Glycaemic control in newly diagnosed diabetes patients and mortality from ischaemic heart disease: 20-year follow-up of the HUNT Study in Norway

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Aims To assess the influence of glycaemic control on long-term mortality from ischaemic heart disease (IHD) in patients with newly diagnosed diabetes.

Methods and results In a large population study in Norway, people ≥40 years with non-fasting glucose ≥8 mmol/L were invited to a fasting glucose test, and if the fasting value was ≤7 mmol/L, an oral glucose tolerance test was also performed. Among people who were diagnosed with diabetes, 205 patients were followed with annual measurements of HbA1c in order to monitor glycaemic control. Stratified Cox regression analysis was used to compare IHD mortality rates during 20 years of follow-up, with comparison of newly diagnosed diabetes patients and a matched group of 205 individuals without diabetes. Among patients, we also assessed the relation of HbA1c with IHD mortality. After adjustment for potentially confounding factors, IHD mortality in the total diabetes group was substantially higher (HR 1.8, 95% CI, 1.0–3.4) compared with the comparison group. However, the increased risk was particularly high in patients with HbA1c in the highest quartile (HR 4.2, 95% CI, 2.1–8.1). Analysing HbA1c as a continuous time-varying variable showed 30% (HR 1.3, CI 1.1–1.5) higher risk per increment of HbA1c among diabetes patients without known CVD at baseline.

Conclusion Poor long-term glycaemic control is associated with a substantial increase in the risk of dying from IHD in patients with diabetes, whereas in patients with reasonably good control, risk of dying from IHD may not substantially differ from that of people without diabetes.

Keywords Diabetes mellitus • Mortality • Ischemic heart diseases • Follow-up • Glycaemic control

Introduction

Type 2 diabetes causes few initial symptoms and is therefore often diagnosed several years after onset.1,2 Typically, the initial disturbance of the glucometabolic control presents itself as impaired glucose tolerance (IGT). It has been estimated that about 50% of people with IGT eventually develop diabetes;3 however, several studies suggest that early intervention may delay or prevent the progression from IGT to diabetes.4,5

It is well known that people with established diabetes are at increased risk of ischaemic heart disease (IHD). Diabetes patients have more than two-fold higher risk of fatal IHD compared to people without diabetes.6–10 In addition, people with IGT, but not yet clinically established diabetes, are at increased risk of
cardiovascular disease (CVD). This suggests that long standing dysfunc-
tional glucose metabolism combined with conventional cardio-
vascular risk factors may cause cardiovascular events that
often precede the diagnosis of diabetes. Maybe one in four
will present with macrovascular complications and microvas-
cular complications are often present in these patients at the time
of diagnosis of diabetes.

Good diabetes control, as monitored by regular HbA1c
measurements, reduces the risk of diabetes retinopathy and
nephropathy. Whether good glucose control reduces long-
term mortality from CVD has not been clearly shown, and it
remains uncertain if there is a universally optimal glucose level.

The results of follow-up studies that used one glucose measure-
ment have shown higher risk of IHD associated with high
blood glucose control, as indicated by annual
measurements, reduces the risk of diabetes retinopathy and
microvascular complications are often present in these patients at the time
of diagnosis of diabetes.

Methods

During 1984–86, a large general health survey (the HUNT Study) was
conducted in Nord-Trøndelag County in Norway. The county is fairly
representative for Norway as a whole, with a stable and ethni-
cally homogeneous population, where only a small proportion (3%) is of
non-Caucasian origin.

The first wave of the HUNT Study has been described in detail else-
where. Briefly, 76,885 (2242 with self-reported diabetes) indivi-
duals responded to a questionnaire and 74,914 (2100 with self-reported dia-
betes) attended a clinical examination that included measurements of
blood pressure, pulse, body weight and height. Among participants
of 40 years and older, a random non-fasting glucose test was taken.
If the glucose concentration in persons without diabetes was
≥8 mmol/L, follow-up examinations were scheduled for fasting
blood glucose measurements and oral glucose tolerance tests, according to
WHO recommendations. Through this procedure, a total of 428
cases of newly diagnosed diabetes were confirmed and flagged as possi-
ble candidates for a long-term follow-up study. Among these patients, 103 were excluded: 20 because they were older than 80 years of age, 12 because they died within the first year of follow-up, 14 due to serious illness at baseline, 2 had moved out of the county, 37 declined to participate in the follow-up, and 18 persons were not followed up for other reasons, leaving 325 patients with newly confirmed diabetes. Due to geographical constraints, it was feasible to follow 235 of these 325 patients, and among them, 205 patients agreed to participate in the follow-up study. From the HUNT Study population, twice as many people without diabetes were frequency matched to the patients by
sex, age, and municipality of residence. Among them, 205 who
agreed to participate in the follow-up study were selected as controls.
The diabetes patients attended an initial comprehensive clinical exam-
ation 6–22 (mean 14) months after the baseline survey, and the
comparison group attended a similar examination 12–32 (mean 22)
months after the baseline survey. The examination included full
medical history and a thorough clinical check-up, including ECG,

Statistics

Baseline characteristics of the study population are displayed by
means and proportions and stratified according to diabetes
status (Table 1).

