Detection of colorectal lesions by using autofluorescence colonoscopy in acromegalics and their relation to serum growth hormone and insulin-like growth factor-1 levels

Violetta Matyja [1], Beata Kos-Kudla [1], Wanda Foltyn [1], Janusz Strzelczyk [1], Wojciech Latos [2], Bogdan Marek [1], Dariusz Kajdaniuk [1], Jacek Karpe [3], Zofia Ostrowska [4], Karolina Sieron-Stoltny [2] & Aleksander Sieron [2]

[1] Department of Pathophysiology and Endocrinology, Silesian Medical University, Zabrze, Poland
[2] Diagnostics and Laser Therapy Centre, Department of Internal Diseases and Physical Medicine, Silesian Medical University, Bytom, Poland
[3] Department of Anaesthesia and Intensiv Care Unit, Silesian Medical University, Zabrze, Poland
[4] Division of Biochemistry, Silesian Medical University, Zabrze, Poland

Correspondence to: Violetta Matyja MD.
Division of Endocrinology,
Department of Pathophysiology and Endocrinology
Silesian Medical University, ul. 3-maja 13/15,
41-800 Zabrze, POLAND
PHONE/FAX: +48 32 3704402
EMAIL: endoklin@slam.katowice.pl

Submitted: July 11, 2006 *Accepted: September 10, 2006*

Key words: **acromegaly; colorectal lesions; autofluorescence-assisted colonoscopy**

Neuroendocrinol Lett 2006; **27**(5):639–643 **PMID:** 17159821 NEL270506A10 **www.nel.edu**

Abstract

OBJECTIVES: Acromegalics have an increased risk of colorectal neoplasm. The aim of this study was to establish the association between acromegaly and colorectal lesions. **MATERIALS AND METHODS**: The study included 51 patients with active acromegaly: 30 women and 21 men (average age 52.95 ± 13.49 years). Growth hormone (GH), insulin-like growth factor I (IGF-I), prolactin (PRL), thyreothropin (TSH), thyroxine (FT4) were measured in the serum when patients were hospitalized for their first diagnosis of acromegaly, before starting the treatment. All patients underwent colonoscopy – in the first phase conventional in white light; in the second phase fluorescence colonoscopy. Autofluorescence of colonic mucosa was assessed by illumination with monochromatic light. Green fluorescence is characteristic for normal colonic mucose, whereas red fluorescence occur in pathological lesions. Material to histopathological examination was taken from every pathological colorectal lesion. **RESULTS**: Using conventional colonoscopy we detected colonic polyps in 21 acromegalic patients (41.17%). Polyps with red fluorescence were found in 7 (13.7%) acromegalics and with green fluorescence in 16 (31.37%) cases of these patients. Histological diagnoses of colorectal lesions are adenoma, hyperplastic and inflammatic polyps. The number of colorectal polyps was dependent on IGF-I, fT4 and sex. **CONCLUSIONS**: Acromegaly is associated with high prevalence of colorectal pathology, mainly hyperplastic polyp and adenoma. There is a relationship between number of colorectal polyps and serum IGF-I levels in acromegaly. Adenomas and hyperplastic polyps were associated with higher levels of IGF-I.

ORIGINAL ARTICLE

Introduction

Acromegaly is a disease which is caused by excessive secretion of growth hormone. It is associated with higher morbidity [8], mainly due to cardiovascular, cerebrovascular, respiratory disorders [14] and with an increased risk of neoplasms by far of the digestive tract [19,9,23,21,7,5,2,1,11,16]. Incidence rates of colon cancer [24,6] and mortality rates in patients with acromegaly are higher than expected. The relative risk of colon cancer in these patients is significantly different depending on the study population and the study design and ranges from 1.7 [12] to 10.4 [20]. Most studies have not adjusted for known colorectal cancer risk factors and so, the true risk of colorectal cancer in acromegalics is not known. That is why we have decided to assess the relation between acromegaly and occurrence of pathological colorectal lesions, taking into consideration serum level of chosen hormones, age, sex of patients, disease duration and the size of pituitary adenoma. Colorectal examination was performed by using colonoscopy in white light and monochromatic light, which has increased the diagnostic sensitivity of the method.

