



LUND UNIVERSITY

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

Östgren, Carl Johan; Lindblad, Ulf; Ranstam, Jonas; Melander, Arne; Råstam, Lennart

Published in:
Diabetic Medicine

DOI:
[10.1046/j.1464-5491.2002.00661.x](https://doi.org/10.1046/j.1464-5491.2002.00661.x)

2002

[Link to publication](#)

Citation for published version (APA):

Östgren, C. J., Lindblad, U., Ranstam, J., Melander, A., & Råstam, L. (2002). Glycaemic control, disease duration and beta-cell function in patients with Type 2 diabetes in a Swedish community. Skaraborg Hypertension and Diabetes Project. *Diabetic Medicine*, 19(2), 125-129. <https://doi.org/10.1046/j.1464-5491.2002.00661.x>

Total number of authors:
5

General rights

Unless other specific re-use rights are stated the following general rights apply:
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

Read more about Creative commons licenses: <https://creativecommons.org/licenses/>

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

LUND UNIVERSITY

PO Box 117
221 00 Lund
+46 46-222 00 00

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

C. J. Östgren*†, U. Lindblad*‡, J. Ranstam§, A. Melander*¶ and L. Råstam*††

*Department of Community Medicine, Malmö University Hospital, Malmö,
†Ödeshög Health Care Centre, Ödeshög,
‡Skaraborg Institute, Skövde,
§Malmö University, Malmö,
¶The NEPI Foundation, Malmö and Stockholm, and
††National Public Health Institute, Stockholm, Sweden

Accepted 25 August 2001

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 $HbA_{1c} < 6.5\%$.

Results Following adjustment for age and gender, $HbA_{1c} \geq 6.5\%$ 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 HbA_{1c} levels and duration remained with adjustment for age, gender, waist-hip ratio (WHR) and serum triglycerides (odds ratio (OR) for $HbA_{1c} \geq 6.5\%$ 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 $HbA_{1c} \geq 6.5\%$ = 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 HbA_{1c} after adjustments for differences in age, gender, WHR, serum triglyceride levels and diabetes duration ($P < 0.001$).

Conclusions Increasing HbA_{1c} by time was associated with declining β -cell function.

Diabet. Med. 19, 125–129 (2002)

Keywords primary care, serum insulin, glucose toxicity

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

Correspondence to: Ulf Lindblad MD, PhD, Department of Community Medicine, Malmö University Hospital, S-205 02 Malmö, Sweden. E-mail: Ulf.lindblad@smi.mas.lu.se

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 HbA_{1c}, 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 HbA_{1c}, were analysed at the central hospital laboratory in the county (Kärnsjukhuset, Skövde, Sweden). HbA_{1c} was measured by ion exchange chromatography HPLC Mono S [13], normal range: 3.7–5.5%. Serum samples for other tests were immediately frozen at –80°C and later analysed for lipids (Lipids Laboratory, Lund University Hospital, Sweden), and insulin using a radioimmunoassay with < 0.3% cross-reactivity for proinsulin [14] (kit from Pharmacia, Uppsala, Sweden; tests performed at the Wallenberg Laboratory, Malmö University Hospital, Sweden). Height (to the nearest cm) and weight (to the nearest 0.1 kg) were measured in light indoor clothes and no shoes. Body mass index (BMI) was calculated by the formula weight/height² (kg/m²) and waist-hip ratio (WHR) by the formula waist circumference (cm)/hip circumference (cm).

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 HbA_{1c} < 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} means with 95% CI and diabetes duration. The association between diabetes duration and HbA_{1c} 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 HbA_{1c} ($P < 0.001$) (Fig. 2). The vast majority of patients with HbA_{1c} $\geq 6.5\%$ were in the lower range of β -cell function, thus illustrating the association between β -cell function and glycaemic control.

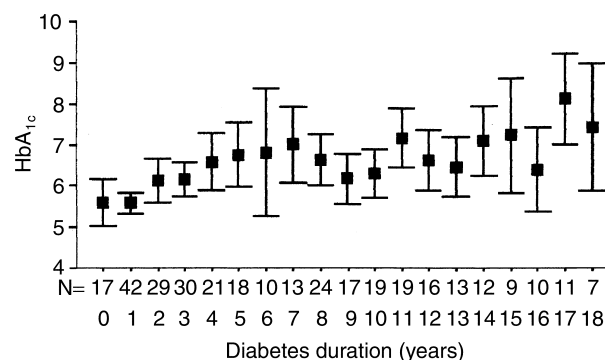


Figure 1 Association between HbA_{1c} and diabetes duration in 190 men and 186 women with Type 2 diabetes. The association between diabetes duration and HbA_{1c} was significant ($P < 0.001$) when adjusted for age and gender. Data are means \pm 95% confidence interval.

