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Prevalence and recurrence rate of colonic lesions in acromegalic patients

Research Article

Dilek Berker[1*], Yasemin Ates Tutuncu[1], Serhat Isik[1], Yusuf Aydin[1], Ufuk Ozuguz[1], Gulhan Akbaba[1], Osman Yuksel[2], Gonul Erden[3], Emin Altiparmak[4], Serdar Guler[1]

[1] *Ministry Of Health, Ankara Numune Research and Training Hospital, Endocrinology and Metabolism Clinic, 06100 Ankara, Turkey*

[2] *Ministry Of Health, Diskapi Yildirim Beyazit Research and Training Hospital, Gastroenterology Clinic, 06200 Ankara, Turkey*

[3] *Ministry Of Health, Ankara Numune Research and Training Hospital, Department of Biochemistry, 06100 Ankara, Turkey*

[4] *Ministry Of Health, Ankara Numune Research and Training Hospital, Gastroenterology Clinic, 06100, Ankara, Turkey*

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Abstract: Acromegaly is associated with an increased prevalence of colonic polyps. The aim of this study was to evaluate the prevalence and recurrence rate of colonic polyps in acromegalic patients. Ninety-six acromegalic patients and 100 irritable bowel syndrome patients (IBS) were enrolled in the study. Twenty patients who were cured exclusively by surgery, and 20 patients that could not be hormonally controlled were re-examined colonoscopically after 36 months. Twenty-nine of 96 acromegalic patients (30.2%) had colonic polyps. In the IBS group, 10 (10.0%) had colonic polyps. The prevalence of colonic polyps was significantly higher in acromegaly. The group of acromegalic patients with and without polyps did not differ significantly with regard to plasma GH, IGF-I, fasting insulin levels and glycemic status. The presence of colonic polyps was correlated with increased patient age and male gender. We did not observe a difference in terms of polyp recurrence frequencies in the patients cured by surgery compared to uncontrolled patients. Acromegalic patients have a higher prevalence of colonic polyps than that of control subjects. We could not identify any factors that could predict polyps within the acromegalic patients – but age and male sex.

Keywords: *Acromegaly • Colon polyp • IGF-I • GH • Insulin*

1. Introduction

Acromegaly is caused by excessive secretion of GH, usually by pituitary somatotropinoma, inducing increased generation of IGF-I. Both these hormones are known to promote cellular growth, proliferation, and proto-oncogene expression [1-3]. In addition, acromegaly is associated with an increased prevalence of abnormal glucose tolerance, and hyperinsulinemia due to insulin resistance [4]. The role of hyperinsulinemia in the pathogenesis of colorectal cancer is well known and the risk of colorectal cancer is increased in diabetic individuals compared to nondiabetic individuals [5-8]. Therefore, we expect to find pathologic colon fidings more frequently in acromegalic patients than the normal population. There are conflicting studies on the correlation between increased colon polyps with GH and IGF-I levels and insulin resistance in acromegalic patients [9-14].

The aim of this study was to evaluate the prevalence and recurrence rate of colonic polyps in acromegalic subjects, and also to detect whether a relationship exists between IGF-I, GH, fasting insulin plasma levels, HOMA-IR and the presence of polyps.

* *E-mail: dberker6@yahoo.com*

2. Material and Methods

2.1. Study design

Ninety-six newly diagnosed acromegalic patients admitted to the Endocrinology and Metabolism Clinic of the Ankara Numune Research and Training Hospital from 2003 to 2008 were enrolled in the study. We performed a retrospective analysis of patients who underwent colonoscopy screening before treatment. Diagnosis of acromegaly was performed on the basis of the following clinical and laboratory conditions: clinical presentation of acromegaly; nadir GH>1 ng/ml after a 75 g oral glucose load and subsequent measurements of GH and glucose every 30 minutes over 2 hours; age and gender-matched increased IGF-I plasma levels, and neuroradiologic findings of pituitary adenoma. Patients with a history of polypectomy, colorectal surgery, and a family history of colorectal cancer were excluded.

We estimated the duration of the disease, bearing in mind the date when the symptoms of patients appeared, and the time they were referred to our clinic. As a control group, we enrolled 100, age- and sex-matched subjects referred to the Endoscopy Unit for symptoms suggesting irritable bowel syndrome (IBS) who were undergoing colonoscopy. The control group was biochemically screened to exclude acromegaly. We followed-up on our patients after 36 months. Twenty patients cured exclusively by surgery, and 20 patients who could not be hormonally controlled by surgery and medical therapy were then re-examined colonoscopically.

