APASL STC 2022 Armenia NAFLD/MAFLD: Non- Infectious Epidemic In XXI Century

ABSTRACT BOOK

Yerevan, Armenia
October 6-8, 2022
www.hepatology.am

Welcome Message,

I have the great pleasure of inviting you to join us at APASL STC on NAFLD/NASH to be held from 6 to 8 October 2022, in Yerevan, Armenia.

Non-alcoholic fatty liver disease (NAFLD) is a very common disorder and refers to a group of conditions where there is accumulation of excess fat in the liver of people who drink little or no alcohol. THE GLOBAL PREVALENCE OF NAFLD: About one-fourth of the world's population has NAFLD, the most common form of NAFLD is a non-serious condition called fatty liver. In the fatty liver, fat accumulates in the liver cells. Although having fat in the liver is not normal, by itself it probably does not damage the liver. A small group of people with NAFLD may have a more serious condition named non-alcoholic steatohepatitis (NASH). In NASH, fat accumulation is associated with liver cell inflammation and different degrees of scarring. NASH is a potentially serious condition that may lead to severe liver scarring and cirrhosis and HCC.

This three-day meeting will focus on all aspects of the management of NAFLD/NASH and will include important topics of epidemiology, Causes

Symptoms, Risk Factors, Screening/Diagnosis as well as optimal current treatment approaches in patients including. Our aim is to invite all experts in the field to present the latest research data and share their experiences as well as to create new plan for the future. STC will be based on active discussion and interactions in order to get necessary results and new challenges in NAFLD/NASH (MAFLD?). We are expecting 500 delegates from the whole world including CIS countries to attend this important conference.

I hope you will enjoy this conference as well as your stay in Armenia, the country with old history, culture and amazing hospitality and traditions.

President of APASL STC 2022

NAFLD/MAFLD

Hasmik Ghazinyan MD, PHD

Secretary of APASL STC 2022

NAFLD/MAFLD

Gagik Hakobyan MD, PHD

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Senior Professor, Hepatology, & Director, Institute of Liver and Biliary Sciences, & Chancellor, Institute of Liver and Biliary Sciences

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Alcohol Associated Liver Disease and HCC

Abstract:

Primary liver cancer is the third most common cause of cancer death as per the WHO. Both Alcohol associated liver disease and NAFLD are among the major contributors. Alcohol is classified as a Group 1 carcinogen by IARC.Chronic alcohol consumption starting at 10g/1 unit/day increases to two times in heavy drinkers (>80g/d) compared with non-drinkers. Alcohol intake also increases the risk of HCC due to other factors; in heavy drinkers, the risk of HCC rises 9.9 in patients with diabetes, and nearly 53.9 fold in patients with HCV infection. Obesity also has a synergistic effect on HCC development. On the other hand, abstinence is associated with a risk reduction in HCC by 6%–7% per year. The pathogenesis of alcohol-induced hepatocarcinogenesis is multifactorial and still ill-understood. Alcohol is metabolized by alcohol dehydrogenase (ADH) into acetaldehyde. Alcohol metabolism increases ROS production via induction of CYP2E1 and impairment of mitochondrial functionality which is carcinogenic as it causes cell injury by forming DNA and protein adducts and also leads to DNA hypomethylation with modifications of oncogenes and tumor suppressor genes. Acetaldehyde and ROS damage cell components through lipid peroxidation, iron accumulation, and DNA mutagenesis via impairment of repair mechanisms. The translocation of gut bacteria and lipopolysaccharides produces pro-inflammatory cytokines and chemokines. Additionally, acetaldehyde causes lipid accumulation in hepatocytes via the transcriptional activity of SREBP-1 and PPAR-r. Alcohol consumption also decreases the sirtuins, the metabolic sensors, which adds to lipid accumulation. Alcohol-induced hepatic fibrosis and cirrhosis also contribute to hepatocarcinogenesis. Alcohol exposure promotes HCC progression and the β-catenin/miR-22-3p/TET2 regulatory axis plays an important role in alcohol-promoted HCC malignancy HCC. Nearly a third of Asians are deficient in aldehyde dehydrogenase 2, an enzyme to detoxify acetaldehyde. This leads to the production of a large amount of oxidized mitochondrial DNA via extracellular vesicles, which can be delivered into neighboring cells and subsequently activate multiple oncogenic pathways, thereby promoting HCC. IL-17A, a tumor-promoting cytokine has also been implicated in HCC pathogenesis. In addition, there is a delay in the detection of the HCC in alcohol users, as, despite known liver disease, such patients are not part of any surveillance program patients. This often results in greater cancer aggressiveness, less amenable to curative options, and worse treatment outcomes. Numerous host factors in patients with ALD modulate the risk of the development of HCC. These include age, gender, liver failure, obesity smoking, and other co-morbidities. Patients with alcoholic cirrhosis should be included in HCC Surveillance programs.

Masao Omata
President, Yamanashi Central and Kita Hospitals
Professor Emeritus, The University of Tokyo

APASL STC Armenia
“The 45 years of APASL and the future”
Masao Omata, Tokyo, Japan

ABSTRACT

APASL was started in 1978 at the initiative of Okuda, Powell, et al and 2022 will mark its 45th anniversary. During that time, several major developments have taken place. The conference used to be held once every two years, but since 2007, an Annual Meeting has been held every year, and in 2006, the Single Topic Conference (STC) was started, which has been held 37 times. The STC has covered three major areas: hepatitis B virus, hepatitis C virus, and hepatocellular carcinoma. 7 meetings have been held for hepatitis B, 8 for hepatitis C, and 6 for hepatocellular carcinoma.
However, the issue of rapidly increasing liver diseases, such as NASH or MAFLD, has emerged. This time, Dr. Hasmik will present the most recent information on this topic.
The APASL, which covers Asia, is celebrating its 45th anniversary and its importance is increasingly being unquestioned. Therefore, this presentation will be a great blessing to 75% of the world's population in Asia, especially those suffering from liver diseases.

Dr. HAN-CHIEH LIN

Executive Council
Member (2013/1-present),
Taiwan Association for the Study of the Liver (TASL)
Councilor (2017/5-present), The Taiwan Liver Cancer Association

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Pathogenesis of NASH and liver fibrosis

ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) has been recognized as a global public health burden. Some patients with NAFLD may progress to non-alcoholic steatohepatitis (NASH) followed by liver fibrosis, cirrhosis or even hepatocellular carcinoma. It is known that dysfunction of lipid metabolism within hepatocytes may cause by genetic factors, diet, and insulin resistance that leads to steatosis. Lipotoxicity, oxidative stress, mitochondrial dysfunction, and ER stress all contribute to hepatocyte apoptosis and death, with subsequent necro-inflammation and hepatic fibrosis. During the development of NASH and liver fibrosis, a dysregulation of the gut-liver axis, adipose-liver axis, and renin-angiotensin system may occur. Translocation of bacteria or its end-products enter the liver would activate hepatocytes, Kupffer cells and hepatic stellate cells, causing exacerbation of hepatic steatosis, inflammation and fibrosis. Increased adipose tissue-derived non-esterified fatty acids would exacerbate hepatic steatosis. Increased leptin also plays a role in hepatic fibrogenesis while decreased adiponectin may contribute to hepatic insulin resistance. In addition, dysregulation of peroxisome proliferator-activated receptors in the liver, adipose and muscle tissues may impair lipid metabolism. Moreover, the renin–angiotensin system could contribute to hepatic fatty acid metabolism, inflammation and fibrosis. Taken together, the development and progression of NASH and live fibrosis involves complex interplay of numerous factors.

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The Global Epidemiology and Outcomes of NAFLD

ABSTRACT

In 2016, data from a meta-analysis suggested that the global prevalence of NAFLD is 25%. In a more recent meta-analysis, the pooled prevalence of NAFLD from 1991-2019 is estimated to be 30%. In both studies, the highest prevalence rates are reported from Middle East and North Africa (MENA) and South America. Nevertheless, very high prevalence rates are reported from Asia and North America. More importantly, assessment of prevalence rates over time suggested an increase from 25.26% (1990-2006) to 38.20% (2015-2019).

In addition to the prevalence of NAFLD, the prevalence of NASH is also high and is now estimated to be around 5.27%. Although the highest prevalence of NASH (6% and 7%) is reported from MENA and South America, most other regions of the world experience 5% prevalence rate of NASH among their general populations.

The meta-analysis also suggested that the overall mortality of NAFLD is 17.15 per 1,000 which is almost twice as high as the mortality in the general population. In this context, CVD, cancer and liver mortality accounted for 64% of all deaths among NAFLD.

The disease presentation and the progression of NAFLD is very heterogenous. In general, it is estimated that 10-15% of patients with underlying NASH can progress to cirrhosis and are at risk for liver cancer and liver-related mortality. This progression is not uniform and may follow a progressive course followed by regression or stability. This type of complex natural history has led to significant placebo rate in clinical trials where patients with NASH treated with placebo experience spontaneous improvement of fibrosis or NASH.

There is significant data documenting the consequences of this progressive nature of NAFLD. In this context, hepatocellular carcinoma (HCC) has been recognized as an important complication of NASH-related cirrhosis. Interestingly, non-cirrhotic patients with NAFLD and NASH can also develop HCC. In this context, the rate of HCC is below the threshold of cost-effective screening for non-cirrhotic NASH and the screening programs are reserved for NASH patients with cirrhosis. In the last decade, NASH-NAFLD has rapidly become the second most common indication for liver transplantation (LT) in the United States. In fact, NASH-NAFLD is now the most common indication for LT among women, those who are in their 50s and possibly HCC LT candidates. Finally, mortality data from the United States suggest that both in men and women, NAFLD is growing as a cause of liver death. These data have been replicated in Europe and other regions of the world.

In addition to country-specific data, Global Burden of Disease data suggest that mortality from cirrhosis and liver cancer related to NAFLD-NASH is increasing in most regions of the world. In fact, disability adjusted years of life (DALYs) related to NAFLD are very high in Asia and the MENA and this rapidly growing burden may be driven by the nutritional and activity habits in these regions of the world.

In addition to these overall epidemiologic aspects of NAFLD, focused areas of assessment include prevalence of NAFLD among children, prevalence among type 2 diabetics (T2DM) and the ethnic and racial diversity issues in NAFLD. In this context, the prevalence of NAFLD is estimated about 7.5%-10% among Children (highest in South America: 25%) and 55% among type 2 diabetics. In the United States, Hispanic population, especially those of Mexican descent, have the highest prevalence of NAFLD. In other countries such as China, these types of ethnic and racial differences have been reported. These differences related to ethnic and racial diversity of NAFLD-NASH are probably related to both environmental factors and genetic factors. Furthermore, these differences can have important implications for understanding disease burden, biomarker discovery and drug development.

It is important to note that NAFLD-NASH is not only associated with significant clinical burden (mortality) but also with impaired patient-reported outcomes (PROs) and tremendous economic burden. In this context, the total burden of NASH-NAFLD on the patients and the society can be enormous.

Finally, a number of factors have been used to predict the outcomes of patients with NAFLD. NAFLD patients with T2DM are at especial high risk of adverse outcomes. In fact, the higher the number of metabolic conditions, the higher the mortality. In addition to these clinical factors, stage of fibrosis (stage 2 or higher) has been associated with mortality. Although initial data about disease stage was generated using histologic data, more recently, non-invasive tests (serum-based and imaging-based) are being validated as prognostic tests or algorithms in NAFLD-NASH.

In summary, NAFLD and NASH have become one of the most common causes of CLD around the world. The prevalence of NAFLD and NASH are rapidly growing due to the pandemic of obesity and T2DM. In addition to high prevalence, mortality, morbidity and economic impact of NAFLD and NASH pose significant burden to the society. Despite this increasing burden, awareness about this disease is quite low among all stakeholders, especially those who are at the forefront of potentially

encountering patients with NAFLD such as primary care providers and diabetes experts. This conundrum of high burden and low awareness is worsened by lack of effective drug treatment which is specifically developed for NASH. In this context, a multi-faceted approach involving patients, providers, industry and policy makers at local and global level is critical.

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Fatigue in Chronic Liver Disease and Non-alcoholic Fatty Liver Disease

ABSTRACT

Fatigue is a non-specific symptom associated with a decrement in performance (physical or psychological) that can be objectively measured or subjectively self-reported. Fatigue is associated with lack of energy, feelings of exhaustion unaided by sleep as well as perception or inability to perform mental and physical activities. Fatigue can be normal when associated with an identifiable cause and relieved by rest. In contrast, pathological fatigue is not relieved by rest and is difficult to manage. Additionally, Fatigue can be classified as central fatigue related central nervous system manifested by decreased motivation and drive and most likely mediated by systemic cytokines. In contrast, peripheral fatigue is related to a reduction in the ability to exert muscular force after exercise. This type of fatigue may be related to muscle, mitochondrial abnormalities and the related pathways. Fatigue can be measured by objective tools that can measure endurance and performance. Fatigue can also be measured by self-reports such as FACIT-F or FSS. Fatigue is a common symptom in patients with chronic liver disease (CLD). It is estimated that 50-85% of patients with CLD experience fatigue. In this context, patients with hepatitis C virus (HCV) infection, primary biliary cholangitis and non-alcoholic fatty liver disease are most notably affected by fatigue. In addition to etiology of CLD, severity of liver disease such as presence of cirrhosis can worsen fatigue. In HCV infected patients, 15-30% have clinically important fatigue. Furthermore, evidence from clinical trials suggest that HCV cure that can be achieved with all oral ant-HCV treatment can lead to improvement of fatigue. In this context, there is some remnant of fatigue that remains after HCV cure and this residual fatigue is associated with comorbidities. In patients with PBC, up to 45% experience significant fatigue and treatment with ursodeoxycholic acid does not seem to improve fatigue. In patents with NAFLD, 35-40% of patients who were enrolled from real world practices reported significant fatigue. Although phase 3 data is not available, improvement of hepatic fibrosis and MRI-
PDFF in patients with NASH and NAFLD seem to improve fatigue. Fatigue has significant negative impact on patients' health related quality of life (HRQL). This has been shown in patients with HCV, PBC and NAFLD who complete both fatigue-specific questionnaire and
HRQL questionnaires. In addition to HRQL, fatigue can negatively impact work productivity which can lead major negative economic burden. Finally, presence of fatigue can have negative impact on patients' prognosis. In one study of patients with advanced NASH-NAFLD, presence of fatigue was associated with adverse clinical events. More recently, data using NHANES suggests that presence of fatigue in patients with NAFLD can be associated with increased mortality. In addition to treatment the primary CLD, management of fatigue should include assessment and correction of other diseases such as anemia, hypothyroidism, cardio-respiratory diseases as well as depression/anxiety. Additionally, level of fitness as well as nutritional, sleep and stress status must be assessed. Although several therapeutic regimens have been assessed for treatment of fatigue but no FDA approved drug regimen is currently available in the US. Some agent that may potentially be of benefit in patients with fatigue include Pentoxifylline (PTX) and Ademetionine. PTX inhibits TNF production and may be associated with some type of CLD and related fatigue. However, the current data does not support the routine use of PTX in CLD-fatigue. Another agent is Ademetionine which has a
broad range of biological effects, including enhancing dopamine synthesis and dopaminergic tone as well as exertion of anti-inflammatory effects by reducing the expression of proinflammatory cytokine TNFα and increasing expression of anti-inflammatory cytokine IL-10. A number of studies from Italy, Russia and India have suggested potential improvement of fatigue in patients with CLD using Nevertheless, Ademetionine is not FDA approved for treatment of CLD-related fatigue in the United States. On the other hand, the drug is available in other countries and used for treatment of fatigue. In summary, fatigue is common among CLD and can have negative impact on clinical outcome (mortality), patient reported outcome (HRQL) and economic outcome (work productivity). Assessment of fatigue can be achieved objectively or subjectively using validated instruments. Treatment should include management of

reversible conditions (depression or anaemia), treatment of CLD (HCV) and assessment of related factors such as sleep and muscle function. Although FDA approved drugs are not available in the US, there is availability of Ademetionine in some countries. Future studies addressing fatigue among patients with NAFLD are important and must be undertaken.

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Noninvasive Tests for MAFLD: A Focus on Imaging:

ABSTRACT

Most NIT reviews focus on blood tests either on line calculators (APRI, FIB3 or NAFLD score) or proprietary makers such as FibroTest/Fibrosure/FibroSpect or ELF (Enhanced Liver Fibrosis). This presentation will look at imaging tests for fibrosis and fat assessment. The major tool used today is standard ultrasound that can qualitatively identify fat and indirectly portal hypertension. Over the last decade data has emerge on the use of elastography in the form of VCTE, TE, 2D SW, 3DSW, ARFI, and newer systems such a Velcur (SonicIncytes, Vancouver, Canada). These tools in combination with CAP, controlled attenuation parameter, we can integrate fat quantification with stiffness to come up with a better complete patient assessment. In addition, we have a new tool maximizing MR imaging: Liver MultiScan (Perspectum, Oxford, England) that uses key information derived from more advanced MR machines to calculation, Fat (PDFF), stiffness in combination with inflammation (cT1) and iron quantification. These new tools will marked improve patient care by more accurate assessment of fat, fibrosis, inflammation, and iron.

