Is there any relation between hyperinsulinemia, insulin resistance and colorectal lesions in patients with acromegaly?

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Abstract

INTRODUCTION: Pathogenesis of colonic lesions in patients with acromegaly remains still unclear. There are suggestions that apart from somatotropin axis hormones (GH and IGF-1), other agents also take part in this process. Molecular and animal studies indicate a vital role of hyperinsulinemia in development of colorectal neoplasms. **AIM OF THE STUDY** was to evaluate a relation between insulin level, insulin resistance and its anthropometric markers and colorectal lesions in patients with acromegaly. **MATERIAL AND METHODS**: The study consisted of 40 patients with active, newly diagnosed acromegaly; 24 women and 16 men aged from 24 to 77 years (mean age 50.1, SD±12.1). The analysis included the results of somatotropin axis function (GH and IGF-1 level), carbohydrate metabolism assessment (fasting serum glucose and insulin levels, oral glucose tolerance test, HOMA-IR for insulin resistance), the results of anthropometric measurement (BMI, WHR) and colonoscopy. **RESULTS:** Colon pathologies (60 polyps and 2 flat lesions) were discovered in 19 (47.5%) patients with acromegaly, 8 of them had multiple polyps. Hyperplastic polyps were revealed in 11 (27.5%), while adenomas in 8 (20%) acromegalics. Patients with colorectal lesions were found to have higher WHR then subjects with normal colon (p=0.033). Positive correlation between the number of hyperplastic polyps in the patients with multiple changes in the colon and IGF-1 (p=0.025), insulin level (p=0.005) and HOMA-IR (p=0.001) was found. Multiple adenomas correlated positively with insulin level (p=0.007), HOMA-IR (p=0.006) and BMI (p=0.015). **CONCLUSIONS:** The study results show a relation between hyperinsulinemia, insulin resistance and colon pathologies in acromegaly. Fasting insulin level and HOMA-IR correlate positively with the number of hyperplastic polyps and adenomas in acromegalic patients with multiply colorectal lesions.

ORIGINAL ARTICLE

INTRODUCTION

Frequent occurrence of colon pathologies in patients with acromegaly in comparison with the general population (Colao et al. 1997, Jenkins et al. 1997, Terzolo et al. 2005) indicates a vital role of somatotropin axis hormones in this process. *In vitro* and *in vivo* studies showed that growth hormone (GH) and insulin-like growth factor type 1 (IGF-1) stimulate proliferation (Jenkins et al. 2000) and suppress the apoptosis (Bogazzi et al. 2004, 2005) of normal and neoplastic cells of the colon epithelium. Additionally, IGF-1 shows mitogenic activity towards the colon mucous cells (Yu and Rohan, 2000) and induces expression of other local growth factors taking part in carcinogenesis process, for example, vascular endothelial growth factor VEGF (Akagi et al. 1998).

According to several authors, colon pathologies appear in 24–48% patients with acromegaly (Colao et al. 1997, Jenkins et al. 1997, Terzolo et al. 1994). The changes most often include hyperplastic polyps, less often adenomas, adenocarcinomas and carcinomas. The fact that colorectal lesions occur in the colon only in some patients with hypersomatotropinemia shows that, apart from somatotropin axis hormones (GH and IGF-1), other agents take part in this process. Hyperinsulinemia, which is a common disorder of patients with acromegaly, seems to be one of them. Molecular and animal studies showed that increased serum insulin level is an independent risk factor of colorectal adenomas (Chang and Ulrich, 2003, Giovannucci, 1995).

Insulin, similarly to IGF-1, stimulates a growth of normal and neoplastic cells of the colon through specific receptors localized on the cell surface (MacDonald et al. 1993a). Moreover, high insulin level can provoke mitogenic activity initiating neoplastic process in the colon or accelerate a transformation of benign adenomas into adenocarcinomas and carcinomas (Corpet et al. 1997, Bjork et al. 1993, Tran et al. 1996). An influence of insulin on IGF-1 bioavailability through changes in proteins binding insulin-like growth factors (IGFBPs) level cannot be neglected (Giovannucci, 2001).

