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Formation process of motor-evacuatory disorders in patients with gastroesophageal reflux disease and concomitant obesity

Mechanizmy vzniku motorických a evakuačních poruch při gastroezofageální refluxní chorobě se souběžnou obezitou

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Summary: **Introduction:** Gastroesophageal reflux disease (GERD) continues to increase worldwide. Its association with concomitant obesity complicates treatment and increases the probability of further complications. **Aim:** The aim of the study was to examine the process via which motor and evacuatory disorders in GERD form in young patients with concomitant obesity. **Materials and Methods:** A total of 105 patients with the non-erosive form of GERD were enrolled in this study. Among these patients, 50 patients had GERD without comorbidity and 55 had GERD with concomitant obesity. In addition to the standard methods of diagnosis, other methods and indicators were used, such as the levels of visfatin and adiponectin, ultrasound, indicators of the state of the nervous system, and questionnaires to determine quality of life. **Results and Discussion:** GERD patients with concomitant obesity showed disturbance of the sympathetic nervous system, significantly higher visfatin levels and lower adiponectin levels, motor and evacuatory oesophageal function disorders, and a lower quality of life index. GERD patients without comorbidities showed disturbance of the sympathetic nervous system, significantly higher rates of gastric juice aggression, and a lower quality of life index. **Conclusion:** In patients with isolated GERD and patients with GERD and concomitant obesity, the mechanisms that lead to the disruption of the lower oesophageal sphincter are different. GERD patients with concomitant obesity showed chronic inflammation of adipose tissue, which is known to lead to a reduction in the protective adipokine (adiponectin) level and an increase in the inflammatory adipokine (visfatin) level. Patients with isolated GERD had a disturbance of the parasympathetic nervous system and higher gastric juice aggression.

Key words: gastroesophageal reflux disease – obesity – visceral adipose tissue – adipokines

Souhrn: **Úvod:** Gastroezofageální refluxní choroba (GERD – gastroesophageal reflux disease) je celosvětově na vzestupu. Výskyt se souběžnou obezitou značně komplikuje léčbu a zvyšuje riziko dalších komplikací. **Cíl:** Cílem zkoumání je studium mechanizmů vzniku motorických a evakuačních poruch při GERD se souběžnou obezitou u osob v mladém věku. **Materiály a metody:** Bylo vyšetřeno 105 nemocných s neerozivní formou GERD, z nichž 50 trpělo GERD bez souběžné patologie a 55 GERD se souběžnou obezitou. Kromě standardních metod diagnostiky byly u nemocných sledovány i další ukazatele, konkrétně hladina visfatinu a adiponektinu, ultrazvukový nález, ukazatele stavu nervového systému a výsledky dotazníků hodnocení kvality života. **Výsledky a diskuze:** U pacientů s GERD se souběžnou obezitou byly pozorovány poruchy sympatického nervového systému, výrazné zvýšení hladiny visfatinu, pokles hladiny adiponektinu, poruchy motorické a evakuační funkce jícnu a nižší hodnoty indexu kvality života. U pacientů s izolovanou GERD byly pozorovány poruchy parasympatického nervového systému, výrazné zvýšení ukazatelů agresivity žaludeční šťávy a snížený index kvality života. **Závěr:** Získané výsledky ukazují rozdílné mechanizmy vedoucí k narušení činnosti dolního jícnového svěrače. U nemocných s GERD se souběžnou obezitou se projevil chronický zánětlivý proces v tukové tkáni, který vede ke snížení hladiny protektivního adipokinu (adiponektinu) a ke zvyšování hladiny zánětlivého adipokinu (visfatinu). U nemocných s izolovanou GERD se tyto procesy vyskytují v důsledku převládání tonu parasympatického nervového systému a zvýšení agresivity žaludeční šťávy.