2.2. Colonoscopy and histological evaluation

Bowel preparation included 4 liters of polyethylene glycol and bisacodyl. All colonoscopies were performed by a single expert endoscopist (OY) using a flexible Fujinon EC-450 WL scope videoendoscope. During colonoscopy, the location of all polyps was determined on the basis of the depth of insertion of the colonoscope and anatomical landmarks, including the hepatic flexure, the splenic flexure, and the junction of the sigmoid and descending colon. A biopsy forceps was used to estimate the diameter of a polyp before polypectomy was performed.

When polyps were discovered, polypectomy was performed after obtaining patients' informed consent. All retrieved polypoid lesions were sent to the pathology laboratory for histological evaluation. We recorded the number, size, sites, and histological types of colonic polyps. The distal colon was defined as the rectum, sigmoid, and descending colon, up to, but not including the splenic flexure. We defined the proximal colon as the splenic flexure and included other more proximal portions of the colon.

2.3. Laboratory Assays

Venous blood was sampled after an overnight fast and centrifuged at 3000 rpm for 30 min at 4°C. Plasma glucose was measured with standard methods. Chemiluminescent immunoassay is used for the quantitative determination of insulin levels in human serum using the Unicel DxI 800 Access Immunoassay Systems (Beckman Coulter, USA). Serum GH levels were measured by immunoradiometric assay (IRMA), using commercially available kits (hGH - IRMA CT; RADIM, Roma, Italy). Serum GH levels were measured by immunoradiometric assay (IRMA), using commercially available kits (hGH - IRMA CT; RADIM, Roma, Italy). The sensitivity of the assay was 0.04 ng/ml. The calibrator has been calibrated against the WHO 80/505 International Standard preparation (1ng hGH = 2 μIU). The reference ranges of GH were 0-16 ng/ml for women and 0-8 ng/ml for men.

Serum IGF-1 was measured with a solid-phase, enzyme-labeled chemiluminescent immunometric assay (Immulite IGF-I, Siemens Medical Solutions Diagnostics, UK), using IMMULITE 1000 System. In our laboratory, the reference ranges of IGF-I in 21–25, 26–30, 31–35, 36-50, 51–60, 61–70, and more than 70-yr-old individuals were 116–358, 117–329,115–307, 94–284, 81–238, 69–212, and 55–188 ng/ml, respectively. The analytical sensitivity of the assay was 20 ng/ml. Calibration was up to 1600 ng/ml (WHO NIBSC 1st IRR 87/518). The within-run coefficients of variation were 3.1, 4.3 and 3.5% for low, medium, and high points of the standard curve, respectively. The total coefficients of variation were 6.1, 6.9, and 5.8% for low, medium, and high points of the standard curve, respectively.

The degree of IR was estimated using the homeostasis model assessment of insulin resistance (HOMA-IR). The homeostasis model assessment of insulin resistance was calculated using the following formula: fasting plasma glucose (mg/dL) x fasting plasma insulin (IU/ml) / 405.

2.4. Statistical analysis

The data were analyzed with SPSS version 11.5 for Windows (Chicago, IL) package program. We determined whether the continuous variables were normally distributed using the Shapiro Wilk test. Continuous variables were expressed as mean ± standard deviation or median (minimum - maximum), where appropriate. Nominal data were shown as number of cases and as percentages. Means were compared by Student's t test, or the Mann Whitney U test where appropriate. Nominal data were tested by Pearson Chi-square or Fisher's Exact test, where applicable. A *p* value of less than 0.05

Table 1. Clinical characteristics and colorectal lesions of acromegalic patients and control group.

