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Activity of glutathione enzyme system in students with gastroesophageal reflux disease

Objective — to determine the antioxidant defense systems (ADS) status based on the activity of glutathione enzyme system parameters in young patients with gastroesophageal reflux disease (GERD).

Materials and methods. The study involved 45 students from Kharkiv universities with GERD and 20 healthy students of similar age and gender who formed the control group. The average age was 21.9 ± 2.7 years, with a predominance of women — 33 (73.3 %). The duration of the disease ranged from «first detected» (17 individuals — 37.8 %) to three years (28 patients — 62.2 %). The presence of the disease was confirmed by patients' complaints and the results of endoscopic examination of the esophagus with biopsy and histomorphological analysis of the mucous membrane.

Results. The esophagogastroduodenoscopy showed that 34 patients (75.6 %) had a nonerosive form of esophageal disease, and 11 (24.4 %) had an erosive form. In patients with the erosive form of GERD, type A was registered in 6 people (54.5 %), type B — 4 (36.4 %) and type C — 1 (9.1 %). It was found that the course of GERD was accompanied by a disturbance in the synthesis of the three components of the glutathione link in the antioxidant defense system (ADS). Thus, glutathione peroxidase (GPX) activity was 1.3 times lower than in the control group ((14.82 ± 0.8 IU/g Hb) versus (18.75 ± 0.9 IU/g Hb)). Glutathione reductase (GTR) content was also reduced by 1.2 times ((1.62 ± 0.3 μmol NADPH/g Hb) versus (1.88 ± 0.4 μmol NADPH/g Hb)), respectively. The activity of reduced glutathione — the main component of the enzyme system — was lowered by 1.2 times (1.53 versus 1.91 mmol/g Hb). A study of these enzymes considering sex, duration of anamnesis and smoking tobacco was conducted. However, these parameters do not affect the indicators. The activity of glutathione system parameters in young patients with GERD depended on the morphological form of esophageal mucosal lesions (it was more pronounced in erosive organ damage). Such changes indicate the formation of cytoprotection defects against the background of a decrease in the activity of the glutathione link of the antioxidant system. The development of GERD at a young age is accompanied by suppression of the level of the glutathione antioxidant system, which promotes chronicity and progression of pathology.

Conclusions. The course of GERD in students is characterized by the presence of predisposing factors for both its occurrence and progression. Unbalanced day under load, chronic stress, lack of timely food intake, poor quality food, admiration for carbonated and low alcohol drinks, and accumulation in large groups with frequent respiratory diseases lead to stress on the body's protective systems and contribute to oxidative stress. Exacerbation of GERD in students leads to impaired antioxidant defense by suppressing the activity of key glutathione system components—glutathione peroxidase, glutathione reductase, and reduced glutathione. This may contribute to both prolonged disease exacerbation and the chronic progression of the pathology.

Keywords: gastroesophageal reflux disease, antioxidant protection system, students, glutathione.

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Chronic diseases among university students have long ceased to be a rarity. Although global studies on the prevalence of chronic illnesses in young people are lacking, individual population-based studies indicate a very high frequency—ranging from 30 % to 41.5 % [6, 12].

Gastroesophageal reflux disease (GERD) is the most common chronic gastrointestinal disorder in young adults. Its prevalence among university students varies from 14.9 % (medical students in Saudi Arabia) and 17.1 % (medical students in Egypt) to 18.5 % (students in South Korea) and 26.2 % (students at the University of Pisa, Italy) [2, 3, 22, 25]. The course of GERD in students is often accompanied by extra-esophageal manifestations, including depression, bronchial asthma, linked angina, and dental erosions [1, 4, 36]. Moreover, early onset of GERD before the age of 30 is associated with an increased risk of developing Barrett's esophagus [4].

Recent studies highlight the significant role of intensified free radical oxidation processes in the development of chronic diseases [24]. Today, the concept of «oxidative stress» is widely used, referring to an imbalance between oxidative and reductive reactions in the body (tissues, cells, or specific organelles) toward excessive formation of reactive oxygen and nitrogen species (RONS), these highly reactive oxidants can damage vital molecules, including enzymes, proteins, membrane phospholipids, and nucleic acids.

