

Islet secretory capacity determines glucose homoeostasis in the face of insulin resistance

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Summary

Background: Debate surrounds the relative importance of impaired β -cell secretory function versus insulin resistance in type 2 diabetes. We therefore defined insulin secretion and sensitivity in patients with impaired glucose homoeostasis of varying aetiology and duration.

Methods: 126 consecutive patients undergoing an oral glucose tolerance test (OGTT) between 1999 and 2003 were included. Whole-body insulin sensitivity index (ISI) and insulinogenic index derived from the OGTT were determined in 32 healthy controls, 65 type 2 diabetic patients, 15 patients with acromegaly, 10 patients with insulinoma, and 4 patients with HAIRAN syndrome.

Results: Median ISI (quartiles Q_{25} – Q_{75}) of healthy controls and of patients with insulinoma were similar (3.5 [2.8–5.6] and 3.2 [1.7–4.2] respectively) but significantly decreased in patients with acromegaly, type 2 diabetes, and HAIRAN syndrome (2.8 [1.8–3.3], 1.9 [1.4–3], and 0.8 [0.6–1.3] respectively). Despite the decrease in ISI, patients with HAIRAN syndrome and acromegaly

maintained normal glucose tolerance by adapting insulin secretion as reflected in the insulinogenic index (106.5 [90.4–127.5] and 49 [24.4–89] in HAIRAN and acromegaly respectively, versus 46.9 [27.3–66.7] in controls). In contrast, type 2 diabetic patients failed to adapt and displayed severely hampered insulin secretion (insulinogenic index of 7.6 [3.8–14.7]). Furthermore, the level of the insulinogenic index correlated significantly with duration of diabetes and HbA_{1c} , which was not the case for the ISI. Insulinoma patients had a decreased insulinogenic index (38.7 [32–83.8]), leading to impaired glucose tolerance despite normal ISI.

Conclusions: The data are compatible with the notion that β -cell function rather than insulin sensitivity determines the evolution of hyperglycaemia.

Key words: diabetes; insulinoma; acromegaly; insulin resistance; insulin secretion

Introduction

Patients with type 2 diabetes usually exhibit both decreased insulin sensitivity and impaired insulin secretion [1, 2]. However, there is debate as to the relative importance of impaired β -cell secretory function versus insulin resistance in the onset and progression of diabetes [3]. In the past, a predominant role has been assigned to insulin resistance in the pathogenesis of impaired glucose homoeostasis, but recently the role of impaired β -cell function in the pathogenesis of type 2 diabetes has aroused fresh interest now that a significant reduction in β -cell mass has been established [4, 5].

The aim of this study was to obtain further insight into the relative contribution of impaired insulin secretion in the development of type 2 di-

abetes. We therefore compared the islet secretory capacity of type 2 diabetic patients with different groups of patients exhibiting various degrees of insulin resistance. Included were patients with the HAIRAN syndrome (triad of hyperandrogenaemia, insulin resistance, and acanthosis nigricans), acromegaly and insulinoma. Patients with the HAIRAN syndrome exhibit genetically determined pronounced insulin resistance of the target tissue [6], whereas patients with acromegaly exhibit acquired decreased insulin sensitivity due to growth hormone excess [7]. The pathology in patients with insulinoma is localised in the pancreas but secondary insulin resistance has been described [8].

Patients and methods

Patients

All Caucasian patients undergoing an oral glucose challenge test (OGTT) between 1999 and 2003 were included. Pregnant women were excluded from this study. The OGTT was performed in 32 healthy individuals, 65 patients with type 2 diabetes, 15 patients with acromegaly, 10 patients with insulinoma, and 4 patients with HAIRAN syndrome. All medication was stopped 12 hours before the OGTT.

Diagnosis of diabetes was based on ADA criteria. Only type 2 diabetic patients treated by diet or oral antidiabetic drugs were included. Patients treated by insulin or glitazones and with known liver or kidney disease were excluded. Subjects treated by sulfonylureas were switched to repaglinide at least five days before the test. Diagnosis of acromegaly was based on clinical findings, elevated age-adjusted serum IGF-I concentrations, and/or sustained elevation of serum GH levels above 1 ng/ml during the OGTT. One patient with acromegaly and diabetes mellitus treated by insulin was excluded. Diagnosis of a GH-secreting pituitary tumour was histologically confirmed in all patients. Diagnosis of HAIRAN syndrome was based on clinical findings including the presence of acanthosis nigricans and hirsutism as well as demonstration of hyperandrogenaemia. Diagnosis of insulinoma was based on the demonstration of endogenous hyperinsulinaemic hypoglycaemia and was histologically confirmed in all patients. Two patients with glucose-sensitive insulinoma and two with islet cell hyperplasia were excluded from the study [9]. Due to unspecific autonomous symptoms most of the healthy individuals were hospitalised for a prolonged fast to rule out a hypoglycaemic disorder. The 72-hour fast was negative in all subjects, with adequate suppression of insulin secretion. The OGTT was performed in these subjects (and patients with insulinoma) at the beginning of the fast to exclude reactive hypoglycaemia; blood samples were collected over 300 minutes. None of the subjects included as controls exhibited evidence of a hypoglycaemic disorder during the evaluation; patients with confirmed reactive hypoglycaemia were excluded.

