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HIF-2α LEVEL IN ADOLESCENTS WITH CHRONIC INFLAMMATORY PATHOLOGY OF THE UPPER GASTROINTESTINAL TRACT

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Chronic inflammatory diseases of the gastrointestinal tract are among the most common pathological conditions in adolescents. A significant role in the pathogenesis of gastrointestinal tract diseases is given to the functioning of the oxygen sensor system, the main mediator of which is hypoxia-inducible factor 2 (HIF-2α). Therefore, the purpose of the study was to determine the level of HIF-2α in the plasma of patients with chronic inflammatory pathology of the gastrointestinal tract, taking into account the endoscopic picture of the lesion, localization of the pathological process, age and gender of the patient. The study involved 70 adolescents aged 8-18 years with chronic gastroduodenitis (CGD), gastroesophageal reflux disease (GERD), gastric or duodenal ulcer and 25 peers who had been classified as healthy. The plasma concentration of HIF-2α was measured by a sandwich-linked ELISA. Helicobacter pylori infection was determined by urease test or by ELISA. According to the data obtained, the HIF-2α plasma level was higher in patients with chronic inflammatory gastrointestinal disease compared to the control group. In boys with chronic gastroduodenal disease, the level of HIF-2α was higher than in girls. CGD and GERD were characterized by a higher HIF-2α level in plasma than gastric and duodenal ulcers. The HIF-2α level did not depend on the age of the patients or the presence of Helicobacter pylori infection.

K e y w o r d s: gastrointestinal tract, HIF-2α, adolescents, chronic gastroduodenitis, gastroesophageal reflux disease.

Chronic inflammatory diseases of the gastrointestinal tract (GIT) are one of the most common pathological conditions among adolescent [1, 2]. Despite modern headways in the diagnosis and treatment of diseases of this group, it is not always possible to achieve stable remission, control the course and prevent the development of complications.

Scientific achievements in gastroenterology continue to search for explanations for the chronicity of processes in the gastroduodenal zone. Thus, recent scientific studies of the pathophysiological processes underlying the progression of inflammation in the gastrointestinal tract have revealed the influence of factors such as cortisol levels on the development of destructive changes in the duodenal mucosa [3], virulence factors of *Helicobacter pylori* infection including vacuolating cytotoxin (VacA), cytotoxin-associated gene A (CagA) [3, 4], decreased levels of vasoactive intestinal peptide (VIP) and calcitonin gene-related peptide (CGRP), and increased levels of substance P (SP), which contribute to pathological changes in the gastric mucosa in children [5, 6].

Of particular scientific interest are the intracellular mechanisms of inflammatory process regulation. Alternative hypotheses regarding the pathogenesis of gastroesophageal reflux disease (GERD) have been presented in several scientific researches. In these studies, considerable attention is paid to the role of the oxygen-sensory system, one of the main mediators of which is the hypoxia-inducible factor 2 (HIF-2). The transcription factor HIF-2 is a heterodimeric protein containing two subunits: HIF-2α and HIF-β. It has been found that, as a result of exposure to reflux acid and bile acid salts, the production of active oxygen species (AOS) by the esophageal squa-

mous epithelium increases. Under the influence of AOS, the catalytic enzymes of proteasomal degradation of HIF-2α, prolylhydroxylases (PHDs) are inactivated, which leads to the stabilization of HIF-2α with its subsequent overactivation. HIF-2α, moving to the cell nucleus, combines with the HIF-β subunit into heterodimers at the loci of target genes. This initiates an increase in the expression of proinflammatory mediators and the development of a powerful inflammatory response [7-9]. Several scientific studies have been devoted to the association of AOS with HIF-2α activity and changes in the proliferation and differentiation of esophageal cells, which may contribute to the progression of the process from Barrett's metaplasia to adenocarcinoma [10, 11].

Whereas gastrointestinal pathology is one of the most common in childhood, starting in preschool age, it can last for several years until adulthood, taking on a stable or progressive character, the study of the contents and role of HIF-2α in children with gastrointestinal diseases needs to be clarified.

Therefore, the purpose of the study was to determine the level of hypoxia-induced transcription factor HIF-2α in the plasma of patients with chronic inflammatory pathology of the upper gastrointestinal tract, taking into account the endoscopic picture of the lesion, localization of the pathological process, age, and gender of the patient.

