

UDC [616.33+616.329]-008.6: 614.253

DOI: 10.15587/2519-4798.2020.220010

GASTROESOPHAGEAL REFLUX DISEASE IN PATIENTS WITH VARIOUS COMORBIDAL PATHOLOGY

A. Oparin, A. Titkova, K. Stepanchenko, V. Tseluyko, M. Kochuieva, O. Korzh

The aim of the work – conduct a literature review to study the most important and complex aspects in the diagnosis and treatment of gastroesophageal reflux disease that are encountered in the practice of a family doctor.

Results. Gastroesophageal reflux disease is becoming an increasingly important disease for the young and able-bodied population, which gives it not only a medical, but also an economic aspect. This is one of the most common pathologies in the practice of not only a therapist, family doctor and gastroenterologist, but – due to the presence of extraesophageal manifestations – in a wider range of medical specialties. Since gastroesophageal reflux disease has many “masks”, this leads to delayed diagnosis and treatment. This disease does not have a “gold standard” in routine diagnostics, and the presence of its refractory forms leads to treatment failures and complications. With a comorbid course of gastroesophageal reflux disease, both diagnosis and treatment require an integrated approach.

Conclusions. Gastroesophageal reflux disease remains one of the most common diseases in the practice of a family doctor. Despite the extensive study of this pathology, it continues to remain difficult in terms of diagnosis and treatment, which is associated with the presence of extraesophageal manifestations, comorbid and refractory course. This requires an additional study of pathogenetic mechanisms and the development of therapeutic and diagnostic measures on the basis of this

Keywords: gastroesophageal reflux disease, extraesophageal manifestations, proton pump inhibitors

Copyright © 2020, A. Oparin, A. Titkova, K. Stepanchenko, V. Tseluyko, M. Kochuieva, O. Korzh.
This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0>).

1. Introduction

At the moment, gastroesophageal reflux disease (GERD) is the most common pathology among diseases of the digestive system, and among diseases of the esophagus its share is 75 % [1]. In the general population it averages 14.8 %, while in European countries this figure reached 17.1 %, in Northern Europe – 15.5 %, in Southern Europe – 21.3 % [2]. Has a steady upward trend [3], annually increasing by 5 %. In addition, with this disease there is a significant decrease in the quality of life [4], patients are in fifth place after hypertension, menopause, angina pectoris and peptic ulcer disease [3].

Today, a particular difficulty in the problem of GERD is the presence of comorbid pathology, which, on the one hand, changes the clinical course of GERD, and on the other, is often masked as extraesophageal manifestations of this disease. All this contributes to the underdiagnosis of comorbid pathology in GERD. Therefore, the study of GERD and its course is an urgent problem not only for gastroenterologists and therapists, but also for a wide range of medical specialists.

The aim of the work – to review the literature to study the most important and complex aspects in the diagnosis and treatment of gastroesophageal reflux disease, which occur in the practice of family medicine.

2. Materials and methods

A review of the modern literature on the diagnosis and treatment of gastroesophageal reflux disease, its extraesophageal manifestations and comorbid course was made. To do this, we conducted a search and analysis of articles and meta-analyses in the PubMed, Google Scholar, Crossref databases.

3. Problems of gastroesophageal reflux disease

Heartburn is the main symptom of GERD in 40–45 % of megalopolises. Every day up to 10 % of the population feel GERD symptoms, weekly – 30 %, monthly – 50 % [5]. Despite the fact that most epidemiological studies show a significant increase in GERD among elderly people (over 50 years old), in recent years it has been significantly rejuvenated [6], and in the age group from 30–39 years old there has been the greatest increase [7]. Since these are people of young working age, this can become not only a medical, but also an economic problem. This disease occurs among students (14–16 %) [8] and children [9] and adolescents [10]. Rejuvenation of the pathology may lead to an increase in the number of complications such as Barrett's esophagus and adenocarcinoma [11] due to a longer history, which also entails a longer treatment with proton pump inhibitors (PPIs). The meta-analysis showed that long-term use of PPIs increases the risk of fractures, bacterial overgrowth and spontaneous bacterial peritonitis, community-acquired pneumonia, and decreased zinc absorption [12].

