Poor Glycemic Control Predicts Coronary Heart Disease Events in Patients With Type 1 Diabetes Without Nephropathy

Seppo Lehto, Tapani Rönnermä, Kalevi Pyörälä, Markku Laakso

Abstract—Patients with type 1 diabetes mellitus, especially those with nephropathy, are at increased risk for coronary heart disease (CHD). However, information on the predictive value of cardiovascular risk factors and the degree of hyperglycemia with respect to CHD events in patients with type 1 diabetes without nephropathy is still incomplete. Therefore, we performed a prospective study on risk factors for CHD in patients with type 1 diabetes free of clinical nephropathy. At baseline examination, cardiovascular risk factor levels of CHD were determined in 177 patients with type 1 diabetes (87 men and 90 women), age 45 to 64 years at baseline and ≥30 years at the time of diagnosis of diabetes. These patients were followed up to 7 years with respect to CHD events. Altogether, 20 patients with type 1 diabetes (13 men [7.3%] and 7 women [3.9%]) died of CHD and 28 patients with type 1 diabetes (17 men [9.6%] and 11 women [6.2%]) had a serious CHD event (death from CHD or nonfatal myocardial infarction). In multivariate Cox regression analysis, a previous history of myocardial infarction (hazard ratio [HR] and its 95% confidence interval, 8.0 [3.1 to 21.0], \( P < 0.001 \)), high glycohemoglobin A1 (>10.4%, the highest tertile, HR 5.4 [1.4 to 20.4], \( P = 0.013 \)), and the duration of diabetes (>16 years, the highest tertile, HR 4.2 [1.3 to 12.9], \( P = 0.013 \)) were the only variables associated with CHD death even after adjustment for other cardiovascular risk factors. These variables also predicted the incidence of all CHD events. Our results indicate that poor metabolic control is a strong predictor of CHD events in patients with late-onset type 1 diabetes without nephropathy, independently of other cardiovascular risk factors. (Arterioscler Thromb Vasc Biol. 1999;19:1014-1019.)

Key Words: type 1 diabetes \( \text{■} \) glucose \( \cdot \) glycohemoglobin A1 \( \text{■} \) coronary heart disease

Several studies have indicated that mortality and morbidity rates of coronary heart disease (CHD) are 2 to 4 times higher among patients with type 1 diabetes than in age-matched nondiabetic subjects.1,2 In particular, patients with clinical diabetic nephropathy and a long duration of diabetes have an extremely high morbidity from macrovascular disease.2–5 Proteinuria and microalbuminuria in patients with type 1 diabetes are known to be associated with several adverse cardiovascular risk factors, including hypertension and lipoprotein abnormalities, characterized mainly by elevated serum total and LDL cholesterol and high total and VLDL triglyceride levels, low HDL cholesterol, and low ApoA1 levels.6–8 Chronic hyperglycemia9–12 and poor glycemic control13–16 have been implicated in the pathogenesis of microvascular complications in patients with type 1 diabetes, but little data are available on the role of these factors for the development of macrovascular complications.

Prospective studies based on representative cohorts of patients with late-onset type 1 diabetes and without clinical diabetic nephropathy, in whom cardiovascular risk factors including serum lipids, lipoproteins, and indicators of glycemic control had been measured at baseline, were not available. This information is, however, particularly relevant because a high occurrence of CHD in patients with type 1 diabetes with nephropathy could be caused mainly by adverse effects of renal disease on cardiovascular risk factors and not by the diabetes state itself.17 Therefore, we performed a prospective study on risk factors for CHD in representative cohorts of Finnish patients with late-onset type 1 diabetes and without nephropathy.