Klíčová slova: refluxní choroba – obezita – viscerální tukové tkáně – adipokiny

Introduction

The high prevalence and rapid increase in the number of patients with gastroesophageal reflux disease (GERD), especially among young people, can testify that GERD is one of the important problems of modern gastroenterology [1,2]. Increased attention to this problem is caused by frequent cases of GERD with comorbid disorders [3,4]. In recent years obesity is one of the leading comorbid pathologies of GERD [1,5]. Concomitant obesity not only contributes to the severity of GERD, but also increases the possibility of further complications, such as oesophageal mucosa metaplasia and oesophageal adenocarcinoma [1,6,7]. For a long time it had been believed that pathogenic mechanisms and processes that could explain the link between obesity and GERD are in mechanical pressure of adipose visceral tissue to the stomach, which increases the internal gastric pressure and weakens the oesophageal sphincter pressure [7–9]. At the same time, there is a strong opinion these days that GERD is a multifactorial disease [6,10]. Some researchers believe that the process of releasing hormone-related factors called adipokines could play a certain role in the pathogenesis of GERD, but at the same time the imbalance of the adipokines can be observed in patients with obesity [10,11]. It should be noted that the motor-evacuatory disorders are some of the most common causes of GERD formation. In addition, they also play a certain role in the pathogenesis of obesity [11,12]. All of the aspects mentioned above have contributed to the purpose of our research.

The purpose of the research is to study the mechanisms of formation of motor-evacuatory disorders in GERD in young adults with concomitant obesity.

Materials and Methods

This study was conducted at the gastroenterological department of Kharkiv Medical Academy of Postgraduate Education (KMAPE), Ukraine. The study was approved by the Institutional Ethic Committee of KMAPE. Written approvals were received from all subjects prior to the start of the research.

During the research examinations of patients with GERD were carried out. The diagnosis of GERD was determined in accordance with ICD-10 and recommendation of the Montreal Consensus of 2006, and by analysing the data collected through endoscopy, radiological and pH-metric methods [13]. The results of the GERD-Q questionnaire were also taken into account [14].

In total 105 patients with non-erosive form of GERD were examined during this research. Two groups of patients were formed based on the presence of associated obesity. Two groups of patients with GERD were similar by age and gender. The first group included 55 patients with GERD and concomitant obesity (30 women and 25 men) whose average age was 22 ± 1.91 years old. The second group included 50 patients with GERD without comorbidity (27 women and 23 men) whose average age was 21 ± 2.06 years old. The case history of GERD ranged from 1 to 4 years. The control group consisted of 20 healthy individuals (11 men and 9 women) aged from 18 to 24 years old.

The patients filled in the questionnaires and all information was received on a voluntary basis. The study excluded patients having any concomitant diseases in addition to obesity. The criteria for exclusion from the examination were as follows – thyroid disease, endocrine forms of obesity and pregnancy.

The Five-point Likert Scale was used to assess the severity of complaints such as heartburn, belching, regurgitation and dysphagia.

The presence of obesity and its level were diagnosed according to ICD-10 with a body mass index (BMI). A normal BMI was considered as 21–24.9, overweight was considered as 25–29.9, obesity with BMI was taken as 30 points or higher according to the World Health Organisation (WHO).

Motor-evacuatory changes were identified by an ultrasound research conducted on ULTIMA pro-30 machine (Ukraine production) – in the patient's left side and on the back; epigastric and projections at hiatus; after fasting and 5, 10 and 15 min after drinking 0.5 L of liquid. The study measured the thickness of the wall of the oesophagus, the diameter of hiatus, and the width of the oesophagus in the lower third, as well as determined by the presence or absence of reflux (reverse fluid flowing from the stomach into the oesophagus) and assessed the extent and duration of stretching the stomach by gastric location relative to the navel (above, at or below) 30, 45 and 60 min after receiving liquid. The method of intragastric pH-metery was used according to a standard technique.

The level of adipokines (adiponectin and visfatin) was studied using ELISA method with AssayPro human adiponectin ELISA kit (US production) and RayBio visfatin enzyme immunoassay kit (US production) by standard methods.

To assess the state of the sympathetic and parasympathetic nervous systems, the Kerdo index calculated by standard methods was used. When the performance index was less than 0, it testified that patients had influence of the parasympathetic nervous system, if it was more than 0 – that of the sympathetic nervous system.

To assess the quality of life (QoL) of patients the international questionnaire The WHOQoL-BREF was used and measured by the standard method, which included evaluation of general state of health, physical health, psychological sphere, social relations and the environment.

