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

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 forms. In 1986 the hypertension and diabetes out-patient 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 out-patient 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 out-patient 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. Blood specimens were drawn in the morning after a 10-h overnight fast. Routine tests, including fasting blood glucose and HbA1c were measured by ion exchange chromatography HPLC Mono S [13], normal range: 3.7–5.5%. Serum samples for women remained for further analyses.

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 means with 95% CI 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.

Figure 1 Association between HbA1c and diabetes duration in 190 men and 186 women with Type 2 diabetes. The association between diabetes duration and HbA1c was significant (P < 0.001) when adjusted for age and gender.

Data are means ±95% confidence interval.
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,
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 blood pressure control [5].

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 support are by a recent study reporting that obesity was not associated with poor glycaemic control [23].

Insulin resistance [1–3] and obesity [23–25] are important in the development of Type 2 diabetes and impaired glucose tolerance [26,27]. However, insulin resistance seems to affect cardiovascular risk factors more strongly than other metabolic abnormalities. Insulin resistance may play a role in the development of Type 2 diabetes [28].

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.

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