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Increased risk of preneoplastic colonic lesions and colorectal carcinoma in acromegaly: multicenter case–control study

Maria Florencia Battistone[1] · Karina Miragaya[2] · Amelia Rogozinski[3] · Monica Agüero[4] · Analia Alfieri[5] · Maria Carolina Ballarino[6] · Laura Boero[7] · Karina Danilowicz[7] · Sabrina Diez[8] · Marina Donoso[5] · Patricia Fainstein-Day[9] · Alejandra Furioso[3] · Natalia Garcia-Basavilbaso[10] · Mariela Glerean[9] · Debora Katz[11] · Monica Loto[12] · Susana Mallea-Gil[6] · Marcela Martinez[13] · Maria Isabel Sabate[14] · Marisa Servidio[15] · Patricia Slavinsky[11] · Graciela Stalldecker[8] · Soledad Sosa[7] · Grabriela Szuman[16] · Julieta Tkatch[1] · Ignacio Caldo[17] · Daniela Lubieniecki[17] · Mirtha Guitelman[1]

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Abstract

Purpose Current international guidelines recommend colonoscopy in patients with acromegaly at the time of diagnosis, even though the risk of developing colorectal neoplasm is still controversial. The main objective of this Argentine multicenter study was to analyze through screening colonoscopy the presence of advanced neoplastic lesions considered as precancerous, in patients with acromegaly compared to a control group.

Methods This is a case–control retrospective study. Full length colonoscopy of 70 acromegalic patients and 128 control subjects were studied. Polyps were classified into non pre-cancerous lesions and advance neoplastic lesions which included advanced adenomas (preneoplastic) and colorectal carcinomas.

Results Thirty three out of 70 acromegalic patients and 32 out of 128 subjects controls presented polyps in the colonoscopy [47.1% vs 25%, p = 0.002, OR 2.68]. Non precancerous polyps were found in 11 (15.7%) and 23 (17.9%) (p = 0.690), while advanced neoplastic lesions were found in 22 (31.4%) and 9 (7.0%) (p = 0,0001 – OR: 6.06) patients and controls respectively. Advanced adenomas and colorectal carcinomas were found in 18 (27.3%) and 9 (7.0%) (p = 0,0006—OR: 4,57), and 4 (5.7%) and 0 (0.0%) p = 0.0063) of patients and controls respectively. The presence of insulin resistance was the only statistically significant associated factor among acromegalic patients with and without colonic polyps.

Conclusions Our findings show an increased risk of preneoplastic colonic lesions and colorectal carcinoma in patients with chronic and sustained GH excess compared to a control group. This supports the recommendation to perform screening colonoscopy at diagnosis of acromegaly.

Introduction

Acromegaly is a progressive disease characterized by the inappropriate secretion of growth hormone with visceromegaly and acral enlargement due to high IGF-1 levels. Without proper treatment and partial control it can lead to serious and disabling complications [1–3]. Considered as a rare disease, both the incidence of 4 cases per million/year and the prevalence of 60 per million/inhabitants increase to 11 and 78 cases respectively according to recent publications [4].

Disease features develop insidiously over decades, often leading to a delay of around 6 to 10 years in diagnosis after the onset of symptoms [5]. The effects of prolonged exposure to supra-physiological GH/IGF-1 levels in several tissues are well known and contribute to increase morbidity and mortality of these patients [3, 5–7].

While some studies show that the main causes of death in acromegaly are cardiovascular disease and malignancies with similar prevalence [5]; other studies show similar cancer incidence in these patients and the general population [8].

Some publications have shown that patients with acromegaly have a high prevalence of colonic neoplasms, which rank second in frequency after thyroid neoplasms [9–11]. However, the risk of developing "de novo" colonic

✉ Maria Florencia Battistone
florencia_batti@hotmail.com

Extended author information available on the last page of the article

malignancies and the direct relation with high levels of GH/IGF-1 in acromegaly is not well documented and it is still controversial in the literature [8, 12–14].

Current International guidelines recommend colonoscopy (CC) screening in patients with acromegaly at the time of diagnosis, but there is no consensus regarding the frequency of repeating colonoscopy during the follow up [3, 6, 7, 15–20]. Lack of a reliable consensus is due to the low number of patients and the absence of an adequate control group in some studies that assess the association between colonic lesions and acromegaly.

