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Short- and long-term gliclazide effects on pancreatic islet cell function and hepatic insulin extraction in non-insulin-dependent diabetes mellitus

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Summary

Nine non-obese males with non-insulin-dependent diabetes mellitus (NIDDM) were evaluated before and after 3 and 12 months (6 patients) treatment with the second generation hypoglycemic sulfonylurea: gliclazide. They underwent an oral glucose tolerance test, intravenous glucose and arginine tests measuring plasma insulin and C-peptide responses. Pre-hepatic insulin production and insulin delivery to peripheral tissues were calculated by deconvolution techniques and hepatic extraction of insulin estimated. An improvement was observed in the β-cell function of the patients on gliclazide treatment: reduction of fasting plasma glucose associated with a progressive increase in C-peptide level but insulin levels decreased at 12 months, suggesting an increase in hepatic insulin extraction at this time. In the same way, while plasma glucose values after oral and i.v. glucose were greatly reduced at 3 and 12 months treatment, insulin did not change but C-peptide levels increased significantly at 12 month treatment. While the prehepatic insulin secretion rate increased progressively on gliclazide during all glucose challenges, the fractional hepatic insulin extraction fell after 3 and increased at 12 month treatment, with opposite changes in insulin delivered to peripheral tissues. Thus the insulinogenic effect of gliclazide could be masked during long-term administration by a concomitant effect of gliclazide which increases hepatic extraction of insulin. The maintenance of the responsiveness to the non-glucose secretagogue, arginine, as evaluated by the C-peptide levels, before and after correction of hyperglycemia, suggested improvement of β-cell sensitivity to glucose after sulfonylurea treatment. When plasma glucose levels during gliclazide therapy were matched by glucose infusion to the pretreatment fasting plasma glucose, the acute insulin and C-peptide responses to arginine were also increased again, indicating that the β-cells were resensitized to the potentiating effect of glucose after sulfonylurea. In conclusion, gliclazide treatment increases insulin secretion and alters hepatic insulin extraction. Because C-peptide kinetic studies were

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not performed, the derived data related to pancreatic insulin secretion and hepatic insulin extraction are tentative and should be accepted with caution.

Key words: Non-insulin-dependent diabetes mellitus; Gliclazide; Oral and i.v. glucose tolerance; Arginine infusion; Hepatic insulin extraction

Introduction

The hyperglycemia of non-insulin-dependent diabetes mellitus (NIDDM) has been attributed to both glucose overproduction by the liver and glucose underutilization by peripheral tissues, which has been ascribed to both deficient insulin secretion and resistance to insulin action. Recent evidence suggests that chronic hyperglycemia leads to progressive impairment in insulin secretion and may also contribute to insulin resistance [1,2]. Several mechanisms have been postulated for the chronic 'hypoglycemic' effects of sulfonylurea therapy in NIDDM. In relation to gliclazide, a second generation hypoglycemic sulfonylurea, there are studies indicating that it has an effect on insulin secretion and an extrapancreatic action related to potentiation of the bioeffects of insulin [3].

In the present study we report the effects of short- and long-term gliclazide therapy on basal insulin, C-peptide levels and glucose and non-glucose-stimulated islet cell responses.

Subjects and Methods

Nine non-obese NIDDM men (body mass index from 21 to 24 kg/m^2), 42–64 years of age, with fasting plasma glucose above 11.1 mmol/l underwent an oral glucose tolerance test (75 g), an intravenous glucose tolerance test (0.3 g/kg, 50% dextrose, injected in 1 min) and measurement of insulin responses to non-glucose stimulant arginine (5 g intravenously). The tests were repeated after 3 months (in all patients) and 12 months (in the 6 patients who continued treatment and which we were able to follow closely) of the second generation sulfonylurea, gliclazide, treatment in a dose of 80–160 mg/day, depending on the response of their fasting plasma glucose measured every 2 weeks. No medication was administered on the morning of the tests. Insulin and C-peptide responses to arginine were also evaluated at a plasma glucose level matched to the fasting plasma glucose before treatment, arginine pulse being given 55 min after the beginning of a 600 mg/min glucose infusion (85 min duration) when steady-state plasma glucose levels similar to untreated values were reached.

