



Acromegaly can be associated with impairment of LES relaxation in the oesophagus

Akromegalia może wiązać się z zaburzeniami rozkurczu dolnego zwieracza przełyku (LES)

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Abstract

Introduction: Although prolonged small intestine and colonic transit time has been demonstrated in acromegaly patients, the influence of acromegaly on oesophagus motility and the pathological mechanisms involved are still not clarified. We aimed to investigate manometric measurements to ascertain whether oesophagus motility is affected in active acromegaly patients.

Material and methods: The study was performed in an institutional referral centre at a tertiary care hospital. Twenty-three acromegaly patients (mean age 43.2 ± 13.2 years) and 25 sex- and age-matched healthy control subjects (mean age 48.6 ± 7.9 years) were recruited to a case-control study. Oesophageal manometry was performed using MMS (Medical Measurement Systems, Netherlands) Solar GI — Air Charged Intelligent Gastrointestinal Conventional Manometry.

Results: In manometric measurements the lower oesophageal sphincter pressure was 18 ± 7 mmHg in acromegaly patients and 15.6 ± 4.4 mm Hg in controls, and there was no significant difference ($p = 0.17$). The percentage of relaxation was 64.8% and 81.8%, respectively, and it was significantly lower in acromegaly patients than in controls ($p < 0.001$). Additionally, the duration of relaxation was found to be 4 ± 1.9 seconds and 5 ± 1.7 seconds in patients and controls, respectively ($p = 0.049$).

Conclusions: Our study has demonstrated a significant reduction in the percentage and duration of lower oesophageal sphincter relaxation in oesophagus motility even in acromegaly patients without any gastrointestinal symptoms. Further clinical and pathophysiological studies are required to clarify the underlying mechanisms of gastrointestinal motility disorders in acromegaly. (*Endokrynol Pol* 2015; 66 (4): 308–312)

Key words: acromegaly; esophagus; motility; manometry

Streszczenie

Wstęp: Chociaż u pacjentów chorujących na akromegalię wykazano wydłużony czas pasażu żołądkowo-jelitowego, wpływ akromegalii na motorykę przełyku oraz powiązane z tym mechanizmy patologiczne nadal nie są wyjaśnione. Celem pracy było zbadanie za pomocą pomiarów manometrycznych czy motoryka przełyku ulega zmianie u pacjentów z aktywną akromegalią.

Materiał i metody: Badanie przeprowadzono w ośrodku referencyjnym w szpitalu specjalistycznym. Dwudziestu trzech pacjentów chorujących na akromegalię (śr. wiek $43,2 \pm 13,2$ lat) oraz w grupie kontrolnej 25 osób dopasowanych pod względem płci i wieku (śr. wiek $48,6 \pm 7,9$ lat) zostało zakwalifikowanych do badania kliniczno-kontrolnego. Manometrię przełyku wykonano za pomocą MMS (Medical Measurement Systems, Holandia) Solar GI.

Wyniki: W pomiarach manometrycznych u pacjentów cierpiących na akromegalię, ciśnienie dolnego zwieracza przełyku wynosiło 18 ± 7 mm Hg, a u osób kontrolnych wynosiło ono $15,6 \pm 4,4$ mm Hg, nie było więc znaczącej różnicy między grupami ($p = 0,17$). odsetek rozkurczu wynosił odpowiednio 64,8% i 81,8% i był on znacznie niższy u pacjentów z akromegalią ($p < 0,001$). Ponadto, długość trwania rozkurczu wynosiła odpowiednio $4 \pm 1,9$ sek. i $5 \pm 1,7$ sek. ($p = 0,049$).

Wnioski: Niniejsze badanie wykazało znaczną redukcję odsetka i czasu trwania rozkurczu dolnego zwieracza przełyku w motoryce przełyku, nawet u pacjentów z akromegalią bez objawów żołądkowo-jelitowych. Należy przeprowadzić dalsze badania kliniczne i patofizjologiczne, aby wyjaśnić mechanizmy leżące u podłoża zaburzeń motoryki żołądkowo-jelitowej u pacjentów chorujących na akromegalię. (*Endokrynol Pol* 2015; 66 (4): 308–312)

