

Prevalence of colonic polyp and its predictors in patients with acromegaly

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ABSTRACT

Background: There are conflicting data regarding the prevalence of colorectal polyp in patients with acromegaly. **Subjects and Methods:** Consecutive forty-seven acromegalic patients (21 men, 26 women), with a mean age of (40 ± 12 years) attending endocrinology outpatient department underwent full colonoscopy. All the patients underwent clinical and biochemical evaluation (glucose suppressed growth hormone (GH), Insulin-like growth factor-1 [IGF-1], fasting insulin, and glucose). The control group ($n = 120$) for colonoscopy was adult subjects undergoing evaluation for symptoms of irritable bowel syndrome. Clinical and biochemical parameters in acromegalic patients with colonic polyp were compared to those without a polyp. **Results:** Patients with acromegaly had significantly higher prevalence of colonic polyp as compared to control subjects (10.6% vs. 0.8%). None of the patients with polyp had skin tags. There was no significant difference between subjects with and without colonic polyp in duration of illness, basal, and glucose-suppressed GH and most recent IGF-1. Fasting blood sugar was significantly higher ($P < 0.05$) in adenoma group after adjusting for age, body mass index (BMI), and insulin levels. Patients in adenoma group showed a trend toward male gender and younger age as compared to those without adenoma. **Conclusions:** Subjects with acromegaly as compared to control have a higher prevalence of colonic polyps. There was no association of polyps seen with age, BMI, skin tags, homeostasis model assessment of insulin resistance index, duration of disease, and basal and glucose-suppressed GH and IGF-1 levels. There were no specific predictive factors detected. Screening full colonoscopy is recommended in all cases with acromegaly.

Key words: Acromegaly, colonoscopy, colon polyp, homeostasis model assessment of insulin resistance index

INTRODUCTION

Acromegaly is characterized by excessive levels of growth hormone (GH) secretion and insulin-like growth factor-1 (IGF-1) levels, usually due to GH-secreting pituitary adenoma. Both GH and IGF-1 play an important role in the regulation of cell proliferation and differentiation.^[1,2]

Cats *et al.* reported increased proliferation index of colonic epithelium proportional to their circulating IGF-1 levels.^[3] Acromegalic patients are shown to have an increased risk for both benign and malignant lesions.^[4] Various studies have reported increased prevalence (9–38%) of colorectal cancer in particular.^[5–13] These variations in the prevalence of colonic tumors may be due to differences in selection of patients, visualization of the entire colon, autoptic versus colonoscopy series, selection of controls, and sample size. Screening guidelines therefore suggest full colonoscopy should be done at first visit in all acromegalic patients irrespective of age and follow-up should be scheduled in

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accordance to presence or absence of colonic adenoma and/or elevated IGF-1.^[14-16] However, a study from North India demonstrated no increased risk of colonic neoplasm in subjects with acromegaly.^[17] There is increased incidence of cancer in general population with age and improved survival of acromegaly patients may be one of the reasons of an increased prevalence of cancer. Other factors such as geographical area and ethnicity may play an important role in the development of colorectal neoplasia rather than elevated GH in acromegalic patients.^[18] We evaluated North Indian subjects with acromegaly for colonic polyp and its clinical and biochemical predictors.

SUBJECTS AND METHODS

Study design and setting: Cross-sectional, comparative, and tertiary care academic university hospital-based study.

Patients

Forty-seven consecutive patients with acromegaly were enrolled from endocrinology outpatients department. Criteria for the diagnosis included clinical features, lack of suppression of GH levels below 1 ng/ml after oral 75-g glucose tolerance test, and elevated serum IGF-1 levels for age- and gender-matched healthy subjects. Exclusion criteria were age <18 years and pregnancy. Cure of acromegaly after pituitary surgery was defined as when serum IGF-1 levels were within the normal age- and sex-matched range and serum GH was suppressed <1 ng/ml at 1 h after 75 g glucose as used in international consensus.^[19]