Plasma glucose, insulin and C-peptide concentrations were determined in all samples. Plasma glucose was measured in a Technicon Autoanalyzer by the ferricyanide method [4]. Insulin was measured by radioimmunoassay using a modification of the method of Desbuquois and Aurbach [5] in which a second antibody was added to the poly(ethylene glycol) to separate free from insulin-antibody-bound fractions. Plasma C-peptide was measured using a radioimmunoassay kit (Biodata C-peptide kit, Serono Diagnostica S.A., Coisins, Switzerland). Glycosylated hemoglobin was determined after elution from an ion-exchange column by a modification of the method of Trivelli et al. [6].

Calculations

The total integrated areas circumscribed by the glucose, insulin and C-peptide response curves during oral GTT were estimated using trapezoidal rule [7].

The acute insulin and C-peptide responses to arginine were expressed as the mean increase in plasma insulin and C-peptide above the prestimulus level 2, 3, 4 and 5 min after the bolus injection as proposed by Judzeswitsch et al. [8].

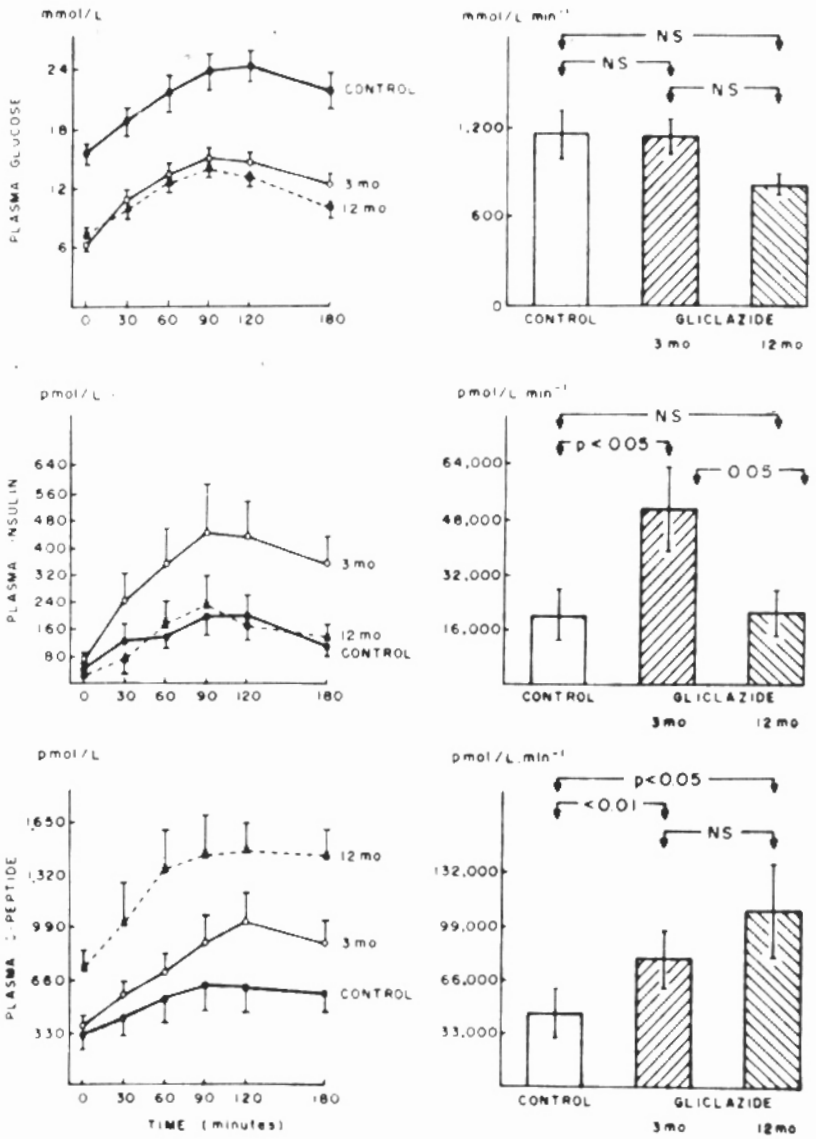

Fig. 1. Mean ± SEM plasma glucose, insulin and C-peptide levels during a 75 g oral glucose tolerance test in 9 NIDDM patients before and after 3 months and 1 year (6 patients) of therapy with gliclazide. Columns and bars indicate mean ± SEM of the incremental total glucose, insulin and C-peptide areas during the glucose tolerance test before (open columns) and after (hatched columns) gliclazide.

