Diabetes, glucose level, and risk of sudden cardiac death

Xavier Jouven1,2*, Rozenn N. Lemaître3, Thomas D. Rea3, Nona Sotoodehnia3, Jean-Philippe Empana2, and David S. Siscovick3

1 Service de Cardiologie, Université Paris-5, Faculté René Descartes, Hôpital Européen Georges Pompidou, 20 rue Leblanc, 75015 Paris, France; 2 Equipe AVENIR et Unité INSERM 258, Hôpital Paul Brousse, Villejuif, France; and 3 University of Washington, Cardiovascular Research Unit, Metropolitan Park, East Tower, Seattle, WA 98101, USA

Aims The prevalence of diabetes mellitus in industrialized countries is rapidly increasing, and diabetes is suspected to carry a particular high risk for sudden cardiac death (SCD).

Methods and results We conducted a population-based case–control study at Group Health Cooperative. Cases (n = 2040) experienced out-of-hospital cardiac arrest due to heart disease between 1980 and 1994. Controls (n = 3800) were a stratified random sample of enrollees. Diabetes status was classified into four exclusive groups: (i) no diabetes, (ii) borderline, (iii) diabetes without microvascular disease (retinopathy or proteinuria), and (iv) diabetes with microvascular disease. When compared with no diabetes, we observed progressively higher risk of SCD associated with borderline diabetes [Odds ratio (OR) = 1.28 (0.98–1.57)], diabetes without microvascular disease [OR = 1.73 (1.28–2.34)], and diabetes with microvascular disease [OR = 2.66 (1.84–3.85)], after adjustment for potential confounders (P-value for trend <0.001). Higher glucose levels were also associated with the risk of SCD both in the absence and in the presence of microvascular disease. However, subjects with microvascular complications but with glucose level <7.7 mmol/L were not at significant increased risk of SCD.

Conclusion These results emphasize the role of diabetes as a strong risk factor for SCD and outline the importance of glucose level at every stage of diabetes severity.

Introduction

Sudden cardiac death (SCD), also known as primary cardiac arrest, is a major problem in industrially developed countries.1–3 Despite a decline in heart disease mortality, hundreds of thousands of people die each year from SCD. Furthermore, although ‘the chain of survival’ outlines opportunities to improve treatment, successful resuscitation remains <5% in most communities.4,5 The ideal solution would be to prevent the disease processes that cause SCD and, strategies aimed at identifying persons or clinical groups at particularly high risk of SCD may represent a major challenge.

Glucose intolerance and diabetes have been associated with an increased risk of coronary heart disease outcomes, and a particular high risk for SCD is suspected.6 However, the (physiological) processes such as microvascular disease, glycaemia, or coronary ischaemia through which diabetes may confer elevated risk of SCD have not been fully evaluated. For example, in the United Kingdom Prospective Diabetes Study, glycaemic control significantly reduced the incidence of microvascular disease, but had more limited effects on cardiovascular events including SCD.7 Although cholesterol-lowering treatment and antihypertensive therapy reduced the risk of macrovascular disease among diabetics, the effects of glucose level control on the risk of macrovascular disease remain discussed.8 We examined whether glucose level and diabetes were associated with an elevated risk of SCD in a large population-based case–control study.

Methods

Design and study subjects

We conducted a population-based case–control study at Group Health Cooperative (GHC) of Puget Sound, a large health maintenance organization with over 400 000 enrollees based in Western Washington State.

Cases were GHC enrollees aged 40–79 who experienced incident, out-of-hospital SCD between 1 January 1980 and 31 December 1994. We defined SCD as a sudden pulseless condition in the absence of evidence of a non-cardiac condition as the cause of cardiac arrest.9 All potentially eligible cases of SCD among GHC enrollees were initially identified from both computerized emergency medical services databases from Seattle and King County Washington and from GHC death records. All cases were confirmed by a review of the ambulatory medical record to ensure that the SCD was of cardiac origin and to confirm the absence of a life-threatening non-cardiac condition prior to the occurrence of cardiac arrest.
Controls were a stratified random sample of GHC enrollees, where the strata were defined in cases by age (decade), gender, calendar year, and treatment with digoxin or nitroglycerin. Stratification on the use of digoxin or nitroglycerin served as a proxy for heart disease in the sampling of controls, as this information was available through automated pharmacy records on all enrollees. However, as stated subsequently, we used ambulatory medical record data for the final classification of each case and control with regard to the presence or the absence of prior physician-diagnosed heart disease.