There are different types of colonic polyps: hyperplastic and low grade of dysplasia adenomatous polyps without any risk for carcinoma development, and high grade dysplasia adenomatous polyps that may be precursor lesions to carcinoma through "adenoma-carcinoma" sequence [21–24]. The "advanced neoplastic lesions" (ANL) are defined as an advanced adenoma (≥ 10 mm diameter, ≥ 25% villous component or high-grade dysplasia), an advanced serrated lesion, or colorectal carcinoma (CRC) [25, 26]. The advanced adenomas and advanced serrated lesions show a high risk of carcinoma development. The positive relationship between colonic polyps, adenomas and colorectal carcinoma in acromegaly is well established in some publications [7, 8, 10, 15, 16, 24, 27, 28], however the association between advanced adenomas and acromegaly has not been studied yet.

The main objective of this study was to compare the presence of advanced neoplastic lesions through colonoscopy between a group of patients with acromegaly and a control group without acromegaly, in a multicenter study in Argentina. The secondary objective was to elucidate associated predictors with the presence of colorectal lesions in patients with acromegaly.

Subjects and methods

It is a case–control retrospective study. We analyzed 145 medical records of patients with acromegaly from 15 hospitals of Buenos Aires city. The control group included 128 non acromegalic subjects from a database of Gastroenterology unit of Carlos G. Durand Hospital, in Buenos Aires city.

For each case, the controls were randomly selected, and matched for age and gender.

Acromegaly diagnosis was made based on clinical suspicion, and biochemical confirmation with high serum levels of IGF-1 matched for age and gender, and lack of serum GH level suppression to < 1 ng/mL during a 75-g oral glucose tolerance test (OGTT) [3].

The information obtained from clinical records is listed as follows (1) personal and first degree family history of adenoma and colorectal carcinoma, (2)insulin resistance index by homeostatic model assessment (HOMA-IR) with a cut off of 2,5 and diabetes mellitus, (3) smoking, (4) time of disease until diagnosis, (5) baseline serum GH and IGF-1 levels. IGF-1 index was calculated (IGF-1 basal level divided by the upper normal limit reported in each assay (IGF-1/UNL).

We also considered acromegaly stage at the time of colonoscopy: *Cured* include patients with normal IGF-1 levels after different treatment modalities, *Controlled* are those patients with normal IGF-1 levels on medical treatment, and *Non-Controlled* is defined when levels of IGF-1 are elevated despite adequate treatments.

Control group included subjects who underwent colonoscopy screening for irritable bowel syndrome suspicion or age screening recommendations.

Inclusion criteria

- Patients ≥ 18 years old.
- Reason for colonoscopy: in patients with acromegaly it was performed as a screening according to international guidelines. In control group it was requested due to age recommendation (> 50 years old) or due to symptoms of irritable bowel syndrome.
- Full-length colonoscopy/satisfactory colonic preparation defined according to Boston scale > = 6 with cecal intubation confirmed by identification of the appendix orifice and the ileocecal valve [29–31]. Boston bowel preparation scale gives objective information on the presence or absence of fecal matter [30, 31].

Exclusion criteria

- Personal history of inflammatory bowel disease, colorectal cancer, familial adenomatous polyposis, hereditary non-polyposis colon cancer.
- Colonoscopy without cecal intubation or inadequate preparation (Boston scale < 6).

Colonoscopy interpretation

Colonoscopy was considered positive when any type of polyps was found and negative in those patients without lesions. Patients and controls were classified according to the histological classification of their colonic lesions: (1) non precancerous polyps (hyperplastic and low grade adenomas, (2) Advanced adenomas (≥ 10 mm diameter, ≥ 25% villous component or high grade dysplasia), (3) advanced serrated lesions and (4) carcinoma colorectal. Colorectal adenomas were classified in low or high grade of dysplasia based on Vienna classification [32, 33]. Patients with multiple lesions were classified according to the most advanced histology.

Statistical analysis

For qualitative variables, the distribution of frequencies, percentages and 95% confidence intervals was calculated. As regards quantitative variables, the average, standard deviation, median, quartiles, minimum and maximum, was calculated. Student test for independent samples was used to compare the two groups with quantitative variables. Independence (Chi-square) test was applied to compare the relationship between qualitative variables. Fisher's exact Test was applied to comparisons of dichotomous variables and with expected frequencies less than 5. Test Binomial for sample independent with Bonferroni correction was used to compare proportions between groups. The risk was expressed in Odds Ratio (OR) with 95% confidence interval. In all cases the applied statistical tests are for independent samples. A less than 5% significance level was used to reject the null hypothesis. p-values < 0.05 were considered statistically significant.