One of the first problems is that official statistics do not reflect the true state of affairs. About 20 % of patients have an asymptomatic course, another large group, in accordance with the “iceberg” phenomenon, does not seek medical help, but self-medicates [13].

Among the risk factors for the development of GERD are the following: age ≥ 50 years, smoking, consumption of nonsteroidal anti-inflammatory drugs, and obesity [2]. Also, according to the results of a meta-analysis, a potential relationship between alcohol consumption and the risk of GERD has been shown [14]. Other authors add genetic factors to this list. It has been

shown that 91 % of the alleles that increase the risk of GERD also increase the risk of Barrett's esophagus and / or adenocarcinoma, which significantly expands the possibilities of detecting genes for these traits [15]. Other studies in this regard call the global acceleration process, pregnancy, overeating, excessive consumption of fatty foods, chocolate, carbonated drinks, flour products, citrus fruits, products containing caffeine, insomnia, the presence of iron deficiency anemia, diabetes mellitus, scleroderma, the effect on the mucous membrane the lining of the esophagus, prostaglandins and other mediators of inflammation (cytokines), which are released during inflammatory processes of the digestive system (peptic ulcer, cholecystitis, pancreatitis), dysfunction of the salivary glands, stress, surgery, increased gastric secretion, duodenostasis, work associated with frequent torso bending and weight lifting [3]. Meta-analysis shows that *H. pylori* eradication is considered one of the risk factors for GERD [16]. In the pathogenesis of GERD, the main role is assigned to impaired nervous regulation and a decrease in the tone of the lower esophageal sphincter (LES), which leads to a decrease in the function of the antireflux barrier LES and an increase in the frequency of gastroesophageal reflux and the volume of refluctate [1]. The autonomic nervous system (ANS) has an important effect on motor skills and secretion. With dysfunction, the tone is shifted to one side or the other, which causes an increase or inhibition of the motor-secretory function, affects the tone of the sphincter and leads to GERD [17]. Not the last role is assigned to neuroregulatory influences. These are the melatonin-serotonin system [18], thyroid hormones [19], ghrelin [20], pro-inflammatory and anti-inflammatory adipokines [21], which play an important role in the regulation of motor secretory function.

In the diagnosis of GERD, especially its non-erosive form, the patient's complaints play the main role. Esophageal symptoms include: heartburn, regurgitation, belching, chest pain, feeling of a lump in the throat, rumination, hypersalivation, rarely hiccups. In addition, along with daytime symptoms, there is nocturnal symptomatology, which is manifested by nocturnal reflux and heartburn, which leads to disturbed sleep and causes sleep fragmentation [22]. Nocturnal manifestations are noted in 89 % of patients with GERD. In addition, nocturnal refluxes are more aggressive than daytime ones, which is associated with prolonged contact of acid with the esophageal mucosa due to a physiological decrease in swallowing movements during sleep, as well as an increase in the number of complications, in particular adenocarcinoma [3]. A meta-analysis showed that there is a significant correlation between obstructive sleep apnoea syndrome and hypopnea and gastroesophageal reflux disease [23].

According to the European guidelines for the management of patients with GERD [24], the diagnostic criterion is the occurrence of symptoms at least twice a week and impaired quality of life due to these symptoms. With the initial visit and the absence of alarming symptoms, the diagnosis can be made without endoscopy, but this approach entails the possibility of missing a more serious illness in the patient, which will also be characterized by the presence of heartburn.