Słowa kluczowe: akromegalia; przełyk; ruchliwość; manometria

Introduction

Acromegaly is a rare disease that is mainly caused by pituitary somatotroph adenomas [1]. Hypersecretion of GH and IGF1 effect the whole body and lead to multi-systemic complications, including those involving the

gastrointestinal system [2, 3]. In terms of organic gastrointestinal disorders, adenomatous polyps and colon carcinoma are the most significant complications associated with acromegaly [4]. Acromegaly has also been related with functional disorders of the gastrointestinal system in several reports. Along with prolonged small



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intestine and colonic transit time, bacterial overgrowth has been demonstrated in acromegaly patients [5, 6]. Additionally, previous studies have shown that somatostatin analogues in the treatment of acromegaly could impair gall bladder emptying, which leads to gallstones [7]. Autonomic intestinal impairment and possible roles of gastrointestinal hormones (e.g. ghrelin) have been postulated to explain the motility dysfunctions [8, 9]. However, the influence of acromegaly on gastrointestinal system motility and the pathological mechanisms involved are still not clarified.

Oesophageal manometry is performed to measure motility function, and it provides the evaluation of the peristalsis and intraluminal pressure of the oesophagus [10]. It is the most relevant technique in the diagnosis of oesophageal functional disorders such as achalasia and diffuse oesophageal spasm. Manometric assessments have also contributed to reveal the pathophysiological mechanisms as well as clinical ground in gastrointestinal manifestations of endocrine diseases such as diabetes and thyroid disorders [11, 12]. Oesophageal manometry is the gold standard technique for the evaluation of oesophageal functional disorders, and to our knowledge no data are available on oesophageal motility in acromegaly patients.

In this study we aimed to investigate the manometric measurements to ascertain whether oesophageal motility is affected in active acromegaly patients.

Material and methods

Subjects

Twenty-three naive acromegaly patients (15 female and 8 male) and 25 age- and sex-matched healthy subjects (17 female and 8 male) were recruited to the study in Bezmialem University Hospital Endocrinology Clinic between 2011 and 2013. Mean age was 43.2 ± 13.2 years in acromegaly patients and 48.6 ± 7.9 years in healthy subjects. All acromegaly patients were newly diagnosed and had no gastrointestinal system symptoms such as dyspepsia, dysphagia, reflux or regurgitation, early satiety, loss of appetite, nausea, abdominal fullness, diarrhoea, or constipation. Based on the clinical features, acromegaly was confirmed by unsuppressed GH to < 0.4 ng/mL after an oral glucose tolerance test and high IGF1 levels, age matched. Magnetic resonance imaging (MRI) of hypophysis was performed for all acromegalic patients and the maximum diameter was determined as the tumour size. The IGF1 values of every patient were adjusted to calculate the IGF1 index using the following formula: $100 \times \text{IGF1} / \text{Upper limit of normal range}$, because the upper limit of the normal range for IGF1 values is variable according to age [13]. Blood GH and IGF1 levels were assayed using a chemiluminescence

immunometric assay (Siemens Advia-Centaur USA). Age-related reference ranges for IGF1 were as follows: 18–20 years old: 197–956; 20–23 years old: 215–628; 23–25 years old: 169–591; 25–30 years old: 119–476; 30–40 years old: 100–494; 40–50 years old: 101–303; and > 50 years old: 78–258 (ng/mL).

Patients with a history of gastrointestinal tract disease, other diseases known to effect gastrointestinal motility (diabetes mellitus, hypothyroidism, etc.), chronic systemic disorders (malignancies, infections), and those taking any medication that could influence gastrointestinal system motility, as well as those smoking or drinking alcohol, were excluded from the study. Complete blood counts, sedimentation rate, routine biochemical blood tests (serum glucose, creatinine, electrolytes, albumin, total protein, liver enzymes) and vitamin B12 level measurements were also performed in all patients.

This study was approved by the local ethics committee of Bezmialem Vakif University, and informed consent was obtained in all cases.

