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# Abnormalities in glucose homeostasis in acromegaly. Does the prevalence of glucose intolerance depend on the level of activity of the disease and the duration of the symptoms?

## Zaburzenia gospodarki węglowodanowej w akromegalii. Czy częstość ich występowania zależy od aktywności choroby oraz czasu trwania objawów?

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## Abstract

**Introduction:** Acromegaly is characterized not only by disabling symptoms, but also by relevant co-morbidities. Insulin resistance, leading to glucose intolerance is one of the most important contributory factors to the cardiovascular mortality in acromegaly.
**Material and methods:** We analysed the records of 220 naïve patients with acromegaly diagnosed at our Department in the years 1995––2007. Diagnosis of active acromegaly was established on the basis of widely recognized criteria. In each patient glucose and insulin concentrations were assessed when fasting and during the 75 g OGTT.
**Results:** Normoglycaemia existed in 46% of acromegalic patients. Among glucose tolerance abnormalities we found impaired fasting glucose in 19%, impaired glucose tolerance in 15% and overt diabetes mellitus in 20%. There was no statistically significant differences in gender, duration of the disease, basal plasma GH, IGF-1 or fasting insulin concentrations between normoglycaemic patients and those with impairments in glucose tolerance. The groups showed statistically significant differences with respect to age at diagnosis ($p < 0.01$). There was no significant correlation between GH, IGF-1 concentrations and fasting plasma glucose. There was no correlation between the duration of the disease and fasting plasma glucose. We found a statistically significant correlation between plasma GH, IGF-1 concentrations and HOMA, QUICKI and $insulin_{AUC}$.
**Conclusions:** The prevalence of diabetes mellitus among acromegalics is much higher than in the general population. The occurrence of glucose tolerance impairments does not depend on the duration of the disease. In patients with acromegaly insulin resistance and hyperinsulinemia are positively correlated with the level of activity of the disease. **(Pol J Endocrinol 2009; 60 (1): 20–24)**

***Key words:*** *acromegaly, insulin resistance, impaired fasting glucose, impaired glucose tolerance, diabetes mellitus*

## Streszczenie

**Wstęp:** Akromegalia charakteryzuje się występowaniem nie tylko typowych objawów klinicznych, ale też licznych powikłań prowadzących do przedwczesnej śmierci. Insulinooporność, prowadząca do zaburzeń tolerancji glukozy, uznana jest za istotny czynnik ryzyka występowania incydentów sercowo-naczyniowych u chorych na akromegalię.
**Materiał i metody:** Badaniem retrospektywnym objęto 220 chorych z akromegalią diagnozowanych w Klinice Endokrynologii CMKP w Warszawie w latach 1995–2007. Rozpoznanie akromegalii zostało potwierdzone na podstawie powszechnie uznanych kryteriów. U każdego pacjenta oznaczono glukozę i insulinę na czczo oraz w OGTT.
**Wyniki:** Prawidłową glikemię stwierdzono u 46% pacjentów. U większości, w momencie rozpoznania choroby, występowały zaburzenia gospodarki węglowodanowej: u 19% nieprawidłowa glikemia na czczo, u 15% nieprawidłowa tolerancja glukozy, a u 20% cukrzyca. Pacjenci z normoglikemią oraz z zaburzeniami tolerancji glukozy nie różnili się pod względem płci, czasu trwania objawów, stężeń GH, IGF-1 i insuliny na czczo. Stwierdzono natomiast różnicę pod względem wieku chorych ($p < 0.01$). Nie wykazano korelacji między stężeniem GH ani IGF-1 a glikemią na czczo. Nie wykazano zależności pomiędzy czasem trwania choroby a glikemią na czczo. Stwierdzono natomiast istotną statystycznie zależność pomiędzy stężeniem GH oraz IGF-1 a wskaźnikami HOMA i QUICKI oraz polem powierzchni pod krzywą dla insuliny.
**Wnioski:** Częstość występowania cukrzycy u chorych z akromegalią jest znacznie wyższa niż w populacji ogólnej. Nie stwierdzono zależności między czasem trwania choroby a nasileniem zaburzeń gospodarki węglowodanowej. U chorych z akromegalią insulinooporność i hiperinsulinemia dodatnio korelują z aktywnością choroby. **(Endokrynol Pol 2009; 60 (1): 20–24)**

