

ORIGINAL ARTICLE

CHANGES IN SERUM GHRELIN AND ITS RELATIONSHIP WITH OF BODY MASS INDEX IN PATIENTS WITH GASTROESOPHAGEAL REFLUX DISEASE AND SPONDYLOARTHRITIS

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Yelyzaveta S. Sirchak, Stanislav A. Tsioka, Andriy S. Chobej, Nelli V. Bedey, Inna S. Borisova

UZHGOROD NATIONAL UNIVERSITY, UZHGOROD, UKRAINE

ABSTRACT

The aim: To determine the features of changes in serum ghrelin levels and its relationship with the body mass index in patients with GERD and spondyloarthritis (SpA) with lesions of the cervical and thoracic spine.

Materials and methods: The examined patients included 80 patients with SpA with cervical and thoracic spine lesions in combination with GERD. The examined patients with SpA with predominant cervical and thoracic spine lesions were divided into two groups depending on the clinical course of GERD, namely: group I included 33 (41.2%) patients with typical esophageal manifestations of GERD (13 males (39.4%), 20 females (60.6%)), and group II consisted of 47 (58.8%) patients with atypical extraesophageal manifestations of GERD (among them were 17 (36.2%) males and 30 (63.2%) females).

Results: All patients were tested for serum ghrelin by enzyme-linked immunosorbent assay. Analysis of clinical manifestations of atypical GERD (group II patients) revealed that most often patients with SpA of the cervical and thoracic spine were diagnosed with dental and otolaryngological forms of reflux disease (40.4% and 25.5% of patients, respectively). Maximum serum ghrelin levels were detected in patients with SpA with cardiac GERD (355.02 ± 4.75 ng/ml), while minimum values were found in patients with dental signs of reflux disease (298.17 ± 5.16 ng/ml – $p < 0.05$).

Conclusions: 1. In patients with SpA with cervical and thoracic spine lesions, GERD often has atypical symptoms (mostly dental and otolaryngological forms in 40.4% and 25.5% of patients). 2. In patients with SpA with esophageal clinical signs of GERD, normal weight or underweight is more common, while in patients with extraesophageal forms of GERD overweight or obesity of varying severity prevails. 3. In patients with SpA and GERD, an increase in serum ghrelin levels was found in patients with cardiac manifestations of reflux disease (355.02 ± 4.75 ng/ml). 4. The relationship between BMI changes in patients with SpA and GERD and increased serum ghrelin levels was found, namely: in group II patients with overweight and obesity a direct correlation was found, and in group I patients with underweight an inverse correlation was found.

KEY WORDS: esophageal, extraesophageal manifestations of gastroesophageal reflux disease, spondyloarthritis, body mass index; ghrelin

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INTRODUCTION

Ghrelin is an orexigenic hormone that regulates neuronal chains that modulate food intake and energy expenditure by binding to specific receptors in the brain [1, 2]. It has a variety of metabolic effects on physiological processes in the body, such as food regulation and satiety, modulation of energy expenditure through regulation of brown fat thermogenesis, regulation of lipid levels and obesity in general, glucose metabolism, inflammation, effects on endothelial dysfunction and many others [3]. Ghrelin, by stimulating growth hormone secretion, may also stimulate increased calorie intake, weight gain, and obesity by activating hypothalamic orexigenic neuropeptide Y (NPY) [4]. Thus, ghrelin is associated with conditions associated with hyperlipidemia, weight gain, abnormal body composition, and fat accumulation [5].

Ghrelin is produced mainly by P/D1 cells of the mucous membrane of the fundus of the stomach [2]. Ghrelin circulates in the human body in two main forms: acylated (about 5.0% of total ghrelin) and deacylated (about 95.0%

% of total ghrelin), which have potential differences in metabolic effects. [4]. Ghrelin as a multifunctional peptide hormone, is involved in the formation of eating behavior, energy balance, regulation of carbohydrate and lipid metabolism, as well as modulation of gastrointestinal function (it stimulates the secretion of hydrochloric acid and affects the motor activity of various digestive systems) [6].