Oral glucose tolerance test

A standard OGTT was performed with a 75-g glucose load after an overnight fast. In the morning, an intravenous catheter was inserted into an antecubital vein. Blood samples were obtained at baseline (mean of two samples) and 30, 60, 90, and 120 min after the glucose load. The subjects spent 2 hours in a semirecumbent posture. Plasma or serum was immediately separated for analysis of glucose and insulin.

Insulin sensitivity and β -cell function indices

Whole body insulin sensitivity index (ISI) was calculated by the method of Matsuda and DeFronzo using the 75-g OGTT values as follows [10]:

Whole body ISI = $10'000/\text{square root of } [(\text{mean plasma insulin} \times \text{mean plasma glucose during OGTT}) \times (\text{fasting plasma glucose} \times \text{fasting plasma insulin})]$.

The insulinogenic index was defined as the ratio of the increment of plasma insulin to that of plasma glucose at 30 min after the glucose load [11, 12].

Laboratory measurements

Venous blood samples were drawn into sodium fluoride-containing tubes for determination of plasma glucose. Plasma glucose was measured by the glucose oxidase technique (Beckman Analyzer; Beckman, Fullerton, CA, USA). Insulin was measured in serum samples by solid-phase radioimmunoassay (CIS Bio international, Oris Industries, Gif-Sur-Yvette, France) with a cross-reactivity of 14% for proinsulin and 0.1% for C-peptide; normal overnight fasting range provided by the manufacturer was 30 to 138 pmol/L; lower limit of detection 14 pmol/L. HbA_{1c} was measured by DCA 2000 (Bayer Diagnostics, Zurich, Switzerland).

Statistics

The statistical difference between the groups of patients was evaluated by Mann-Whitney U-test, $p < 0.05$ was considered significant. In patients with type 2 diabetes, correlation of age, BMI, diabetes duration, and HbA_{1c} with whole-body ISI and insulinogenic index was done by Spearman Rank Correlation, these results being considered significant at $p < 0.0125$ ($p < 0.05$ with a Bonferroni correction for 4 comparisons with control).

Results

Demographic characteristics and the results of the OGTT are shown in Table 1. The median age (quartiles Q₂₅–Q₇₅) of patients with type 2 diabetes was 62 (51–67) years, BMI was 29 (26–32) kg/m², duration of diabetes 5 (2–10) years, and HbA_{1c} 7.3 (6.8–8) %. Patients with type 2 diabetes and acromegaly were significantly older than healthy individuals. Patients with diabetes, acromegaly and insulinoma were overweight and patients with HAIRAN syndrome obese. In the 32 healthy individuals, fasting and 2 h plasma glucose concentrations during the OGTT were 4.6 (4.4–5) and 5.6 (4.5–7) mmol/L respectively. In the 65 patients with type 2 diabetes the fasting plasma glucose concentration was 8.0 (6.5–9.9) mmol/L; in eight of them it was normal (i.e. < 5.6 mmol/L), in ten

impaired (i.e. 5.6 to 6.9 mmol/L), and in 47 above 6.9 mmol/L. The median 2 h plasma glucose concentration in type 2 diabetic patients was 15.5 (12.8–18) mmol/L; two patients had normal glucose tolerance (i.e. < 7.8 mmol/L), one had impaired glucose tolerance (7.8 to 11.0 mmol/L) and 62 patients a 2 h plasma glucose concentration above 11.0 mmol/L. In acromegalic patients the fasting plasma glucose concentration was 5.7 (5.5–6); in five of 15 patients it was normal and in ten impaired. The median 2 h plasma glucose concentration in patients with acromegaly was 6.6 (4.6–7.8) mmol/L; 11 patients had normal and four impaired glucose tolerance. In patients with insulinoma the fasting and 2 h plasma glucose concentrations were 3.7 (3.1–4.7) and 8.4 (7.8–9.3)