***Słowa kluczowe:*** *akromegalia, insulinooporność, nieprawidłowa glikemia na czczo, nieprawidłowa tolerancja glukozy, cukrzyca*

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## Introduction

Acromegaly, a chronic and systemic disease caused by growth hormone (GH )and insulin-like growth factor 1 (IGF-1) hypersecretion, is characterized not only by disabling symptoms, but also by relevant co-morbidities which contribute to the premature death observed in this condition [1–4]. Many studies have shown increased mortality of acromegalic patients compared with the general population, particularly as a result of cardiovascular incidents [1–5]. Insulin resistance, leading to glucose intolerance is one of the most important contributory factors to cardiovascular diseases in acromegaly. In recent years it has been revealed, that patients with acromegaly and co-existing hypertension and diabetes mellitus experience the most severe alteration in cardiac function [6, 7]. It is well established that GH excess may cause insulin resistance, and that is why glucose homeostasis impairments are frequently associated with acromegaly. The prevalence of diabetes mellitus in acromegaly is unknown, but ranges from 19–56% in different series [8–10]. Similarly, the prevalence of the most well-known intermediate form of altered glucose metabolism, referred to as impaired glucose tolerance (IGT), ranges from 16 to 46% [8–10]. To date, there have been few data about the prevalence in acromegalic patients of impaired fasting glucose (IFG), the second pre-diabetic condition, and one which is known to occur less frequently than IGT in the general population. In the only study published so far, this condition was not detected among patients with acromegaly [8].

The aim of our study was to assess the impairments of glucose homeostasis in naïve acromegalic patients and to find the association between the level of activity of the disease, the duration of symptoms and the severity of glucose intolerance.

## Material and methods

In this retrospective study we analysed the records of 220 naïve acromegalic patients aged 22–79 years who had been diagnosed at our Department in the years 1995–2007. Diagnosis of active acromegaly was established on the basis of elevated plasma GH above 1 ug/L during the 75 g oral glucose tolerance test (OGTT) and elevated plasma IGF-1 above the normal range for age and gender. In each patient, glucose and insulin concentrations were assessed fasting and after 30′, 60′, 90′, 120′ of the 75 g OGTT. Abnormalities in plasma glucose concentrations were categorised according to recent WHO criteria. Insulin resistance was assessed on the basis of homeostasis model assessment (HOMA-IR), which was calculated by using fasting insulin and glucose values: HOMA-IR = fasting insulin ($\mu$IU/ml) × fasting glucose (mmol/l)/22.5 [11]. The normal HOMA-IR range was < 2.77. Insulin sensitivity was assessed by calculating the quantitative insulin sensitivity check index (QUICKI) calculating by using the following formula: QUICKI = 1/[ (log fasting insulin ($\mu$IU/ml) + log fasting glucose (mg/dl)].

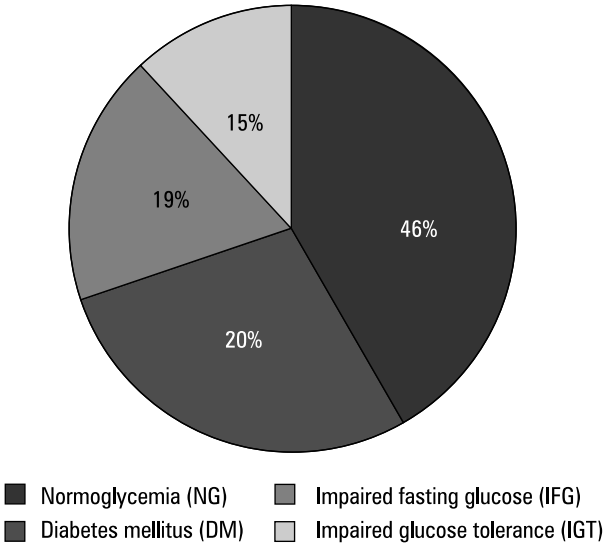


**Figure 1.** *Impairment in glucose homeostasis in the group studied*
**Rycina 1.** *Zaburzenia gospodarki węglowodanowej w badanej grupie pacjentów*

### *Statistical analysis*

Each variable was checked for normality of distribution by the Shapiro-Wilk test. Values are presented as mean ± ± standard deviation (SD) or median (and range) if not normally distributed. Statistical significance in the differences was evaluated using a non-parametric method, the Kruskal-Wallis ANOVA test. For nominal variables chi-square test was performed. Spearman's correlation analysis ($r_s$) was applied to assess the relationships between the parameters examined . Differences were considered statistically significant at $p < 0.05$.

