on mortality was more profound in type 1 diabetic participants than in type 2 diabetic participants.

Our study is in agreement with the Early Treatment Diabetic Retinopathy Study, which showed that 5-year all-cause mortality rates were quite similar regardless of the type of diabetes and sex.

Table 2—*Increment of the risk of CVD mortality (%) (Cox model) per increase of one unit (%) of GHb*

	Type 1 diabetes	Type 2 diabetes
Men	80.1 (37.5–135.8)	6.0 (1.0–11.1)
Women	48.4 (7.8–104.3)	10.2 (5.4–15.2)
All	52.5 (28.4–81.3)	7.5 (4.3–10.8)

Adjusted for age, sex (in the analyses of all participants), area of residence, BMI, current smoking, use of alcohol, systolic blood pressure, total cholesterol, HDL cholesterol, duration of diabetes, Cockroft-Gault estimate of creatinine clearance, and urinary protein (log).

All-cause mortality rate per 1,000 person-years was 15.3 in type 1 diabetic men, 10.3 in type 1 diabetic women, 15.6 in type 2 diabetic men, and 16.1 in type 2 diabetic women in the age-group of 50–59 years (13). In contrast, the World Health Organization Multinational Study of Vascular Disease in Diabetes Study demonstrated that type 2 diabetic women had lower relative CVD mortality compared with that in type 1 diabetic subjects and type 2 diabetic men (14).

We observed a higher hazard ratio of GHb for CVD in type 1 than in type 2 diabetic participants. Because the risk of CVD did not differ between the types of diabetes, this implies that nonglycemic related risk factors have to play a significant role in the risk of CVD in type 2 diabetes. Indirect evidence for this notion comes from the adjustment for major CVD risk factors, because it substantially reduced the hazard ratio for CVD in type 2 diabetic women but increased it in type 1 diabetic women. Similar results have been observed in previous studies (15,16), particularly in women with type 2 diabetes. This underlies the importance of multiple risk intervention in type 2 diabetic subjects (17) and possibly even more importantly in type 2 diabetic women.

A marked increase in the relative risk of CVD in women has been observed not only in type 2 diabetes (15) but also in type 1 diabetic subjects, with higher diabetes-related relative risk for all-cause, CVD, or CHD mortality in women than in men (18–23). Also in our study diabetes-related relative risk was, to a greater extent, increased in women (10- to 13-fold) than in men (3- to 4-fold).

A recent comparative analysis on CVD and coronary artery disease risk in type 1 diabetes, based on findings from the Pittsburgh Epidemiology of Diabetes Complications Study, suggested that glycemia may have a stronger effect on coronary artery disease in patients without albuminuria than in those with albuminuria (24). Our results were different because glycemia had a prominent effect on CVD mortality in type 1 diabetic subjects with proteinuria.

Poorly controlled and long-lasting glycemia in type 1 diabetes leads to the development of nephropathy. Even milder abnormalities of renal function are known to lead to dyslipidemia, raised blood pressure, and thus contribute to the high risk of CVD in type 1 diabetes (21,25). Similar pathways of vascular complications are likely to be shared in type 1 and type 2 diabetes. On the basis of our observations and previous epidemiological studies, it is not surprising that the treatment of hyperglycemia has been shown to reduce long-term complications in type 1 diabetic patients (26). A recent meta-analyses of randomized trials demonstrated comparable benefits of improving glycemic control to reduce the incidence of macrovascular events in both type 1 and type 2 diabetes (27). Intensive therapy of diabetes decreases the risk of complications, including CVD, as demonstrated in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study in subjects with type 1 diabetes (8).

This study has limitations. The glucometabolic status was not reevaluated in the nondiabetic study cohort during the study period. No repeated GHb measurements were performed. Therefore, the effect of hyperglycemia on the risk of CVD mortality may be underestimated. Because the age of onset of diabetes in our study participants was >30 years, our results cannot be generalized to early-onset type 1 diabetes. Furthermore, the number of type 1 diabetic participants was limited.

In summary, our findings indicate similarities in the risk of CVD related to type 1 and type 2 diabetes in people with diabetes diagnosis after the age of 30 years. Based on our results, hyperglycemia is the key risk factor for mortality in both main types of diabetes, with a greater hazard ratio per unit change of GHb in type 1 than in type 2 diabetes. Our findings imply that intensified therapy aimed at achieving near normoglycemia in both type 1 and type 2 diabetes is warranted.

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