Prehepatic insulin production was calculated by the deconvolution technique proposed by Eaton et al. [9] from kinetic analysis of peripheral C-peptide behavior. The deconvolution technique consists of fitting the C-peptide plasma data to a combination of exponential equations in such a way as to obtain a single smooth curve approximating the data. This suggested a two-compartment model consisting of intravascular and extravascular C-peptide exchanging pools. The fractional turnover constant rates for both compartments were provided experimentally by the injection of synthetic C-peptide in normal and diabetic patients by Faber et al. [10] which was

used to define the removal characteristics of C-peptide in man. With this information and knowledge of C-peptide behavior in plasma it is possible to determine the production of C-peptide. Since C-peptide and insulin are released by the pancreas in equimolar concentrations and C-peptide is not extracted by the liver, its prehepatic production is a marker of β-cell secretory activity.

Insulin delivery to peripheral tissues was also calculated by deconvolution of the peripheral insulin levels, as described by Polonsky et al. [11].

Hepatic insulin extraction was estimated by utilizing a three-compartment model comprising hepatic, vascular and extravascular spaces. By this method, solution in the vascular space was fit to the peripheral plasma insulin data by least-squares criteria, and endogenous insulin secretion into the hepatic pool was obtained by deconvolution as described above [9]. Since no C-peptide was injected to assess kinetics, the fractional turnover constants were derived from the literature [12]. The only model parameters which were allowed to vary during the fitting process were the fractional loss from the liver compartment and the fractional return to the plasma compartment [12]. In view of the fact that C-peptide kinetic studies were not performed, the data relative to prehepatic insulin production, hepatic extraction and insulin delivered to peripheral tissues are tentative and should be accepted with caution.

Statistics

All data are expressed as the mean ± SEM. Student's *t*-test for paired and unpaired data was used for comparing the diabetic subjects before and during sulfonylurea treatment.

Informed consent was obtained from all patients, and approval was granted by the Ethical Committee from Hospital das Clinicas.

Results

Body weight did not change after 3 and 12 months of gliclazide treatment. Fasting plasma glucose (FPG) fell significantly from 16.1 ± 0.6 to 6.4 ± 0.3 mmol/l ($P < 0.001$) at 3 months and remained significantly lower at 12 months (6.7 ± 0.4 mmol/l) ($P < 0.001$). The corresponding glycosylated hemoglobin levels fell from 14.0 ± 1.1 to 7.2 ± 0.4% ($P < 0.001$) and to 7.5 ± 0.4% ($P < 0.001$), respectively. Fasting plasma insulin levels obtained during the study increased significantly from 31.5 ± 6.5 to 94.7 ± 13.6 pmol/l at 3 months ($P < 0.0001$) and returned towards baseline being 37.3 ± 7.9 pmol/l ($P < 0.01$) after 1 year of treatment. Corresponding fasting plasma C-peptide levels increased from 281.4 ± 53.0,

TABLE 1

Estimated prehepatic insulin secretion, hepatic insulin extraction and insulin delivered to peripheral tissues during oral and intravenous glucose tolerance tests in 9 NIDDM patients before and after 3 months and 1 year (6 patients) of gliclazide therapy

	Prehepatic insulin secretion		Fractional hepatic extraction (%)		Insulin delivered to peripheral tissues	
	Oral GTT (nmol 180 min)	i.v. GTT (nmol/20 min)	Oral GTT	i.v. GTT	Oral GTT (nmol/180 min)	i.v. GTT (nmol/20 min)
Control	38.1 ± 8.5	1.4 ± 0.4	48 ± 10	42 ± 16	19.3 ± 5.0	0.8 ± 0.2
Gliclazide: 3 months	52.9 ± 8.6	3.0 ± 0.7	16 ± 8	26 ± 8	44.4 ± 7.9	1.9 ± 0.3
12 months	87.1 ± 11.3	4.5 ± 0.9	65 ± 8	53 ± 12	23.7 ± 5.3	1.5 ± 0.5
Control vs. 3 months	$P < 0.01$	< 0.05	< 0.01	NS	< 0.01	< 0.05
Control vs. 12 months	$P < 0.01$	< 0.05	< 0.05	NS	NS	NS
3 vs. 12 months	$P < 0.05$	< 0.05	< 0.01	NS	< 0.05	NS

NS, not significant.

