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COMPLICATIONS OF ALCOHOLIC LIVER DISEASE AND DIAGNOSTIC MARKERS

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Alcoholism is one of the leading diseases affecting people's health and immunity worldwide. Nearly 30 thousand people in the USA die from chronic liver damage. The liver is the central organ in the metabolism of alcohol. Alcohol is primarily a hepatotoxic agent. Hepatotoxicity of alcohol is clinically manifested by the development of alcoholic fatty liver, alcoholic hepatitis and alcoholic cirrhosis. It is characterized by appropriate symptomatology, depending on the degree of liver damage. Excessive use of alcohol for a long period of time, along with malnutrition, genetic and ethnic predisposition, leads to alcoholic cirrhosis and the development of its complications. Portal hypertension damages other organs and organ systems, causing hepatopulmonary syndrome, hepatorenal syndrome, hepatic encephalopathy, spontaneous bacterial peritonitis, etc.

For these reasons, alcoholism reduction is given priority, as well as reduction of morbidity and mortality of people with alcoholic chronic liver damage. Therefore, early diagnosis of alcohol abuse is necessary, as well as timely diagnosis of different degrees of alcoholic liver damage.

The diagnosis of chronic alcoholic liver damage is set on the basis of confirmed data of alcohol consumption; liver function test (serum markers aminotransferase, gamma-glutamyl transferase, prothrombin time, serum bilirubin and albumin level); serum markers of liver fibrosis. Fibrosis markers are directly involved in sedimentation and dissolution of extracellular matrix, i.e. in the process of fibrogenesis and fibrinolysis of liver tissues. They include markers and enzymes of metabolism, as well as cytokines and chemokines. *Acta Medica Medianae 2011;50(4):55-61.*

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Introduction

Alcoholism is the third most common cause of death, after cardiovascular and oncologic diseases. According to epidemiological data, the number of alcoholics encompasses about 5% of people in general population, i.e. 10% of adult males. The largest number of alcoholics is in the most productive period of live, from thirty to the fifty years of age.

Chronic alcohol consumption causes liver damage. Nearly 30 thousand people die of chronic liver damage every year in the USA (1, 2). Liver damage may appear in the form of alcoholic fatty infiltration, alcoholic hepatitis and alcoholic cirrhosis. Alcoholic fatty liver and alcoholic hepatitis are reversible changes after cessation of alcohol use, whereas alcoholic cirrhosis is an irreversible liver damage. The degree of liver damage depends on the dose, or alcohol concentration, as well as the length of alcohol use. Liver damage depends on gender and ethnicity, genetic predisposition and nutrition (3, 4).

Fatty liver develops in about 20% of severe alcoholics. In many cases there are no clinical symptoms, except liver enlargement (hepatomegaly). In more than 60% of cases there are no predispositions for serious liver damage if a person abstains from alcohol use.

Alcoholic hepatitis develops with long and continuous alcohol use. Clinical signs of alcoholic hepatitis include: liver enlargement, nausea, vomiting, jaundice and stomach ache. In abstinence, it represents an acute form of liver damage. In biochemical terms, in about 10-30% of cases, it encompasses a spectrum of asymptomatic disorders. If excessive alcohol use is continued, hepatitis will develop into cirrhosis in about 40% of cases. Mortality in severe liver damage is about 50% (5-7).

Alcoholic cirrhosis of the liver represents a terminal condition of a serious liver damage. It is present in 15-20% of case of alcoholic liver damage. Liver cirrhosis is characterized by diffuse fibrosis of the liver connective tissue, which causes deterioration of its structure, degeneration and destruction of hepatocytes. Liver

cirrhosis is also characterized by inflammation process, associated with the release of cytokines and inflammation mediators, as well as the activation of lymphocytes and macrophages. They stimulate the creation of fibroblasts and connective-collagenous tissue. It is a progressive disease which leads to many complications associated with other organs and systems. The final complication of liver cirrhosis is portal hypertension. It is characterized by increased pressure in the liver sinuses, development of varices in the esophagus and stomach, splenomegaly, spider angioma, abdominal collateral veins and liquid buildup in peritoneal cavity (8). Portal hypertension further causes disorders in arteriovenous circulation in the lungs, hypoxemia, i.e. hepatopulmonary syndrome with the development of cyanosis. Hepatic encephalopathy is a disorder of the brain function, which develops because the liver is unable to remove toxic materials, such as ammonia from the blood.