Variables	Control (n=100)	Acromegalic patients (n=96)	p
Age (years)	44.5±10.1(25.0-69.0)	44.7±11.2(18.0-65.0)	0.838[a]
Gender-Female (%)	56 (56.0)	58 (60.4)	0.315[b]
BMI (kg/m^2)	29.2±4.6	29.5±4.9	0.918[a]
GH (ng/ml)	2.0±0.7 (0.90-4.52)	19.5±22.2(4.96-97.56)	<0.001[c]
IGF-I (ng/ml)	180.3± 60.3(67.0-305.0)	969.4±400.3(493.0-2170.0)	<0.001[c]
Insulin (μIU/ml)	5.9±2.4(2.5-15.0)	11.3±10.3(1.6-53.8)	0.017[c]
HOMA-IR	1.2±0.5(0.4-2.7)	3.5±5.1(0.3-27.0)	0.001[c]
Polyp number (%)	10 (10.0)	29 (30.2)	<0.001[b]
Proximal localization (%)	6/10 (60.0)	23/29 (79.3%)	0.228[b]
Polyp diameter (mm)	5.1±1.9	5.2±2.8	0.548[c]
Histological findings (%)			-
Hyperplastic	6 (60.0)	13 (%44.8)	
Adenomatous	4 (40.0)	14 (%48.3)	
Leiomyoma	-	2 (%6.9)	

[a] *Student's t test.*
[b] *Pearson Chi-square test.*
[c] *Mann Whitney U test.*
BMI: body mass index; DM: diabetes mellitus; GH: growth hormone; HOMA-IR: homeostasis model assessment insulin resistance; IGF-I: insulin like growth factor-1

was considered statistically significant. To assess the risk of colorectal lesions in acromegalic patients, we calculated the odds ratio for colorectal lesion with 95% confidence intervals (CI).

We evaluated the optimal cut-off points for age to determine colonic lesions with Receiver Operator Characteristics (ROC) analysis, considering the maximum sum of sensitivity and specificity for the significance test. Sensitivity *(q)* and specificity *(p)* are both functions of some cut-point, with maximum {q(c)+p(c)-1} occurring at the optimum cut-point, *c*. The cut-point that achieves this maximum is referred to as the optimal cut-point (*c*) because it is the cut-point that optimizes the biomarker's differentiating ability when equal weight is given to sensitivity and specificity. We also calculated the area under curve (AUC) and 95% confidence intervals (CIs).

3. Results

The mean age of the acromegalic patients was 44±11.2 years (38 males and 58 females, mean duration of disease 47.6±43.7 months) and the mean age of the IBS patients was 44.5 ± 10.0 years (44 males and 56 females) (Table 1). The mean age, gender distribution, and BMI values of both groups were similar. However, GH, IGF-1, insulin levels and insulin resistance (HOMA-IR values) were significantly higher in the patient group (Table 1). In the acromegaly group, 20 patients (28.2%) had diabetes mellitus, while there were no diabetic patients in the control group.Twenty-nine of 96 acromegaly patients (30.2%) had colonic polyps,13 (44.8%) had hyperplastic polyps, 14 (48.3%) had adenomatous polyps, and 2 (6.9%) had leiomyoma. In the IBS group, 10 (10.0%) had colonic polyps; six (60.0%) had hyperplastic polyps, and 4 (40.0%) had adenomatous polyps. The prevalence of colonic polyps was significantly higher in acromegalic patients (p<0.001). We did not find a significant difference between the acromegaly patients and the control group in terms of polyp dimensions.

We did not observe a significant difference between the control group and acromegalic individuals considering the settlement of polyps (proximal localization 60.0%, and 79.3%, respectively; p=0.228). We also did not observe any difference in acromegaly patients in terms of the distribution of hyperplastic polyps (4 transverse colon, 4 descending colon, 1 cecum, 1 rectum and 3 sigmoid) and adenomatous polyps (2 sigmoid, 5 transverse colon, 2 descending colon and 2 cecum) (p=0.439).

The group of acromegalic patients with and without polyps did not differ significantly with regard to duration of disease, body mass index, polyp size, plasma GH, IGF-I, fasting insulin levels, HOMA-IR values, and impaired glucose tolerance, impaired fasting glucose and diabetes mellitus (Table 2). The average age of the acromegalic patients with polyps was higher (p<0.001) and the ratio of male patients was higher (p=0.012). In the control group we did not determine a significant difference between the individuals with or without polyps in terms of age or gender (40.0±4.9 vs. 45.0±10.4 years, p=0.137; %60 vs. %50 male gender, p=0.333).

Table 2. Comparison of acromegalic patients with and without polyps.

