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

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**Running title:** Cardiovascular mortality in type 1 and type 2 diabetes

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ABSTRACT

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 1294 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 1000 person-years (95% CI) were 23.1 (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 ratio (95% CI) for CVD mortality in participants with type 1 diabetes vs no diabetes was 3.6 (2.2-5.7) in men and 13.3 (6.9-22.5) in women, and in participants with type 2 diabetes vs. no diabetes 3.3 (2.5-4.5) in men and 10.1 (6.7-17.4) in women. Increment of 1 unit (%) of GHb increased CVD mortality by 52.5% (28.4-81.3%) in type 1 diabetic 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 diabetic than in type 2 diabetic subjects.
Diabetes mellitus is a heterogeneous group of disorders characterized by high blood glucose levels (1). Type 1 diabetes is primarily due to destruction of pancreatic beta cells resulting in absolute insulin deficiency. Type 2 diabetes, accounting for over 80% of all diabetes 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. Neither 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 diabetes diagnosis after the age of 30 years.

RESEARCH DESIGN AND METHODS

The original study population included 211 type 1 diabetic subjects, 1059 type 2 diabetic subjects and 1373 corresponding nondiabetic subjects. A detailed description of study participants has been published previously (10). The selection of the diabetic study cohort was based on drug reimbursement registry, maintained by the Social Insurance Institution. All participants were aged from 45 to 64 years. Diabetic participants fulfilled the WHO diagnostic criteria for diabetes (11). Their age at the onset of diabetes was over 30 years. Type 1 diabetes was verified by the performance of glucagon-stimulated C-peptide measurement, with the 6-minute stimulated level less than 0.20 nmol/l. A random control-population sample of non-diabetic subjects of same age was invited to participate in the study.

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). The creatinine clearance was estimated by the 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 non-traumatic lower extremity amputation) at baseline were excluded from the study.

Finally, altogether 173 type 1 diabetic participants (83 men and 90 women), 834 type 2 diabetic participants (429 men and 405 women), and 1294 nondiabetic participants (581 men and 713 women) were included in the statistical analyses.

**Follow-up study.** The follow-up period lasted until January 1, 2001. Copies of death certificates of those participants who had died before January 1st 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., S.L.). Hospital records, and autopsy records when available, were used in the final classification of the causes of death. According to the International Classification of Diseases, 9th revision (ICD-9), codes 390-459 were used to record CVD death, and codes 410 - 414 to record coronary heart disease (CHD) death.

**Definition of endpoints.** The endpoints 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.

**Approval of the Ethics Committees.** The Ethics Committees of the Kuopio University Hospital and the Turku University Central Hospital approved the study. All study participants gave informed consent.

**Statistical methods.** Data analyses were conducted with the SPSS 14.0.1 program (SPSS,
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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 Chi-square test. Logarithmic transformations were used for triglycerides and urinary protein to correct their skewed distribution. Group-specific incidence rates per 1000 person-years (95% CIs) were calculated. Cox proportional hazards models were used to compare the study groups adjusted for age, area of residence, gender (in the analyses of all subjects), current smoking, use of alcohol (user vs. non-user), systolic blood pressure, body mass index, total cholesterol, HDL cholesterol, duration of diabetes (in comparisons of type 1 vs. type 2 diabetes), Cockcroft-Gault estimate of creatinine clearance, and urinary protein (log.). The association of GHb with event-rates per 1000 person-years was evaluated with linear trend test by group-specific tertiles. The interaction of GHb tertile x diabetes type was evaluated for CVD and total mortality. Risk increase per a unit increase of GHb was calculated as 100% x (hazard ratio - 1) (95% CIs) for the study groups. The rates of CVD deaths per 1000 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 cut-offs (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 less than 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 participants (43 men, 45 women), 567 type 2 diabetic participants (291 men, 276 women) and 252 nondiabetic participants (164 men and 88 women) died. Respectively, 54 type 1 diabetic participants (31 men, 23 women), 366 type 2 diabetic participants (179 men, 187 women) and 100 nondiabetic participants (77 men and 23 women) died of CVD, and 43 type 1 diabetic participants (25 men and 18 women), 258 type 2 diabetic participants (134 men and 124 women), and 66 nondiabetic participants (52 men and 14 women) died of CHD.

