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# Acromegaly : irreversible clinical consequences

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**Citation**
Wassenaar, M. J. E. (2010, June 10). *Acromegaly : irreversible clinical consequences*. Retrieved from https://hdl.handle.net/1887/15664

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|---|---|
| Version: | Corrected Publisher's Version |
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| Downloaded from: | https://hdl.handle.net/1887/15664 |

**Note:** To cite this publication please use the final published version (if applicable).

Chapter 9.

# ACROMEGALY IS ASSOCIATED WITH AN INCREASED PREVALENCE OF COLONIC DIVERTICULA: A CASE-CONTROL STUDY

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*Accepted for publication in The Journal of Endocrinology and Metabolism, 2010 Mar 9 [Epub ahead of print].*

## ABSTRACT

**Objective:** In acromegaly, overproduction of GH and IGF-I causes abnormal extracellular matrix regulation. We hypothesized that this may predispose to the development of colonic diverticula. Since the relation between acromegaly and colonic diverticula is unknown, the study aim was to assess the prevalence of colonic diverticula in patients with cured acromegaly.

**Design:** We conducted a case-control study.

**Methods:** We screened reports of colonoscopies performed for the purpose of screening for polyps in 107 patients with cured or biochemically controlled acromegaly and in 214 age- and sex-matched controls for the presence of diverticula, dolichocolon, and polyps. In patients, the findings were related to GH/IGF-I concentrations at the time of diagnosis of acromegaly and to the duration of GH/IGF-I excess.

**Results:** In acromegaly, colonic diverticula were present in 37% of patients, dolichocolon in 34%, and adenomatous polyps in 34%, which was increased compared with controls (OR 3.6, 95% CI: 1.4, 5.7; 12.4, 95% CI: 6.8, 18.0; 4.1, 95% CI: 1.9, 6.4, respectively). The presence of colonic diverticula was associated with both GH and IGF-I concentrations at the time of diagnosis of acromegaly, when adjusted for the duration of active disease. The presence of dolichocolon and adenomatous polyps was associated with higher IGF-I concentrations at diagnosis.

**Conclusions:** Acromegaly is associated with an increased prevalence of colonic diverticula. In addition to the known irreversible effect of GH excess on collagen of joints and cardiac valves, this observation indicates an irreversible effect of GH and/or IGF-I on the collagen in the colon.

# INTRODUCTION

Diverticular disease is common in Western and industrialized societies [1;2]. Diverticula are most often found in the sigmoid and descending colon[1;3]. Although the pathophysiology of colonic diverticula is still incompletely understood, it is generally assumed that aging and low dietary fibre are the main pathogenic factors involved in this disease. Aging might be associated with altered motility and weakening of the colonic wall and low fibre diet leads to a small amount of stool, resulting in colonic segmentation. The intraluminal pressure tends to be high in the segmented colon and causes mucosal and submucosal herniation through the weakened muscle layer, and, consequently, colonic diverticula develop[4;5].

Acromegaly is a chronic, slowly developing disease caused by a growth hormone-secreting pituitary adenoma leading to increased circulating growth hormone (GH) levels and increased insulin-like growth factor-I (IGF-I) secretion by peripheral tissues, especially the liver. Well known gastro-intestinal manifestations associated with acromegaly are colon carcinoma, adenomatous polyps, and dolichocolon[6-8].

GH is involved in matrix regulation, since GH increases gene expression of the matrix metalloproteinases (MMPs), that are capable of altering the composition of the extracellular matrix[9]. Recently, changes have been found in heart valves and aortic root in patients with acromegaly, comparable to those observed in patients with Marfan's syndrome, which is a connective tissue disease[10;11]. Marfan's syndrome is also associated with colonic diverticula[12-14]. Therefore, we hypothesized, that in acromegaly abnormal extracellular matrix regulation caused by overproduction of GH and IGF-I may also predispose to the development of diverticula.