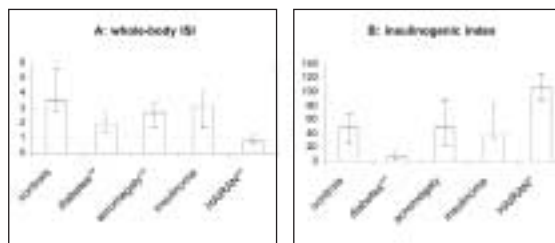
Table 1

Demographic characteristics of patients and results of the OGTT. Demographic characteristics and data from the OGTT in 32 healthy controls, 65 type 2 diabetic patients, 15 patients with acromegaly, 10 insulinoma patients and 4 patients with HAIRAN syndrome. Data are shown as median and quartiles (Q_{25} – Q_{75}). PG = plasma glucose.

	Controls (n = 32)	Diabetes (n = 65)	Acromegaly (n = 15)	Insulinoma (n = 10)	HAIRAN (n = 4)
Female sex (%)	62	35	73	70	100
Age (yr)	37 (30–53)	62 (51–67)	47 (39–67)	62 (54–73)	26 (21–31)
BMI (kg/m ²)	22 (20–27)	29 (26–32)	28 (26–29)	27 (24–29)	35 (32–43)
0 min PG (mmol/L)	4.6 (4.4–5)	8.0 (6.5–9.9)	5.7 (5.5–6)	3.7 (3.1–4.7)	5.0 (4.8–5.5)
30 min PG (mmol/L)	7.7 (6.3–9.5)	13.6 (11–14.9)	9.4 (8.4–10.1)	7.2 (6.7–8.8)	9.2 (8.1–10.4)
60 min PG (mmol/L)	7.9 (6.8–8.9)	15.9 (13.7–18.8)	9.9 (7.8–11.3)	8.2 (5.4–9.6)	9.2 (8.9–9.8)
90 min PG (mmol/L)	6.6 (5.9–7.9)	16.5 (13.6–18.5)	8.6 (5.5–9.7)	7.7 (7.2–10.1)	7.8 (7.7–8.7)
120 min PG (mmol/L)	5.6 (4.5–7)	15.5 (12.8–18)	6.6 (4.6–7.8)	8.4 (7.8–9.3)	6.7 (6.4–7.6)
0 min insulin (pmol/L)	106 (63–140)	140 (106–176)	114 (104–170)	163 (144–214)	435 (258–618)
30 min insulin (pmol/L)	487 (293–629)	269 (178–367)	619 (329–968)	493 (370–766)	1657 (1419–1719)
60 min insulin (pmol/L)	448 (355–792)	330 (213–502)	667 (576–993)	377 (369–726)	1903 (1750–2207)
90 min insulin (pmol/L)	460 (280–651)	357 (255–683)	546 (337–688)	598 (391–668)	1650 (1331–1867)
120 min insulin (pmol/L)	273 (147–553)	283 (194–421)	295 (195–736)	409 (187–651)	1393 (688–2056)

Figure 1

Whole-body insulin sensitivity index and insulinogenic index. Whole-body insulin sensitivity index and insulinogenic index derived from the OGTT in 32 healthy controls, 65 type 2 diabetic patients, 15 patients with acromegaly, 10 insulinoma patients, and 4 patients with HAIRAN syndrome. Data are shown as median and quartiles (Q_{25} – Q_{75}), the indexes are compared with healthy controls. (* $p < 0.05$, ** $p < 0.005$).



mmol/L respectively. All 10 insulinoma patients had fasting plasma glucose concentrations below 5.6 mmol/L. Four insulinoma patients had normal glucose tolerance, five impaired glucose tolerance, and one a 2 h plasma glucose concentration above 11.0 mmol/L. In patients with HAIRAN syndrome, fasting and 2 h plasma glucose concentrations were 5.0 (4.8–5.5) and 6.7 (6.4–7.6) mmol/L respectively. 3 out of 4 patients had normal fasting and 2 h plasma glucose concentrations; and one

patient had impaired fasting glucose as well as impaired glucose tolerance. Fasting insulin levels were significantly higher in patients with diabetes (140 [106–176] pmol/L), insulinoma (163 [144–214] pmol/L), and HAIRAN syndrome (435 [258–618] pmol/L) compared with controls (106 [63–140] pmol/L). 30 and 60 min after the oral glucose intake absolute insulin concentrations were significantly lower in patients with type 2 diabetes than in healthy controls.

