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THE ROLE OF INFLAMMATORY RESPONSE AND ANTIOXIDANT PROTECTION MARKERS IN THE PATHOGENESIS OF ABDOMENALGIA IN PATIENTS WITH CHRONIC PANCREATITIS COMORBID WITH HYPERTENSIVE DISEASE

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Modern medicine is gradually losing the mononosological nature of the disease course, and the trend towards polymorbidity is becoming more and more noticeable. The combination of multi-organ changes has a negative effect on the clinical course of all diseases. A frequent common combination in clinical practice is a combination of chronic pancreatitis and hypertension. The purpose of our study was to determine the effect of laboratory parameters of the antioxidant defense system and markers of inflammatory response on the intensity of abdomenalgia in patients with chronic pancreatitis comorbid with hypertension disease. The results of our study are complementary to the fundamental knowledge on the pathogenesis of combined pathology, namely the element of a subjective parameter formation - abdomenalgia. It has been proven that leukocytes, ESR, α1-antitrypsin, glutathione peroxidase, selenium and zinc are key parameters in the formation of abdominal pain. Based on these laboratory parameters activity level, it is recommended to expand the basic set of medical measures in order to accelerate removing of abdomenalgia.

Key words: chronic pancreatitis, hypertension, abdomenalgia, markers of inflammation, antioxidants.

The work is a fragment of the research project "Polymorbid pathology in diseases of the digestive system, features of pathogenesis, possibility of correction", state registration No. 0118U004365.

One of the major problems in modern medicine is comorbid (multimorbid) conditions, which occupy a leading place in the daily practice of clinicians. This is due to many reasons, because the combination of two or more diseases mutually complicate the course of each other, significantly impair the quality of patients' life, complicate the diagnostic process and require using a whole arsenal of drugs, which are often incompatible with each other [1].

Therapeutic nosologies, which can often be combined, include chronic pancreatitis (CP) and hypertension disease (HD) [2]. At first sight, these diseases are pathogenically difficult to associate with each other. However, a number of researchers point out to the presence of common etiopathogenetic links in the formation of combined pathology [2, 6, 7]. One of them is the presence of a systemic inflammatory response that causes the continuity of pathological changes and promotes disease progression [9]. Equally important is the role of oxidative stress, which, according to current scientific claims, is considered a significant pathophysiological mechanism for many diseases formation. Intensification of lipid peroxidation processes under the conditions of imbalance or insufficiency of the antioxidant system is the basis for excess free radicals accumulation with subsequent damage to the vascular wall and deepening ischemic changes in organs and tissues [3].

In our opinion, a detailed study of the abdominal pain syndrome in patients with a combination of CP and HD is interesting. This is primarily due to the fact that abdominal pain is a leading complaint in almost all patients with chronic pancreatic disease (CP). The mechanisms of the abdomenalgia syndrome formation are diverse, however, the main role belongs to the focus of inflammation present in the parenchyma of the pancreas gland [4]. Activation and persistence of the inflammatory response certainly disrupts the equilibrium in the pro- and antioxidant (AO) system. With the imbalance of the antioxidant system, the most favorable conditions for triggering oxidative stress are formed, which in the long run significantly worsens the course of the disease and determines the severity of the clinical picture.

The purpose of the study was to identify key indices of inflammatory response and antioxidant defense system that are leading in the abdominal pain onset in patients with comorbid pathology (chronic pancreatitis and hypertension disease).

Materials and methods. In order to achieve this purpose, we have performed a comprehensive general clinical and laboratory examination of 102 patients with stage II CP and HD who were hospitalized at Khust Central District Hospital within 2017-2018. The diagnosis of CP was based on the positions of "Unified Clinical Protocol of Primary, Secondary (Specialized) Medical Assistance and Medical Rehabilitation. Chronic pancreatitis ", approved by the MOH of Ukraine's order No. 638 of 10.09.2014;

HD – on the requirements of the "Unified Clinical Protocol for Primary, Emergency and Secondary (Specialized) Medical Care. Hypertension", approved by the MOH of Ukraine's order No. 384 of 24.05.2012, clinical recommendations for hypertension by the European Society of Hypertension (ESH) and the European Society of Cardiologists (ESC) (2013 and 2018).