The prevalence, localization, and severity of colonic diverticula in acromegaly is currently unknown. Therefore, the aim of our study was to quantify the presence of colonic diverticula in a well-characterized cohort of cured acromegalic patients, and in age- and sex-matched controls. In addition, we related the prevalence of colonic diverticula, cecal intubation rate, increased bowel length referred to as dolichocolon, and adenomatous polyps to parameters of initial disease activity of acromegaly, in order to gain more insight into the pathophysiological processes involved in the colonic complications of acromegaly, including colonic diverticula.

## PATIENTS AND METHODS

### Patients

We screened the medical records of all acromegaly patients currently in our database for eligibility in the current analysis. Since 1992 all acromegaly patients were advised to undergo a colonoscopy to screen for colonic polyps[15]. Patients were eligible when a colonoscopy had been performed in our center (n=110) and after biochemical control or cure of acromegaly had been achieved (n=107).The included patients did not differ from the excluded patients in age at diagnosis, gender, BMI, GH and IGF-I concentrations at diagnosis, or type of treatment.

The initial diagnosis of acromegaly was based on the characteristic clinical signs and symptoms and confirmed by insufficient suppression of GH during a glucose tolerance test (normal response: GH nadir <0.38 μg/L), elevated age- and gender-adjusted IGF-I levels, and the presence of a pituitary adenoma on radiological imaging. The first treatment option in the majority of patients was transsphenoidal surgery (TPS) performed by a single specialized neurosurgeon. If necessary, adjuvant treatment was given by radiotherapy (prior to 1985) or somatostatin (SMS) analogs (from 1985 onwards). This treatment approach resulted in early postoperative control in 66% and late control in 90% of patients[16]. From 1998, in some patients primary treatment was given in the form of depot formulations of SMS analogs. From 2003, patients with inadequate control by surgery and/or long-acting SMS analogs were treated with pegvisomant.

Disease activity was assessed yearly by oral glucose tolerance tests (except in patients treated with SMS analogs or pegvisomant), measurement of fasting serum GH and IGF-I concentrations, and evaluation of other pituitary functions. Remission of acromegaly was defined as a normal glucose suppressed serum GH less than 1.25 ( RIA assay until 1992) or 0.38 μg/L (IFMA assay from 1992 onwards), serum GH levels less than 1.9 μg/L (all years) and normal IGF-I levels for age (from 1986 onwards) at yearly follow-up visits[16-18]. Hypopituitarism was treated promptly with thyroxine, hydrocortisone, testosterone or estrogens (in pre-menopausal women) when deficiencies were documented using appropriate basal hormone and dynamic tests[19].

Disease duration was calculated from the estimated date of onset, using start of signs and symptoms, facial changes on photographs and, in case of disease cure or remission, to the

date of normalization of serum IGF-I concentration after transsphenoidal surgery or additional treatment. GH and IGF-I concentrations at diagnosis and at colonoscopy were used for analyses. The GH concentration at diagnosis was calculated as the mean of several random fasting GH concentrations prior to diagnosis. Since IGF-I measurements were performed since 1986, pre-treatment IGF-I concentrations were available in 69 of the 107 patients. We combined the duration and severity of exposure to the high circulating concentrations of GH and IGF-I SD by multiplying the duration of active disease (in years) with the natural logarithm of the pre-treatment GH and IGF-I SD concentrations These products of pre-treatment exposure to GH or IGF-I will be referred to as: duration*lnGH or duration*lnIGF-I SD.

## Controls

We included an age- and sex-matched control population consisting of 214 patients who had colonoscopic evaluation with the primary aim to screen for colorectal polyps. In these controls colonoscopy was also performed with the primary aim to screen for colorectal polyps, because of rectal blood loss, a positive family history of colon cancer, or aspecific abdominal complaints. Each acromegalic patient was matched to 2 controls. Patients and controls were compared on the presence of diverticula, cecal intubation rate, dolichocolon, and on colorectal polyps. All colonoscopies were performed at the Leiden University Medical Center using a strict protocol, under the same conditions as the patients, and from 1995 onward. All controls were derived from the same geographical area as the patients. The medical ethical committee approved the review the medical records and did not require informed consent for this retrospective analysis.