Materials and Methods

The study involved 95 adolescents aged from 8 to 18 years (average age 14.5 ± 2.33 years) who were examined at the Department of Paediatrics and Rehabilitation of the SI "Institute for Children and Adolescents Health Care at the National Academy of Medical Sciences of Ukraine" and the City Children's Clinical Hospital No 19. The main group consisted of 70 adolescents with chronic gastroduodenitis (CGD), GERD, and gastric or duodenal ulcer, which was confirmed by endoscopic examination. The diagnosis of the disease was made by the Unified clinical protocol for the diagnosis and treatment of digestive diseases in children (Order of the Ministry of Health of Ukraine No. 59 of 29.01.2013). Study inclusion criteria: adolescents aged from 11 to 18 years, patients with chronic gastroduodenitis, esophagitis, GERD, gastric or duodenal ulcer with different disease duration. Exclusion criteria: age under 11 years, patients with organic disorders of the cardiovascular system, central nervous system and congenital gastrointestinal diseases, patients with chronic diseases of other organs and systems in the acute period, absence of consent to participate in the study. The results were compared with the control group, which included 25 peers who had no significant health abnormalities, which allowed them to be classified as healthy.

The study was conducted by the requirements of bioethics in compliance with the provisions of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the School of Medicine of V. N. Karazin Kharkiv University, Kharkiv, Ukraine (protocol number 5 of 13.03.2024). All patients over 14 years old and/or their family members (parents/guardians) gave written informed consent to participate in the study.

The body mass index (BMI) of children was calculated using the formula "BMI = weight/(height)^2 (kg/m^2)". The assessment was carried out using percentile tables following the WHO Child Growth Standards recommendations of the World Health Organization (WHO). Underweight was defined as BMI at or below the 2nd percentile, normal weight between the 2nd and 91st percentiles, overweight between the 91st and 98th percentiles, and obesity from the 98th percentile and above.

All patients underwent instrumental and laboratory tests (video esophagogastroduodenoscopy (VEGDS), intragastric express PH-metry, enzyme-linked immunosorbent assay (ELISA) test for total antibodies to *Helicobacter pylori* (HP) and/or biopsy URE test). VEGDS was performed on patients using the Olympus CV-140 endoscopic video system and the Olympus GIF P-140 video gastroscope. The pH was assessed using the IKZH-2 gastric acidity indicator during the VEGDS, and pH values were measured in the esophagus, body, and antrum. *Helicobacter pylori* infection was determined by a urease test for HP in biopsy specimens (URE test) or by ELISA (total anti-HP antibody test).

The plasma concentration of HIF-2α was measured by a sandwich-linked ELISA using a Human ELISA kit (Elabscience, catalog number: E-EL-H2468). Plasma samples for ELISA analysis were frozen in liquid nitrogen and stored at -80°C. The concentration of human HIF-2α in the samples is calculated by comparing the samples to the standard curve. Units of measurement: ng/ml.

The treatment of patients in the main group was carried out according to the protocols for diagnosis and treatment in the specialty "Paediatric Gastroenterology" (Order of the Ministry of Health

of Ukraine No. 59 of 29.01.2013) and included drugs aimed at eradicating *Helicobacter pylori* infection (if applicable), proton pump inhibitors, antispasmodics, prokinetic agents, antacids and adsorbents.

All data are presented as median [range] for continuous variables and number (*n*; %) for categorical variables. Student's and Fisher's *t*-tests and ANOVA tests were used. Differences were considered statistically significant at a *P*-level of < 0.05. Spearman's rank correlation test was used to assess the relationship between quantitative variables. Statistical analysis was performed using STATISTICA 7 software.

Results and Discussion

The main group included 70 patients with chronic inflammatory gastrointestinal disease. The majority of patients were males (*n* = 42; 60%, *P* < 0.05). The demographic characteristics of the patients are presented in Table 1.

A positive family history of digestive system diseases was found in 64 % of children, mostly through the first line of kinship. The main and control groups were comparable in BMI, however, sixteen children were underweight and four patients were overweight in the main group. Among the pathological conditions of the gastrointestinal tract, chronic gastroduodenitis prevailed (80%, *P* < 0.01). Eleven adolescents were diagnosed with GERD in combination with CGD, and three children were diagnosed with gastric or duodenal ulcers in the exacerbation period.