We divided all patients into two groups. The basis for the division was the assessment of abdominal pain on a ten-point visual-analogue scale of pain (J. J. Bonica, 1990). Group I (n = 17) included patients who indicated pain intensity of five or less points; group II (n = 85) included patients with pain intensity of six or more points. Duration of CP in patients of group I was 5.71±2.37 years, HD - 5.24±2.01 years, in group II - 6.14±3.04 years and 5.95±2.79 years, respectively. The gender distribution of the study groups indicated a predominance of males in group I (n = 10 vs. n = 7) and female dominance in group II (n = 50 versus n = 35).

For the study of the pancreas exocrine secretion function, determination of the fecal elastase-1 (FE-1) level was performed by ELISA test (Pancreatic Elastase 1 Stool Test).

In order to diagnose the activity of inflammatory response markers in the examined patients, we measured the content of the following parameters in the patients' blood: leukocytes, erythrocyte sedimentation rate (ESR), albumin, interleukin-4 (IL-4) and interleukin-6 (IL-6) (by means of enzyme-linked immunosorbent assay), fibrinogen (R.A. Rutberg's gravimetric method), α1-antitrypsin (α1-AT) (immunoturbidimetric method), and cortisol (enzyme immunoassay).

Out of a wide arsenal of known representatives of the antioxidant system, we determined the levels of such antioxidants (AO) in the blood of our patients with CP in combination with HD: glutathione peroxidase (GPO) by enzyme immunoassay, transferrin by immunoturbidimetric method, selenium (Se) by spectrofluorometry and zinc (Zn) by means of atomic absorption spectroscopy.

All studies were carried out in compliance with the main provisions of the World Health Association Declaration on Ethical Principles for Human Research (1964-2000), GCP (1996), the Council of Europe Convention on Human Rights and Biomedicine of 04.04.1997.

Data Processing. Statistical analysis of the study results was performed with a personal computer using Microsoft Office Excel and Statistica for Windows 10.0 software packages. The difference between the data was considered significant at $p < 0.05$. The statistical significance (p) of the mean values in the studied samples with normal distribution was assessed using the Student's test and, in the absence of signs of normal distribution, the Wilcoxon test.

Results of the study and their discussion. In all of our patients, the syndrome of abdominal pain was dominant, but not the only one in the clinical course. Thus, in addition to abdomenalgia, dyspeptic syndrome, exocrine secretion failure syndrome, asthenovegetative and hypertension syndromes were recorded.

Concerning the level of blood pressure, it met the criteria of 1-2 degree arterial hypertension (in group I – 153.98±10.18 / 95.27±9.25 mm Hg, in group II of patients – 155.35±9.49 / 93.53±9.17 mm Hg) and did not differ significantly between groups (p (SAT) = 0.59; p (DAT) = 0.48).

It is well known that in the presence of chronic pancreatitis, special attention of clinicians is focused on the detection of exocrine hypofunction of the pancreas and the possibilities of its correction. In patients of our study groups, the exocrine secretion failure of the pancreas fluctuated on the border of moderate and mild degree according to the results of the analysis on the elastase-1 content in feces without statistically significant difference between the groups (in patients of group I - 158.94±21.86 mcg / g, in the surveyed of group II - 157.60±16.37 µg / g (p = 0.77), fig. 1).

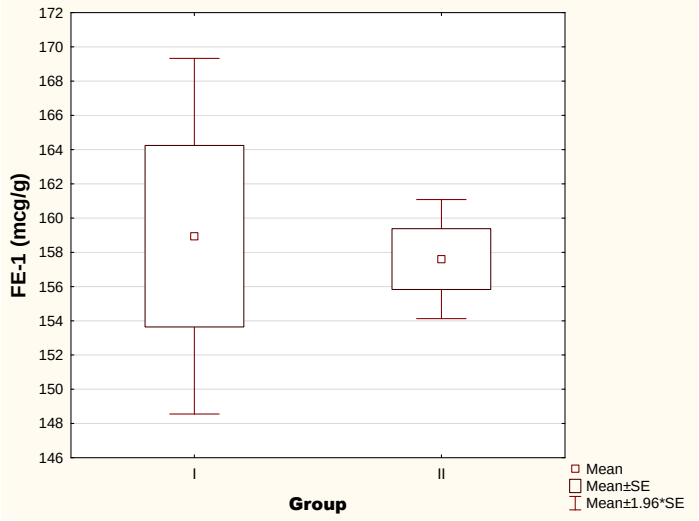

Fig. 1. Elastase-1 content in feces

Despite the lack of a significant difference between the results obtained, it is important to analyze the range of FE-1 content variations in patients of group I, whose subjective sensation of pain in the abdomen was less intense. In our opinion, this is primarily due to the fact that in patients with mild exocrine secretion failure, the focus of inflammatory acinocytes is lower, therefore, the intensity of abdomenalgia is lower. In addition, in patients with more pronounced exocrine secretion failure, a lower intensity of abdomenalgia is caused by more widespread fibrosis of the parenchymal organ tissue than in patients with mild exocrine dysfunction.

