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ALCOHOLIC LIVER DISEASE

ALKOHOLNA BOLEST JETRE

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Summary

Introduction. Alcoholic liver disease is one of the most common liver disorders in Europe and in the United States of America. This paper highlights the clinical-pathological concept of alcoholic liver disease with an overview of current therapeutic approaches. **The spectrum** of alcoholic liver disorders includes liver steatosis, alcoholic steatohepatitis, alcoholic cirrhosis with a potential to culimate in hepatocellular carcinoma. Alcoholic steatohepatitis is a rapidly-progressive disorder that may be associated with severe clinical manifestations of alcoholic hepatitis and high mortality. There are large variations in alcohol consumption and consequent morbidity and mortality around the world. In addition to the amount of alcohol intake, different individual manifestations of alcoholic liver disease are affected by genetic and other risk factors. **Pathogenesis** with a potential to culminate in hepatocellular carcinoma of the disease is based on the toxic effects of acetaldehyde, oxidative stress, lipid metabolism disorders and alcohol-induced inflammation. **Diagnosis of alcoholic liver disease.** In the diagnosis of alcoholic liver disease, apart from clinical picture and laboratory findings, ultrasonography, transient elastography, magnetic resonance imaging, serum biomarkers and liver biopsy are important. **Therapy of alcoholic liver disease** includes abstinence, nutritional support, corticosteroid treatment and liver transplantation. New therapeutic modalities are being investigated. **Conclusion**. Despite abundant knowledge of the epidemiology, pathophysiology and clinical diagnostics of alcoholic liver disease, the therapy has not changed over the past few decades. The development of novel therapeutic modalities requires a multidisciplinary approach and close cooperation of doctors and pharmacists. The emphasis must be put on the disease prevention at both individual and community level.

Key words: Liver Diseases, Alcoholic; Hepatitis, Alcoholic; Liver Cirrhosis; Acetaldehyde; Lipid Metabolism; Inflammation; Diagnosis; Therapeutics; Risk Factors

Sažetak

Uvod. Alkoholna bolest jetre jedna je od najčešćih bolesti jetre u Evropi i Sjedinjenim Američkim Državama. U radu je istaknut kliničko-patološki koncept alkoholne bolesti jetre sa osvrtom na aktuelnu terapiju. **Spektar** alkoholne bolesti jetre čine steatoza jetre, alkoholni steatohepatitis i alkoholna ciroza jetre, koja može rezultirati hepatocelularnim karcinomom. Alkoholni steatohepatitis može biti rapidno progresivan i manifestovati se ozbiljnom kliničkom slikom alkoholnog hepatitisa sa visokom smrtnošću. Širom sveta postoje velike varijacije u konzumaciji alkohola i posledičnom morbiditetu i mortalitetu. Osim količine alkohola, na različito individualno ispoljavanje alkoholne bolesti jetre utiču genetski i drugi faktori rizika. **Patogeneza** alkoholne bolesti jetre zasniva se na toksičnom dejstvu acetaldehida, oksidativnom stresu, poremećaju metabolizma lipida i alkoholom indukovanoj inflamaciji. **U dijagnostici alkoholne bolesti jetre**, osim kliničke slike i laboratorijskih nalaza, značajni su ultrasonografija, tranzijentna elastografija, magnetna rezonancija, serumski biomarkeri i biopsija jetre. **Standardna terapija** alkoholne bolesti jetre uključuje apstinenciju, nutritivnu podršku, primenu kortikosteroida i, uz ispunjavanje kriterijuma, transplantaciju jetre. Istražuju se novi terapijski modaliteti. **Zaključak.** Iako se mnogo zna o epidemiologiji, patofiziologiji i kliničkoj dijagnostici alkoholne bolesti jetre, terapija se nije mnogo promenila tokom proteklih decenija. Potrebno je angažovanje kliničara i farmaceuta sa ciljem iznalaženja novije terapije alkoholne bolesti jetre. Lečenje alkoholne bolesti jetre mora biti multidisciplinarno. Akcenat mora biti na prevenciji bolesti na populacionom i individualnom nivou.