Gastroesophageal reflux disease (GERD) is a common digestive disease based on pathological gastroesophageal (GE) reflux, which occurs due to esophageal cardia insufficiency and impaired barrier function of the lower esophageal sphincter [7]. The prevalence of GERD in Western populations over the past 30 years has a clear tendency to increase and varies from 10.0% to 30.0% [8, 9]. The relevance of GERD is also due to the presence of both typical and atypical (bronchopulmonary, cardiac, dental, otolaryngological) clinical manifestations that complicate the diagnosis of GERD [10].

The search for new factors that play a role in the formation of GERD is especially relevant in patients with

polymorbid pathology, the treatment of which requires medications that may adversely affect the condition of the mucous membrane of the upper gastrointestinal tract, as well as its functional activity. Therefore, the study of the clinical course, as well as factors and levels of various biologically active substances that may play an important role in the pathogenetic mechanism of GERD in patients with combined pathology, including inflammatory lesions of the spine, namely spondyloarthritis (SpA), is an extremely relevant problem of modern clinical medicine.

THE AIM

The aim of the study is to determine the features of changes in serum ghrelin levels and its relationship with the body mass index in patients with GERD and spondyloarthritis with lesions of the cervical and thoracic spine.

MATERIALS AND METHODS

The examined patients included 80 patients with SpA with cervical and thoracic spine lesions in combination with GERD who were hospitalized in Rheumatology and Gastroenterology Departments of Municipal Non-Profit Enterprise "Transcarpathian Regional Clinical Hospital named after Andrii Novak" of Transcarpathian Regional Council, and patients who were on outpatient observation by family doctors at the place of residence, as well as underwent dental treatment at Dental Plus Clinic in the period of 2019–2022. All studies were performed with the consent of patients, and their methodology was in line with the Helsinki Declaration of Human Rights of 1975 and its revision in 1983, the Council of Europe Convention on Human Rights and Biomedicine, and the legislation of Ukraine.

The control group included 20 healthy individuals: 9 males (45.0%) and 11 females (55.0%) without musculoskeletal and upper gastrointestinal tract lesions. The average age was 48.8 ± 4.1 years.

All patients were examined using general clinical, anthropometric, instrumental and laboratory methods. To verify the diagnosis, attention was paid to the nature of the complaints and medical history. In anthropometric research, height and waist circumference were determined, and body mass index (BMI) was calculated. According to WHO recommendations, the patients were distributed depending on the BMI, at which BMI 16.0 or less indicates a pronounced deficit of body weight; 16.0–18.5 underweight; 18.5–24.9 normal weight; 25.0–29.9 overweight; 30.0–34.9 obesity Class 1; 35.0–39.9 obesity Class 2; 40.0 and more obesity Class 3 (morbid obesity) [11].

The diagnosis of GERD was established according to the criteria of the unified clinical protocol (order of the Ministry of Health of Ukraine dated 31.10.2013 № 943) taking into account complaints, endoscopic examination data, etc. To confirm the diagnosis, the examined patients underwent fibroesophagogastroduodenoscopy (FEGDS) using endoscopy equipment Pentax ERM-3300 video

processor and flexible fiber endoscopes Pentax E-2430, GIF-K20. Also, 24-hour pH monitoring according to Prof. V.N. Chernobrov's method was performed. The Los Angeles (LA) classification (1998) was used for endoscopic assessment of the degree of damage to the esophagus: Grade A – single erosion ≤ 5 mm; Grade B – ≥ 1 erosion > 5 mm long that does not occupy the entire space between 2 adjacent folds of the esophagus; Grade C – ≥ 1 erosion that occupies the entire space between ≥ 2 folds of the esophagus and $\leq 75\%$ of the perimeter of the esophagus; and Grade D – erosions or ulcers occupying $\geq 75\%$ of the esophageal perimeter [12].

The diagnosis of SpA was established on the basis of diagnostic criteria of the American College of Rheumatology (ACR, 2018) and the European League Against Rheumatism (European League Against Rheumatism, EULAR, 2018) [13, 14].

All patients were tested for serum ghrelin by enzyme-linked immunosorbent assay (ELISA) using a test system from BioChemMac, RayBio® Human/Mouse/Rat Ghrelin Enzyme Immunoassay Kit.

The examined patients with spondyloarthritis with predominant cervical and thoracic spine lesions were divided into two groups depending on the clinical course of GERD, namely: group I included 33 (41.2%) patients with typical esophageal manifestations of GERD (13 males (39.4%), 20 females (60.6%), with the average age 49.8 ± 5.2 years), and group II consisted of 47 (58.8%) patients with atypical extraesophageal manifestations of GERD (among them were 17 (36.2%) males and 30 (63.2%) females, with the average age 46.7 ± 4.9 years).

