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Implementation mechanisms of psychosomatic disorders in gastroesophageal reflux disease with concomitant chronic obstructive pulmonary disease

Mehanizmi za realizaciju psihosomatskih poremećaja kod gastroezofagealne refluksne bolesti s komorbidnom kroničnom opstruktivnom bolešću pluća

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Summary

Nowadays, gastroesophageal reflux diseases and chronic obstructive pulmonary diseases are among the most commonly occurring diseases. In most cases these diseases occur combined. Considering the fact that psychosomatic disorders play a major role in the formation of gastroesophageal reflux diseases and chronic obstructive pulmonary diseases, researching their implementation with the combined course of these diseases represents scientific and practical interest. Therefore, the aim of our research was to investigate the mechanisms of implementation of psychosomatic disorders in this comorbidity. During our research, we took two groups of patients. The first group consisted of patients with gastroesophageal reflux disease combined with chronic obstructive pulmonary disease. The second group consisted of patients with isolated gastroesophageal reflux disease. In addition to the standard methods of research, gastroesophageal reflux disease and chronic obstructive pulmonary disease, the level of melatonin, norepinephrine, and psychosomatic status indicators were also researched. As a result, it was found that patients with comorbid pathology had significantly higher indicators of depression, but indicators of melatonin and respiratory function significantly lower not only with persons in the control group, but also in patients with isolated gastroesophageal reflux disease. At the same time, patients with gastroesophageal reflux disease without comorbidity pathology had significantly higher indicators of reactive and personal anxiety, norepinephrine, and pH meters not only in the control group, but also in comparison with gastroesophageal reflux disease patients with concomitant chronic obstructive pulmonary disease. Thus, the obtained results indicate that patients with gastroesophageal reflux disease combined with concomitant chronic obstructive pulmonary disease have psychosomatic disorders, primarily due to depressions, that lead to the decreasing of melatonin levels and external respiration parameters which leads to the reduction of protective properties of the esophagogastric junction. Psychosomatic disorders of patients with isolated gastroesophageal reflux disease lead to increased production of norepinephrine and hydrochloric acid, first of all, due to increasing reactive and personal anxiety level, and thereby contribute to the increase in aggression factor level. The acquired data testify the role of psychosomatic disorders in creating the basic and accompanying pathology which requires differentiated treatment, aimed at increasing of protective properties of the first group of patients, and reducing aggression factors of the second group of patients.

Key words: gastroesophageal reflux disease, chronic obstructive pulmonary disease, psychosomatic disorders, melatonin, norepinephrine

Sažetak

Gastroezofagealna refluksna bolest i kronična opstruktivna bolest pluća najčešće su bolesti koje se u značajnom postotku javljaju zajedno. S obzirom da psihosomatski poremećaji igraju veliku ulogu, kako u formiranju gastroezofagealne refluksne bolesti, tako i kronične opstruktivne bolesti pluća, proučavanje njihove pojave predstavlja znanstveno-primijenjeni interes. Stoga je cilj našega istraživanja proučavanje mehanizama utjecaja psihosomatskih poremećaja u ovoj komorbidnoj patologiji. Tijekom našeg istraživanja