Hepatorenal syndrome is a disorder in the function of the kidneys. It is characterized by reduced renal circulation, retention of sodium and water, as well as the development of azotemia. Spontaneous bacterial peritonitis is the most significant complication of cirrhosis with ascites. It is characterized by fever, abdominal pain and leukocytosis. Hematologic disorders in cirrhosis include leukopenia, thrombocytopenia, anemia, coagulopathy and hemosiderosis. Endocrine complications in liver cirrhosis include gynecomastia, testicular atrophy, feminism, sexual impotence in men, whereas infertility and amenorrhea develop in women (9-13).

Hepatocellular liver carcinoma is a serious, late complication of chronic liver disease. In the majority of cases it develops in alcoholic liver cirrhosis. Hepatocellular carcinoma develops in 10-15% of patients with alcoholic cirrhosis. It is the fifth most frequent malignant disease in the world. In about 90% of cases, in patients with cirrhosis who stop drinking, survival is around 5 years, whereas in 70% of cases, in patients who do not stop drinking, survival is less than 5 years. In patients with cirrhosis and developed ascites, the survival rate is higher if they stop drinking, compared to patients who do not stop drinking (14).

General diagnostic markers

The diagnosis of chronic alcoholic liver damage is established by noninvasive and invasive methods. Synthetic liver function test is a noninvasive method. This test includes the determination of serum marker activity (transaminases, glutamyltranserases, concentration of albumin and total protein) and determination of serum bilirubin and prothrombin time. SVS test can confirm the symptoms of liver damage as well as anemia. It is assumed that alcohol is the cause of liver damage in patients whose alcohol consumption is chronic and excessive. The dose for men is more than 60 g a day, while for women it is 40 g a day.

Aminotransaminases. In the serum of healthy people the AST/ALT ratio is less than 1. In liver parencyma damage caused by alcohol, transaminases activity in serum is moderately increased. In alcoholic hepatitis the AST/ALT ratio is higher than 2 because Alt activity is reduced. AST is a specific marker of alcoholic liver damage and an increase in its activity is more persistent in serum. However, in the progression of chronic hepatitis with significant hepatocyte necrosis, ALT activity is increased by 5-6 times. AST activity increases by 10-20 times above normal (15).

Gamma glutamyl transferase (γ-GT) is the most important enzyme in the diagnosis of alcoholic liver damage. A quick increase of γ-GT in serum is characteristic in alcoholics with alcoholic hepatitis in acute stage of liver damage. In this stage, increase in ALT and glutamate dehydrogenase is slower.

In the early stage of liver damage, the increase in γ-GT in serum is the only sign of liver damage. Activity of γ-GT is higher due to increased metabolism of ethanol which is done by this enzyme, as well as because of cholestasis which develops as a consequence of taking other narcotics or medicines.

In chronic alcohol consumers who do not have serious liver damage, the values of γ-GT in serum are 2 to 3 times higher. However, in chronic alcohol consumers with liver damage the values of γ-GT in serum are 10 to 20 times higher (16).

Serum albumin can be low, which is usually a consequence of malnutrition or liver damage with reduced albumin synthesis function.

Prothrombin time (PT) is lengthened in severe liver damage. The reason for this is a coagulation disorder developed due to reduced synthesis of coagulation factors, reduced number of thrombocytes and vitamin K deficit. Reduced number of thrombocytes is caused by hypersplenism, whereas vitamin K deficit is a consequence of cholestasis, digestion disorders and liposoluble vitamin absorption.

Serum bilirubin is an indicator of secretory liver function. In the beginning of the disease, at low degree of damage, conjugated bilirubin is dominant in serum.

Macrocytosis with MCV above 100 is a consequence of direct effects of alcohol on the bone marrow. Malnutrition, which leads to folate deficiency, is also a cause of macrocytic anemia. Thrombocytopenia can be a consequence of either direct toxic effect of alcohol on the bone marrow or splenomegaly. Neutrophile lukocytosis can be present in alcoholic hepatitis and can be an indicator of an infection, primarily of severe pneumonia or severe peritonitis (17, 18).