Materials and methods

Study population

The study included 51 patients with active acromegaly, diagnosed for the first time because of acromegaly, in the Department of Endocrinology, Silesian Medical University in Zabrze in Poland, aged 24–78 years (the mean age at diagnosis was 52.95 ± 13.49 years). There were 30 women with median age 57.6±12.1 years (range 34–78) and 21 men with average age 46.6±13.3 years (range 24–67). All patients were measured for serum GH, IGF-I, PRL, TSH, FT4 levels and were given a standard oral glucose (75g) tolerance test. The inability to suppress plasma GH to less than 1 mU/l was the criterion of acromegaly diagnosis. The size of pituitary adenoma was assessed by using magnetic resonance scanning.

Serum hormone levels measurements

GH, IGF-1, PRL, TSH, FT4 were measured in the serum samples obtained in the morning after 8 hs fasting. Serum GH was assessed by immunoradiometric assay (IRMA) (DSL, USA). The assay sensitivity was 0.01 ng/ml. Serum IGF-I level was measured, after acid-aceton extraction, by an immunoenzymatic assay (DSL). The assay sensitivity was 0.03 ng/ml. Concentrations of PRL, TSH, FT4 were assayed by luminiscent electrochemistry (Elecsy 2010 kit, Roche). Assay sensitivities were for PRL 0.023 ng/dl; for TSH 0.005 mIU/ml; for FT4 0.023 ng/dl.

Colonoscopy

All patients included in this study underwent colonoscopy. Total colonoscopy was performed after careful bowel preparation with 4 Ls of a polyethylene glycol oral lavage solution (Fortrans, Beolufor Ipsen International), which the patient drank in 4 hours duration before the day of this study. Colonoscopy was performed by a gastroenterologist from the Diagnostics and Laser Therapy Centre, Department of Internal Diseases and Physical Medicine, Silesian Medical University in Bytom. The colon was examined from rectum through cecum by colonoscopy – in the first phase conventional colonoscopy in white light (using colonoscope: Olympus CF-EL; light source: Olympus CLF-U40). Examination was performed using standard optical equipment. In the second phase fluorescence colonoscopy was performed using monochromatic light (Xillix LIFE Lung, used for assessment of tissue autofluorescence in vivo). The source of monochromatic light was Olympus CLF U40 with an in-built filter cutting light in the 425–455 nm wavelength segment. Green fluorescence is characteristic for normal colonic mucose, whereas red fluorescence in different intensitivities occur in pathological lesions. All pathological lesions visualised by both techniques (by performing white-light endoscopic polypectomy or monochromatic-light hot biopsy) were registered and the material was taken to histopathological examination. Histological verification of this material diagnosed adenomas in different stages of dysplasia, hyperplastic polyps and inflammatic polyps.

The acceptance of the proposed examination has been obtained from the Local Ethics Committee of the Silesian Medical University.

Results

The clinical characteristics and colorectal lesions of our acromegalic patients are summarized in Table 1 and Table 2.

Among the cases, none had a past history of colorectal adenoma or cancer, none had a positive family history of colorectal cancer. 23 out of 51 cases had one or more colorectal lesions, visualised by both techniques; six patients (11.5%) had multiple pathological lesions of the same kind.Using conventional colonoscopy (Tab.2) we detected colonic polyps in twenty-one (41.17%) patients; using fluorescence colonoscopy – polyps with red fluorescence were found in 7 (13.7%) acromegalics and with green fluorescence in 16 (31.37%) cases of these patients. Table 2 shows the relevant results.

Among 7 (13.7%) acromegalics with red polyps all polyps in histological examination were adenomas (6 acromegalics had tubular adenomas and 1 acromegalic had tubulovillous adenoma), whereas among 16 (31.4%) acromegalics with green polyps, 9 (17.3%) patients were diagnosed with hyperplastic polyps, 4 (7.7%) patients with inflammatic polyps, and 3 (5.8%) with adenomas at different stages of dysplasia.

Figure 1 presents histological diagnoses of all found polyps (56) in study group.