## Results

The majority of the studied group were women (63%). The mean age at the moment of diagnosis was 46.55 (SD ± 14.07) years. The duration of the disease from the onset of the first symptoms was 7.37 (SD ± 5.30) years. Normoglycaemia existed in 46% of the acromegalic patients. Among the glucose tolerance abnormalities we found impaired fasting glucose (IFG) in 19%, impaired glucose tolerance (IGT) in 15% and overt diabetes mellitus in 20% (Fig. 1). The groups did not differ with respect to gender and the duration of symptoms.

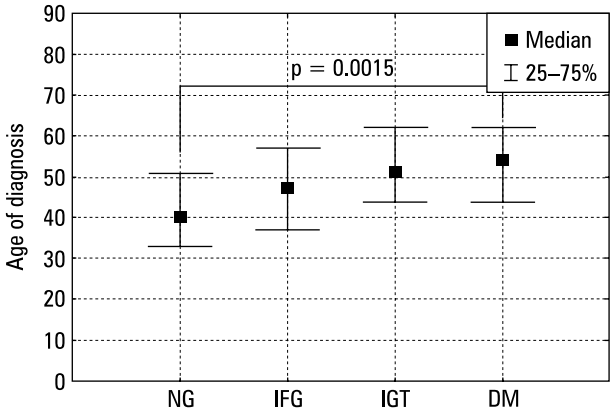


**Figure 2.** *Age of acromegalic patients with normoglycaemia (NG), impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and diabetes mellitus (DM) at the moment of diagnosis*

**Rycina 2.** *Wiek pacjentów z akromegalią w momencie rozpoznania choroby z prawidłową glikemią (NG), nieprawidłową glikemią na czczo (IFG), nieprawidłową tolerancją glukozy (IGT) oraz cukrzycą (DM)*

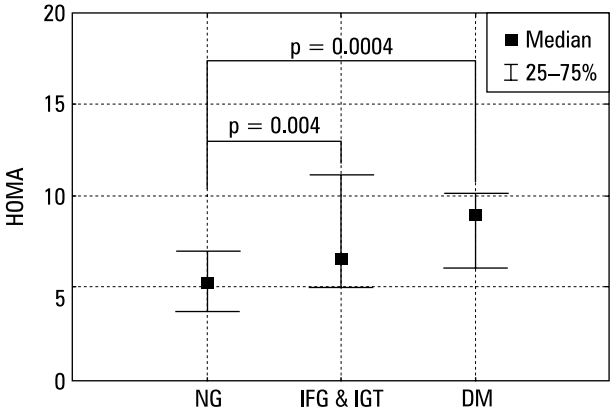


**Figure 3.** *HOMA-IR in acromegalic patients with normoglycaemia (NG), impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and diabetes mellitus (DM)*

**Rycina 3.** *Współczynnik HOMA-IR w grupie pacjentów z akromegalią i prawidłową glikemią (NG), nieprawidłową glikemią na czczo (IFG), nieprawidłową tolerancją glukozy (IGT) oraz cukrzycą (DM)*

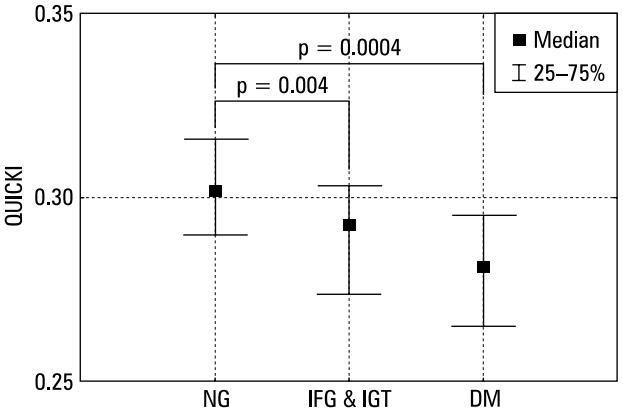


**Figure 4.** *QUICKI in acromegalic patients with normoglycaemia (NG), impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and diabetes mellitus (DM)*