At baseline type 1 diabetic participants, when compared to 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 to nondiabetic participants were older, heavier, more often non-users of alcohol, 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 to type 2 diabetic participants were younger, leaner, less frequently non-users of alcohol, 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% in type 1 diabetic participants, 19.5, 7.7 and 5.1% in nondiabetic participants, and 68.0, 43.9 and 30.9% 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 per 1000 person-years (95% CI) were 37.7 (28.0-50.8), 54.6 (47.2-63.2) and 11.7 (10.2-13.4) for total mortality, 23.1 (16.8-31.9), 35.3 (30.8-40.4) and 4.6 (3.8-5.7) for CVD mortality and 18.4 (13.0-26.0), 24.9 (21.5-28.8) and 3.1 (2.4-3.9) for CHD mortality, in the combined analysis of both genders.

Table 1 presents Cox model hazard ratios (HRs) of men, women and all participants for all-cause, CVD, CHD, and non-CVD mortality in three comparisons: type 1 vs. no diabetes, type 1 vs. type 2 diabetes and type 2 vs. 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 3-4-fold increased in men and 10-13-fold increased in women. Diabetes-related risk of CHD was 4-5-fold increased in men and 11-17-fold increased in women. Total and CVD mortality rates are illustrated in Figure 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 non-significant (HR 1.8; 95% CI 0.9-3.4).
The effect of glycemia on mortality in type 1 diabetic men and women compared to that in type 2 diabetic men and women is illustrated in Figure 2, which shows CHD, CVD, non-CVD and all-cause mortality per 1000 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, 0.146 in type 1 diabetic women, <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 gender. The effect of GHb on total mortal mortality was stronger in type 1 diabetic participants than in type 2 diabetic participants, with P-value of 0.024 for the interaction of diabetes type x tertile of GHb after adjustment for age, gender, 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 model. In Model 3, 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% (95%CI 4.3-10.8%) in type 2 diabetic participants. In gender-specific analyses, the corresponding increment of cardiovascular risk was 80.1% (95%CI 37.5-135.8%) in type 1 diabetic men, 48.4% (95%CI 7.8-104.3%) in type 1 diabetic women, 6.0% (95%CI 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 introducing also the renal variables into the model.

To evaluate the effect of high GHb on CVD mortality in participants with high or low urinary protein, the groups were dichotomised 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 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 diabetes 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 (ETRDS), which showed that 5 year all-cause mortality rates were quite similar regardless of the type of diabetes and gender. All-cause mortality rate per 1000 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 to 59 years (13). In contrast, the WHO Multinational Study of Vascular Disease in Diabetics (WHO MSVDD) Study demonstrated that type 2 diabetic women had lower relative CVD mortality compared both to that in type 1 diabetic subjects and to type 2 diabetic men (14).

We observed a higher hazard ratio of GHb for CVD in type 1 diabetic participants than in type 2 diabetic participants. Because the risk of CVD did not differ between the types of diabetes, this implies that non-glycemic 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 reduced substantially 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 particularly in women with type 2 diabetes (15-16). 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 risk of 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
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A greater extent increased in women (10-13-fold) than in men (3-4-fold).

A recent comparative analysis on cardiovascular and coronary artery disease risk in type 1 diabetes, based to findings in 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 in 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 (DCCT/EDIC) study in subjects with type 1 diabetes (8).

This study has limitations. The glucometabolic status was not re-evaluated 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 of the age of onset of diabetes in our study participants was over 30 years, our results can not be generalized to early-onset type 1 diabetes. Furthermore, the number of type 1 diabetic participants was limited.

In summary, our findings indicate similarity 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 diabetes 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.

ACKNOWLEDGMENTS
This study was supported by the Academy of Finland.
REFERENCES

**TABLE 1.** Cox model hazard ratio (HR) (95% CI) of total, cardiovascular disease (CVD), coronary heart disease (CHD), and non-cardiovascular (non-CVD) mortality according to the presence and type of diabetes. Adjusted for age, gender (in the analyses of all participants), area of residence, body mass index, current smoking, use of alcohol, systolic blood pressure, total cholesterol, HDL cholesterol, duration of diabetes (in comparison of type 1 diabetes vs. type 2 diabetes), Cockroft-Gault estimate of creatinine clearance, and urinary protein (log.).

