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Risk factors for glucose intolerance in active acromegaly

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Abstract

In the present retrospective study we determined the frequency of glucose intolerance in active untreated acromegaly, and searched for risk factors possibly supporting the emergence of the diabetic condition. Among 43 patients, 8 (19%; 95% CI: 8-33%) had diabetes mellitus and 2 (5%; 1-16%) impaired glucose tolerance. No impaired fasting glycemia was demonstrable. The frequency of diabetes was on average 4.5 times higher than in the general Slovak population. Ten factors suspected to support progression to glucose intolerance were studied by comparing the frequency of glucose intolerance between patients with present and absent risk factors. A family history of diabetes and arterial hypertension proved to have a significant promoting effect ($P<0.05$, chi-square test). A significant association with female gender was demonstrated only after pooling our data with literature data. Concomitant prolactin hypersecretion had a nonsignificant promoting effect. In conclusion, the association of active untreated acromegaly with each of the three categories of glucose intolerance (including impaired fasting glycemia, not yet studied in this connection) was defined as a confidence interval, thus permitting a sound comparison with the findings of future studies. Besides a family history of diabetes, female gender and arterial hypertension were defined as additional, not yet described risk factors.

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Introduction

Acromegaly, a clinical syndrome caused by autonomous hypersecretion of growth hormone, is frequently associated with glucose intolerance. While the occurrence of diabetes mellitus has been repeatedly evaluated in patients with acromegaly, with estimates of 19 to 56% (1-6), that of the intermediate form of disturbed glucose metabolism, referred to as impaired glucose tolerance, was analyzed, to the best of our knowledge, only in two recent studies (6,7). No evaluation of impaired fasting glycemia - a new category of the intermediate disorder of glucose metabolism (8,9) - in acromegaly has been performed thus far.

A well-known major cause of glucose intolerance in acromegaly is insulin resistance (10-12) induced by growth hormone and its mediator, insulin-like growth factor type 1. Other risk factors (e.g., a long duration of active acromegaly and older patient age) may promote the development of glu-

cose intolerance. Nevertheless, relevant clinical studies are scarce (2,6).

Therefore, the aim of the present study was to assess the frequency of all three categories of diabetic disease (i.e., diabetes mellitus, impaired glucose tolerance, impaired fasting glycemia) in Slovak patients with acromegaly, and to extend the few existing scrutinies of possible risk factors for glucose intolerance in acromegaly.

Patients and Methods

The records of 43 patients with active untreated acromegaly (10 males and 33 females aged 20-71 years, on average 45.7 years), diagnosed during the years 1990-99 at the Institute of Endocrinology (Lubochna, Slovak Republic) were reviewed. Typical signs of acromegaly were present in all 43 patients. The diagnostic investigation at the Institute of Endocrinology was performed over a period of 1-15 years, on average 5.8 years since the onset of the signs of acromegaly. The diagnosis of active acromegaly was based on sustained elevation of serum growth hormone levels that were not suppressible below 4 mU/l in the 75 g oral glucose tolerance test. This test was not performed in patients with a history of diagnosed diabetes mellitus. The diagnosis of active acromegaly was then based on integrated serum growth hormone values (mean of five measurements during 24 h) above 10 mU/l. The morning level of serum prolactin was routinely determined in every patient.

Plasma glucose concentrations were determined by the glucose oxidase method (Beckman Glucoanalyser, Beckman Instruments, Fullerton, CA, USA). The results were retrospectively reviewed according to the diagnostic criteria of the American Diabetes Association (8). In patients with a history of already diagnosed diabetes mellitus, the daily glucose levels (morning fasting plasma glucose plus 3 to 7 additional glycemia readings) were measured several times during the patients' stay at the Institute of Endocrinology. Repeated morning fasting plasma glucoses values ≥7.0 mmol/l confirmed the diagnosis of known diabetes mellitus. In all other patients, the 75 g oral glucose tolerance test was routinely performed. The diagnostic criterion for diabetes mellitus was a 2-h plasma glucose value ≥11.1 mmol/l. A 2-h plasma glucose value ≥7.8 mmol/l but <11.1 mmol/l indicated impaired glucose tolerance, and fasting plasma glucose ≥6.1 but <7.0 mmol/l indicated impaired fasting glycemia.