Diagnostic markers of fibrosis

Alcoholic liver cirrhosis is characterized by changes in serum enzymes present in alcoholic

fatty liver and alcoholic hepatitis, as well as the appearance of specific markers of fibrosis. Fibrosis is an unspecific response to damage which includes synthesis of extracellular matrix (ECM). ECM represents a group of macro-molecules, collagenous and non-collagenous glyco-proteins, growth factor of matrix, glycosamino-glycans, proteoglycans and matrix proteins (19). During the process of fibrinogenesis, both quantitative and qualitative changes take place. Total collagen content in the liver increases 3-10 times. Qualitative changes include increase in filament-forming collagen (type I, III and IV), non-filament-forming collagen (type IV and VI), glycoproteins (fibronectin, laminin, osteonectin, tenascin, von Willebrand factor), protoglycans and glycosaminoglycans (perlecan, decorin, aggrecan, lumican and fibromodulin).

The result is the replacement of low-density matrix by high-density matrix of interstitial type. Metabolism, synthesis and function of hepatocytes, and stellate and endothelial cells are disturbed in the liver parenchyma.

The central leading event in liver pathology is the activation of liver stellate liver cells which leads to liver fibrosis.

Activation of stellate cells includes two steps; initiation of 'preinflammatory phase' and changes such as proliferation, chemotaxis, fibrogenesis, contractility, matrix degradation, loss of retinoid and release of WBC chemokines and cytokines. Fibrosis markers are directly included in sedimentation and dissolution of ECM, i.e.in the process of liver fibrogenesis and fibrolysis (20, 21).

They include the markers and enzymes of the metabolism of matrix sedimentation and dissolution, proliferation of connective tissue, as well as cytokines and chemokines. Every phase of liver fibrosis demands the presence of specific cytokines, chemokines or other biologically active mediators. Fibrosis markers can be classified according to their molecular structure. These are mostly the components of fibrous tissue, various types of collages and their precursors, fibrillary proteins, and enzymes included in the dissolution of connective tissue (22-26). Fibrosis markers are divided into: sedimentation markers in the matrix, matrix dissolution markers and cytokines with chemokines (Table 1).

Markers of disposal in the matrix

Collagen I is a fibril-forming type of collagen which develops by post-translation modification of procollagen I. During collagen synthesis, under the effect of procollagen C and N proteinase enzyme, procollagen undergoes enzymatic changes at carboxyl and amino terminal ends. Peptides are released I serum as procollagen type I carboxyl-terminal peptide and procollagen type III amino-terminal peptide. They are used as a measure of sedimentation in the matrix (26).

Procollagen type I carboxyl-terminal peptide (P I CP) is a fragment obtained by procollagen I breakdown by the effect of peptidase before secretion from fibrocytes. For this reason, the determination of C-terminal peptide procollagen I can be used as a measure of disposal of collagen I. Collagen I with collagen III is the major component of total collagen in fibrous liver. Collagen types I and III are broken down proteolytically. Procollagen type I carboxyl-terminal peptide is significantly increased in cirrhosis and points to liver damage of alcoholic etiology (27).

Procollagen type III amino-terminal peptide (P III NP). Procollagen III is synthesized in firoblasts as biosynthetic precursor of collagen III. N-terminal peptide is obtained at the conversion of procollagen III into collagen III in extracellular space. There is a correlation between the level of this marker and the degree of liver fibrosis in alcoholic liver damage, viral hepatitis and primary biliary cirrhosis (28).

Collagen IV is the major component of basal membranes. It appears in the form of tetramer aggregates. Compared to collagen type I and III which are porteolytically processed, collagen type IV is deposited intact in the extracellular matrix.

Type IV collagen maintains the condition of extracellular matrix. It increases 14 times during fibrogenesis in the liver. It is most often used in practice.

Type IV collagen in serum is in a positive correlation with the degree of liver fibrosis in patients with chronic viral hepatitis and alcoholic liver damage. It is a sensitive indicator of the presence of hemochromatosis in alcoholic cirrhosis. Values above 110 ng/ml indicate phase F2, while values above 130 ng/ml indicate phase F3 cirrhosis (29, 30).

Table 1. Markers of fibrosis

Markers of disposal in the matrix	Collagens	Procollagen type I , III и IV, Type IV collagen
	Glycoproteins and Glycosaminoglycans	Laminin and Hyaluronic acid
Matrix dissolution markers	Enzymes	collagenpeptidase, prolilhydroxylase, monoamineoxidase, lizilhydroxylase
	Matrix-metaloproteinase and their inhibitors	MMP-2 , TIMP-1, TIMP-2, cICAM-1, cVCAM-1 …
Cytokines and chemokines of liver fibrosis	Transforming growth factor-β1	TGF-β1
	Platelet growth factor	PGF

Prolyl hydroxylase catalyses the process of hydroxylation of prolyl remains in procollagen into hydroxyprolyl. The deficit in vitamin E and selenium with increase in aminoterminal procollagen III peptide points to active hepatic fibrosis.