On the basis of the contribution of oxidative stress in the pathogenesis of individual chronic diseases, a classification of the condition is proposed: first, oxidative stress as the main cause of pathology (eg atherosclerosis); second, oxidative stress as a secondary factor of disease progression (e.g., chronic obstructive pulmonary disease, arterial hypertension) (e.g., chronic obstructive pulmonary disease, arterial hypertension) [11, 14].

Today the classical ideas about GERD ethiopathogenesis, as a disruption of the locking function of the lower esophageal sphincter with subsequent blocking of the contents of the stomach and acid and pepsin damage to the esophageal mucosa, are substantially supplemented by inflammatory «cytokine sizzle» model [35]. This model suggests that inflammation of the esophageal mucosa caused by reflux is initiated by cytokines from T-lymphocytes, not by acid burn as such. Active oxygen forms are involved in this process by activating hypoxia-inducible factor-2α, which causes the secretion of proinflammatory cytokines and triggers migration of T-lymphocytes [8, 34]. Thus, it is oxidative stress that initiates the pathological process of inflammatory damage to the esophageal mucosa.

During inflammation, the fat cells, macrophages and leukocytes are involved in the site of damage and under conditions of increased oxygen uptake, a «respiratory burst» is formed, further amplifying the production of free radicals [29]. Thus, between oxidative stress and inflammation a vicious cycle is formed. In addition, oxidative stress plays one of the main roles in GERD progression, namely in the formation of Barret's esophagus and esophageal adenocarcinomas [15, 17, 29].

Cells are protected by a multi-level system of bio-antioxidants — antioxidant defense systems (ADS). There are four lines of antioxidant protection in the body that consistently restore (neutralize) active oxygen forms (free radicals), peroxidation fat and protein products [16, 23]. The advertisement includes the enzyme (dimethylated superoxide, catalase, peroxidase, glutathione etc.) and non-enzyme components. The non-enzyme components of the advertisement contain hydrophilic (neutralizing free radicals inside the cell) and hydrophobic antioxidants (act on the external plasmaleme). The first group includes: ascorbic acid, carnosine, reduced glutathione, and anserine. In the second group, there is a precursor of vitamin A — β-carotene, α-tocopherol, carotenoids of group K, vitamins of group K, and ubiquinone [10].

The first line of the ADS, whose work is related to the activities of dismutase superoxide, catalase, ceruloplasmin and a number of other enzymatic and non-enzymatic components, is considered the initial (primary) barrier that provides support at a continuously controlled level of free radical oxidation. The glutathione system is an important component of the first ADS line, which includes glutathione (GSH), glutathione peroxidase (GPX), glutathione transferase (GTF) and glutathione reductase (GTR). GSH can act as a non-enzymatic free absorber of RONS, GSH as an electron donor, leading to the oxidation of GSH as an end product [16, 18, 31]. In the second line of the ADS, intermediate metabolic products undergo conjugation with endogenous molecules, resulting in the formation of polar compounds, which are then excreted from the body through specialized elimination mechanisms. The key antioxidants of this second line include ascorbic acid, alpha-tocopherol, ubiquinone, and glutathione. The third line of ADS consists of proteolytic enzymes present in the cytosol and mitochondria, which recognize, degrade, and remove oxidatively modified proteins. The fourth line of ADS (adaptive response) is responsible for generating signals in response to RONS exposure, which regulate the synthesis and transport of specific antioxidants to the required site [16, 23].

GSH is a unique antioxidant. He is active on all the lines of ADS. It serves as the «main antioxidant» of our body and is involved in antioxidant protection,

detoxification of xenobiotics, cysteine transmission/storage, cellular signaling, protein folding, gene expression, cell differentiation/proliferation [21, 32].