The research design suggested that patients in the main group be divided into two subgroups based on the results of the VEGDS: the first subgroup included patients (*n* = 25; 35.71%) with erosive and ulcerative changes in the gastrointestinal mucosa, and the second subgroup included patients with non-destructive changes of esophagus, stomach and duodenum mucosa (*n* = 45; 64.29%, *P* = 0.0002), who were a significant majority.

In the group of patients with erosive and ulcerative changes, the following variants of pathology were observed: duodenal bulb erosion (*n* = 15; 60%), isolated erosive gastropathy (*n* = 2; 8%), erosive esophagitis (*n* = 5; 20%), and gastric and/or duodenal ulcer in three children (12%). In some patients (*n* = 19; 28.79%), gastroduodenitis was characterized by duodenogastric reflux (DGR) of II-III degree.

According to the results of intragastric PH-metry in children from the main group, destructive inflammatory changes of the gastrointestinal tract developed significantly more often in patients with the increased acid-forming function of the stomach (72%; *P*(F) < 0.05). *Helicobacter pylori* positivity was detected only in 39.22% of children with chronic gastrointestinal inflammation disorders.

The assessment of the concentration of HIF-2α revealed a significant increase in the level in patients of the main group who were diagnosed with chronic inflammatory gastrointestinal pathology (median 0.110 ng/ml [range 0.019-0.760 ng/ml]) compared with the control group (median 0.044 ng/ml [range 0.001-0.206 ng/ml]; *P* = 0.001) (Fig. 1).

Table 1. Clinical characteristics of the examined adolescents (mean ± SD)

Indicator	The main group, *n* = 70	Control group, *n* = 25
Age, years	14.97 ± 1.93	13.58 ± 2.37
median	15.85	13.56
range	10-18	10-17
Gender, boys/girls	42/28	11/14
BMI, kg/m^2	20.20 ± 3.22	18.63 ± 1.25
Distribution of patients by pathological condition:		
Chronic gastroduodenitis in the acute stage,	56 (80.00%)[1]	–
including erosive changes	17 (24.29%)	–
GERD (in combination with CGD) in the acute stage,	11 (15.71%)	–
including the erosive changes	5 (7.14%)	
Gastric or duodenal ulcer	3 (4.29%)	

Note. [1]*P* < 0.01 – differences between the number of patients with CGD and GERD, Ulcer. Values are the number (%). CGD – chronic gastroduodenitis, GERD – gastroesophageal reflux disease

At the same time, the level of HIF-2α in the blood of boys in the main group was significantly higher than in the girls of the main group and the control group ($P = 0.001$). These patterns were not observed in the control group ($P = 0.695$) (Table 2).

No correlation was found between patients' age[1], BMI[2] and HIF-2α levels ($r^1 = 0.16$; $r^2 = - 0.003$; $P > 0.05$). Also, the concentrations of HIF-2α in patients with a positive gastrointestinal heredity history and those without a burdened history did not differ significantly ($P > 0.05$).

Depending on the type of pathological process of the digestive system, significantly higher levels of HIF-2α in the blood were found in patients with GERD and chronic gastroduodenitis compared to the control group (Table 3). At the same time, patients with peptic ulcer disease did not differ from the control group.

Taking into account the endoscopic picture of gastrointestinal lesions, it was found that in patients with both destructive changes[1] of the gastrointestinal tract and non-destructive changes[2], HIF-2α levels were higher compared to the control group ($P^1 = 0.027$; $P^2 = 0.009$). However, there was no significant difference between the two subgroups of patients ($P > 0.05$) (Table 4).

Depending on the localization of erosive and ulcerative changes, a significant increase in HIF-2α levels was found in patients with erosive esophagitis as opposed to patients with destructive lesions of the gastric mucosa ($P < 0.05$). It can also be noted that there was a clear tendency towards higher levels of HIF-2α in destructive esophageal lesions compared to erosive duodenal lesions ($P = 0.067$) (Fig. 2).

Patients with gastric motility disorders such as grade I-III DGR had significantly lower HIF-2α levels (median 0.083 ng/ml [range 0.023-0.452]) versus patients without DGR (median 0.129 ng/ml [range 0.019-0.760]; $P = 0.009$).