<table>
<thead>
<tr>
<th></th>
<th>Men HR (95% CI)</th>
<th>Women HR (95% CI)</th>
<th>All (95% CI)</th>
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<tbody>
<tr>
<td><strong>Type 1 diabetes vs. no diabetes</strong></td>
<td></td>
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</tr>
<tr>
<td>Total mortality</td>
<td>2.2 (1.5-3.2)</td>
<td>4.5 (3.0-6.8)</td>
<td>2.9 (2.2-3.8)</td>
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<tr>
<td>CVD mortality</td>
<td>3.6 (2.2-5.7)</td>
<td>13.3 (6.9-25.5)</td>
<td>5.2 (3.6-7.5)</td>
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<tr>
<td>CHD mortality</td>
<td>4.9 (2.9-8.4)</td>
<td>16.9 (7.6-37.2)</td>
<td>6.6 (4.3-10.1)</td>
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<tr>
<td>Non-CVD mortality</td>
<td>1.0 (0.5-2.0)</td>
<td>2.5 (1.4-4.3)</td>
<td>1.7 (1.1-2.5)</td>
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<tr>
<td><strong>Type 2 diabetes vs. no diabetes</strong></td>
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<tr>
<td>Total mortality</td>
<td>2.6 (2.1-3.2)</td>
<td>4.5 (3.4-5.9)</td>
<td>3.2 (2.7-3.7)</td>
</tr>
<tr>
<td>CVD mortality</td>
<td>3.3 (2.5-4.5)</td>
<td>10.1 (6.7-17.4)</td>
<td>4.9 (3.8-6.3)</td>
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<tr>
<td>CHD mortality</td>
<td>3.7 (2.6-5.3)</td>
<td>10.8 (5.9-19.7)</td>
<td>5.1 (3.8-6.9)</td>
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<tr>
<td>Non-CVD mortality</td>
<td>1.9 (1.4-2.6)</td>
<td>2.1 (1.4-3.1)</td>
<td>2.0 (1.6-2.5)</td>
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<tr>
<td><strong>Type 1 diabetes vs. type 2 diabetes</strong></td>
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<tr>
<td>Total mortality</td>
<td>0.8 (0.6-1.2)</td>
<td>0.9 (0.6-1.3)</td>
<td>0.9 (0.6-1.1)</td>
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<tr>
<td>CVD mortality</td>
<td>1.1 (0.7-1.7)</td>
<td>0.7 (0.4-1.1)</td>
<td>0.8 (0.6-1.2)</td>
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<tr>
<td>CHD mortality</td>
<td>1.1 (0.7-1.9)</td>
<td>0.7 (0.3-1.3)</td>
<td>0.9 (0.6-1.3)</td>
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<tr>
<td>Non-CVD mortality</td>
<td>0.5 (0.2-1.0)</td>
<td>1.2 (0.7-2.3)</td>
<td>0.8 (0.5-1.3)</td>
</tr>
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</table>
TABLE 2. Increment of the risk of cardiovascular disease mortality (%) (Cox model) per increase of one unit (%) of GHb. Adjusted for age, gender (in the analyses of all participants), area of residence, body mass index, 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.).

<table>
<thead>
<tr>
<th></th>
<th>Type 1 diabetes</th>
<th>Type 2 diabetes</th>
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<tr>
<td>Men</td>
<td>80.1% (37.5 - 135.8%)</td>
<td>6.0% (1.0 – 11.1%)</td>
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<tr>
<td>Women</td>
<td>48.4% (7.8 - 104.3%)</td>
<td>10.2% (5.4 - 15.2%)</td>
</tr>
<tr>
<td>All</td>
<td>52.5% (28.4 - 81.3%)</td>
<td>7.5% (4.3 - 10.8%)</td>
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</table>
FIGURE LEGENDS

Figure 1. Total and cardiovascular disease (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, age, current smoking, use of alcohol, systolic blood pressure, body mass index, total cholesterol, and HDL cholesterol, Cockcroft-Gault estimate of creatinine clearance, and urinary protein (log.).

Figure 2. Coronary heart disease, cardiovascular disease, non-cardiovascular and total mortality according to the status of diabetes and glycemia. Deaths per 1000 person-years (y-axis) by GHb (x-axis) plotted by group-specific medians of tertile ranges. Black lines: type 1 diabetic participants; Grey lines: type 2 diabetic participants. Solid lines: men and women; Long dashes: men; Short dashes: women.
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FIGURE 1

Total mortality

CVD mortality

Time of follow-up (years)

T2D M, T1D M
T2D W, T1D W
Non-D M
Non-D W

T1D M
T2D M
T2D W
T1D W
Non-D M
Non-D W
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FIGURE 2

Coronary heart disease mortality

Cardiovascular disease mortality

Non-cardiovascular mortality

Total mortality