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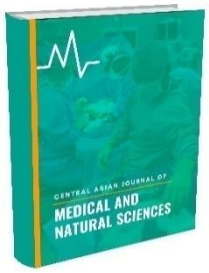

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Assessment of Biochemical Parameters in Patients with Non-Carious Lesions Associated with the Disease of the Hepatobiliary System

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Abstract: The wide prevalence of hepatobiliary pathology (GBP) (from 3 to 15 per 1000 examined), the steady increase in morbidity, disability and mortality determines the relevance of this problem. In the pathogenesis of diseases of the hepatobiliary system and its progression, violation of intrahepatic hemodynamics is of great importance, which may be associated with damage to the endothelial lining of hepatic sinusoids and endothelial dysfunction (ED). The processes of progression of liver damage, in particular, neoangiogenesis and fibrosis in the liver are also closely related to the functional viability of the endothelium. It is relevant to study the pathogenesis of liver damage in non-carious diseases of the hard tissues of teeth and to develop methods for assessing the severity of combined pathology.

The purpose of the study. To study some biochemical parameters in patients with non-carious lesions associated with the disease of the hepatobiliary system.

Material and methods of research.

68 patients with non-carious lesion of the hepatobiliary system associated with the disease were examined. Among the examined persons, 40 (58.8%) women and 28 (41.2%) men, the average age was 48.3±18.6 years and 12 persons with non-carious lesions without concomitant pathology. The control group consisted of 10 healthy individuals comparable in gender and age.

The criteria for inclusion in the study were an increase in serum levels of alkaline phosphatase, GGTP and functional studies, where focal liver changes and biliary hypertension were excluded, the presence and degree of hepatomegaly and portal hypertension were assessed.

In the blood serum, the activity of alkaline phosphatase and GGTP in the blood serum was determined using a biochemical analyzer "Mindray" using reagents from "HUMAN" companies. The content of endothelin-1 (endothelin-1, Et-1), the activity of von Willebrand factor (vWF) was carried out on an enzyme immunoassay "Mindray MR-96 A". The number of DECs was calculated using the Hladovec method (1978).

Statistical processing of the results was carried out using computer programs Statistica 6.0 and Biostatistics 4.03. To establish the relationship and measure the closeness of the relationship between the parameters, correlation analysis was used with the calculation of the Pearson correlation coefficient (r). Statistical analysis of quantitative features was carried out using the Student's criterion. The values of $p<0.05$ were considered highly significant and reliable.

Results and discussion.

The analysis of the results of the studies presented in Table 1 showed that the functional state of the endothelium in non-carious lesions of the teeth associated with pathology of the hepatobiliary system significantly differed from similar parameters in practically healthy individuals with intact dentitions.

A significant increase in the concentration of endothelin-1 in combined pathology by 3 times indicates an imbalance of compounds affecting vascular tone. An increase in the content of desquamated endothelial cells in the blood (DEC) in patients with associated pathology of the hepatobiliary system indicates damage to the endothelium, which, combined with an increase in the activity of Willebrand factor in combined pathology, indicates stimulation of neoangiogenesis and increased thrombogenicity of the vascular endothelium.

Table 1. Indicators of endotoxemia and enzyme systems in the blood plasma of patients with non-carious lesions of the hard tissues of the teeth associated with the disease of the hepatobiliary system

Indicators	Healthy faces (n=10)	associated with the disease of the GB system n=68	without pathology of the GB system n=12
Endothelin -1 fmol/ml	0,24 ± 0,03	0,71 ± 0,13 *	0,37 ± 0,02*
The Willebrand Factor %	78,54 ± 6,29	112,10 ± 11,34*	89,11 ± 7,43
Desquamated endothelial cells 104/l	2,24 ± 0,21	8,69 ± 0,76*	3,51 ± 0,33*

Note: *- the significance of the differences is $P<0.05$

Involvement of vascular endothelial cells in destructive processes in NP associated with GB diseases is an integral and one of the key components in the development of vasculopathy. We assume that biologically active molecules involved in the activation and damage of vascular endothelial cells may be indicators and potential biomarkers of these processes. Among such biomarkers are cytokines, vascular endothelial growth factors, fibroblasts, platelets and glycoproteins, which are involved in the initiation and regulation of inflammation and neoangiogenesis. It seems promising to further study the complex of biomarkers in patients with a combined form of the disease.