Ključne reči: alkoholna bolest jetre; alkoholni hepatitis; ciroza jetre; acetaldehid; metabolizam lipida; inflamacija; dijagnoza; terapija; faktori rizika

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Abbreviations

ALD – alcoholic liver disease
ASH – alcoholic steatohepatitis
AH – alcoholic hepatitis
HCC – hepatocellular carcinoma
AFL – alcoholic fatty liver
DNA – deoxyribonucleic acid
NAD – nicotinamide adenine dinucleotide
IL – interleukin
TNF-α – tumor necrosis factor-α
SREBP1 – sterol regulatory element-binding protein 1
PPAR-α – peroxisome proliferator-activated receptor-alpha

Introduction

Alcoholic liver disease (ALD) is one of the most common liver disorders in Europe and the United States of America. The disease is caused by chronic alcohol overconsumption at amounts exceeding standard daily quantities, which vary significantly between individuals. It commonly affects the working population resulting in extensive socio-medical consequences [1, 2]. As early as the 18th century, physicians drew the connection between heavy drinking and the distribution of liver diseases in population [3, 4].

Spectrum and epidemiology of alcoholic liver disease

The ALD spectrum includes alcoholic fatty liver (AFL), alcoholic steatohepatitis (ASH) and alcoholic cirrhosis with a potential to culminate in hepatocellular carcinoma (HCC). The ASH may manifest as a slowly-progressing condition, when chronic liver injury and inflammation lead to progressive fibrosis and liver cirrhosis. In some patients with ALD (with or without cirrhosis), ASH may progress rapidly and may be accompanied by severe clinical manifestations of alcoholic hepatitis (AH). Short-term mortality of AH remains high (20–30%), as well as six-month mortality, that can reach 40% in severe disease conditions [5, 6].

The majority (90–100%) of heavy chronic alcoholics develop liver steatosis. Those who consistently and excessively abuse alcohol are at risk of developing progressive ALD. Fibrosis is likely to occur in some 20% to 40% of patients with steatosis, while 8% to 20% of these patients will develop liver cirrhosis [7].

A large variation in alcohol consumption and related morbidity and mortality exists worldwide. According to the European Association for the Study of the Liver HEPAHEALTH Report, Serbia is categorized as a country with a stable alcohol consumption at low levels (on average below 10 L pure alcohol per person annually) [8]. A group of authors from Novi Sad reported that alcohol consumption in Vojvodina region is lower than in other regions of Serbia, but with significant health consequences [9].

In 2012, it was estimated that 3.3 million deaths, or 5.9% of all deaths worldwide, were attributable to alcohol consumption. An estimated 5.1% of the global burden of disease, as measured in disability-adjusted life-years, is attributed to alcohol consumption [10].

Global liver cirrhosis deaths increased from around 676,000 (95% uncertainty interval: 452,863 - 1,004,530) in 1980 to over 1 million (1,029,042; 670,216 - 1,554,530) in 2010 (about 2% of the global total) [11]. Due to cirrhosis and chronic liver disease, there were 1,256,900 deaths in 2016. Out of these, 334,900 (27%) were attributable to alcohol [12].

Risk factors for the development of ALD

Considering that a relatively small percentage of chronic alcoholics develop advanced ALD, the course of the disease is most likely determined not only by the amount of alcohol intake, but also by the predisposing factors such as genetics, female sex, underlying viral and metabolic liver diseases, overweight, use of some drugs and supplements (paracetamol, isoniazid, methotrexate, beta-carotene, vitamin A) and smoking [5–7].

The measurement of alcohol consumption includes determination of daily alcohol intake in grams and duration of drinking period. According to relevant guidelines, standardizing a "drink" to a measure of 10 g of alcohol is recommended. The number and type of alcoholic drinks are recorded and calculation to grams of alcohol per day is done [5–7].

Rehm et al. reported a continuous curve displaying increased risk for the development of liver cirrhosis proportional to increased alcohol consumption; however, increased risk is also associated with chronic consumption of small amounts of alcohol (12 g/day to 24 g/day) [14].

Chronic consumption of more than 40 g of alcohol per day over a period of several consequent years was identified as a risk factor for AFL by Seitz et al. [5]. The majority of patients with AH reported heavy drinking (more than 100 g of alcohol per day) during ten years and over, with escalated consumption as a response to recent life events and crisis [15].