The analysis of HIF-2α levels in patients with increased gastric acid-forming function did not significantly differ from adolescents in the main group with normal secretion ($P = 0.984$). There was also no significant difference between patients diagnosed

Table 2. Plasma levels of HIF-2α in patients of the main group and children of the control group depending on gender

Indicator	Number of cases	Plasma HIF-2α level (ng/ml) (median, range)
Main group of children ($n = 70$)		
Girls	28 (40.00)	0.083 [0.33 - 0.369]
Boys	42 (60.00)	0.110[1] [0.019 - 0.760]
Control group ($n = 25$)		
Girls	14 (56.00)	0.044 [0.020 - 0.134]
Boys	11 (44.00)	0.061 [0.001 - 0.206]

Note. [1]$P = 0.030$ – differences between the indicators of boys and girls in the main group. Values are the number (%), unless otherwise indicated

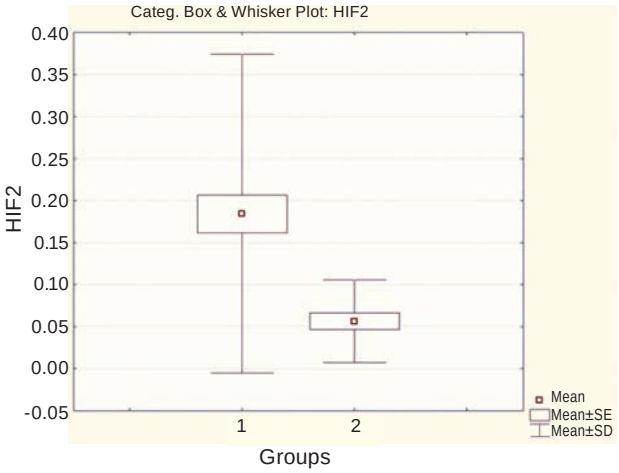

Fig. 1. Plasma levels of HIF-2α in adolescents of the main and control groups (results are presented as a comparison of the mean HIF-2α level of the main group – 1 with the control group – 2)

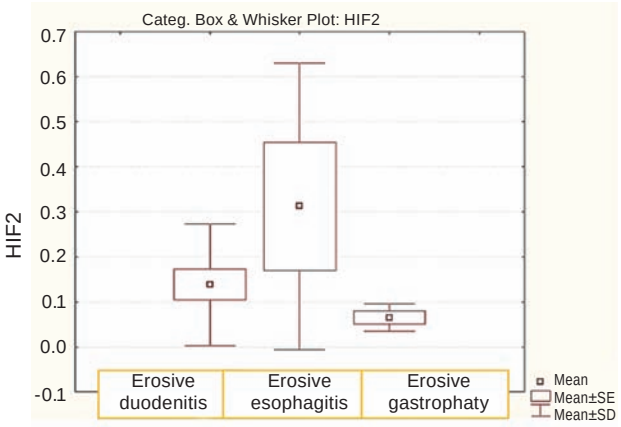

Fig. 2. Plasma concentrations of HIF-2α in patients of the main group depends on the location of erosive and ulcerative changes

Table 3. Plasma levels of HIF-2α in patients of the main group, taking into account the clinical type of the disease

Clinical type	Number of cases	HIF-2α level (ng/ml) in plasma (median, range)
Chronic gastroduodenitis	56 (80.00)	0.106[1] [0.019 - 0.720]
GERD	11 (15.71)	0.117[2] [0.053 - 0.760]
Gastric or duodenal ulcer	3 (4.29)	0.101 [0.080 - 0.112]
Control group	25 (100.00)	0.044 [0.001 - 0.206]

Note. [1]$P = 0.002$ – differences between the indicators in patients with CGD and the control group. [2]$P = 0.019$ – differences between the indicators in patients with GERD and the control group. Values are the number (%), unless otherwise indicated

Table 4. Plasma levels of HIF-2α in patients of the main group according to the results of endoscopic examination

Indicator	Number of cases	Plasma HIF-2α level (ng/ml) (median, range)
Distribution of patients by type of gastrointestinal mucosa lesion		
Subgroup 1 (erosive/ulcerative changes)	28 (40.00)	0.092[1,2] [0.033 - 0.760]
Subgroup 2 (erythematous changes)	42 (60.00)	0.125[3] [0.019 - 0.720]
Distribution of patients by localisation of erosive and ulcerative changes ($n = 25$)		
Erosive duodenopathy, or duodenal ulcer	16 (64.00)	0.092 [0.033 - 0.452]
Erosive esophagitis	5 (20.00)	0.110[4] [0.059 - 0.760]
Erosive gastropathy, or stomach ulcer	4 (16.00)	0.061 [0.040 - 0.101]