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COVID-19 and Liver Steatosis

ABSTRACT

The pandemic of coronavirus disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has resulted in over 55 million confirmed cases and over 6 million deaths globally. Although disseminated lung injury with the development of acute respiratory distress syndrome (ARDS) is the main cause of mortality in COVID-19, liver impairment has been frequently reported as a common manifestation.1,2 Our studies showed that patients with non-alcoholic fatty liver diseases (NAFLD) had a higher risk of progression to severe COVID-19, higher likelihood of abnormal liver function from admission to discharge and longer viral shedding time compared to patients without NAFLD.[3] Acute on chronic liver failure (ACLF) can also occur in patients with pre-existing NAFLD who had COVID-19.[4] The liver contains the largest number of macrophages (Kupffer cells) in the body and is a potent cytokine producer. We postulate that in patients with NAFLD, the polarization status of hepatic macrophages might be skewed from inflammation-promoting M1 macrophages to inflammation-suppressing M2 macrophages, leading to progression of COVID-19. We also observed that the prevalence of deep vein thrombosis (DVT) and D-dimer levels were significantly higher in COVID-19 subjects with NAFLD compared with those without NAFLD.[5] It may be possible that the hypercoagulable state in NAFLD contributes to the high incidence of thrombosis in these subjects during COVID-19 infections. Further understanding of the role of NAFLD in COVID-19 will have therapeutic implications.

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Genetics and epigenetics of MAFLD

ABSTRACT

Metabolic (dysfunction) associated fatty liver disease (MAFLD) affects 30-40% of people in affluent societies and is a primary cause of cirrhosis and hepatocellular carcinoma. MAFLD resembles a complex disease trait resulting from the dynamic interaction of environmental factors (e.g., caloric intake and composition, energy expenditure, the microbiome) acting on a susceptible polygenic background, with a key role for epigenetics in mediating this interaction.
Genome-wide association studies (GWAS) and candidate gene studies have enriched our understanding of genetic factors contributing to the known inter-individual variation in MAFLD in terms of disease spectrum and outcomes. In spite of the enthusiasm for using single genetic markers as a predictor of liver diseases in clinical practice such as *PNPLA3*, it should be noted that it is unlikely that this SNP alone or potentially any other SNP alone will allow meaningful discrimination between patients with and without significant liver damage. Yet, it can be projected that as more risk variants are identified, the predictive value of cumulative polygenic scores will increase, especially if it is incorporated with other clinical variables in novel models. Furthermore, the identification of risk genes and their regulatory regions provides the essential framework for an integrated and systems-based approach to understanding the molecular basis of MAFLD. Furthermore, the high plasticity of epigenetic modifications in response to environmental cues renders epigenetics a novel area for therapeutic drug discovery. Such information will be essential for the development of new therapies, which are ultimately likely to require personalized approaches. The recent advances in our ability to access large phenotypically well-characterized clinical cohorts, the availability of new technology platforms, better study designs, and statistical algorithms have us well placed to significantly improve our understanding of MAFLD development and its progression and to identify additional genetic ad epigenetic risk factors with modest effect and to correlate these with epigenetic factors. In this talk, I will provide an overview of the field as it pertains to MAFLD, with an emphasis on data about the potential clinical utility of polygenic scores. These advances have not yet been fully capitalized upon; hence, I will also discuss the promises and challenges of using genetics as a predictor of liver diseases and for gene-based stratification in clinical trials.

From NAFLD to MAFLD: a year in a review

ABSTRACT

Perhaps the greatest conceptual advance in thinking about fatty liver diseases over the last several decades has been the drive to rename and redefine the disease based on positive criteria. This advance was led by an international group of research leaders across the world, including from the Asia Pacific, Europe, North and South America, and the Middle East and Africa. While the terms non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) have been in use for over 4 decades, there are numerous problems with the definition. First and foremost, NAFLD is a disease of exclusion, without a set of positive criteria. Any such definition introduces heterogeneity to the clinical phenotype and ultimately, poor responses in clinical trial ecosystems. Secondly, the term NAFLD trivializes and discriminates on the one hand with the use of the word alcohol in the name, but also implies that a person who has alcohol-related liver disease or for that matter, any other liver disease, cannot concomitantly have a fatty liver disease associated with metabolic dysfunction. Indeed, moderate alcohol consumption has been reported in up to 2 thirds of people from many countries, while fatty liver disease related to metabolic dysfunction is present in up to a quarter of the population. Hence, liver disease with a dual etiology can and does frequently coexist. Conceptually then, the tasks for the international consensus were first to come up with a new and more appropriate name and secondly to come up with a positive definition and set of criteria for diagnosis of the disease. Importantly, the goals of such a definition had to include that it reflects pathophysiology and can be useful for clinical research studies, but most importantly, should have utility in daily clinical practice. The name that has been proposed by international consensus is metabolic (dysfunction) associated fatty liver disease or MAFLD, which refers to the pathophysiology of the disease, but is distanced from both alcohol and obesity. The new definition is simple to use in clinical practice even in resource-limited settings, the latter being critical for widespread acceptance in what is a very common disorder. Since publication, MAFLD has been accepted by international liver associations (APASL, ALEH, and the Middle East), patient groups, and allied health alike. Critically, in moving from a concept to evidence, multiple studies indicate that MAFLD outperforms NAFLD for the identification of patients with more advanced liver disease, and for risk stratification both for liver and extrahepatic complications. Based on these transformational changes, in future, we will witness better patient stratification leading to precision medicine, the development of multidisciplinary models of care, and innovative clinical trial designs.

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Liver fibrosis and HCC in the Era of MAFLD

Abstract

Metabolic (dysfunction) associated fatty liver disease (MAFLD) is defined as evidence of hepatic steatosis with invasive or noninvasive methods and the presence of at least 1 of 3 metabolic dysfunctions, such as excess weight or obesity, type 2 diabetes mellitus or evidence of metabolic dysfunction (increased waist circumference and an abnormal glycemic and lipid profile) . MAFLD is a complex condition that led to series complications such as liver failure as well as HCC.

Currently, MAFLD is the second leading etiology of patients listed for transplantation because of HCC, and from 2004 to 2015 the number of MAFLD patients on the transplantation list in the USA has almost tripled. The burden of patients with MAFLD, MAFLD -cirrhosis and its associated complications is also growing. The estimated annual HCC incidence in the progressive form of MAFLD is about 0.3%. The risk of HCC development is higher in men and increases with age, more advanced fibrosis, progressive obesity, insulin resistance and diabetes mellitus. several features seem to be particularly important in this hepatocarcinogenic process the insulin resistance which is associated with high levels of insulin which is an important growth factor; the dysfunction of the Akt/mTOR pathway which bridges metabolism control with cell proliferation; the oxidative stress; and a dysbiosis with quantitative and qualitative changes of the gut microbiota. Also, advanced fibrosis and cirrhosis are at increased risk of HCC in patients with MAFLD, though HCC can also arise in the absence of advanced fibrosis

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Liver Transplantation and MAFLD

ABSTRACT

The liver is the largest gland in the human body, which is responsible for hundreds of critical functions to keep the body free from toxins and harmful substances. Besides fighting infections and illness, the liver is responsible for removing toxins, such as alcohol, from the body and controls cholesterol levels. It produces a special liquid, known as bile, which helps break down fat and boosts digestion. The liver also helps your body fight infections by removing bacteria from the blood. There are various liver diseases that are detrimental to human health.

The common liver diseases include:
• Alcoholic liver disease
• Nonalcoholic Steatohepatitis
• Liver Cirrhosis
• Fatty Liver Disease
• Hepatitis - A, B, C
• Fatty Liver of Pregnancy

We are one of the very few liver units in the country having the ability to manage sick patients and undertake liver transplantation on an emergency basis. In our hospital, we get many patients with Acute Liver Failure, which refers to a severe failure of liver function within a matter of days to weeks in a previously healthy person. The most common cause of ALF i is viral infection due to hepatitis viruses. Other causes of ALF are overdose of paracetamol, consumption of poisonous materials like phosphorus compounds (found in rat killer poison), autoimmune hepatitis, and Wilson's disease. Patients with acute liver failure usually present with jaundice, bleeding problems, and altered behavior. Patients with acute liver failure need urgent transfer to a hospital with liver transplant service to have a successful outcome. Some of these patients may recover with medical treatment alone. This treatment has to be provided in an intensive care unit with careful monitoring by liver physicians and intensive care specialists. Patients who reach certain criteria on blood tests need urgent liver transplantation as they will not survive with medical treatment. Urgent living donor or deceased donor liver transplantation is lifesaving in this situation and Sanar International Hospital is one of the best liver transplant hospitals in India.

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Why the MAFLD Name and Definition is the Way Forward

ABSTRACT

Metabolic (dysfunction) associated fatty liver disease or MAFLD is the most common liver disease globally, affecting the latest analysis, up to 50% of the population. The pathogenesis of the disease is complex and multifactorial representing the interaction of genes and epigenetics with the environment, and the metabolic milieu of the individual. This results in the meta-inflammation of multiple tissues. With this understanding of pathophysiology and the observation that the liver is but one target organ affected by metabolic dysregulation, it follows, that patients with MAFLD will concomitantly have competing risks for adverse outcomes from other chronic diseases. This not only includes cardiovascular and cerebrovascular disease but also extra-hepatic cancers as well as chronic kidney and respiratory disease. As the extent of metabolic dysregulation increases as measured by common parameters including dyslipidemia, hypertension, dysglycaemia, and inflammation (hsCRP), so does the stage of liver disease and the risk of adverse liver-related outcomes. Equally, these patients are at risk of competing in extrahepatic events. The ratio of hepatic to extrahepatic risks for adverse outcomes increases with the increasing liver disease stage. Among the categories of metabolic risk that define MAFLD, type 2 diabetes confers the greatest risk for liver fibrosis stage and for adverse liver outcomes.

The close association of MAFLD, and metabolic steatohepatitis (MeSH) with the extrahepatic disease has been reported in multiple studies and meta-analyses. In all, the MAFLD term identifies patients with more advanced disease and with a greater risk of hepatic and extrahepatic adverse outcomes than the outdated term NAFLD. Using the MAFLD definition, it will be possible in future studies, to more clearly delineate the role of this disease in contributing to clinical outcomes in the presence of concomitant liver diseases such as viral hepatitis or alcohol-related liver disease. Ultimately, for treating patients, therapies that target metabolic dysregulation with systemic activity will be the ones most likely to result in the greatest benefit, rather than just focusing on liver disease risk reduction. Based on all these data, there is no doubt that the name MAFLD and its definition is the way forward to increase awareness and improve the care of patients.

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Predicting outcomes and monitoring patients with NAFLD/MAFLD

ABSTRACT

Among patients with metabolic dysfunction associated with fatty liver disease (MAFLD), the degree of fibrosis is predictive of clinically relevant outcomes such as decompensation, hepatocellular carcinoma (HCC), and liver-related mortality. FIB-4 is recommended as the first-line screening test for fibrosis due to its widespread validation, low cost, and availability as well as having a slightly higher accuracy compared to the NAFLD Fibrosis Score (NFS). Although FIB-4 is associated with the development of liver-related outcomes at a population level, it is relatively insensitive, lacks specificity with increasing age, and has reduced accuracy in type 2 diabetes. Combining two or more non-invasive fibrosis tests (eg serum test with Fibroscan) is recommended for the detection of advanced liver fibrosis, although has modest positive predictive values (62-66%). Magnetic resonance elastography (MRE) is the most accurate non-invasive technique to assess liver fibrosis in MAFLD, and also predicts prognosis, however, is limited by expense and accessibility. Prognostication of outcomes in MAFLD patients with cirrhosis can be performed using cirrhosis-specific scores such as ABIDE. The prediction of HCC in MAFLD remains challenging with scores from the US Veterans Affairs data sets having modest accuracy but higher than scores based on genetic variants. Monitoring MAFLD patients over time also remain challenging. Changes in FIB4, NFS, fibroscan, or MRE, correlate with changes in fibrosis over time, however, their predictive value at an individual patient level is modest. Persistently normal or low values have the greatest utility in confirming the absence of fibrosis progression whereas increasing values are less predictive of fibrosis progression.

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Abstract

Patient Guidelines Focusing on Non-alcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the United States and in other industrialized nations. It has increased in prevalence in parallel with rising in obesity and metabolic syndrome, and NAFLD now represents a leading indication for liver transplantation in the United States.

A streamlined approach to the prevention, diagnosis and treatment of the disease remains of utmost importance. All societies have provided recommendations for the management of NAFLD.

Guidance for diagnosis of NAFLD suggests the following: (1) evidence of hepatic steatosis by imaging or histology, (2) no significant alcohol consumption, (3) no competing causes of hepatic steatosis, and (4) no co-existing causes of chronic liver disease.

One notable change in guidance, compared to previous years is a stronger emphasis on assessment for metabolic risk factors in patients with incidental findings of hepatic steatosis and normal liver chemistries but lacking liver-related symptoms. There is evidence that patients with NAFLD have increased cardiovascular morbidity and mortality. In addition, advanced fibrosis is associated with an increasing number of metabolic co-morbidities. Thus, early identification and treatment of individual components of the metabolic syndrome are critical in preventing both cardiovascular and liver-related mortality.

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Current Available Pharmacological Therapeutic Options for NAFLD

ABSTRACT

Pharmacological treatment for non-alcoholic fatty liver disease (NAFLD) remains an area of active research with many drugs that are under various stages of development and testing. There are no FDA-approved treatments currently. Medications that have been evaluated in controlled clinical trials and demonstrated potential benefit include Vitamin E, Pioglitazone, and Liraglutide.

With regards to Vitamin E in patients with NASH, there have been multiple randomized controlled trials with variable endpoints, durations, and formulations. There has been modest histological improvement with variable impact on fibrosis. There has been a suggestion of all-cause mortality with a high dose of Vitamin E. Current recommendation is for non-diabetic patients. Thiazolidinediones, in this group pioglitazone, has been approved for use in patients with biopsy-proven NASH and can also be used in patients with diabetes.

Liraglutide which is a GLP-1 agonist has shown potential benefit in patients with NASH in small randomized controlled trials. Interestingly weight loss may have accounted for the difference that was noted in patients with NASH. Statins have been shown to be safe in use for patients with NAFLD/NASH since many of these patients have cardiovascular risk factors. Cardiovascular risk factor modification is an important part of patients but there has not been any documentation of histological improvement.

Many drugs remain in the pipeline for NASH and the most promising in development or pending FDA decisions are Obeticholic acid, Elafibranor, and antifibrotics.

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MAFLD, A New Disease

Abstract

Non-alcoholic fatty liver disease (NAFLD) is described as evidence of hepatic steatosis, at least 5% or higher of hepatocytes, either by imaging or histology. In this definition, the lack of secondary causes of hepatic fat accumulation including significant alcohol consumption, viral, autoimmune, or genetic disorders. Several variants in different genes are associated with the susceptibility to the progression of NAFLD. Discrimination of NAFLD with NASH or without NASH is a matter of debate. However, the definition of Metabolic Associated Fatty Liver Diseases (MAFLD) would help to overcome the dichotomization of NASH and Non-NASH.

MAFLD is described as hepatic steatosis, at least 5% or higher of hepatocytes, either by imaging or histology. Besides that, the patients must have at least two of three criteria such as 1- the patients must be overweight or obese 2 the patients must have type 2 diabetes mellitus 3- The patients with lean/normal weight must have at least two metabolic risk abnormalities as follows: a-Waist circumference ≥102/88 cm in Caucasian men and women or ≥ 90/80 cm in Asian men and women. b-Blood pressure ≥ 130/85 mmHg or specific drug treatment. c-Plasma triglycerides ≥ 150 mg/dl (≥ 1.70 mmol/L) or specific drug treatment. d- Plasma HDL cholesterol < 40mg/dl (<1.0 mmol/L) for men and < 50 mg/dl (<1.3 mmol/L) for women or specific drug treatment. e-Prediabetes f- HOMA score ≥ 2.5 g-Plasma high-sensitivity C-reactive protein level > 2 mg/L.

The heterogeneous nature of fatty liver diseases suggests that cannot be considered or managed as a single condition with a “One size fit all “approach to therapy. The definition of MAFLD facilitates the assessment of disease severity in clinical practice. Definition of MAFLD increases of awareness of physicians regarding the management of the diseases. Diagnosis of cryptogenic cirrhosis attributable to metabolic derangements would be easier using the definition of MAFLD. The definition of MAFLD increases public attention and improves health policy actions. The definition of MAFLD reduces confusion and stigma regarding the disease.

In several clinical trials, MAFLD identifies patients with high cardiovascular risk, significant fibrosis, high proportions of metabolic co-morbidities, with severe liver steatosis. All causes of mortality, cardiovascular diseases related mortality, cancer-related mortality, and other cause mortalities are higher in patients with MAFLD compared to NAFLD. However, the definition of MAFLD may underestimate the actual prevalence of the disease. It may exclude patients without metabolic disturbances. Metabolic derangement may be absent in 30% of the patients with NAFLD. There should be definitive guidelines regarding the inclusion of genetic risk factors, phenotypic measurements, dietary intake, visceral adiposity, and alterations in the microbiota in the definition.