**Rycina 4.** *Współczynnik QUICKI w grupie pacjentów z akromegalią i prawidłową glikemią (NG), nieprawidłową glikemią na czczo (IFG), nieprawidłową tolerancją glukozy (IGT) oraz cukrzycą (DM)*

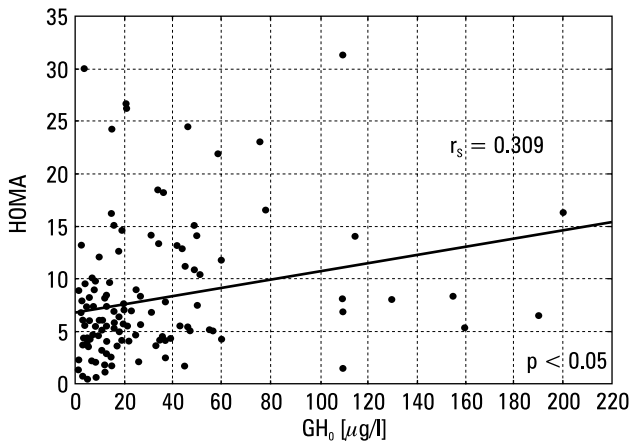


**Figure 5.** *Correlation ($r_S$) between basal plasma GH concentrations and HOMA-IR*

**Rycina 5.** *Korelacja ($r_S$) pomiędzy podstawowym stężeniem GH a współczynnikiem HOMA-IR*

There was no statistically significant difference in basal plasma GH, IGF-1 or fasting insulin concentrations between normoglycaemic patients and those with impairments in glucose tolerance. The groups showed statistically significant differences as far as the age of diagnosis was concerned ($p < 0.01$) (Fig. 2). The acromegalic patients with coexisting diabetes mellitus were 10 years older than the normoglycaemic acromegalics. The median HOMA-IR in patients with normoglycaemia, glucose intolerance and overt diabetes was 5.1, 6.5 and 8.9, respectively ($p < 0.01$) (Fig. 3). The median QUICKI in patients with normoglycaemia, glucose intolerance and overt diabetes was 0.30, 0.29 and 0.28, respectively ($p < 0.01$) (Fig. 4). There was no significant correlation either between basal plasma GH concentration and fasting plasma glucose or between IGF-1 concentration and fasting plasma glucose. There was no correlation between the duration of the disease and fasting plasma glucose. HOMA-IR was positively correlated with basal plasma GH ($GH_0$) , nadir GH during OGTT ($GH_{min}$) and IGF-1 concentrations: $r_S = 0.309$, $r_S = 0.309$, $r_S = 0.429$, respectively ($p < 0.05$) (Fig 5, 6, 7). QUICKI was negatively correlated with plasma $GH_0$, $GH_{min}$ and IGF-1 concentrations: $r_S = –0.309$, $r_S = –0.309$, $r_S = –0.429$, respec-