The aim of the study was to evaluate a relation between insulin level, insulin resistance, its anthropometric expression and colorectal lesions in patients with acromegaly.

MATERIAL AND METHODS

The study included 40 patients with newly diagnosed active acromegaly, 24 women aged from 33 to 73 years (mean age 56.2±11.4) and 16 men aged 23–61 years (mean age 44.1±13.3). Duration of symptoms was for women from 3 to 23 years (mean 9.2±6.5) and for men 1–13 years (mean 7.1±4.5). The patients qualified for the study did not have any family history of colorectal pathology.

The diagnosis of acromegaly was based on clinical symptoms, laboratory test results, such as increased serum level of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) above the normal range for age and sex, lack of suppression of serum GH levels below 1 ng/ml during on oral 75-g glucose tolerance test and presence of adenoma in the pituitary, confirmed by magnetic resonance imaging (MRI).

All patients had carbohydrate metabolism evaluated – fasting serum glucose and insulin levels were marked, 75g glucose oral tolerance test was performed, insulin resistance was assessed by using Homeostasis Assessment Model method (HOMA-IR). Moreover, anthropometric examination, closely linked to the syndrome of insulin resistance was applied, like BMI (Body Mass Index), a reliable marker of obesity and WHR (Waist to Hip Ratio), that define the distribution of fat tissue.

Colonoscopy was performed in all patients after their written consent, first in white and then in monochromatic light. A colonoscope by Olympus, CC-EL with Xillix LIFE Lung set for tissue autofluorescence examinations *in vivo* was used. A device by Olympus, CLF-U40 with an in-built filter selecting light in the range 425–455nm was the source of monochromatized light. The polyps removed by endoscopy and specimens taken from flat lesions were sent for routine histopathology.

RESULTS

The resume of the results of colonoscopy and histopathology in patients with acromegaly is presented in Table 1. Colorectal lesions were discovered in 19 (47.5%) patients with acromegaly, in 8 (20%) of them multiple polyps (from 2 to 26) were found. The localization of colon pathologies is shown in Figure 1. Histopathology revealed mucous membrane hyperplasia within 42 polyps in 11 (27.5%) patients. Tubular, tubular-villous and villous adenomas were discovered within 18 polyps and in 2 flat lesions in 8 (20%) patients. In 3 cases, the co-occurrence of hyperplastic polyp and adenoma were depicted.

Carbohydrate disturbances were found in 18 (45%) acromegalics, which included diabetes in 9 patients and impaired glucose tolerance in the remaining 9 subjects. The patients with diabetes had higher levels of GH ($p=0.03$) and insulin ($p<0.001$), higher HOMA-IR index ($p<0.001$) and longer duration of acromegaly ($p=0.012$) than nondiabetic subjects (Fig.2)

Obesity (related to BMI) was diagnosed in 17 (42.5%) acromegalic patients. Central distribution of fat tissue was found in 19 patients (18 women and 1 man). Significantly higher value of WHR was found in patients with colorectal pathology in comparison to the subjects with normal colon (0.89 vs. 0.84, $p=0.033$). No significant differences within parameters such as: GH, IGF-1, glucose, insulin levels, BMI, HOMA-IR, patients' age and duration of acromegaly symptoms were shown between those groups. Correlation analysis revealed that the

Table 1. Results of colonoscopy and histopathology assessment of colonic lesions in the group of acromegalic patients.

Number of patients	Colorectal lesion		Histopathology assessment	
	polyps	**flat lesions**	**hypertrophy**	**adenoma**
Female N=24	N=9 (42 polyps)	N=2 (2 flat lesions)	N=4 (31 polyps)	N=5 (13 polyps, 2 flat lesions)
Male N=16	N=10 (18 polyps)		N=7 (11 polyps)	N=3 (5 polyps)
N=40	N=19 (60 polyps)	N=2 (2 flat lesions)	N=11 (42 polyps)	N=8 (18 polyps, 2 flat lesions)

Table 2. Correlation between number of hyperplastic polyps, adenomas and exponents of hormonal and metabolic condition in acromegalic patients with multiply colonic lesions (r - Pearson coefficient, NS - not significant).