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Bariatric Surgery and MAFLD
Abstract

The prevalence of obesity and metabolic diseases such as type 2 diabetes and
Non-alcoholic fatty liver disease (NAFLD)/Metabolic associated fatty liver disease (MAFLD) has risen dramatically over the past decades. Bariatric surgery (BS)/Metabolic surgery(MBS) is very effective for obesity and metabolic comorbidities including NAFLD/MAFLD. Indications for BS/MBS vary across Asia-Pacific Countries. East/South East/South Asian countries have a lower BMI cut-off for BS/MBS (as compared to the Western/Caucasian population). BS/MBS have effects on food intake, gut hormone secretion, metabolic signaling pathways, and adipose tissue dysfunction. A reduction in hepatic fat content and an improvement in hepatic insulin resistance are among the earliest beneficial effects of bariatric surgery, which has therefore emerged as an attractive treatment option for NAFLD/MAFLD. BS/MBS provides long-term resolution of NASH and fibrosis regression. BS/MBS is associated with a significantly lower risk of incident major adverse liver outcomes and major adverse cardiovascular events in NASH and obesity. BS/MBS also reduces cancer risk (including HCC) in adults with NAFLD and severe obesity. BS/MBS has high mortality in decompensated cirrhosis. BS/MBS can safely be performed in selected patients with liver cirrhosis and is an attractive option in carefully selected transplant candidates with severe obesity. Sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) are equivalently effective for treating NAFLD/MAFLD. However, SG has become the preferred procedure in the last decade, especially for patients with cirrhosis. Reports of liver failure following BS/MBS (especially with older bypass procedures) have been reported. BS/MBS may be a risk factor for alcohol abuse. BS/MBS should be used after appropriate screening and with close follow-up, and the beneficial effects generally far outweigh the risks.

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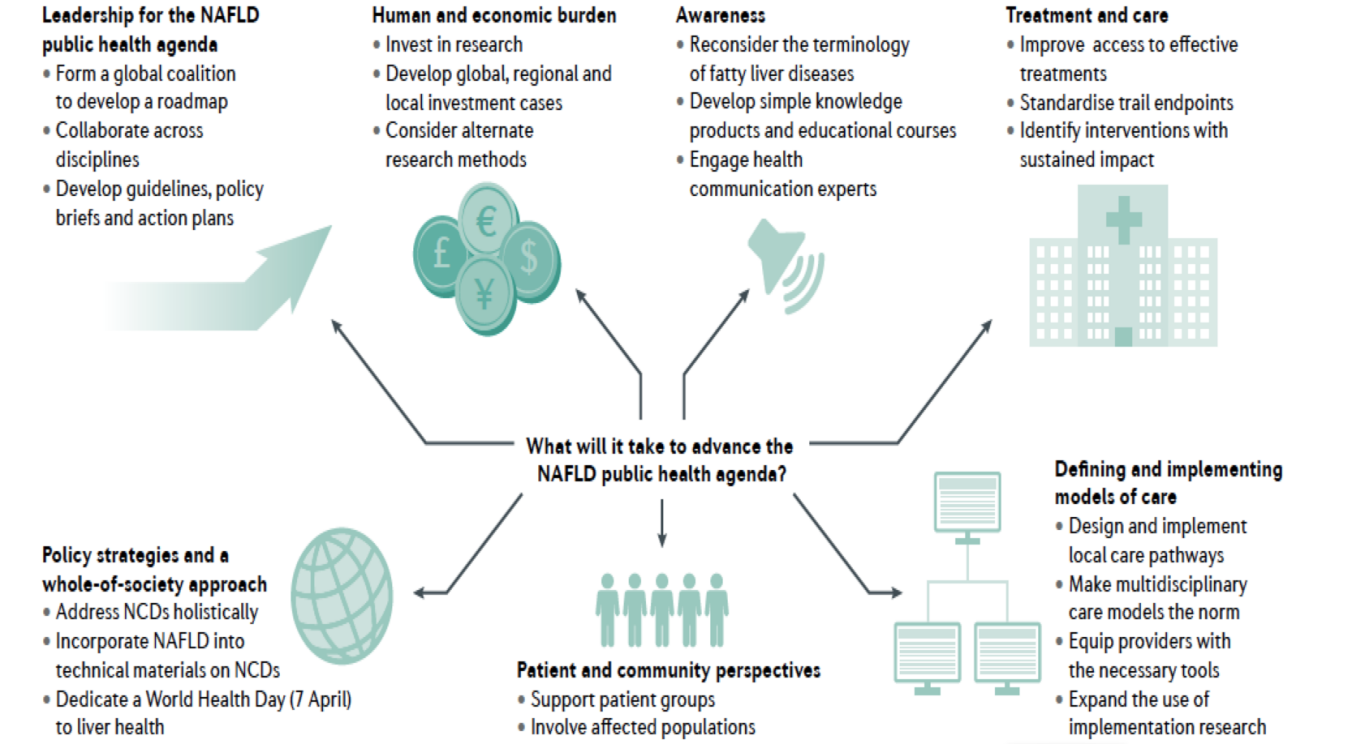
Abstract

Advancing the global public health and policy agenda for NAFLD

Non-alcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease globally but is widely absent from public health and policy agendas. In response, in 2021 more than 200 experts from around the world developed a global NAFLD public health consensus statement and recommendations (Figure), including advancing the NAFLD public health agenda by forming a global coalition to develop a roadmap; collaborating across disciplines; developing action plans, guidelines and policies that address NAFLD and linked non-communicable diseases holistically; monetary investment in NAFLD research; raising disease awareness, and improving models of care (MoCs).

The 'what, where who, and how' of NAFLD MoCs should include: developing guidance on screening and testing using non-invasive methods and on treatment strategies, establishing pathways that are patient-centered and tailored to the disease stage; properly articulating the care roles of and interactions between primary, secondary and tertiary care providers; and establishing where co-location of services for the treatment of NAFLD and common comorbidities would be feasible, integrating and coordinating care across the whole healthcare system. Effectively tackling NAFLD will also entail engaging patients and revising its terminology. AASLD and EASL with APASL, ALEH, and others have been leading an inclusive, global multi-stakeholder process, including patient groups, to examine nomenclature options and ramifications to inform agreeing on a name that addresses stigma and advances the understanding of disease subtypes, its natural history and its response to treatment, so as to help in battling this public health crisis.

Figure. NAFLD public health consensus statement recommendations.


Leadership for the NAFLD public health agenda
• Form a global coalition to develop a roadmap
• Collaborate across disciplines
• Develop guidelines, policy briefs and action plans
Human and economic burden
• Invest in research
• Develop global, regional and local investment cases
• Consider alternate research methods
Awareness
• Reconsider the terminology of fatty liver diseases
• Develop simple knowledge products and educational courses
• Engage health communication experts
Treatment and care
• Improve access to effective treatments
• Standardise trail endpoints
• Identify interventions with sustained impact
What will it take to advance the NAFLD public health agenda?
Policy strategies and a whole-of-society approach
• Address NCDs holistically
• Incorporate NAFLD into technical materials on NCDs
• Dedicate a World Health Day (7 April) to liver health
Patient and community perspectives
• Support patient groups
• Involve affected populations
Defining and implementing models of care
• Design and implement local care pathways
• Make multidisciplinary care models the norm
• Equip providers with the necessary tools
• Expand the use of implementation research

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MULTIDISCIPLINARY APPROACHES FOR THE MANAGEMENT OF NAFLD (MAFLD)

Abstract

NAFLD (MAFLD) is usually associated with obesity, dyslipidemia, insulin resistance (IR) or T2DM, and arterial hypertension which are defined as a metabolic syndrome (MS). Apart from these MS components, there are some other established linkages of NAFLD such as atherosclerosis, cardiovascular diseases (heart failure, arrhythmia), chronic kidney disease (CKD), obstructive sleep apnea, polycystic ovarian syndrome, and hypothyroidism. Furthermore, recent evidence has increased the broad spectrum of other extra-hepatic emerging linkages, including vitamin D deficiency, osteoporosis, male sexual dysfunction, coronary artery calcification, carotid artery, and aortic valve sclerosis, IHD, cardiomyopathy, ischemic stroke and fatigue, albuminuria and urolithiasis, periodontitis, psoriasis, and tumors (namely HCC), colorectal and breast cancer. Treatment of NAFLD encompasses lifestyle modification, targeting MS components, liver-directed pharmacotherapy, and managing liver cirrhosis complications. Mediterranean diet, low in saturated fats and animal protein, high in antioxidants and fibers, omega-3, and polyphenols, is suggested to be effective in NAFLD. Due to its anti-inflammatory, antioxidant, lipid-lowering, prebiotic, and probiotic properties, it reduces weight, insulin resistance functional liver tests, and steatosis, and as a result, risks of CVD, MS, DM, and dyslipidemia. Physical activity leads to increase peripheral insulin sensitivity with a reduction of lipogenesis, visceral fat, and lipid supply to the liver, and as a result, a rise in VLDL clearance, a decrease in lipid storage, and liver triglyceride content. Targeted therapies for MS and other associated comorbidities in patients with NAFLD may also have a positive impact on the liver. In particular, pioglitazone improves liver histology in patients with biopsy-proven NASH with and without T2DM (PIVENS study), GLP-1 agonists (liraglutide) lead to histological resolution of non-alcoholic steatohepatitis in 39%, as well as to decrease ALT and body weight (LEAN study), SGLT2 inhibitors (empagliflozin) help to reduce the liver fat fraction evaluated by MRI-PDFF from 16 % to 11% as well as ALT level (E-LIFT study). In some trials, statin treatment led to a decrease ALT, AST, GGT, and ALP, as well as ballooning, lobular inflammation, and collagen deposition in the liver. Fibrates may reduce triglycerides, IR, ALP, gamma-GT, and transaminases, as well as ballooning and liver stiffness. PUFAs were demonstrated to reduce, ALT, AST, GGT, TG, glucose, IR, and liver fat. RAS blockers (especially angiotensin receptor blocker Telmisartan) were shown to decrease IR and liver fibrosis in some studies. In summary, some interventions and targeted therapies for MS and other NAFLD-associated comorbidities have or may have some potential benefits for liver health.

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Abstract

Safety and Efficacy of Glucagon-like Peptide Type 1 in NASH

Background. Dulaglutide has been approved as a hypoglycemic agent for the treatment of patients with T2DM. A positive effect on carbohydrate metabolism and body weight was shown in RCT. It was found that GLP-1 agonists may prevent the progression of NAFLD directly affecting lipid metabolism and inflammation. Aim. To assess the effect of dulaglutide on carbohydrate and hepatic metabolism in patients with T2DM and NAFLD in real clinical practice in the Moscow Region. Design. An open observational prospective cohort study of real clinical practice. After approval by LEC 45 pts with T2DM and NAFLD, BMI ≥ 27 kg / m2, receiving basic therapy at the time of inclusion with a daily dose of metformin ≥ 1,500 mg as monotherapy or as part of combination therapy were conducted in the study with the treatment of dulaglutide subcutaneous injections 1,5 mg weekly for 26 weeks. Mean age 55,6±10,6 лет, 16(36%) men. All patients undergo a physical examination with height, weekly weight, waist and hip circumference measurement, monthly blood sampling tests (HbA1c, FPG, ALT, AST, GGT, lipids, hematology), ultrasound, elastometry using Fibroscan before and after 26 weeks of treatment. Also FIB4, and FLI were calculated before and after 26 weeks of treatment. Statistical analysis was done using by MedCalc Version 19.1 using the Wilcoxon test for nonparametric and the Fisher test for parametric data. Results presented in the median with interquartile range (IQR). Results. In real clinical practice weekly visits, it was found statistically significant difference in weight loss. 5%weight loss was found in 56,0 % pts, 10% weight loss - in 7,0 % of patients, median weight loss was -5 kg in 26 weeks. A statistically significant decrease in weight, BMI, waist circumference, HbA1c, and ALT levels were detected in the whole group, despite the fact that the goal of more than 5% of the initial weight loss has reached only 56,0% of patients. There was no statistical difference in hip circumference, FPG, AST, GGT, or lipids levels. Median of HbA1c decreased from 7,4% (6,1-8,4) to 6,3 (5,6-6,8), ALT median decreased from 67.2 (IQR 35.5-96.9) to 38.2 (IQR 22.6-62.9). A downward trend in FLI and TE was also noted, although absolute values corresponded to a high risk of steatosis. Conclusion. In real clinical practiceDulaglutide may have a positive effect on weight loss, and metabolic and hepatic parameters in patients with NAFLD and T2DM.

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Abstract

Drug Development Overview and Clinical Pharmacology

Non-alcoholic fatty liver disease is a spectrum of pathological changes in the liver: excessive accumulation of triglycerides, the development of inflammation, fibrosis, and cirrhosis. NAFLD is the most common chronic disease in the world. The pathogenesis and progression of the disease are often described by the "multiple hit hypothesis". The first "hit" is the accumulation of excess triglycerides in hepatocytes. The deposition of highly toxic free fatty acids in the background of insulin resistance leads to lipid peroxidation and oxidative stress. Consistently or simultaneously with the first "hit", the second one develops - in the background of increased peroxidation processes, reactive oxygen species accumulate, and the production of pro-inflammatory cytokines increases. The ongoing shift in the cytokine balance towards the overproduction of pro-inflammatory cytokines plays an important role in the development and progression of NAFLD by stimulating hepatic inflammation, cell necrosis, apoptosis, and fibrosis induction. Genetic and epigenetic factors can contribute to the chronicity of the inflammatory process, the death of hepatocytes, the activation of liver stellate cells, and their increased production of the extracellular collagen matrix. Thus, inflammation is one of the key links in the pathogenesis of NAFLD and the most important factor in its progression. Therefore, it is extremely important to recognize the inclusion of anti-inflammatory drugs in therapy. One such drug is glycyrrhizic acid, which is marketed as fixed combinations with phospholipids or UDCA. The results of the studies indicate that glycyrrhizic acid has anti-inflammatory activity associated with an inhibitory effect on the production of TNFα and IL-6, as well as an antifibrotic effect due to the suppression of the activity of liver stellate cells and their production of collagen. The efficacy and favorable safety profile of glycyrrhizic acid have been proven in two multicenter, double-blind, randomized, placebo-controlled, post-registration clinical trials "GEPARD" and "JAGUAR", which included 300 patients.

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Abstract

Life Style and NAFLD

The development of non-alcoholic fatty liver disease is closely related to lifestyle factors, namely excessive calorie intake combined with reduced physical activity and exercise. The presentation gives evidence for lifestyle modification as a tool to improve liver steatosis and liver histology in patients with non-alcoholic fatty liver disease/non-alcoholic steatohepatitis and strategies to overcome these obstacles in the clinical setting. The development of non-alcoholic fatty liver disease (NAFLD) is closely related to lifestyle factors, namely excessive consumption of high-calorie foods combined with reduced physical activity and exercise. Global urbanization and modernization in the 20th and 21st centuries have been associated with unhealthy lifestyle changes. Consequently, over the past 3 decades, there has been a significant increase in the average global body mass index (BMI) and the prevalence of obesity, which are pathophysiological factors in NAFLD. An example of this is the rapid increase in the prevalence of NAFLD in Asia over the past 15 years, associated with urbanization and the transition to "Western" food. The drivers behind unhealthy lifestyles and choices are complex and multifaceted, but they can be successfully addressed to reap significant health benefits. If successful, lifestyle changes leading to weight loss are very effective in reducing fibrosis and necroinflammatory changes in non-alcoholic steatohepatitis (NASH). However, sustainable lifestyle changes and weight loss are difficult to achieve, and unfortunately, lifestyle changes alone do not bring success to every person. Lifestyle interventions can be very effective in treating NAFLD across the spectrum of disease and managing not only liver health but also cardiovascular and metabolic disease. It is often difficult for our patients to achieve lifestyle changes, but with individual support, significant long-term changes are possible. Further research is needed to determine optimal nutritional therapy in combination with physical activity/exercise that improves liver damage and fibrosis; More evidence is needed to determine which patients are most likely to benefit from lifestyle interventions and, in particular, whether the initial stage of fibrosis affects the effectiveness of lifestyle changes. If lifestyle changes are achieved and maintained, the benefits to liver, heart and metabolic health may outweigh the effectiveness of drugs. Therefore, lifestyle modification should remain the main focus for all patients with NAFLD.

Conclusion: The main treatment for NAFLD is diet and lifestyle changes. An individual approach should be taken, combining diet and gradual increase in aerobic/strength load.

Identification and correct diagnosis at the onset of NAFLD disease prevent irreversible consequences and reduce mortality.

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Abstract

NAFLD in Children

Nonalcoholic fatty liver disease (NAFLD), defined as the abnormal hepatic accumulation of macrovesicular fat in the absence of other etiologies, such as infection, autoimmune processes, hepatotoxic drugs, and storage disorders, is the most common cause of liver disease in children and teenagers. NAFLD represents a spectrum of diseases from simple hepatic steatosis to steatohepatitis that may develop into progressive hepatic fibrosis and even cirrhosis. It is the most rapidly increasing indication for liver transplantation in adults, and also a highly prevalent liver disease in children. The incidence of NAFLD has increased over the past decade. NAFLD is a common disease in children, with a prevalence rate between 5% and 10%. Prevalence is higher in older children, boys, and children of Hispanic ethnicity or Asian race compared with younger children, girls, or children of the black race. Obesity is one of the strongest risk factors for NAFLD in children, but most children with obesity do not have NAFLD. The prevalence rate of NASH and advanced fibrosis in children with NAFLD is ~20% to 50% and between 10% and 20%, respectively. The majority of children with NAFLD are overweight or obese, there is an increasing subset of children with normal body mass index with so-called lean NAFLD. NAFLD in children is associated with several extrahepatic manifestations, including hyperlipidemia, insulin resistance, and obstructive sleep apnea. The pathogenesis of NAFLD in children involves a multifactorial interaction among genetics, in-utero exposures, early childhood exposures, and ongoing nutritional exposures. Although there are some similarities between pediatric NAFLD and adult NAFLD, liver biopsies in children show histologic differences between the two. The current standard-of-care treatment of NAFLD in children is a lifestyle change to decrease caloric intake and increase physical activity. There are no medications currently approved for the treatment of NAFLD in children.