## Colonoscopic evaluation

Colonoscopy was performed routinely in all patients with an established diagnosis of acromegaly. The records of colonoscopies performed in the Leiden University Medical Center between 1992 and 2008 were used for the present analysis. Structured reports of the colonoscopy were retrospectively analyzed and scored for the presence of diverticula, cecal intubation rate, dolichocolon and colorectal polyps. In case of biopsies, the histopathology was recorded. In case of more than one colonoscopy, the most recent colonoscopy was used for analysis, although polyps taken by biopsies in previous colonoscopies were also taken into account.

All patients and controls were prepared with four liters of hypertonic polyethylene glycol solution (Kleanprep; Helix Bio-pharma Corp., Aurora, Ontario, Canada). The proce-

dures were performed under conscious sedation using midazolam and/or fentanyl. Cecal intubation was confirmed by identification of the orifice of the appendix and the ileocecal valve.

## Hormone assays

Serum GH levels were measured with a sensitive immunofluorometric assay (IFMA) (Wallac, Turku, Finland), specific for the 22 kDA GH protein, calibrated against World Health Organisation International Reference Preparation (WHO IRP) 80/505 (detection limit 0.01 μg/l; intra-assay coefficient of variation (CV) 1.6-8.4% of 0.01-15.38 μg/l) from 1992 onwards. For conversion of μg/l to mU/l, multiply by 2.6. Before 1992, GH was measured by RIA (Biolab, Serona, Coissins, Switzerland) calibrated against WHO IRP 66/21(detection limit 0.5 mU/L, interassay coefficient of variation <5%, for conversion from μg/l to mU/l, multiply by 2).

From 1986 up till 2005, serum IGF-I concentrations were determined by a radioimmunoassay (RIA) (Incstar; Stillwater, MN, USA) with a detection limit of 1.5 nmol/l and an inter-assay CV below 11%. IGF-I is expressed as SD scores (SD score) for age- and gender-related normal levels determined in the same laboratory[20]. From 2005 onwards serum IGF-I concentration (ng/ml) was measured using an immunometric technique on an Immulite 2500 system (Diagnostic Products Corporation, Los Angeles, CA, USA). The intra-assay CV was 5.0 and 7.5% at mean plasma levels of 8 and 75 nmol/l, resp. IGF-I levels were expressed as SD score, using lambda-mu-sigma (LMS) smoothed reference curves based on measurements in 906 healthy individuals[21;22].

## Statistical analysis

SPSS for Windows version 16.0 (SPSS inc., Chicago, IL) was used for data analysis. Data are presented as mean (SEM). We dichotomized the data according to the presence or absence of colonic diverticula, dolichocolon, cecal intubation, or polyps. First, we performed comparisons between acromegalic patients and controls by binary logistic regression analysis, with adjustments for age at colonoscopy and gender, to estimate odds-ratios (OR) shown with corresponding 95% confidence intervals (CIs), see *Table 2*. Second, within patients with acromegaly we performed binary logistic regression analysis with presence of diverticula as dependent variable adjusted for several factors and covariates. OR's reflected in page 9 and 10 are the result of these analysis. Third, Multinomial logistic regression analysis was used, with disease duration in tertiles as dependent variable, to estimate OR's with corresponding 95% CIs. The lowest tertile

was the reference category, see *Table 4*. Colonic diverticula and gender were entered in the model as factors and the covariates were lnpre-treatment GH concentrations, lnpre-treatment IGF-I SD scores, age at colonoscopy, and BMI. The OR's and 95% CIs are not displayed, but were subsequently transformed to risk ratios (RR) and corresponding 95% CI using the approximation formulae described by Zhang *et al*.[23]. This approach was chosen because the OR's for common outcomes in a closed cohort is no good approximation of the RR.

# RESULTS

## Patient and treatment characteristics

We studied 107 patients, 60 men (56%) and 47 women (44%), with long term cure/biochemical control of acromegaly. At the time of diagnosis of acromegaly the mean age was 46.8 ± 1.2 yr, and at time of the most recent colonoscopy mean age was 56.4 ± 1.2 yr. The treatment characteristics of acromegaly are provided in *Table 1*.