Serum growth hormone levels were measured by immunoradiometric assay (GH IRMA kit, Immunotech, a Beckman Coulter Company, Marseille, France). The sensitivity of the assay was 0.10 mU/l and the intra- and interassay coefficients of variation were 1.5 and 14.03%, respectively. Serum prolactin levels were estimated by immunoradiometric assay (IRMA-mat Prolactin kit, Byk-Sangtec Company, Dietzenbach, Germany). The sensitivity of the assay was <10 mU/l and the intra- and interassay coefficients of variation were 8.3 and 10.6%, respectively.

As to the pituitary tumor staging, computed tomographic scan or magnetic resonance imaging revealed intrasellar pituitary microadenomas (diameter <10 mm) in 11 patients, intrasellar macroadenomas in 10, expansive macroadenomas in 15, and invasive macroadenomas in 7.

The variables studied possibly promoting glucose intolerance were as follows: patient gender (females versus males), patient age at the time of diagnostic investigation (≥40 years versus <40 years), duration of acromegaly at this time (≥6 years versus <6 years), a family history of diabetes (positive versus negative), obesity (body mass index ≥30 kg/m^2 versus <30 kg/m^2), arterial hypertension (≥140/90 mmHg versus absent), hirsutism in female patients (≥8 points according to Ferriman and Galwey's estimate (13) versus absent), integrated serum growth hormone value (≥50 mU/l versus <50 mU/l),

hyperprolactinemia (prolactin level ≥400 mU/l versus <400 mU/l), and pituitary macroadenoma (adenoma diameter ≥10 mm versus <10 mm).

All proportions, e.g., those of subjects with glucose intolerance in relation to the total group, were expressed as point estimates of percentage with the 95% confidence intervals (95% CI) based on binomial distribution (14).

In the search for factors playing a role in the manifestation of glucose intolerance, the data were always divided according to the presence or absence of each variable into two groups, e.g., female versus male subjects. In either group, the percentage of subjects with glucose intolerance and its 95% CI were calculated. The difference in percentage between groups was evaluated by the chi-square test.

Results

Glucose intolerance was present in 10 subjects, i.e., in 23% (95% CI: 12-39%) of the total of 43 acromegalics. Eight (19%; 95% CI: 8-33%) of them had diabetes mellitus, confirmed by our glycemia measurements. Diabetes mellitus manifested at the onset of acromegaly in 2 subjects and developed after its onset in 6. Of these 8 diabetics, 4 were treated with insulin, 2 were on oral hypoglycemic agents and 2 on diet alone. Two cases (5%; 95% CI: 1-16%) of impaired glucose tolerance were revealed *de novo*. Impaired fasting glycemia was not detected.

Table 1 lists the outcome of the study of the influence of ten factors putatively promoting the development of glucose intolerance.

Discussion

This is the first study of all three categories of glucose intolerance in acromegaly, i.e., of diabetes mellitus, impaired glucose tolerance and impaired fasting glycemia. It is also the first study of this kind performed in Slovakia. The frequency of diabetes mellitus (19%) found in patients with active untreated acromegaly was on average 4.5 times higher than the prevalence of diabetes mellitus reported to be 4.18% (95% CI: 4.16-4.19%) by the Institute of Health Information and Statistics of the Slovak Republic (15) for the whole population of Slovakia (5,387,650 inhabitants).

The 19% frequency of diabetes, and particularly its confidence interval (8-33%) compare well with the 19% frequency of diabetes mellitus reported for the sample of acromegalics in the United Kingdom by

Table 1. Association of ten factors with glucose intolerance (GI%) in 43 acromegalics.