Patient characteristics

Detailed clinical history included presenting symptoms and duration, systemic complications of acromegaly and gastrointestinal symptoms as malena, altered bowel habits, abdominal pain were obtained. All subjects underwent complete general physical and systemic examination. Demographic and anthropometric data viz. (height, weight, body mass index [BMI], and waist-hip ratio [WHR]) were recorded. Waist circumference was measured midway between the iliac crest and the lowermost margin of the ribs at the end of normal expiration, and the hip girth was measured at the intertrochanteric level according to the World Health Organization guidelines.^[20] WHR was calculated, and a WHR ratio of 0.9 in males and 0.8 in females was taken as a cutoff for abnormal WHR.^[21] BMI was calculated (weight [kg]/height [m²]) and the obesity was considered ≥ 25 kg/m².^[22] Blood sample was obtained after an overnight fast. Plasma blood glucose (fasting and postprandial), serum albumin, adjusted total calcium, phosphorous, alkaline phosphatase, lipid profile, total cholesterol, triglyceride, high-density lipoprotein, low-density lipoprotein, electrolytes, renal function

tests, and liver function tests. Endocrine evaluation included serum T4 or FT4, GH suppression (taken at 0 min and after 1 h of 75 g of glucose), IGF-1, follicle stimulating hormone, prolactin (PRL), testosterone (in males), basal and stimulated cortisol (taken 1 h after intramuscular injection with 250 μ g of synthetic ACTH (1–24), glycosylated hemoglobin (HbA1c), and fasting insulin. Homeostasis model assessment of insulin resistance index (HOMA-IR) was calculated. Stool examination for occult blood was performed. All patients underwent imaging of sella and suprasellar regions using gadolinium-enhanced magnetic resonance, direct ophthalmoscopy for fundus examination, and automated perimetry for visual field defects.

Colonoscopy

Bowel preparation was done using a polyethylene glycol-based electrolyte solution (Peglec-Powder, Tablets India Limited). Full colonoscopy was performed using a video colonoscope (Q180AL, 2008483, and OLYMPUS EVIS EXERA II). All colonoscopies were performed by the same endoscopist. Tumor sites were classified as the right colon (cecum, ascending, and transverse colon), left colon (descending and sigmoid colon), and rectum (distal 18 cm). Location and size of polyps were noted before removal [Figure 1]. All lesions were removed and/or biopsied. Histopathological examination was performed by independent pathologists blinded to clinical findings. Polyps were classified as neoplastic (adenomas and adenocarcinomas) or nonneoplastic (i.e., hyperplastic polyps).^[23] No complications occurred during colonoscopy.

Controls

The control group consisted of 120 patients (65 males and 55 women, mean age 39 ± 14) attending gastroenterology outpatient with a diagnosis of irritable bowel syndrome. Hemogram, liver function test, and renal function test were normal. Subsets with diabetes mellitus and hypothyroidism were excluded.

Analytic methods

Serum chemistries were performed on autoanalyzer (Imola™ Randox, UK) within 24 h of sample collection. Serum GH was measured by immunoradiometric assay using commercially available kit (IRMA GH; ©2015 Beckman Coulter, Inc. IMMUNOTECH S.T.O.) with analytical sensitivity of 0.10 mIU/L. Serum IGF-1 was done with (IRMA-IGF-1; Beckman Coulter) after extraction. Analytical sensitivity was 4.5 ng/mL, intra- and inter-assay coefficient of variation (CV) was $\leq 5.6\%$ and $\leq 8.3\%$, respectively. Serum testosterone was done using radioimmunoassay and had analytical sensitivity of 0.02 ng/ml and below 15% and 5.6% was inter- and intra-assay CV. Serum cortisol, PRL, T4, FT4, and insulin

were done using chemiluminescent assay (IMMULITE® 1000, SIEMENS) which had an analytical sensitivity of 5.5 nmol/L, 11 mIU/L, 1.67pmol/L, and 2 µIU/ml, respectively. HbA1c was done using (Bio-Rad Variant™ II, hemoglobin A_{1c} Program, USA) which utilizes principles of ion-exchange high-performance liquid chromatography. The range of average values was 3.5–18.6%. Type 2 diabetes mellitus, impaired fasting glucose (IFG), and impaired glucose tolerance (IGT) were defined as per the American Diabetes Association guidelines.^[24] IR was determined with the HOMA by HOMA-IR.^[25] HOMA-IR = fasting serum insulin (mU/L) × fasting serum glucose (mg/dl)/(22.5 × 18). We used HOMA-IR values higher than 2.5 for indicating IR based on published literature.^[26]