Oesophageal manometry

The parameters of oesophageal manometry were measured by using MMS (Medical Measurement Systems, Netherlands) Solar GI — Air Charged Intelligent Gastrointestinal Conventional Manometry. A four-channel air charged circumferential pressure catheter (Latitude Gastrointestinal Manometry Catheter Clinical innovations, Inc. 747 West 4170, South Murray, Utah) with a 5-cm distance between sensors was inserted via a nostril and then placed to straddle the gastroesophageal junction. After an overnight fast, oesophageal motility in patients with acromegaly and healthy subjects were performed in the supine position. The lower oesophageal sphincter pressure (LESP) was measured as the difference between the end-expiratory LESP and the end-expiratory gastric pressure, applying the station pull-through technique. All pressure values were given in mm Hg and referred to atmospheric pressure. The four sensors positioned 3, 8, 13, and 18 cm above the lower oesophageal sphincter (LES) were used to calculate contractions in the oesophageal body. Ten consecutive wet swallows at 30-second intervals (5 mL of water) were measured. Dry swallows were excluded in the analysis. Only one investigator performed all tracings.

The wave amplitude from the mean intraoesophageal baseline pressure to the peak of the wave was included in the measurements. The duration of individual contractions was calculated from the initiation of the major upstroke to the termination of the wave. The percentage of peristalsis was recognised among the 10 consecutive wave forms.

Statistical analysis

Statistical analyses were performed with SPSS software, version 20.0 for windows (SPSS Inc., Chicago, IL, USA). Since the distribution of values was normal, Student's *t* test was used for comparison of the means of two groups. Pearson's correlation was applied to evaluate the relationship between the studied parameters. Statistical significance was set at $p < 0.05$. The quantitative variables are presented as mean \pm standard deviation.

Results

Table I summarises the demographic characteristics of acromegaly patients and healthy controls. Age and gender were similar in both groups. Body mass index was 29.1 ± 4.4 in acromegaly patients and 27.7 ± 3.3 in healthy subjects, and there was no significant difference ($p > 0.05$). Mean GH level was 8.7 ± 10.8 ng/mL and mean IGF1 level was 788.4 ± 332.3 ng/mL in acromegaly patients. Adjusted IGF1 levels according to the upper limit of normal range was 3.2 ± 1.4 ng/mL. Sixteen (69.6%) patients had macroadenomas and 7 (30.4%) had microadenomas in the acromegaly group. Laboratory findings and clinical assessment showed no hypopituitarism or any other endocrinological disorders except for acromegaly in the patient group.

All parameters in oesophageal manometric measurements were compared between acromegaly patients and control group. The mean lower oesophageal sphincter pressure (LESP) was 18 ± 7 mm Hg in acromegaly patients and 15.6 ± 4.4 mm Hg in controls, and there was no significant difference between these two groups ($p = 0.17$) (Fig. 1). The duration of contraction was 3.7 ± 0.8 seconds in acromegaly patients and 3.7 ± 0.6 seconds in healthy subjects ($p > 0.05$). Maximum upstroke

Table I. Demographic Characteristics of Acromegaly Patients and the Control Group

Tabela I. Cechy demograficzne grupy pacjentów z akromegalią i grupy kontrolnej

	Acromegaly Patients (n = 23)	Control Group (n = 25)	p
Age (y)	43.2 \pm 13.2	48.6 \pm 7.9	N.S.
Gender	Female (n)	15	N.S.
	Male (n)	8	
BMI [kg/m ²]	29.1 \pm 4.4	27.7 \pm 3.3	N.S.
GH [ng/mL]	8.7 \pm 10.8		
IGF1 [ng/mL]	788.4 \pm 332.3		
IGF1 index	3.2 \pm 1.4		
Tumour Size (n, %)			
Macroadenoma	16 (69.6)		
Microadenoma	7 (30.4)		

Data are mean \pm Standard Deviation
IGF1 index: $100 \times \text{IGF1} / \text{Upper limit of normal range}$

also displayed no significant difference between groups (71.5 ± 21.1 mm Hg in acromegaly patients and 68.1 ± 24.6 mm Hg in healthy subjects). The percentage of relaxation for acromegaly patients and control group was 64.8% and 81.8%, respectively, which was significantly lower for acromegaly patients than for healthy subjects ($p < 0.001$) (Fig. 2). Furthermore, the duration of relaxation was found to be 4 ± 1.9 seconds in acromegaly patients and 5 ± 1.7 seconds in the control group, and it was significantly shorter in patients with acromegaly than in controls ($p = 0.04$). No correlation was observed between manometric measurements and disease characteristics, including GH, IGF1, adjusted IGF1, and tumour size.