Results

Seventy out of 145 patients with acromegaly met inclusion criteria; 40 women (57.1%; mean age 51.7 ± 11.2) and 30 men (42.9%; mean age 50.9 ± 11). Control group included 128 subjects, 76 women (59.4%; mean age 51.5 ± 11.2) and 52 men (40.6%; mean age 49.7 ± 11.1). All patients with acromegaly underwent CC for screening. In contrast, in the control group 64.1% was performed for age screening and 35.9% due to irritable bowel syndrome symptoms.

No statistical differences were observed in gender, age, first degree family history of adenoma or colorectal cancer, smoking and diabetes between patients with acromegaly and control group. (Table 1).

Thirty three out of 70 patients with acromegaly and 32 out of 128 in the control group, harbored colonic polyps in the CC. Comparing to controls, patients with acromegaly had a significant higher risk of developing colonic polyps [47.1% vs 25%, p = 0.002, OR 2.68 (CI 95% 1.44–4.96)].

The histopathological findings in patients and controls were as follows: (1) non precancerous polyps in 11 (15.7%) and 23 (17.9%) in patients and controls respectively, (2) Advanced adenomas in 18 (27.3%) and 9 (7.0%) in patients with acromegaly and controls respectively, (3) CRC in 4 (5.7%) and 0 (0.0%) in patients with and controls respectively. ANL (AA + CRC) were found in 22 (31.4%) and 9 (7.0%) acromegalic and controls respectively. None advanced serrated lesion was found in either group. (Table 2).

The prevalence of preneoplastic colonic lesions in our acromegalic population was significantly higher than in the controls subjects, being the OR of 6.06 (CI 95% 2.60–14.10) and 4.57 (CI 95% 1.92–10.85) for ANL and AA respectively. The risk of CRC was significant p = 0.0063 with an OR non measurable due to the lack of patients with CRC in the control group. Interestingly, when non precancerous polyps were separately analyzed

Table 1 Clinical characteristic of patients with acromegaly compared to controls

	Acromegaly n = 70	Controls n = 128	P
Women/Men; n (%)	40 (57.1%) / 30 (42.9%)	76 (59.4%) / 52 (40.6%)	0.760
Age; mean (range)	51.3 (22–72)	50.8 (21–73)	0.754
Family history adenoma; n (%)	3 (4.3%)	3 (2.3%)	0.435
Family history CRC; n (%)	7 (10.1%)	17 (13.3%)	0.521
Smoking; n (%)	11 (15.7%)	19 (14.8%)	0.870
Diabetes; n (%)	9 (12.9%)	8 (6.2%)	0.113

Table 2 Colonoscopy: pathological findings

	Acromegaly n = 70	Controls n = 128	P
No lesions (Normal CC)	37	96	
Total polyps	33	32	p = 0.002
No precancerous polyps	11	23	p = 0.690
AA	18	9	p = 0.0006
CRC	4	0	p = 0.0063
ANL (AA + CRC)	22	9	p = 0.0001

Non Precancerous lesions: hyperplastic polyps and low grade adenomas

AA advanced adenomas, *CRC* colorectal carcinoma, *ANL* Advanced Neoplastic lesions

Table 3 Profile of acromegalic patients with or without colorectal neoplasm

	Polyps	No polyps	
Women/Men; n	15/18	25/12	p = 0.062
Basal IGF-1/UNL	3.0 (2.6–3.4)	2.8 (2.2–3.3)	p = 0.438
Basal GH (ng/ml)	24.5 (14.8–36)	23.3 (11.4–35.3)	p = 0.792
Age CC (years)	53 (29–71)	49.8 (22–72)	p = 0.231
Controlled disease n (%)	17 (45.9)	20 (54.1)	p = 0.737
Insulin-resistance (%)	18 (62.1)	11 (37.9)	p = 0.023
Disease duration (years)	8.3 (6.3–10.4)	6.9 (4.6–9.2)	p = 0.343

Data are shown as mean (range)—CC: colonoscopy

we found that there was no increase risk between patients and controls.

The age of patients with acromegaly was not significantly different in the group with or without polyps (p = 0.231), while in the control group subjects with polyps were older (p = 0.012). The median age of the patients with acromegaly and colonic lesions was 53 years with a range of 29–71 years (Table 3).