Quite often, patients with a non-erosive form of GERD show extraesophageal symptoms in the form of oropharyngeal, dental, respiratory, pseudocardial symptoms. According to some reports, almost a quarter of patients with GERD have exclusively extraesophageal symptoms that obscure the GERD itself. Such patients often turn to "specialized doctor", which creates the prerequisites for making an incorrect diagnosis, little or even ineffective treatment, and most importantly, the progression of the underlying disease and the development of complications [3]. For example, sometimes instead of heartburn, patients complain of a feeling of pain behind the breastbone, which requires diffiagnosis with ischemic heart disease, reflex angina pectoris, and retrosternal symptoms. Also, more than one third of cases of bronchial asthma are caused by GERD [1]. Oropharyngeal symptoms occur when the organs of the oral cavity and pharynx are affected by the acidic contents of the stomach. These include inflammation of the nasopharynx and sublingual tonsils, pharyngitis, a feeling of a lump in the throat, and malignant lesions of the pharynx. Otolaryngological symptoms are manifested by laryngitis, hoarseness, granulomas, ulcers, vocal cord polyps, otalgia, rhinitis, otitis media. The results of a meta-analysis confirm a significant association of GERD with chronic rhinosinusitis, with both acid and non-acid reflux being risk factors for this pathology [25]. Dental symptoms include tooth decay, tooth enamel erosion, periodontal disease, and aphthous stomatitis. Bronchopulmonary manifestations are the development of chronic bronchitis with bronchiectasis, bronchial asthma, aspiration pneumonia, lung abscess, paroxysmal sleep apnea [1]. The pseudocardial symptoms of GERD are manifested by chest pain syndrome, which is not associated with heart disease. Cardiac symptoms are accompanied by arrhythmias and pain in the heart. Elderly patients are characterized by atypical symptoms of GERD. Despite the insignificant severity of symptoms, they may exhibit pronounced morphological changes in the mucous membrane of the esophagus [3].

Thus, pulmonologists, otolaryngologists, dentists, and cardiologists should add GERD with its extraesophageal manifestations to their list of differential diagnoses. Extraesophageal reflux manifestations are most effectively diagnosed using a step-by-step approach that includes empirical treatment and antisecretory therapy, 24-hour multichannel intraluminal esophageal impedance monitoring in combination with pH-metering, and surgery [26].

Thus, using traditional research methods, it is not always possible to diagnose GERD, especially its non-erosive form. At the moment, a search is underway for new methods for diagnosing this pathology. A study of salivary pepsin has been proposed, but a meta-analysis showed that salivary pepsin has moderate diagnostic value for GERD and is not as useful as previously thought [27]. Also, the scientific study of the ultrasound method for examining the stomach and the upper third of the esophagus with water loading is being carried out. This method is minimally invasive, at the same time, quite informative and easily applicable in the routine practice of a doctor [21].

Another difficult point in the diagnosis is the presence of a comorbid pathology. GERD occupies a leading place among the pathologies that occur in multimorbid patients [28]. Chronic obstructive pulmonary disease [29], bronchial asthma [30], diabetes mellitus [31], ischemic heart disease [32], thyroid pathology [19], and other diseases may accompany GERD. A feature of the comorbid course is mutual burdening, changes in the clinical picture, difficulty in diagnosis and treatment.

Despite the increased prevalence of GERD in patients with asthma and COPD, a causal relationship has not been established. Sources confirm that GERD is a risk factor for exacerbations of COPD [29]. GERD has been shown to impair COPD control and enhance bronchial reactivity and microaspiration. The risk of bacterial colonization of the lower respiratory tract increases and, as a consequence, the risk of exacerbations of COPD increases [33].

The data on the problem of the comorbid course of GERD with type 2 diabetes mellitus (T2DM) are contradictory, while some authors believe that GERD can be considered as a complication of T2DM. Possible pathogenetic mechanisms include diabetic nephropathy and diabetic gastropathy, which lead to movement disorders of the upper digestive tract and thereby increase the development of pathological gastroesophageal reflux. The presence and severity (frequency of erosive lesions of the esophagus) of GERD are directly related to the duration of T2DM. Patients with T2DM are more likely to suffer from asymptomatic GERD as a result of visceral neuropathy, which greatly complicates the diagnosis [34].

