Effect of growth hormone releasing hormone on growth hormone secretion in Type 2 (non-insulin-dependent) diabetes mellitus

P. Pietschmann and G. Schernthaner

Department of Medicine II, Division of Metabolism and Endocrinology, University of Vienna, Vienna, Austria

Summary. Growth hormone levels following an intravenous bolus injection of 1 µg/kg body weight growth hormone releasing hormone were measured in 21 non-obese and 26 obese patients with Type 2 (non-insulin-dependent) diabetes mellitus and in 13 control subjects. Growth hormone responses in non-obese Type 2 diabetic patients were not statistically different from control subjects. However, obese Type 2 diabetic patients had significantly decreased growth hormone responses to growth hormone releasing hormone when compared with non-obese Type 2 diabetic patients ($p < 0.02$). In 9 Type 2 diabetic patients growth hormone releasing hormone tests were performed both during hyperglycaemia and after metabolic improvement by insulin treatment. Growth hor-

mone responses before and after insulin treatment were not statistically different. Our data demonstrate that (1) growth hormone responses to growth hormone releasing hormone in non-obese Type 2 diabetic patients do not differ significantly from control subjects; (2) obesity blunts growth hormone responses to growth hormone releasing hormone in Type 2 diabetes mellitus; and (3) growth hormone responses following growth hormone releasing hormone administration in Type 2 diabetes mellitus are not influenced by the state of metabolic control.

Key words: Growth hormone, growth hormone releasing hormone, diabetes mellitus, Type 2 diabetes mellitus, obesity.

Various disturbances of growth hormone (GH) secretion in diabetes mellitus have been reported. Hansen and co-workers [1, 2] demonstrated a growth hormone hyper-responsiveness to physical exercise in Type 1 (insulin-dependent) and non-obese Type 2 (non-insulin-dependent) diabetic patients. Type 1 diabetic patients show a failure of glucose-mediated suppression of growth hormone releasing hormone (GHRH)-induced GH levels [3].

In a preliminary investigation, Richards et al. [4] reported decreased GH responses to GHRH in eight Type 2 diabetic patients compared with four control subjects. It is unclear, however, whether this impaired GH response to GHRH in Type 2 diabetes is caused by the obesity frequently associated with Type 2 diabetes or by the disease itself. We have therefore studied a larger number of obese and non-obese Type 2 diabetic patients than hitherto investigated. In addition, we have examined the effect of improved metabolic control upon GHRH-induced GH levels in this disorder.

Subjects and methods

We studied 21 non-obese and 26 obese patients with Type 2 diabetes mellitus according to the classification of the NIH Data Group [5]. Clinical characteristics of Type 2 diabetic patients and control sub-

jects are shown in Table 1. All subjects gave their informed consent. After an overnight fast the subjects were recumbent for at least 2 h, after which an intravenous catheter was placed in a suitable antecubital vein. No medication was given on the morning of the test. Blood samples were obtained before (–30 and 0 min) and after (15, 30, 45, 60 and 90 min) an intravenous bolus injection of 1 µg/kg body weight human pancreatic growth hormone releasing hormone 1–44 (hpGHRH 1–44, Bissendorf Peptides, Wedemark, FRG). Nine Type 2 diabetic patients with secondary failure of oral hypoglycaemic treatment (sulfonylurea) (mean age 65 ± 5 years, mean BMI $23 \pm 1\%$ in males, mean BMI $27 \pm 1\%$ in females) were tested both during hyperglycaemia and after metabolic improvement by insulin treatment.

GH was measured by radioimmunoassay (Tandem β HGH, Hybritech, Liège, Belgium). Intraassay and interassay coefficients of variation were 3.8% and 5.2%, respectively (at 8.1 ng/ml and 7.8 ng/ml, respectively). The minimum detectable concentration was 0.2 ng/ml.

Statistical analysis

Statistical evaluation was performed using the non-parametric Mann-Whitney U-test and Wilcoxon signed rank test for paired comparisons. Data are presented as the mean $\pm$ SEM, with the exception of the basal GH levels and the increase in GH levels, which are presented as the median value and the lower quartile (25% point = Q_1) and the upper quartile (75% point = Q_3). A value of $p < 0.05$ was considered statistically significant.