CONCLUSIONS AND RESEARCH NEEDS: The emergence of NAFLD has been an important change in the landscape of the pediatric liver disease. It is necessary to recognize the risk factors of NAFLD for prevention in childhood since NAFLD is asymptomatic in the early stage. Keywords Nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, obesity, children, chronic liver disease

Hepatocellular Carcinoma Emergence in Armenia
The outcome of Multiple Risk Factors

January 2019 to March 2020

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Abstract

Background: According to the most recent estimates of GLOBOCAN, primary liver cancer (PLC) emerged as a major health threat in Armenia. We intend to provide the first detailed description of PLC risk factors and clinical presentation in Armenia.

Methods: A series of 69 patients were diagnosed with PLC. Demographic data, risk factors, histology, PLC work-up, symptoms, and biological variables were collected at the time of diagnosis and patient survival was determined long-term.

Results: HCC was found in the majority of cases of PLC (95.6%) while tumors appeared in patients with cirrhosis in most cases (90.3%). The sex ratio of this series was (M: F=3.9) with the mean age of patients (56. 9±11.4 years). HCV was the main risk factor (68.1% of cases) followed by heavy alcohol consumption (51.7%) followed by HBV (18.8%). Metabolic disorders were prevalent in 63.7% of the patients with obesity being the most common (BMI≥30). The median overall survival time was 10 months (IQR:6-14). Younger patients (≤57.0 years) were characterized by an even high proportion of male sex (94.1% vs 65.7% for patients over >57 years old, P<0.01), as were frequent tobacco consumption (85% vs 58.8%, P<0.05). We noticed that HBV-infected patients self-reported significantly higher rates of somatic cancers in their families (92.3% vs 58.6%, P<0.05).

Conclusion: The current problem of HCC in Armenia seems to be due to the presence of HCV spread with metabolic disorders and to the alcohol/tobacco use disorders. Further studies are warranted to characterize viral characteristics and molecular alterations that may promote liver tumorigenesis in Armenia.

Keywords: Hepatocellular carcinoma, metabolic disorders, HCV, HBV alcohol consumption

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Abstract

The current situation with NAFLD in Armenia

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NAFLD is the leading cause of chronic liver disease in the Western world. The prevalence of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) in Armenia is not known. We reviewed the published data on the prevalence of known risk factors for NAFLD/metabolic syndrome, including obesity, diabetes, and hypertension. We also surveyed focus groups of primary care physicians in order to assess the common practices in the diagnosis and treatment of patients with fatty liver detected by ultrasound. According to Global Nutrition Report, 53.7% of men and 53.9% of women in Armenia were overweight in 2016, and the prevalence of obesity was 17.1% among men and 23.0% among women. Obesity rates were predicted to reach 19.4% in men and 29.6% in women by 2020. Based on the official national statistical report, the prevalence rate of diabetes among adults in Armenia was 4.6% in 2021, and this number has been steadily increasing over the past 16 years. Hypertension has been officially reported to be prevalent in 6.2% of the Armenian adult population; however, cross-sectional studies have produced a prevalence rate of 28.6% among adults. The survey of physicians and observation of common practices has shown that in patients with ultrasound-confirmed fatty liver there is inadequate scrutiny regarding history taking (alcohol consumption patterns), lack of awareness of non-invasive fibrosis measurement scores, as well as widely observed unwarranted prescription of so-called “hepatoprotective” which has not shown any Effectiveness.

In summary, the high prevalence of NAFLD risk factors and commonly observed gaps in the care for these patients call for studies to assess the prevalence of NAFLD/NASH in Armenia and develop and implement locally adapted guidelines.

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Alcoholic and non-alcoholic fatty liver disease: a comparative analysis

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Abstract:

The most common causes of fatty liver are excessive alcohol consumption leading to alcoholic liver disease (ALD) and insulin resistance manifested as non-alcoholic fatty liver disease (NAFLD). These two disease entities have clearly distinct etiologies; however, they share many pathogenetic factors such as activation of lipogenesis transcription factors and suppression of lipolysis, and assembly of very low-density lipoproteins. There are also strikingly similar histologic features in different stages of the two diseases, including steatosis, steatohepatitis, and fibrosis.The reasons behind these similarities are yet to be fully understood. However, there are data pointing to a higher ethanol lever in plasma of NAFLD patients compared to healthy controls, without preceding alcohol consumption. One possible explanation is the increased endogenous ethanol production by gut microbiota of patients with non-alcoholic steatohepatitis (NASH). Other studies suggest a different mechanism, such as modulation of alcohol dehydrogenase enzyme in the liver by insulin resistance. Several differences are observed in the natural history, concerning the rate of progression of simple steatosis to hepatic fibrosis and cirrhosis. In patients with ALD, the estimated 5-year risk of cirrhosis was 6.9% in case of steatosis and 16.0% in steatohepatitis. Liver cirrhosis developed in 0%-8% of NAFLD patients without hepatic fibrosis over a mean follow-up period of 3.2-13.8 years. A long-term (about 20 years) follow-up study reported that among patients with simple hepatic steatosis, 22% in the ALD group and 1.2% in the NAFLD group developed liver cirrhosis. Autopsy-based results indicated the ratios of simple hepatic steatosis to steatohepatitis or liver cirrhosis to be 2.33:1 in ALD patients and 3.60:1 in NAFLD patients.
In conclusion, studying the similarities and differences in pathogenesis, natural course and clinical manifestations of ALD and NAFLD may yield important clues to the understanding of the underlying mechanisms and developing effective treatment strategies for both disorders.

Keywords: alcoholic liver disease, non-alcoholic liver disease, insulin resistance, steatosis, steatohepatitis, liver fibrosis, cirrhosis

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Abstract

Nonalcoholic fatty liver disease and Diabetes Mellitus

The global prevalence of the not-alcohol fatty liver disease is considerably higher than previously estimated and is continuing to increase at an alarming rate. Nearly one-third of the adult population has the nonalcoholic fatty liver disease (NAFLD), with men much more likely to have the disease than women. Although the pathogenesis of the disorder is not fully clarified, insulin resistance (IR) is widely considered a central feature of NAFLD, which is strongly and independently associated with an increased risk of type 2 diabetes mellitus (T2DM) and cardiovascular disease. The most important link between NAFLD and T2DM is insulin resistance. The most recent recommendation is to screen patients with NAFLD for T2DM. T2DM increases the risk of NAFLD progression. Patients who presented with NAFLD and T2DM have shown a greater risk of chronic liver disease, fibrosis, and cirrhosis compared to non-DM patients., Moreover, NAFLD in DM patients increases the risk of cardiovascular disease and other diabetic complications. NAFLD also increases the risk of DM complications. There are common management options for the two diseases. Lifestyle changes can be important in the initial management of both diseases. Medications that are used to treat T2DM are also used in the management of NAFLD, such as metformin, thiazolidinediones (TZD), glucagon-like peptide-1 (GLP-1) analogs, and dipeptidyl peptidase-4 (DPP4) inhibitors. Bariatric surgery is often used as a last resort and has shown promising results. CONCLUSIONS AND RESEARCH NEEDS: It is important to raise awareness among clinicians about the relationship between T2DM and NAFLD and how the presence of one disease is suspicious of the existence of the other. It would be interesting and of great necessity to know the prevalence of NAFLD in T2DM patients in the Republic of Armenia.

Keywords: Nonalcoholic fatty liver disease, diabetes mellitus, insulin resistance, hypoglycemic medicines, obesity.

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Abstract

METABOLIC SYNDROME AND HYPERFERRITNEMIA IN PATIENTS WITH NAFLD

Objectives: NAFLD is the commonest liver disease in Western countries, affecting 17–46% of adults. It correlated with the prevalence of metabolic syndrome, which increases the risk of more advanced liver disease, both in adults and in children. Metabolic risk factors/components of Metabolic Syndrome are following:
1. Waist circumference ⩾94/⩾80 cm for Europid men/women.
2. Arterial pressure ⩾130/85 mmHg or treated for hypertension.
3. Fasting glucose ⩾100 mg/dl (5.6 mmol/L) or treated for T2DM.
4. Serum triacylglycerols >150 mg/dl (>1.7 mmol/L).
5. HDL cholesterol <40/50 mg/dl for men/women (<1.0/<1.3 mmol/L).
The aim of the study is evaluation of correlation BMI, liver function tests, and lipid profile with NAFLD in small Armenian cohort.
Methods: 50 patients with ultrasound-diagnosed NAFLD (hepatic steatosis) were involved in the study (56.4% male), from 27 to 76 years old (51.9±12.8), BMI 34.2±6.4 kg/m^2. We evaluated following biochemical and lipids profile parameters: AST, ALT, GGT, fasting glucose, triglycerides (TG), cholesterol (CHOL), high density lipoprotein (HDL), low density lipoprotein (LDL). We also checked ferritin (FERR) and Vitamin D-25OH level. Atherosclerosis risk, metabolic syndrome and high blood pressure also were part of report.
Statistical analysis was done by SPSS 11.0.
Results: 41% had metabolic syndrome, 36% had diabetes, 31% had High blood pressure. F4 had 12.8% of patients. Range and mean±SD or SE of evaluated parameters: FERR 60.14-1946.80 ng/mL (527.70±129.49); TG 0.75-7.98 (2.67±1.71), CHOL 2.85-9.24 (5.68±1.61), HDL 0.43-1.79 (0.98±0.26), LDL.1.38-7.66 mmol/L (3.72±1.41), GGT 18-318 U/L (68.11±9.29), ALT 15-339 (71±9.96), AST 12-192 (46.69±6.51). Atherosclerosis risk from 10.2 to 35.8 (17.6±6.0).
Conclusion: In ultrasound-diagnosed NAFLD average level of enzymes and ferritin is high. Presence of metabolic syndrome and high risk of atherosclerosis is reveled in more than third of ptients with NAFLD.

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NAFLD considerations as a part of the global hepatitis C elimination effort

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Abstract

The World Health Organization (WHO) is planning to eradicate HCV, setting up specific goals to reduce new cases of the infection by 80% and lower the number of related deaths to 65% by 2030. However, other liver diseases can lead to increased severity of liver damage up to the development of hepatocellular carcinoma (HCC), regardless of sustained virologic response (SVR) acquired after the antiviral treatment. Along with the decrease of HCV prevalence, there has been a significant uptick in non-alcoholic fatty liver disease (NAFLD) cases. NAFLD is diagnosed in 30-40% of HCV patients.
We have reviewed the potential interaction of HCV and NAFLD.
Reviewing the data about HCV and NAFLD interaction in related literature.
HCV therapy has a significant impact on fibrosis development. However, the impact of direct acting antivirals (DAA) on steatosis hasn't been thoroughly researched. NAFLD is a risk factor for HCC development in patients with HCV. The latest data suggests, that steatosis is an independent risk factor for HCC development even after the eradication of the virus. Fatty liver causes lipotoxicity and oxidative stress, which are known factors for hepatocarcinogenesis and is considered a predictor in all causes of mortality in post-DAAs treat-
ment SVR-acquired HCV patients, regardless of the fibrosis levelO Therefore, PNPLA3 can be a useful surro-
gate marker for the steatosis dynamic changes as well as a prognostic biomarker for HCC after SVR.
International experts underline the importance of complete and multidiscipline approach toward the growing number of post-treatment HCV patientsO

Conclusions:

1. NAFLD management and treatment is vital for the evaluation of disease outcome, the decrease of morbidi-
ty and mortality in HCV patients.

2. This will strengthen and improve the care cascade for patients, decrease the cost associated with the disease,
improve the quality of life for patients following successful DAAs therapy.

Non alcoholic fatty liver disease in patients with acute hepatitis B virus

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ABSTRACT

Non alcoholic fatty liver disease (NAFLD) is a disease that affects multiple organs with a 30-40% prevalence. It is one of the global problems for worldwide healthcare. There's a 9% yearly increase in NAFLD-associated HCC.

The purpose of the study is to research the changes in the phospholipid (PL) spectrum of erythrocyte membranes (EM) in patients with acute hepatitis B (AHB) and NAFLD combined AHB (NAFLD+AHB).

Materials and methods: In groups of NAFLD+AHB (n = 24) and AHB (n = 24) patients we studied the relative content of PL in EM using thin layer chromatography.

Results and Discussion: The changes in FL fractions manifested in monoinositide phospatides (MIP), lysophosphatidylcholine (LPC), phosphatidylserine and cardiolipins increase, on account of phosphatidylethanolamine (PE), phosphatidylcholine (PC) and sphingomyelin decrease, which was more apparent in NAFLD+AHB patients during the study. Although PL levels tend to decrease, it has yet to reach normal levels in early stages of convalescence. For example: in NAFLD+AHB patients MIP was significantly higher (13.8±0.16), than in AHB patients (12.9±0.06, P≤0.01). In both groups MIP levels gradually decreased, however staying significantly over the norm (N=8.51±0.18) even after being discharged from hospital. NAFLD+AHB patients had a double increase of LPC, making up 21.3±0.19%, whereas in AHB patients the index was 20.6±0.09% (P<0.001). And vice versa the PC and PE levels were decreased in both groups, but in the NAFLD+AHB group it was significantly lower: PC - 16.7±0.21 (P<0.05), PE - 4.5±0.15 (P<0.05) and in the AHB group: PC - 17.5±0.10, PE - 5.0±0.08.

Conclusion

NAFLD complicates the course of the disease in AHB patients and slows the rate of clinical and biochemical recovery.

FI specter imbalance leads to increase in membrane penetrability and necrotic inflammation because of liver cell damage, which threatens to activate fibrogenesis and oncogenesis in NAFLD and AHB patients.

Key words: Non-alcoholic fatty liver disease, acute hepatitis B, phospholipids, erythrocyte membranes.

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Key words:

NAFLD,NASH,Cirrhosis,HCV, HBV,ascites,portal hypertension

Abstract

Consuming a Mediterranean diet rich in minimally processed plant foods has been associated with a reduced risk of developing multiple chronic diseases and increased life expectancy. Data from several randomized clinic trials have demonstrated a beneficial effect in the primary and secondary prevention of cardiovascular disease, type 2 diabetes, atrial fibrillation, and breast cancer. The exact mechanism by which an increased adherence to the traditional Mediterranean diet exerts its favorable effects is not known. However, accumulating evidence indicates that the five most important adaptations induced by the Mediterranean dietary pattern are: (a) lipid-lowering effect, (b) protection against oxidative stress, inflammation and platelet aggregation, (c) modification of hormones and growth factors involved in the pathogenesis of cancer, (d) inhibition of nutrient sensing pathways by specific amino acid restriction, and (e) gut microbiota-mediated production of metabolites influencing metabolic health. More studies are needed to understand how single modifications of nutrients typical of the Mediterranean diet interact with energy intake, energy expenditure, and the microbiome in modulating the key mechanisms that promote cellular, tissue, and organ health during aging.

Keywords: Mediterranean diet, Cardiovascular disease, Cancer

References

Metabolic and Molecular Mechanisms Valeria Tosti, MD,1 Beatrice Bertozzi, PhD,1 and Luigi Fontana, MD, PhD1,2 1 Department of Medicine, Division of Geriatrics and Nutritional Science, Washington University, St. Louis, Missouri. 2 Department of Clinical and Experimental Sciences, Brescia University Medical School, Italy. Address correspondence to Luigi Fontana, MD, PhD, Washington University School of Medicine, 4566 Scott Avenue—Campus Box 8113, St. Louis, MO 63110. E-mail: lfontana@wustl.edu Received: November 1, 2017; Editorial Decision Date: November 10, 2017 Decision Editor: Rafael de Cabo, PhD

ABSTRACT

The incidence of liver diseases in Armenia

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Key words: NAFLD,NASH,Cirrhosis,HCV, HBV,ascites,portal hypertension

Background: There are various liver diseases that may lead to the damage of liver cells. Liver disease is a progressive deterioration of liver functions. Liver functions include the production of clotting factors and other proteins, detoxification of harmful products of metabolism, and excretion of bile. The damage is a continuous process of inflammation, destruction, and regeneration of liver parenchyma leading to fibrosis and cirrhosis. Liver cirrhosis is the final stage of fibrosis of liver cells, that results in disruption of liver architecture, the formation of widespread nodules, vascular reorganization, neo-angiogenesis, and deposition of an extracellular matrix. The cause may vary from chronic HBV hepatitis, chronic HCV hepatitis, autoimmune hepatitis, non-alcoholic steatohepatitis (NASH) to non-alcoholic fatty liver disease (NAFLD).

Aims: The aim of this study is to establish the incidence of liver cirrhosis in Armenia. Moreover, we will discuss the crucial reasons of cirrhosis among these patients, the incidence of hospitalization in intensive care unit and deaths. Nonetheless, we will review the relation between the incidence of liver cirrhosis and gender.

Methods: We studied the etiology and complications of liver diseases in patients admitted to Erebouni Medical Center (EMD) from 2018 to 2019. The outcomes were based on clinical, biochemical, serological, virological and diagnostic imaging (CT, ultrasound).