Regarding the size of the polyps, 58.6% and 29.0% of them were ≥ 1 cm in the acromegalic and control group respectively (p = 0.021—Odds ratio: 3.45).

When comparing patients with acromegaly, the presence of insulin resistance (p: 0.023 OR: 3.147) was the only statistically significant difference between patients with and without colonic polyps. No differences were found in IGF-1 index or GH levels, years of disease evolution before diagnosis, age and disease stage at the time of performing CC. (Table 3).

Patients with higher baseline levels of GH had polyps greater than 1 cm (p = 0.031). This relationship was no statistically significant in patients with higher baseline IGF-1 levels or longer period of disease progression.

The most frequent location of the polyps in both groups was descending and rectum colon; however in control group had a higher tendency to have a location preferably at this place (18/33 acromegaly vs. 23/32 controls). Regarding advanced adenomas, the most frequent location in both group was the rectum and the descending colon (9/18 acromegaly and 8/9 controls). In the control group, 1 lesion was found in the transverse colon, while in the acromegaly group 3 were located in the transverse colon and 3 in the ascending colon, with no information in the remaining 3 patients (Table 4).

In patients with acromegaly three out of four adenocarcinomas were in descending colon and rectum, 1 without information.

Table 4 Site distribution of polyps and advanced neoplastic lesions

	Acromegaly	Controls
Polyps		
Cecum/ascending colon (%)	5/33 (15.15%)	4/32 (12.50%)
Transverse colon (%)	4/33 (12.12%)	4/32 (12.50%)
Descending colon/rectum (%)	18/33 (54.54%)	23/32 (71.87%)
Without information (%)	6/33 (18.19%)	1/32 (3.13%)
Advanced adenomas		
Cecum/ascending colon (%)	3/18 (16.66%)	0/9 (0%)
Transverse colon (%)	3/18 (16.66%)	1/9 (11.11%)
Descending colon/rectum (%)	9/18 (50%)	8/9 (88.88%)
Without information (%)	3/18 (16.66%)	–
Colorectal carcinoma		
Descending colon/rectum (%)	3/4 (75%)	–
Without information (%)	1/4 (25%)	–

Discussion

Patients with acromegaly have a high prevalence of colorectal lesions, being the second most frequent after thyroid carcinoma according to the latest publications. Several studies evaluate the prevalence of benign and malignant colonic neoplasms in acromegaly, in order to review the recommendation of colonoscopy screening at diagnosis which is still controversial in the different international guidelines [11, 15, 16, 18, 28, 34–38]. Colorectal carcinoma in most cases evolves from an adenomatous polyp, through the so-called "adenoma-carcinoma sequence". It is a multi-step process of mutations and genetic aberrations that begins at stem cells level of the epithelium, and then develops a balance disorder between proliferation and apoptosis at the colonic crypt (the intestinal epithelium functional unit), which ends in tumor development [18, 21, 22, 39, 40].

Hyperplastic polyps are considered non-neoplastic lesions, and like the adenomatous polyps with low grade dysplasia have no risk of carcinoma progression. Conversely, large size adenomatous polyps with higher dysplasia grade, mainly those considered advanced adenomas, constitute a greater risk for malignant neoplasm development. The progression to cancer in this type of polyps is estimated at just over 5 years [23, 24, 27].

Experimental studies have shown that both normal colonic mucosa cells and tumor cells express the IGF-1 receptor and even IGF-1 mRNA has been identified in these cells, demonstrating its proliferative and anti-apoptotic action on tumor cells in colorectal carcinomas [41–43]. The relationship between IGF-1 and abnormal cell proliferation in colonic crypts with rapid cellular renewal from pluripotential stem cells has also been demonstrated [44, 45]. In patients with acromegaly, the length of the colon and the sigma are generally greater than in non-acromegalic

subjects. On the other hand, epithelial cells in the sigmoid crypts have a greater proliferation pattern, a preliminary step for adenoma formation, which correlates with the circulating levels of IGF-1 [44–46]. Both circulating and local GH, acting through the GHR, attenuate p53 stability, and blocking GH signaling results in p53 induction. GH excess suppresses p53 levels, with subsequent decreased p21 expression, suppressed PTEN, APC, and apoptosis, and enhanced EMT transcription factors, thereby enabling cell survival and motility [13]. It can then be speculated that in acromegaly, GH and IGF-1 excess increases cell proliferation in the colonic epithelium and decreases apoptosis, while larger intestine increases the amount of exposed stem cells, susceptible to aberrant mutations, which could predispose to the accumulation of mutations that can culminate in the development of pre-cancerous lesions and carcinomas [6, 18]. There are sufficient reports on the higher prevalence of colon polyps and colorectal cancer in patients with acromegaly, however, advanced adenomas and pre-neoplastic lesions in these patients were never studied [8, 10, 11, 15, 28, 34, 36, 38].