The aim of the research was also to check if there are any relations between the prevalence of these lesions and

Table I: The clinical characteristic of 51 patients with acromegaly with and without polyps

	All acromegalics (n=51) mean (SEM)	Acromegalics with polyps (n=21) mean (SEM)	Acromegalics without polyps (n=30) mean (SEM)
Age (years)	52.9 (13.6)	55.6 (7.6)	50.9 (16.6)
GH (ng/ml)	28.8 (33.6)	29.9 (35.5)	28.1 (32.7)
IGF-1 (ng/ml)	990.4 (530.6)	1020.2 (446.5)	968.6 (591.3)
PRL (ng/dl)	18.9 (16.4)	18.9 (19.5)	19.0 (14.1)
TSH (uIU/ml)	1.7 (1.5)	1.9 (1.7)	1.5 (1.3)
FT4 (ng/dl)	1.3 (0.4)	1.5 (0.6)	1.2 (0.2)
Size of pituitary adenoma (mm)	18.0 (11.0)	20.0 (10,0)	16.0 (11.0)
Disease duration (years)	8.7 (5.9)	9.73 (6.9)	7.9 (4.9)

GH, growth hormone; IGF-I, insulin-like growth factor I; PRL, prolactin; TSH, thyreothropin; fT4, thyroxine.

Table 2: Prevalence of colorectal lesions in colonoscopy (conventional and autofluorescence)

No. of acromegalics	Sex	Colorectal lesions			
		Conventional colonoscopy in white light	Autofluorescence colonoscopy in monochromatic light		
		No. of acromegalics with polyps	No. of acromegalics with polyps		Other lesion
			green	red	
51		21	16	7	1*
30	female	10	7	3	1*
21	male	11	9	4	–

No., numer; * small flat lesion – nonspecyfic chronic colitis.

serum levels of GH, IGF-I, PRL, TSH, FT4, age of patients, disease duration and the size of pituitary adenoma. We showed the multiple-factor association between the number of colorectal polyps and the concentration of IGF-I, FT4, and the gender (increased number of polyps was in women with increased levels of IGF-I and decreased levels of FT4). Figure 2 shows the magnitude of relation between the dependent variable (number of polyps) and the other values (IGF-I, FT4, TSH, sex). Beta – value sign indicates the proportionality of this dependence. Positive beta value – the higher number of polyps, the higher concentration of IGF-I. Negative beta value–the higher number of polyps, the smaller concentration of FT4.

Acromegalics with a hyperplastic polyp and an adenoma had a significantly elevated mean serum IGF-I level compared with those patients with either an inflammatic polyp or a nonscecific colitis, which has been presented in Figure 3.

It has been shown in our study group that parameters like levels of GH, TSH, PRL, as well as the size of pituitary adenoma had no relation to the presence or number of colorectal polyps.

Discussion

Acromegaly usually occurs with an increased risk for colorectal neoplasm in large intestine. Our study has assessed the prevalence of pathological colorectal lesions in acromegalic patients. We showed the presence of colorectal polyps in 22 (42, 3%) patients including adenomas in 11 (21%) acromegalics (Fig. 1). The first research by Klein et al. [3] documented a 30% prevalence of colon adenomatous polyps in acromegalics. Nowadays their prevalence is described with 24% mean of patients [23] – from 9% to 38% depending on the study population [23, 17]. Acromegaly occurs with both sexes in the same frequency. Most previous studies have described more frequent occurrence of colorectal polyps in males, which we have also confirmed in our patients group; however, the number of polyps was higher in females. Every red polyps in autofluorescence in histopathological examination was an adenoma, which may potentially undergo neoplasm transformation. The mechanism of relation between GH/IGF-I and colorectal neoplasms thoroughly examined has not been and probably is associated with mucosal hyperproliferation. IGF-I regulates the process of tumor composition on different levels, decreases apoptotic activity, increases epithelial cell proliferation, both in healthy as well as in neoplastic cell