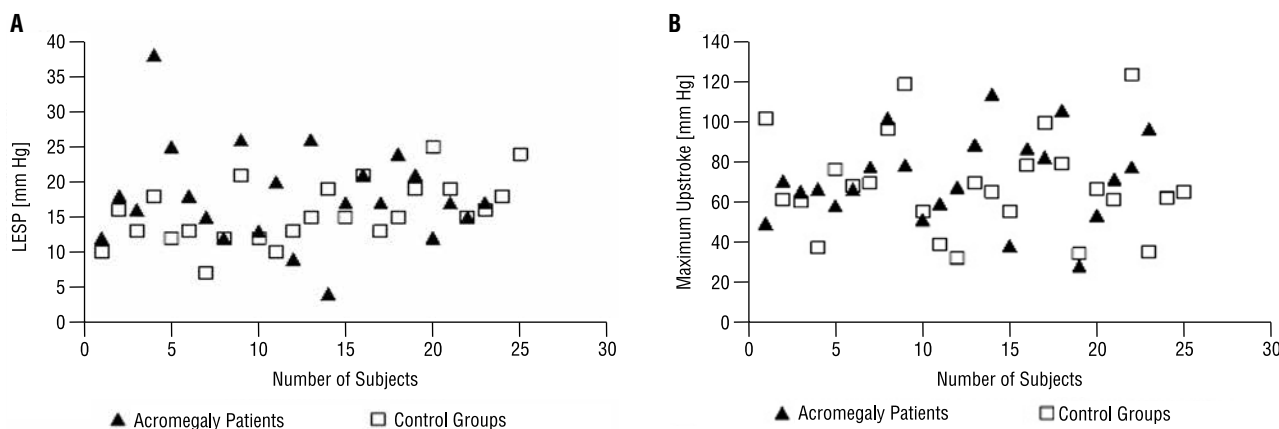


Figure 1. Distribution of (A) LESP and (B) maximum upstroke in acromegaly patients and control group ($p > 0.05$ for both manometric parameters)

Rycina 1. Rozkład (A) ciśnienia dolnego zwieracza przełyku oraz (B) maksymalnej relaksacji u pacjentów z akromegalią i grupy kontrolnej ($p > 0,05$ dla obu parametrów manometrycznych)

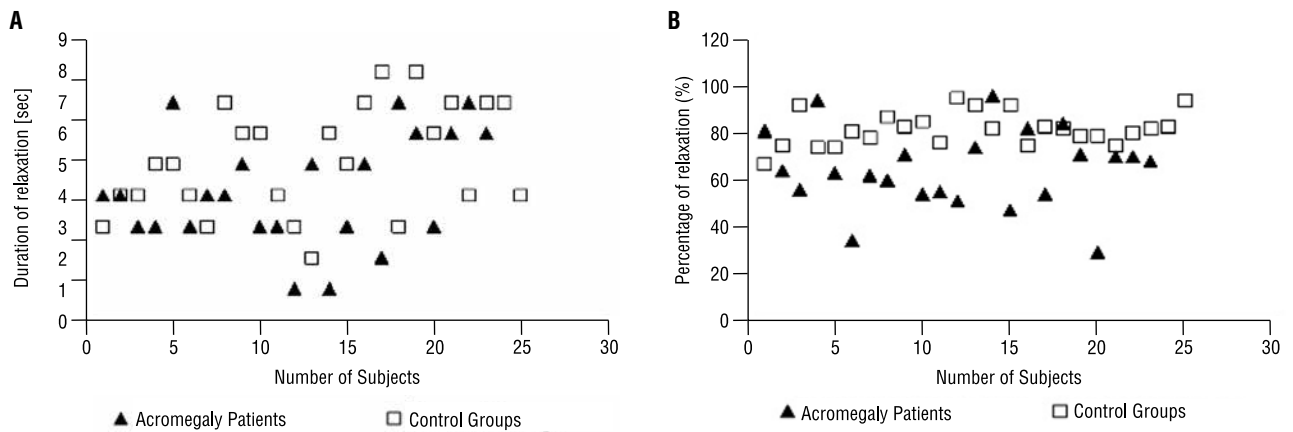


Figure 2. Distribution of (A) duration of LES relaxation and (B) percentage of LES relaxation in acromegaly patients and control group ($p < 0.05$ and $p < 0.001$, respectively)