Laminin. One of the major glycoproteins of basal membrane is laminin which is synthesized in hepatocytes and sinusoid cells. Laminin increases during fibrosis because of increased synthesis of laminin in the liver and lack of its degradation by endothelial liver cells. During fibrosis, it accumulates around blood vessels perisinusoidally and around portal tract.

It is in correlation with the progression of liver fibrosis and the degree of inflammation in chronic hepatitis. It is also correlated with serum level of ALT which reflects the degree of liver damage, especially in cirrhosis. It is superior in reflecting the degree of liver damage than serum level of ALT. Serum level of laminin reflects the gradient of portal pressure in the liver, as well as in vena porta (31, 32). It has been suggested that the measurement of laminin concentration in serum be a sensitive test for determining the degree of liver damage, as well as the degree of portal hypertension development.

Hyaluronic acid (HA) is glycosaminoglycan, a component of ECM, which is synthesized in hepatocytes. In normal circumstances, endothelial cells of liver sinusoids synthesize and degrade the hyaluronic acid. The high level of serum HA has been discovered in patients with liver disease of various etiologies. It is significantly higher in patients with cirrhosis. When serum level of HA is below 60 mg/l, serious liver cirrhosis is excluded, as well as serious vein fibrosis. Early fibrosis is identified. When serum level is around 85 mg/l of serum, HA has the sensitivity of 64.5% for the development of severe liver fibrosis. When the values are around 110 mg/l, HA has the sensitivity of 79.2% for the development of severe liver fibrosis (33, 34). The determination of the level of laminin and HA has prognostic significance in the complication of liver cirrhosis, such as hepatic encephalopathy, ascites and portal venous thrombosis.

Matrix dissolution markers

Extracellular matrix is an active tissue where a dynamic process takes place, such as synthesis and dissolution of matrix. This leads to ECM remodulation. It is very difficult to make a clear distinction between sedimentation markers and dissolution markers of ECM. In serum, these markers reflect both processes simultaneously, and the total mass of ECM goes through the process of adaptation (35).

The products of matrix dissolution are a result of activity of a family of matrix metaloproteinase (MMPs) enzymes. Synthesized intracellularly, they are secreted as MMPs proenzymes. They are activated by proteolytic effect of membrane type 1 matrix metaloproteinase (MT1-MMP) or by the effect of plasmin, and inhibited by bonding to specific tissue inhibitors (TIMPs).

Considering the specificity by substrate, there are five categories of MMPs: interstitial collagenase (MMP-1, 8, 13), gelatinase (MMP-2, 9 and proteins of fibroblast activation), stromelysin (MMP-3, 7, 10, 11), membrane type (MMP-14, 15, 16, 17, 24, 25) and metalloelastase (MMP-12). MMPs and their inhibitors are included in the control of matrix degradation.

The research of chronic liver disease is directed at MMP-2 and metalloproteinase membrane type 1 or 2, which activate latent MMP-2, TIMP-1 and TIMP-2 (36). MMP-1 shows specificity for interstitial collagen type I and III substrate, while MMP-2 shows specificity for collagen type IV, V, VII, X, elastin and fibronectin substrate.

TIMPs may irreversibly bond with proenzyme or active forms of MMPs and inactivate them. An excess of synthesized TIMPs in relation to MMPs can be an important factor in liver fibrosis progression. Stellate liver cells are a major source of MMP-2 in the human liver. The activation of MMP-2 requires hepatocyte reaction. TIMP-1 are also produced by stellate cells and hepatocytes (37, 38).

One study has shown that the level of MMP-2 is increased only in developed cirrhosis, while TIMP-1 has diagnostic significance in discovering an early phase of fibrosis. Serum level of TIMP-1 can also be significant in estimating liver fibrosis which is associated with active inflammatory activities. This study has shown that TIMP-1 level has a strong correlation with the inflammatory process, and that MP-2 level is not connected with the phase of fibrosis in non-cirrhotic liver (39). Other studies have demonstrated that the level og serum MMP-1 decreases with the degree of liver fibrosis and inflammation. High level of MMP-1 in serum is present in patients with late phase of fibrosis. The ratio between TMP-1 and MMP-1 can be useful in the diagnosis of liver fibrosis (39).