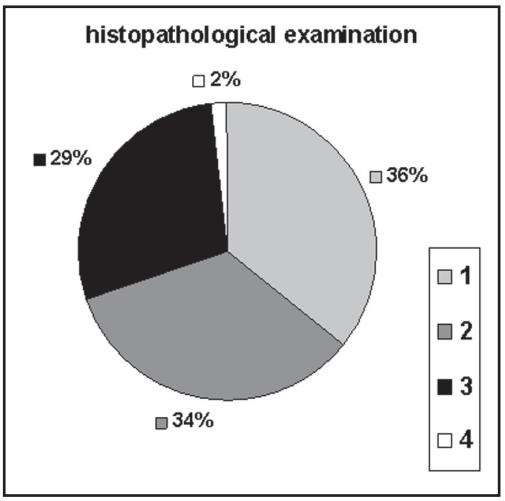

Figure 1: Prevalence of histological examination of colorectal lesions in colonoscopy.
1- hyperplastic polyp (35.7%)
2- adenoma (33.9%)
3- inflammatic polyp (28.6%)
4- nonspecyfic chronic colitis (1.8%)

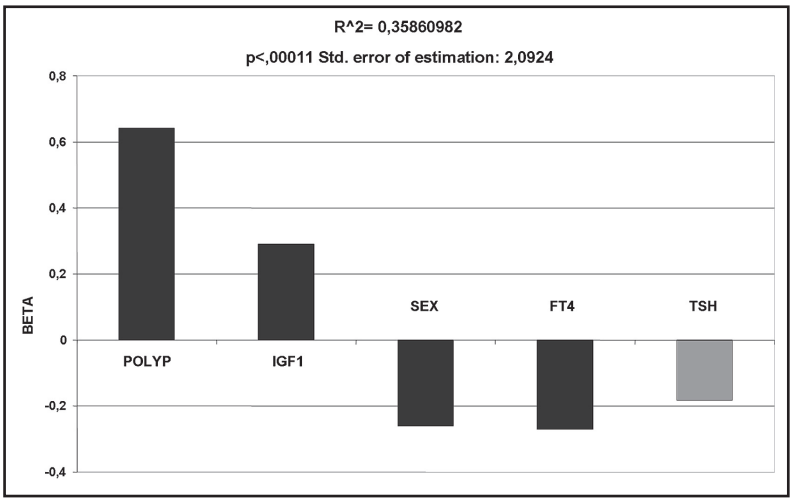

Figure 2: Association between number of polyps and serum IGF-1 levels, FT4 levels and sex.

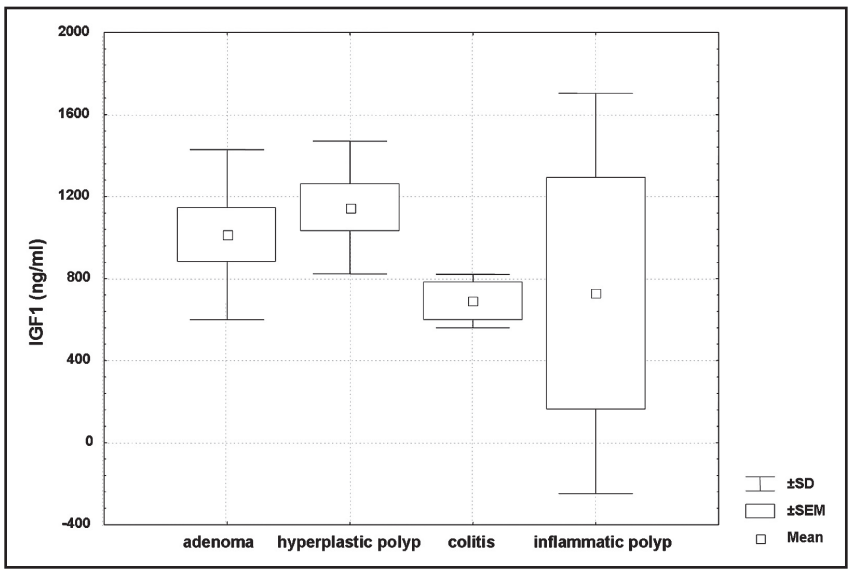

Figure 3: The mean serum IGF-1 in acromegalics with colorectal adenomas (10 acromegalics), hyperplastic polyps (9 acromegalics), inflammatic polyps (4 acromegalics) or nonspecific colitis (1acromegalic).

lines, previously transformed by viral, cellular, and/or chemical oncogenes [22, 15]. Jenkins et al. [11] showed increased mitotic numbers and decreased apoptosis in acromegalic patients compared to control group. Cats et al. [18] also showed that the index in the crypts of colonic mucosa was elevated in acromegalics in comparison with healthy control groups and positively correlated with levels of GH/IGF-I.