Due to a change in the thyroid status, a violation of the motor and secretory functions of the upper alimentary canal develops. With hypothyroidism, symptoms such as pain in the chest and in the epigastric region, belching, intensify. An increase in the level of thyroid hormones causes an increase in the level of gastrin and, as a consequence, an increase in the tone of the lower esophageal sphincter [19].

The symptoms of chest pain caused by GERD are similar to those of heart pain, and thus the 2 types of pain can be confused. In addition, GERD and coronary artery disease (CAD) can interact with each other to cause chest pain. Studies have shown that stimulation of the esophagus can cause heart pain, causing cardiac arrhythmias or coronary spasms with impaired coronary blood flow. It is also known that myocardial ischemia can aggravate GERD by causing impaired esophageal motility or relaxation of the lower esophageal sphincter. Research results indicate that GERD has been associated with an increased risk of coronary heart disease [35]. Based on this, it can be concluded that the study of the comorbid course of GERD, the features of combined pathogenesis, etiology and clinical manifestations, is very relevant for creating diagnostic algorithms and treatment regimens, taking into account all the features and applying an individual approach.

Complications of GERD include esophageal strictures, peptic ulcers of the esophagus, bleeding from ulcers of the esophagus, Barrett's esophagus (BE), and esophageal adenocarcinoma. A systematic review and meta-analysis found a significant association between reflux disease and the presence of malignant neoplasms

of the larynx [36]. Identified the following risk factors for the development of BE: GERD – 3 %; GERD plus any risk factor – 12.2 %; family history – 23.4 %; age > 50 years – 6.1 %; obesity – 1.9 %; male sex – 6.8 % [37].

According to the Gstaad treatment guidelines, GERD PPIs are the drugs of choice. H2 receptor antagonists can only be used for a short time, as tachyphylaxis develops rapidly to them. PPIs dosage and duration of treatment depend on the severity of reflux esophagitis according to the Los Angeles classification. Studies have shown that the use of proton pump inhibitors was associated with a lower risk of exacerbation and mortality in patients with COPD and symptomatic GERD, although other reports of treatment outcomes for patients with asthma, COPD and GERD have been mixed [33]. Acid suppression is an effective therapy for chronic laryngitis associated with GERD. An increase in the effect was noted in patients with a surgical method of treatment and longer therapy [38]. At the same time, there are reports that the use of PPIs for more than 1 year may increase the risk of CHD [35].

Patients with severe erosive esophagitis require long-term PPIs therapy or surgical treatment (Nissen fundoplication) [24]. A systematic review and network meta-analysis of studies of patients with GERD found that Nissen fundoplication has the greatest ability to improve physiological parameters of GERD, including an increase in LES pressure and a decrease in percentage pH <4 [39].

Another meta-analysis showed that obese patients had more frequent recurrence of GERD symptoms and a longer operative time associated with laparoscopic anti-reflux surgery compared with non-obese patients [40]. Prevention of a recurrence of GERD may include on-demand or short courses.

With erosive esophagitis, the use of clarithromycin 250 mg and amoxicillin 500 mg twice a day is indicated, for a course of 1 week.

Prokinetics are used as an adjunct in the treatment of GERD.

Recently, there has been a revival of interest in alginates in the treatment of GERD, including the refractory form. The meta-analysis results show that alginates have a stronger advantage over antacids and therefore can be considered as the initial therapy for patients with mild GERD symptoms, for whom long-term acid suppression is undesirable [41].

3. Results

Thus, a review of the literature indicates that gastroesophageal reflux disease is becoming increasingly relevant for the young and able-bodied population, which gives it not only a medical, but also an economic aspect. This pathology is encountered not only by therapists, family doctors and gastroenterologists, but – due to the presence of extraesophageal manifestations – also by cardiologists, pulmonologists, dentists, otolaryngologists. The presence of comorbid pathology and extraesophageal manifestations alters the clinical course of GERD, which significantly complicates the diagnosis of GERD. This disease does not have a “gold standard” in routine diagnostics, which creates prerequisites for the search for new diagnostic methods. With a comorbid course of gas-

troesophageal reflux disease, both diagnosis and treatment require an integrated approach.