Methods

Baseline Study
A cross-sectional study aiming to compare the prevalence of atherosclerotic vascular disease and its risk factors in middle-aged diabetic patients and in nondiabetic subjects was performed from 1982 to 1984 in eastern and western Finland. A detailed description of the procedure of obtaining representative study populations has been reported elsewhere.18 The study population was chosen from the national register of the Social Insurance Institution, which includes all Finnish citizens who receive antidiabetic medication. In brief, the inclusion criteria were the following: (1) age from 45 to 64 years, (2) diabetes diagnosed at...
the age of 30 years or later, and (3) area of residence and place of birth in the Kuopio University Hospital district (eastern Finland) or in the Turku University Hospital district (western Finland). Altogether, 567 diabetic patients from eastern Finland and 639 diabetic patients from western Finland participated (participation rates were 83% and 73%, respectively). Of these diabetic patients, 120 from eastern Finland and 158 patients from western Finland had insulin treatment at the time of examination. C-peptide measurements after intravenous glucagon were performed in 112 of the insulin-treated patients from eastern Finland and in 151 patients from western Finland (93% and 96%, respectively). In 228 patients, type 1 diabetes was diagnosed by postglucagon C-peptide measurement (<0.20 nmol/L) and a history of ketoacidosis. In all of these patients insulin treatment had been initiated within the first year after diagnosis. The cutoff point of 0.20 nmol/L was chosen because postglucagon C-peptide values below this limit have been shown to be associated with the occurrence of ketoacidosis in insulin-treated diabetic subjects.19 These 228 patients (113 men and 115 women) formed the study population. Fifty-one patients (26 men and 25 women) with urinary protein measurements after intravenous glucagon were performed in 112 of the insulin-treated patients from eastern Finland and in 151 patients from western Finland (93% and 96%, respectively). In 228 patients, type 1 diabetes was diagnosed by postglucagon C-peptide measurement (<0.20 nmol/L) and a history of ketoacidosis. In all of these patients insulin treatment had been initiated within the first year after diagnosis. The cutoff point of 0.20 nmol/L was chosen because postglucagon C-peptide values below this limit have been shown to be associated with the occurrence of ketoacidosis in insulin-treated diabetic subjects.19 These 228 patients (113 men and 115 women) formed the study population. Fifty-one patients (26 men and 25 women) with urinary protein excretion >300 mg/L and/or serum creatinine >110 μmol/L in women and 120 μmol/L in men were excluded. Thus, the final study population comprised 177 patients (87 men and 90 women).

The study program previously described in detail18 was performed during 1 outpatient visit at the Clinical Research Unit of the University of Kuopio or the Rehabilitation Research Center of the Social Insurance Institution in Turku. The visit included an interview regarding the history of chest pain symptoms suggestive of CHD, smoking, alcohol intake, physical activity, and the use of drugs. All medical records of those subjects who reported during the interview that they had been admitted to the hospital because of chest pain symptoms were reviewed. Review of the medical records was performed by 2 of us (M.L. in Kuopio and T.R. in Turku) after a careful standardization of the methods between the reviewers. The World Health Organization criteria for verified definite or possible myocardial infarction (MI) based on chest pain symptoms, ECG changes, and enzyme determinations were used in the ascertainment of the diagnosis of previous MI.20

Smoking status was based on an interview. In all statistical analyses, subjects were classified as nonsmokers or current smokers.

With the subject in a sitting position after a 5-minute rest, blood pressure was measured with a mercury sphygmomanometer and read to the nearest 2 mm Hg. A subject was classified as having hypertension if he or she was receiving drug treatment for hypertension or if his or her systolic blood pressure was at least 160 mm Hg or diastolic blood pressure at least 95 mm Hg.

Biochemical Methods

All laboratory specimens were drawn after a 12-hour fast at 8 AM. Fasting plasma glucose was determined by the glucose oxidase method (Boehringer). Glycohemoglobin A1c (GHbA1c) was determined by affinity chromatography (Isolab) (reference range, 5.5% to 8.5%). The plasma C-peptide response to glucagon was determined according to the method of Faber and Binder.21 Serum lipids and lipoproteins were determined from fresh serum samples drawn after a 12-hour overnight fast. Serum total cholesterol and triglycerides were assayed by automated enzymatic methods (Boehringer). Serum HDL cholesterol was determined enzymatically after precipitation of LDL and VLDL lipoproteins with dextran sulfate/MgCl2.22 LDL cholesterol was calculated by using the Friedewald formula as follows: LDL cholesterol = total cholesterol − HDL cholesterol − 0.45 × total triglycerides.