	Number of hyperplastic polyps		Number of adenomas	
	r	***p***	***r***	***p***
IGF-1	0.3587	0.025	0.2839	NS
Insulin	0.4369	0.005	0.4236	0.007
HOMA-IR	0.5003	0.001	0.4632	0.003
BMI	0 .1283	NS	0.3298	0.038

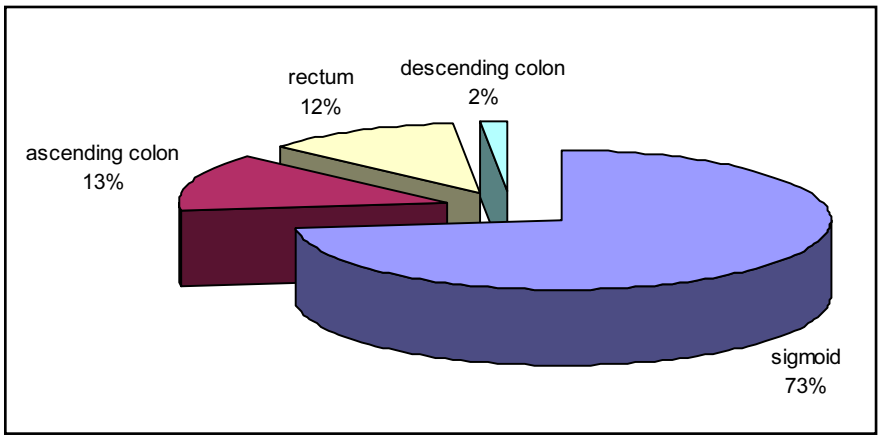

Figure 1. Localization of colorectal lesions in patients with acromegaly.

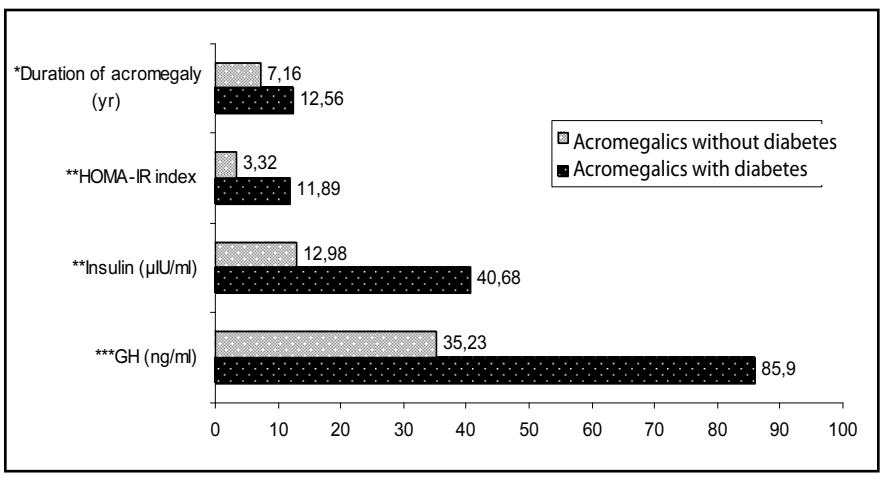

Figure 2. Significant differences in assessed parameters (age, BMI, WHR, GH, IGF-1, insulin level, HOMA-IR, duration of acromegaly symptoms) between acromegalics with and without diabetes (*p=0.012, **p<0.001, ***p=0.03).

number of hyperplastic polyps in patients with multiple colonic lesions was directly proportional to the levels of IGF-1 (p=0.025), insulin (p=0.005) and HOMA-IR index (p=0.001) however, the number of adenomas correlated positively with insulin level (p=0.007), HOMA-IR (p=0.006) and BMI (p=0.015) – Table 2. Multiple regression analysis showed significant influence of factors such as HOMA-IR (R^2=0.21; p=0.003) and BMI (R^2=0.082; p=0.047) on occurrence of multiple adenomas of the colon and significant influence of HOMA-IR (R^2=0.25; p=0.001) on appearance of multiple hyperplastic polyps.