The first evidence of the increased prevalence of premalignant polyps in the colon was provided by Klein et al. in 1982, showing about 30% prevalence of adenomatous polyps in a prospective analysis of colonoscopies in 17 patients with acromegaly and a total of 4 carcinomas in a retrospective study in 44 patients [47]. While subsequent studies did not show an increase in the development of colon malignancies [8, 12], other reports showed an increase in the incidence and prevalence of colonic malignancies in patients with acromegaly [10, 11, 15, 34, 36, 48–50]. Perhaps one of the most representative studies is the meta-analysis published in 2008 by Rokkas et al. that included 9 studies with 701 acromegalic patients and a control group with a similar number of individuals. They demonstrated a statistically significant higher prevalence of hyperplastic polyps, adenomas and colorectal carcinomas among patients with acromegaly vs. controls (relative risk (RR) 3.6, 3.3 and 4.4 respectively) [28].

A more recent Japanese study revealed an even higher risk of colorectal malignancies in patients with acromegaly versus controls. This study reports OR of 4.0, 8.7, and 17.5, for hyperplastic polyps, adenomas, and adenocarcinomas, respectively, using an historical control group of Chinese patients with irritable bowel syndrome as a control group [48].

Our study demonstrated a higher prevalence of polyps in patients with acromegaly than in control subjects (OR 2.68) in agreement with most publications. We found an increased risk of advanced neoplastic lesions (advanced adenomas and CRC) with an OR of 6.06, but we did not find an increased risk of non-preneoplastic lesions (hyperplasic polyps or low-grade adenomas) among patients with acromegaly vs controls ($p = 0.69$). These findings allow us to reinforce the hypothesis that the excess of GH/IGF-1 are predisposing factors for malignant colonic neoplasm.

Baseline IGF-1 levels, years of evolution of acromegaly and disease stage at the time of CC were not associated with increased risk of colorectal lesions in the present study. Patients with higher baseline levels of GH showed polyps greater than 1 cm, this relationship was not seen with higher baseline IGF-1 levels, according to recent publications [13]. Only insulin resistance was higher in the group with colonic lesions (p: 0.023), similar to what is reported in the literature [12, 16, 51, 52]. We also observed that the polyps in the patients with acromegaly were almost 4 times larger than in the controls; and that in the acromegaly group the prevalence of polyps in young patients was higher than in the control group.

Despite the findings in the literature that demonstrate a greater location of polyps in the cecum and ascending colon in patients with acromegaly [12, 17, 28], our data show that the rectum and descending colon are the preferred locations in both controls and patients. We only found some cases of advanced adenomas in the ascending colon and none in that location in the control group. In any case, a complete colonoscopy is the established recommendation for patients with acromegaly.

Screening for colonic neoplasms in patients with acromegaly continues to be controversial, as well as the time to perform it and the subsequent interval. According to the international acromegaly guidelines published in 2013 [7] and 2014 [3], colonoscopy is recommended at the time of diagnosis of the disease. The follow-up colonoscopy should be requested every 10 years according to the guidelines of general population in case of patients with no lesions and controlled disease, and at lower intervals for those uncontrolled. In the presence of polyps, follow-up should be performed according to the general population gastroenterology guidelines [17]. The latest clinical practice guidelines supported colonoscopy screening at diagnosis in acromegaly, without agreement on the subsequent intervals [3].

The drawbacks affecting this study comprise the low number of patients recruited, the potential risk of selection bias, the retrospective nature of the study and the fact that colonoscopy screenings in acromegaly patients were performed in several different centers. On the other hand, the evaluation of insulin resistance through the HOMA index is imprecise. Unfortunately we lacked data on visceral obesity, insulin peak during the OGTT, triglycerides/C-HDL index or triglycerides and glucose index which are other surrogates markers of insulin resistence.