The inclusion criteria were as follows: the presence of clinical symptoms (typical and atypical) of GERD, detection of FEGDS changes in the esophageal mucosa characteristic of GERD, and spondyloarthritis of the cervical and thoracic spine.

The exclusion criteria were as follows: functional or organic diseases of the esophagus, stomach and duodenum, non-erosive form of GERD, Barrett's esophagus, Helicobacter pylori positive patients, and patients with psychiatric and oncological diseases.

Analysis and processing of the results of the examinations was carried out by the computer program Statistics for Windows v.10.0 (StatSoft Inc, USA) using parametric and non-parametric methods of evaluation of the results.

RESULTS

The leading clinical manifestations of lesions of the upper gastrointestinal tract in patients of group I (with typical esophageal manifestations of GERD) were acid regurgitation, heartburn and dysphagia. As shown in Figure 1, esophageal signs of GERD were diagnosed in 41.2 % of patients, while atypical clinical forms of reflux disease were detected in 58.8 % of SpA patients.

Analysis of clinical manifestations of atypical GERD (group II patients) revealed that most often patients with SpA of the cervical and thoracic spine were diagnosed with

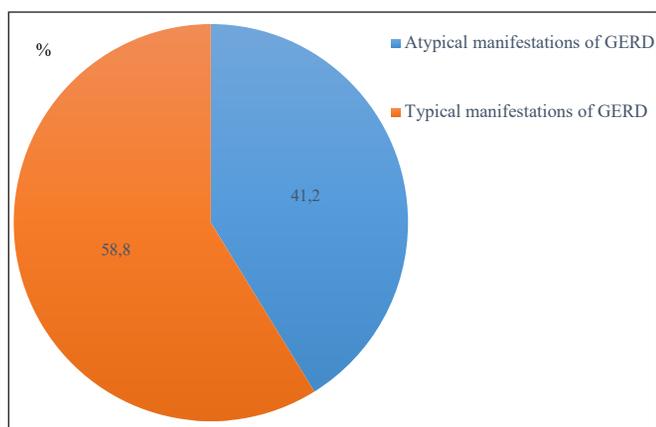


Fig. 1. Distribution of the examined patients with SpA depending on the clinical form of GERD

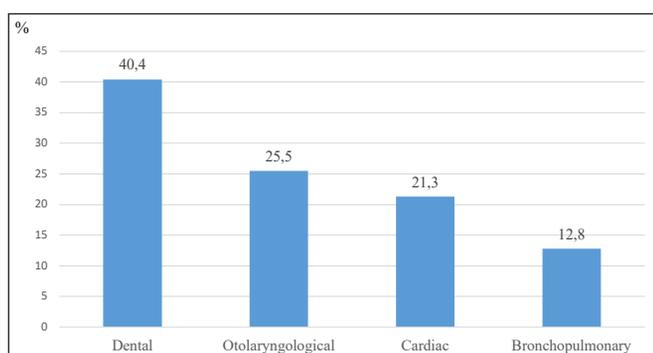


Fig. 2. Distribution of the examined SpA patients of group II depending on atypical clinical forms of GERD

dental and otolaryngological “masks” of reflux disease (40.4 % and 25.5 % of patients, respectively) – Fig.2. At the same time, dental signs of GERD were manifested by dental caries, stomatitis and periodontitis. Otolaryngological changes, which were considered atypical manifestations of GERD, were indicated by sore throat, hoarseness of voice, lump in the throat, as well as chronic coughing.

Cardiac form of GERD, manifested by chest pain along the esophagus, heart failure, as well as its bronchopulmonary “mask”, which was clinically manifested by dry cough and sleep apnea, was found in 21.3 % and 12.8 % of patients.

Determination of BMI allowed to establish differences in body mass in the examined patients with SpA with different clinical forms of GERD – Table I.