Results: The study showed that 226 patients were hospitalized (n=226) with liver diseases. The mean age of patients was 55.9. The incidence of liver cirrhosis was 78% (n=177). The main cause of cirrhosis was HCV infection 30.2% (n=78). HBV infection was detected in 2.7% of patients (n=7). NASH and NAFLD were detected in 45 patients (17.4%). Child Pugh A class was in 3.4%, class B in 14.7% and class C in 2.7%. Liver failure was obtained in 17.4% of patients **(n=45). Also, 8.9% of patients were moved to intensive care unit (ICU), 0.77% (n=2) of patients had died from complications of cirrhosis.**

Conclusion: The results showed that HCV was the major reason for liver cirrhosis among Armenian patients. Noteworthy, the second reason that led to liver cirrhosis among evaluated patients was NASH/NAFLD. Moreover, liver diseases were more common in males than females.

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NAFLD and Malignancy

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Abstract:

Nonalcoholic fatty liver disease (NAFLD) has become one of the most prevalent chronic liver diseases globally. Currently, it has an estimated overall prevalence of 25.2% worldwide, and 29.62% in Asians. Hepatocellular carcinoma(HCC) represents the most common primary liver cancer and is known to be caused by a variety of risk factors. In light of a global rise in obesity and type 2 diabetes, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis (NASH) represent an increasingly important underlying aetiology of hepatocellular carcinoma (HCC). One of these is NAFLD most HCC cases develop in the presence of advanced chronic liver disease related to chronic hepatitis C virus (HCV) infection, chronic hepatitis B (HBV) infection, and alcohol abuse. Approximately 50% of HCC cases are classified as idiopathic, suggesting that other risk factors are responsible for its rising incidence. After development of hepatic steatosis, other factors such as obesity, insulin resistance (IR) and genetic mutations act as a 'second hit' at molecular level, leading to hepatocarcinogenesis .Clinical presentation of NAFLD/NASH HCC are similar to HCC of other aetiologies. Non-invasive diagnosis of HCC laid down alpha-fetoprotein (AFP) more than 350 ng/ml or arterialization of the liver mass seen on multiphasic computed tomography (CT) or magnetic resonance imaging (MRI). In the absence of raised AFP, arterial enhancement on two imaging modalities could also satisfy the diagnosis. Prevention of sedentary life style is mandatory for preventing progression of NAFLD to NASH and further to HCC. All patients with risk factors for developing HCC need surveillance; however, there are no established surveillance protocols for NAFLD/NASH patients.

CONCLUSION

NAFLD/NASH-associated HCC is a huge problem in the present era and has a strong association with metabolic syndrome (MS). Focusing on lifestyle modifications is mandatory for preventation.There is specific criteria for diagnosis HCC. There are no surveillance protocols for NAFLD/NASH patients.

KEYWORDS: Non-alcoholic Fatty Liver Disease, Non-alcoholic Steatohepatitis, Hepatocellular Carcinoma, Metabolic Syndrome.

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The role of innate immune response in non-alcoholic fatty liver disease

Abstract:

Non-alcoholic fatty liver disease (NAFLD) is a rising worldwide public health problem which includes a wide spectrum of clinicopathological conditions with increasing prevalence in the developed world. Early stages of NAFLD represent simple steatosis and appears to have benign course, although in some patients this condition progresses to nonalcoholic steatohepatitis (NASH), and may proceed to development of cirrhosis which in turns shapes the basis for hepatocellular carcinoma occurrence.

The prevalence of NASH among individuals diagnosed with NAFLD is about 30%. These patients have a high likelihood of developing advanced fibrosis and cirrhosis. The metabolic syndrome was found to be a strong predictor of NAFLD development, however the mechanisms leading to progression to NASH are still obscure. Inflammation is considered as main contributor to hepatic tissue damage during NAFLD progression, but the process of inflammatory mechanisms initiation is still not well understood. Available data indicate that the complex interactions between the cellular components of the innate immune system and the resident cell types of the liver play an essential role in maintaining and modulating the inflammatory response in the liver.

The innate immune cells in the liver recognize cell damage or pathogen invasion via intracellular or surface-expressed pattern recognition receptors (PRRs). These receptors detect either damage-associated molecular patterns (DAMPs) released from injured cell, or pathogen associated molecular patterns (PAMPs) which originate from gut-derived microbial products. These DAMPs and PAMPs can activate the innate immune system through PRRs, thereby subsequently initiating signaling cascades that trigger the release of factors promoting the inflammatory response during NAFLD progression.

Conclusion:

The innate immune response in the liver plays a crucial role during NAFLD progression. Furthermore, changes in the intestinal microbial balance and bacterial translocation can affect disease progression. Therefore, the understanding of the inflammatory response that control the transition between the disease stages during NAFLD is important for the design of disease-modifying therapies.

Keywords: non-alcoholic fatty liver disease, nonalcoholic steatohepatitis, innate immune response, intestinal microbiota

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NONINVASIVE BIOMARKERS IN NAFLD AND NASH

ABSTRACT

Introduction: Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver condition worldwide and affects 25% of the global adult population. The active form of NAFLD is nonalcoholic steatohepatitis (NASH), with histological lobular inflammation and with association of faster fibrosis progression. In the USA, NASH has already in the third leading cause of hepatocellular carcinoma (HCC) and end-stage liver disease, which makes it economic and public health burden. On the other hand, the prevalence of NAFLD is unfortunately increasing with a 10% rise in a last fiveyear period. As the number of patients with NASH-related end-stage liver disease is increasing globally and pharmacological treatments have paramount importance, there is a crucial need to define NAFLD and NASH biomarkers for prognosis, patients' selection for drug therapy and monitoring. This makes defined biomarkers more required as the utility of liver biopsy is limited due to its invasive nature and lack of patient acceptability. Nevertheless, biopsy is taken on a small sample of liver that may not be well presenter of the pathology of the other part of the organ tissue.

Blood transaminases are the most practically used liver function tests, however have not been selected to be dependable and satisfactory in predicting of NAFLD progression. Currently literature suggests following non-invasive blood tests for NASH/NAFLD diagnosis: Hepatic Steatosis Index, Fatty Liver Index , the Steatotest and the Liver Fat Score. Non-invasive scoring systems such as Fibrosis-4, NAFLD Fibrosis score, Hepamet Fibrosis Score, and Platelet Ratio Index commonly are used to monitor progression risk of NAFLD, however have lack of sensitivity to identify early stages of NASH and fibrosis. Regarding biochemical blood markers of NASH, the most extensively evaluated test for diagnosis of NASH is CK18, but overall accuracy is low to moderate.

Nowadays, there is no defined NASH/NAFLD biomarker for clinical use. Nevertheless, further researches in the field will add value in the practice. Biomarkers related to metabolic changes, inflammation, fibrogenesis or apoptosis have highest associations.

Keywords

Nonalcoholic fatty liver disease, NASH, Biomarkers, Non-invasive markers

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Lipid metabolism, insulin resistance and NAFLD

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ABSTRACT

The development of non-alcoholic fatty liver disease (NAFLD) is related to major abnormalities of hepatic lipid metabolism. Lipid abnormalities directly or indirectly contribute to NAFLD, especially fatty acid accumulation, arachidonic acid metabolic disturbance, and ceramide overload. The mechanism(s) underlying the accumulation of fat in the liver may include excess dietary fat, increased delivery of free fatty acids to the liver, inadequate fatty acid oxidation, and increased de novo lipogenesis. Insulin resistance may contribute these metabolic changes. NAFLD is considered the hepatic component of the metabolic syndrome and insulin resistance represents its pathophysiological hallmark. Insulin resistance in NAFLD is characterized by reduced whole-body, hepatic, and adipose tissue insulin sensitivity. Insulin resistance is often associated with chronic low-grade inflammation, and numerous mediators released from immune cells and adipocytes may contribute liver damage and liver disease progression. Understanding the molecular mediators of liver injury would promote the development of mechanism-based therapeutic interventions.

Abnormal lipid metabolism is also associated with NAFLD progression from steatosis to NASH, and therefore, alterations in liver and serum lipidomic signatures are good indicators of the disease's development and progression. NASH is distinguished from steatosis by the presence of inflammation and hepatocyte injury. Most patients with NASH have insulin resistance (IR), and there is a near-universal association between NASH and IR. The contribution of IR to the pathogenesis of liver injury and inflammation ("hepatitis") as well as to fibrosis in patients with NASH needs to be further investigated, and the indications for prevention as well as treatment merit further consideration.

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NON ALCOHOLIC FATTY LIVER DISEASE AND EXTRAHEPATIC MALIGNANCY

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Abstract:
Non alcoholic fatty liver disease (NAFLD) is closely tied with various illnesses, including diabetes mellitus, cardiovascular disease, kidney disease and cancer. The data from previously conducted studies points to a connection between NAFLD and extrahepatic cancer. Obesity, insulin resistance, metabolic syndrome can increase the risk of cancer development. In the last decades there have been studies about the connection between NAFLD and colorectal (CRC), esophageal, gastric, bile duct, pancreatic and breast cancers. The OR values of CRC and adenoma risks were, respectively 1.75 (95% CI: 1.40-2.11) and 1.37 (95% CI:1.25-1.46). CRC cases in NAFLD patients make up 18.6%, while in non-NAFLD patients it is 5.5% (P=0.002). The risk of CRC increases with NAFLD connected with liver fibrosis. Obesity is associated with Barrett's esophagus and esophageal adenocarcinoma. NAFLD along with obesity are risk factors for gastric cancer. In NAFLD patients with liver tumors the risk of malignization is the highest, followed by uterine and gastric tumors. NAFLD has 3 times more correlation with the development of intrahepatic cholangiocarcinoma (OR 3.52; 95% CI, 2.87-4.32, P<0.0001) and extrahepatic cholangiocarcinoma (OR 2.93; 95% CI, 2.42-3.55; P<0.0001). The connection between metabolic syndrome and pancreatic cancer is most evident in women and younger individuals. The overall risk of breast cancer in NAFLD patients was 1.69 (95% CI; 1.44-1.99). Breast cancer in women has a 45.2% prevalence, relapse is most common in postmenopause. The prevalence of prostate cancer in NAFLD patients is 12.6%. NAFLD is also closely tied to melanoma, kidney and bladder cancer risks.

Conclusion
NAFLD is a complex multifactorial disease closely interrelated with obesity and type 2 diabetes, and shares with them a significant increased risk of several types of cancer. Beyond the risk of HCC, clearly mediated by NASH, substantial evidence is accumulating for a role of NAFLD as independent risk factor for cancers, particularly in the gastrointestinal tract
All data convey that NAFLD patients require a multidisciplinary evaluation with a particular attention to the development of extra-hepatic complication

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The role of gut microbiota in the pathogenesis of NAFLD and NASH

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ABSTRACT

The human gut microbiota comprises the trillions of microorganisms from different species that reside in gastrointestinal tract, of which bacteria constitute the vast majority. This large community of microbes establishes a symbiotic relationship with the host and is able to perform various functions that significantly influence its physiology and pathology. Several different studies have described a beneficial role of the commensal microbiota in maintaining liver homeostasis and preventing liver fibrosis. As such, a disturbed imbalance of the endogenous microbiota, has been associated with a range of chronic liver conditions such as NAFLD, NASH, alcoholic liver disease as well as cirrhosis and its complications (hepatic encephalopathy, HCC).

NAFLD is nowadays the first cause of liver disease worldwide, and in the near future it will emerge as the leading cause of end-stage liver disease. Indeed, NAFLD should be considered as a spectrum of chronic liver diseases that ranges from simple steatosis to NASH and cirrhosis. Several different mechanisms have been proposed to explain the role of the gut microbiota in the pathogenesis of NAFLD, including a dysbiosis-induced increased intestinal permeability, an increased dietary energy harvest, the regulation of choline metabolism, the production of short chain fatty acids and the bile acids metabolism.

Once this close relationship is established, the microbiome has proposed as a useful tool to determine liver disease severity in NAFLD, and the risk of disease progression from NAFLD toward NASH and more severe fibrosis. In other words, gut microbiota is emerging as a potential non-invasive marker of disease-severity in NAFLD.

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NAFLD in Lean Individuals

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Abstract:

Non-alcoholic fatty liver disease (NAFLD) is a major cause of chronic liver disease worldwide, with an estimated global prevalence of approximately 25% , encompassing a spectrum of clinical-histological phenotypes from non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH) which can progress to fibrosis, cirrhosis. Although non-alcoholic fatty liver disease (NAFLD) is usually associated with obesity, patients who are not obese can also present with NAFLD. The prevalence of lean NAFLD varies from 7-20% of the Western population and 5-26% of the Asian population . Lean NAFLD is defined as NAFLD that develops in patients with a body mass index (BMI) <23 kg/m2 in Asians and (BMI) <25 kg/m2 in Europeans. This subset of individuals, known to have 'lean NAFLD' or 'non-obese NAFLD', is growing increasingly prevalent. Risk factors for NAFLD in lean patients include genetic predisposition, metabolic dysregulation, the gut microbiota, and the gut liver axis changes, drugs, body weight gain even within normal weight limits. The pathogenesis of the NAFLD is multifactorial and the underlying mechanisms yet to be fully understood. Most mechanisms for developing NAFLD are linked with changes in lipid metabolism and development of insulin resistance. The role of factors like diet, ethnicity and gut microbiota came into light. Although NAFLD in lean individuals is generally considered a less severe form of liver disease than NAFLD in obese patients, this conception has recently been challenged.Lifestyle modification, including diet and physical activity remains the mainstay in the management of patients with non-obese NAFLD. Treatment options for NAFLD include pioglitazone and vitamin E but they have a limited role for the management of lean NAFLD.

CONCLUSIONS AND RESEARCH NEEDS:

Non-alcoholic Fatty Liver Disease (NAFLD) is an emerging public health problem. It is necessary to recognize the risk factors and to develop appropriate management approaches.

Keywords

Non-alcoholic Fatty Liver Disease, Non-alcoholic Steatohepatitis, Body Mass Index, non-obese NAFLD, lean NAFLD

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The role of iron in MAFLD. The mysterious relationship

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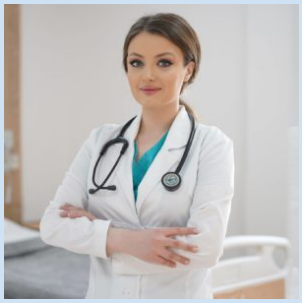
Abstract

Metabolic associated fatty liver disease (MAFLD) is the most prevalent liver disease worldwide, with an association to obesity, insulin resistance and the metabolic syndrome. Approximately one-third of patients with MAFLD develop elevated serum ferritin and hepatic iron overload, a condition known as the dysmetabolic iron overload syndrome (DIOS). DIOS defines a condition characterized by increased body iron unrelated to hereditary haemochromatosis (HH), but associated with presence of fatty liver and/or metabolic features typical of insulin resistance. Indeed, deregulated iron metabolism presenting with hyperferritinaemia with normal transferin saturation is commonly observed in MAFLD and the metabolic syndrome. Increased iron stores could be of pathogenic importance in MAFLD, since it may increase the risk of hepatocyte balloning, inflammation and fibrosis, which are features of liver damage seen in metabolic associated steatohepatitis (MASH) which is the more severe form of MAFLD. The role of hepatic iron in MAFLD pathogenesis has largely focussed on the generation of oxidative stress by iron. Regulated cell death is intrinsically associated with inflammatory liver disease and is pivotal in governing outcomes of metabolic liver disease. Different types of cell death may coexist as metabolic liver disease progresses to inflammation, fibrosis, and ultimately cirrhosis. In addition to apoptosis, lytic forms of hepatocellular death, such as necroptosis, pyroptosis and ferroptosis elicit strong inflammatory responses due to cell membrane permeabilisation and release of cellular components, contribuiting to the recruitment of immune cells and activation of hepatic stellate cells. Although associations of modest iron overload with MAFLD and diabetes appear reasonably well established, causality is difficult to determine. The available data suggest that venesection is unsuitable as a general treatment for all patients with MAFLD. Further studies are needed to assess the role of therapeutic iron depletion and cell death regulation for MAFLD treatment.

Conclusion
In patients with chronic liver disease, iron metabolism changes result in iron overload. Manipulating iron stores is an attractive treatment option, however more rigorous data is needed.

Keywords
Iron, dysmetabolic iron overload syndrome, ferroptosis, insulin resistance.



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Liver Cirrhosis and NAFLD: Clinical Implications

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NAFLD is the world's most common chronic liver disease, and its increasing prevalence parallels the global rise in diabetes and obesity. The prevalence of NAFLD is up to 30% in developed countries and nearly 10% in developing nations. It is characterised by fat accumulation in the liver evolving to non-alcoholic steatohepatitis (NASH), an inflammatory subtype that can lead to liver fibrosis and cirrhosis. Cirrhosis is a terminal stage of chronic liver disease. Only one in three people with cirrhosis knows they have it. Most patients with cirrhosis remain asymptomatic until the onset of decompensation. When clinical signs, symptoms, or abnormal liver function tests are discovered, further evaluation should be pursued promptly. During progression from the compensation period to the decompensation period, various complications occur and the life prognosis is significantly reduced. Cirrhosis can lead to many complications, including ascites, varices, hepatic encephalopathy, hepatocellular carcinoma, hepatopulmonary syndrome, and coagulation disorders. The most common causes of cirrhosis are viral hepatitis, alcoholic liver disease, and nonalcoholic steatohepatitis. Insulin resistance, occurring in the context of metabolic syndrome, is a well-established independent pathophysiological driver for the development of non-alcoholic fatty liver disease (NAFLD) It is also well established that an unhealthy diet rich in calories, sugars, and saturated fats and low in polyunsaturated fatty acids, fibre, and micronutrients plays a critical role in the development and progression of non-alcoholic fatty liver disease.