4. Conclusions

Thus, gastroesophageal reflux disease is the leading disease of the gastrointestinal tract. Recently, there has been a significant rejuvenation of this pathology, which can give an economic dimension to this problem. Increased morbidity among children and adolescents can lead to more complications (Barrett's esophagus, adenocarcinoma).

The main difficulties in diagnosis are patients with non-erosive form of GERD. The comorbid course of GERD, as well as the presence of extraesophageal manifestations, significantly complicates the identification of

this pathology. To improve diagnosis, it is necessary to take into account not only esophageal, but also extraesophageal manifestations, as well as nocturnal symptoms. The use of ultrasound examination of the stomach and upper third of the esophagus with water load, which is currently being studied in scientific works, may be promising in the diagnosis of this form of GERD.

The presence of a comorbid pathology requires additional study of pathogenetic mechanisms and the development of therapeutic and diagnostic measures based on this.

Conflict of interests

The authors declare that they have no conflicts of interest.

References

- Shcherbynina, M. (2013). *Hastroezofahealna refliuksna khvoroba*. Kyiv: Medknyha, 105.
- Eusebi, L. H., Ratnakumaran, R., Yuan, Y., Solaymani-Dodaran, M., Bazzoli, F., Ford, A. C. (2017). Global prevalence of, and risk factors for, gastro-oesophageal reflux symptoms: a meta-analysis. *Gut*, 67 (3), 430–440. doi: <http://doi.org/10.1136/gutjnl-2016-313589>
- Zviahintseva, T. D., Serhienko, O. I., Chernobai, A. I., Sharhorod, I. I., Hridnieva, S. V. (2017). *Hastroezofahealna refliuksna khvoroba ta yii refrakterni forma: suchasni uiavlennia pro diahnostyku i likuvannia*. Kharkiv: Drukarnia Madryd, 109.
- Guan, X.-L., Wang, H. (2015). Quality of life scales for patients with gastroesophageal reflux disease: A literature review. *International Journal of Nursing Sciences*, 2 (1), 110–114. doi: <http://doi.org/10.1016/j.ijnss.2015.02.003>
- El-Serag, H. B., Sweet, S., Winchester, C. C., Dent, J. (2013). Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut*, 63 (6), 871–880. doi: <http://doi.org/10.1136/gutjnl-2012-304269>
- Yamasaki, T., Hemond, C., Eisa, M., Ganocy, S., Fass, R. (2018). The Changing Epidemiology of Gastroesophageal Reflux Disease: Are Patients Getting Younger? *Journal of Neurogastroenterology and Motility*, 24 (4), 559–569. doi: <http://doi.org/10.5056/jnm18140>
- Kim, G. H. (2018). It Is Time to Meet the Challenges of the Changing Epidemiology of Gastroesophageal Reflux Disease. *Journal of Neurogastroenterology and Motility*, 24 (4), 507–509. doi: <http://doi.org/10.5056/jnm18152>
- Bordbar, G. & Bolandnazar, N. S. (2015). Gastroesophageal reflux disease (GERD): prevalence and association with Psychological Disorders among medical sciences students. *International journal of pharmtech research*, 8 (7), 120–130.
- Rybak, A., Pesce, M., Thapar, N., Borrelli, O. (2017). Gastro-Esophageal Reflux in Children. *International Journal of Molecular Sciences*, 18 (8), 1671. doi: <http://doi.org/10.3390/ijms18081671>
- Poddar, U. (2018). Gastroesophageal reflux disease (GERD) in children. *Paediatrics and International Child Health*, 39 (1), 7–12. doi: <http://doi.org/10.1080/20469047.2018.1489649>