Statistic analysis of the results was carried out using Microsoft Office Excel 2007 and the system of statistical data processing using Statistica 6.0. When normal distribution was shown, t-Student test was used for analyses; in case of deviation from the normal distribution, nonparametric criteria was used. Reliable differences were considered at $p < 0.05$. The results were presented as M ± m, with M as the median, and m as standard deviation.

Results and Discussion

During the study it was found that heartburn was the most pronounced complaint in both groups of patients with GERD (3.73 ± 0.98 points on the Likert scale were measured in patients with GERD with concomitant obesity and 3.88 ± 0.85 points in patients with GERD without comorbidity).

Patients with GERD with concomitant obesity had expressed more complaints to belching air compared to GERD patients without comorbidity (4.35 ± 0.58 points in group 1 and 3.78 ± 0.8 points in group 2), dysphagia (3.8 ± 0.52 points in group 1 and 3.45 ± ± 0.71 points in group 2) and regurgitation (3.88 ± 0.33 points in group 1 and 3.5 ± 0.72 points in group 2).

It is important to note that during the determination of the degree of severity of complaints of heartburn, the study failed to identify significant differences between the group of patients with GERD without comorbidity and the group of GERD patients with concomitant obesity.

In the course of the ultrasound examination of the stomach and the lower third of the oesophagus it was found that the width of the oesophagus in the lower third in patients of group 1 was 2.9 ± 0.2 cm, and in group 2 2.56 ± 0.26 cm, in the control group 2.13 ± 0.16 cm. The diameter of hiatus in patients of group 1 was 2.03 ± 0.15 cm, in group 2 1.79 ± 0.09 cm, in the control group 1.51 ± 0.08 cm. The thickness of the wall of the oesophagus in patients of group 1 was 0.46 ± 0.05 cm, in group 2 0.40 ± 0.03 cm and in the control group 0.31 ± 0.07 cm. Thus, it was found that the rates of the diameter of hiatus and thickness of the wall of the oesophagus were significantly greater in patients with GERD with concomitant obesity than the corresponding figures in the group of patients with isolated GERD ($p < 0.05$). Besides, patients with GERD had gastroesophageal reflux, the amount of which averaged 6.1 ± 0.2 mL in group 1, 4.8 ± 0.12 mL in group 2.

In assessing the relative position of the stomach after 60 min of the water load the stomach was below the navel, indicating gastrostasis in 84% of group 1 and only in 2.75% of group 2.

The acidity of the gastric juices in the stomach in group 1 averaged 1.3 ± 0.11, in group 2 1.1 ± 0.09 (in the control group 1.8 ± 0.1). Indicators of acidity in the antrum were 5.8 ± 0.29 in group 1, 5.0 ± 0.24 in group 2 (6.75 ± 0.55 in the control group).

Thus, the pH of gastric juice in both groups of patients with GERD were significantly lower than that in the control group ($p < 0.05$). The acidity of gastric juice in the group of patients with GERD with concomitant obesity was significantly lower than that in the group of patients with isolated GERD ($p < 0.05$). Between the acidity of antrum of the stomach in the group of patients with isolated GERD and GERD with concomitant obesity there was no significant difference.

Using ELISA, it was found that the levels of visfatin and adiponectin in patients with GERD with concomitant obesity were resp. 29.5 ± 3.6 ng/mL and 8.5 ± 1.5 mg/mL, in patients with isolated GERD 19.6 ± 2.2 ng/mL and 14.1 ± 1.9 mg/mL, and 17.8 ± 1.8 ng/mL and in the control group 19.7 ± ± 2.0 mg/mL, resp. So, it was found that the level of visfatin was significantly higher and the level of adiponectin was significantly lower in patients with GERD with concomitant obesity compared to the group of patients with isolated GERD and the control group. The level of adiponectin was significantly lower in patients with GERD compared to the control group ($p < 0.05$). Also the levels of visfatin in patients with isolated GERD were slightly higher than in patients in the control group, but those differences were not significant statistically ($p > 0.05$).

When studying characteristic features of the state of the parasympathetic and sympathetic systems using Kerdo indexes, the following data were obtained. For the patients of group 1 the indicator was 6.5 ± 4.2 points, indicating prevalence of influence of the sympathetic system in patients of this group. The indicator in group 2 was 4.3 ± 3.8 points, indicating influence of the parasympathetic nervous system. In the control group it was 0.3 ± 2.5 points.