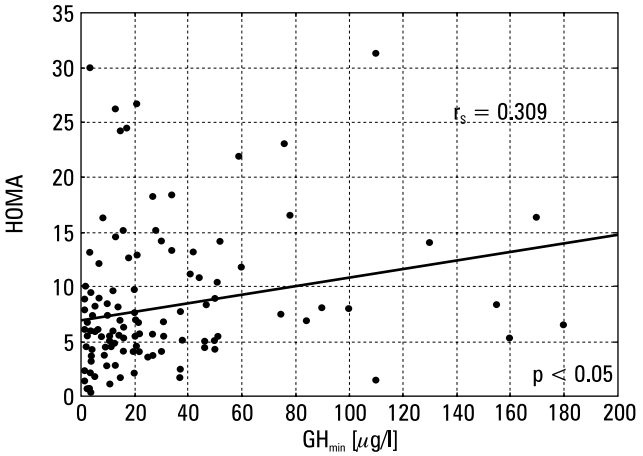


**Figure 6.** *Correlation ($r_S$) between minimal plasma GH concentration during OGTT and HOMA-IR*

**Rycina 6.** *Korelacja ($r_S$) pomiędzy minimalnym stężeniem GH w OGTT a współczynnikiem HOMA-IR*

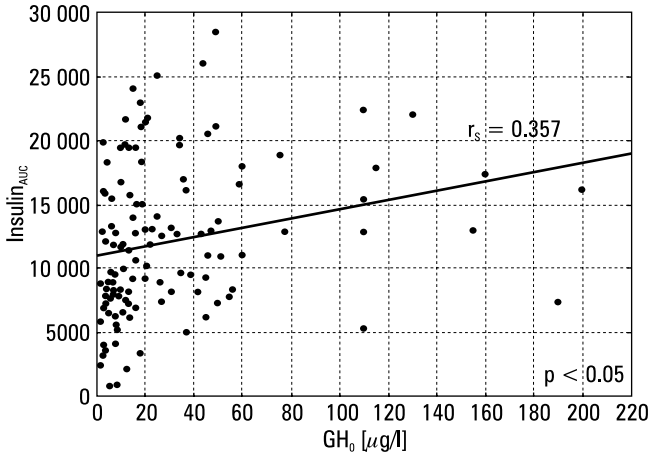


**Figure 8.** *Correlation ($r_S$) between basal plasma GH concentration and insulinAUC*

**Rycina 8.** *Korelacja ($r_S$) pomiędzy podstawowym stężeniem GH a polem pod krzywą dla insuliny (insulinAUC)*

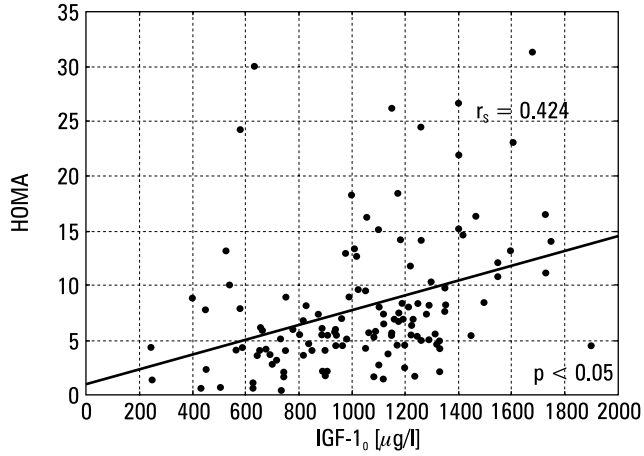


**Figure 7.** *Correlation ($r_S$) between plasma IGF-1 concentration and HOMA-IR*

**Rycina 7.** *Korelacja ($r_S$) pomiędzy stężeniem IGF-1 a współczynnikiem HOMA-IR*

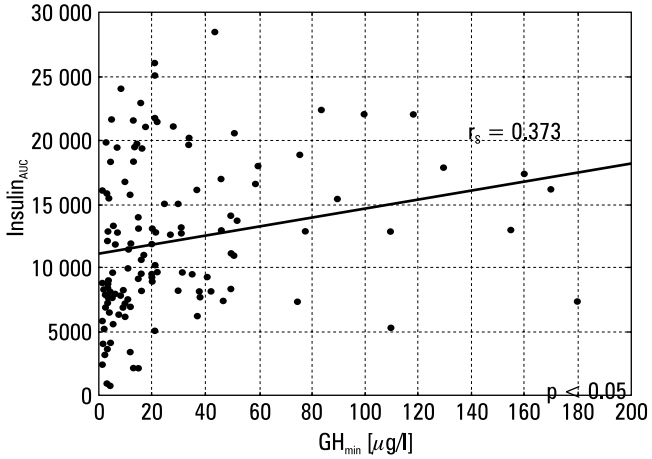


**Figure 9.** *Correlation ($r_S$) between minimal plasma GH concentration during OGTT and insulinAUC*

**Rycina 9.** *Korelacja ($r_S$) pomiędzy minimalnym stężeniem GH w OGTT a polem pod krzywą dla insuliny (insulinAUC)*

tively ($p < 0.05$). The area under the curve for insulin ($insulin_{AUC}$) also positively correlated with plasma $GH_0$, $GH_{min}$ and IGF-1 concentrations: $r_S = 0.357$, $r_S = 0.373$, $r_S = 0.322$, respectively ($p < 0.05$) (Fig. 8, 9, 10).

