Glycaemic control, disease duration and beta-cell function in patients with Type 2 diabetes in a Swedish community. Skaraborg Hypertension and Diabetes Project.

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Introduction
Type 2 diabetes mellitus is usually preceded by a long period of asymptomatic hyperinsulinaemia consequent to insulin resistance [1,2], a condition characterized by a cluster of risk factors [3]. Eventually, the pancreatic β-cell fails to compensate for the insulin resistance, a state referred to as impaired fasting glycaemia (IFG) or impaired glucose tolerance (IGT). Finally, Type 2 diabetes becomes overt [4]. In some cases Type 2 diabetes exclusively evolves as β-cell insufficiency [5]. The UKPDS and the Belfast Diet Study showed that Type 2 diabetes by time is accompanied by increasing hyperglycaemia explained by progressive β-cell deterioration [6,7]. In the light of these recent reports we decided to analyse data from a cross-sectional community-based survey, including the vast majority of subjects with

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Abstract
Aims To examine determinants for glycaemic control in primary care patients with Type 2 diabetes.
Methods In a community-based surveillance of primary care patients with Type 2 diabetes, 190 men and 186 women were consecutively identified and examined for cardiovascular risk factors. Insulin resistance and β-cell function were estimated using homeostasis model assessment (HOMA). Good glycaemic control was defined as HbA1c < 6.5%.
Results Following adjustment for age and gender, HbA1c ≥ 6.5% was associated with duration of diabetes (10.6 vs. 6.4 years, \( P < 0.001 \)), lower levels of serum insulin (6.3 vs. 8.0 mU/l, \( P = 0.012 \)), higher serum triglyceride levels (2.0 vs. 1.7 mmol/l, \( P = 0.002 \)) and impairment of β-cell function (HOMA index 19.5 vs. 45.8, \( P < 0.001 \)). The association between HbA1c levels and duration remained with adjustment for age, gender, waist-hip ratio (WHR) and serum triglycerides (odds ratio (OR) for HbA1c ≥ 6.5% by 5 years diabetes duration = 1.7; 95% confidence interval (CI) 1.4–2.1) but was lost following additional adjustment for β-cell function (OR for HbA1c ≥ 6.5% = 1.3; 95% CI 0.96–1.7). In a separate linear regression with β-cell function as the dependent variable there was a significant association with HbA1c after adjustments for differences in age, gender, WHR, serum triglyceride levels and diabetes duration (\( P < 0.001 \)).
Conclusions Increasing HbA1c by time was associated with declining β-cell function.

Keywords primary care, serum insulin, glucose toxicity
Type 2 diabetes in the area, aiming to examine determinants for glycaemic control.

Patients and methods

Skara Hypertension and Diabetes Project

Since the 1970s, structured treatment and education programmes for patients with hypertension and Type 2 diabetes, respectively, have been organized at the Health Care Centre in the city of Skara and annual check-ups of these patients have been performed [8–12]. Information has been registered according to structured protocols. In 1986 the hypertension and diabetes outpatient clinics in Skara merged, forming a joint clinic with nurses educated on both diseases, supervised by the family physician.

Subjects

Skara Health Care Centre is the only available primary health care facility in the community and serves a total population of about 19 000 residents. Patients with Type 2 diabetes who completed an annual check-up at the hypertension and diabetes outpatient clinic in Skara from June 1992 through September 1993 were eligible for the present study. The study enrolled 433 patients with diabetes mellitus. After exclusion of 33 patients with Type 1 diabetes and 24 subjects with missing analyses of HbA1c, 376 patients with Type 2 diabetes (190 men and 186 women) remained for further analyses.

Methods

Nurses at the hypertension and diabetes outpatient clinic who were specially trained for this task performed the study visit. The procedure has been described in detail previously [8]. The structured protocol for follow-up of these patients included information on the date when a patient was first diagnosed with diabetes mellitus, smoking habits, current alcohol consumption and physical exercise habits. A structured interview by the nurses dealt with medical history and current medications. The participants completed a detailed questionnaire about smoking habits, current alcohol consumption and physical exercise habits.

Diabetes duration was defined as time since diagnosis of Type 2 diabetes. Good glycaemic control was defined as HbA1c < 6.5% [15].