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uzeli smo dvije skupine bolesnika. Prvu skupinu čine bolesnici koji pate od gastroezofagealne refluksne bolesti, uz prateću kroničnu opstruktivnu bolest pluća, a drugu oni s izoliranom gastroezofagealnom refluksnom bolešću. Osim standardnih metoda istraživanja gastroezofagealne refluksne bolesti i kronične opstruktivne bolesti pluća, provedena su istraživanja razine melatonina, noradrenalina, te pokazatelja psihosomatskog statusa kod bolesnika. Kao rezultat provedenih istraživanja utvrđeno je da su kod bolesnika s komorbidnom patologijom pokazatelji depresije bili značajno veći, a pokazatelji melatonina i funkcije disanja znatno niži, ne samo kod osoba kontrolne grupe, nego i kod bolesnika s izoliranom gastroezofagealnom refluksnom bolešću. U isto vrijeme, kod bolesnika s gastroezofagealnom refluksnom bolešću bez komorbidne patologije, pokazatelji reaktivne i osobne anksioznosti, noradrenalina i ph-metara bili su značajno viši, ne samo kod kontrolne grupe, nego i kod bolesnika gastroezofagealne refluksne bolesti s komorbidnom kroničnom opstruktivnom bolešću pluća. Dobiveni rezultati pokazuju da je kod bolesnika od gastroezofagealne refluksne bolesti s kroničnom opstruktivnom bolešću pluća, psihosomatski poremećaj, prvenstveno depresija, doveo do smanjene razine melatonina i pokazatelja funkcije disanja, te smanjenja zaštitnih svojstava ezofago-gastričnog sfinktera. Kod bolesnika s izoliranom gastroezofagealnom refluksnom bolešću, psihosomatski poremećaji dovode do povećanja razine noradrenalina i klorovodične kiseline, tj. doprinose povećanju čimbenika agresije, prvenstveno kroz povećanje pokazatelja reaktivne i osobne tjeskobe. Dobiveni podaci svjedoče o ulozi psihosomatskih poremećaja u formiranju, kako osnovne, tako i popratne patologije, što zahtijeva diferenciranu terapiju koja je usmjerena na bolesnika iz prve skupine za povećanje zaštitnih svojstava, a iz druge skupine na smanjenje čimbenika agresije.

Ključne riječi: gastroezofagealna refluksna bolest, kronična opstruktivna bolest pluća, psihosomatski poremećaji, melatonin, noradrenalin.

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Introduction

The problem of comorbid pathology is one of the leading ones in modern medicine today.[1-2] The most frequent diseases, which usually occur combined with other pathology, are gastroesophageal reflux disease (GERD) and chronic obstructive pulmonary disease (COPD).[3-6] The prevalence of such comorbid diseases in the Asian continent, according to the data of Jinhee et all, is up to 28%,[7] in America, according to the data of Smith and Wrobel from 7.7% to 30%[4], and in Western Europe, according to Velanovich from 3% to 16%.[8] In their turn, these diseases are the most prevalent among the structure of diseases of the gastrointestinal tract from 20% to 60%, and of the respiratory organs from 10% to 25% respectively.[9-11] A particular problem is the pathogenesis of the combined course of GERD and COPD.[12-14] Moreover, the question of which disease is primary and which develops on its background is still being studied.[15-18] At the same time, many medications, which are used during the treatment of COPD, particularly, theophylline and inhalation forms of glucocorticosteroids and adrenomimetics, have a negative effect on the esophageal mucosa and tone of esophageal sphincter.[19-20]

Thus, researches of common pathogenic mechanisms, that create the basis for GERD and COPD, will contribute not only to the discovery of their pathogenesis, but also the development of therapy, considering these common pathogenetic components.[21] Considering that psychosomatic disorders play an important role in the formation of GERD[22] by regulating the motor and secretory function of the digestive tract, as well as in the formation of COPD[23] by regulating the processes of the bronchial tree tone, the study of the features of their pathological implementation in case of comorbidity will be of scientific interest and practical importance.

The main goal of the research is to examine the role of psychosomatic disorders in the mechanism of formation of GERD with concomitant COPD.

Materials and methods of research

Proceeding from the stated objective, we took two groups of patients. The first group of patients consisted of 40 people (18 women and 22 men) aged from 20 to 35, who were sick with nonerosive GERD with concomitant COPD of I-II degree. Patients with the other concomitant disease were not included in the study. The second group included 45 patients (26 men and 19 women) aged from 19 to 33 years, who were sick with nonerosive form of GERD without comorbidity. The control group consisted of 20 almost healthy persons of the same age and sex.

During the study, an examination of young patients with GERD was performed on clinical basis of the Department of Therapy, Rheumatology and Clinical Pharmacology of the Kharkov Medical Academy of Postgraduate Education. The research was approved by the Institutional Ethics Committee

of the Kharkov Medical Academy of Postgraduate Education and Clinical Bases. Written informed consent was obtained from all the study subjects. The GERD diagnosis was established in accordance with ICD-10, considering the Montreal Consensus 2006 and Gstaad guidelines for GERD treatment.