Statistical methods

Statistical analyses were performed using SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). Komlogorov–Smirnov test or Shapiro–Wilks test was used to assess the normal distribution. Continuous variables were expressed as a mean ± standard deviation. Z-test of proportion was done to compare proportions between two groups (cases vs. control). Chi-square test and Fischer Exact test were used to assess the association or to compare two categorical values. Logistic regression analysis was done to determine various parameters known to affect the presence of a polyp. Those which were significant on univariate analysis were then analyzed using multiple regression. Independent sample *t*-test or Mann–Whitney test was used to compare variables between two groups. A *P* < 0.05 was taken as significant.

RESULTS

Forty-seven subjects with mean age of 40 ± 12.3 were enrolled. The colon was visualized fully till caecum in 45 (95%) patients and in two patient it could be done up to hepatic flexure. Of the 47 patients, eight were treatment naive, 24 (65.9%) underwent transsphenoidal surgery (TSS) or transcranial surgery like craniotomy as per neurosurgical indication, while twenty patients had received radiotherapy following TSS. Three subjects took octreotide along with TSS and radiotherapy. One patient was given only octreotide who had ectopic source that was not localized.

There was a median delay of 5 years (range: 1–15) from the onset of symptoms and diagnosis of acromegaly. Anthropometry showed mean BMI of 28 kg/m² and WHR in male and female was 0.91, respectively. Hypertension was seen in 18 (38%) patients at presentation and eight (17%) had the onset of hypertension before the diagnosis of acromegaly. Type 2 diabetes mellitus was present in 7 and IFG/IGT was present in 12.8% of patients [Tables 1 and 2].

Table 1: Clinical and biochemical features of patients at baseline (n=47)

Variables	Mean±SD (%)	Range
Age (years)	40±12.3	20-68
<40	24 (51)	
40-49	13 (28)	
50-59	6 (13)	
60-69	4 (8)	
Male	21 (45)	
Female	26 (55)	
Overweight (BMI 23-24.9 kg/m ²)	4 (8.5)	
Obesity (BMI ≥25 kg/m ²)	36 (77)	
WHR (waist hip ratio)		
>0.9 in males	11 (52.4)	
>0.8 in females	22 (84.6)	
Total disease duration (years)	9.9±6.8	1-30
Disease activity		
Active	32 (68)	
Inactive	15 (32)	
At time of colonoscopy		
GH (ng/ml) 0 min*	16.6±15.8	0.17-49
GH (ng/ml) after OGTT	15.8±15.8	0.17-49
IGF-1 (ng/ml)*	558±388	24-1279

Values are expressed as mean±SD or percentage in parentheses. Normal ranges in our laboratory are as follows: GH: 0.10–35 ng/ml*. IGF-1-288 ng/ml for 20-30 year, 245 ng/ml for 30-40 year, 199 ng/ml for 40-50 year, 147 ng/ml for 50-60 year, 141 ng/ml for 60-70 year, 117 ng/ml for 70-80 year

Table 2: Clinical profile of patients at presentation (n=47)

Variables	n (%)
Headache	32 (68.1)
Visual field defects	15 (31.9)
Acral enlargement	44 (93.6)
Excess of sweating	40 (85.1)
Skin tags	16 (34)
No. of skin tags ≥5	12 (25.5)
Hyperpigmentation	32 (68.1)
Change in voice	34 (72.3)
Teeth gap	30 (63.8)
Abdominal pain	2 (4.3)
Snoring	31 (66)
Clinical features of OSA	14 (29.8)
Galactorrhea	4 (8.5)
Hypertension	18 (38.3)
Diabetes mellitus	7 (14.9)
IFG/IGT	6 (12.8)