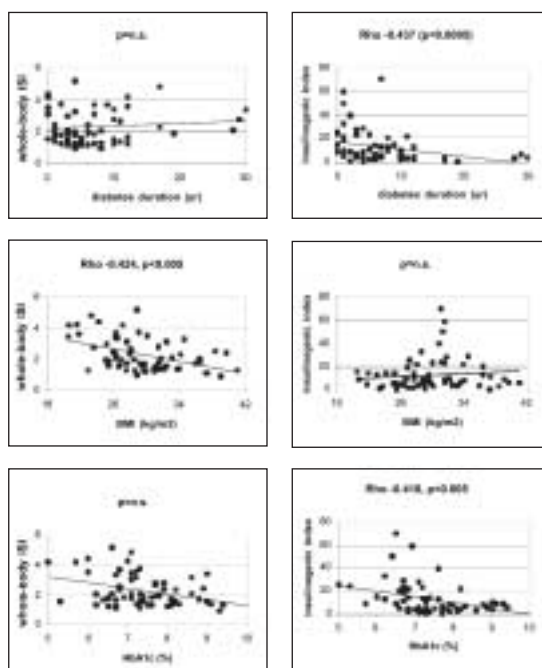
The whole-body insulin sensitivity indexes (ISI) and the insulinogenic indexes are shown in Figure 1. ISI were lower in patients with type 2 diabetes, acromegaly, and HAIRAN syndrome than in younger and leaner healthy individuals, indicating decreased insulin sensitivity in these groups of patients. Median ISI was 3.5 (2.8–5.6) in controls and significantly lower in patients with acromegaly (2.8 [1.8–3.3]; $p < 0.005$), type 2 diabetes (1.9 [1.4–3]; $p < 0.0005$), and HAIRAN syndrome (0.8 [0.6–1.3]; $p < 0.005$). The whole-body ISI in patients with insulinoma was 3.2 (1.7–4.2), not significantly lower than that of healthy controls.

The insulinogenic index as an assessment of β -cell secretory function was 46.9 (27.3–66.7) in healthy controls. A higher insulinogenic index of 106.5 (90.4–127.5, $p < 0.05$) was observed in patients with HAIRAN syndrome. The insulinogenic indexes in patients with acromegaly and insulinoma were 49.0 (24.4–89, ns) and 38.7 (32–83.8, ns) respectively. In contrast, the insulinogenic index of patients with type 2 diabetes was dramatically impaired (7.6 [3.8–14.7], $p < 0.0005$).

Within the group of type 2 diabetic patients no significant correlation was found between patients' age and whole-body ISI or insulinogenic index (not shown). The correlation of diabetes duration, BMI, and HbA_{1c} with both the whole-body ISI and the insulinogenic index is shown in Figure 2. The duration of diabetes did not correlate with whole-body ISI whereas there was a significant correlation between diabetes duration and the in-

Figure 2

Patients with type 2 diabetes. Spearman rank correlation for whole-body insulin sensitivity index (ISI) and insulinogenic index with duration of diabetes, BMI, and HbA_{1c} in 65 patients with type 2 diabetes.



sulinogenic index ($Rho -0.437$, $p < 0.0005$), indicating decreased insulin secretion in patients with a longer duration of diabetes. Higher BMI correlated significantly with lower whole-body ISI ($Rho -0.424$, $p < 0.005$), indicating decreased insulin sensitivity in obese patients. In contrast, BMI did not correlate with the insulinogenic index. HbA_{1c}

tended to correlate negatively with whole-body ISI ($Rho -0.275$, $p = 0.03$), indicating a trend towards lower insulin sensitivity in patients with increased HbA_{1c} . Finally, a significant negative correlation was found between HbA_{1c} and insulinogenic index ($Rho -0.418$, $p < 0.005$), indicating decreased insulin secretion in patients with increased HbA_{1c} .

Discussion

Our data illustrate the crucial role of impaired β -cell function in the pathogenesis of glucose intolerance. Analysing oral glucose tolerance tests from groups of patients with quite distinct underlying diseases, we found that despite higher fasting insulin levels in all groups of patients with decreased insulin sensitivity, insulin secretion during the OGTT was variable and determined the resultant glucose tolerance status. In patients with HAIRAN syndrome, for example, a marked decrease in insulin sensitivity was compensated by a marked increase in insulin secretion during the OGTT and normal glucose tolerance could be preserved. In contrast, the markedly decreased insulinogenic index in patients with type 2 diabetes was associated with impaired glucose homeostasis despite a less pronounced decrease in insulin sensitivity. On the same lines, absolute insulin levels at 30 and 60 minutes following the glucose intake were markedly lower in patients with type 2 diabetes when compared with healthy controls. Thus, absolute insulin deficiency during the OGTT in the presence of decreased insulin sensitivity characterised the impaired glucose tolerance status, whereas normal glucose tolerance could be preserved by increased (or preserved) insulin secretion.