Patients with SpA with a typical clinical course of GERD (group I) more often had normal BMI and overweight (45.5 % and 24.2 % of patients). Obesity I and II was found in only 9.1 % and 3.0 % of patients. Also, underweight was 7.9 % more often found in patients of group I ($p < 0.01$) than in patients with atypical clinical forms of GERD. Group II patients most often had overweight (34.0% of subjects), as well as obesity of Class 1 and Class 2 (25.5 % and 17.1 %, respectively). Thus, SpA patients with atypical clinical forms of GERD are more likely to be overweight and obese (Class 1-2), while patients with typical esophageal manifestations of reflux disease are more likely to be diagnosed with normal or overweight or underweight.

Table I. Distribution of examined patients with SpA and different clinical forms of GERD depending on BMI

Indicator	Examined patients with SpA.	
	group I (n=33)	group II (n=47)
Underweight (BMI: 16.0 – 18.5)	18.2 % **	4.3 %
Normal weight (BMI: 18.5 – 24.9)	45.5 % **	19.1 %
Overweight (BMI: 25.0 – 29.9)	24.2 %	34.0 % *
Obesity Class 1 (BMI: 30.0 – 34.9)	9.1 %	25.5 % *
Obesity Class 2 (BMI: 35.0 – 39.9)	3.0 %	17.1 % **

Note: the difference between the indicators in the examined patients of groups I and II is statistically significant: * – $p < 0.05$; ** – $p < 0.01$.

Determination of ghrelin levels in the blood serum revealed differences in its level in the patients we examined for SpA depending on different clinical forms of GERD – Table II.

A significant increase in serum ghrelin levels was found in patients with SpA and GERD. In patients with SpA with esophageal manifestations of GERD its level was 223.21 ± 4.16 ng/ml against 105.11 ± 3.25 ng/ml in the control group ($p < 0.05$), while in patients with atypical forms a 3.0-fold increase was detected ($p < 0.01$).

Further analysis determined the differences in the level of this orexigenic hormone depending on the clinical course of atypical manifestations of GERD and established a dependence on changes in BMI in patients with SpA – tables III and IV.

Maximum serum ghrelin levels were detected in patients with SpA with cardiac GERD (355.02 ± 4.75 ng/ml), while minimum values were found in patients with dental signs of reflux disease (298.17 ± 5.16 ng/ml – $p < 0.05$). Almost the same serum ghrelin levels were found in patients with SpA with otolaryngological and bronchopulmonary signs of GERD.

In patients of group I, ghrelin levels correlated with BMI, which corresponds to normal weight and overweight and inversely correlated with underweight. In patients with SpA with atypical manifestations of GERD, a relationship was found between increased ghrelin levels and obesity Class 1-2, as well as BMI which corresponded to overweight ($r = 0.72$; $p < 0.05$).

The results of an experimental study by Kraft EN et al. (2019) indicate that ghrelin and its isoforms directly affect fatty acid oxidation and lipolysis. This may be the reason why patients with UCTD with high ghrelin levels have an asthenic constitution and poor nutrition. In particular, their BMI was often lower than normal. The results of this study also show that ghrelin stimulates the transport of fatty acids, affecting not only lipolysis but also skeletal muscle. Probably because of this, patients with UCTD are characterized by proximal muscle weakness, hypotension and /

Table II. Serum ghrelin levels in patients with SpA and GERD and the control group

Indicator	Controlgroup (n=20)	SpA patients	
		Typical form of GERD (n=33)	Atypical form of GERD (n=47)
Ghrelin, ng/ml	105.11±3.25	223.21±4.16 *	316.77±3.89 **, ^

Note: a statistically significant difference was found between the control group and the examined patients: * - p <0.05; ** - p <0.01; statistically significant difference between indicators in patients of group I and group II: ^ - p <0.05.

Table III. Serum ghrelin levels in patients with SpA and GERD and control group

Indicator	SpA patients of group II (with atypical forms of GERD) (n = 47)			
	Dental (n=19)	Otolaryngological (n=12)	Cardiac (n=10)	Broncho-pulmonary (n=6)
Ghrelin, ng/ml	298.17±5.16	305.70±5.26	355.02±4.75*	308.04±4.25

Note: a statistically significant difference was found between the indicators in patients with dental and cardiac “masks” of GERD: * - p <0.05.