To validate the GERD diagnosis, patients were subjected to endoscopy by fibergastroscope Olympus XP-20 (made in Japan), intragastric pH monitoring, performed on acidogastrometer (indicator of acidity of the stomach) "Gastric acidity indicator – 2" (made in Ukraine), and GERD questionnaire. The diagnosis of COPD was validated according to ICD-10, and considering recommendations of Global initiative for obstructive lung diseases (GOLD) 2016. External breathing function was defined using spirograph (produced in Ukraine) by standard methodics. During the spirography, pharmacological tests were performed with a short-acting bronchodilator to determine its influence on lung function. To avoid distortions of bronchodilation test results patients stopped using bronchodilators in accordance with the pharmacological properties of used drug.

The level of melatonin in blood serum was determined by ELISA, using the reagents from the IBL standard kit (made in Germany). The level of norepinephrine in blood plasma was determined by ELISA, using the reagents from the IBL standard kit (made in Germany).

The psychosomatic condition of patients was determined by Spielberg's questionnaire of personal and reactive anxiety, Beck depression questionnaire, Eysenck personality questionnaire, which allows to determine the features of a patient's character: extrovert, introvert, neurotic, Sheehan anxiety questionnaire.

The results were processed by methods of variation statistics using PC software Statystyka. Data were presented in a conventional form of (M ± m), where M – the arithmetic average, and m – the error of arithmetic average. The results were considered statistically significant when the probability of error was less than 5% ($p < 0.05$). To analyze the significance of differences between two groups was used ± (Student's t-test). As required to compare the values of the indicator inside two or more groups simultaneously, analysis of variance with the definition of the Fisher coefficient were used.

Results

The research resulted in both groups having significant change of psychosomatic status compared with the individuals of the control group. Patients with GERD concomitant COPD had indicators of depression 35.7 ± 2.1 points and patients with GERD without comorbidity had 26.8 ± 1.9 points at norm or rate 8.1 ± 1.1 points. Simultaneously, the patients of the first group indicated reactive and personal anxiety values 39.7 ± 0.91 and 38.4 ± 1.05 points at norm or rate 22.7 ± 1.4 and 23.5 ± 1.3 points. At the same time, patients with GERD without comorbidity, indicated reactive and personal anxiety values 43.4 ± 0.85 and 45.8 ± 1.6 points respectively. Patients with GERD concomitant COPD had indicators of trouble 52.4 ± 2.8 points, patients with isolated GERD had 45.27 ± 2.7 points. The level of the trouble indicators in the control group was 19.5 ± 1.4 points (Table 1).

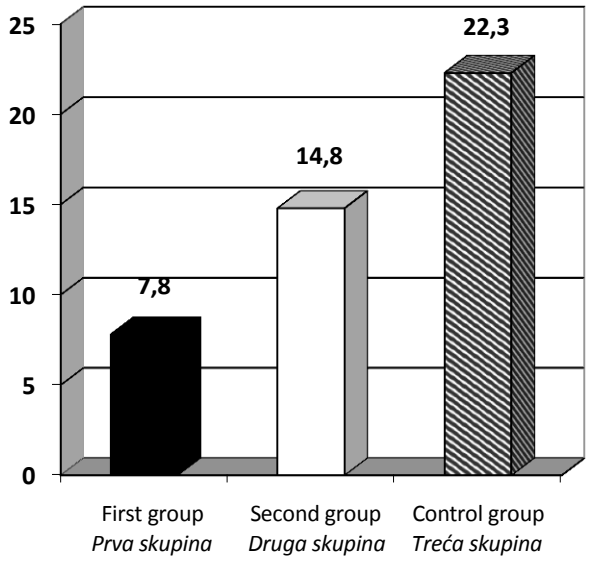
It was thus registered that patients with GERD concomitant COPD revealed a significant increase in depression and anxiety level not only compared with the control group, but compared also with GERD patients without comorbidity.