Cirrhosis and its complications not only impair quality of life but also decrease survival. Managing patients with cirrhosis can be a challenge and requires an organized and systematic approach.

Keywords: End stage liver disease, Diabetes mellitus, Liver cirrhosis, Insulin resistance, Non-alcoholic fatty liver disease

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Hypothyroidism and Nonalcoholic Fatty Liver Disease

ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is an emerging worldwide problem. NAFLD is a complex clinical entity which can be secondary to many other diseases including hypothyroidism, characterized by lowering of thyroid hormones and increased thyroid stimulating hormone (TSH). Prevalence of primary hypothyroidism is between 0.3% and 3.7% in the general population of the USA and 0.2 and 5.3% of the European general population. It is defined by biochemical increase of thyroid-stimulating hormone (TSH) and lowering of the thyroid hormones thyroxine and triiodothyronine, as clinical or overt hypothyroidism, and as subclinical hypothyroidism if only TSH is increased and thyroid hormones are in reference interval. Thyroid hormones have a significant role in hepatic lipid metabolism; acting through the thyroid hormone β receptors, they can lead to hepatic fat accumulation and stimulate hepatic lipogenesis. Also, thyroid hormones modify lipid accumulation in the liver, affecting leptin and adiponectin; cytokines that also have significance in the pathogenesis of hepatic steatosis. Obesity, dyslipidemia and insulin resistance, the main features of metabolic syndrome which are also common in patients with overt and subclinical hypothyroidism are strongly associated with NAFLD. Replacement therapy with levothyroxine can significantly decrease serum lipids and decrease body mass, thus improving clinical features of metabolic syndrome. It has been reported that implementation of levothyroxine replacement therapy in patients with subclinical hypothyroidism and dyslipidemia can decrease prevalence of NAFLD.

Keywords: Non-alcoholic fatty liver disease, Hypothyroidism, Metabolic syndrome, Thyromimetics

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Acute fatty liver disease of pregnancy

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ABSTRACT

Acute fatty liver of pregnancy (AFLP) is a rare disorder that is an obstetric emergency, which can lead to liver failure due to micro-vesicular fatty infiltration of hepatocytes. It usually occurs in the third trimester. There is a significant increase in maternal and fetal mortality. One of the breakthroughs in understanding acute fatty liver of pregnancy pathophysiology was the discovery that fetal fatty acid oxidation disorders are linked to acute fatty liver in the mother.

Long-chain 3-hydroxyacyl-coenzyme A dehydrogenase is a part of a complex mitochondrial enzyme involved in the β-oxidation of fatty acids in mitochondria. Deficiencies in this enzyme result in an accumulation of hepatotoxic long-chain fatty acid metabolites in the fetus that can cross into the maternal circulation, leading to maternal hepatotoxicity and mitochondrial dysfunction. High levels of free fatty acids increase reactive oxygen species production and caspase activity and induce apoptosis.

Fatty acid oxidation disorders have autosomal recessive inheritance, so when present in the fetus, the mother is usually a carrier for the disorder. Symptoms include malaise, nausea, vomiting, polyuria, polydipsia, abdominal pain, jaundice and encephalopathy. Hypoglycaemia is a poor prognostic sign. Common biochemical changes include leukocytosis renal dysfunction, raised aminotransferases, prothrombin time, serum uric acid and bilirubin. Raised serum ammonia concentration and lactic acidosis are indications of severe disease. The Swansea diagnostic criteria are used to aid diagnosis of AFLP.

Management is supportive and expedited delivery, if diagnosed antenatally. Liver transplantation is warranted in cases of failure of recovery of liver function and severe hepatic encephalopathy.

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«Mediterranean fatty liver»? An unexpected cause of cryptogenic cirrhosis

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ABSTRACT

Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease (AID) affecting mainly the ethnic groups originating from Mediterranean basin. FMF is caused by mutations in the MEFV gene coding for pyrin, which is a component of inflammasome functioning in inflammatory response and production of interleukin-1β (IL-1β). Although liver involvement in FMF has long been known, its pathogenesis remains incompletely understood. Our purpose is to figure out the interaction between FMF and fatty liver disease.

It is well known, that IL-1β has an important role in pathogenesis of all stages of fatty liver disease, including steatosis, steatohepatitis and fibrosis. IL-1β contributes to accumulation of fatty acids, triglycerides and cholesterol. Moreover, IL-1 signaling stimulates hepatic lipogenesis by upregulating fatty acid synthase. Besides acting on lipogenesis, the increase in circulating IL-1β levels also results in inflammation by overexpressing ICAM1 on sinusoidal endothelial cells, which attracts neutrophils.

Chronic inflammatory states lead to fibrosis. Patients with FMF that carry M694V/M694V mutation, patients that have received Colchicine at highest acceptable dose but still have subclinical inflammation and those who received suboptimal dose of Colchicine because of side effects, are at increased risk for developing fatty liver disease due to high levels of circulating IL1-β. In these patients it would be appropriate to use IL1-β antagonists, but unfortunately those are not available in Armenia. There is a need for further investigation to understand the possibility of developing fatty liver disease in patients with FMF and without metabolic risk factors.

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NAFLD (MAFLD) and cardiovascular diseases - risk factor or protective effect?

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Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in Western countries and affects approximately 25% of the adult population. NAFLD is more prevalent in patients with major cardiovascular risk factors (e.g., type 2 diabetes mellitus, obesity and hypertension), the association between NAFLD and cardiovascular disease appears to be independent of these risk factors.

However, NAFLD also appears to increase the risk for ischemic stroke, a leading cause of mortality and long-term disability worldwide. Moreover, emerging data suggest that patients with NAFLD experience more severe ischemic stroke and have more unfavorable prognosis after an acute ischemic stroke in terms of functional dependency and short- and long-term mortality. One study suggests that the potential causal effect of NAFLD on ischemic stroke may be confined to the large artery atherosclerosis and small vessel occlusion subtypes. However, there are some unclarified questions.

There is limited information on the relationship between non-alcoholic fatty liver disease (NAFLD) and the severity or functional outcomes of ischemic stroke or transient ischemic stroke (TIA). The other study shows that a higher burden of liver steatosis seems to be associated with less severe stroke and better functional outcome after ischemic stroke or TIA. These differences suggest that further research will help many discoverers.

Keywords: Non-alcoholic fatty liver disease; stroke; stroke functional outcome; cardiovascular disease.

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Drug-associated fatty liver disease

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ABSTRACT

Drug induced liver injury is an underestimated cause of liver disease. Diagnosis of drug induced liver injury is one of the most challenging problems faced by hepatologists because of its relatively low incidence, the variety in its clinical phenotype and the absence of specific biomarkers. Drug induced liver injury is one of the most common reasons for withdrawal of an approved drug. Pharmacological therapy has been associated with wide variety of alterations in the structure and functions of the liver and biliary system. Drugs have been associated with acute and chronic hepatitis, chronic cholestasis, steatohepatitis, hepatic fibrosis, cirrhosis, and benign and malignant liver tumors.

Steatosis and steatohepatitis are rare but well documented types of drug induced liver injury. Drug-associated fatty liver disease is a secondary cause of hepatic steatosis. The complex mechanism leading to hepatic steatosis are caused by commonly used drugs such as tamoxifen, amiodarone, methotrexate, glucocorticoids, chemotherapy. It relates not only to induction of the metabolic changes caused by some drugs but also to their impact on important molecular pathways including increased hepatocytes lipogenesis, decreased secretion of fatty acids, interruption of mitochondrial β-oxidation and altered expression of genes responsible for drug metabolism. We also can have cases of acute fatty liver.

On the other hand, the underlying metabolic condition causing a fatty liver may change the drug metabolism and exacerbate the risk of drug induced liver injury. A detailed understanding of the molecular mechanisms of drug-associated fatty liver disease is useful to minimize adverse effects in susceptible patients and to recommend alternative treatment solutions that reduce hepatotoxicity without interrupting the therapy.

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Mean platelet volume ascardiovascular Risk Factorin patients with acute Myocardial infarctioncomorbid with non-alcoholic fatty liver

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Keywords: acute myocardial infarction, non alcoholic fatty liver disease, mean platelet volume, cardiovascular risk ,mortality

Abstract

Background: Nonalcoholic liver disease represents most common cause of chronic liver disease in western countries and associated with diabetes, atherosclerosis, metabolic syndrome and increased cardiovascular risks due to systemic inflammation, increased oxidative stress Mean platelet volume (MPV) is a marker of platelet activation and a validated predictor of cardiovascular risk. The purpose of study to assess MPV in patients with acute myocardial infarction and NAFLD and determine relation between MPV and cardiovascular events after acute myocardial infarction in such patients.

Methods; We included all admitted to University Hospital (from October 1, 2013 to October1, 2014) non fatal acute myocardial infarction patients (totally 176) .NAFLD was diagnosed by ultrasound examination.

Results: Patients with NSFLD had higher MPV values .

Non-alcoholic fatty liver diseases characterized by lipid accumulation in hepatocytes and has been regarded as the hepatic phenotype of metabolic syndrome (1-3).The association of NAFLD with dyslipidemia, diabetes and atherosclerosis provide evidence that this pathology has prevalence and incidence of cardiovascular disease(2;4;5).

Mean platelet volume (MPV) is a marker of platelet activation and established risk of cardiovascular events..(6,7) and represents simple,inexpensive test in everyday practice.

MPV has been associated with dyslipidemia, diabetes, hypertension (8-9) .

Larger platelets are enzymatically more active than small platelets, produce thromboxane A2 and have more prothrombotic potential (10, 13, 14). Both NAFLD and acute myocardial infarction are associated with higher values of MPV (11, 12).

Thus, the aim of study was two-fold: first to assess MPV values in patients with acute myocardial infarction and NAFLD compared to those without NAFLD and second to determine relation between MPV and cardiovascular events in such patients.

From October 1, 2013 to October 1, 2014 176 patients with acute myocardial infarction admitted to the General and Invasive Cardiology Clinic at University Hospital 1 passed primary PCI or medical treatment. All patients passed abdominal ultrasound within the first 12 hours of

admission for diagnosing fatty liver. Patients who died within the first 48 hours after admission, had severe liver failure, documented hepatitis B and C viruses in blood, history of alcohol intake more than30mg/day in men and 20 mg/day in women have not been included in the study(totally 21 patients).

The diagnosis of NAFLD was made if typical ultrasound pattern with increased echogenicity of liver, vascular blurring, increased echogenicity compared with kidney and attenuation of echogenicity at deep parts images (15). Only grade 2 and grade 3 level of NAFLD were taken as clear diagnosis to escape misdiagnosis.

Continuous variables were expressed as mean ± standard error of mean and compared using one way analysis. Categorical variables were expressed as number and percentages. Pearson chi square test was used to evaluate correlation analysis.

The comparative analysis of patients with and without non-alcoholic fatty liver showed thatMPV was 10.6 ± 0.093 in patients with NAFLD and 9.5 ± 0.13 without NAFLD ($p<0.01$) respectively.

Conclusions

Our study suggests that MPV is significantly higher in patients with acute myocardial infarction who has NAFLD, which indicates increased platelet activity in these patients.

High MPV values are associated in these patients with increased predictive cardiovascular risk after 12 months from acute myocardial infarction. We strongly believe that it is important to consider MPV as well as NAFLD as risk factors for risk stratification in patients with acute myocardial infarction.

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Role of myeloid-derived suppressor and other myeloid cells in diminished immune response to vaccinations in obese individuals

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Obesity is a chronic inflammatory condition associated with an increased production of cytokines and exacerbated immune response. However, obese subjects are susceptible to infections and respond poorly to vaccines. This study evaluated the immune responses of obese mice and the underlying mechanisms by explor-ing the roles of myeloid cells. Diet-induced obese (DIO) mice were prepared from C57BL/6J mice fed a high-calorie and high-fat diet for 12 weeks. Humoral and cel-lular immune responses of DIO mice to a hepatitis B vaccine containing the hepatitis B surface antigen (HBsAg) were assessed in sera and via a lymphoproliferative assay, respectively. The effects of CD11b+GR1+ myeloid-derived suppressor cells (MDSC) and CD11b+GR1− non-MDSC on T cell proliferation and cytokine production were com-pared via a cell culture system. The production of cytokines, expression of activation and exhaustion markers, and proportions of apoptotic T cells were estimated with flow cytometry. Increased T and B lymphocyte proliferation and higher interferon-and tumor necrosis factor- _ levels were detected in spleen cells and liver non-parenchymal cell cultures of DIO mice compared to controls ($p < 0.05$). However, antibody to HBsAg (anti-HBs) levels and HBsAg-specific T cell proliferation were signifi-cantly lower in DIO mice compared to controls ($p < 0.05$). The addition of MDSC, but notnon-MDSC, induced a decrease in HBsAg-specific T cell proliferation, lower cytokineproduction, decrease in T cell activation, and increase in T cell exhaustion and apo-ptosis ($p < 0.05$). MDSC play an important role in mediating impaired antigen-specificimmunity.

Laparoscopic sleeve gastrectomy in a patient with NAFLD and grade 2 obesity.

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Case Presentation

Introduction:

Obesity is associated with non-alcoholic fatty liver disease (NAFLD), one of the most common causes of chronic liver disease. NAFLD is a condition in which excess fat is stored in the liver. This build-up of fat is not caused by heavy alcohol use. The condition usually doesn't cause symptoms and is most often found when blood tests indicate elevated liver enzymes. NAFLD is more common in people who have certain conditions, including obesity and conditions that may be related to obesity, such as type 2 diabetes. Researchers have found NAFLD in 40% to 80% of people who have type 2 diabetes and in 30% to 90% of people who are obese.

Case Presentation:

The patient is a 35-year-old young woman with 2nd degree obesity, non-alcoholic fatty liver dystrophy (FLI-99, BARD- -0.701), dyslipidaemia, hyperuricemia. The patient was diagnosed with NAFLD at the age of 32, which was asymptomatic, but laboratory and instrumental data revealed elevated liver enzymes and hepatomegaly and sonographic data of fatty liver dystrophy. Over the years, despite attempts to change the nature of lifestyle, attempts to regulate body mass, drug treatments, negative dynamics were observed in the patient laboratory-instrumentally as well as clinically. It was manifested by a progressive increase in body mass from 78 kg in 2018 to 86 kg in 2022, elevations or non-normalization of liver enzymes and aging of the liver and worsening of ultrasound indicators of fatty liver dystrophy. Considering the ineffectiveness of the measures implemented during the last 4 years, the dynamic increase in body mass, the negative dynamics of laboratory and instrumental data and the magnitude of FLI, it was decided to perform a bariatric intervention - sleeve gastrectomy.

The patient underwent laparoscopic sleeve gastrectomy and liver biopsy. The postoperative period, a significant decrease in liver enzymes, a decrease in the size of the liver and a significant decrease in the amount of fatty tissue, and the elimination of the pain symptom were observed.

Conclusion:

These results suggest that bariatric surgery and particularly laparoscopic sleeve gastrectomy may represent an effective therapeutic approach to NAFLD.

Sleeve gastrectomy is associated with a significant improvement in liver steatosis and fibrosis.

Bariatric surgery has a beneficial effect on non-alcoholic fatty liver disease in patients with obesity and NAFLD and it should be applied to the treatment of NAFLD as soon as possible after the consensus of a multidisciplinary discussion, to prevent the progression of fibrosis and necrosis and to obtain the best functional outcome.

Keywords: Bariatric surgery; Fatty liver; obesity; Non-alcoholic fatty liver disease, NAFLD..

Levon Grigoryan

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Case Presentation

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Keywords: Bariatric surgery; Fatty liver; obesity; Non-alcoholic fatty liver disease, NAFLD.

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The role of multiparametric examination of the liver of patients with NAFLD in the differentiation of fibrotic changes and steatosis.

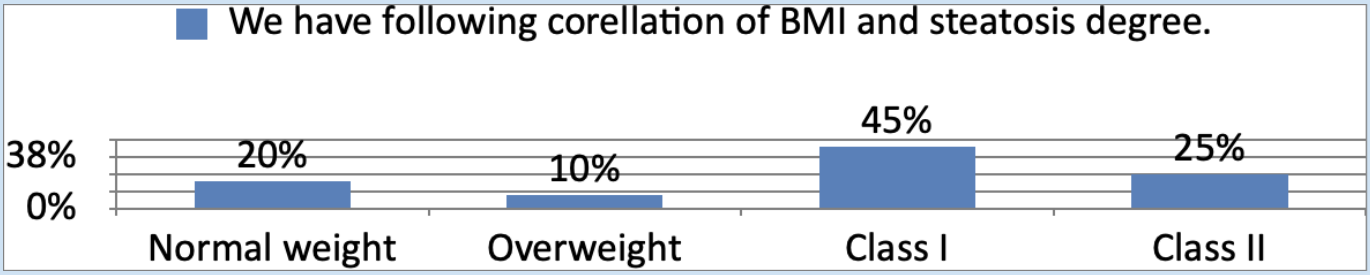
According to statistics, over the past 20 years, the number of patients with non-alcoholic fatty liver has doubled. Naturally, interest in him grew among hepatologist and radiologist. The issues of diagnosing NAFLD or NASH and its conditions in the form of fibrosis, cirrhosis and hepatocellular cancer have become actual.