IGF-I/IGF-I-R system also causes angiogenesis within tumoral tissues and in the surrounding areas [22, 13]. In vitro IGF-I does not promote cellular transformation, but proliferation of transformed cell clones and the development of preexisting tumor tissues. Does acromegaly increase the colorectal cancer risk? It has been verified that acromegaly especially stimulates the colon adenomatous polyps development. The cellular architecture separates adenomas into tubular, tubulovillous as well as villous (the two first ones predominate in acromegaly). In our study group a tubulovillous adenoma was found in one patients and tubular adenomas were recognized in ten. Adenomas are benign glandular dysplastic lesions with a high cellular proliferation rate [4] and from them most of all colon carcinomas develop. The mean time of neoplasm transformation into cancer is 10–15 years. Adenomas and hyperplastic polyps were the most frequently affirmed pathological lesions in large bowel

(and prevailed in sigmoid colon and rectum), which has also been found by other researches, too [9, 23]. Single hyperplastic polyps are most frequently benign changes, whereas multiple large and proximal located hyperplastic polyps may potentially develop into neoplasm. Our study did not show the association between the prevalence or a number of colorectal polyps and concentration of GH, TSH, PRL and the size of pituitary adenoma. What seems to be especially interesting is that no studies so far have described the multi-factor association between increased colorectal polyps number in women and decreased concentration of fT4 and with increased concentration of IGF-I (Fig. 2). On the basis of existing data, factors such as male gender, age ≥ 40 years [12] or ≥50 years [19], current smoking, and higher levels of GH/IGF-I might be potential colorectal neoplasm predictors with acromegalics [19, 15]. By Jenkins and Fairclough [10] acromegalics after age 40 should have regular colonoscopy. It is important to individualize methods and intervals between these colonoscopies including by far such clinical information as smoking and concentration of GH, IGF-I in serum, the number, the size and the lesions localisation in the first colonoscopy. In this study we have confirmed that acromegaly is associated with the colorectal polyps prevalence (adenomas with different stages of dysplasia and hyperplastic polyps), which can potentially increase the risk of neoplasm. The study also suggests that GH/IGF-I axis activity may be associated with the prevalence of pathological lesions in large bowel, especially with an increased number of them. An assertained relation between increased number of colorectal polyps in women with decreased level of FT4 and increased level of IGF-I needs confirmation in further studies, which will provide relevant information.

Statistics

Statistical analyses were conducted using Stat View Statistical software version 6.0.

Data was reported as mean ± standard deviation. Normality of data was assessed by the Kolmogorov-Smirnov test. One-factor variation ANOVA analysis with RIR Tukey test was used for comparison of the two groups. To assess the relationship between serum levels of GH, IGF-I, PRL, TSH, FT4 and the number of polyps a multiple regression analysis with dependent variable was performed. Differences were considered statistically significant when p-values were less than 0.05.

REFERENCES

1 Archambeaud-Mouveroux F, Geffray I, Teissier MP, Galinat S, Sautereau D, Pillegand B. Prevalence of colorectal carcinoma and polyps in acromegaly [abstract]. In 80th Annual meeting of The Encocrine Society; June 24–27, 1998; New Orleans. Bethesda, MD: The Endocrine Society; 1998: 504.

2 Baris D, Gridley G, Ron E. Acromegaly and cancer risk: A cohort study in Sweden and Denmark. Cancer Causes Control 2002; **13**:395–400.

3 Baserga R. The contradictions of the insulin-like growth factor 1 receptor. Oncogene 2000; **19**: 5574–5581.

4 Besser GM, Fairclough PD. Colorectal neoplasia in acromegaly. Gut 1999; **44**:585–7.

5 Burt RW, Samowitz WS. The adenomatous polyp and the hereditary polyposis syndromes. Gastroenterol Clin North Am 1988; **17**:657–78.