Structurally, glutathione is a tripeptide composed of glutamine, cysteine, and glycine, with its biologically active L-isomer. The sulfhydryl (-SH) group is the key functional element responsible for its antioxidant and detoxifying properties, acting as an electron donor in neutralizing over 3,000 oxidized toxic substrates in the body. GPX catalyzes the recovery of hydrogen peroxide and organic peroxide using reduced GSH. The regeneration of GSH, which is used for the detoxification of peroxide, takes place in the presence of GTR. Another important enzyme of the Glutathione system is GTF. When GPX and GTF are present, hydroperoxides are reconstituted, which prevents the progression of peroxidation and its secondary metabolites [18, 26, 28]. When free radicals are over-produced, the GSH is rapidly depleted. Sufficient GSH concentration is critical for cell survival under oxidative stress [21].

Although significant progress has been made in understanding the functioning of individual components of the ADS in the most common chronic diseases, the role of this system in young patients with GERD is not known for certain. The available data on changes in glutathione activity in esophageal lesions are fragmentary and contradictory [19].

Objective — to determine the state of antioxidant defense based on the activity of the glutathione enzyme system markers in young patients with gastroesophageal reflux disease.

Materials and methods

This study was conducted in accordance with the ethical principles World Medical Association Declaration of Helsinki (1975, 1983). The Kharkiv National Medical University ethics committee approved the study design, and all patients signed informed consent forms.

The study involved 45 young patients with GERD — university students from the city. The average age in the group was 21.9 ± 2.7 years, with a predominance of women (33 individuals, 73.3 %). The duration of the disease ranged from «first diagnosed» to three years, which was determined by the specific characteristics of the study cohort. The clinical examination of the patients included: collection of complaints, medical and life history, objective examination, and laboratory-instrumental diagnostic methods.

In diagnosing GERD, the Montreal Consensus (2006) recommendations were used, along with the «Unified Clinical Protocol for Primary and Secondary (Specialized) Medical Care for Gastroesophageal Reflux Disease» and ICD-10 code K21. The disease form was determined based on visual changes in the esophageal mucosa (non-erosive or erosive) as assessed by esophagogastroduodenoscopy (EGDS) using the «Fuginon» system, in accordance with the Los Angeles classification recommendations. All patients underwent histomorphological examination of biopsy samples, which allowed the identification of the inflammatory response features in the esophageal mucosa.

Patients with diabetes mellitus, cardiovascular diseases, kidney diseases, oncology of any localization, mental disorders, pregnant women, and minors were excluded from the study. Control values for the study were obtained from 20 healthy individuals who were representative of the main group across all parameters. Activity of GTR, GPX and GSH was investigated by spectrophotometry using commercial test systems of «Elabscience» (USA).

Statistical processing of the results of the study was carried out by a variation statistics method using the Stata 12.1 license software. The distribution of indicators studied was different from the usual one, therefore non-parametric methods were used for statistical data processing. For comparing the indices of patients from study groups and healthy people, the Mann-Whitney (U) criterion was used. The level of statistical significance was not lower than 95 % ($p < 0.05$).

Results and discussion

The study was selected by students of the city's universities, which allowed to limit age fluctuations, duration of the disease history, compare social affiliation, features of mental and physical stress and eating behavior. Thus, the following results were established in the distribution of patients with a history of GERD: 17 (37.8 %) cases had the disease diagnosed for the first time; y 28 (62,2,1 %) — for 1—3 years. Treatment of students to the doctor from the moment of onset of clinical manifestations of the disease at time period of 7—8 months to 1.5 years. Such «later» contact with the doctor was caused by the following reasons: moderate clinical symptoms or careless treatment of oneself, treating clinical signs as temporary, insignificant problems associated with «poor quality food or drink», «lack of time to see a doctor during daily classes or sessions» etc.

The main complaint of patients with GERD was heartburn, which was recorded in all cases, but its manifestations had different intensity, frequency, time and duration (Table 1).

The duration of symptoms of heartburn was different: from 30—40 minutes to 2—3 hours and quite often its appearance was stopped by alkaline solutions.