Table 1 Indicators of psychosomatic status in GERD patients with concomitant COPD and without comorbidity.
Tablica 1. Pokazatelji psihosomatskog stanja kod GERD pacijenata s pratećim COPD i pacijenata bez komorbiditeta

Psychosomatic disorders *Psihosomatski poremećaji*	First group *Prva skupina*	Second group *Druga skupina*	Control group *Kontrolna skupina*
Depression *Depresija*	35.7 ± 2.1	26.8 ± 1.9	8.1 ± 1.1
Reactive anxiety *Reaktivna tjeskoba*	39.7 ± 0.91	43.4 ± 0.85	22.7 ± 1.4
Personal anxiety *Osobna tjeskoba*	38.4 ± 1.05	45.8 ± 1.6	23.5 ± 1.3
Trouble *Nevolja*	45.27 ± 2.7	52.4 ± 2.8	19.5 ±

At the same time, patients with GERD without comorbidity indicators of reactive and personal anxiety were significantly higher compared not only with the indicators of the control group, but also compared with indicators of patients with GERD with concomitant COPD. The trouble level indicators were significantly higher inside the group of patients with isolated GERD comparing both with the indicators of the GERD patients group with concomitant COPD and with the control group. It was also found that among patients with GERD with concomitant COPD, the majority were introverts (57%), while in patients with GERD without comorbidity dominated extroverts (32%) and neurotics (49%).

In researching the melatonin level, it was found that the first group of patients had average values 7.8 ± 0.9 pg/ml and at the second group of patients 14.8 ± 1.2 pg/ml at norm rate 22,3 ± 1,4 pg/ml (Picture 1).

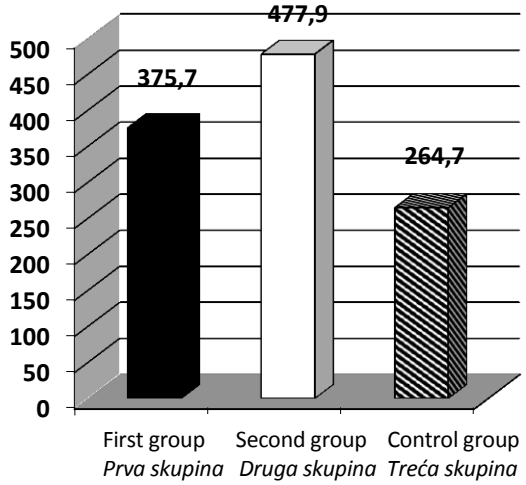


Picture. 1 Indicators of serum melatonin (pg / ml) in patients with GERD concomitant COPD, with isolated GERD and in the control group

Slika 1. Pokazatelji melatonin seruma (pg/ml) kod pacijenata s GERD popratnim COPD s izoliranim GERD i u kontrolnoj skupini

Thus, it was noted that patients with GERD with concomitant COPD had a significant decrease in melatonin level, compared with a control group of persons, and patients with GERD without concomitant pathology. Along with this, the melatonin level of the second group patients was statistically significantly lower than with the controlled individuals.

Analyzing the norepinephrine level, it was found that patients of the first treatment group had average value 375.7 ± 6.8 pg / ml and patients with GERD without comorbidity 477.9 ± 8.1 pg/ml at the established normal rate 264.7 ± 6.3 pg/ml (Picture 2). Thus, patients with GERD concomitant COPD indicators of norepinephrine had significantly lower indicators values, compared with patients with GERD without comorbidity ($p < 0.001$), though these indicators were significantly higher in the control subjects ($p < 0.001$).