Bellentani and Tiribelli reported development of ALD in patients consuming more than 30 g of alcohol per day during ten years. The incidence of cirrhosis increases linearly with increasing alcohol intake above this threshold [16]. Alcoholics taking 80 g of alcohol per day in the last 10 years are nearly certain to develop an advanced form of ALD [17]. As reported by Dunn and Shah, AH is associated with female sex and an irregular (i.e. binge drinking) pattern of alcohol consumption. Cirrhosis is associated with female sex, heavy alcohol use over a period of 15 years, and consuming over 200 g of alcohol per day [18].

In the United States, the type of alcohol and the prevalence of binge drinking changed during the period of 2000 – 2013, with a substantial increase observed in the consumption of distilled spirits,

wine and binge drinking. Binge drinking is particularly concerning in young adults [6, 19]. Early onset of alcohol consumption is a predictor of alcohol problems in adulthood. Today, many more young people drink at younger ages. Psychosocial factors play an important role [20]. Certain childhood risk factors may lead to alcohol addiction later in life [21].

Patatin-like phospholipase domain-containing protein 3 (PNPLA3) may be implicated in the genetic background of ALD. The PNPLA3 is associated with the development of ALD even in cases of significantly shorter drinking history and exposure to alcohol [5, 6, 18].

Females are more prone to alcohol than men. They develop ALD after consuming lesser amounts of alcohol over a shorter period. It may be due to their decreased gastric metabolism of alcohol, lower total body water content and alcohol-mediated increase of serum estrogen levels [5, 6].

Pathogenesis of ALD

Alcohol oxidation includes conversion of ethanol to acetaldehyde by alcohol dehydrogenase (ADH) in hepatocytes. Acetaldehyde is further metabolized down to acetate. Another pathway of alcohol conversion to acetaldehyde involves cytochrome P450 2E1. Acetaldehyde is a highly toxic and carcinogenic substance. It binds to the proteins leading to structural and functional damage predominantly in mitochondria and microtubules [5, 22].

Consumption of alcohol is also associated with oxidative stress. Formation of reactive oxygen species can be generated through *CYP2E1* induced by alcohol metabolism as well as alcohol-induced inflammation. The reactive oxygen species bind with proteins and deoxyribonucleic acid (DNA) either directly or via lipid peroxidation products, thus resulting in formation of DNA adducts [6, 7, 18, 23, 24].

Alcohol-induced epigenetic modifications include acetylation, phosphorylation, DNA hypomethylation as well as dysregulation of micro-ribonucleic acid (miRNAs) [25–27].

Lipid metabolism impairments in ALD

Early pathophysiological response to chronic alcohol consumption includes accumulation of lipids (triglycerides, phospholipids and cholesterol esters) in the hepatocytes. Alcohol drinking induces lipolysis resulting in elevation of circulating fatty acids and their accumulation in the liver, while increasing the lipid supply from the small intestines into the liver [28].

Alcohol consumption increases the reduced to oxidized forms of nicotinamide adenine dinucleotide reduced (NADH) and nicotinamide adenine dinucleotide(NAD) (NADH/NAD+) ratio in hepatocytes, thus disturbing the mitochondrial fatty acid β-oxidation. It also increases hepatic expression of sterol regulatory element-binding protein 1 (SREBP1c), a transcription factor stimulating the expression of lipogenic genes and consequent increase of fatty acid synthesis [29]. Alcohol inhibits the effects of negative SREBP1c regulators, such as adenosine monophosphate activated protein kinase and some other ones [6, 7, 18, 30, 31].

Alcohol inactivates the peroxisome proliferator-activated receptor-alpha (PPAR-α), a nuclear hormone receptor that, under physiological conditions, increases the expression of several genes involved in fatty acid transport and oxidation. Alcohol can reduce the activity of PPAR-α either directly (via acetaldehyde) or indirectly (via oxidative stress, adiponectin decrease and zinc deficiency) [18, 32].

Alcohol is an established cause of oxidative stress, inflammation and cell death in the adipose tissue. It induces an increase in serum leptin and decreases adiponectin levels. Alcohol inhibits the activation of farnesoid X-receptor, thus negatively affecting the lipogenesis via SREBP1 and positively regulating fatty acid oxidation via PPARα [6, 18, 33].