In order to take the matched design into account, stratified Cox
regression analysis was used to estimate hazard ratios (HRs) and
95% confidence intervals (CIs) of death from IHD, CVD, and all
cases in the group of diabetes patients and the comparison
group. All analyses were adjusted for age (continuous) and sex
(by strata), and in subsequent multivariable analyses, we assessed
potential confounding by factors such as BMI, history of CVD,
smoking habits, hypertension, exercise level, and education. Only
variables that influenced the associations of diabetes status with
cardiovascular mortality were included in the presented tables.
Statistical tests were two-sided, and all statistical analyses were conducted using Stata for Windows (version 10 © StataCorp LP 1985–2007).

**Results**

Patients with newly diagnosed diabetes were more often hypertensive, had higher BMI, and were less likely to exercise compared with the group without diabetes (Table 1). Established CVD at baseline, indicated by history of stroke, myocardial infarction or angina, was more frequent in the diabetes group compared with the control group.

During follow-up, patients with diabetes were more likely to die from IHD (adjusted HR, 1.8; 95% CI, 1.0–3.4) compared with people without diabetes (Table 2). For cardiovascular deaths as a whole and for total deaths, the associations were weaker than for IHD mortality, but showed consistently higher HRs for patients with diabetes.

HbA1c levels were measured during the first 10 years of follow-up in the diabetes group and were used as an indicator of glycaemic control (Table 3). After multivariable adjustment, patients in the highest quartile of HbA1c were at much higher risk of death from IHD compared with the comparison group without diabetes (HR, 4.2; 95% CI, 2.1–8.1), and in this group, risk was more than two-fold higher than in diabetes patients with lower levels of HbA1c (Table 3). We also analysed the linear association of HbA1c (as a time-varying continuous variable) and mortality among diabetes patients; this analysis showed that one unit increase in HbA1c was associated with 20% higher risk of death from IHD compared with the comparison group.

**Discussion**

During 20 years of follow-up, we found that patients with newly diagnosed diabetes had a higher risk of dying from IHD compared with people without diabetes at baseline, but the higher risk was most evident in patients with poorly controlled diabetes, as indicated by high level (highest quartile) of HbA1c during the first 10 years of follow-up. In patients with lower HbA1c, mortality was only slightly higher compared with people without diabetes at baseline.

Several studies have shown that the increased cardiovascular risk associated with diabetes may not only be due to conventional risk factors, but that intrinsic factors related to diabetes or pre-diabetes are likely to be important. This hypothesis has been supported by studies showing that hyperglycaemia is positively associated with CVD, also after adjustment for potentially confounding factors.

People with newly diagnosed diabetes more often had prevalent CVD at baseline compared with the control group, and this could explain the differences in life expectancy between the groups. However, among the diabetes group, we found that patients with good glucose control (indicated by HbA1c values) were more likely to have prevalent CVD than patients with poorer control. Possibly, good glucose control may, at least to some