In each stratum, the ratio of controls to cases was 2:1.

As the focus of this investigation was SCD due to heart disease, we excluded cases and controls with life-threatening non-cardiac conditions including metastatic cancer, brain tumour, end-stage liver disease, or respiratory failure. We also excluded subjects who had been enrolled in the Health Maintenance Organization for <1 year or had less than four ambulatory care visits prior to the index/event date. For these analyses, we excluded patients with type 1 diabetes (22 cases and 7 controls) and subjects who did not have a plasma glucose measurement (167 cases and 366 controls). The study population for this report thus included 2040 cases and 3800 controls.

Data collection

Each study subject was assigned an index date. The index date was the date of SCD for cases. Controls, within the same strata as cases, were randomly assigned an index date from the same calendar year.

We reviewed the ambulatory medical record of GHC to obtain information about various clinical characteristics before the index date. The record includes not only notes from the ambulatory care visits, but also results (and dates) of diagnostic and laboratory tests, discharge summaries of hospitalizations, consultant reports, responses to annual GHC questionnaires, and updated problem lists. We collected the plasma glucose level measured most recently before the index date from the ambulatory care medical record. Information on whether the glucose measurement was obtained during fasting or non-fasting state was not consistently available.

We used the GHC pharmacy database to assess medications. The pharmacy database includes all prescriptions filled for enrollees since 1976. Previous surveys suggest that 98% of all prescriptions for enrollees were filled at pharmacies included in the database.

Definitions

We defined four mutually exclusive categories of diabetes status: (i) no diabetes defined as plasma glucose <7.7 mmol/L without physician diagnosis of diabetes; (ii) borderline diabetes defined as plasma glucose between 7.7 and 11.1 mmol/L without physician diagnosis of diabetes; (iii) diabetes without microvascular disease defined as physician diagnosis of diabetes or blood glucose >11.1 mmol/L but no evidence of microvascular disease; and (iv) diabetes with microvascular disease. Diabetes-related microvascular disease was defined as physician diagnosis of diabetes-associated retinopathy (non-proliferative retinopathy or proliferative retinopathy or macular oedema) or a urine analysis with at least 1+ proteinuria.

Clinically recognized heart disease was defined as physician-diagnosed myocardial infarction, angina pectoris (stable and unstable), coronary revascularization (coronary artery bypass surgery and graft and percutaneous transluminal angioplasty), atrial or ventricular arrhythmia, congenital or valvular heart disease, cardiomyopathy, or congestive heart failure.

Statistical analyses

Statistical analyses were made on Stata 7.0 software (Stata Corporation, College Station, TX, USA) and all tests were two-sided. In descriptive analyses, we compared the prevalence of risk factors between cases and controls using \( \chi^2 \) tests for categorical variables and t-tests for continuous variables. Consistent results were observed with and without Bonferroni corrections for multiple testing, so that the statistics of descriptive analysis were reported without such a correction. We used conditional logistic regression to obtain estimates of the odds ratio (OR) for SCD. The conditional logistic regression analyses accounted for the sampling variables (age decade, gender, calendar year, and use of digoxin or nitroglycerin). To estimate the OR of SCD associated with progressively more severe diabetes, we included three indicator variables for diabetes (borderline diabetes, diabetes without microvascular complications, and diabetes with microvascular complications) using the non-diabetes category as reference. We also combined glucose categories (<7.7, 7.7–11.1, and >11.1 mmol/L) with the presence or absence of microvascular complications, so that we estimated the associated OR of SCD for each category using non-diabetics subjects with glucose level <7.7 mmol/L as the reference category. Logistic regression was systematically adjusted for major risk factors for sudden coronary death including current smoking status, systolic blood pressure, anti-diabetic treatment, and history of myocardial infarction and congestive heart failure. Other known potential risk factors such as body mass index, serum cholesterol and creatinine levels, and heart rate were subsequently added to multivariate models after imputing missing data by the mean of each corresponding variable (taken from controls). Analyses were also stratified on clinically recognized heart disease and gender, and interaction terms between diabetes categories and clinically recognized heart disease and gender respectively were included in the models. All continuous variables included in regression analysis verified the linearity assumption (assessed by plotting the proportion of cases by deciles of continuous variables).