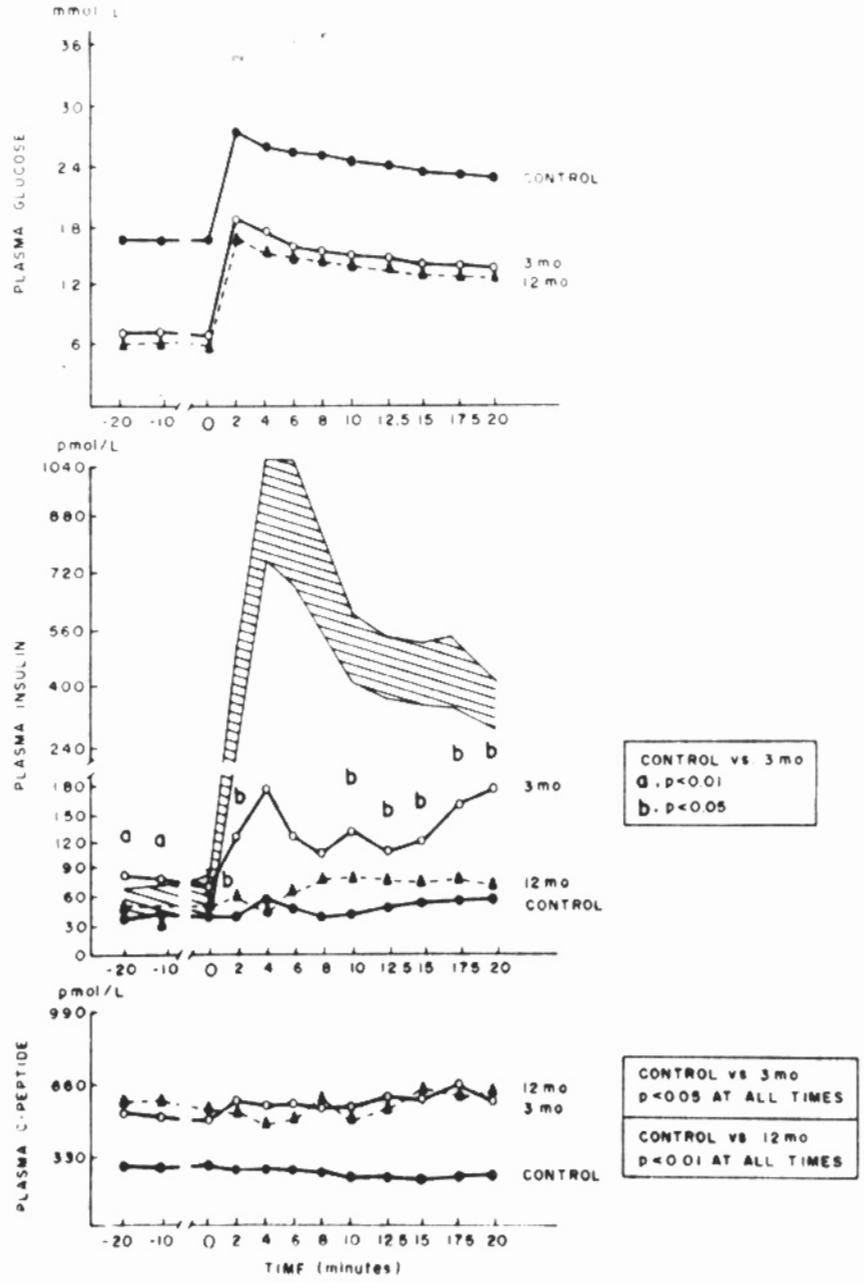

Fig. 2. Mean plasma glucose, insulin and C-peptide levels in 9 NIDDM patients in response to an intravenous glucose tolerance test before and after 3, and 12 months (6 subjects) of gliclazide therapy. Hatched area indicates mean ± SEM of plasma insulin in 8 normal subjects.

before therapy, to 436.9 ± 56.3 ($P < 0.005$) and 665.3 ± 99.3 pmol/l ($P < 0.002$) at 3 and 12 months, respectively (3 vs. 12 months, $P < 0.05$).

Oral glucose tolerance (Fig. 1)

As can be seen in Fig. 1, there was a significant decrease in mean plasma glucose levels after gliclazide, attaining similar values at 3 and

12 months. Mean insulin levels were not significantly different from control at 3 and 12 months, except at 180 min at 3 months. C-peptide values at 3 months were similar to the untreated control study but they were significantly higher at 12 months therapy.

The plasma glucose incremental areas above fasting did not change significantly after gliclazide. The corresponding insulin and C-peptides areas increased at 3 months and while the insulin area decreased significantly at 12 months the C-peptide area was kept elevated.

The calculated prehepatic insulin secretion, the corresponding amount of insulin delivered to the peripheral tissues and hepatic insulin extraction changes during gliclazide therapy are indicated in Table 1.