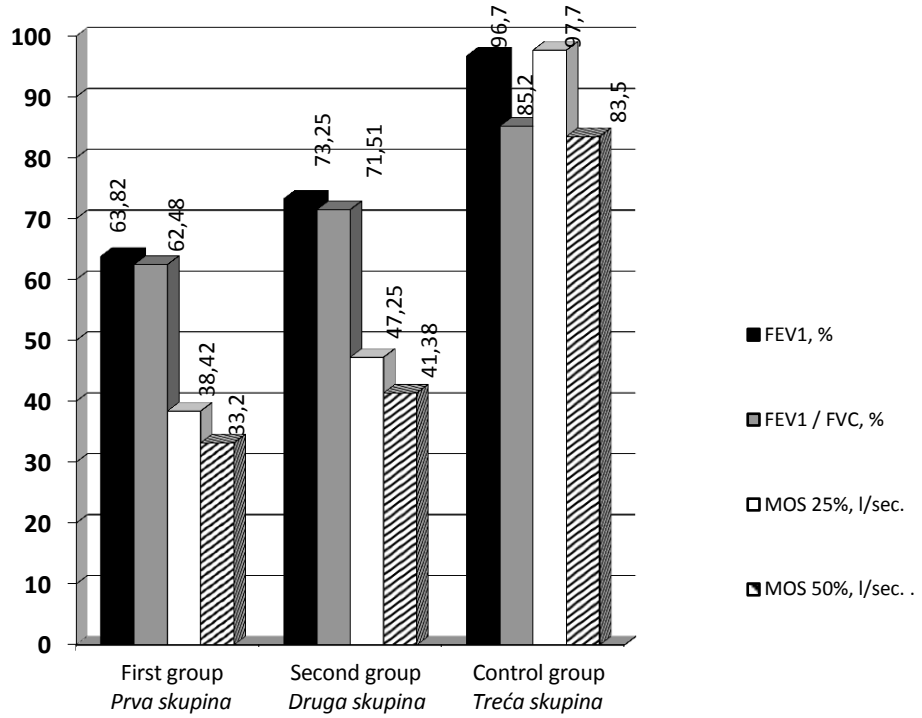


Picture 2 Indicators of norepinephrine levels in the blood plasma (pg/ml) in GERD patients with concomitant COPD, without comorbidities, and control group

Slika 2. Pokazatelji razina norepinefrina u krvnoj plazmi (pg/ml) kod GERD pacijenata s popratnim COPD, bez komorbiditeta i kontrolna skupina

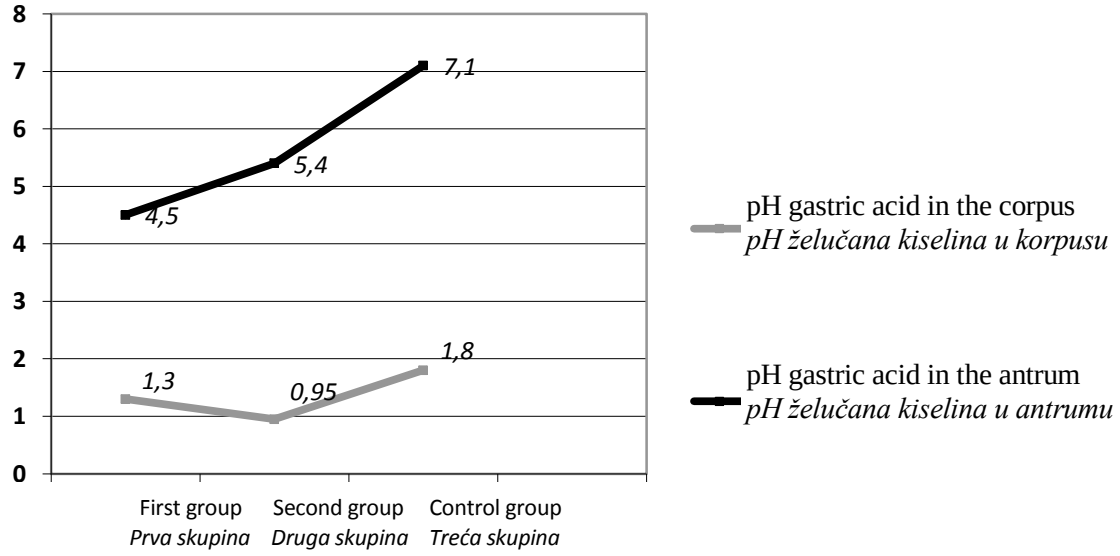
Analyzing spirography data, it was found that patients of the first group had a more distinct decrease in the respiratory function as compared with those in the control group and patients with GERD without comorbidity. Index FEV1 averaged 63.82 ± 2.70% at a rate of 96.7 ± 3.2% and 73.25 ± 3.1% of GERD patients without comorbidity. Indicators FEV1 / FVC in patients of the first group was 62.48 ± 1.57% at a rate of 85.2 ± 2.3% and 71.51 ± 1.91% of GERD patients without comorbidity. Indicators MOS and MOS 25% to 50% of the first group patients amounted, on average, 38.24 ± 2.31 l / sec and 33.21 ± 2.42 l / sec, whereas with the second group of patients the figures were 47.25 ± 2.32 l /sec. and 41.38 ± 2.37 l/sec. at a rate of 97.7 ± 2.61 l/sec. and 83.5 ± 2.29 l / sec (Picture 3).