As regards the strengths, we should mention that the control group was recruited at the same center, that only full-length colonoscopy screenings were included in the study,

and the fact of analyzing preneoplastic lesions separating of those without risk of transformation into carcinoma.

Conclusion

Our findings show an increased risk of preneoplastic colonic lesions and colorectal cancer in patients with acromegaly, with larger polyps in younger patients compared to control group. Our previous research is reinforced by this current study with a larger number of patients [53].

Even though future prospective studies with a greater number of patients are necessary, our findings support the recommendation to perform colonoscopy screening in patients with acromegaly at diagnosis.

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Data Availability All data is available in the text.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest.

References

1. Sanno N, Teramoto A, Osamura RY et al (2003) Pathology of pituitary tumors. Neurosurg Clin N Am. 14(1):25–39
2. Scacchi M, Cavagnini F (2006) Acromegaly. Pituitary 9(4):297–303
3. Katznelson L, Jr EL. (2014) Acromegaly An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab.2014–2700.
4. Burton T, Le Nestour E, Neary M, Ludlam WH (2016) Incidence and prevalence of acromegaly in a large US health plan database. Pituitary 19(3):262–267
5. Arosio M, Reimondo G, Malchiodi E et al (2012) Predictors of morbidity and mortality in acromegaly an Italian survey. Eur J Endocrinol. 167(2):189–198
6. Colao A (2004) Systemic Complications of Acromegaly Epidemiology, Pathogenesis, and Management. Endocr Rev. 25(1):102–152
7. Melmed S, Casanueva FF, Klibanski A et al (2013) A consensus on the diagnosis and treatment of acromegaly complications. Pituitary 16(3):294–302
8. Petroff D et al (2015) The incidence of cancer among acromegaly patients: Results from the German acromegaly registry. J Clin Endocrinol Metab. 100(10):3894–3902
9. Gullu BE, Celik O, Gazioglu N, Kadioglu P (2010) Thyroid cancer is the most common cancer associated with acromegaly. Pituitary 13(3):242–248
10. Ruchała M, Szczepanek-Parulska E, Fularz M, Woliński K (2012) Risk of neoplasms in acromegaly. Contemp Oncol (Pozn). 6(2):111–117
11. Baris D, Gridley G, Ron E et al (2002) Acromegaly and cancer risk a cohort study in Sweden and Denmark. Cancer Causes Control. 13(5):395–400
12. Renehan AG, Bhaskar P, Painter JE et al (2000) The prevalence and characteristics of colorectal neoplasia in acromegaly. J Clin Endocrinol Metab. 85(9):3417–3424
13. Chesnokova V, Zonis S, Zhou C et al (2016) Growth hormone is permissive for neoplastic colon growth. Proc Natl Acad Sci. 113(23):E3250–E3259
14. Melmed S (2001) Acromegaly and cancer: not a problem? J Clin Endocrinol Metab. 86(7):2929–2934
15. Dworakowska D, Gueorguiev M, Kelly P et al (2010) Repeated colonoscopic screening of patients with acromegaly 15-year experience identifies those at risk of new colonic neoplasia and allows for effective screening guidelines. Eur J Endocrinol. 163(1):21–28
16. Terzolo M, Reimondo G, Gasperi M et al (2005) Colonoscopic screening and follow-up in patients with acromegaly: a multicenter study in Italy. J Clin Endocrinol Metab. 90(1):84–90
17. Lois K, Bukowczan J, Perros P, Jones S, Gunn M, James RA (2014) The role of colonoscopic screening in acromegaly revisited: review of current literature and practice guidelines. Pituitary 18(4):568–574
18. Dworakowska D, Grossman AB. Colonic Cancer and Acromegaly. (2019) *Front Endocrinol (Lausanne)*. 10: 390.
19. Parolin M, Dassie F, Russo L et al (2018) Guidelines versus real life practice: the case of colonoscopy in acromegaly. Pituitary 21(1):16–24
20. Iwamuro M, Yasuda M, Hasegawa K et al (2018) Colonoscopy examination requires a longer time in patients with acromegaly than in other individuals. Endocr J. 65(2):151–157
21. Gualdrini. Cancer colorrectal en la Argentina. Organización, cobertura y calidad de las acciones de prevención y control. (2012) *Misnisterio Salud, Pres la Nación - Argentina*.
22. Bujanda L, Cosme A, Gil I, Arenas-Mirave JI (2010) Malignant colorectal polyps. World J Gastroenterol. 16(25):3103–3111
23. Sack. Colorrectal cancer: Natural history and Management. (2000) *Hosp Physician*. October:64–73.
24. Strum WB (2016) Colorectal Adenomas. Nejm 374:1065–1075
25. Baik SJ, Park H, Park JJ et al (2017) Advanced Colonic Neoplasia at Follow-up Colonoscopy According to Risk Components and Adenoma Location at Index Colonoscopy A Retrospective Study of 1974 Asymptomatic Koreans. Gut Liver. 11(5):667–673
26. Rigter LS, Spaander MCW, Aleman BMP et al (2019) High prevalence of advanced colorectal neoplasia and serrated polyposis syndrome in Hodgkin lymphoma survivors. Cancer 125(6):990–999
27. Laiyemo (2008) Postpolypectomy colonoscopy surveillance guidelines: predictive accuracy for advanced adenoma at 4 years. *Ann Intern Med*. 148–419.
28. Rokkas T (2008) Risk of colorectal neoplasm in patients with acromegaly: A meta-analysis. World J Gastroenterol 14(22):3484
29. Fletcher R. The quality of colonoscopy servicies responsibilities of referring clinicians: a consensus statement of the quality assurance task gruop, National Colorectal Cancer Roundtable. (2010) *J Gen Intern Med*. 1225–1230.
30. Lai EJ, Calderwood AH, Doros G, Fix OK, Jacobson BC (2008) The Boston bowel preparation scale: a valid and reliable instrument for colonoscopy-oriented research. Gastrointest Endosc. 69(32):620–625
31. Calderwood AH, Jacobson BC (2010) Comprehensive validation of the Boston Bowel Preparation Scale. Gastrointest Endosc. 72(4):686–692
32. Schlemper RJ (2000) The Vienna classification of gastrointestinal epithelial neoplasia. Gut 47(2):251–255