Results

Characteristics of cases and controls are compared in Table 1, stratified on the presence (\( n = 3493 \)) or the absence (\( n = 2347 \)) of clinical heart disease. Among both study subjects with or without clinically recognized heart disease, a greater proportion of cases were current smokers and heavy alcohol drinkers, cases had on average a higher basal heart rate and higher levels of cholesterol, creatinine, and blood glucose than controls, and a greater proportion of cases had pharmacologically treated diabetes. Body mass index and systolic blood pressure were higher in cases than controls among study subjects without heart disease but lower in cases than controls among study subjects with heart disease. The proportion of borderline diabetic subjects was similar among cases and controls, although the proportion of diabetic subjects with microvascular complications (including retinopathy and urine protein) was greater among cases than among controls (Table 1).

The ORs (95% CI) for SCD of 1 SD increase of glucose level (2.7 mmol/L in controls) and for the presence of microvascular complications were 1.20 (1.12–1.28) and 1.64 (1.22–2.22), respectively, after adjustment for current smoking status, systolic blood pressure, anti-diabetic treatment, and history of myocardial infarction and congestive heart failure. When compared with no diabetes, we observed progressively higher risk of SCD associated with borderline diabetes [OR = 1.24 (0.98–1.57)], diabetes without microvascular disease [OR = 1.73 (1.28–2.34)], and diabetes with microvascular disease [OR = 2.66 (1.84–3.85)], after adjustment for current smoking status, systolic blood pressure, anti-diabetic treatment, and history of myocardial infarction and congestive heart failure (P-value for trend <0.001; Table 2). The ORs
associated with diabetes were higher among subjects without clinically recognized heart disease than among subjects with heart disease (P-value for interaction = 0.005). However, the ORs increased in a stepwise fashion across diabetes status categories both among persons without heart disease (P-value for trend = 0.001) and among persons with heart disease, (P-value for trend = 0.001, Table 2). Similarly, the ORs associated with diabetes were higher among women than among men (P-value for interaction <0.001); however, the stepwise increase in OR was observed both among women (P-value for trend <0.001) and among men, (P-value for trend = 0.001, Table 3). We generally observed higher ORs among men without heart disease than among men with heart disease and among women without heart disease than among women with heart disease, although the 95% CI were large and overlapping (P-value for interaction with heart disease in men is 0.19 and in women is 0.06; data not shown).

We observed higher risk of SCD associated with higher levels of glucose both in the presence and in the absence of microvascular disease after adjustment for current smoking status, systolic blood pressure, anti-diabetic treatment and for those with heart disease and for myocardial infarction and congestive heart failure (Table 4). When compared with study subjects without microvascular disease and with glucose <7.7 mmol/L, the ORs increased progressively and significantly in subjects with glucose level between 7.7 and 11.1 mmol/L, in the absence and in the presence of microvascular disease. However, subjects with microvascular complications but with glucose level <7.7 mmol/L were not at significant increased risk of SCD (Table 4).
As in the previous analyses, ORs were higher among study subjects without heart disease (P-value for interaction with heart disease is 0.01) and among women (P-value for interaction with sex, 0.001); however, similar patterns of increasing ORs across categories of glucose levels were generally observed among subjects without and with heart disease (Table 4) and among men and women (Table 5).

Further adjustments for body mass index, serum cholesterol and creatinine levels, and heart rate did not change the results. Similar results were obtained in subjects younger or older than 65 years.

**Discussion**

In this population-based case–control study, diabetes and diabetes-related microvascular complications as well as high level of hyperglycaemia were associated with an elevated risk of SCD. Given the increasing prevalence of diabetes and the considerable health burden of SCD, these results have potentially important public health implications. Subjects with diabetes-related microvascular complications but glycaemia <7.7 mmol/L did not have a significant increased risk of SCD, underscoring the prognostic importance of keeping glycaemia within the normal range at all stages of diabetes.