During the study of QoL it was found that the group of GERD patients with concomitant obesity had shown the following QoL indexes: general health 46.8 ± 6.1 points, physical health 50 ± ± 9.6 points, psychological sphere 34.4 ± 8.74 points, social relations 39.4 ± ± 8.0 points, environment 45.9 ± ± 6.2 points. In patients with GERD: general health 55.0 ± 5.1 points, physical health 64.4 ± 7.6 points, psychological sphere 44.8 ± 6.0 points, social relations 41.5 ± 9.7 points, environment 40.2 ± 6.5 points. In the control group: general health 79.1 ± ± 10.1 points, physical health 83.2 ± ± 7.3 points, psychological sphere 75.0 ± 4.2 points, social relations 61.13 ± 8.3 points, environment 68.7 ± 5.5 points. A significant decrease in QoL by all parameters in groups 1 and 2 compared to the control group was found ($p < 0.05$). More reduction was observed in the QoL in terms of general health, physical health, psychological sphere and environment in patients with GERD with concomitant obesity

compared to the group of patients with GERD ($p < 0.05$); there were no significant differences in terms of social relations between group 1 and group 2 ($p > 0.05$).

We found a significant correlation between visfatin and adiponectin levels and characteristics of the motor-evacuation disorders of the gastrointestinal tract of GERD patients with concomitant obesity and between pH-metric data and the degree of influence of the parasympathetic nervous system of GERD patients without comorbidity.

Thus, frequent and prolonged transient lower oesophageal sphincter relaxations, resulting in stretching of the stomach (compared to the group of patients with isolated GERD and to the control group) were found in patients with GERD with concomitant obesity. This was illustrated by ultrasound methods. These data suggest that in patients with GERD with obesity we can observe a chronic inflammatory process that occurs in visceral adipose tissue. It is characterised by a lower level of protective adipokine (adiponectin) and an increased level of proinflammatory adipokine (visfatin). As a result, the patients had shown a reduction of the tone of the lower oesophageal sphincter, which increases the frequency of its transient relaxation and could be considered as one of the major causes of GERD. However, in patients with GERD without comorbidity the study observed a slight increase in proinflammatory adipokine (visfatin) and a lower level of protective adipokine (adiponectin). The study had shown that in patients with GERD without comorbidities the decrease of QoL could lead to disorders of the sympathetic and parasympathetic nervous system, which regulates the activity of the lower oesophageal sphincter. The results suggest various mechanisms or processes that could lead to the disruption of the lower oesophageal sphincter.

Conclusion

1. It was found that GERD patients with concomitant obesity have more pronounced complaints of belching and regurgitation, compared to the group of GERD patients without comorbidity. At the same time, there was no evidence of significant differences of the severity of heartburn in both groups of patients with GERD.
2. During the study of motor and evacuatory disorders using the ultrasound method, it was found that patients with GERD with concomitant obesity have shown significantly bigger diameter of the hiatus, thickness of the lower third of the oesophagus, oesophageal wall thickness and in performance of gastrostasis, compared to patients without concomitant GERD pathology. Then, during internal gastric pH-metery it was found that acidity of gastric juice in the group of patients with GERD with concomitant obesity was significantly lower than in the group of patients with isolated GERD.
3. During the study of QoL it was found that the patients with GERD and concomitant obesity have a significant reduction in terms of general health, physical health, psychological state of the environment, compared to the group of patients with GERD. It was also found that patients with GERD with concomitant obesity had influence of the sympathetic nervous system, and in patients with GERD without comorbidity – of the parasympathetic nervous system.
4. It was found that GERD patients with concomitant obesity had shown a significantly higher level of proinflammatory adipokine (visfatin) and a significantly lower level of protective adipokine (adiponectin) than GERD patients without comorbidity and the control group, however, the patients with isolated GERD still have a significantly lower level of adiponectin compared with the control group.
5. A clear correlation was found between indicators of motor-evacuatory disorders, pH-metric data, the state of the sympathetic and parasympathetic nervous systems, and levels of adiponectin and visfatin and the presence of concomitant obesity in patients with GERD.

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