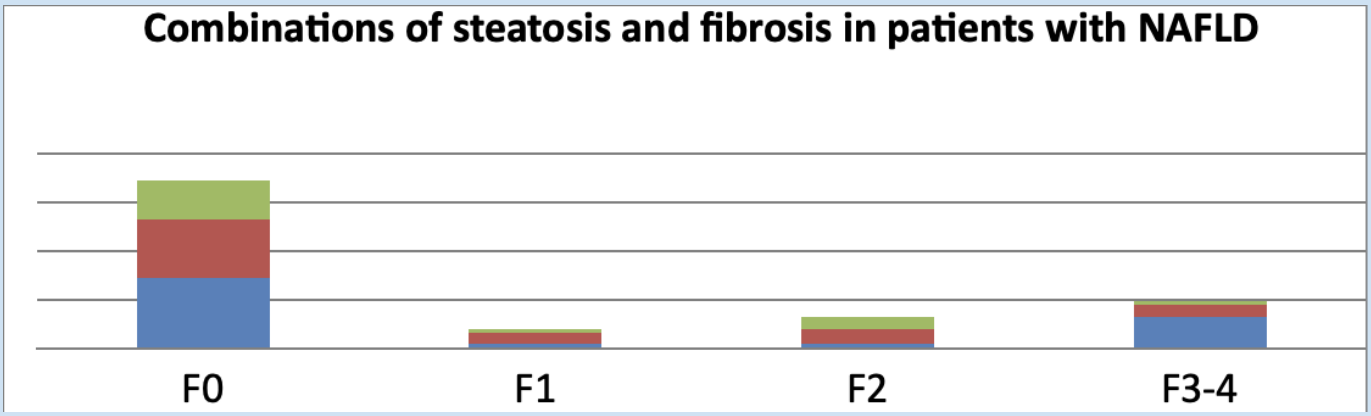
B-mode ultrasound imaging can detect the liver fatty infiltration, but we know, that US gives less information about mild steatosis.

On the other hand, radiologists are well aware that with ultrasound it is often impossible to differentiate fibrotic changes in the liver that develop against the background of steatohepatitis, if liver cirrhosis has not yet developed. It is also quite difficult to diagnose combined changes in the liver, fibrosis and fatty infiltration.

The method of elastography (Quantitative US) for determining the degree of liver fibrosis has made a great breakthrough in hepatology. And the recently appeared method of quantitative assessment of the degree of steatosis (Attenuation) also solved the issue of combined liver damage.

In 2021-2022, we examined 369 patients (120women, 249 men) with elevated liver enzymes with a multiparametric method. 48% of patients did not have viral hepatitis, 31% had Hepatitis B, 21% had Hepatitis C.





Conclusion:

1 Multiparametric study of the liver reveals:

- fibrotic changes veiled under steatosis
- liver fatty infiltration veiled under fibrosis

2 Steatosis of the third degree is more often observed in patients with the second degree of obesity than with the third, which may indicate a complex etiology of the occurrence of steatosis.

Molecular characterization of hepatocellular carcinoma in Armenia, 2019-2020: initial observations

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According to the most recent data of the IARC, Armenia is, within a large region encompassing Caucasus, Middle East, and Central Asia, the country where the incidence of liver cancer is the highest for both sexes. Risk factors responsible for this situation as well as molecular changes occurring in liver tumors are poorly known for Armenian patients. To shed light on these issues, we conducted a case-control study on plasma samples of 110 cases of hepatocellular carcinoma (HCC) and 167 cases of non-tumor chronic liver disease (CLD). These series were dominated by hepatitis C with 67.2% and 41.8% of positive cases in HCC and CLD while hepatitis B (HBsAg) was far less prevalent (13.6% and 5.1%). We explored using a 3rd generation PCR technique, free circulating DNA in the plasma of patients for the presence of a mutated TERT gene promoter, the most frequent mutation in HCC worldwide. It was found in 20.0% of HCC cases and 1.7% only of CLD patients (OR=13.5, P=2.5 E-07). In contrast, TP53 R249S mutant, the hallmark of exposure to aflatoxin B1 in the intertropical regions was rare (1.8% vs 3.6%, ns). Albeit minimal, this presence of TP53 mutation suggests for some patients a previous contact with the carcinogenic toxin. Concerning hepatitis B virus (HBV), 6 HCC patients were infected with subtype D1 (66.6%), one with D3 (11.1%), and two with A2/D1 recombinant viruses (22.2%). In CLD, we observed two D1 and a single A2 subtypes. Subtype 3A of hepatitis C virus (HCV) was representing 64.0% (n=16/25) of isolates characterized in HCC patients. It was followed by subtype 1b (32%, n=8/25), and a single subtype 2a strain (4.0%). No HCV intergenotypic recombinant frequent in neighboring countries was found. Further studies are now warranted to extend our results and to identify the molecular determinants of chronic hepatitis aggressiveness in Armenia.

ROLE OF POLYAMINES IN ORGAN REJECTION AFTER TRANSPLANTATION Harutyunyan H.V. 1 , Barseghyan H.A. 1 , Voskanyan A.A. 2 1 Department of General Surgery, Yerevan State Medical University, Yerevan, Armenia 2 Department of Endoscopic and Endocrine Surgery, Yerevan State Medical University, Yerevan, Armenia

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KEYWORDS: polyamines, organ transplantation, rejection

Introduction

Polyamines, such as Spermine, Spermidine, and Putrescine, are Organic Polycationic Alkylamines, which are synthesized from L-ornithine or by the decarboxylation of amino acids. They are found in all living cells [Sharma S et al., 2017; Handa A K et al., 2018; Firpo M et al., 2020]. Mammalian cells contain a millimolar concentration of Polyamines [Pegg A, 2016]. In 1678, Spermine was first identified by Van Leeuwenhoek as crystals in dried semen but not in fresh ones. In 1791, Vauquelin identified these crystals as an unknown phosphate-derived compound [Vauquelin L N, 1791]. In 1878, Ladenburg and Abel proposed its name “Spermine” [Schreiner P, 1878; Ladenburg A, Abel J,, 1888]. Further, in 1888 Schreiner reported Spermine as a basic compound. After one decade (in 1898), Poehl suggested the use of Spermine for the treatment of several diseases [Poehl A V, 1898] and finally, in 1924, Spermine, Spermidine, and Putrescine were synthesized by Rosenheim, which led to the foundation of the modern science of Polyamines [Rosenheim O, 1924]. Moreover, Putrescine was discovered in the microorganisms in ~1800s, and Spermidine was identified in the 20 th century. Polyamines have been found to be involved in various important biochemical roles and are an integrated part of the cellular and genetic metabolism such as synthesis, functioning, maintenance, and stability of nucleic acids (DNA and RNA), and proteins [Park M, 2006]. They also play a pivotal role in cell differentiation, cell proliferation (Rapidly dividing cells contain a higher level of Polyamines), gene expression and regulation (Polyamine control expression and stability of p53, a nuclear phosphate protein which regulates different genes associated with growth and death of the cell), cell signalling, apoptosis, DNA binding, transcription, RNA splicing, and functioning of cytoskeletons, and also stimulate post- translational modification with the help of ‘eukaryotic initiation factor 5A’ (eIF5A). [Hesterberg R et al., 2018; Flynn A, Hogarty M, 2018; Mathews M, Hershey J,, 2015; Thomas T, 2018; Pällmann N, et al., 2015]. It is currently an undeniable fact that polyamines play a role in the development and healing of various wounds [Lim H et al., 2018; Nishimura K et al., 2006; Maeno Y et al., 1990]. It has been shown that from the very first moment of wound formation, the activity of ornithine decarboxylase, the enzyme that regulates the synthesis of polyamines (Putrescine) increases in the wound area [Hardbower D et al., 2017; Casero R et al., 2009; O’Brien T et al., 1997]. The role of spermidine is unique in wound healing [Casero R et al., 2009; Pegg A, 2016]. Due to the disruption of polyamine synthesis regulation in wounds, the risk factors increase the appearance of neoplasms in the wound foci [Casero R et al., 2018, Shi C et al., 2012; Wei G et al., 2007]. Of particular note in this regard are the studies that examined the quantitative shifts of polyamines in 1990s and their diagnostic significance in the context of organ transplantation [Seiler N, Knodgen B, 1985; Carrier M et al., 1986; Thai P et al., 1994; Terakura, M et al., 1995]. Several studies on cardiac allograft rejection linked with increased urinary polyamines were conducted between the period of 1985 up to 1994 including hypothesis testing on humans and dogs. Also, some other investigations have been conducted on role of Polyamines during post-organ transplantations. Here, in this review, based on the investigations conducted both on Humans and Animals (Specifically, Dogs and Rats), our aim is to prove that polyamines levels are increased and are linked with allograft rejection. According to the Cardiac Allograft Rejection Study was stated that, “Histological Evaluation done by Endomyocardial Biopsy

specimen for monitoring organ rejection after transplantation gave a discontinuous evaluation of recipient's immunological status, it is an expensive and invasive method, this procedure cannot be done on a daily basis as a monitor of organ rejection" [Carrier M et al., 1986]. It was thus discussed that, "Because of these difficulties, a predictive non-invasive approach is needed. To be clinically useful the latter should be accurate, sensitive, simple, and easy to perform, available daily, and finally acceptable to the patients. Ideally, it should also predict the rejection process so that an immediate treatment can prevent cell necrosis and damage to the transplanted heart and would permit a more continuous monitoring than the biopsy technique" [Carrier M et al., 1986, 1988a, 1988b]. So, Urinary Polyamines as a non-invasive marker was considered for hypothesis testing as its excretion reflects cellular proliferation or degeneration and, as a marker of cellular metabolic activity, may also reflect lymphocyte proliferation and organ rejection. Aim Given the new developments in the diagnostic methods in medicine, it is necessary to study the quantitative shifts of polyamines not only in the urine but also in various components of the blood, particularly in RBCs. At the same time, in order to make a targeted diagnosis, it is necessary to combine the quantitative research of polyamines with the study of other compounds of biological importance. The Role of Polyamines in Heart Transplantation Investigation on role of Urinary Polyamines in rejection of Cardiac Allograft in Human as conducted from July 1985 to December 1986, 17 Patients having heart transplantation and one patient having heart- lung transplantation (two women, 16 men) were studied. Their Urinary polyamine levels were measured during the period of hospitalization for transplantation. Urine specimens for polyamine measurement were collected every morning and stored at –80.0 C until assayed. Urinary polyamines were measured by high-pressure liquid chromatography [Seiler N, Knodgen B, 1985]. Role of Urinary Polyamines in rejection of Cardiac Allograft in Animals (1987, 1988 and 1994): Back in the 80s during the dog's cervical heterotopic heart transplantation, comparative studies were conducted between daily percutaneous transmural biopsy of the transplanted heart and urine samples: Animals which did not receive immunosuppression therapy were studied [Carrier, M. et al., 1987], as well as Animals treated with cyclosporine or cyclosporine and steroids were studied. The urinary excretion of N-Acetylputrescine and N-Acetylspermidine was also studied in 36 dogs. Two groups underwent heterotopic heart transplantation. Three other groups were given different immunosuppression treatments without having any surgery and one group had a sham cervical operation [Carrier, M. et al., 1988]. [Thai, P. et al., 1994]. During the research it was revealed that allograft rejection by the non-invasive method was defined as an increase of N-Acetylputrescine and total polyamine excretion associated with a daily variability of 28% or more. This indicates increased metabolic cellular activity and predicts rejection in the next 8 days (occurring 0 to 8 days) before a positive histologic finding. Based on these definitions, the sensitivity of polyamine analysis to predict histologic rejection was 85% (17/20), the specificity 88% (59/67), the positive predictive value 79% (30/38), and the negative predictive value 95% (59/62). Thus authors have proved that serial measurements of urinary polyamines may provide daily information on the recipient's immunologic status after cardiac transplantation [Carrier M et al., 1986]. The study by the authors showed that between 2 to 4 days after transplantation, all allografts by histologic picture had a mild to moderate rejection. The urinary excretion of total polyamines and putrescine fraction increased during the rejection process after transplantation, attaining a maximum from the first to the third day after operation. This early elevation suggests that urinary polyamines are markers of immune activation and unmodified heart allograft rejection [Carrier M et al., 1987]. Another study by the authors showed that between 2 to 4 days after transplantation, the transplanted hearts of all animals without immunosuppression had histological rejection. An early increase in putrescine levels and total urinary polyamine levels was observed in this group. In the treated groups, histological rejection appeared from the second to the eighth day after transplantation [Carrier M et al., 1988]. The studies showed that immunosuppression of the transplanted dogs with Cyclosporine, Imuran and Prednisone during the postoperative period caused a significant increase in the excretion of N- Acetylspermidine averaging 512 +/- 122 nmol/mg of creatinine respectively compared to 197 +/- 31 nmol/mg of creatinine in Sham (fake operation conducted like placebo) group. The excreted levels of N- Acetylputrescine for the same group were 594 +/- 202, nmol/mg of creatinine compared to 71 +/- 24 nmol/mg of creatinine in Sham group [Thai P et al., 1994].

Thus, the authors have proved a significant excretion of N-Acetylspermidine and N-Acetylputrescine in transplanted dogs after immunosuppression. Other Recent Scientific Investigations The Role of Polyamines in Other Transplantations According to the study conducted in the year 1990: 'Red blood cell polyamine level changes following heart transplantation in Man' which is based on study of 'Urinary Polyamines as a non-invasive marker for cardiac allograft rejection' by Carrier, M et al., 1986. The results stated that, "Follow-up of orthotopic heart transplanted patients has revealed the existence of abnormally high RBC (Red Blood Cells) Spermidine levels during the first two months after surgical procedure (A-period). From the third month after heart transplantation (B-period), RBC Spermidine concentrations went back to normal values in an Early Cardiac Rejection (ECR) patient. During A and B-periods, significantly higher Spermidine levels and Spermidine/Spermine ratios were observed in Late Cardiac Rejection (LCR) patients than ECR ones." Thus, it was concluded that, "The lack of a direct relationship between the histological grade of rejection and RBC Spermidine levels leads us to consider these Polyamine blood levels as a new biological instrument in the diagnosis of heart rejection" [Moulinoux, J-Ph et al., 1990]. In correspondence to the research conducted in July 1995 which aimed at studying "Clinical importance of erythrocyte polyamine (Spermine and Spermidine) level determination during bone marrow transplantation in children". An interest was developed in finding an early blood criteria of Bone Marrow regeneration based on the chemotherapy induced post-transplant aplasia period. The results stated that, "After Bone Marrow transplantation, two main periods were observed: first (A-period) which corresponded to abnormally low Spermidine levels in the beginning, later ended with increased amount of Spermidine reaching normal values with inversion in Spermidine/Spermine ratio which became greater than 1, and Second (B-period) which was usually linked to an abnormally high RBC Spermidine concentrations and a Spermidine/Spermine ratio greater than 1 in the beginning, this later was characterised by an increase in granulocyte count (reaching 0.5 x 10(9) cells/l)". Thus, it was concluded that, "Since the A and B-periods are considered as a post-transplant aplasia period (only according to leukocyte count) and since normal RBC Spermidine levels occurred 14 days after Bone Marrow transplantation and 16 days before granulocyte rise, these data led us to consider erythrocyte polyamine levels to be an earlier biological criteria of bone marrow engraftment than the number of circulating granulocytes" [Bergeron, C et al., 1995]. In accordance with the study conducted in 1995 on "Polyamine metabolism in the rat liver after orthotopic liver transplantation". The results stated that, "The activities of Aspartate aminotransferase (AST), Alanine aminotransferase (ALT) and Lactate dehydrogenase (LDH) elevated and peaked 4 hrs after liver transplantation. Hepatic Ornithine decarboxylase and Spermidine/Spermine N1- acetyltransferase activities were also elevated and peaked 8 hrs after the operation. In agreement with the increases in Ornithine decarboxylase and Spermidine/Spermine N1-acetyltransferase activities, the Putrescine content increased and Spermidine content decreased in the transplanted liver. Putrescine administrated intraperitoneally improved the survival rate, decreased serum transaminase level, and increased the 3H-thymidine incorporation into the liver DNA". Thus, it was concluded that, "These findings suggest that both biosynthetic and biodegradative pathways are stimulated in liver transplantation, resulting in the increase in the formation of putrescine from Ornithine and from Spermidine, and that putrescine administration improve the survival rate by protecting the damaged graft after cold ischemia and reperfusion and by stimulating liver regeneration" [Terakura, M et al., 1995]. Based on the study conducted in the year 1997 on 63 children suffering from acute lymphoblastic leukemia. It was discussed to establish Erythrocyte Spermine levels as a prognostic parameter in childhood common acute lymphoblastic leukemia. It was stated that, "Polyamines have been implicated to play a role in cell proliferation and in cancer development and Ninety percent (90%) of the circulating Spermidine and Spermine are transported by RBCs (Red Blood Cells). Also, that Spermidine and Spermine levels were not correlated with WBC count and enhancement of specifically Spermine concentrations in RBC could be the sign of an important quantity of leukemia cell death before any treatment." Based on the results, it was concluded that, "An RBC Spermine level could be used as a parameter of prognosis at the time of diagnosis, particularly for patients with intermediary WBC count" [Bergeron, C et al., 1997]. With reference to the research conducted in the year 2000 aiming at studying "Polyamines as biochemical indicators of radiation injury". It was stated that, "In rats