Values are expressed percentage ()

Table 3: Localization of colonic adenomas

Age/ gender	Location of adenoma	Number of polyp	Histopathology
35/Female	Caecum	1	Simple polyp (Inflammatory)
27/Male	Transverse colon	1	Adenomatous polyp (Low grade dysplasia)
32/Male	Descending colon	1	Hyperplastic polyp (Figure 1)
65/Female	Rectum	1	Adenomatous polyp (Low grade dysplasia Figure 2)
32/Male	Rectum	1	Simple polyp (Inflammmatory)

Patients were categorized into two groups (with polyp and those without polyp). Colonic adenoma was documented in five (10.6%) patients. All had single lesion only. In control group ($n = 120$) only one patient was detected to have polyp (0.8%). Thus, the risk of colonic polyp was significantly higher in patients with acromegaly as compared to control population ($P = 0.003$). On histopathology, we observed adenomatous polyps with low-grade dysplasia ($n = 1$) [Figure 2], hyperplastic ($n = 1$) [Figure 3], and simple polyp with no evidence of dysplasia ($n = 2$) [Table 3]. All patients with polyp had active disease at the time of colonoscopy. There was no significant difference in the duration of illness, basal GH levels, GH suppression ($P = 0.822$), and IGF-1 levels between acromegaly subjects with or without polyp [Table 4]. No significant difference was seen in serum fasting insulin levels and calculated HOMA-IR (with polyp vs. without polyp 4.3 ± 4.2 vs. 3.1 ± 3.3 , $P = 0.501$). None in the polyp group was found to have skin tags. One out of five in a polyp group had a history of intermittent abdominal pain and malena with a positive stool for occult blood. No one had a family history of gastrointestinal malignancies [Table 5].

In univariate analysis, fasting blood sugar had a significant association with polyp. In multivariate analysis, it continued to be significant ($P < 0.05$) after adjusting for age, BMI, gender, and serum insulin [Table 6].

DISCUSSION

Colonic polyps were observed in 10.6% of acromegalic patients, significantly higher as compared to age- and sex-matched control population. This is in concordance with other studies that have shown increased prevalence of colonic polyp in acromegaly patients.^[11,27-29] A large meta-analysis by Rokkas *et al.* further highlighted increased risk of developing colorectal adenomatous polyps, as well as colorectal cancer in these patients.^[13] In contrast, three studies have shown no association between colonic polyps and acromegaly. In these studies, patients were predominantly younger and colonoscopy was incomplete.^[17,18,30]

The mean age of our patients who had polyp was 38 ± 15 years. Of the five patients who had polyp, four (80%) were <40 years of age. Two studies^[10,27] reported a higher prevalence of adenoma in younger age group (<55 years) who usually display more aggressive course. None had a family history of colorectal cancer. Males were found to harbor polyp greater than females (60% vs. 40%) although it was statistically not significant. This is consistent with other studies.^[7,27]

None of our patients with a polyp had skin tags. The lack of correlation between polyp and skin tags is in agreement with the study done by Terzolo *et al.*^[27] There was no

Table 4: Clinical features of patients between two groups

Variables	Polyp present	Polyp absent	P value
Case	5	42	
Age (year)	38±15	40.3±11.9	0.758 (-16.5-21)
Male	3 (60%)	16 (40.5)	
Female	2 (40%)	23 (59.5)	0.644
Duration of illness (year)	8.2±3.4 (5-14)	10.1±7.2 (1-30)	0.755
Preoperative duration (year)	6.6±1.9 (4-8)	5.4±3.6 (1-15)	0.191
Disease activity			
Active	5	26	0.157
Inactive	0	15	
Skin tags ≥5	0	12	
Acanthosis nigricans	3	23	1
Abdominal pain	1	0	0.217
Stool for occult blood	1	3	0.394
GH secreting-pituitary adenoma			
Microadenoms	0	3	0.77
Macroadenoma	5	38	
Ectopic	0	1	