Rycina 2. Rozkład (A) czasu trwania rozkurczu LES oraz (B) procentowej relaksacji LES u pacjentów z akromegalią i grupy kontrolnej (odpowiednio, $p < 0,05$ i $p < 0,001$)

Discussion

Colorectal neoplasms are the most prevalent and clinically well-known gastrointestinal complications of acromegaly [14, 15]. In clinical studies and reviews, functional disorders of the gastrointestinal system in acromegaly have been overshadowed by organic disorders. Moreover, there are a very limited number of studies focused on gastrointestinal functional disorders in acromegaly, and it has been shown that active acromegaly may induce impairment of the intestinal motility [16]. Resmini et al. revealed prolonged oro-cecal transit time and small intestinal bacterial overgrowth in acromegaly patients [5], and Catnach et al. found that gall bladder motor function was severely impaired in untreated acromegaly patients [17]. In another study reporting on gall bladder emptying and small intestinal transit in acromegaly patients, Hussaini et al. showed that intestinal transit and gall bladder volume were significantly different between acromegaly patients and controls [18]. Our results contribute to previous studies by indicating motility abnormalities of the oesophagus and by suggesting that acromegaly could have unfavourable effects on oesophageal motility through the mechanisms of reduced percentage and duration of LES relaxation in patients without any clinical gastrointestinal symptoms. Moreover, LESP was also found to be slightly higher in acromegaly patients than in control subjects, albeit insignificantly.

Plausible mechanisms have been elucidated that might explain gastrointestinal motility alterations in acromegaly, and the underlying pathogenesis remains unclear. Motility disorders in acromegaly could be linked to the presence of autonomic dysfunction, similar to that which have been previously demonstrated in the cardio-

vascular system [8, 19, 20]. LES is comprised of smooth muscle, and vagal efferent nerve induces its relaxation mediated by NO, which is the main neurotransmitters in the gastrointestinal tract [21–23]. It was shown that acromegaly can precipitate low levels of NO [24, 25]. Ronconi et al. found significantly decreased levels of NO concentrations in 13 acromegalic patients, compared to 12 sex- and age-matched controls, and an inverse correlation of NO levels with GH and IGF1 [26]. LES is also stimulated by postganglionic sympathetic nerves, although vagal innervation is responsible for the main regulator action. Previous studies showed sympathetic hypertonia indicating sympathovagal imbalance in acromegaly patients [19]. In our study, the decreased percentage and duration of LES relaxation in acromegaly patients could be related to sympathovagal imbalance due to sympathetic hypertonia and decreased NO levels, which contribute to the impairment of relaxation and increase of LES basal tone in acromegaly [23]. Other studies have also shown that alterations in gastrointestinal hormones, including ghrelin and somatostatin (SS), can cause motility dysfunctions. Ghrelin enhances upper gastrointestinal motility and gastric emptying through the vagus nerves [27–29]. It has been shown that there is a feedback mechanism between ghrelin, SS, and GH, which might be considered one of the possible reasons for oesophageal motility dysfunction in patients with acromegaly [9, 30–32]. Arosio et al. indicated that GH stimulates hypothalamic SS production, as found in acromegaly, and that it may influence circulating SS levels, which might play a role in gastrointestinal motility disorders such as prolonged bowel transit in acromegaly patients [33]. However, the pathophysiological mechanisms of gastrointestinal motility disorders still need clarification, and further studies are required.

Correlations between well-known complications and levels of GH and IGF1 are still a matter of debate. Along with increased risk for mortality and morbidity in acromegaly patients, non-biochemical parameters do not necessarily correlate with biochemical activity of acromegaly [34, 35]. Correlations between levels of GH and IGF1 and motility parameters were not reported in previous acromegaly studies. In this study no correlation was found between the level of biochemical activity of acromegaly and manometric parameters. These results suggested that acromegaly impairs the relaxation of LES independently of levels of GH and IGF 1 hypersecretion.

In conclusion, we investigated for the first time oesophageal motility manifestations in naive acromegalic patients. This study has demonstrated a significant reduction of the percentage and duration of LES relaxation in oesophagus motility even in acromegaly patients without any gastrointestinal symptoms. Further clinical and pathophysiological studies are required to clarify the underlying mechanisms of gastrointestinal motility disorders in acromegaly.

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