33. Dixon M (2000) Gastrointestinal epithelial neoplasia: Vienna revisited. Gut 51:130–131
34. Koksal AR, Ergun M, Boga S et al (2014) Increased Prevalence of Colorectal Polyp in Acromegaly Patients: A Case-Control Study. Diagn Ther Endosc 2014:1–4
35. Ruchala M, Skiba A, Gurgul E, Uruski P, Wasko R, Sowinski J. (2009) The occurrence of thyroid focal lesions and a need for fine needle aspiration biopsy in patients with acromegaly due to an increased risk of thyroid cancer. *Neuro Endocrinol Lett*. 30(3):382–386.
36. Gonzalez B, Vargas G, Mendoza V, Nava M, Rojas M, Mercado M (2017) The prevalence of colonic polyps in patients with acromegaly a case-control, nested in a cohort colonoscopy study. Endocr Pract. 23(5):594–599
37. Kurimoto M, Fukuda I, Hizuka N, Takano K (2008) The prevalence of benign and malignant tumors in patients with acromegaly at a single institute. Endocr J. 55(1):67–71
38. Ron E (1991) Acromegaly and gastrointestinal cancer. Cancer 68:1673–1677
39. Cappell (2008) Reducing the incidence and mortality of colon cancer: mass screening and colonoscopic polypectomy. *Gastroenterol Clin N Am*. 37:129–160.
40. Winawer (1993) Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *Nejm*. 1993:329–1977.
41. Freier S, Weiss O, Eran M et al (1999) Expression of the insulin-like growth factors and their receptors in adenocarcinoma of the colon. Gut 44(5):704–708
42. Lahm H, Amstad P, Wyniger J et al (1994) Blockade of the insulin-like growth-factor-I receptor inhibits growth of human colorectal cancer cells evidence of a functional IGF-II-mediated autocrine loop. Int J Cancer. 58(3):452–459
43. Boguszewski CL, da Boguszewski MC (2019) Growth Hormone's Links to Cancer. Endocr Rev. 40(2):558–574
44. Cats A, Dullaart RP, Kleibeuker JH et al (1996) Increased epithelial cell proliferation in the colon of patients with acromegaly. Cancer Res. 56(3):523–526
45. Renehan AG, O'Connell J, O'Halloran D et al (2003) Acromegaly and colorectal cancer a comprehensive review of epidemiology, biological mechanisms, and clinical implications. Horm Metab Res. 35(11–12):712–725
46. Dutta P, Bhansali A, Vaiphei K et al (2012) Colonic neoplasia in acromegaly: increased proliferation or deceased apoptosis? Pituitary 5(2):166–173
47. Klein I, Parveen G, Gavaler JS, Vanthiel DH (1982) Colonic polyps in patients with acromegaly. Ann Intern Med. 97(1):27–30
48. Yamamoto M, Fukuoka H, Iguchi G et al (2014) The prevalence and associated factors of colorectal neoplasms in acromegaly: a single center based study. Pituitary 18(3):343–351
49. Dal J, Leisner MZ, Hermansen K et al (2018) Cancer Incidence in Patients With Acromegaly A Cohort Study and Meta-Analysis of the Literature. J Clin Endocrinol Metab. 103(6):2182–2188
50. Terzolo M, Reimondo G, Berchialla P et al (2017) Acromegaly is associated with increased cancer risk a survey in Italy. Endocr Relat Cancer. 24(9):495–504
51. Colao A, Pivonello R, Auriemma RS et al (2007) The association of fasting insulin concentrations and colonic neoplasms in acromegaly a colonoscopy-based study in 210 patients. J Clin Endocrinol Metab. 92(10):3854–3860
52. Delhougne B, Deneux C, Abs R et al (1995) The prevalence of colonic polyps in acromegaly a colonoscopic and pathological study in 103 patients. J Clin Endocrinol Metab. 80(11):3223–3226
53. Battistone MF, Loto MKD et al (2017) Riesgo aumentado de lesiones colónicas preneoplasicas en acromegalia estudio miltricentrico casa control Resultados preliminares. Rev Argentina Endocrinol y Metab RAEM. 54(4):169–175