The next step in our study was to determine the levels of the laboratory parameters in the inflammatory response. In general, pain is one of the five classic signs of inflammation and its occurrence is the result of the direct or indirect action of activators, mediators of the inflammatory process on the sensitive nerve endings. The assessment of indices that reproduce the of the inflammatory response activity in the groups of patients examined by us represents the following features (table 1).

Table 1

Activity of inflammatory markers in the blood of patients with CP combined with HD

Indices	Group 1 (n=17)	Group II (n=85)	Difference reliability (p)
Leukocytes 4.0-9.0, g/L	6.10±1.91	9.36±2.69	$0.7*10^{-5}$
ESR 2-15, mm/hour	6.06±2.79	10.53±5.54	0.002
Albumin 38-51, g/L	40.29±3.41	39.25±2.71	0.17
Fibrinogen 1.8-3.5, g/L	2.83±0.43	2.95±0.56	0.39
IL-4 0-4, pg/ml	2.01±0.16	1.91±0.22	0.11
IL-6 0-10, pg/ml	11.71±1.50	11.99±1.62	0.52
α1- antitrypsin 0.9-2.0, g/L	1.41±0.16	1.54±0.25	0.04
Cortisol in the morning 190-690, nmol/L	898.82±250.34	975.48±222.65	0.21

Visual data indicate a pronounced activity of inflammatory response in patients of group II, whose intensity of abdominal pain was higher than in patients of group I. This was confirmed by the presence of statistically significant differences between the groups in terms of: ESR (p = 0.002), leukocyte level (p = 0.7 * 10-5) and α1-AT (p = 0.04). Therefore, we can assume that these laboratory markers of inflammation are active participants in the formation of pain. Increased leukocyte levels and acceleration of ESR are a direct consequence of the activation and synthesis of a number of inflammatory mediators. As for the involvement of α1-AT in the cascade of the inflammatory response, its role is also unambiguous, as it is one of the most active inhibitors of lysosomal proteases released from granules of activated and damaged polymorphonuclear leukocytes, as well as a regulator of leukocyte migration and leukocyte balance. Although the levels of the interleukins under study did not manage to achieve cross-group differences, however, in Group I, there was a tendency for more active involvement of anti-inflammatory IL-4 and lower concentration of pro-inflammatory IL-6, which also explains the lower severity of abdomenalgia.

Harmony and consistency in the system of prooxidants and AO provides homeostasis of the body. In the presence of chronic inflammation and in conditions of comorbidity, the balance of this system is broken. This may be due to both the excessive amount of oxidants and the insufficient capacity of the AO. In our study, we tried to determine the activity of the antioxidant system in patients with CP associated with HD, depending on the severity of abdominal pain. The results obtained are summarized in table 2.

Table 2

Level of antioxidants in the blood of patients with a combination of CP and HD

Indices	Group I (n=17)	Group II (n=85)	Difference reliability (p)
Glutathione peroxidase 12.5-200, ng/ml	51.46±10.84	43.97±10.58	0.009
Selenium 23-190, µg/L	72.53±15.59	61.91±18.58	0.03
Zinc 543-1130, µg/L	874.18±222.06	714.42±188.67	0.003
Transferrin 2.0-3.6, g/L	2.34±0.29	2.33±0.24	0.89

The results indicate statistically significant higher glutathione peroxidase activity in patients of group I. The involvement of transferrin in the elimination of abusive stress in patients of the both groups was almost the same, so we cannot speak about the true significance of this AO in the development of pain syndrom. Let us dwell on the analysis of the Se and Zn effect on the severity of abdomenalgia. One of the properties of selenium, as AO, is its ability to accumulate in the focus of ischemia, which necessarily arises under the conditions of oxidative stress, and to produce active membranous resistance. The antioxidant property of zinc is related to its ability to inhibit the formation of H_2O_2 and hydroxyl radicals.