The few previous studies that have assessed the risk of SCD associated with diabetes mellitus have provided mixed results. Interestingly, positive association was found in studies with long-term follow-up (typically >20 years). For instance, Curb et al. found an increased relative risk of SCD in diabetic middle-aged Japanese American men when compared with non-diabetic subjects. In the Paris Prospective Study I, a study of middle-aged men free of clinical heart disease working for the city of Paris, the risk of SCD, but not of fatal myocardial infarction, was increased in diabetes when compared with normal subjects. In the Framingham study, diabetes was strongly associated with the incidence of SCD and the association was stronger in women than in men. In a case–control study by Escobedo et al. diabetes was related to sudden coronary death only in subjects with prior coronary heart disease. However, in this latter study, diabetes (and other risk factors) was self-reported and sudden death cases were identified through death certificates and interview of informants. Likewise, in another Australian case–control study, diabetes was strongly associated with SCD. However, in two other prospective studies of middle-aged men from Finland and England, diabetes and glucose level were not associated with SCD.

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### Table 3 Association of diabetes status with out-of-hospital cardiac arrest among men and women

<table>
<thead>
<tr>
<th>Diabetes status</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case/control OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>No diabetes</td>
<td>1032/2135</td>
<td>1</td>
</tr>
<tr>
<td>Borderline diabetes</td>
<td>112/184</td>
<td>1.25</td>
</tr>
<tr>
<td>Diabetes without microvascular disease</td>
<td>177/211</td>
<td>1.63</td>
</tr>
<tr>
<td>Diabetes with microvascular disease</td>
<td>122/100</td>
<td>2.42</td>
</tr>
</tbody>
</table>

*Conditional logistic regression adjusted for age, current smoking status, systolic blood pressure, and antidiabetic treatment and for those with heart disease and for myocardial infarction and congestive heart failure.

### Table 4 Association of out-of-hospital cardiac arrest with non-fasting glycaemia level and microvascular disease

<table>
<thead>
<tr>
<th>Non-fasting glycaemia (mmol/L)</th>
<th>Overall</th>
<th>No heart disease</th>
<th>Heart disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case/control OR</td>
<td>95% CI</td>
<td>Case/control OR</td>
</tr>
<tr>
<td>No microvascular disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7.7</td>
<td>1516/3290</td>
<td>1</td>
<td>575/1526</td>
</tr>
<tr>
<td>7.7–11.1</td>
<td>170/249</td>
<td>1.26</td>
<td>42/73</td>
</tr>
<tr>
<td>&gt;11.1</td>
<td>151/135</td>
<td>2.08</td>
<td>39/24</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7.7</td>
<td>42/41</td>
<td>1.48</td>
<td>9/8</td>
</tr>
<tr>
<td>7.7–11.1</td>
<td>61/38</td>
<td>2.62</td>
<td>12/8</td>
</tr>
<tr>
<td>&gt;11.1</td>
<td>100/47</td>
<td>3.23</td>
<td>20/11</td>
</tr>
</tbody>
</table>

*Conditional logistic regression adjusted for age, current smoking status, systolic blood pressure and antidiabetic treatment and for those with heart disease and for myocardial infarction and congestive heart failure.

Stratification on clinically diagnosed heart disease.

As in the previous analyses, ORs were higher among study subjects without heart disease (P-value for interaction with heart disease is 0.01) and among women (P-value for interaction with sex <0.001); however, similar patterns of increasing ORs across categories of glucose levels were generally observed among subjects without and with heart disease (Table 4) and among men and women (Table 5).

Further adjustments for body mass index, serum cholesterol and creatinine levels, and heart rate did not change the results. Similar results were obtained in subjects younger or older than 65 years.
follow-up, 8 and 11 years, respectively, when compared with 20 years of follow-up in previous prospective studies cited earlier.

Moreover, most previous studies were restricted to men and were conducted in middle-aged subjects without prevalent coronary heart disease. In addition, these studies were not able to investigate the role of microvascular disease complications.

The results of the current investigation support an association between diabetes and an elevated risk of SCD overall as well as among demographic (age/gender) and clinical subgroups (with and without heart disease). The estimated OR between diabetes and SCD was particularly large among women and persons without clinically recognized heart disease. This is consistent with the Framingham study in which the association between diabetes and SCD was stronger in women independent of age.13 Moreover, in the British Heart Regional Study, other risk factors, such as heavy alcohol consumption and heart rate, were particularly associated with SCD in men without pre-existing ischaemic heart disease.14 However, in the current study, the larger relative risks in these subgroups (gender and pre-existing ischaemic heart disease) should be considered with respect to the lower incidence and lower absolute risk of SCD for women compared with men and for persons without heart disease compared with persons with heart disease. Furthermore, direct comparison of the OR for SCD between gender and subjects with and without heart disease is difficult, because the reference category (first level of diabetes category of each subgroup) may not carry the same absolute risk of SCD. In addition, the presence of heart disease is a strong risk factor of SCD by itself, which may attenuate the effect of other risk factor including diabetes.