Follow-Up Study

In 1990, a postal questionnaire containing questions about hospitalization because of acute chest pain was sent to every surviving participant of the original study cohort. All medical records of those subjects who died between the baseline examination and December 31, 1989, or who reported in the questionnaire that they had been admitted to the hospital because of chest pain symptoms between the baseline examination and December 31, 1989, were reviewed by 1 of us (S.L.). To ensure that the data collection with regard to hospital-treated MIs was complete, a computerized hospital discharge register was used to check hospital admissions of all participants of the baseline study, and in case of hospitalization for an acute CHD event, medical records were checked. The modified World Health Organization criteria for definite or possible MI based on chest pain symptoms, ECG changes, and enzyme determinations were used in the ascertainment of the diagnosis of MI similarly as in the baseline study.20 Copies of death certificates of those patients who had died were obtained from the files of the Central Statistical Office of Finland. In the final classification of the causes of death, hospital records and autopsy records were used, if available. The mortality data included in the present article are mortality from CHD (International Classification of Diseases 9, Codes 410 to 414).

Statistical Methods

Data analyses were conducted with the SPSS and SPSS/PC+ programs (SPSS Inc). The results for continuous variables are given as mean±SEM values or percentages. The differences between the groups were assessed by the χ2 test, or Student’s 2-tailed t test for independent samples when appropriate. The univariate and multivariate Cox regression model23 was used to investigate the association of cardiovascular risk factors with the incidence of CHD events.

Approval of Ethics Committee

This study was approved by the Ethics Committee of Kuopio University Central Hospital and the Turku University Central Hospital. All study subjects gave informed consent.

Results

During 7-year follow-up (mean follow-up was 7.2 years in men and women), 20 patients (13 men [7.3%] and 7 women [3.9%]) with type 1 diabetes died of CHD. Altogether, 28 patients with type 1 diabetes (17 men [9.6%] and 11 women [6.2%]) had a serious CHD event (death from CHD or nonfatal MI).

Table 1 summarizes baseline characteristics of patients with type 1 diabetes, in relation to cardiovascular mortality and morbidity during the 7-year follow-up, by sex. Data from eastern and western Finland were combined, because no significant differences existed between these areas in the levels of cardiovascular risk factors with respect to CHD events. Men with CHD were significantly older and had more often a history of previous MI and had higher GHbA1c than men without CHD. Women with CHD had more often a history of previous MI and higher levels of GHbA1c and a longer duration of diabetes than women without CHD.

Table 2 reports unadjusted and adjusted hazard ratios (HRs) for cardiovascular risk factors. The highest or lowest (for HDL cholesterol) tertile limit was used as a cutoff point for continuous variables. In univariate analysis, a previous history of MI and GHbA1c and the duration of diabetes were the only variables associated with the risk of CHD death (P<0.001) and all CHD events (P<0.01). Figure 1 demonstrates that poor glycemic control was associated with the incidence of CHD death similarly throughout the follow-up period. In multivariate analysis, a previous history of MI (HR 8.0 [3.1 to 21.0], P<0.001), high GHbA1c (>10.4%, HR 5.4 [1.4 to 20.4], P=0.013), and the duration of diabetes (>16 years, HR 4.2 [1.3 to 12.9], P=0.013) were associated with CHD death even after adjustment for other cardiovascular risk factors (age, sex, area of residence, previous MI, smoking, body mass index, hypertension, total cholesterol, total
triglycerides, and HDL cholesterol). In a similar manner, previous MI, high GHbA1, and a long duration of diabetes were associated significantly with all CHD events in univariate analyses. Multivariate Cox analyses demonstrated that HRs for previous MI (3.4 [1.5 to 7.9], \(P=0.004\)), high GHbA1 (2.8 [1.2 to 6.9], \(P=0.021\)), and long duration of diabetes (HR 3.9 [1.6 to 9.3], \(P=0.002\)) remained almost unchanged when adjusted for other cardiovascular risk factors. Because lipids and lipoproteins were not associated with the risk for CHD, we included these variables into the Cox regression models also as continuous variables. In addition, we used different cutoff points to confirm that the use of the highest tertile limit does not underestimate the significance of these variables. Dyslipidemia was not a significant risk factor in any of these analyses.