DISCUSSION

Numerous studies among patients with acromegaly provide divergent results on the prevalence of colon pathologies. According to the opinion of most authors, acromegaly is conductive to neoplasm development in the distal part of the alimentary tract. A resume of 14 prospective studies carried out in 800 patients with acromegaly shows a 6–7 fold increase of the risk of colon cancer in comparison with the control group (Jenkins et al. 2006). According to other investigators the risk of colorectal neoplasm in patients with acromegaly is not higher than in general population (Bhansali et al. 2004, Renehan et al. 2000).

In order to evaluate the colon more precisely, two techniques of endoscopy, described in our previous paper (Matyja et al. 2006, Zieleznik et al. 2001), were used. Traditional white light colonoscopy showed presence of 60 polyps in 19 (47.5%) patients. Monochromatic light colonoscopy performed at the second stage revealed two additional flat lesions (adenomas), invisible in classic colonoscopy. Colon pathologies in 27% patients were of hyperplastic polyp character, in 20% of the subjects adenomas were diagnosed.

The results are similar to those received by other authors. Colao et al. (1997) in their study of 50 patients with acromegaly found polyps of the colon in 46% of the subjects, which included hyperplastic polyps in 24%, colon adenomas in 22%, and adenocarcinoma in 2% patients. Jenkins et al. (1997), in a group of 129 acromegalics, found adenomas in the colon in 26% subjects, and adenocarcinoma in 5%. On the other hand, Bogazzi et al. (2006), in a recently published study including 79 patients with acromegaly showed a distinctly higher percentage of patients with colon adenomas (33%) and relatively fewer patients with hyperplastic polyps (9%). Contrary to the above mentioned studies, we have not found adenocarcinomas which could be a result of a smaller number of patients in our study.

Analyzing localization of colon pathologies, it was noticed that both hyperplastic polyps and adenomas occurred mainly in the distal part of the colon (sigmoid, descending colon and rectum); only 8 polyps, including 3 hyperplastic polyps and 5 adenomas, were placed in the ascending colon. These results confirm the observations of other authors who claim that hyperplastic lesions are usually situated in the distal part (Colao et al. 2004, Khan et al. 2002), and adenomas in the proximal part of the colon (Cats et al. 1996, Jenkins et al. 1997).

Similarly to other authors, we did not see a significant difference in GH and IGF-1 levels between the group of acromegalics with colon pathology and the one with normal colon. However, numerous *in vitro* and *in vivo* studies proved that IGF-1 exerts proliferative, mitogenic and antiapoptotic activity to normal and neoplastic cells of the colon epithelium (Bogazzi et al. 2005, Jenkins et al. 2000, MacDonald et al. 1993a, Yu and Rohan, 2000). Not only levels of somatotropin axis hormones but also time of exposure to growth factors activity might have considerable influence on pathology of the colon. Most epidemiological studies, including ours, have retrospective character, therefore complete information about the duration of the disease process and the levels of GH and IGF-1 in the patients before diagnosis is not available. Moreover, the existence of other additional agents which contribute to development of pathologic changes in the colon of acromegalic patients should be considered.