Values are expressed as mean±SD or percentage (%)

Table 5: Anthropometric and biochemical features of patients between two groups

Variables	Polyp present (n=5)	Polyp not present (n=42)	P
BMI (kg/m ²)	28±5 (22-35)	28.7±5.3 (18.4-42)	0.824
WHR (waist hip ratio)			
Male	0.89±0.08	0.92±0.04	0.751
Female	0.92±0.07	0.90±0.08	0.920
*GH (ng/ml)			
0 min	16.7±13.6 (2.1-33)	16.6±16.2 (0.17-49)	0.729
60 min	14.1±13.3 (1.79-33)	16.09±16.2 (0.17-49)	0.822
†IGF-1 (ng/ml)	734±322 (449-1175)	537±393 (24-1279)	0.183
Fasting blood sugar (mg/dl)	140±82	95.5±21	0.290
Postprandial sugar (mg/dl)	179±117	136±54	0.468
Fasting Insulin (mIU/L)	11.4±6.3	11.9±9.2	0.923
HOMA-IR	4.3±4.2	3.1±3.3	0.501

Values are expressed as mean±SD or percentage; Normal ranges in our laboratory are as follows: GH: 0.10-35 ng/ml*. †IGF-1-288 ng/ml for 20-30 year, 245 ng/ml for 30-40 year, 199 ng/ml for 40-50 year, 147ng/ml for 50-60 year, 141 ng/ml for 60-70 year, 117 ng/ml for 7080 year

correlation seen between the presence or absence of stool for occult blood and polyps.

Increasing evidence supports IR as the underpinning of the obesity-colorectal neoplasia link. HOMA-IR is a good marker of IR and for central obesity. The presence of adenoma was not influenced with glucose intolerance, fasting insulin levels, HOMA-IR, and WHR. This is in contrast to the study done by Colao *et al.*,^[31] which showed significant association seen with fasting insulin levels, HOMA-IR, and prevalence of polyp. Small sample size could be a plausible explanation. In our study, there was