## Discussion

The prevalence of diabetes mellitus in acromegaly is much higher than in the general population [12]. As already mentioned, the incidence of overt diabetes mellitus in acromegaly differs widely between studies, probably owing to different patient series and ethnicity [8, 9, 13, 14]. Moreover, the majority of the studies were conducted before currently accepted criteria for the diagnosis and classification of diabetes mellitus had been established, and that is why some data may be underestimated [15]. Our study revealed that the incidence of diabetes mellitus in acromegalics is 3.7 fold higher than in the general Polish population (20% *vs.* 5.37%) [16]. We would like to emphasize that this was the first analysis of glucose homeostasis alterations performed in a Polish population of acromegalic patients. The study was based on the most numerous group of patients with this condition treated in a single department.

In the study by Nabarro et al. [14], the analysis of the risk factors promoting the development of glucose

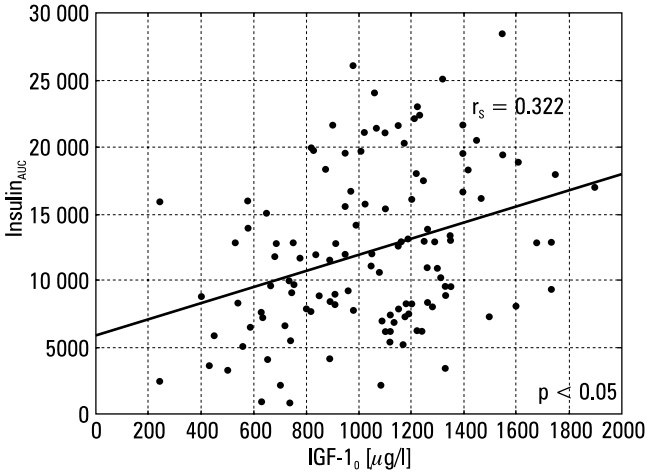


**Figure 10.** *Correlation ($r_S$) between plasma IGF-1 concentration and insulinAUC*

**Rycina 10.** *Korelacja ($r_s$) pomiędzy stężeniem IGF-1 a polem pod krzywą dla insuliny (insulinAUC)*

intolerance revealed that higher GH levels, higher age, and longer duration of the disease significantly predicted a tendency to develop symptomatic diabetes. In the study by Biering et al. [9], ageing was the only variable that significantly predisposed patients to an increase in the severity of this complication. Results from a study by Kreze et al. [8] suggested that the development of glucose intolerance appeared to be associated with a family history of diabetes mellitus and with the concomitant presence of arterial hypertension. Colao et al. revealed that the prevalence of glucose intolerance is similar in men and women with acromegaly [12]. Our study revealed that age is the only predisposing factor and that the mean age of the patients with diabetes mellitus is 10 years higher than the age of normoglycaemic acromegalics. In our group of patients there was no difference between men and women in prevalence of diabetes mellitus. We found that the severity of glucose intolerance does not depend on the duration of the disease. We found no differences between patients with and those without glucose impairments in relation to the level of activity of acromegaly. Fasting plasma glycaemia did not correlate with either plasma $GH_0$, $GH_{min}$ or IGF-1 concentrations. It is noteworthy that the majority of patients with acromegaly are insulin resistant at the moment of diagnosis. In this large cohort of patients we showed that insulin resistance (HOMA-IR) is correlated with the level of activity of the disease: the higher the plasma GH and IGF-1 concentration, the more significant insulin resistance. The highest insulin resistance was found in diabetic and the lowest in normoglyaemic patients, but there was no statistically significant difference between the groups with respect to fasting plasma insulin. This is in contrast to what was postulated in some studies, namely that insulin sensitivity in acromegaly is reduced to a similar extent in acromegalic patients with normal glucose tolerance as in those with IGT or diabetes mellitus, suggesting that a compensatory hyperfunction of pancreatic $\beta$-cells might counterbalance the reduced insulin sensitivity in the patients with normal glucose tolerance, but not in those with IGT or diabetes [8].

## Conclusions

The prevalence of diabetes mellitus in acromegaly is much higher than in the general population. The occurrence of glucose tolerance impairments does not depend on the duration of the disease. In patients with acromegaly insulin resistance and hyperinsulinaemia are positively correlated with the level of activity of the disease.

The high prevalence of diabetes and intermediate forms of glucose intolerance in acromegalics should urge clinicians to treat this condition not only with the aim of reducing growth factors but also to maintain the favourable effects on metabolism and metabolism-related mortality.

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