Table IV. Comparison of changes in serum ghrelin levels in patients with SpA and GERD with BMI

Indicator	Ghrelin levels (ng/mL)	
	group I (n=33)	group II (n=47)
Insufficient weight	r= -0.60; p<0.05	-
Normal weight	r= 0.56; p<0.05	-
Overweight	r= 0.64; p<0.05	r= 0.72; p<0.05
Obesity Class 1	-	r= 0.70; p<0.05
Obesity Class 2	-	r= 0.52; p<0.05

or malnutrition. According to the same authors, ghrelin does not independently change lipolysis, but, apparently, there are some additional sites for the regulation of lipid oxidation, which need to be further investigated [Kraft EN, Cervone DT].

DISCUSSION

Scientific research of pathogenetic mechanisms of GERD formation at comorbid pathological states is carried out, including its combination with backbone lesions of various genesis. At the same time, of great interest are studies aimed at determining the effect of various biologically active substances on the tonus of the lower esophageal sphincter (LES) with subsequent formation of GERD. It is known that such peptide hormones as ghrelin, adipokines, which regulate food intake, also play an important role in the formation of GERD, due to their effect on gastric acid secretion and gastrointestinal motility [15].

The results of experimental studies by Nahata M. et al. (2012) indicate an increase in peripheral ghrelin levels in rats with GERD against the background of reduced gastric emptying, food intake and antral motility [16]. The results of experimental studies in recent years (Kraft EN et al., 2019) indicate that ghrelin and its isoforms directly affect fatty acid oxidation and lipolysis. The authors explain this by the fact that patients with undifferentiated connective tissue dysplasia have high ghrelin levels, an asthenic constitution and underweight. The results of this study also

show that ghrelin stimulates the transport of fatty acids, affecting not only lipolysis but also skeletal muscle. The authors believe that ghrelin does not independently change lipolysis, but, apparently, there are some additional sites for the regulation of lipid oxidation, which need to be further investigated [17].

The results of the study also indicate high serum ghrelin levels in patients with SpA in combination with GERD. At the same time, the maximum values were registered in patients with atypical course of GERD (its increase of 3.0 times – p <0.01), especially in the cardiac “mask” of reflux disease (increase of 3.4 times – p <0.01). The results of our study also indicate a relationship between an increase in serum ghrelin levels and an increase in BMI, mainly in patients with atypical forms of GERD.

In the group of patients with SpA and GERD who have clinically typical esophageal signs, there was also an increase in ghrelin levels (2.1 times – p <0.05 compared with the control group). In this group of patients, ghrelin levels were negatively correlated with BMI, which corresponded to underweight (-0.60; p <0.05) and coincided with the results of Kraft EN et al.

Thus, the mechanism of GERD formation and features of its clinical course is multifactorial, but not fully understood process, especially in patients with comorbid conditions. Further research is needed in this direction to understand the processes underlying the lesions of the upper gastrointestinal tract in patients with comorbid conditions, especially lesions of the spine of inflammatory origin (in SpA). Particular attention needs to be paid to the detection of atypical forms of GERD, such as dental, otolaryngological and cardiac “masks” for their timely correction.

CONCLUSIONS

1. In patients with SpA with cervical and thoracic spine lesions, GERD often has atypical symptoms (mostly dental and otolaryngological forms in 40.4% and 25.5% of patients).
2. In patients with SpA with esophageal clinical signs of GERD, normal weight or underweight is more common,

- while in patients with extraesophageal forms of GERD overweight or obesity of varying severity prevails.
- In patients with SpA and GERD, an increase in serum ghrelin levels was found in patients with cardiac manifestations of reflux disease (355.02 ± 4.75 ng/ml).
 - The relationship between BMI changes in patients with SpA and GERD and increased serum ghrelin levels was found, namely: in group II patients with overweight and obesity a direct correlation was found, and in group I patients with underweight an inverse correlation was found.

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ORCID and contributionship:

Yelyzaveta S. Sirchak: 0000-0001-6738-0843 ^{A, F}
 Stanislav A. Tsioka: 0000-0002-2790-1357 ^{B, D, E}
 Andriy S. Chobej: 0000-0002-0700-5934 ^B
 Nelli V. Bedey: 0000-0002-8885-0258 ^B
 Inna S. Borisova: 0000-0003-4254-6004 ^C

Conflict of interest:

The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Yelyzaveta S. Sirchak

Uzhhorod national university
 14 Universitetskaya st., 88000 Uzhhorod, Ukraine
 tel: +380509761794
 e-mail: sirchakliza777@gmail.com

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