Note. [1]$P > 0.05$– differences between the indicators of 1 and 2 subgroups of patients. [2]$P = 0.027$ – differences between the patients' indicators of subgroup 1 and the control group. [3]$P = 0.001$ – differences between indicators patients of subgroup 2 and control group. [4]$P = 0.048$ – differences between the indicators in patients with erosive esophagitis and erosive gastropathy. Values are the number (%), unless otherwise indicated

with HP-associated pathology and patients with negative HP tests ($P = 0.255$).

Discussion

Over the past decades, the understanding of the pathogenesis of GERD and other chronic recurrent inflammatory diseases of the gastrointestinal tract has changed, starting from the influence of aggression factors (hydrochloric acid, bile acid salts, *Helicobacter pylori* infection), impaired epithelial barrier permeability to various molecular mechanisms [5, 8, 14]. However, recent studies have attributed a key role in gastrointestinal epithelial damage to a cytokine-mediated mechanism involving IL-8 and IL-1β, with hypoxia-inducible factor as a key mediator [7, 12]. HIFs are associated with a powerful inflammatory response, activation of fibrogenesis, angiogenesis, effects on tissue differentiation, proliferation and development of Barrett's metaplasia, as well as the progression of metaplasia to adenocarcinoma [10, 11]. It is known that HIF-2α is expressed predominantly in highly vascularised organs such as the heart, liver, lungs, brain, kidneys, intestines, and pancreas and contributes to the control of oxidative stress, RNA transport, cell cycle progression, and vascular remodeling [14]. In addition, the role of HIF-2α activation in the pathogenesis of not only GERD but also colitis and increased colon carcinogenesis has been shown [15]. Although several studies have established the importance of HIF-2α in developing GERD, there is still little information on the clinical significance of HIF-2α expression in other gastrointestinal diseases, especially in adolescence.

Our study showed that the levels of HIF-2α in the plasma of adolescents with chronic inflammatory

gastrointestinal disease exceeded those of the control group by almost 69% in terms of average values. The obtained results demonstrated higher levels of the transcription factor in males, which makes them more vulnerable to developing unfavorable variants of the disease's course and complications than in females. The results are compatible with the epidemiological data of the systematic review from 2014 to 2023 in the United States, which showed a slightly higher prevalence of GERD among men at the same time, women with GERD symptoms more often suffering from non-erosive forms, and men with prolonged GERD symptoms more likely to develop Barrett's esophagus [16]. Men are more likely to suffer from duodenal ulcers [17]. Also, according to our previous studies, there was a slight prevalence of gastroduodenitis among male adolescents [2].

The risk factors for developing gastrointestinal pathology, such as family history, age, obesity or overweight, did not affect plasma levels of HIF-2α compared to adolescents who did not have these risk factors. Although, according to the literature, there is a positive correlation between the prevalence of GERD and BMI among adult patients [18].

The study found that among the diseases associated with HIF-2α activation are not only GERD, which corresponds to the data of Rhonda F. Souza and colleagues, but also CGD. At the same time, HIF-2α concentrations were highest in patients with GERD. It should be noted that there were no significant differences in the levels of HIF-2α between patients with peptic ulcer disease and the control group. Hiroshi Hashimoto and colleagues studied the level of HIF-1α subunit during gastric ulcer healing. They found that it tends to increase during the active stage of the ulcer, while no data on the level of HIF-2α were available [19]. Kayla J. Steinberger et al. in a recent study made the following conclusions: HIF-1α is degraded more rapidly than HIF-2α, and during chronic episodes of hypoxia a switch from HIF-1α to HIF-2α occurs; HIF-1α expression rapidly deteriorates upon tissue reoxygenation, while HIF-2α remains elevated during reoxygenation [20]. These features of HIF-2α may explain its increase in recurrent chronic gastrointestinal inflammation.

Damage to the gastrointestinal mucosa in adolescents can vary, from superficial to destructive changes, as confirmed by endoscopic examination, and does not always correlate with the clinical picture. However, the peculiarity of plasma levels of HIF-2α in adolescents was the dependence on the location of destructive changes, with the highest levels recorded in esophageal wall lesions.