The acidity of the gastric juice in the corpus of the first group patients averaged 1.3 ± 0.11 at a rate of 1.8 ± 0.21 and 0.95 ± 0.12 in the second group of patients. Acidity indicators in the antrum in patients with the first group averaged 4,5 ± 0,31 at a rate of 7,1 ± 0,35 and 5,4 ± 0,33 of the second group (Picture 4).



Picture 3 Indicators of external respiration function in GERD patients with concomitant COPD, without comorbidities and control group

Slika 3. Pokazatelji vanjske respiratorne funkcije kod GERD pacijenata s popratnim COPD bez komorbiditeta i kontrolne grupe



Picture 4 Indicators of gastric acidity in the corpus and antrum in GERD patients with concomitant COPD, without comorbidities and control group

Slika 4. Pokazatelji želučane kiseline u korpusu i antrumu kod GERD pacijenata s popratnim COPD bez komorbiditeta i kontrolne grupe

Analyzing the correlation, the following was detected. GERD patients with concomitant COPD degree of manifestation of psychosomatic disorders, and especially indicators of depression, were in close correlation (r = 0.75) with the level of melatonin and indicators of respiratory function. The higher was the level of psychosomatic disorders the lower were the level of melatonin and indicators of respiratory function. Patients with isolated GERD had a clear correlation (R = 0.73) between the severity of psychosomatic disorders, primarily reactive and personal anxiety, with higher levels of norepinephrine and pH of gastric juice.

Discussion

Our results on the prevalence and severity of GERD with concomitant COPD found confirmation in the works of Lee et al.[12] The authors examined the prevalence of symptomatic and clinically silent proximal and distal gastroesophageal reflux (GER) in adults with chronic obstructive pulmonary disease (COPD) and gastric aspiration. The prevalence of GERD in COPD was 37%. Of those diagnosed with GERD, clinical reflux was detected in 20% patients with COPD.

Psychosomatic disorder researches with a combination of GERD with COPD have been the subject of several works.[5,24,25] One of the latest works was conducted by Smith and Wrobel,[4] where the authors have shown the influence of psychosomatic disorders, such as depression and anxiety, on the worsening of COPD and GERD courses. However, as in other similar works, authors have not studied how these psychosomatic changes affect the acidity and lung function.

The correlation of melatonin level inpatients with psychosomatic disorders has been described in the work of Nagane et al.[26] In this work, it is noted that circadian rhythm disorders have effect on the presence and severity of psychosomatic disorders, and evidenced by a decrease of melatonin levels in the test group. However, these works were not devoted to the study of the level of melatonin and psychosomatic disorders in any particular disease.

The level of noradrenaline, along with the presence of psychosomatic disorders in middle-aged females, was studied by Hughes et al.[27] Ninety-one women aged 47-55 years were evaluated in this study. Depression symptoms were assessed with the Beck Depression Inventory and state anxiety was assessed with the state anxiety portion of the Spielberger State-Trait Anxiety Inventory. Twenty-four-hour urine collections were assayed for epinephrine, norepinephrine and cortisol. These results suggested that higher levels of depression symptoms on a scale Beck ($\geq$ 10) and state anxiety on Spielberg questionnaire were associated with increased 24-hour norepinephrine excretion (r = .27. P = .009) and (r = 0.28, P = 0.01), respectively. The current findings suggest that depression and anxiety may be associated with increased sympathetic nervous system activity and, in particular, with the level of noradrenaline.

Finding the pathophysiological mechanisms of depression and anxiety were the task of Paine et al. research.[28] This research involved 140 patients with average age 45.5 years; females accounted for 38.5%. Research was performed on the concentration of noradrenaline in daily urine, as indicator of activity of the simpatoadrenal system. Depressive symptoms were assessed using the Beck Depression Inventory, with anxiety symptoms assessed using the Spielberger State-Trait Anxiety Inventory.

It has been shown that the points of depression and anxiety were intercorrelated (R = 0.76, p < 0.001), and the noradrenaline level of daily urine correlated with anxiety (R = 0.10, p = 21) and depression (r = 0.07, p = 0.39). As a conclusion, authors determined that anxiety was associated with heightened sympatho-adrenal activity, suggesting a biological pathway through which anxiety could increase the risk of internal diseases.