Variables	Without polyp (n=67)	With polyp (n=29)	p
Age (year)	41.6±11.4(18-65)	51.9±6.6(43-64)	<0.001[a]
Gender-Male (%)	21 (31.3)	17 (58.6)	0.012[b]
BMİ	28.8±4.5	31.1±5.3	0.090[a]
Disease duration (month)	48 (6-144)	36 (2-240)	0.744[c]
GH (ng/mL)	23.3±17.7(4.9-97.5)	24.9±18.5(11.9-85.6)	0.336[c]
IGF-I (ng/mL)	934.1±415.8 (493.0-2170.0)	1050.8±355.5(448.0-1827.0)	0.154[c]
Insulin (μIU/mL)	18.2±11.8(1.6-38.4)	26.0±10.7(13.1-43.3)	0.080[c]
HOMA-IR	4.43±3.3(0.32-10.87)	6.5±3.5(2.6-12.1)	0.070[c]
Pituitary adenoma volume (cm3)	1.20(0.04-14.54)	3.20(0.01-78.0)	0.188[c]
IFG (%)	14 (20.8)	8 (27.6)	0.448[b]
IGT (%)	6 (8.9)	1 (3.4)	0.309[d]
DM (%)	13 (19.4)	7 (24.1)	0.425[d]

[a] *Student's t test.*
[b] *Pearson Chi-square test.*
[c] *Mann Whitney U test.*
[d] *Fisher's Exact Probability test.*
DM: diabetes mellitus; GH: growth hormone; HOMA-IR: homeostasis model assessment insulin resistance; IFG: impaired fasting glucose; IGF-I: insulin like growth factor-1; IGT: impaired glucose tolerance

Diabetes prevalence was higher in patients with polyps compared to patients with no polyps, although it was not significant (35.7% and 20.0% respectively, p=0.237). We did not observe a difference between acromegalic patients with hyperplastic polyps and acromegalic patients with adenomatous polyps in terms of age, size, duration of disease insulin, baseline GH and IGF-I levels and HOMA-IR values. Finally, we did not observe a difference between patients with proximal polyps and distal polyps in terms of IGF-I, GH and insulin levels, HOMA-IR values, age, and gender (p>0.05 for all parameters).

While no correlation was determined in acromegaly patients in terms of other parameters, the presence of colonic polyps correlated with patients' age (r: 0.371, p<0.001) and male gender (r: 0.271, p=0.01). However, there was no correlation in the control group between colon polyp presence and of the parameters.

When the relationship between colon polyp presence and age was evaluated in acromegaly patients, the area under the curve (AUC) of the Receiver Operator Characteristics (ROC) and the 95% CI were assessed to be 0.774 (0.683-0.864). The most likely age in acromegaly patients to determine colon polyp presence was determined as 44.5 years (93.1% sensitivity and 64.2% specificity). We observed colon polyps in 6.4% (3 patients) of the patients at a younger age than the cut-off value, colon polyps were observed in 53.0% (26 patients) of the patients at less than or equal to 45 years of age (p<0.001).

The odds ratio and the 95% confidence interval of acromegaly presence for the development of colon polyps were 2.7 and 95% CI 0.501-14.585 respectively. At the end of the 36-month follow-up period, there were 20 patients who have been cured only by surgery, and another 20 patients who could not be hormonally controlled with any treatment methods. These two patient subgroups were compared in terms of polyp numbers in repeated colonoscopies.We did not detect any significant difference between patients who were cured and hormonally uncontrolled regarding prevalence (2 (10%) and 7 (35%), p=0.058, respectively) and recurrence rate (1 (5%), 3 (15%), p=0.381, respectively) of the colonic polyps (Table 3).

4. Discussion

We found that the frequency of colonic polyps is increased in the acromegalic patient group, which had a higher level of GH, IGF-I, insulin and which consisted of a higher number of diabetic individuals. However, we did not identify any factors that could predict polyps within the acromegalic patients – except the established risk factors of colonic polyps such as age and male sex.

Studies conducted on the correlation between acromegaly and the risk of cancer focus more on colorectal cancers; however, findings obtained from previously performed studies are unsatisfactory on the issue. Colorectal cancer in acromegaly is still debated in literature [15-17]. In a study performed on 210 acromegalic patients, Colao et al. found colonic lesions in 38.6% of their persions, with 2.8% being adenocarcinoma [18]. The in-depth analysis of the

Table 3. Comparison between the cured acromegalic patients and the patients unable to be hormonally controlled.