Naturally, the most informative way is to determine the concentration of trace elements in the tissue of the pancreas, but such research is invasive, which limits the possibility of its use in daily practice. Instead, determining the level of essential trace elements studied in the blood is a direct reproducing the mean value of their recent entry into the human body with food. In addition, the pancreas belongs to a

group of parenchymal organs that have the ability to deposit both Se and Zn. Both microelements under study are structural components of potent AO of enzymatic origin (Se - glutathione peroxidase, Zn - superoxide dismutase). Due to the higher content of Se in the blood of group I patients in comparison with the results obtained in patients of group II, the level of GPO is also naturally higher. This is due to the fact that four Se atoms are required for the synthesis of one GPO molecule. The role of GPO in multifactor protection of the whole body from the products of free radical peroxidation is leading. And this is confirmed by a number of scientific studies.

In our opinion, the lower concentration of Se, Zn, GPO in the blood of patients of group II, unlike the examined group I, causes insufficient ability of the antioxidant protection system to suppress oxidative stress. Therefore, due to insufficient intensity regulation of radical formation, patients will subjectively have a more pronounced level of abdomenalgia, which will significantly impair the quality of their life and contribute to the deepening of pathological changes.

Our statements clearly correlate with the scientific view of prof. L.S. Babinets, who also indicates the dominance of deep deficiency of antioxidant system in patients with comorbid pathology (CP and osteoarthritis) [1]. A study by K. Venardos et al, performed in rats, demonstrated that Se deficiency contributes to damage of the endothelium of the vascular wall and myocardium by enhancing protein and lipid peroxidation [8]. B. N. Girish et al assessed the content of zinc in patients with CP and studied their relationship with exocrine and endocrine failure of pancreas. The study involved 101 patients with CP and 113 healthy controls. The mean Zn level was significantly lower in patients with CP compared to the group of healthy persons [5]. According to prof. T.M. Khristich for the treatment of abdominal pain in CP it is promising to use antioxidants that are able to actively inhibit oxidation, block catalysts of free radical oxidation, activate antiradical enzymes of the protection system [4].

Thus, as a result of the study, we have managed to determine which indices of inflammatory response and AO system most actively affect the pain intensity in patients with a combination of CP and HD, which will permit to apply comprehensive pathogenetically justified therapy with the possibility of reducing the abdominal pain intensity in clinical practice.

Conclusions

1. Subjective perception of abdomenalgia in chronic pancreatic injury depends on the features of the inflammatory response course and homeostasis of the antioxidant system.

2. Among laboratory parameters that identify the of the inflammatory response activity, leukocytes, erythrocyte sedimentation rate, and α1-antitrypsin play a leading role in the severity of pain.

3. Glutathione peroxidase, selenium and zinc are the key laboratory parameters of the antioxidant group that significantly affect the abdominal pain intensity in patients with chronic pancreatitis and hypertension disease.

Prospects of further research are as follows. In order to deepen and improve the knowledge gained during this study, we consider it necessary to further increase the number of patients with comorbid pathology in the study groups and to expand the spectrum of diagnostic search with involvement of more laboratory parameters.

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Реферати

РОЛЬ МАРКЕРІВ ЗАПАЛЬНОЇ ВІДПОВІДІ ТА АНТИОКСИДАНТНОГО ЗАХИСТУ У ПАТОГЕНЕЗІ АБДОМЕНАЛГІЇ У ПАЦІЄНТІВ ІЗ ХРОНІЧНИМ ПАНКРЕАТИТОМ, КОМОРБІДНИМ ІЗ ГІПЕРТОНІЧНОЮ ХВОРОБОЮ

Архій Е.Й., Прилипко Л.Б., Горленко О.М. Москаль О.М.