**Table 1:** Clinical characteristics of patients with biochemical control of acromegaly

| | Males N=60 (56 %) | Females N=47 (44 %) | P-value |
|---|---|---|---|
| **Age at diagnosis (yr)** | 45.1 (1.6) | 49.9 (1.7) | 0.02 |
| **Age at colonoscopy (yr)** | 54.7 (1.6) | 58.5 (1.8) | 0.17 |
| **BMI at diagnosis (kg/m$^2$)** | 27.2 (0.6) | 26.4 (0.7) | 0.20 |
| **Pre-treatment GH (ug/l)** | 31.6 (4.4) | 24.9 (5.3) | 0.33 |
| **Pre-treatment IGF-I SD score (n=69)** | 7.6 (0.74) | 7.0 (0.8) | 0.62 |
| **Treatment for acromegaly** | | | |
| Surgery | 38 (63 %) | 22 (47 %) | 0.09 |
| Surgery + RT | 9 (15 %) | 7 (15 %) | 0.89 |
| Surgery + RT + SMS | 3 (5 %) | 2 (4 %) | 0.82 |
| Surgery + SMS | 7 (12 %) | 8 (17 %) | 0.42 |
| Primary SMS | 3 (5 %) | 6 (13 %) | 0.38 |
| Primary SMS + pegvisomant | - | 2 (4 %) | - |
| **Duration of active disease (yr)** | 10.2 (1.3) | 9.0 (1.3) | 0.80 |
| **Duration of disease remission (yr)** | 9.9 (1.3) | 10.2 (1.7) | 0.43 |

Data are shown as mean (SEM), unless mentioned otherwise. P<0.05 was considered significant. Pre-treatment IGF-I SD score was only available in 69 patients. Abbreviations: SEM: standard error of the mean, SD: standard deviation, yr: year, BMI: body mass index, RT: radiotherapy, SMS: somatostatin (analogs), kg: kilogram, m: meter. Bold P-values reflect significant difference.

The mean estimated duration of active disease prior to diagnosis was 9.7 ± 1.0 yr and the mean duration of remission was 9.8 ± 0.9 yr. At the time of diagnosis of acromegaly, mean serum GH concentration was 29.1 ± 2.7 μg/l and mean IGF-I SD score was 7.4 ± 0.5 SD. At the time of colonoscopy, mean serum GH concentration was 1.01 ± 0.2 μg/l and mean IGF-I SD score was 0.58 ± 0.2 SD.

Patients were compared with 214 age- and sex-matched non-acromegalic controls, 120 men (56%) and 94 women (44%). In controls, the mean age at colonoscopy was 57.0 ± 1.8 yr, which was comparable to that of the patients. The percentage Caucasians in patients and controls was comparable (95% *vs.* 94%, p=0.91).

## Prevalence of diverticular disease

As demonstrated in *Table 2*, diverticula were reported in 40 patients (37%), left-sided in 38 patients and right-sided in 4 patients.





**Table 2**. Increased prevalence of diverticular disease and other colon abnormalities in patients with acromegaly compared with controls.

| | **Acromegalic patients n=107** | **Controls n=214** | **OR (95% CI)** |
|---|---|---|---|
| **Diverticula** | 40 (37 %) | 41 (19 %) | 3.6 (1.4, 5.7) |
| Left-sited | 38 (36 %) | 39 (18 %) | 3.6 (1.4, 5.6) |
| Right-sited | 4 (4 %) | 11 (5 %) | 1.3 (0.4, 4.0) |
| **Dolichocolon** | 36 (34 %) | 2 (1 %) | 12.4 (6.8, 18.0) |
| **Cecal intubation rate** | 83 (78 %) | 205 (96 %) | 0.14 (0.1, 0.3) |
| **Colonic polyps** | 51 (48 %) | 47 (22 %) | 3.6 (2.1, 5.2) |
| Hyperplastic | 15 (14 %) | 19 (9 %) | 1.8 (0.9, 2.8) |
| Adenomatous | 36 (34 %) | 28 (13 %) | 4.1 (1.9, 6.4) |
| Low grade | 30 (28 %) | 21 (10 %) | |
| Intermediate grade | 3 (3 %) | 4 (2 %) | |
| High grade | 3 (3 %) | 3 (1 %) | |
| **Colonic malignancy** | 3 (3 %) | 9 (4 %) | 0.91 (0.1, 1.9) |

Data are shown as number (%). Data were compared by binary logistic regression analysis, with adjustments for age at colonoscopy and gender. Results are demonstrated as odds ratio (OR) with 95% confidence interval (CI). Controls were the reference category. Bold OR's reflect significant difference.