We did all statistical analyses also by including patients with nephropathy in our analyses (data not shown). These analyses also demonstrated that poor glycemic control (high

### TABLE 1. Levels of Cardiovascular Risk Factors (Mean±SEM or Percentages) in Relation to the Incidence of CHD Events (Death From CHD or Nonfatal MI) During 7-Year Follow-Up in Patients With Type 1 Diabetes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men Without CHD (n=79)</th>
<th>Men With CHD (n=17)</th>
<th>Women Without CHD (n=79)</th>
<th>Women With CHD (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>53.5±0.5</td>
<td>58.6±1.4†</td>
<td>56.2±0.6</td>
<td>56.4±1.8</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.1±0.4</td>
<td>24.4±0.8</td>
<td>25.5±0.5</td>
<td>26.1±1.4</td>
</tr>
<tr>
<td>Insulin dose (IU/d)</td>
<td>45±2</td>
<td>51±6</td>
<td>40±2</td>
<td>43±4</td>
</tr>
<tr>
<td>Previous MI (%)</td>
<td>4.3</td>
<td>35.3§</td>
<td>5.1</td>
<td>27.3‡</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>28.6</td>
<td>23.5</td>
<td>45.6</td>
<td>36.4</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>25.7</td>
<td>35.3</td>
<td>11.4</td>
<td>9.1</td>
</tr>
<tr>
<td>Urinary protein (mg/L)</td>
<td>114.2±0.1</td>
<td>132.0±0.2</td>
<td>99.0±0.1</td>
<td>161.0±0.3*</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>6.27±0.15</td>
<td>6.76±0.47</td>
<td>6.94±0.15</td>
<td>7.36±0.22</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>4.22±0.13</td>
<td>4.54±0.38</td>
<td>4.59±0.13</td>
<td>4.91±0.20</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.47±0.05</td>
<td>1.56±0.14</td>
<td>1.76±0.05</td>
<td>1.83±0.14</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.40±0.09</td>
<td>1.56±0.22</td>
<td>1.44±0.15</td>
<td>1.48±0.17</td>
</tr>
<tr>
<td>Plasma glucose (mmol/L)</td>
<td>9.7±0.6</td>
<td>11.7±1.0</td>
<td>10.4±0.5</td>
<td>11.8±1.8</td>
</tr>
<tr>
<td>GHb A1 (%)</td>
<td>9.4±0.2</td>
<td>10.5±0.4*</td>
<td>10.1±0.2</td>
<td>11.1±0.4</td>
</tr>
<tr>
<td>Duration of diabetes (y)</td>
<td>13.8±1.0</td>
<td>15.7±1.6</td>
<td>13.0±0.8</td>
<td>22.4±2.0‡</td>
</tr>
</tbody>
</table>

*P<0.05; †P<0.01; ‡P<0.001.

### TABLE 2. Unadjusted and Adjusted HRs and Their 95% Confidence Intervals (CI) for Cardiovascular Risk Factors to Increase the Risk for CHD Events During 7-Year Follow-Up in Patients With Type 1 Diabetes (Cox Regression Model)