Сучасна медицина поступово втрачає мононозологічний характер перебігу захворювань, і все помітніше стає тенденція до поліморбідності. Поєднання мультиорганних змін негативно відбивається на клінічному перебігу всіх захворювань. Досить частим поєднанням в практиці клініцистів є поєднання хронічного панкреатита і гіпертонічної хвороби. Мета нашого дослідження полягала у визначенні впливу лабораторних параметрів системи антиоксидантного захисту та маркерів запальної реакції на інтенсивність абдоменалгії у хворих на хронічний панкреатит в поєднанні з гіпертонічною хворобою. Результати нашого дослідження є доповненням фундаментальних знань патогенезу поєднаної патології, а саме елементу формування суб'єктивного параметра - абдоменалгії. Доведено, що лейкоцити, ШОЕ, α1-антитрипсин, глутатионпероксидаза, селен і цинк є ключовими параметрами формування болю в животі. На основі рівня активності зазначених лабораторних параметрів рекомендовано розширювати базовий комплекс медикаментозних заходів з метою прискорення нівелювання абдоменалгії.

Ключові слова: хронічний панкреатит, гіпертонічна хвороба, абдоменалгія, маркери запалення, антиоксиданти.

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РОЛЬ МАРКЕРОВ ВОСПАЛИТЕЛЬНОГО ОТВЕТА И АНТИОКСИДАНТНОЙ ЗАЩИТЫ В ПАТОГЕНЕЗЕ АБДОМЕНАЛГИИ В ПАЦИЕНТОВ С ХРОНИЧЕСКИМ ПАНРЕАТИТОМ, КОМОРБИДНЫМ С ГИПЕРТОНИЧЕСКОЙ БОЛЕЗНЬЮ

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Современная медицина постепенно теряет мононозологический характер течения заболеваний, и все заметнее становится тенденция к полиморбидности. Сочетание мультиорганных изменений негативно отражается на клиническом течении всех заболеваний. Достаточно частым сочетанием в практике клиницистов является сочетание хронического панкретатита и гипертонической болезни. Цель нашего исследования состояла в определении влияния лабораторных параметров системы антиоксидантной защиты и маркеров воспалительной реакции на интенсивность абдоменалгии у больных хроническим панкреатитом в сочетании с гипертонической болезнью. Результаты нашего исследования являются дополнением фундаментальных знаний патогенеза сочетанной патологии, а именно элемента формирования субъективного параметра – абдоменалгии. Доказано, что лейкоциты, СОЭ, α1-антитрипсин, глутатионпероксидаза, селен и цинк являются ключевыми параметрами формирования боли в животе. На основе уровня активности указанных лабораторных параметров рекомендовано расширять базовый комплекс медикаментозных мероприятий с целью ускорения нивелирования абдоменалгии.

Ключевые слова: хронический панкреатит, гипертоническая болезнь, абдоменалгия, маркеры воспаления, антиоксиданты.

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EFFICACY OF PHARMACOLOGICAL CORRECTION OF MAGNESIUM DEFICIENCY IN PATIENTS WITH ARTERIAL HYPERTENSION AND TYPE 2 DIABETES

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The purpose of the study was to assess the efficacy of therapy with addition of magnesium orotate (MO) in patients (pts) with AH and type 2 DM with hypomagnesemia. The total of 62 pts with AH and DM with hypomagnesemia were examined. After registration of the baseline data, baseline therapy was prescribed to all pts, 32 of them (group 1) obtained an additional MO for 8 weeks and 28 pts were included in the comparison group. It was found that antihypertensive efficacy had been more significant in group 1. In group 1 showed significant positive changes in lipid and carbohydrate metabolism and along with an improvement in the quality of life. Thus, an addition of MO in the complex therapy of pts with AH and DM with hypomagnesemia increases the efficacy of antihypertensive therapy, positively affects glucometabolic parameters and the quality of life in this category of patients.

Keywords: magnesium deficiency, arterial hypertension, type 2 diabetes mellitus, daily blood pressure monitoring, treatment.

The work is a fragment of the research project "Development of methods for early diagnosis and drug prevention of fibrosis processes in patients with comorbid pathology (hypertension and type 2 diabetes mellitus) based on the assessment of cardiohemodynamics and renal function", state registration No. 0120U102062.

Significant data have been collected on high prevalence of arterial hypertension (AH) in patients with type 2 diabetes mellitus (type 2 DM) [2]. The combination of hypertension and type 2 DM leads to the mutual influence on the course of the diseases, nature and severity of complications, often aggravates diagnosis, determines a specific choice of drug therapy. It has been demonstrated that the combination of AH and type 2 DM is associated with earlier disability of this cohort of patients, increased risk of development of cardiovascular complications and higher mortality rate compared to the whole population [6].