- Boeckxstaens, G., El-Serag, H. B., Smout, A. J. P. M., Kahrilas, P. J. (2014). Symptomatic reflux disease: the present, the past and the future. *Gut*, 63 (7), 1185–1193. doi: <http://doi.org/10.1136/gutjnl-2013-306393>
- Hatemi, I., Esatoglu, S. N. (2017). What is the long term acid inhibitor treatment in gastroesophageal reflux disease? What are the potential problems related to long term acid inhibitor treatment in gastroesophageal reflux disease? How should these cases be followed? *The Turkish Journal of Gastroenterology*, 28 (1), 57–60. doi: <http://doi.org/10.5152/tjg.2017.15>
- Lee, S. P., Sung, I.-K., Kim, J. H., Lee, S.-Y., Park, H. S., Shim, C. S. (2016). The Clinical Features and Predisposing Factors of Asymptomatic Erosive Esophagitis. *Digestive Diseases and Sciences*, 61 (12), 3522–3529. doi: <http://doi.org/10.1007/s10620-016-4341-9>
- Pan, J., Cen, L., Chen, W., Yu, C., Li, Y., Shen, Z. (2018). Alcohol Consumption and the Risk of Gastroesophageal Reflux Disease: A Systematic Review and Meta-analysis. *Alcohol and Alcoholism*, 54 (1), 62–69. doi: <http://doi.org/10.1093/alcal/agy063>
- An, J., Gharakhani, P., Law, M. H., Ong, J.-S. et al. (2019). Gastroesophageal reflux GWAS identifies risk loci that also associate with subsequent severe esophageal diseases. *Nature Communications*, 10 (1). doi: <http://doi.org/10.1038/s41467-019-11968-2>
- Wang, X., T., Zhang, M., Chen, C., Y., Lyu, B. (2016). *Helicobacter pylori* eradication and gastroesophageal reflux disease: a Meta-analysis, 1 (55 (9)), 710–716. doi: <http://doi.org/10.3760/cma.j.issn.0578-1426.2016.09.011>
- Kseneva, S. I., Borodulina, E. V., Udut, V. V. (2018). Discoordination of Autonomic Support of Functions in the Pathogenesis Gastroesophageal Reflux Disease. *Bulletin of Experimental Biology and Medicine*, 166 (1), 19–21. doi: <http://doi.org/10.1007/s10517-018-4279-3>
- Ferracioli-Oda, E., Qawasmi, A., Bloch, M. H. (2013). Meta-Analysis: Melatonin for the Treatment of Primary Sleep Disorders. *PLoS ONE*, 8 (5), e63773. doi: <http://doi.org/10.1371/journal.pone.0063773>
- Yarantseva, N. A. (2020). Clinical-pathogenetic parallels in the combined course of autoimmune tyreoiditis and gastroesophageal reflux disease among young adults. *Shidnoevropejskij Zurnal Vnutrisnoi Ta Simejnoi Medicini*, 1, 106–110. doi: <http://doi.org/10.15407/internalmed2020.01.106>
- Oparin, O. A., Oparin, A. G., Kudriavtsev, A. A. (2019). The role of ghrelin in the formation of the comorbide flow of gastroesophageal reflux disease with type 2 diabetes in young people. *Problems of Uninterrupted Medical Training and Science*, 3, 48–56. doi: <http://doi.org/10.31071/promedovsity2019.03.048>
- Korniienko, D., Oparin, A. (2016). The use of ultrasound methods for the diagnosis of motor and evacuation disorders in gastroesophageal reflux disease with concomitant obesity. *Oxford Review of Education and Science*, 1 (11), 414–419.
- Okuyama, M., Takaiishi, O., Nakahara, K., Iwakura, N., Hasegawa, T., Oyama, M. et al. (2016). Associations among gastroesophageal reflux disease, psychological stress, and sleep disturbances in Japanese adults. *Scandinavian Journal of Gastroenterology*, 52 (1), 44–49. doi: <http://doi.org/10.1080/00365521.2016.1224383>