<table>
<thead>
<tr>
<th>CHD Mortality (20/177) HR (95% CI)</th>
<th>All CHD Events (28/177)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>Multiple Adjusted*</td>
</tr>
<tr>
<td>Previous MI (7.2 mmol/L)</td>
<td>6.0 (2.9–12.7)§</td>
</tr>
<tr>
<td>Total cholesterol (7.2 mmol/L)</td>
<td>1.6 (0.7–4.0)</td>
</tr>
<tr>
<td>LDL cholesterol (4.82 mmol/L)</td>
<td>1.0 (0.4–2.7)</td>
</tr>
<tr>
<td>Total triglycerides (1.4 mmol/L)</td>
<td>0.8 (0.3–2.2)</td>
</tr>
<tr>
<td>HDL cholesterol (1.40 mmol/L)</td>
<td>1.2 (0.6–2.5)</td>
</tr>
<tr>
<td>Fasting plasma glucose (12.6 mmol/L)</td>
<td>1.7 (0.7–4.2)</td>
</tr>
<tr>
<td>Glycated hemoglobin A1 (10.4%)</td>
<td>6.8 (2.5–19.0)§</td>
</tr>
<tr>
<td>Duration of diabetes (16 y)</td>
<td>5.0 (2.0–12.4)§</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, area, previous MI, smoking, body mass index, hypertension, total cholesterol, triglycerides (log), HDL cholesterol, GHbA1, and duration of diabetes. Total cholesterol was not adjusted for LDL cholesterol and vice versa. HDL was not adjusted for plasma glucose and vice versa.

†P<0.05; ‡P<0.01; §P<0.001.
metabolic control (Figure 2).

The 7-year incidence (%) of CHD death, by median baseline GHbA1 (≥10.4% versus ≤10.4%) during the 7-year follow-up (univariate Cox regression model).

Figure 1. Survival curves for CHD death in patients with type 1 diabetes, by baseline GHbA1 (≥10.4% versus ≤10.4%) during the 7-year follow-up (univariate Cox regression model).

GHbA1 (10.0%) and known duration of diabetes (13.0 years) were used as cutoff points. The impact of poor glycemic control on the risk for CHD death was seen independently of diabetes duration. Although the long duration of diabetes increased the risk for CHD death, this effect was much weaker than that exercised by poor metabolic control (Figure 2).

Discussion

Our 7-year follow-up study is the first population-based study demonstrating the important role of glycemic control as a predictor of CHD mortality and morbidity in patients with late-onset type 1 diabetes without nephropathy. In univariate analysis, the risk for CHD death was 7-fold and the risk for all CHD events (CHD death or nonfatal MI) 3-fold among patients with type 1 diabetes with high GHbA1 (≥10.4%) compared with those with better glycemic control. The association remained statistically significant even after adjustment for other cardiovascular risk factors (Table 2). Furthermore, the impact of poor glycemic control was independent of diabetes duration. Because our study was based on only 1 single measure of glycemic control at baseline, it is likely that our results are even an underestimation of the deleterious effects of hyperglycemia on the risk for CHD.

Several previous studies have indicated that hyperglycemia predicts microvascular complications in patients with type 1 diabetes.10–12 Data on the risk for macrovascular complications have been much more limited. Deckert et al24 followed 259 patients with type 1 diabetes and with slightly elevated urinary albumin excretion (age range, 19 to 51 years at baseline) for 11 years. Elevated albumin excretion rate, but not GHbA1c, predicted the incidence of atherosclerotic vascular disease (CHD, stroke, and peripheral vascular disease). GHbA1 was also not a predictor for CHD in the Pittsburgh Epidemiology of Diabetes Complications Study.25 These 2 recent studies have significant differences compared with our study. Both included a much younger cohort of type 1 patients with early-onset diabetes. Furthermore, the study by Lloyd et al25 included patients with overt nephropathy, and the study by Deckert et al24 combined all manifestations of atherosclerotic vascular disease as their end point, which makes it impossible to clarify risk factors for CHD in their study. That poor metabolic control is causally associated with the risk for macrovascular complications in type 1 diabetes has recently gained substantial support by the Diabetes Control and Complications Trial.26 This trial demonstrated that not only microvascular complications, but also macrovascular complications, were reduced (by 41%) in patients with type 1 diabetes with good glycemic control compared with conventionally treated diabetic patients, although the reduction in macrovascular events was not statistically significant.