According to the results of this study, the levels of these biomarkers are not related to the gender, age of patients and etiology of the underlying disease, but the level of individual biomarkers correlates with laboratory indicators of the risk of vascular diseases: an increase in the concentration of cholesterol, fibrinogen, a decrease in the content of high-density lipoproteins, etc.

It has been established that the development of pathology of hepatobiliary pathology is accompanied by a significant increase in complaints: weakness, bitterness in the mouth, jaundice, itching, heaviness or pain in the right hypochondrium. In the pathology of GBS, the level of all components of bile, and primarily bile acids, increases in the blood serum. An increase in the content of serum bile acids makes it possible to assess the interaction between their absorption in the intestine and capture in the liver (Sherlock Sh., Dooley J. 1999). This is due to a lesion of the parenchyma, the presence of portocaval shunts and a violation of the removal of bile acids (LC) from the blood of the portal vein. In addition, the LC is fed back into the blood from damaged hepatocytes. It is obvious that an increase in the

concentration of serum LC indicates hepatobiliary disease. It has been established that LC causes apoptosis and cell necrosis through damage to mitochondria. Thus, it is the mitochondria that are the main target of the toxic effects of bile acids.

In everyday practice, routine laboratory indicators of the presence of intrahepatic cholestasis are primarily an increase in the activity of enzymes: aspartate amintransferase (AST), alkaline phosphatase (alkaline phosphatase), gamma-glutamyltranspeptidase (GGTP), which we observed in our studies (Table 2). The main reason for the increase in the hepatic fraction of alkaline phosphatase is an increased synthesis of the enzyme in the liver due to a block of intestinal—hepatic circulation, as well as a delay in the release of the enzyme into bile. The increase in the activity of alkaline phosphatase reflects an increase in its synthesis by hepatocytes and epithelial cells of the biliary tract and to a lesser extent — the reverse flow of the enzyme into the blood due to obstruction of the biliary tract. LC, on the one hand, induce the synthesis of alkaline phosphatase, and on the other — contribute to its cleavage from cell membranes.

Gamma-glutamyltranspeptidase is an enzyme that catalyzes the transition of the glutamyl group from gamma-glutamyl peptides to alpha-amino acids and other peptides. The low-molecular component of the enzyme is localized in the cytoplasm, and the high-molecular component is closely related to the membranes of the microsomal fraction of the hepatocyte and the membranes of the smallest bile tubules. Therefore, the enzyme is sensitive to alcohol and drug intoxication, as well as to pressure fluctuations in the bile ducts. The activity of the enzyme increases due to the intensification of its synthesis under the influence of LC. The main clinical significance of GGTP research is the diagnosis of cholestatic conditions, especially in combination with other enzymes.

Table 2. Indicators of the activity of enzyme systems and the content of bile acids in the blood serum of patients with associated GBS disease

Indicators	Healthy faces (n=10)	Patients associated with GBS pathology n=68	Patients without pathology of GBS n=12
Bile Acid Content (mmol/ml)	13,4+3,01	41,36+4,02*	18,5+3,45
Aspartate Aminotransferase (IU/L)	16,11+0,57	64,89+4,18*	27,08+2,11*
Gamma glutamyltransferase (IU/L)	54,27+3,93	203,93+8,92*	73,41+5,92
Alkaline phosphatase (IU/L)	56,83+2,71	207,94+9,94*	76,93+5,03*

Note: * -the reliability of the differences is $P < 0.05$

The analysis of the obtained research results showed that the activity of the determined serum enzymes in the combined form of the disease (ALP and GGTP) significantly increases with the increase of cholemia (Table 2). As can be seen from the presented research results, the examined patients associated with the pathology of GBS showed an increase in the level of bile acids in the blood serum by 3 times when compared with a group of healthy individuals. With an increase in the concentration of serum LC, cholesterol levels (HC) significantly increase to 6-8 mmol / l (at a rate of 5.2 mmol/ l).

Thus, serum levels of enzymes, bile acids and HC are criteria for the pathology of GBS in patients. We hope that the revealed research results are intended to help the practitioner to differentially assess the condition of a patient with non-carious disorders in order to improve his treatment and improve the prognosis.

It should be noted that impaired absorption of vitamin D and calcium in the intestine due to a deficiency of LC may be one of the causes of osteoporosis and osteopenia, one of the mechanisms of which is a violation of the phosphorus-calcium imbalance. It should be borne in mind that the violations of phosphorus-calcium metabolism revealed in our work against the background of an increase in the content of bile acids and the activity of marker enzymes in the blood serum had no clinical manifestations at the time of examination of the patient. This indicates that patients, regardless of the severity and etiology of the underlying disease, require increased attention, a full-fledged comprehensive examination and treatment aimed at reducing the severity of cholestasis to reduce the risk of occurrence and reduce the severity of complications.