Affiliations

Maria Florencia Battistone[1] · Karina Miragaya[2] · Amelia Rogozinski[3] · Monica Agüero[4] · Analia Alfieri[5] · Maria Carolina Ballarino[6] · Laura Boero[7] · Karina Danilowicz[7] · Sabrina Diez[8] · Marina Donoso[5] · Patricia Fainstein-Day[9] · Alejandra Furioso[3] · Natalia Garcia-Basavilbaso[10] · Mariela Glerean[9] · Debora Katz[11] · Monica Loto[12] · Susana Mallea-Gil[6] · Marcela Martinez[13] · Maria Isabel Sabate[14] · Marisa Servidio[15] · Patricia Slavinsky[11] · Graciela Stalldecker[8] · Soledad Sosa[7] · Grabriela Szuman[16] · Julieta Tkatch[1] · Ignacio Caldo[17] · Daniela Lubieniecki[17] · Mirtha Guitelman[1]

1 División Endocrinología, Hospital Carlos G. Durand, Buenos Aires, Argentina

2 Servicio de Endocrinología, Sanatorio Güemes, Buenos Aires, Argentina

3 División Endocrinología, Hospital Ramos Mejía, Buenos Aires, Argentina

4 Grupo de trabajo Endocrinología, Hospital Tornú, Buenos Aires, Argentina

5 Servicio de Endocrinología, Hospital Nacional Profesor A. Posadas, El Palomar, Buenos Aires, Argentina

6 Servicio de Endocrinología, Hospital Militar Central, Buenos Aires, Argentina

7 División Endocrinología, Hospital de Clínicas José de San Martin UBA, Buenos Aires, Argentina

8 Servicio de Endocrinología, Hospital General de Agudos Dr. Ignacio Pirovano,, Buenos Aires, Argentina

9 Servicio de Endocrinología, Hospital Italiano, Buenos Aires, Argentina

10 Servicio de Endocrinología, Sanatorio Las Lomas, San Isidro, Buenos Aires, Argentina

11 Sección Neuroendocrinología, FLENI, Buenos Aires, Argentina

12 Servicio de Endocrinología, Hospital Británico, Buenos Aires, Argentina

[13] Servicio de Endocrinología, Hospital C. Milstein, Buenos Aires, Argentina

[14] Servicio de Endocrinología, Hospital Universitario Austral, Pilar, Buenos Aires, Argentina

[15] Unidad de Endocrinología, Hospital Teodoro Alvarez, Buenos Aires, Argentina

[16] Servicio de Endocrinología, Sanatorio Municipal Dr. J. Mendez, Buenos Aires, Argentina

[17] Unidad de Gastroenterología, Hospital Carlos G. Durand, Buenos Aires, Argentina