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**Table 1 Baseline characteristics of the study participants**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Not diabetes</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>205</td>
<td>205</td>
</tr>
<tr>
<td>Male/female ratio</td>
<td>106/99</td>
<td>106/99</td>
</tr>
<tr>
<td>Age at baseline, years, mean (SD)</td>
<td>66.7 (9.8)</td>
<td>66.6 (9.7)</td>
</tr>
<tr>
<td>Random glucose (mmol/L), mean (SD)</td>
<td>5.2 (1.2)</td>
<td>10.6 (3.7)</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L), mean (SD)</td>
<td>5.0 (1.0)</td>
<td>6.9 (1.9)</td>
</tr>
<tr>
<td>Cholesterol (mmol/L), mean (SD)</td>
<td>7.28 (1.53)</td>
<td>6.68 (1.23)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg), mean (SD)</td>
<td>152.2 (25.8)</td>
<td>161.7 (24.7)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg), mean (SD)</td>
<td>89.8 (11.3)</td>
<td>91.4 (12.5)</td>
</tr>
<tr>
<td>Body mass index (kg/m²), mean (SD)</td>
<td>26.1 (3.5)</td>
<td>29.7 (4.9)</td>
</tr>
<tr>
<td>Waist–hip ratio, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>0.83 (0.06)</td>
<td>0.88 (0.08)</td>
</tr>
<tr>
<td>Men</td>
<td>0.92 (0.04)</td>
<td>0.94 (0.05)</td>
</tr>
<tr>
<td>Hypertension*, n (%)</td>
<td>102 (50)</td>
<td>140 (68)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No smoking</td>
<td>140 (68)</td>
<td>140 (68)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>35 (17)</td>
<td>42 (21)</td>
</tr>
<tr>
<td>Unknown</td>
<td>30 (15)</td>
<td>23 (11)</td>
</tr>
<tr>
<td>Education, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 years</td>
<td>144 (70)</td>
<td>155 (76)</td>
</tr>
<tr>
<td>10–12 years</td>
<td>25 (12)</td>
<td>20 (10)</td>
</tr>
<tr>
<td>≥13 years</td>
<td>9 (4)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>27 (13)</td>
<td>25 (12)</td>
</tr>
<tr>
<td>Exercise frequency, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 per week</td>
<td>59 (29)</td>
<td>93 (45)</td>
</tr>
<tr>
<td>1–3 per week</td>
<td>82 (40)</td>
<td>61 (30)</td>
</tr>
<tr>
<td>≥4 per week</td>
<td>31 (15)</td>
<td>26 (13)</td>
</tr>
<tr>
<td>Unknown</td>
<td>33 (16)</td>
<td>25 (12)</td>
</tr>
<tr>
<td>Prevalence of cardiovascular disease, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total with prevalent CVD, n</td>
<td>27 (13)</td>
<td>44 (22)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>16 (8)</td>
<td>30 (15)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>11 (5)</td>
<td>14 (7)</td>
</tr>
<tr>
<td>Stroke</td>
<td>5 (2)</td>
<td>12 (6)</td>
</tr>
</tbody>
</table>

CVD, cardiovascular disease.

*Hypertension, ≥140/90 mmHg, or antihypertensive medication.

†Participants may have more than one disease.

We also estimated the association of HbA1c with mortality from CVD and IHD. These analyses were done in two separate ways: first, we estimated the risk of death in quartiles of HbA1c compared with the reference group without diabetes, and second, we analysed HbA1c as a time-varying continuous variable among diabetes patients. The proportional hazards assumption was evaluated using graphical procedures (log–log plots). All statistical tests were two-sided, and all statistical analyses were
Influence of glycaemic control on long-term mortality from IHD

Table 2 Hazard ratios of deaths from all causes, and specifically from cardiovascular disease, and from ischaemic heart disease, in people with newly diagnosed diabetes at baseline, and people without diabetes at baseline

<table>
<thead>
<tr>
<th>Diabetes status</th>
<th>Person years</th>
<th>All causes</th>
<th>Cardiovascular diseases</th>
<th>Ischemic heart disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Deaths</td>
<td>Adjusted HR (95% CI)</td>
<td>Deaths</td>
</tr>
<tr>
<td>No</td>
<td>2693</td>
<td>125</td>
<td>1.0 (reference)</td>
<td>64</td>
</tr>
<tr>
<td>Yes</td>
<td>2456</td>
<td>146</td>
<td>1.2 (0.9–1.7)</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45</td>
</tr>
</tbody>
</table>

Twenty-year mortality follow-up. CI denotes confidence interval.

Table 3 Hazard ratios of deaths from cardiovascular disease and from ischaemic heart disease, according to the level of HbA1c measured during 10 consecutive years after the diagnosis of diabetes

<table>
<thead>
<tr>
<th>Diabetes status and HbA1c (%)</th>
<th>Person years</th>
<th>Cardiovascular disease</th>
<th>Ischemic heart disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Deaths</td>
<td>Adjusted HR (95% CI)</td>
</tr>
<tr>
<td>No diabetes</td>
<td>2693</td>
<td>64</td>
<td>1.0 (Reference)</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First quartile HbA1c (&lt;6.41)</td>
<td>596</td>
<td>25</td>
<td>1.6 (1.0–2.5)</td>
</tr>
<tr>
<td>Second quartile HbA1c (6.41–7.20)</td>
<td>606</td>
<td>20</td>
<td>1.4 (0.9–2.4)</td>
</tr>
<tr>
<td>Third quartile HbA1c (7.21–8.20)</td>
<td>715</td>
<td>18</td>
<td>1.2 (0.7–2.0)</td>
</tr>
<tr>
<td>Fourth quartile HbA1c (≥8.21)</td>
<td>539</td>
<td>23</td>
<td>2.6 (1.5–4.3)</td>
</tr>
<tr>
<td>HbA1c, per unit increaseb</td>
<td>2456</td>
<td>86</td>
<td>1.1 (1.0–1.3)</td>
</tr>
</tbody>
</table>

Twenty-year mortality follow-up. CI denotes confidence interval.