23. Wu, Z.-H., Yang, X.-P., Niu, X., Xiao, X.-Y., Chen, X. (2018). The relationship between obstructive sleep apnea hypopnea syndrome and gastroesophageal reflux disease: a meta-analysis. *Sleep and Breathing*, 23 (2), 389–397. doi: <http://doi.org/10.1007/s11325-018-1691-x>
24. Voutilainen, M. (2016). Nastanova 00170. Gastroezofagealna refluksna khvoroba. 18.11.2016. Available at: https://guidelines.moz.gov.ua/?fbclid=IwAR3Lz_a3yd8Y0r9a-HVVb7M33U1emjSh_VJ9gFcpl7BUCgAinIuSSEPTie0
25. Leason, S. R., Barham, H. P., Oakley, G., Rimmer, J., DelGaudio, J. M., Christensen, J. M. et al. (2017). Association of gastro-oesophageal reflux and chronic rhinosinusitis: systematic review and meta-analysis. *Rhinology Journal*, 55 (1), 3–16. doi: <http://doi.org/10.4193/rhino16.177>
26. Sidhwa, F., Moore, A., Alligood, E., Fisichella, P. M. (2017). Diagnosis and Treatment of the Extraesophageal Manifestations of Gastroesophageal Reflux Disease. *Annals of Surgery*, 265 (1), 63–67. doi: <http://doi.org/10.1097/sla.0000000000001907>
27. Guo, Z., Wu, H., Jiang, J., Zhang, C. (2018). Pepsin in Saliva as a Diagnostic Marker for Gastroesophageal Reflux Disease: A Meta-Analysis. *Medical Science Monitor*, 24, 9509–9516. doi: <http://doi.org/10.12659/msm.913978>
28. Ahmadi, B., Alimohammadian, M., Yaseri, M., Majidi, A., Boreiri, M., Islami, F., Malekzadeh, R. (2016). Multimorbidity: Epidemiology and risk factors in the golestan cohort study, Iran a cross-sectional analysis. *Medicine*, 95 (7), e2756. doi: <http://doi.org/10.1097/md.0000000000002756>
29. Broers, C., Tack, J., Pauwels, A. (2017). Review article: gastro-oesophageal reflux disease in asthma and chronic obstructive pulmonary disease. *Alimentary Pharmacology & Therapeutics*, 47 (2), 176–191. doi: <http://doi.org/10.1111/apt.14416>
30. Kim, S. Y., Min, C., Oh, D. J., Choi, H. G. (2019). Bidirectional Association Between GERD and Asthma: Two Longitudinal Follow-Up Studies Using a National Sample Cohort. *The Journal of Allergy and Clinical Immunology: In Practice*, 8 (3), 1005–1013.e9. doi: <http://doi.org/10.1016/j.jaip.2019.10.043>
31. Sakitani, K., Suzuki, N., Ihara, S., Hirata, Y., Kawazu, S., Iwamoto, Y., Koike, K. (2018). Decline in perception of acid regurgitation symptoms from gastroesophageal reflux disease in diabetes mellitus patients. *PLOS ONE*, 13 (3), e0194466. doi: <http://doi.org/10.1371/journal.pone.0194466>
32. Drozd, V. Y., Khukhlina, O. S., Mandryk, O. E., Hryniuk, O. E. (2016). Certain unsolved questions of pathogenetic interrelation between gastroesophageal reflux disease and chronic forms of ischemic heart disease (review of the references). *Bukovinian Medical Herald*, 20 (2 (78)), 191–193. doi: <http://doi.org/10.24061/2413-0737.xx.2.78.2016.106>
33. Su, V. Y.-F., Liao, H.-F., Perng, D.-W., Chou, Y.-C., Hsu, C.-C., Chou, C.-L. et al. (2018). Proton pump inhibitors use is associated with a lower risk of acute exacerbation and mortality in patients with coexistent COPD and GERD. *International Journal of Chronic Obstructive Pulmonary Disease*, 13, 2907–2915. doi: <http://doi.org/10.2147/copd.s157761>
34. Maev, I., V., Iurenev, G., L., Kakhramanova D., A. (2012). Peculiarities of gastroesophageal reflux disease in patients with type 2 diabetes mellitus. *Klin Med*, 90 (9), 53–56.
35. Chen, C.-H., Lin, C.-L., Kao, C.-H. (2016). Association between gastroesophageal reflux disease and coronary heart disease. *Medicine*, 95 (27), e4089. doi: <http://doi.org/10.1097/md.0000000000004089>
36. Parsel, S. M., Wu, E. L., Riley, C. A., McCoul, E. D. (2019). Gastroesophageal and Laryngopharyngeal Reflux Associated With Laryngeal Malignancy: A Systematic Review and Meta-analysis. *Clinical Gastroenterology and Hepatology*, 17 (7), 1253–1264. doi: <http://doi.org/10.1016/j.cgh.2018.10.028>
37. Qumseya, B. J., Bukannan, A., Gendy, S., Ahemd, Y., Sultan, S., Bain, P. et al. (2019). Systematic review and meta-analysis of prevalence and risk factors for Barrett's esophagus. *Gastrointestinal Endoscopy*, 90 (5), 707–717.e1. doi: <http://doi.org/10.1016/j.gie.2019.05.030>
38. Yang, Y., Wu, H., Zhou, J. (2016). Efficacy of acid suppression therapy in gastroesophageal reflux disease-related chronic laryngitis. *Medicine*, 95 (40), e4868. doi: <http://doi.org/10.1097/md.0000000000004868>
39. Richter, J. E., Kumar, A., Lipka, S., Miladinovic, B., Velanovich, V. (2018). Efficacy of Laparoscopic Nissen Fundoplication vs Transoral Incisionless Fundoplication or Proton Pump Inhibitors in Patients With Gastroesophageal Reflux Disease: A Systematic Review and Network Meta-analysis. *Gastroenterology*, 154 (5), 1298–1308. doi: <http://doi.org/10.1053/j.gastro.2017.12.021>
40. Bashir, Y., Chonchubhair, H. N., Duggan, S. N., Memba, R., Ain, Q. ul, Murphy, A. et al. (2019). Systematic review and meta-analysis on the effect of obesity on recurrence after laparoscopic anti-reflux surgery. *The Surgeon*, 17 (2), 107–118. doi: <http://doi.org/10.1016/j.surge.2018.05.001>
41. Leiman, D. A., Riff, B. P., Morgan, S., Metz, D. C., Falk, G. W., French, B. et al. (2017). Alginate therapy is effective treatment for GERD symptoms: a systematic review and meta-analysis. *Diseases of the Esophagus*, 30 (5), 1–9. doi: <http://doi.org/10.1093/dote/dow020>