Although some studies have demonstrated the role of Helicobacter infection and its virulence factors in the development of gastrointestinal pathology and carcinogenesis [4, 21], our results did not reveal differences in the concentration of HIF-2α in patients with HP-associated and HP-negative disease, which probably indicates different pathogenetic mechanisms of chronic inflammation. These results are compatible with the findings of Pavle Matak et al., who studied the levels of HIF-1 and HIF-2 in biopsy samples of patients with gastritis with *H. pylori* infection and found that epithelial expression of HIF-2 even gradually decreased with the severity of *H. pylori*-associated gastritis, and, therefore, is unlikely to be dependent on HIF-2 [22].

Conclusions.

1. The concentration of hypoxia-induced factor HIF-2α was higher in patients with chronic inflammatory gastrointestinal disease compared to the control group.

2. In boys with chronic gastroduodenal disease, the level of HIF-2α transcription factor was higher than in girls in the main group and adolescents in the control group, so they are at risk.

3. No correlation was found between HIF-2α levels and patients' age and BMI.

4. The concentration of HIF-2α did not depend on family history for gastrointestinal diseases.

5. Chronic gastroduodenitis and GERD were characterized by higher levels of HIF-2α in plasma than gastric and duodenal ulcers.

6. The HIF-2α level did not significantly differ from the degree of mucosal damage according to the results of the endoscopic examination, the type of gastric secretory function and the presence of *Helicobacter pylori* infection.

7. In patients with existing duodenogastric reflux, plasma HIF-2α levels were significantly lower.

8. The plasma HIF-2α level differed significantly in patients depending on the location of the destructive process, and was higher in adolescents with erosive esophagitis.

Thus, the transcription factor HIF-2α is increased in adolescents with chronic inflammatory pathology of the upper gastrointestinal tract and may affect the further course and chronicity of the process, the prognosis of the disease in terms of the development of complications, in particular, epithelial metaplasia. Therefore, patients with high levels

of HIF-2α constitute a risk group that should be subject to careful additional observation and reasonable pathogenetic treatment.

Conflict of interest. The authors have completed the Unified Conflicts of Interest form at http://ukrbiochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

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РІВЕНЬ HIF2-α У ПІДЛІТКІВ ІЗ ХРОНІЧНОЮ ЗАПАЛЬНОЮ ПАТОЛОГІЄЮ ВЕРХНІХ ВІДДІЛІВ ШЛУНКОВО-КИШКОВОГО ТРАКТУ

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Хронічні запальні захворювання органів травлення є одними із найпоширеніших патологічних станів серед підлітків. Значна роль у патогенезі захворювань шлунково-кишкового тракту відводиться функціонуванню кисневої сенсорної системи, основним медіатором якої є гіпоксією-індукований фактор 2 (HIF-2α). Метою дослідження було визначення рівня HIF-2α у плазмі крові пацієнтів із хронічною запальною патологією шлунково-кишкового тракту з урахуванням ендоскопічної картини ураження, локалізації патологічного процесу, віку та статі пацієнта. У дослідженні взяли участь 70 підлітків віком 8-18 років із хронічним гастродуоденітом (ХГД), гастроезофагеальною рефлюксною хворобою (ГЕРХ), виразковою хворобою шлунка або дванадцятипалої кишки та 25 однолітків, яких було віднесено до категорії здорових. Концентрацію HIF-2α у плазмі крові визначали за допомогою сендвіч-зв'язаного ІФА. Інфекцію *Helicobacter pylori* визначали за допомогою уреазного тесту або ІФА. Згідно з отриманими даними, рівень HIF-2α у плазмі крові був вищим у пацієнтів із хронічною запальною патологією шлунково-кишкового тракту порівняно з контрольною групою. Серед пацієнтів із зазначеною патологією у хлопчиків рівень HIF-2α був вищим, ніж у дівчаток. ХГД і ГЕРХ характеризувалися вищим рівнем HIF-2α у плазмі крові, ніж виразкова хвороба шлунка і дванадцятипалої кишки. Рівень HIF-2α не залежав від віку пацієнтів або наявності інфекції *Helicobacter pylori.*

Ключові слова: шлунково-кишковий тракт, HIF-2α, підлітки, хронічний гастродуоденіт, гастроезофагеальна рефлюксна хвороба.

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