Liver inflammation in ALD

Pathogen-associated molecular patterns from the gastrointestinal tract, which stimulate the expression of cytokines and chemokines from Kupffer cells, as well as damage-associated molecular patterns released from dying hepatocytes, are implicated in the development of ASH [5]. Excessive use of alcohol results in alterations of intestinal microbiome composition. Intestinal barrier damage leads to increased intestinal permeability and small intestinal dysmotility, resulting in increased translocation of bacterial products from the gut towards the liver via the portal circulation [34].

Endotoxin (lipopolysaccharide) is sensed by immune system cells via the Toll-like receptor 4 leading to the activation of nuclear factor kappa B and formation of proinflammatory chemokines (chemokine (C-C motif) ligand 2 and interleukin (IL-8) and cytokines (tumor necrosis factor-α (TNFα) and IL-6) [5]. Processing of Pro-IL-1β to its active form (IL-1β) and its release is mediated by caspase activity and requires activation of inflammasome. The IL-1β amplifies the production of proinflammatory cytokines, renders hepatocyte susceptibility to cell death signals, increases synthesis of fatty acids and stimulates liver fibrosis [18, 35]. The IL-17 induces recruitment of neutrophils into the liver and stimulates production of IL-8 and chemokine (C-X-C motif) ligand 1 by hepatic stellate cells. Increased activity of other cytokines and chemokines has also been established [6, 7].

The loss of proteasome or inhibition of ubiquitin-proteasome pathway may result in cell damage, proliferation, apoptosis and formation of cellular inclusions comprising keratin aggregates [5]. Alcohol induces hepatocyte apoptosis by activating mitochondrial (intrinsic) apoptotic pathways, caspase-dependent and caspase-independent pathways, as well as by endosplasmic reticulum stress [36].

Progression of ALD - liver fibrosis and liver cirrhosis

Hepatic fibrosis is a wound-healing response, which may regress following absolute abstinence from alcohol. Continuation of alcohol consumption leads to a progressive course resulting in the replacement of the liver parenchyma by a scar tissue. In liver injury, hepatic stellate cells undergo complex activation processes and become the major source of excessive deposition of extracellular matrix. Activated hepatic stellate cells play a role in regulating the inflammatory response [37].

Cirrhosis is characterized by the formation of regenerative nodules of hepatic parenchyma surrounded by fibrous septa. It is associated with the development of portal hypertension and vascular abnormalities. Vasoconstriction occurs in the liver and kidneys, whereas vasodilatation is present in multiple vascular beds. Impairments occurring in individual vascular beds involve specific clinical manifestations thus requiring specific therapeutic modalities [38, 39].

Diagnosis of alcoholic liver disease

The diagnosis of ALD is frequently suspected upon documentation of excessive alcohol consumption (more than 40 g per day to 50 g per day) and the presence of clinical and/or biological abnormalities suggestive of liver injury. In its early stages, ALD is a silent disease and can only be detected by laboratory tests or imaging techniques [40].

Simple abdominal ultrasonography can be used to screen for AFL, but it has only moderate sensitivity and specificity. By contrast, ultrasonography techniques based on attenuation of shear waves such as controlled attenuation parameter are more accurate for the quantification of AFL. Magnetic resonance imaging has excellent accuracy for detecting liver fat [22].

Laboratory finding in ALD reveals aspartate aminotransferase/alanine aminotransferase ratio higher than 2, increased AST values at least twice the upper normal limit, increased gamma-glutamyl transferase and mean corpuscular volume. Decreased synthetic function of the liver, increased bilirubin and leukocyte counts and acute renal failure can occur. Liver biopsy is indicated in aggressive forms of ALD, if prospective modification of therapeutic options or establishment/confirmation of the accurate diagnosis is needed. Transjugular approach is the preferred biopsy method in cases with coagulopathy and ascites [13, 40].

Acute AH should be distinguished from decompensated alcoholic cirrhosis or acute or chronic liver disease [18]. Differential diagnosis may include severe sepsis, biliary obstruction, diffuse HCC, drug-induced liver injury and ischemic hepatitis [22]. The diagnosis of AH is frequently overlooked, especially in patients admitted for gastrointestinal bleeding or sepsis. The AH patients at significantly high risk for early mortality are identified according prognostic models such as Maddrey's discriminant function, the Model for End-Stage Liver Disease, the Glasgow AH score, and the age-bilirubin-International normalized ratio-creatinine score. After 7 days of medical therapy with prednisolone, physicians may identify responders using the Lille model [7, 40].