Received date 06.08.2020

Accepted date 22.09.2020

Published date 30.11.2020

Aleksey Oparin, MD, Professor, Department of Therapy, Rheumatology and Clinical Pharmacology, Kharkiv Medical Academy of Postgraduate Education, Amosova str., 58, Kharkiv, Ukraine, 61176
E-mail: oparinaa@ukr.net

Anna Titkova, PhD, Associate Professor, Department of General Practice-Family Medicine, Kharkiv Medical Academy of Postgraduate Education, Amosova str., 58, Kharkiv, Ukraine, 61176,
E-mail: ann.titkov@gmail.com

Kostiantyn Stepanchenko, MD, Professor, Department of Neuropathology and Neurosurgery, Kharkiv Medical Academy of Postgraduate Education, Amosova str., 58, Kharkiv, Ukraine, 61176

Vira Tseluyko, MD, Professor, Department of Cardiology and Functional Diagnostics, Kharkiv Medical Academy of Postgraduate Education, Amosova str., 58, Kharkiv, Ukraine, 61176

Maryna Kochuieva, MD, Professor, Department of Tuberculosis, Pulmonology and Family Medicine, Kharkiv Medical Academy of Postgraduate Education, Amosova str., 58, Kharkiv, Ukraine, 61176

Oleksii Korzh, MD, Professor, Department of General Practice-Family Medicine, Kharkiv Medical Academy of Postgraduate Education, Amosova str., 58, Kharkiv, Ukraine, 61176