Thus, the analysis of recent works demonstrates a clear relationship of psychosomatic disorders with the contents of melatonin and noradrenaline. And, at the same time, a noticeable lack of true researches of these indicators in patients with comorbid disorders of GERD and COPD and definition of their role in the pathogenesis of these diseases. This was the aim of our research.

Analysis of research results conducted by us shows that GERD patients with concomitant COPD had psychosomatic disorders primarily at the expense of depression, leading to decreasing melatonin level and external respiration parameters. This led to a reduction of the protective properties of the esophagogastric junction. Patients with isolated GERD, psychosomatic disorders, first of all, due to increasing of reactive and personal anxiety, led to the increased production of norepinephrine and hydrochloric acid and thereby contributed to an increase of the aggression factor. Data obtained during research evidenced the role of psychosomatic disorders during the formation of both diseases: the main and concomitant and required differentiated treatment, aimed at patients of the first group to improve the protective properties, while in the second group of patients to reduce aggression factors.

Conclusions

It was detected that both groups under research had significant psychosomatic disorders, compared with the control group. GERD patients with concomitant COPD had depression indicators that were significantly higher (35,7 ± 2,1) compared with indicators of the control group (8.1 ± 1.1) and GERD patients without comorbidity (26.8 ± 1.9). Reactive and personal anxiety indicators of GERD patients without comorbidity were significantly higher (43.4 ± 0.85 and 45.8 ± 1.6) than the indicators of the control group (22.7 ± 1,4 and 23.5 ± 1.3) and the indicators of the GERD with concomitant COPD group (39.7 ± 0.91 and 38.4 ± 1.05). At the same time, indicators of trouble were significantly higher in group patients with isolated GERD (52.4 ± 2.8) than the indicators of the control group (19.5 ± 1.4) and the indicators of the group with the GERD concomitant COPD (45.27 ± 2.7).

It was found that GERD patients with concomitant COPD (7.8 ± 0.9 pg/ml) had significantly decreased melatonin level, as compared with the norm (22.3 ± 1.4 pg/ml), as with patients without GERD comorbidity (14.8 ± 1.2 pg/ml). Patients with comorbid disorder indicators of norepinephrine levels were significantly higher (375.7 ± 6.8 pg/ml), than normal (264.7 ± 6.3 pg/ml) but significantly lower than the level of norepinephrine of GERD patients without comorbidity (477.9 ± 8.1 pg/ml).

Patients with GERD with concomitant COPD indicators of respiratory function were significantly lower (OFV1 – 63.82 ± 2.70%, OFV1/FVC – 62.48 ± 1.57%, MOS 25% – 38.24 ± 2.31 l/sec, MOS 50% – 33.21 ± 2.42 l/sec) than indicators of the control group (OFV1 – 96.7 ± 3.2%, OFV1/FVC – 85.2 ± 2.3%, MOS 25% – 97.7 ± 2.61 l/sec, MOS 50% – 83.5 ± 2.29 l/sec) and GERD without comorbidity patients (OFV1 – 73.25 ± 3.1%, OFV1/FVC – 71.51 ± 1.91%, MOS 25% – 47.25 ± 2.32 l/sec, MOS 50% – 41.38 ± 2.37 l/sec). Patients with GERD without comorbidity indicators of gastric acidity in the corpus were significantly higher (0.95 ± 0.12) than the control group (1.8 ± 0.21) and GERD patients with concomitant COPD (1.3 ± 0.11). The highest indicators of gastric acidity in the antrum were in the group of patients with GERD concomitant COPD (4.5 ± 0.31), while in the second group (4.5 ± 0.31) these indicators were approaching the control group indicators (7.1 ± 0.35).

It was revealed that a clear correlation was established among the severity of psychosomatic disorder, the prevalence of increased depression level in patients, indicators of reactive and personal anxiety, indicators of respiratory function, of pH levels, increasing the level of melatonin and norepinephrine. The last is indicative for those GERD patients with concomitant COPD due to psycho-somatic disorders leading to decreasing melatonin level and indicators of respiratory function. This led to decreasing protection factors of esophagogastric junction (r = 0.75). Patients with isolated GERD, due to increased reactive and personal anxiety, had higher levels of norepinephrine, gastric pH. It meant that it led to the activation of aggression factors (r = 0.73).

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