Insulin resistance and insulin secretion were assessed from fasting glucose and fasting insulin concentrations using the homeostasis model assessment (HOMA) [16,17]. The HOMA model is not applicable to subjects treated with insulin, and 65 patients were excluded from the HOMA analysis for this reason. Due to skewed distributions, HOMA IR, HOMA BC, serum insulin and serum triglycerides were log transformed in analyses and re-transformed for tabulations. Differences in means were assessed by analysis of covariance (ANCOVA). Associations between categorical data were analysed by logistic regression and expressed as odds ratios (OR) with 95% confidence interval (95% CI). Associations between continuous variables were analysed by linear regression. The association between diabetes duration and HbA1c was explored by partial correlation controlling for differences in age and gender.

The study protocol was approved by the Research Ethics Committee of the Medical Faculty, Göteborg University.

Results

Mean HbA1c in men and women were 6.5% and 6.6%, respectively (P = 0.26). The observed range of diabetes duration was 1–18 years. Figure 1 illustrates the association between HbA1c and diabetes duration. The association between diabetes duration and HbA1c was significant (P < 0.001) when adjusted for age and gender.

Characteristics of the 376 study subjects with Type 2 diabetes (190 men, 186 women) with respect to glycaemic control are shown in Table 1. When stratified for genders a similar pattern in both genders was found. Thus we considered it justified to analyse both genders together and adjust for gender differences. Subjects with poor glycaemic control had longer disease duration, lower β-cell function, lower levels of serum insulin, higher levels of serum triglycerides but lower systolic and diastolic blood pressure than subjects with good glycaemic control. β-cell function (HOMA index) was associated with HbA1c (P < 0.001) (Fig. 2). The vast majority of patients with HbA1c ≥ 6.5% were in the lower range of β-cell function, thus illustrating the association between β-cell function and glycaemic control.

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The association between poor glycaemic control and diabetes duration was challenged by adjustments for age, gender, WHR and triglyceride levels (Table 2). Disease duration remained a significant determinant of poor glycaemic control. However, when β-cell function was accounted for, this association was lost.

In a separate linear regression with impaired β-cell function as the dependent variable, there was a significant association with HbA1c (P < 0.001) after adjustments for differences in age and gender. After further adjustment for WHR, serum triglyceride levels and diabetes duration, the associations between HbA1c and impaired β-cell function remained. These results were confirmed in a subanalysis of subjects (n = 168) having a diabetes duration ≤ 6 years.

### Discussion

The main finding in this population-based study, involving virtually all subjects in the population diagnosed with Type 2 diabetes at that time, was a successive increase in HbA1c by time associated with a corresponding decline in β-cell function. However, there were no associations between glycaemic control and age, markers for insulin resistance or obesity. Accordingly, it seems reasonable to conclude that the increasing hyperglycaemia was consequent to deterioration of β-cell function [18]. An additional explanation could be glucose toxicity, i.e. down-regulation of β-cell function by chronic hyperglycaemia [19].

In Type 2 diabetes the risk of macrovascular disease is already increased when blood glucose exceeds 5.4 mmol/l [20]; indeed, with HbA1c (P < 0.001) after adjustments for differences in age and gender. After further adjustment for WHR, serum triglyceride levels and diabetes duration, the associations between HbA1c and impaired β-cell function remained. These results were confirmed in a subanalysis of subjects (n = 168) having a diabetes duration ≤ 6 years.

### Table 1

Characteristics of subjects with Type 2 diabetes mellitus with respect to glycaemic control

<table>
<thead>
<tr>
<th>Variables</th>
<th>HbA1c &lt; 6.5% (n = 196)*</th>
<th>HbA1c ≥ 6.5% (n = 180)†</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69.6 (10.4)</td>
<td>70.9 (9.8)</td>
<td>0.202</td>
</tr>
<tr>
<td>Duration of Type 2 diabetes (years)</td>
<td>6.4 (5.8)</td>
<td>10.6 (6.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Fasting blood glucose (mmol/l)</td>
<td>7.3 (1.4)</td>
<td>10.3 (2.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Fasting serum insulin (mU/l)‡</td>
<td>8.0 (1.9)</td>
<td>6.3 (2.8)</td>
<td>0.012</td>
</tr>
<tr>
<td>HOMA β‡§</td>
<td>45.8 (2.1)</td>
<td>19.5 (1.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HOMA IR‡¶</td>
<td>2.5 (2.0)</td>
<td>2.8 (2.8)</td>
<td>0.295</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.0 (4.4)</td>
<td>28.3 (4.8)</td>
<td>0.377</td>
</tr>
<tr>
<td>Waist–hip ratio</td>
<td>0.92 (0.09)</td>
<td>0.93 (0.09)</td>
<td>0.168</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.8 (1.2)</td>
<td>6.0 (1.1)</td>
<td>0.122</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)‡</td>
<td>1.7 (0.9)</td>
<td>2.0 (1.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>162 (19.9)</td>
<td>157 (23.3)</td>
<td>0.011</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>85 (9.4)</td>
<td>83 (9.6)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