Analysis of the results of our study did not show any significant difference in parameters evaluating carbohydrate metabolism (serum glucose and insulin levels and HOMA-IR index) between the group with pathology and without pathology in the colon. However, positive correlation between the number of colon adenomas and hyperplastic polyps and the insulin level and value of HOMA-IR index in the patients with multiple colorectal lesions was found. These results suggest that hyperinsulinemia and insulin resistance participate in pathogenesis of colonic lesions of acromegalic patients. Many epidemiological studies related to the increasing number of colon tumours in highly developed countries consider hyperinsulinemia and hyperglycemia to be risk factors for these diseases. Chang and Ulrich (2003) and Larsson SC et al. (2005) reviewed papers related to this subject and concluded that there is a minor increase of colon cancer risk in patients with type 2 diabetes or insulin resistance. Recently published papers confirmed a correlation between the level of insulin and presence of hyperplastic polyps and adenomas in the colon (Schoen et al. 2005, Yoshida et al. 2006).

What is the role of insulin in development of colon pathology? Molecular studies and studies of animal models showed that insulin is an important growth factor for normal and neoplastic cells of colon epithelium. These cells possess receptors both for insulin and for IGF-1 (Guo et al. 1992, MacDonald et al. 1993b). Insulin is thought to be conductive to carcinogenesis process directly, through own receptor activation and indirectly, through stimulation of receptors for IGF-1 and hybrid receptors IGF-1/insulin (Khandwala et al. 2000). The insulin influence on the increase of IGF-1 bioavailability as a result of synthesis inhibition of the proteins binding insulin-like growth factors (IGFBPs) in the liver

(Giovannucci, 2001, Mounier and Posner, 2006, Sandhu et al. 2002) is of vital importance. The mechanism of direct insulin mitogenic activity has not been fully explored yet. Studies at molecular level showed that this process can involve activation of the *ras* protein. It was found that insulin stimulates violent increase of activity of this protein in cells containing insulin receptors (Burgering et al. 1991, Jhun et al. 1994). Apart from mitogenic activity, insulin exerts inhibiting influence on the process of colon epithelium cell apoptosis, which additionally contributes to increased pathology risk in this part of the alimentary tract (Keku et al. 2005).

Hyperinsulinemia and insulin resistance often coexist with obesity, especially with abdominal type. WHR ratio reflects the central distribution of fat tissue and is an anthropometric expression of insulin resistance. Visceral adipose tissue is a place of synthesis of numerous peptides, cytokines and factors such as Tumour Necrosis Factor alfa (TNFα) [Hotamisligil et al. 1996], leptin (Ahren et al. 1997), angiotensinogen (Engeli et al. 1999) and plasminogen activator inhibitor type I (PAI-I) [Alessi et al. 1997] which are involved in the pathogenesis of chronic diseases including diabetes and neoplasms. It can be an explanation of the relation between colon polyps and a value of waist-to-hip ratio which was observed among acromegalic patients in our study. Additionally, multifactor regression analysis showed that BMI is an essential factor conductive to development of colon multiple adenomas in this group of patients. According to some researchers, BMI and WHR are independent risk factors of colon adenoma and carcinoma (Giovannucci et al. 1996, Kono et al. 1999).

Summing up, hyperinsulinemia and insulin resistance can be of some importance in the development of colorectal lesions in acromegalic patients. However, the pathogenesis of those lesions is still unclear, which indicates a necessity for further study.

CONCLUSION

The study results showed a relation between hyperinsulinemia, insulin resistance and colon pathologies in acromegaly. Fasting insulin level and HOMA-IR correlate positively with the number of hyperplastic polyps and adenomas in acromegalic patients with multiply colorectal lesions.

Statistical analysis

After distribution analysis with W Shapiro-Wilk test for the data of normal distribution, t-Student test was applied for the unconnected values or U Mann-Whitney test was used for the data with distribution different than normal. The multiple regression analysis by the method of step by step regression for dependent variables "Number of hyperplastic polyps" and "Number of adenomas" was made; the GH, IGF-1, glucose, insulin levels, HOMA-R, BMI, WHR, patient's age and disease duration were independent variables. The correlation analysis applied Pearson linear correlation method and Spearman rank–order correlation in specified cases. The results were presented in the form of mean value and standard deviation (SD). Value $p<0.05$ was assumed to be statistically significant.

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