Cytokines and chemokines of liver fibrosis

Transforming growth factor-β1 (TGF-β1) is a homodimetric polypeptide which is secreted as inactive form that demands activation. It has a pleiotropic effect on the receptors of membranes of wide spectrum of cells. In liver pathology, TGF-β1 is the most important stimulant of ECM synthesis by stellate cells and it is also an inhibitor of growth and hepatocyte proliferation.

In liver biopsy of patients with chronic liver damage, TGF-β1 and RNA levels are in correlation with messenger RNA of type I collagen (40, 41). There are limitations of TGF-β1 serum level because TGF-β1 bonds with location of damaged ECM and damaged vascular endothelium. The limitations are associated with seizure by soluble proteins and complication in TGF-β1 sample purification.

These factors explain why plasma level of TGF-β1 has diagnostic significance. Some studies have shown a good correlation between total level of TGF-β1 in serum and the degree of fibrosis progression. Some authors give prognostic value to the border value of TGF-β1 level in patients without fibrosis progression, compared to those in whom the disease has progressed. The level of TGF-β1 below 75 ng/ml points to a stable course of the disease (42, 43).

Platelet growth factor (PGF) is the major stimulant in the proliferation and migration of stellate cells after liver damage. PGF-BB is the main subunit with the most important role in path signalization to stellate cells. One study has shown that serum level of PGF-BB has the highest significance in the assessment of liver fibrosis (44).

It can be concluded that the analysis of serum biomarkers can assess the risk of health problems in alcoholics. Biomarker analysis contributes to understanding disease pathogenesis caused by alcohol, monitoring the natural development of the disease, as well as the diagnosis and disease prognosis. Thereby, both treatment and outcome can be improved. Simultaneous use of combination of sedimentation and ECM dissolution markers improves the accuracy in diagnosing the degree of fibrosis development. In this way, the process of remodeling and adaption of matrix can be estimated. Determination of serum markers is performed in order to control the intake of alcohol which should influence the reduction of alcoholic liver damage.

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KOMPLIKACIJE ALKOHOLNE BOLESTI JETRE I DIJAGNOSTIČKI MARKERI

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Alkoholizam predstavlja jednu od vodećih bolesti u većini zemalja u svetu. Od hroničnog oštećenja jetre u SAD svake godine umre blizu 30 hiljada ljudi. Jetra je centralni organ metabolizma alkohola. Alkohol je primarno hepatotoksični agens. Klinički se hepatotoksičnost alkohola manifestuje pojavom alkoholne masne jetre, alkoholnim hepatitisom i alkoholnom cirozom. Karakteriše se odgovarajućom simptomatologijom, zavisno od stepena oštećenja jetre. Prekomerno konzumiranje alkohola u dužem vremenskom periodu, pored malnutricije, genske i etničke predispozicije dovodi do alkoholne ciroze i razvoja njenih komlikacija. Portalna hipertenzija dovodi do oštećenja i drugih organa i sistema organa, kao što su hepatopulmonalni sindrom, hepatorenalni sindrom, hepatična encefalopatija, spontani bakterijski peritonitis i dr.

Iz tog razloga prioritet se daje smanjenju alkoholizma, kao i smanjenju morbiditeta i mortaliteta obolelih od alkoholnog hroničnog oštećenja jetre. Zato je potrebno rano postavljanje dijagnoze zloupotrebe alkohola, kao i pravovremena dijagnoza različitog stepena alkoholnog oštećenja jetre.

Dijagnoza hroničnog alkoholnog oštećenja jetre postavlja se na osnovu potvrđenog podatka o konzumiranju alkohola; testa funkcije jetre (serumski markeri aminotransferaza, gama glutamil transferaza, protrombinsko vreme, serumski bilirubin i nivo albumina); serumskih markera fibroze jetre. Markeri fibroze su direktno uključeni u taloženje i razlaganje ekstracelularnog matriksa, odnosno u proces fibrogeneze i fibrolize tkiva jetre. Oni uključuju markere i enzime metabolizma, kao i citokine i hemokine. *Acta Medica Medianae 2011;50(4):55-61.*

Ključne reči: *alkoholno oštećenje jetre, serumski markeri*