Variables	Cured (n=20)	Uncontrolled (n=20)	p
Age (year)	40.1±9.6	42.9±12.7	<0.001[a]
Gender-Male (%)	2 (10.0)	6 (30.0)	0.114[b]
Disease duration (month)	12 (6-120)	48 (2-240)	0.744[c]
GH (ng/mL)	22.6±27.8	20.2±16.0	0.336[c]
	(3.2-97.5)	(4.3-50)	
IGF-I (ng/mL)	912.5±312.4	1087.7±468.7	0.154[c]
	(493.0-1400.0)	(449.0-2170.0)	
Pituitary adenoma volume (cm^3)	3.47	2.77	0.188[c]
	(0.01-14.54)	(0.05-78.0)	
Polyp number at diagnosis (%)	2 (10.0)	7 (35.0)	0.058[b]
Polyp number at control (%)	1 (5.0)	3 (15.0)	0.381[b]

[a] *Student's t test.*
[b] *Pearson Chi-square test.*
[c] *Mann Whitney U test.*
GH: growth hormone; IGF-I: insulin like growth factor-1

aforementioned study revealed that colon polyps and adenocarcinoma were correlated with the presence of diabetes mellitus and insulin levels, but not with IGF-I and GH levels. Interestingly, the reported GH and IGF-I levels of acromegalic patients without polyps were higher, although not significantly, compared to patients with polyps.

Researchers tried to explain this unexpected conflict by improbably low IGFBP-3 levels that may accompany high levels of GH/IGF-I. In one study, the rate of colonic lesions was 51.7%, and 10.3% of it was colon carcinoma [19]. In our study, the colonic lesion prevalence was observed as 30.2%, and no carcinoma was found.

The difference in age and disease duration in patient populations in both of the studies mentioned above, and in our patients, can explain the difference observed in colonic lesion prevalence. The average ages of the patients in studies by Colao et al., and by Kurimoto et al., and in our study, were 44 years (20-82 years), 55 years (21-86 years), and 44 years (18-65 years), respectively; and disease durations were 96 months (12-360 months), 11.8 years (2-43 years), and 47.6 months (2-240 months). We observed that patients in both studies were older compared with our patient population, and furthermore, acromegaly had been diagnosed much earlier.

It is well-known that colon pathology and colorectal cancer prevalence increases with age. In previous studies, it was shown that the incidence of colon adenoma in acromegaly patients increases after the age of 50 [18]. When we evaluated the relation between colon polyp presence and age in the acromegaly patients in our study, we determined that the most likely age to determine colon polyp presence in acromegaly patients was 44.5 years (93.1% sensitivity and 64.2% specificity). The youngest patient to determine colon polyp presence was 43 years old. The American Cancer Society recommends sigmoidoscopy and fecal occult blood screening for colon lesions in the normal population over 50 years [20]. However, in accordance with our findings, we believe that colon lesion screening in acromegalic patients should be conducted at an earlier age.

Again, in case of a prolonged duration without any treatment, more frequent and severe complications are expected in an acromegalic patient due to prolonged exposure to higher GH and insulin levels. In this respect, our findings of less colon pathologies, and no incidence of colon cancer in our younger patient population with shorter disease duration does not conflict with the findings of previous studies.

There is evidence showing that DM is related with a gradually increasing risk of colon cancer [21-27]. A meta-analysis found that the colorectal cancer risk among diabetics is 30% higher than that of non-diabetics [28]. The main factor causing increased risk of colon cancer in DM is hyperinsulinemia [1,2]. Insulin in vitro is a significant growth factor for colonic mucosa cells and has a mitogenic effect on colon carcinoma cells [1-3]. Insulin-like growth factor-1 (IGF-I) inhibits apoptosis. IGF-I receptors exist in both colorectal epithelium and colon cancer tissue [29,30]. This means that both the pre-malignant and cancerous stages may be influenced by IGF-I. Insulin-like growth factor 1 also builds up the vascular endothelial growth factor production necessary for angiogenesis and tumor growth [31]. Such findings were supported by demonstrating the independent correlation of high IGF-I and quite low insulin-like growth factor binding protein-3 (IGFBP-3) concentrations in circulation with advanced colorectal adenoma and an

increase in cancer risk [32].