All analyses adjusted for age and gender with ANCOVA. *One hundred and two men (52%) and 94 women (48%). †Eighty-eight men (49%) and 92 women (51%). ‡Geometric mean. §β-cell function estimated by the homeostasis model assessment. ¶Insulin resistance estimated by the homeostasis model assessment.

### Table 2

Association between duration of Type 2 diabetes mellitus and glycaemic control with different sets of covariates

<table>
<thead>
<tr>
<th>Duration and different sets of co-variates</th>
<th>OR for HbA1c ≥ 6.5%</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 years duration of Type 2 DM</td>
<td>1.7</td>
<td>1.4–2.0</td>
</tr>
<tr>
<td>Adjusted for age, gender</td>
<td>1.7</td>
<td>1.4–2.1</td>
</tr>
<tr>
<td>Adjusted for age, gender, WHR</td>
<td>1.7</td>
<td>1.4–2.1</td>
</tr>
<tr>
<td>Adjusted for age, gender, WHR, triglycerides</td>
<td>1.7</td>
<td>1.4–2.1</td>
</tr>
<tr>
<td>Adjusted for age, gender, WHR, triglycerides, HOMA β*</td>
<td>1.3</td>
<td>0.96–1.7</td>
</tr>
</tbody>
</table>

OR for HbA1c ≥ 6.5% corresponding to 5 years duration of diabetes Type 2 analysed with logistic regression. WHR, Waist–hip ratio. *β-cell function estimated by the homeostasis model assessment.
Type 2 diabetes often exists subclinically before being diagnosed. Thus, our definition of diabetes duration equating time from diagnosis is an approximation that confers some misclassification. However, associations found should rather be underestimates of the true relations than false-positive findings.

The current antidiabetic treatment in the study population has been described before [21]; the most frequent treatments being dietary recommendations (42%) and treatment with sulphonylurea (31%). The most frequently used anti-hypertensive drugs were β-blockers and diuretics.

The relation between blood pressure and glycaemic control in subjects treated for Type 2 diabetes [22]. Our data are supported by a recent study reporting that obesity was not associated with poor glycaemic control, but one should keep in mind that this study was conducted on a population that had already developed Type 2 diabetes. Patients with Type 2 diabetes but without hypertension seem to constitute a subgroup of Type 2 diabetes with predominantly impaired β-cell function and worse glycaemic control than hypertensive patients with Type 2 diabetes who were characterized by risk factors resembling the insulin resistance syndrome [21]. Probably, β-cell deterioration is a stronger determinant for poor glucose control than insulin resistance, which, on the other hand, is a stronger determinant for increased blood pressure.

Markers for insulin resistance such as hypertension, elevated insulin, HOMA IR and obesity were not associated with poor glycaemic control, but one should keep in mind that this study was conducted on a population that had already developed Type 2 diabetes. Our data are supported by a recent study reporting that obesity was not associated with poor glycaemic control in subjects treated for Type 2 diabetes [22].

Insulin resistance [1–3] and obesity [23–25] are important in the development of Type 2 diabetes and impaired glucose tolerance [26,27]. In Type 2 diabetes, these factors do not seem to be associated with poor glycaemic control, at least not in a population of Type 2 diabetes treated in primary care. The steady decline in β-cell function associated with poor glycaemic control seems inevitable [18] and has been demonstrated particularly in the UKPDS and the Belfast Diet Study [6,7].

This is an observational study and not a clinical trial, and thus other explanations cannot be excluded. However, our results are consistent with the findings in UKPDS and valid in an ethnically homogeneous primary care population that involved the vast majority of people with Type 2 diabetes in a geographically defined area.

Acknowledgements

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