In patients with type 1 diabetes, total cholesterol, HDL cholesterol, and total triglycerides are usually within normal limits when blood glucose is controlled.27,28 Good glycemic control in type 1 diabetes usually reduces LDL and VLDL to normal levels29 and may raise HDL even above the normal range.28 Abnormal lipoprotein metabolism could theoretically contribute to premature atherosclerosis in patients with type 1 diabetes. However, in our study, high levels of total and LDL cholesterol and total triglycerides and low levels of HDL cholesterol failed to predict CHD events in patients with type 1 diabetes although our study population included a substantial number of patients with poor metabolic control (Table 2). This could be the result of a limited number of CHD events in our study population, but it may also indicate that in late-onset type 1 diabetes without nephropathy, abnormalities in lipids and lipoproteins do not play such a crucial role in the development of CHD compared with the effects of poor glycemic control. Smoking, hypertension, and insulin dose were no different among patients with type 1 diabetes with and without CHD (Table 1). Our study population including patients with type 1 diabetes without nephropathy provided an excellent opportunity to assess the relation between glycemic exposure and the risk for CHD in type 1 diabetes. Based on our findings, it is suggested that the crucial factor in the development of CHD in patients with late-onset type 1 diabetes is hyperglycemia, because the only factors that significantly predicted CHD events in our patients were...
high GHbA1c and the long duration of diabetes (duration of hyperglycemia). This implies that the risk for CHD in our study must be explained by direct effects of hyperglycemia itself, because clinical and biochemical characteristics were not otherwise different between those who had a CHD event compared with those who did not (Table 1). However, long-lasting hyperglycemia often leads to diabetic kidney disease and cardiovascular risk factors become abnormal when microalbuminuria, proteinuria, or elevation of creatinine level is present. Therefore, in addition to direct harmful effects of hyperglycemia, indirect effects on cardiovascular risk factors also take place that probably explain the massive increase in the risk for CHD in patients with type 1 diabetes and overt nephropathy.

Many potential biochemical and clinical mechanisms may explain why hyperglycemia itself, independently of changes in cardiovascular risk factors, can increase the risk for CHD.30 Hyperglycemia is related to abnormalities in lipoprotein particle composition, which in turn are known to be atherogenic. Furthermore, hyperglycemia has been reported to accelerate oxidation of lipoproteins31 and to induce and worsen insulin resistance and hyperinsulinemia, both of these effects being linked with an increased risk for atherosclerotic vascular disease.32–35 Hyperglycemia can also accelerate thrombus formation among diabetic patients.36,37 Finally, long-lasting hyperglycemia can cause irreversible glycation of proteins in the arterial wall, which may also contribute to the development of vascular complications.37

Significant differences exist between type 1 diabetes and type 2 diabetes regarding cardiovascular risk factors predicting CHD. In type 2 diabetes, dyslipidemia (high LDL cholesterol, high total triglycerides, and low HDL cholesterol) is the most important determinant of CHD events.38 According to recent studies, hyperglycemia is also associated with the risk for CHD in type 2 diabetes but it is a weaker risk factor for CHD than is dyslipidemia.39 In contrast, according to the present study, poor metabolic control dominates other risk factors, including dyslipidemia, in patients with type 1 diabetes without diabetic kidney disease. Whether the relation between GHbA1c and the risk for CHD is linear or nonlinear cannot be solved by this study because of a limited number of CHD events.

Because poor glycemic control plays an important role in the development of macrovascular complications in type 1 diabetes, it is reasonable to assume that its treatment reduces the risk for CHD in patients with type 1 diabetes. The findings of the Diabetes Control and Complications trial are also in accordance with this view.40 Therefore, the correction of hyperglycemia seems to be rational, not only because of the prevention of microvascular complications, but also because it may decrease the risk for atherosclerotic vascular disease in patients with type 1 diabetes.

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References


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