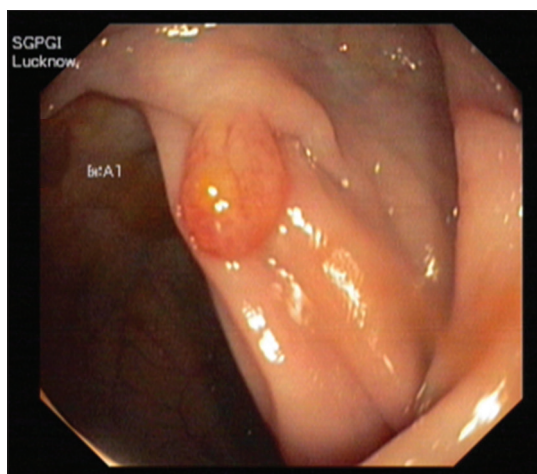


Figure 1: Colonoscopy-pedunculated rectal polyp

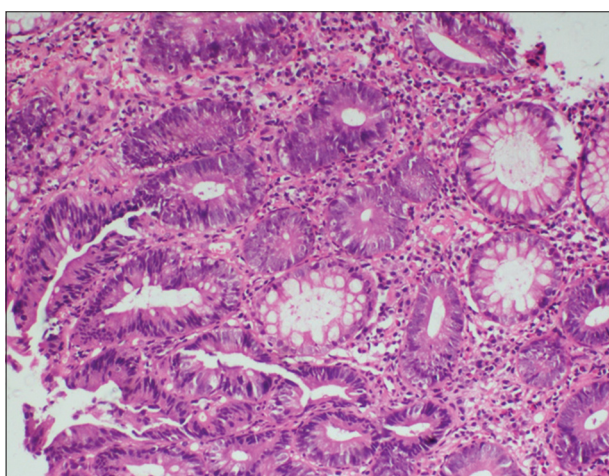


Figure 2: Histopathology-adenomatous colonic polyp

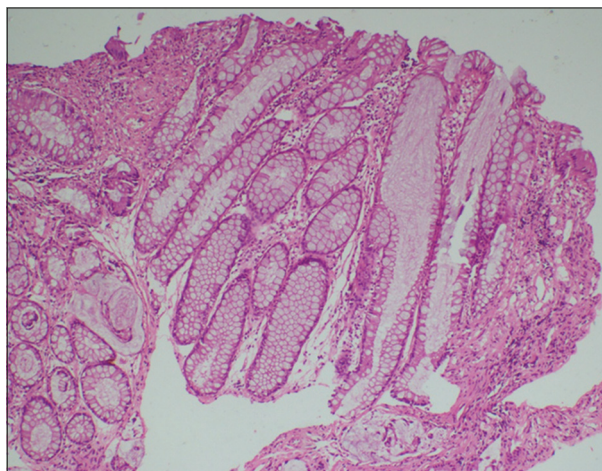


Figure 3: Histopathology-hyperplastic colonic polyp

a significant association with fasting blood sugars and it persisted after correction for BMI, age, and insulin levels.

Interestingly, three out of five patients with polyp had <5 years of duration of illness. We failed to demonstrate a significant

Table 6: Logistic regression of variables that can determine development of polyp

Variables	P value	Odds ratio	Confidence interval
Age (years)	0.683	0.983	0.907-1.066
Gender	0.428	2.15	
Total duration of illness (years)	0.556	0.953	0.811-1.119
Preoperative duration (years)	0.474	1.093	0.857-1.393
GH levels			
0 min	0.988	1.000	0.943-1.061
60 min	0.794	0.992	0.934-1.054
IGF-1 (ng/ml)	0.289	1.001	0.999-1.004
Fasting insulin level	0.918	0.995	0.898-1.102
Fasting blood sugar (mg/dl)	0.047	1.016	1.000-1.032
Postprandial sugar (mg/dl)	0.364	1.005	0.995-1.014
HOMA-IR	0.469	1.083	0.872-1.345
BMI	0.818	0.979	0.813-1.177

correlation between the duration of disease, GH, IGF-1 levels, disease activity, and the prevalence of polyps. Similar findings were noted with previous observations.^[27] It did not discredit the hypothesis that prolonged and exaggerated secretion of growth-promoting factors, increase cellular mitotic activity of colonic mucosa, thereby predisposing to the development of neoplastic lesions. It has to be considered that hormone measurement in a certain moment of a long-lasting disease such as acromegaly may not give a reliable picture of the degree of hypersecretion during the preceding years. The trend (not significant) toward a greater prevalence of polyps in patients with active disease and pituitary GH-secreting macroadenoma, both conditions associated with more aggressive disease, is consistent with a pathogenic role of GH and/or IGF-1.

Data from India suggest that the prevalence of colonic polyp is 2% which is relatively lower.^[32] This has been speculated to be due to high dietary fiber intake and predominantly vegetarian habits.^[33] This is against the notion that increase in the prevalence is due to increase in life expectancy of patients with acromegaly. Higher prevalence of colonic polyps in patients with acromegaly as compared to control population adds more morbidity and hence, warrants colonic screening in these patients at the time of diagnosis. Further follow-up studies are required to determine how frequently pancolonoscopy be repeated in these patients.

CONCLUSION

The present study demonstrated increased prevalence of colon polyp in acromegaly patients as compared to general population. The prevalence of polyp showed a trend toward males and younger population. This was against the previous notion that with an increase in life expectancy incidence of polyps has increased. There were no specific predictors for the development of polyp. Polyps were detected at different

sites without any specific predilection. Hence, all acromegalic patients of any age and duration of illness should undergo screening full colonoscopy at the time of diagnosis.

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Conflicts of interest

There are no conflicts of interest.

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