Table 1. **Clinical characteristics of the main clinical symptom GERD — heartburn — in patients examined (p = 45)**

Characteristics	Number of patients
Intensity of manifestation	
Weak	25 (55.6 %)
Mild	16 (35.6 %)
Expressed	4 (8.9 %)
Frequency of occurrence	
Daily	23 (51.1 %)
More than twice a week	22 (48.9 %)
By time of occurrence	
In the daytime	31 (68.9 %)
At night	14 (31.1 %)

Table 2. **Frequency of individual clinical symptoms of GERD in young patients**

Clinical sign	Number of patients
Discomfort in the epigastrial area	6 (13.3 %)
Pain in the epigastric region	6 (13.3 %)
Dysphagia	2 (4.4 %)
Nausea	4 (8.9 %)
Vomit	3 (6.7 %)
Growling	21 (46.7 %)
Feeling of rapid satiation after eating	11 (24.4 %)
Gas buildup	14 (31.1 %)
Cough	3 (6.7 %)
Hoarseness	1 (2.2 %)

Almost half of the patients had growling (46.7 %). Other GERD symptoms were noted somewhat less frequently (Table 2).

The EGDS showed that in 34 (75.6 %) patients a non-erosive form of esophageal injury was diagnosed, while 11 (24.4 %) patients had an erosive form. In patients with the erosive form of GERD, type A was registered in 6 (54.5 %) people, type B — 6 (36.4 %) and type C — 1 (9.1 %). A diaphragmatic hernia was identified in 4 (8.9 %) patients.

It is recognized that in antioxidant protection the glutathione system and its constituent enzymes occupy a prominent place [21, 32]. These components protect cells from free-radical oxidation products and xenobiotics, so they are considered important representatives of the system for the detoxification of toxic metabolites. Thus, the following results were obtained when determining the activity of these enzymes in patients with GERD (Table 3).

That is, in the active phase of the disease there is a suppression of glutathione enzymes, which can be both the result of an expressed inflammatory reaction in the esophagus, and high reactivity of the organism, characteristic for young people.

The activity of the indicators of the glutathione system was determined, taking into account the duration of the disease history (Table 4).

Thus, the duration of the anamnesis did not affect the changes in the glutathione system.

We also did not determine changes in activity of these indicators, taking into account the effect of harmful factors, namely smoking (Table 5).

Table 3. **Glutathione enzyme activity in patients with GERD**

Indicators	Control group (n = 20)	GERD patients (n = 45)	U	p
GTR, μmol NADPH/g Hb	1.88 (1.85; 1.98)	1.62 (1.44; 1.80)	257	< 0.01
GSH, μmol/g Hb	1.91 (1.49; 2.55)	1.53 (1.44; 1.60)	1217	< 0.01
GPX, IU/g Hb	18.75 (16.02; 19.80)	14.82 (13.30; 15.58)	948	< 0.01

Table 4. **Contents of the glutathione system indicators depending on the duration of GERD**

Indicators	Newly diagnosed (n = 17)	From 1 to 3 years from diagnosis (n = 28)	p
GTR, μmol NADPH/g Hb	1.51 (1.42; 1.63)	1.53 (1.46; 1.56)	> 0.05
GSH, μmol/g Hb	1.59 (1.42; 1.79)	1.63 (1.39; 1.81)	> 0.05
GPX, IU/g Hb	14.69 (13.37; 15.15)	14.83 (13.23; 15.61)	> 0.05

We believe this is due to the extremely high prevalence of passive smoking in the student environment, which eliminates the difference in glutathione activity of the advertising binder between schoolchildren who smoke and those who do not.

Thus, the development of GERD in young people is accompanied by a suppression of the antioxidant protection system, which manifests itself in the decrease of activity of the enzyme glutation system. That is, oxidative stress is formed, which will promote the death of cells with the accumulation of cellular oxidants. Thus, the complex cascade of events is indirectly stimulated, leading to the formation and constant «support» of pathological apoptosis.