We found that diabetic patients with reasonable glucose control, as indicated by their annual measurements of HbA1c, had much lower risk of fatal IHD compared with poorly controlled patients. Although many studies have shown that the glucose concentration at baseline is positively associated with future risk of cardiovascular events, few studies have assessed how risk may vary according to the level of HbA1c. One recent meta-analysis demonstrated that the association of glucose with cardiovascular risk may have an exponential shape and that the risk increase starts below the thresholds that are typically used for diagnosing IGT and diabetes.

Andersson and Svärdshult followed 411 newly diagnosed diabetic patients for more than 7 years with annual fasting glucose measurements and found that having glucose levels ≥7.8 mmol/L was associated with a 50% higher mortality compared with having glucose levels <7.8 mmol/L. In a recent meta-analysis of randomized controlled trials of type 1 and type 2 diabetes patients, it was concluded that in type 1 diabetes, strict glycaemic control was associated with a reduction in both macro- and microvascular complications, whereas in type 2 diabetes, good glycaemic control was associated with only a modest reduction in macrovascular complications.

We found that diabetic patients with reasonable glucose control, as indicated by their annual measurements of HbA1c, had much lower risk of fatal IHD compared with poorly controlled patients. Although many studies have shown that the glucose concentration at baseline is positively associated with future risk of cardiovascular events, few studies have assessed how risk may vary according to the level of HbA1c. One recent meta-analysis demonstrated that the association of glucose with cardiovascular risk may have an exponential shape and that the risk increase starts below the thresholds that are typically used for diagnosing IGT and diabetes.

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benefited most in relation to mortality. The DIGAMI 2 study, using a similar design, monitored HbA1c for a median of 2.1 years, but mortality did not clearly differ between the treatment groups, and HbA1c concentrations were also similar between the groups.

In the UKPD Study, HbA1c was measured annually during 10 years of follow-up in patients with newly diagnosed type 2 diabetes and showed a reduction in microvascular complications associated with a reduction in blood glucose; however, no reduction in macrovascular complications was observed. During 17 years of follow-up of the DCCT/EDIC Study of patients with type 1 diabetes, the group that received intensive treatment had substantially lower risk of cardiovascular events compared with patients who received conventional treatment.

The present study is one of a few that has monitored HbA1c over a long period of time. Our finding that IHD mortality is higher in poorly controlled diabetes patients indirectly supports that good glucometabolic regulation reduces the risk of macrovascular events in patients with type 2 diabetes. Adverse effects of diabetes in relation to development of atherosclerosis have been attributed to several factors including disturbed lipid metabolism, impaired endothelial function, increased platelet, and coagulation activity. Interestingly, the duration of diabetes is more strongly linked to IHD than to other diseases of the cardiovascular system and the coronary artery circulation may be more vulnerable to the accelerated atherothrombotic process induced by these abnormalities than other parts of the circulatory system.

In our study, the newly diagnosed diabetes patients were identified within a population survey, and the comparison group was recruited from the same population, matched to the patients by gender, age, and place of residence. The number of patients of the study is moderate, but annual measurements of HbA1/HbA1c were made for a median of 8 years. Another strength of this study is that only patients who were diagnosed with diabetes as part of a large baseline population survey were included. Diabetes patients in our study were all diagnosed after the age of 40 years, and therefore assumed to have diabetes type 2. Due to the long follow-up period, the standard methods to measure HbA1/HbA1c have changed over time, and the values from different assays had to be recalculated into comparable units. The methods that we used have been shown to be reliable, but we cannot exclude a possible misclassification of patients according to category of glucose control, and it is a weakness that we do not have updated data on treatment throughout the follow-up period.

In this 20-year mortality follow-up of patients with newly diagnosed diabetes, we found that patients with poor glucometabolic control, as indicated by repeated HbA1c measurements, had four times higher risk of dying from IHD compared with a matched group without diabetes. Among patients whose glucose was reasonably well controlled, the risk was only slightly higher. This finding is compatible with the hypothesis that good glucose control reduces the risk of coronary complications in patients with diabetes.

Contributors
A.C.D. and R.W. conceived the idea analysed the data and wrote the paper. L.J.V. and T.I.N. analysed the data, interpreted the findings, and wrote the paper. K.M. was responsible for the original planning and collection of data in the diabetes study and contributed to the writing of the paper. R.W. is guarantor of this study.

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Conflict of interest: none declared.

References