This prevalence in acromegalic patients was higher compared with the prevalence in controls (19%) (p=0.002). In acromegaly, diverticula were identified at a younger age than in controls (58.0 ± 1.7 yr *vs.* 72.3 ± 1.8 yr, p<0.001). Thirty-five percent of controls had colonoscopy for symptomatic complaints. Exclusion of these controls from analysis did not affect our outcome.

### *Factors influencing diverticular disease in acromegaly patients*

Age, gender, and BMI.

There was a positive correlation between female gender and the risk for diverticula (OR 3.1, 95% CI: 1.3,7.4). However, after adjustment for age at colonoscopy and BMI, this positive association was not statistically significant (OR 2.2, 95% CI: 0.8,6.1). Age at colonoscopy was positively associated with diverticula, even when adjusted for gender and BMI (OR 1.09, 95% CI 1.0,1.2). Age at diagnosis was not associated with diverticula when adjusted for gender and BMI.

**Table 3.** Differences in clinical characteristics and biochemical finding between acromegaly patients with and without diverticular disease.

| | Diverticular disease | | |
|---|---|---|---|
| | **No n=68** | **Yes n=39** | **P-value** |
| **Gender (% males)** | 58 % | 42 % | 0.03 |
| **Age at diagnosis (yr)** | 45 (1) | 51 (2) | 0.01 |
| **Age at colonoscopy (yr)** | 54 (2) | 63 (2) | 0.01 |
| **BMI at diagnosis (kg/m$^2$)** | 27 (1) | 27 (1) | 0.91 |
| **Pre-treatment GH (ug/l)** | 29 (4) | 29 (4) | 0.92 |
| **Pre-treatment IGF-I SD score** | 7 (2) | 7 (1) | 0.86 |
| **Duration of active disease (yr)** | 9 (1) | 14 (3) | 0.02 |
| **Duration of disease remission (yr)** | 10 (1) | 11 (2) | 0.65 |

Data are shown as mean (SEM), unless mentioned otherwise. P<0.05 was considered significant. Abbreviations: SEM: standard error of the mean, SD: standard deviation, yr: year, BMI: body mass index, kg: kilogram, m: meter. Bold P-values reflect significant difference

GH/IGF-I concentrations at diagnosis and duration of active disease

Duration of active disease was almost twice as long in patients with diverticula (14.3 ± 3.1 yr) when compared with patients without diverticula (8.7 ± 0.9 yr) (p<0.001) and when adjusted for age, gender, and BMI logistic regression analysis demonstrated a significant positive relation between disease duration and diverticular disease (OR 1.09, 95% CI 1.0, 1.2). Pre-treatment

GH concentrations and IGF-I SD scores were not different between patients with and without diverticula (*Table 3*). However, when entered in the regression model together with duration of active disease, the relation between disease duration and diverticular disease became even stronger (OR 1.11, 95% CI: 1.1-1.2). As shown in *Table 4,* patients with the longest disease duration had increased relative risks (RR) for diverticula (highest tertile: >11 years).

The prevalence of hypopituitarism, initial treatment modalities, current use of SMS analogs or pegvisomant, and duration of remission were not associated with diverticula.

**Table 4. Risk of presence of diverticular disease of patients with acromegaly in relation to tertiles of duration of acromegaly.**

| | Tertiles | Patients with diverticula (%) | Adjusted RR (95% CI) | p-value |
|---|---|---|---|---|
| **Disease duration** | **<5.0** | **18** | **1** | |
| **(years)** | 5.0 – 11.0 | 23 | 2.01 (0.8, 3.6) | 0.08 |
| | >11.0 | 29 | 4.21 (2.4, 5.4) | <0.01 |

N=69. Data were analyzed by multinomial logistic regression analysis with tertiles of disease duration as dependent variable and the lowest tertile as reference category. Colonic diverticula and gender were entered in the model as factors and the covariates were ln pre-treatment GH concentrations, ln pre-treatment IGF-I SD scores, age at colonoscopy and BMI. Abbreviations: RR: relative risk, CI: confidence interval.