Factor	Factor present			Factor absent			Chi-square for difference
	N	GI%	95% CI	N	GI%	95% CI	
Female gender	33	27	(13-46)	10	10	(0-45)	1.5918
Age (>40 years)	28	29	(13-49)	15	13	(2-40)	1.4127
Duration (>6 years)	17	35	(14-62)	26	15	(4-35)	2.2336
Family history of diabetes	13	46	(19-75)	30	13	(4-31)	5.0504*
Obesity	17	35	(14-62)	26	15	(4-35)	2.2336
Hypertension	13	46	(19-75)	30	13	(4-31)	5.0504*
Female hirsutism	6	50	(12-88)	27	22	(9-42)	1.7032
Growth hormone (>50 mU/l)	12	42	(15-72)	31	16	(5-34)	2.8782
Hyperprolactinemia	15	33	(12-62)	28	18	(6-37)	1.2545
Pituitary macroadenoma	32	22	(9-40)	11	27	(6-61)	0.1290

N = sample size; 95% CI = 95% confidence interval.
*P<0.05 compared to acromegalics with absent factor (chi-square test).

Table 2. Association of the factor female gender with glucose intolerance before and after recalculation by summing the data from two sources.

Source	Factor present			Factor absent			Chi-square for difference
	N	GI%	95% CI	N	GI%	95% CI	
Present paper	33	27	(13-46)	10	10	(0-45)	1.5918
Nabarro (2)	123	23	(16-31)	133	15	(9-22)	2.5127
Present paper + Nabarro (2) (pooled)	156	24	(17-31)	143	15	(9-22)	3.9736*

N = sample size; GI = glucose intolerance; 95% CI = 95% confidence interval.
*P<0.05 compared to male acromegalics (chi-square test).

Nabarro (2), with the 20% frequency found among acromegalics of Maryland (USA) by Emmer et al. (1), with the 24% frequency found in Italian acromegalics by Arosio et al. (3), and with the 32% frequency ascertained among German patients by Biering et al. (6). On the other hand, the frequency rates of diabetes mellitus were well above our upper confidence limit in acromegalic patients of Indian origin and in patients from Hong Kong (56 and 50%, respectively (4,5)). The differences in the size of patient samples and in ethnicity may have contributed to these discrepant findings.

The category of impaired glucose tolerance, an intermediate form of disturbed glucose metabolism, was assessed in only two studies on acromegaly. In both of them the frequency rates were above our upper 95% confidence limit (16%), being 31% in German acromegalics (6) and 46% in Japanese acromegalics (7). The second, recently recognized (8,9) intermediate form of glucose intolerance, named impaired fasting glycemia, was not detected in the present study. Since the presence of this category of glucose intolerance in acromegaly has not been assessed by other investigators, a comparison could not be made. In general population studies, impaired fasting glycemia has been found less frequently than impaired glucose tolerance (16-18). Our negative outcome in acromegaly is therefore not a surprise.

As to the risk factors promoting the development of glucose intolerance in acromegaly, Nabarro (2) claimed a significant tendency towards the occurrence of symptomatic diabetes in the presence of higher levels of growth hormone, older age and longer duration of acromegaly. Biering et al. (6) found a predisposing influence for older age only. Analysis of our sample shows similar but statistically nonsignificant associations. The significant results obtained in the present study indicate that glucose intolerance in acromegaly develops in association with a family history of diabetes and with the presence of arterial hypertension. The predisposing influence of family history of diabetes on diabetes mellitus development in acromegaly is suggested by some textbooks (19-21), although this statement was not corroborated by quantitative data. The association with arterial hypertension has not been described previously. We have no explanation for such an association. The expected connection between hyperprolactinemia and glucose intolerance appeared to be nonsignificant while the connection with pituitary macroadenoma was completely absent. A positive association between glucose intolerance and female gender, found to be nonsignificant by ourselves and Nabarro (2), reached a significant level after the samples reported in the two studies were pooled (Table 2).

In conclusion, the association of active untreated acromegaly with each of the three categories of glucose intolerance (including impaired fasting glycemia, not yet studied in this connection) was defined as confidence interval, thus permitting sound comparison with future studies. Female gender and arterial hypertension were identified as newly recognized risk factors. Other reasonable associations found to be nonsignificant in the present study, possibly because of the small sample size, might become significant after pooling the samples, as shown for female gender.

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