Table 1 Characteristics of subjects with Type 2 diabetes mellitus with respect to glycaemic control

Variables	HbA _{1c} < 6.5% (n = 196)*		HbA _{1c} ≥ 6.5% (n = 180)†		P
	Mean	(SD)	Mean	(SD)	
Age (years)	69.6	(10.4)	70.9	(9.8)	0.202
Duration of Type 2 diabetes (years)	6.4	(5.8)	10.6	(6.9)	< 0.001
Fasting blood glucose (mmol/l)	7.3	(1.4)	10.3	(2.6)	< 0.001
Fasting serum insulin (mU/l)‡	8.0	(1.9)	6.3	(2.8)	0.012
HOMA β‡§	45.8	(2.1)	19.5	(3.2)	< 0.001
HOMA IR‡¶	2.5	(2.0)	2.8	(2.8)	0.295
Body mass index (kg/m ²)	28.0	(4.4)	28.3	(4.8)	0.377
Waist–hip ratio	0.92	(0.08)	0.93	(0.09)	0.168
Total cholesterol (mmol/l)	5.8	(1.2)	6.0	(1.1)	0.122
Triglycerides (mmol/l)‡	1.7	(0.9)	2.0	(1.3)	0.002
Systolic blood pressure (mmHg)	162	(19.9)	157	(23.3)	0.011
Diastolic blood pressure (mmHg)	85	(9.4)	83	(9.6)	0.013

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.

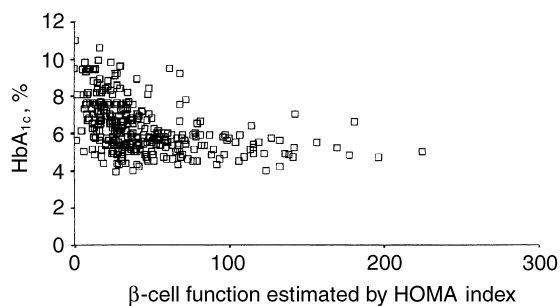


Figure 2 HbA_{1c} as a function of β-cell function estimated by the homeostasis model assessment index (HOMA) in 166 men and 153 women with Type 2 diabetes.

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 HbA_{1c} ($P < 0.001$) after adjustments for differences in age and gender. After further adjustment for WHR, serum triglyceride levels and diabetes duration, the associations between HbA_{1c} 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 HbA_{1c} 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,

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

Duration and different sets of co-variates	OR for HbA _{1c} ≥ 6.5%	95% confidence interval
5 years duration of Type 2 DM	1.7	1.4–2.0
Adjusted for age, gender	1.7	1.4–2.1
Adjusted for age, gender, WHR	1.7	1.4–2.1
Adjusted for age, gender, WHR, triglycerides	1.7	1.4–2.1
Adjusted for age, gender, WHR, triglycerides, HOMA β*	1.3	0.96–1.7

OR for HbA_{1c} ≥ 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 equalling 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 this population has been described before. Patients with Type 2 diabetes but without hypertension seem to constitute a subgroup of Type 2 diabetes with predominately 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], but once diabetes is established, these factors do not seem to be associated with 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

This study was supported by grants from the Swedish Heart Lung Foundation, the Swedish Medical Research Council, the National Public Health Institute, the Skaraborg Institute and Skaraborg County Council, the NEPI Foundation (The Swedish Network for Pharmacoepidemiology), and the Faculty of Medicine, Lund University.