## Cecal intubation rate and dolichocolon

The cecal intubation rate was significantly lower in patients (78%), compared with controls (96%) (p<0.001). Dolichocolon was present in 43 patients (34%), but only in 3 controls (1%) (p<0.001). Cecal intubation rate was significantly lower in patients with dolichocolon (64%) when compared with patients with normal colon length (89%, p<0.001).

### *Factors influencing dolichocolon*

The presence of dolichocolon was not associated with age at colonoscopy, age at diagnosis of acromegaly, gender, or BMI. LnIGF-I SD scores at the time of diagnosis were associated with dolichocolon (OR 1.3, 95% CI 1.1-1.4) also when adjusted for the duration of pre-treatment exposure (OR 1.3, 95% CI: 1.1-1.5). LnGH at diagnosis was not associated with dolichocolon, nor when adjusted for disease duration.

There was no influence of hypopituitarism, type of treatment for acromegaly, or duration of remission on dolichocolon. Dolichocolon was more frequently present in patients with

diverticula than in patients without diverticula (odds 1.4, 95% CI: 1.2-1.7).

### Colorectal polyps

In 51 patients (48%) polyps were found and biopsy or polypectomy was performed, with an equal distribution in men (46%) and women (49%). Histopathological examination showed hyperplastic polyps in 14% of patients and adenomatous polyps in 34% of patients (82% low grade, 4% intermediate grade, and 4% high grade dysplasia).

Patients had a higher prevalence of adenomatous polyps compared with controls (28% vs. 13%, $p<0.001$), whereas there were no differences between both groups with respects to the grades of dysplasia. Thirty-five percent of controls had colonoscopy for symptomatic complaints. Exclusion of these controls from the analysis did not affect the difference in the prevalence of polyps between patients and controls (28% vs. 12%, $p<0.001$).

#### *Factors influencing colorectal polyps*

Age at colonoscopy, age at diagnosis of acromegaly, gender, or BMI were not associated with adenomatous polyps. LnIGF-I SD concentration at diagnosis was associated with adenomatous polyps (OR 1.1, 95% CI: 1.01-1.14), even when entered in the regression model together with disease duration (OR 1.1, 95% CI: 1.03-1.12). LnGH concentrations at diagnosis were not associated with adenomatous polyps. There was no influence of hypopituitarism, type of treatment for acromegaly, or duration of remission on adenomatous polyps. There was no difference in the presence of diverticula and dolichocolon between patients with and without adenomatous polyps.

## DISCUSSION

This case-control study in patients with cured/controlled acromegaly is the first to report that acromegaly is associated with colonic diverticula. In addition, we observed an association between colonic diverticula and duration/severity of previous exposure to increased circulating GH and IGF-I concentrations. The highest tertile of disease duration, adjusted for pre-treatment concentrations of GH and IGF-I SD scores, was associated with a more than four-fold increased risk for diverticula. This observation adds diverticular disease to the currently recog-

nized, irreversible effects of acromegaly.

Dolichocolon was also increased in the patient group and associated with IGF-I concentrations at diagnosis, when adjusted for the duration of active acromegaly. Dolichocolon is a well known feature of acromegaly[24]. However, we are the first to systematically evaluate the prevalence of this manifestation in a large population of patients with controlled acromegaly. Therefore, these observations stress that the severity of acromegaly is a determinant of the various manifestations of acromegaly with respect to colonic diseases, which also appears to include diverticular disease.