The content of these indicators was not dependent on disease duration, sex of patients, or action of harmful factors, but depended on morphological form of GERD (Table 6).

The determination of the glutathione system indicators was carried out taking into account the presence of reflux esophagitis. The results obtained from GSH, GPX and GTR activities did not depend on the Los Angeles Classification of Esofagitis ($p > 0.05$) and the presence of hernia of the esophageal aperture.

Studies of the level of activity of glutathione in patients with GERD have been conducted at many research centers before this. B. Modzelewski found decreased GPX activity in the serum [27]. Low levels of GSH were determined in the proximal esophageal mucosa by J. Räsänen et al. [30]. The expression of glutathione S-transferase-theta-2 mRNA in patients with Barrett esophagus and esophageal adenocarcinoma was studied by D. Ferrer-Torres et al. [9]. Our study differs positively from the above studies in a comprehensive approach — we studied three main components of ADS glutathione binding under the conditions of monomorphic of young patients with GERD simultaneously.

The appearance of GERD in the student environment can be explained by such points. The student environment chosen for research has certain characteristics. First, these are young people of about the same age living and studying in a large gathering of people with special daily and night loads, with frequent lack of quantity and quality of sleep. Secondly, university education always takes place against the background of chronic stress with periods of its intensification during tests and classes. Meanwhile, sleep problems and chronic stress are the causes of oxidative stress [7, 20, 33]. Also students are characterized by frequent careless eating (dry foods, widespread use of fast food, energy and carbonated drinks), wrong habits (smoking, alcoholic beverages), etc. [2, 3, 25]. All this leads to the introduction into the body of a large number of exogenous oxidants (trans-unsatisfied fatty acids, tobacco products) [13]. In such conditions, the body's regulatory systems (immune, antioxidant) work with overload and eventually become exhausted. As a result, detoxification processes are slowed down, the eso- and endogenous prooxids accumulate and «explode» as oxidative stress, followed by initiation or activation of a chronic pathological process — GERD.

Thus, the totality of these factors is a negative basis for the formation of GERD [33]. That is, the suppression of references to glutathione, despite a short history of the disease, should be considered as a result of the high reactivity of the body, characteristic for students, against the background of imbalance of regulatory systems.

Table 5. **The activity of glutathione peroxidase, glutathione reductase and glutathione in patients with GERD taking into account the bad habit — smoking**

Indicators	Smokers (n = 16)	Non-smokers (n = 29)	p
GTR, μmol NADPH/g Hb	1.55 (1.44; 1.61)	1.52 (1.29; 1.51)	> 0.05
GSH, μmol/g Hb	1.54 (1.39; 1.74)	1.62 (1.47; 1.79)	> 0.05
GPX, IU/g Hb	14.86 (13.57; 15.87)	14.56 (13.22; 15.47)	> 0.05

Table 6. **Glutathione and glutathione-dependent enzyme content in the serum of students with GERD, depending on the status of the esophageal mucosa**

Indicators	Erosion (n = 11)	No erosion (n = 34)	U	p
GTR, μmol NADPH/g Hb	1.54 ± 0.09	1.54 ± 0.10	144	0.2616
GSH, μmol/g Hb	1.55 ± 0.04	1.80 ± 0.03	103	< 0.01
GPX, IU/g Hb	14.21 ± 0.02	15.43 ± 0.03	89	< 0.01

Conclusions

The formation of GERD in young individuals, particularly those in the student cohort, is characterized by the presence of predisposing factors for both its onset and progression. Among them are: an unbalanced daily routine with respect to mental and physical workload, chronic stress, the lack of timely meals, on-the-go nutrition, excessive consumption of carbonated and low-alcoholic beverages, and the accumulation of individuals in large groups with frequent respiratory illnesses. These factors together place a load on the controlling homeostasis systems — namely, the immune and antioxidant systems.