Cytokine-mediated liver damage against the background of a systemic inflammatory process is accompanied by the release of fragments of hepatocyte membranes, enzymes and various polypeptides into the bloodstream. At the same time, the size of polypeptides and oligopeptides, medium-weight molecules are different, which are captured at different wavelengths on a spectrophotometer. Otherwise, they are called endogenous intoxication products or medium-weight molecules.

As can be seen from the presented research results, in the patients we examined with non-carious lesions of the hard tissues of the teeth associated with the disease of the hepatobiliary system, a significant increase in the average molecular peptides E254 was noted by 1.8 times when compared with a group of healthy individuals and by 1.5 times when compared with a group of patients without liver pathology. The average molecular weight peptides detected at the wavelength of E280 were also increased in patients with the combined form of the disease by 1.6 times when compared with a group of healthy individuals, which indicates endogenous intoxication and an increase in blood plasma of peptides of various weights, which is one of the causes of cytokine-mediated damage to the hepatobiliary system of the liver. Liver damage caused by activation of TNF-R-1 receptors observed as a result of endotoxemia leads to activation of lysosomal enzymes of hepatocytes and premature death of liver mitochondria. This condition is detected by the release of the mitochondrial enzyme - aspartate aminotransferase into the bloodstream.

As can be seen from the results of the studies presented in the table, the activity of aspartate aminotransferase significantly increases in patients with GBS associated with the disease by an average of 4 times when compared with healthy individuals. The involvement of hepatocyte mitochondria in the pathological process is also accompanied by an increase in the activity of the mitochondrial enzyme-glutamate dehydrogenase in the blood of the subjects. The activity of the latter exceeded the baseline level by an average of 2.3 times ($P<0.05$).

Table 3. Analysis of indicators of endotoxemia, enzyme systems and maleic anhydride in blood plasma in the examined patients

Indicators	Healthy individuals (n=10)	Patients associated with GB system disease n=68	Patients without GB system pathology n=12
Medium Molecular weight Peptides E254 (usl.units)	0,21+0,01	0,38+0,01*	0,25+0,01
Medium molecular weight peptides E280 (usl.units)	0,30+0,01	0,49+0,03*	0,36+0,02
Aspartate Aminotransferase (IU/L)	16,11+0,57	64,89+4,18*	27,08+2,11*
Gamma glutamyltransferase (IU/L)	54,27+3,93	203,93+8,92*	73,41+5,92
Alkaline phosphatase (IU/L)	56,83+2,71	207,94+9,94*	76,93+5,03*

Glutamate Dehydrogenase (mmol/hr/L)	15,42+0,91	35,18+3,21*	19,65+1,67*
Malondialdehyde (nmol/ml)	3,74+0,21	4,91+0,13*	4,04+0,21

Note: *- the significance of the differences is P<0.05

Endogenous intoxication and activation of the cytokine system in combined pathology is accompanied not only by damage to liver hepatocytes, but also affects the bile-forming function of the liver, i.e. synthesis and secretion are disrupted, as well as bile outflow at the level of the bile tubules due to the death of bile capillary cells and the release of enzymes into the blood plasma. To assess this condition, we studied the activity of the enzyme gammaglutamyltransferase and alkaline phosphatase. As can be seen from the obtained research results, in patients with non-carious lesion, combined with GBS disease, there was a significant increase in the activity of gammaglutamyltransferase by an average of 3.8 times (P<0.0.5).

A similar dynamics is observed with respect to the enzyme alkaline phosphatase, the activity of which in the blood plasma of the examined individuals is increased by 3.7 times when compared with healthy individuals. The reason for this is the location of the enzymes studied close to each other in the epithelial membrane of the bile ducts. Therefore, the observed destruction of the membranes of the bile ducts under the influence of endogenous toxins contribute to the release of membrane enzymes GGT and alkaline phosphatase into the bloodstream simultaneously and almost equally.

Thus, in patients with non-carious lesions of the hard tissues of the teeth associated with the disease of the hepatobiliary system, an increase in endogenous toxins in the blood was noted, which leads to a violation of the bile-forming function of the liver. Endogenous intoxication and oxidative stress in the examined patients is accompanied by an increase in the activity of markers of the hepatobiliary system, thereby indicating the depth of damage to hepatocytes of the liver.

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