The assessment of liver fibrosis in patients with ALD is done by using non-invasive methods such as serum markers and liver stiffness measurements. The AST to platelet ratio index, FibroTest®, Fibrometer®, Hepascore®, and Fibrosure® can be useful in patients with ALD. Liver cirrhosis is diagnosed by clinical evaluation, using hepatic imaging techniques and, in some instances, liver biopsy. Esophagogastroduodenoscopy is used to assess the presence of esophageal varices, whereas liver/spleen ultrasound elastography is applicable for quantifying portal hypertension [40–42].

Therapy of alcoholic liver disease

Therapeutic strategies in the early stages of ALD implicate antioxidant administration, neutralization of intestinal bacterial endotoxins, and recovery of intestinal permeability by applying zinc, balancing the disturbed gut flora by using probiotics and specific antibiotics [7, 36].

Administration of inflammatory cytokines (e.g. TNF-α) blockers did not prove effective in patients with ALD, which is probably due to the fact that the majority of cytokines exhibit hepatoprotective properties besides their inflammatory effects. Corticosteroids reduce systemic inflammatory response, yet increasing the risk of infection and sepsis [36].

Inhibition of inflammasome signaling pathways by applying caspase inhibitors may be a new therapeutic target [35]. Preclinical studies open novel promising therapeutic options such as application of IL-22, anakinra, and IL-1 receptor antagonists. Potential application of farnesoid X receptor agonists also gains increased attention [6, 7, 36, 43, 44].

Key points in the therapy of ALD

The first and most important step in the therapy of ALD is absolute abstinence from alcohol. Combination of psychosocial intervention, pharmacotherapy and medical management is the most effective strategy in the treatment of patients with alcohol use disorders and ALD [45, 46].

Patients with advanced ALD manifest with severe clinical signs of protein-calorie malnutrition, so relevant nutritional support is needed. Reduced intake of vitamins and minerals and consequent impairment of their bioavailability results in clinical deficiency syndromes that require adequate supplementation [46–48].

Pharmacotherapy of ALD has not considerably changed over the past few decades as compared with tremendous advancements of treatment options for other liver diseases [7, 46]. Corticosteroids still remain the first-line therapy in AH. The majority of therapy protocols include 40 mg prednisolone per

day during a one-month period, with or without dose reduction [40]. After 7 days of prednisolone administration, Lille model can be used to identify the nonresponders, in which the risk greatly overwhelms the benefits of further corticosteroid therapy [13, 49]. Intravenous administration of N-acetylcysteine along with prednisolone (40 mg/day) can improve the 30-day survival of patients with severe AH. Pentoxifylline is not recommended in the treatment of AH any more [50].

Liver transplantation, as a rescue therapy in selected AH patients who do not respond to medicamentous therapy, dramatically improves their survival. Strict adherence to the rule of 6-month abstinence period before acceptance to the transplantation list is widely applied; however, the majority of AH patients die before the expiration of this period [51].

Decompensated alcoholic liver cirrhosis is most commonly manifested by portal hypertension complications such as ascites with or without complication and esophageal varices with or without bleeding. Treatment regimens for such clinical conditions are clearly defined [52].

Alcoholic liver cirrhosis is one of the most common indications for liver transplantation. Such patients often display multi-system manifestations of long-term ethanol consumption (peripheral and central nervous system disorders, alcoholic myopathy, hepatic osteodystrophy, and alcoholic cardiomyopathy, etc) [46, 47, 53, 54]. Treatment of alcoholic liver cirrhosis and preparing the patient for liver transplantation requires a multidisciplinary approach [46, 55].

Conclusion

Despite the abundant knowledge of the epidemiology, pathophysiology and clinical diagnostics of alcoholic liver disease, the therapy has not changed much over the past few decades. The development of novel therapeutic modalities for alcoholic liver disease requires a multidisciplinary approach and close cooperation of doctors and pharmacists. The emphasis must be put on the disease prevention at both individual and community level.

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