The course of GERD in students occurs against the backdrop of suppression of the antioxidant defense system due to reduced activity of the glutathione system enzymes, which «opens access» to the cellular membrane. Oxidative stress thus acts both as a factor that initiates the disease and as a factor that contributes to its chronicity. The activity of glutathione system indicators in young patients with GERD was not dependent on age, disease duration, or harmful factors (e.g., smoking), but it was dependent on the morphological form of esophageal mucosal damage—it was more pronounced in cases of erosive lesions. These changes indicate the formation of a defect in cytoprotection due to reduced activity of the glutathione component of the antioxidant defense system. A reduction in the activity of the glutathione system—glutathione peroxidase, glutathione transferase, and reduced glutathione — can contribute to both the prolongation of the GERD exacerbation phase and the chronicization of the pathology.

Conflicts of interest: none.
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Активність глутатіонової ферментної системи в студентів із гастроезофагеальною рефлюксною хворобою

Мета — визначити стан антиоксидантного захисту (АОЗ) за показниками активності ферментної системи глутатіону в пацієнтів молодого віку з гастроезофагеальною рефлюксною хворобою (ГЕРХ).

Матеріали та методи. У дослідженні взяли участь 45 студентів університетів м. Харкова, хворих на ГЕРХ, та 20 здорових студентів відповідного віку та статі, які утворили контрольну групу. Середній вік становив (21,9 ± 2,7) року. Серед обстежених переважали жінки — 33 (73,3 %). Тривалість захворювання варіювала від «уперше виявленого» (17 (37,8 %) осіб) до трьох років (28 (62,2 %)). Наявність захворювання підтверджено скаргами пацієнтів і результатами ендоскопічного дослідження стравоходу з біопсією та гістоморфологічним дослідженням слизової оболонки.

Результати. Під час езофагогастродуоденоскопії в 34 (75,6%) хворих виявлено неерозивне ураження стравоходу, в 11 (24,4%) — ерозивний езофагіт (типу А в 6 (54,5%) осіб, типу В — у 4 (36,4%), типу С — у 1 (9,1%). Установлено, що перебіг ГЕРХ супроводжувався порушенням синтезу трьох компонентів глутатіонової ланки системи АОЗ. Активність глутатіонпероксидази була в 1,3 разу нижчою, ніж показник контрольної групи ((14,82 ± 0,8) та (18,75 ± 0,9) МО/г Hb), вміст глутатіонредуктази — у 1,2 разу ((1,62 ± 0,3) і (1,88 ± 0,4) мкмоль НАДФН/г Hb), активність відновленого глутатіону — основного компонента ферментної системи — в 1,2 разу (1,53 та 1,91 мкмоль/г Hb). Проведено дослідження цих ферментів з урахуванням статі, тривалості анамнезу та куріння тютюну. Установлено, що ці чинники не впливають на показники глутатіонової системи. Активність показників глутатіонової системи у хворих на ГЕРХ молодого віку залежала від морфологічної форми ураження слизової оболонки стравоходу (вона була виразнішою при ерозивному ураженні органа). Такі зміни свідчать про утворення дефектів цитопротекції на тлі зниження активності глутатіонової ланки АОЗ. Розвиток ГЕРХ у молодому віці супроводжується пригніченням глутатіонової ланки системи АОЗ, що призводить до хронізації та прогресування патології.

Висновки. Перебіг ГЕРХ у студентів характеризується наявністю чинників, що зумовлюють як її виникнення, так і прогресування. Незбалансований за навантаженням день, хронічний стрес, несвоєчасний прийом їжі, неякісна їжа, часте використання газованих та слабоалкогольних напоїв, перебування у великих групах з підвищеним ризиком респіраторних захворювань навантажують захисні системи організму та спричиняють окислювальний стрес. Загострення ГЕРХ у студентів призводить до порушення антиоксидантного захисту шляхом пригнічення активності ключових компонентів глутатіонової системи — глутатіонпероксидази, глутатіонредуктази та відновленого глутатіону. Це може спричинити як тривале загострення захворювання, так і хронічне прогресування патології.

Ключові слова: гастроезофагеальна рефлюксна хвороба, система антиоксидантного захисту, студенти, глутатіон.

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