6 Cats A, Dullaart RP, Kleibeuker JH, Kuipers F, Sluiter WJ, Hardonk MJ, et all. Increased epithelial cell proliferation in the colon of patients with acromegaly. Cancer Res 1996; **56**:523–6.

7 Colao A, Balzano A, Ferone D, Panza N, Grande G, Marzullo P, et al. Increased prevalence of colonic polyps and altered lymphocyte subset pattern in the colonic lamina propria in acromegaly. Clin Endocrinol 1997; **47**: 23–8.

8 Delhougne B, Deneux C, Abs R, Chanson P, Fierens H, Laurent-Puig P, Duysburgh I, at all. The prevalence of colonic polyps in acromegaly: A colonoscopic and pathological study in 103 patients. J Clin Endocrinol Metab 1995; **80**:3223–6.

9 Extabe J, Gaztambide S, Latorre P, Vasquez JA. Acromegaly: An epidemiological study. J Endocrinol Invest 1993; **16**:181–7.

10 Holdway IM, Rajasoorya RC, Gamble GD. Factors influencing mortality in acromegaly. J Clin Endocrinol Metab 2004; **89**:667–74.

11 Jenkins PJ. Acromegaly and colon cancer. Growth Horm IGF Res 2000: 35–6.

12 Jenkins PJ, Besser M. Acromegaly and cancer: A problem. J Clin Endocrinol Metab 2001; **86**: 2935–41.

13 Jenkins PJ, Fairclough PD. Screening guidelines for colorectal cancer and polyps in patients with acromegaly. Gut 2002; **51** (Suppl V):v13–4.

14 Jenkins PJ, Fairclough PD, Richards T, Lowe DG, Monson J, Grossman A, et al. Acromegaly, colonic polyps and carcinoma. Clin Endocrinol(Oxf). 1997; **47**:17–22.

15 Jenkins PJ, Frajese V, Jones AM, Camacho-Hubner C, Lowe DG, Fairclough PD, et al. Insulin-like growth factor I and the development of colorectal neoplasia in acromegaly. J Clin Endocrinol Metab 2000; **85**:3218–21.

16 Khandwala HM, McCutcheon IE, Flyvbjerg A, Friend KE. The effects of insulin-like growth factors on tumorigenesis and neoplastic growth. Endocr Rev 2000; **21**:215–244.

17 Klein I, Parveen G, Gavaler JS, VanThiel DH. Colonic polyps in patients with acromegaly. Ann Intern Med 1982; **97**:27–30.

18 Klein I, Parveen G, Gavaler JS, Vanthiel DH. Colonic polyps in patients with acromegaly. Ann Intern Med 1982; **97**:27–30.

19 Liu X, Lin CS, Spencer EM, Lue TF. Insulin-like growth factor-I promotes proliferation and migration of cavernous smooth muscle cells. Biochem Biophys Res Commun 2001; **280**:1307–15.

20 Orme SM, McNally RJ, Cartwright RA, Belchetz PE. Mortality and cancer incidence in acromegaly: A retroprospective cohort study. J Clin Endocrinol Metab 1998; **83**:2730–4.

21 Renehan AG, Bhaskar P, Painter JE, O'Dwyer ST, Haboubi N, Varma J, at al. The prevalence and characteristics of colorectal neoplasia in acromegaly. J Clin Endocrinol Metab 2000; **85**:3417–24.

22 Ron E, Gridley G, Hrubec Z, Page W, Arora S, Fraumeni JF Jr. Acromegaly and gastrointestinal cancer. Cancer 1991; **68**:1673–7.

23 Terzolo M, Tappero G, Borretta G, et al. A high prevalence of colonic polyps in patients with acromegaly. Influence of sex and age. Arch Intern Med 1994; **154**:1272–6.

24 Tzoiti M, Akriviadis A, Papadopoulou E. Colon polyps prevalence in acromegalic patients. Proceedings of the 82nd Annual Meet of The Endocrine Society. 2000; 2028.