References

- Lillioja S, Mott DM, Spraul M, Ferraro R, Foley JE, Ravussin E *et al.* Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus. Prospective studies of Pima Indians. *N Engl J Med* 1993; **329**: 1988–1992.
- Martin B, Warram J, Krolewski A, Bergman R, Soeldner S, Kahn R. Role of glucose and insulin resistance in development of type 2 diabetes mellitus: results of a 25-year follow-up study. *Lancet* 1992; **340**: 925–929.
- Reaven GM. Role of insulin resistance in human disease. Banting Lecture 1988. *Diabetes* 1988; **37**: 1595–1607.
- Watanabe RM, Laws A, Rewers M, Bergman R. Impaired glucose tolerant subjects exhibit a beta-cell defect despite normal fasting glycemia. *Diabetes* 1995; **44**: 5A.
- Tuomi T, Carlsson A, Li H, Isomaa B, Miettinen A, Nilsson A *et al.* Clinical and genetic characteristics of type 2 diabetes with and without GAD antibodies. *Diabetes* 1999; **48**: 150–157.
- UK Prospective Diabetes Study (UKPDS) Group. U.K. Prospective Diabetes Study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. *Diabetes* 1995; **44**: 1249–1258.
- Levy J, Atkinson AB, Bell PM, McCance DR, Hadden DR. Beta-cell deterioration determines the onset and rate of progression of secondary dietary failure in type 2 diabetes mellitus: the 10-year follow-up of the Belfast Diet Study. *Diabet Med* 1998; **15**: 290–296.
- Bøg-Hansen E, Lindblad U, Bengtsson K, Ranstam J, Melander A, Råstam L. Risk factor clustering in patients with hypertension and NIDDM. *J Int Med* 1998; **243**: 223–232.
- Berglund G, Isacson S-O, Rydén L. The Skaraborg Project—a controlled trial regarding the effect of structured hypertension care. *Acta Med Scand* 1979; **205**: 64–68.
- Råstam L, Berglund G, Isacson S-O, Rydén L. The Skaraborg Hypertension Project 3. Influence on blood pressure of a medical care program for hypertension. *Acta Med Scand* 1986; **219**: 261–269.
- Lindblad U, Råstam L, Rydén L, Ranstam J, Berglund G, Isacson S-O. Reduced stroke incidence with structured hypertension care: The Skaraborg Hypertension Project. *J Hypertension* 1990; **8**: 1147–1153.
- Lindblad U, Råstam L, Rydén L, Ranstam J, Isacson S-O, Berglund G. Control of blood pressure and risk of myocardial infarction: Skaraborg Hypertension Project. *BMJ* 1994; **308**: 681–686.
- Eckerbom S, Bergqvist Y, Jeppson JO. Improved method for analysis of glycated haemoglobin by ion exchange chromatography. *Ann Clin Biochem* 1994; **31**: 355–360.
- Andersen L, Dinesen B, Jørgensen PN, Poulsen F, Røder ME. Enzyme immunoassay for intact human insulin in serum or plasma. *Clin Chem* 1993; **38**: 578–582.
- European Diabetes Policy Group 1999. A desktop guide to Type 2 diabetes mellitus. *Diabet Med* 1999; **16**: 716–730.
- Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β -cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; **28**: 412–419.
- Haffner S, Miettinen H, Stern M. The homeostasis model in the San Antonio Heart Study. *Diabetes Care* 1997; **20**: 1087–1092.
- Kahn SE. The importance of the beta-cell in the pathogenesis of type 2 diabetes mellitus (1). *Am J Med* 2000; **17** (Suppl. 1): 2–8.
- Yki-Järvinen H. Glucose toxicity. *Endocr Rev* 1992; **13**: 415–431.
- Fuller JH, Shipley MJ, Rose G, Jarrett RJ, Keen H. Coronary-heart-disease risk and impaired glucose tolerance. The Whitehall study. *Lancet* 1980; **1**: 1374–1376.
- Östgren CJ, Lindblad U, Bøg-Hansen E, Ranstam J, Melander A, Råstam L. Differences in treatment and metabolic abnormalities between normo- and hypertensive patients with type 2 diabetes. *Diabetes Obes Metab* 1999; **1**: 105–112.
- Bruno G, Cavallo-Perin P, Bargerò G, Borra M, D'Errico N, Pagano G. Glycemic control and cardiovascular risk factors in type 2 diabetes: a population-based study. *Diabet Med* 1998; **15**: 304–307.
- Pi-Sunyer X. Weight and non-insulin-dependent diabetes mellitus. *Am J Clin Nutr* 1996; **63**: 426S–429S.

- 24 Wannamethee G, Shaper G. Weight change and duration of overweight and obesity in the incidence of type 2 diabetes. *Diabetes Care* 1999; **22**: 1266–1272.
- 25 Colditz G, Willett W, Rotnitzky A, Manson J. Weight gain as a risk factor for clinical diabetes mellitus in women. *Ann Intern Med* 1995; **122**: 481–487.
- 26 Fujimoto WY. The importance of insulin resistance in the pathogenesis of type 2 diabetes mellitus. *Am J Med* 2000; **17** (Suppl. 1): 9–14.
- 27 Haffner S, Miettinen H, Gaskill SP, Stern MP. Decreased insulin action and insulin secretion predict the development of impaired glucose tolerance. *Diabetologia* 1996; **39**: 1201–1207.