Intravenous glucose tolerance (Fig. 2)

Mean plasma glucose levels fell significantly after gliclazide treatment, with no significant differences between 3 and 12 months. The mean insulin and C-peptide levels were significantly higher after 3 months of treatment, except at 4, 6 and 8 min for insulin levels. However, at 12 months the mean insulin levels decreased, although they were not significantly different from untreated controls and 3 months, whereas the mean C-peptide values were still higher than the controls but not different from the 3-month levels.

Prehepatic insulin secretion, the corresponding amounts of insulin delivered to peripheral tissues and the estimated hepatic insulin extraction before and during gliclazide treatment are indicated in Table 1.

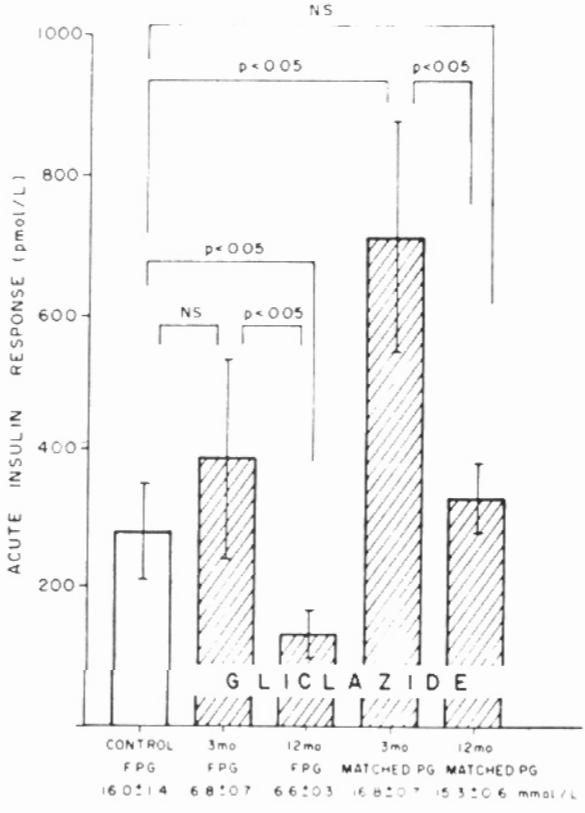

Fig. 3. Acute insulin responses (mean ± SEM) to arginine before and after 3 months (9 patients) and 1 year (6 patients) gliclazide therapy in NIDDM. Columns and bars indicate mean ± SEM of the insulin responses during testing before (open columns) and after (hatched columns) gliclazide.

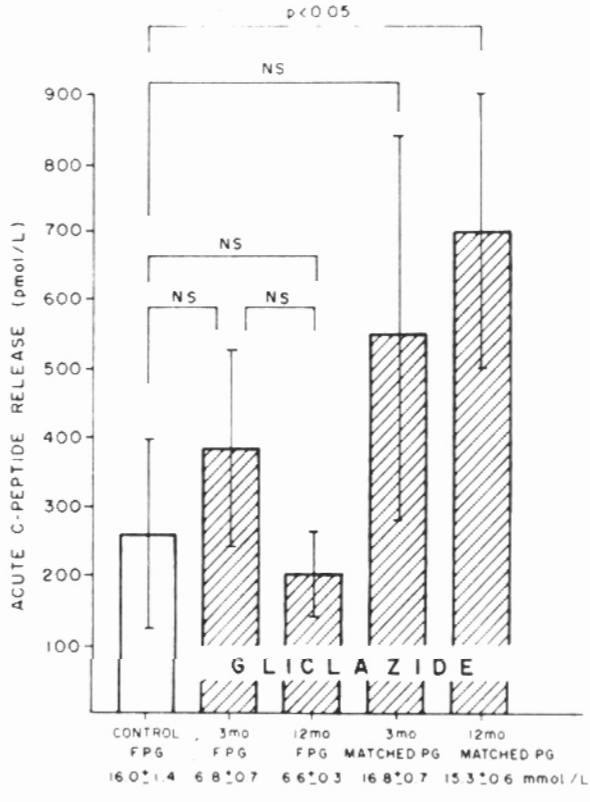

Fig. 4. Acute C-peptide responses (mean ± SEM) to arginine before and after 3 months (9 patients) and 1 year (6 patients) gliclazide therapy in NIDDM. Columns and bars indicate mean ± SEM of the C-peptide responses during testing before (open columns) and after (hatched columns) gliclazide.

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