Suspected mechanisms

The association between SCD and diabetes may be due to either microvascular processes including cardiac autonomic dysfunction, macrovascular disease such as coronary atherosclerosis or some combination of macro- and microvascular processes. Microvascular disease may produce autonomic neuropathy that manifests as a prolonged QT interval, increased QT dispersion, or decreased heart rate variability, which in turn may contribute to the occurrence of ventricular arrhythmias.18-21 In the current study, some evidence supports the role of microvascular processes: risk increased stepwise for those with diabetes with clinical microvascular disease when compared with those with diabetes without microvascular disease. This elevated risk of SCD among persons with diabetes and microvascular disease was evident among persons with and without clinical heart disease and did not appear to be due to confounding factors. Alternatively, the presence of microvascular disease might have been a marker for duration of diabetes, a factor that might increase macrovascular disease. The design (stratified on clinical heart disease) of the current study limits the ability to evaluate the macrovascular contribution to SCD among persons with diabetes; though prior investigations have established that coronary heart disease is more prevalent in persons with diabetes and that coronary lesions are present in >80% of SCD victims.22 Some data also suggest an accelerated coronary atherosclerosis.23-26 Moreover, a prothrombotic state has been reported as a mechanism linking diabetes and SCD.27

Blood glucose level

In the current study, an increasing level of blood glucose was associated with an elevated risk of SCD, a relationship that was present among those with and without clinical evidence of microvascular disease. Several factors may explain the relationship of hyperglycaemia and SCD. Hyperglycaemia may promote microvascular disease that was not clinically apparent (or documented) and that in turn may contribute to SCD risk. Hyperglycaemia may be a surrogate for other health markers such as poor health behaviours or medical care that may be associated with the risk of SCD. Finally, hyperglycaemia may confer risk through some other yet unknown mechanisms. Moreover, in the present study, subjects with microvascular complications but with glucose level <7.7 mmol/L were not at statistically significant increased risk of SCD after multivariate adjustment. This argues in favour of a tight control of blood glucose level even in more severe diabetes.

Limitations

In this study, it was not possible to determine whether the measure of blood glucose in the medical record was performed in the fasting state, a characteristic that may have produced some misclassification, if some.
measurements were fasting and others were not fasting. Random misclassification would have attenuated the associations observed. Thus, the results of this investigation may underestimate the risk of SCD associated with diabetes and hyperglycaemia. This underestimation of the association might also be due to our definition of diabetes status, which was strongly physician-dependent. Unfortunately, HbA1c measurements were not available in the present study.

We addressed the possibility of confounding by matching (at group level), stratification, and multivariate adjustment. We used ambulatory medical record data for the final classification of each case and control with regard to the presence or absence of prior physician-diagnosed heart disease. With this design, the association of heart diseases such as myocardial infarction with SCD cannot be evaluated. However, the current design minimized the possibility that the observed association of diabetes and SCD was confounded by prior heart disease. In addition, analyses stratified by heart disease produced consistent results. The possibility of residual confounding by an unknown factor is possible in this observational study. However, the association was independent of major risk factors for SCD and an unknown factor would not likely account for the entire association.28

Although the presence of 1+ proteinuria is a highly sensitive criterion for microvascular renal disease, it lacks specificity due to a substantial proportion of false positive. However, similar results were obtained when a cut-off value of 2+ was chosen for proteinuria. In addition to be a marker of microvascular kidney disease, proteinuria might also reflect to some extent macrovascular kidney disease.29

The present analysis did not address the issue of a decrease in the risk of SCD with a decrease in the level of glycaemia. Although the results of this study suggest that the level of glycaemia itself may be important as a risk factor for SCD, the relative importance of glycaemic control requires confirmation from clinical trials.

**Conclusion**

In this investigation, diabetes was associated with an elevated risk of SCD. Moreover, diabetes with clinically recognized microvascular disease appeared to confer an even greater risk. Because subjects with random glycaemia <7.7 mmol/L did not have a significant increased risk of SCD even in the presence of diabetes-related microvascular complications, the importance of glycaemia control is outlined. The results raise the hypothesis that efforts to prevent diabetes and its microvascular complications may reduce the health burden of SCD.

**References**