Diverticula are left-sided out-pouchings of colonic mucosa and submucosa that emerge through the muscularis propria[1;5]. Although risk-factors for diverticular disease including physical inactivity, constipation, obesity, smoking, and non-steroidal anti-inflammatory drugs (NSAIDs) have been described, the development of diverticula is mainly related to three essential precipitating factors: low fibre diet, altered motility, and colonic wall resistance. On a microscopic level colons with diverticulosis may have increased elastin in the taenia[25], and structural changes in the collagen that mimic those seen with aging[26]. This concerns not so much the total amount of collagen, but the cross-linking and an increase in type 3 fibres[27;28], which may decrease the tensile strength of the circular muscle, facilitating the formation of diverticula. Support for a pathophysiological role of alterations in connective tissue characteristics in diverticula are derived from observations in patients with connective tissue diseases like Marfan's and Ehlers-Danlos syndromes, who develop diverticula throughout the colon at a precocious age[12-14;28].

Diverticula in Marfan's syndrome are caused by an abnormally weak bowel wall, due to a mutation in the fibrillin gene, leading to disturbed connective tissue[13]. This same mechanism also leads to degeneration of cardiac valves and aortic root in these patients[10]. GH is also involved in matrix regulation. GH increases gene expression of the matrix metalloproteinases (MMPs), that are capable of altering the composition of the extracellular matrix[9]. In acromegaly, this altered matrix is thought to be responsible for changes found in heart valves and the aortic root[11], a mechanism known from Marfan's syndrome[10]. A crucial role of GH and IGF-I in the regulation of matrix regulation is further strengthened by the observations that both cardiac valve pathology and the presence of diverticula are strongly associated with the duration of exposure to abnormal GH and IGF-I concentrations[29].

In addition, in this study in patients with long-term follow-up of acromegaly, colonic

adenomatous polyps were associated with IGF-I SD concentrations at diagnosis of acromegaly, even when adjusted for the estimated duration of active acromegaly. In accordance with previous studies, documenting a high prevalence of adenomatous polyps in patients with acromegaly[30;31], we observed a higher prevalence of adenomatous polyps in comparison with our control group, even though our controls underwent colonoscopy for a medical reason, i.e. because of rectal blood loss, a positive family history of colon cancer, or aspecific abdominal complaints. The adenomatous polyp frequency in the controls was comparable with the frequency observed in general Caucasian population[32].

Some potential limitations of this study have to be addressed. Since the indication of colonoscopy in both patients and controls was screening for colorectal polyps, diverticular disease may have been underreported, despite the use of a structured protocol for colonoscopy reports. However, this may have underestimated, rather than overestimated diverticula and dolichocolon, and therefore does not affect our conclusions[33;34]. Moreover, it is unlikely this effect will be different between patients and controls. Thus, the control group is appropriate for comparison of prevalences of diverticular disease and dolichocolon. Second, although all patients and controls underwent colonoscopy for the purpose of polyp screening, the *a priori* chance for the presence of polyps and colorectal cancer will be different between patients and controls and also within the control group, dependent on the indication for colonoscopy, i.e. rectal bleeding, (symptomatic) or family history of colorectal cancer (asymptomatic). However, the prevalence of polyps in the controls is comparable to literature reports. Moreover, exclusion of symptomatic controls from the analysis did not affect our conclusions on the frequency of polyps or diverticula. Moreover, a potentially higher polyp prevalence in the controls due to the indication of rectal bleeding or familiar cancer risk, would decrease, rather than increase, the difference between patients and controls. Third, the fact that in 20% of colonoscopies in acromegaly cecal intubation failed, may potentially have underestimated the prevalence of diverticula and polyps in acromegaly. However, this would result in an underestimation of the prevalence of diverticular disease, which does not affect our conclusions with respect to the increased prevalence of colonic diverticula in acromegaly.

In conclusion, colonic diverticular disease is increased in patients with acromegaly compared with controls and diverticula were present at a significantly younger age. Diverticulosis in acromegaly was primarily associated with the duration of active disease, which became even stronger when adjusted for the extend of previous GH and IGF-I excess. In addition,

dolichocolon and adenomatous polyps were increased in patients when compared with controls, which were both associated with IGF-I concentrations at the time of diagnosis of acromegaly. We hypothesize that in patients with acromegaly diverticula develop due to disturbed matrix regulation caused by previous excess of GH and/or IGF-I.

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