Results

Median basal GH levels in non-obese Type 2 diabetic patients (0.6; Q_1 : 0.2; Q_3 : 1.5 ng/ml), obese Type 2 dia-

Table 1. Clinical characteristics of non-obese and obese Type 2 diabetic patients and control subjects

	Age (years)	Sex (m/f)	BMI (kg/m ²)		FPG ^a mmol/l	HbA _{1c} (%)	Diabetes duration (years)	Treatment		
			(m)	(f)				D ^b	OHA ^c	I ^d
Non-obese patients (n=21)	65±2	11/10	24±1	22±1	9.6±0.7	8.3±0.4	14±2	0	12	9
Obese patients (n=26)	62±2	8/18	29±1	29±1	9.0±0.8	8.9±0.4	13±2	2	12	12
Control subjects (n=13)	65±3	7/ 6	24±1	22±1	4.3±0.3	5.2±0.1	-	-	-	-

^a Fasting plasma glucose; ^b diet alone; ^c oral hypoglycaemic agents; ^d insulin

Fig. 1. Median increase of growth hormone (GH) levels after growth hormone releasing hormone (GHRH) in control subjects, non-obese patients and obese Type 2 diabetic patients. Vertical lines indicate lower and upper quartiles. Δ GH was significantly decreased ($p < 0.02$) in obese compared with non-obese Type 2 diabetic patients.

betic patients (0.5; Q_1 : 0.1; Q_3 : 0.6 ng/ml) and control subjects (0.5; Q_1 : 0.1; Q_3 : 1.0 ng/ml) were not statistically different. The increase in GH levels (Δ GH = peak level – basal level) following GHRH was less marked in obese Type 2 diabetic patients compared with non-obese Type 2 diabetic patients ($p < 0.02$; Fig. 1). The GH responses to GHRH in non-obese diabetic patients and in control subjects were not significantly different (Fig. 1).

In the Type 2 diabetic patients who had 2 GHRH tests, the mean fasting plasma glucose was 13.7 ± 0.8 mmol/l before insulin treatment and 7.3 ± 1.0 mmol/l after insulin treatment. The increase in GH levels (Δ GH) following GHRH injection at hyperglycaemia (median Δ GH 2.6; Q_1 : 0.8; Q_3 : 4.3 ng/ml) and after insulin treatment (median Δ GH: 3.1; Q_1 : 1.7; Q_3 : 9.2 ng/ml) was not significantly different.

GHRH injection was well tolerated in all subjects, with the exception of 2 diabetic patients who experienced facial flushing.

Discussion

Our data demonstrate that GH responses to GHRH in non-obese Type 2 diabetic patients are comparable to these in control subjects. These data are consistent with those of Fatourechhi et al. [6], who reported normal GH responses to insulin-induced hypoglycaemia in patients with Type 2 diabetes mellitus. GH levels following GHRH administration were significantly blunted in obese compared with non-obese Type 2 diabetic patients. In normal subjects GH responses to GHRH are influenced by age [7] and obesity [8]. Since age, fasting plasma glucose levels, HbA_{1c} and diabetes duration were comparable in obese and non-obese Type 2 diabetic patients (Table 1), obesity seems to be the factor predominantly responsible for the blunted GH responses in these patients. We recently demonstrated that GH responses to GHRH in overweight Type 2 diabetic patients irrespective of the presence or lack of diabetic retinopathy are not different from control subjects with comparable body mass index [9]. Richards et al. [4] reported decreased GH responses to GHRH in a small number of patients with Type 2 diabetes mellitus. Since these Type 2 diabetic patients were more obese than the control subjects, these data are not inconsistent with ours; in fact, they provide further evidence that obesity in Type 2 diabetes mellitus blunts GH responses to GHRH. In rats with genetic obesity, the release of somatostatin from hypothalami is higher than in non-obese rats [10]. Thus, blunted GH responses in obese Type 2 diabetic patients to GHRH may be due to enhanced secretion of (hypothalamic) somatostatin.

In the Type 2 diabetic patients studied both before and after insulin treatment, GH responses to GHRH were not statistically different during hyperglycaemia and after metabolic improvement. These data are consistent with the finding in Type 1 diabetes mellitus that GH responses to GHRH are comparable in hyperglycaemic and euglycaemic patients [3].

In conclusion, our data demonstrate that (1) GH responses to GHRH in non-obese Type 2 diabetic patients do not differ significantly from control subjects; (2) GH responses to GHRH are blunted in obese compared

with normal weight Type 2 diabetic patients; and (3) GH responses to GHRH in Type 2 diabetes mellitus are not influenced by the state of metabolic control.

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Professor G. Schernthaner
Department of Medicine II
Division of Metabolism and Endocrinology
University of Vienna
Garnisongasse 13
A-1090 Vienna
Austria