In patients with type 2 diabetes, longer duration of diabetes and higher HbA_{1c} levels, but not age and BMI, correlated with decreased β -cell function. The decrease in insulin secretion with increasing diabetes duration is in line with the known decrease in β -cell mass in type 2 diabetes and could be the rationale for the correlation with higher HbA_{1c} levels and the observed progressive character of type 2 diabetes [5, 13]. As well as reflecting decreased insulin secretion, higher HbA_{1c} levels may also be responsible for the decreased secretory capacity of β -cells due to glucotoxicity. Whatever the relation of HbA_{1c} to β -cell function turns out to be, our data are in line with the concept of early insulin treatment in poorly controlled type 2 diabetic patients treated by oral antidiabetic drugs [14]. Insulin sensitivity indices did not correlate significantly with diabetes duration, HbA_{1c} or age. As expected, higher BMI values correlated with lower insulin sensitivity, confirming the well-recognised reduced insulin sensitivity in overweight patients. In contrast, the correlation between BMI and insulinogenic index was not signif-

icant, indicating absolute insulin deficiency during the OGTT not only in lean but also in obese type 2 diabetic patients. A limiting factor in our study was that patients and control subjects were not matched for age or BMI. However, neither age or BMI correlated significantly with insulinogenic index.

A previous study in acromegalic patients showed that insulin sensitivity is reduced to a similar extent in acromegalic patients with normal glucose tolerance and those with impaired glucose tolerance or diabetes [15]. However, impaired insulin secretion was found in acromegalic patients with impaired glucose tolerance or diabetes. Thus, the degree of impaired β -cell function determined the glucose tolerance status in patients with acromegaly in that study. These data were obtained by HOMA model assessment derived from fasting plasma glucose and serum insulin concentrations. Our data derived from the OGTT confirm and extend these findings to patients with reduced insulin sensitivity due to varying causes.

The aetiology of HAIRAN syndrome is not known, but a defect "downstream" from the insulin receptor in target tissue has been suggested [16, 17]. In previous studies the decrease in insulin sensitivity has been shown to be more pronounced than in individuals of comparable weight [18]. Our data show that the marked increase in insulin secretion during the OGTT allows these patients to preserve normal glucose tolerance and highlight the fact that normal β -cells are able to compensate even for marked insulin resistance.

The decreased insulinogenic index in our insulinoma patients compared to patients with acromegaly was associated with an impaired glucose tolerance status despite less reduced insulin sensitivity. These data highlight the crucial role of impaired β -cell function in glucose homeostasis.

In conclusion, our data illustrate the fact that impaired β -cell function in the face of decreased insulin sensitivity determines the degree of glucose intolerance in patients with reduced insulin sensitivity, i.e. patients with type 2 diabetes, acromegaly, insulinoma, and HAIRAN syndrome. In patients with type 2 diabetes a longer duration of diabetes and higher HbA_{1c} correlated with decreased β -cell function and absolute insulin deficiency during the OGTT. Hence, in addition to therapeutic approaches targeting insulin resistance, other inno-

vative therapies designed to preserve or even improve functional β -cell mass are desirable.

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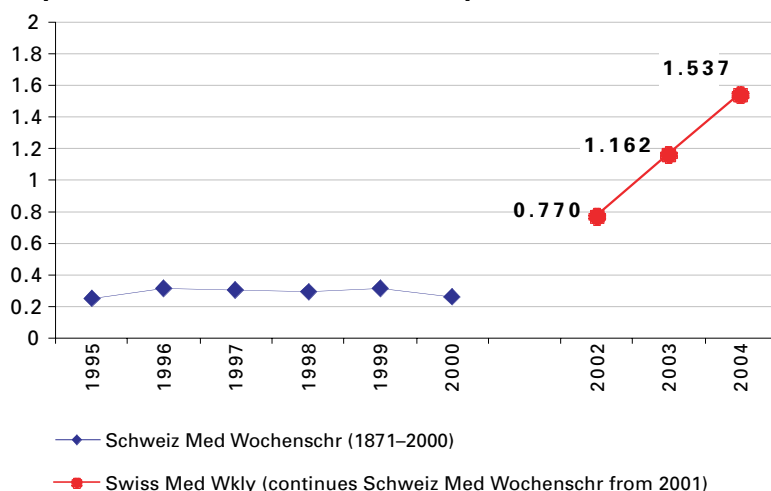
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