Some of these studies found that high IGF binding protein-3 (IGFBP-3) levels are preventive in terms of cancer [32,33]. In acromegaly, IGF-I levels increase and IGFBP-3 concentrations decrease due to excessive GH; thus, the IGF-I/IGFBP-3 rate increases in parallel with GH concentration [34,35]. It is plausible that the increased IGF-I/IGFBP-3 rate observed in acromegaly escalates the risk of cancer [33,36].

Studies on the issue demonstrated that although proliferation-inducing effects of IGF-I on the colorectal cancer cell series were shown empirically, increased insulin levels are active in increased colonic pathology pathogenesis of acromegalic patients. In our study, patients with polyps had higher insulin and HOMA-IR levels compared with patients without polyps, but this difference relation was not statistically significant (26.0±10.7 and 18.2±11.8 respectively, p=0.080). Again in our study, diabetes prevalence was higher in patients with polyps compared with patients with no polyps, but it was also not significant (35.7% and 20.0% respectively, p=0.237). In addition, insulin demonstrated mitogenic activity by affecting colonic mucosa cells through insulin and IGF-I receptors, and it induced colonic lesion development by repressing the synthesis of IGFBP levels especially in supraphysiological doses [37,38].

In our study, GH, IGF-I, fasting insulin levels, and HOMA-IR values of acromegalic patients were significantly higher than in the control group. We claim that the reason for the higher prevalence of colon polyps in acromegalic patients in our study, compared with the control group, is due to greater IGF-I and insulin levels. However, we are of the opinion that these humoral and metabolic factors may play a triggering role in colon pathology pathogenesis in acromegalic patients because IGF-I and insulin levels did not have any correlation

in acromegalic individuals. Nevertheless, there may be other unknown, but necessary factors waiting for a pathological development.

Previous studies found an increase in the risk of colorectal adenomatous and hyperplastic polyps and also colorectal cancer development in acromegalic patients [9,18,39,40]. The correct approach in this issue is to determine risk factors (race, cancer history in family, disease duration, presence of DM, etc.) through comprehensive studies, and to conduct routine examinations on these patients. Since proximal colon pathology is more prevalent in some studies, colonoscopies should be performed to examine acromegalic patients [14,41,42].

At the 36-month follow-up, which may be considered a short follow-up period, when patients cured exclusively by surgery were compared with patients who could not be controlled by any method, we did not find any differenced in colonoscopies performed at the time of diagnosis and later, and also no difference was observed in terms of polyp recurrence frequencies in colonoscopies at repeated follow-ups. The patients who could not be hormonally controlled were using a somatostatin analog. Maybe, these patient in spite of not being able to have hormonal control, did not have any increase in the recurrence of colonic lesions compared with the patients cured by surgery due to the effects of somatostatin analogs on colon pathology. In an animal study, a finding of suppression on the activity of tyrosine kinases with octreotide (OCT) is noteworthy [43]. In the long-term follow-ups of acromegalic patients, investigations of the somatostatin analogs regarding these effects will give explanations to our results.

4.1. Study limitations

A limitation of our study was the inability to check IGFBP-3 levels due to technical difficulties. There is a clear relation between the average duration of the disease and possible colonic lesion development. However, other studies showed the co-occurrence of a large number of colonic lesions comprising histopathologic malignancy during longer disease period. Therefore, instead of limitation, we perceived shortness of the average disease duration in our study as a mandatory and beneficial outcome in the progress made in acromegaly diagnosis and treatment. However, a short follow-up period to assess colon polyp recurrence is another limitation of the study. We believe that more precise data can be obtained with regard to colonic lesion recurrence rates in acromegaly patients through longer follow-up periods. In our study, we evaluated the comparison between 20 patients who were cured after the surgery, and the 20 patients who could not be cured through the surgery and had already been using somatostatin analogs. In this respect, studies should be conducted with more extensive patient series and longer follow-up periods to determine the effects of somatostatin analogs on colon lesions.

5. Conclusion

Our study shows that acromegaly is associated with a statistically higher prevalence rate of colonic polyps compared to the control group. Acromegalic patients have a higher prevalence of colonic polyps than IBS subjects. We did not find any association between IGFI, GH, fasting insulin plasma levels, glycemic status, HOMA-IR and the presence of colonic polyps in acromegalic patients. Greater IGF-I and insulin

levels may explain higher colon polyp prevalence in acromegalic patients. However, we believe that randomized, controlled studies are necessary to show the possible other unknown factors in colon pathology pathogenesis, in addition to humoral and metabolic factors in acromegalic individuals.

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