submitted to Total Body Irradiation (TBI) with 3 Gy of Gamma radiation, tissue polyamines significantly decrease during the early phases of the injury in tissues with high proliferative activity (small intestine and spleen) and showed no modifications in kidney. Also, in patients submitted to radiation therapy, polyamines have been determined in urine and in RBC of patients with carcinoma of uterine cervix, head and neck and prostate, treated by external radiotherapy, and with thyroid cancer treated with iodine-131 therapy. It should be noted that polyamine levels before treatment appeared significantly higher than in healthy controls. After TBI the RBC polyamines show a dramatic fall to extremely low levels during the phase of marrow aplasia. The values show an increase corresponding to the engraftment of transplanted cells and to the following marrow repopulation. These evidences make the RBC polyamines very interesting parameters to monitor the radiation effects on humans." Thus, it was concluded that, "Polyamines demonstrates the ability to monitor both cell-death during acute radiation damage, and the following repopulation of highly proliferative tissues" [Porciani, S et al., 2000]. In the light of the study conducted in the year 2001. Effect on Ornithine decarboxylase (the main enzyme in Polyamine biosynthesis) and Total protein synthesis 24 hrs following partial hepatectomy was analysed in livers of rats treated with a pharmacological dose of recombinant IFN alpha-2b (Interferon alpha-2b). Results of the study stated that, "De novo Ornithine decarboxylase (ODC) synthesis by isolated hepatocytes was reduced significantly in the Interferon alpha-2b treated hepatectomized group 12 hr after surgery, the mean percentage of this diminution being 79%. Twenty-four hours after the operation, Ornithine decarboxylase (ODC) synthesis was undetectable and there are marked reduction observed in Polyamine levels." Also, it was discussed that, "DNA and Protein synthesis peak around 24 hrs after partial hepatectomy, but after therapeutic doses of IFN alpha-2b, DNA synthesis was not modified but surprisingly there was decrease in Total protein synthesis 24 hrs post-hepatectomy. In addition, there was reduction of Putrescine and Spermidine concentrations in regenerating liver by 40- 50%". Thus, it was concluded that: "The protein synthesis rate in regenerating liver was impaired by therapeutic doses of IFNa-2b. In addition, the results presented in this study suggest that IFNa-2b negatively regulates Ornithine decarboxylase synthesis, causing a reduction in polyamine levels during liver regeneration" [Cristián, F et al., 2001]. A study was conducted in 2016 investigating the impact of polyamines (Spermidine and Spermine) on ischemia/reperfusion injury (IRI) and liver regeneration. In this study 2 groups of Male Lewis Rats were created: A Polyamine group given polyamines before and after operation as treatment and A Vehicle group given distilled water as 'placebo'. The levels of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) at 6, 24, and 48 hours after reperfusion were significantly lower in the polyamine group compared with those in the vehicle group. Polyamine treatment reduced the expression of several proinflammatory cytokines and chemokines at 6 hours after reperfusion. Histological analysis showed significantly less necrosis and apoptosis in the polyamine group at 6 hours after reperfusion. In addition, the regeneration of the remnant liver at 24, 48 and 168 hours after reperfusion was significantly accelerated, and the Ki-67 labelling index and the expressions of proliferating cell nuclear antigen and phosphorylated retinoblastoma protein at 24 hours after reperfusion were significantly higher in the polyamine group compared with those in the vehicle group" Thus, it was concluded that, "Perioperative oral polyamine administration attenuates Liver Ischemia/Reperfusion Injury (IRI) and promotes liver regeneration. It might be a new therapeutic option to improve the outcomes of partial Liver Transplantation" [Okumura, S et al., 2016]. Conclusion Based on the Investigations conducted on Humans and Animals (Dogs) from the entire period of 1985 till 1994, increased level of urinary polyamines was detected. Polyamines were found to be increased in their levels in the early post-transplantation period (between 0 to 8 days after transplantation) and before acute rejection phase of the transplanted organ. Specifically, N-Acetylputrescine and N-Acetylspermidine elevations were responsible for the increase of total polyamine content in the urine after operation, before acute allograft rejection, and during Methylprednisolone therapy. It is thus concluded that, increased urinary polyamine measurements provide a daily evaluation of recipient's immunologic status which might be valuable to the diagnosis of organ rejection during the early post-transplantation period. Also, proving that Polyamines are useful as a non-invasive marker for lymphocyte activity and cardiac allograft rejection compared to invasive endomyocardial biopsy

specimen method. Thus, based on all the investigations conducted, it is clear that Polyamine levels (Spermidine, Spermine and Putrescine) are helpful in indicating allograft rejection at the earlier stage of post-transplantation period. Also, in one of the investigations, the use of therapeutic doses of IFN alpha-2b inhibited the total protein synthesis and Polyamines formation. After the study analysis, if the therapeutic doses of IFN alpha-2b are not used, there will be a significant increase in Total Protein synthesis and Ornithine decarboxylase activity thereby increasing Putrescine and Spermidine levels within 24 hrs in partially hepatectomised rats. Thereby, proving our aim that, Polyamine levels are increased in early post- transplantation period. Critical point to note is that there are no extensive studies until now conducted on role of Polyamines in Liver, Kidney, or other transplants. Only study on cardiac allograft rejection linked with increased urinary polyamine levels has been conducted from period of 1985 up to 1994 on Humans and specifically, Dogs. Polyamines importance specifically in organ rejection has not been researched extensively. So, we need to conduct more new scientific investigations, experiments and test the hypothesises on organ rejection and increased Polyamines levels after Liver, Kidney transplantation too. Further studies and active research are necessary to be conducted to define a potential clinical application of Urinary Polyamines as markers of cellular metabolic activity of the immune system and allograft rejection. Polyamines have potential to be a powerful marker to prevent the allograft rejections beforehand during the early
post-transplantation period.

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HEPATOCELLULAR CARCINOMA RISK ASSESSMENT IN CHRONIC HEPATITIS C PATIENTS TREATED WITH ANITVIRALS

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Liver diseases make up a significant percentage among causes of disability and death worldwide. Furthermore, rates of sickness are noticeably on the rise, especially in working age people with chronic liver problems. Intense research of the latter is caused by its social impact. Chronic Hepatitis C (HC) has a special place among liver diseases. Chronic hepatitis C virus (HCV) is unique because it can stay hidden and thus undiagnosed for a long time. Simultaneously, it progresses gradually, leading to development of liver cirrhosis (LC) and/or hepatocellular carcinoma (HCC) [1, 2, 3].

Presently, the antiviral drugs used for treating chronic HC have a 95% effectiveness in treating the disease, which leads to the decrease of mortality from LC and HCC, but alas the level of accessibility of chronic HC diagnosis and treatment remains low. According to WHO data the number of HCV-infected individuals rises every year, reaching to, for example, 1.5 million, with 290000 lethal cases, mainly from LC and/or HCC, in 2019 [4].

The statistics in Armenia are being recorded since 2015. Armenia is considered a country with medium HC prevalence. The burden of disease makes up 4.5% (about 100.000 people), amongst those only 10% have knowledge of being infected. The problem is the low number of informed and diagnosed patients and an even lower number of patients who have started treatment or have been cured. For example, in 2017 in Armenia there have been 711 recorded cases of HC, in 2018 - 1351 new cases.

A number of factors have a negative impact on the natural course and the effectiveness of antiviral treatment of HCV. Among such factors are advancing age, male gender, obesity, liver steatosis, insulin resistance, severe fibrosis and LC, accompanying diseases, early menopause, patient's commitment towards the treatment [5, 6, 7, 8, 9, 10].

HCV is the second most common etiological factor for HCC worldwide and the first in Western Europe, the USA and Japan. In the case of HCV infection, HCC develops in the majority of cases, preceded by LC, with 1-4% yearly frequency, and 13% in patients with Child-Pugh class A cirrhosis after 5 years of observation, which point to the development of primary liver cancer [11].

The risk factors for the development of HCC in HCV infected patients are male gender, patient's age - over 50, high histologic grade, severe fibrosis, HCV 1b genotype. The nodules are separate, small, have a capsule, as opposed to tumors developed in chronic hepatitis B patients, which have multiple nodules and frequently have infiltrative growth [12].

For patients with said risk factors it is recommended to determine serum alpha-fetoprotein (AFP) levels and conduct abdominal ultrasound imaging every six months for the purpose of early HCC detection. However, in 40-50% of patients the levels of AFP don't rise even after the tumor has shown significant growth, only in 1/5 of patients it reaches high, diagnosable levels (400 ng/ml) and is considered a negative predictive value. Only in 1/5 of patients the AFP level correlates with the stage of the disease [13, 14, 15]. Currently, three types of AFP have been discovered, of which ACE L3 is mainly present in HCC patients' serums [16]. In the case of HCC detection,

ACE L3 sensitivity fluctuates between 45% with 2cm or smaller tumors and 90% with tumors bigger than 5cm [17, 18]. The diagnostic value of computer tomography (CT) and magnetic resonance imaging (MRI) is also dependent on the size of the tumor. MRI precision surpasses 90% if the tumor is 2cm in diameter or bigger, however this value decreases to 33% if the tumor is smaller than 2cm.

Still the majority of researchers agree that the diagnostic value of ultrasound is lower than that of CT and MRI [19, 20], despite the fact, that the latter are not used for HCC screening because of their high cost and cumulative negative risk: x-ray radiation (CT) and the risk of kidney function loss in patients with hepatorenal syndrome caused by iodine containing contrast use (MRI) [21].

Des-gamma-carboxyprothrombin, also known as PIVKA-II (Protein induced by vitamin K absence or antagonist II) is a relatively new HCC marker. Its level increase is observed in 67% of HCC patients, but only in 8% in cases, where the size of the tumor is small (<2cm). Unlike AFP, PIVKA-II levels do not increase in patients with benign tumors in the liver, including hepatitis and cirrhosis [22,23]. T. Nakagawa and co-authors have shown that in HCC diagnostics PIVKA-II sensitivity is 48-62%, and its specificity is 81-98% [24]. PIVKA-II diagnostic value is comparable to AFP. It has been shown that PIVKA-II and AFP are independent of each other and the use of both (PIVKA-II and AFP) markers leads to a significant increase in sensitivity (74.3%) and specificity (87.2%).

In recent times research has shown that 5% of HC patients have a risk of developing HCC within two years of finishing treatment with direct-acting antivirals (DAA) [26, 27].

Based on this information, the goal of our work was to examine serum markers for HCC (PIVKA-II and AFP) in patients with chronic HC before and after treatment.

Patients and methods

The study included 35 untreated patients (30 males and 5 females, mean age 56,23±1,45) diagnosed with HCV-related chronic hepatitis. Patients participating in the study were selected from applicants to infection and/or gastroenterology-hepatology centers based on their hepatitis C diagnosis. Patients were divided into two groups. The first group (HCV+HCC) included 15 patients diagnosed with HCC along with HCV, all males, mean age 57,06±2,42. The second group (HCVnon-HCC) included the remaining 20 patients (15 males and 5 females, mean age 55,20±1,80)

Diagnosis in patients was based on clinical (medical history, clinical examination), instrumental (ultrasonography, liver elastography, CT scan, liver biopsy) and laboratory (serum HCV antibodies, HCV-RNA and liver function tests, AFP, PIVKA-II test) data. Patients with autoimmune diseases, alcohol abuse, and hepatotropic drug-induced liver injury were excluded from the study. According to the recommended screening strategy, patients with other chronic or acute infectious processes (altered white blood cells count, temperature, urinary tract infection, airway infections, etc.) were also excluded. Patients' plasma des-gamma-carboxyprothrombin levels were determined by sensitive enzyme immunoassay (ARCHITECT PIVKA-II, Japan, cut-off 50.9mAU1/ml) according to the manufacturer's instructions. Informed consent was obtained from all patients. While fasting in the morning, a blood sample was withdrawn from all subjects, and the testing was conducted by Prom-Test laboratories.

There has been no need to determine HCV genotype in this study, since the treatment was conducted with pangenotypic DAAs. However medical history has shown that the majority of patients had undergone testing before and in most cases HCV 1b genotype was present, which is the most prevalent in Armenia.

Liver ultrasound elastography was conducted in all patients with the CANON Medical Systems APLIO I900 device. Fibrosis level was expressed in kPa: F2 - mild fibrosis (6.3 - 10.7 kPa), F3 - severe fibrosis (8.1 – 13.5 kPa), F4 - cirrhosis (18.5 - 30.7 kPa). In the first group, the results

showed F3 in 6.7%, F3-F4 in 13.3%, F4 in 80.0% of patients, while in the second group F2 in 10.0%, F3 in 10.0%, F3-F4 in 15.0%,and F4 in 65.0%. For the purpose of precisely determining the fibrosis stage, some patients underwent liver biopsy.

Subjects were studied 3 times: before antiviral therapy, after 12 weeks (end of treatment) and after 24 weeks. After the end of treatment patients were tested for HCV RNA with negative results. The overwhelming majority of patients had undergone treatment with DAAs under a government program according to international guidelines (WHO 2018, EASL 2018) - Sofosbuvir/Velpatasvir, Sofosbuvir/Daclatasvir - 1 per day and/or 1 of each for 12 weeks. All patients with 1b genotype in the stage of cirrhosis had undergone treatment with Sofosbuvir/Ledipasvir for 12 weeks (EASL 2018).

HCC diagnosis was based on serum PIVKA-II and AFP levels, liver ultrasonography and CT scan data. Liver biopsy was performed for some patients.

Statistical analysis of the data was performed using the STATIST.5 program. The results of biochemical studies were processed with the statistical dispersion method using the Student Fisher test. The relationship between continuous variables was studied using Spearman's correlation test. Statistical significance was estimated $P<0.05$.

Results

In the first group (HCV+HCC) before starting antivirals, high serum PIVKA-II, AST, GGT levels were recorded: ALT in 86.7% of patients, AFP in 73.3% of patients. The overwhelming majority had low PLT (93.3%) and PT% (86.7%) count. After the treatment PIVKA-II levels remained high in all subjects, while AFP levels were increased in 60.0% of patients. The ALT and GGT levels decrease was the most significant - 53.3% and 40.0% accordingly. PLT count was unchanged, PT% continued to remain low in 66.7% of patients. After the third examination (24 months) we recorded high levels of PIVKA-II in 86.7%, AFP in 40.0%, AST in 80.0% of patients. In this timeframe a significant normalization of GGT in 73.3% and ALT in 66.7% of patients was recorded, as well as PT% normalization in 40.0% of the cases. PLT count remained low in 73.3% of patients.

The second group (HCVnon-HCC) before starting antivirals also showed high serum PIVKA-II and AST levels, however GGT levels were high only in 75% of the patients. The rest of the comparable indexes were as follows: high ALT in 85.0% and AFP in 50.0% of cases, low PLT (85.0%) and PT% (55.0%) count. After the treatment PIVKA-II levels remained high in 80.0% of the patients, while AFP levels were above normal only in 25.0% of cases. ALT decrease was the most significant, it was above normal only in half of the patients (50.0%), while AST and GGT levels remained high in 80.0% and 60.0% of the cases accordingly. PLT count was low in 60.0% and PT% in 35.0% of patients. After the third examination it was recorded that PIVKA-II levels remained high in 40.0%, AFP only in 15.0% of the cases, however AST was high in 55.0%. In this timeframe PT% countin 90.0%, ALT in 85.0%, GGT in 70.0% and PLT in half of the patients reached normal levels.

Following this, we calculated average values of studied indexes in this timeframe, which are presented in the following table.

The table shows that PIVKA-II values were high in both groups before the treatment and during the study we recorded their decrease, however, only the second group had statistically significant decrease in values after the treatment ($P<0.05$) and after 24 weeks ($P<0.01$)

Table. The changes of serum values in different groups (HCV+HCC and HCVnon-HCC) in different timeframes of the study

Serum Values (normal distribution)	Statis-tical values	Research timeframe					
		First group (n=15) (HCV+HCC)			Second group(n=20) (HCVnonHCC)		
		Before treatment	After 12 months	After 24 months	Before treatment	After 12 months	After 24 months
PIVKA II (< 50.9)	$\overline{X}$	11237.87	3087.65	816.77	355.67	151.55	56.99
	m	8363.67	1753.78	519.90	85.05	33.26*	°°9.15**
AFP (≤8.78)	$\overline{X}$	426.84	728.10	34.28	522.60	71.04	20.73
	m	333.39	672.23	20.68	464.22	54.95	12.87
Bil. Total (3.4 – 20.5)	$\overline{X}$	65.25	38.87	27.88	48.20	27.07	15.01
	m	13.69	7.20	7.17*	11.70	5.79	°1.07**
Bil. Direct (0 – 8.6)	$\overline{X}$	38.70	21.52	14.47	27.112	11.46	7.085
	m	10.35	5.56	5.31*	7.76	2.37	*0.94*
ALP (40-150)	$\overline{X}$	162.72	123.93	92.10	141.46	108.13	85.69
	m	16.24	12.51	°7.91***	14.34	9.21	6.85**
ALB (35-50)	$\overline{X}$	30.32	33.90	38.85	34.60	37.27	40.32
	m	1.44	1.42	°1.15***	0.94	*0.93*	°0.98***
AST (5-34)	$\overline{X}$	152.57	157.07	64.82	149.18	75.1	38.75
	m	17.76	68.65	7.38***	20.61	13.24***	°**5.51***
ALT (<55)	$\overline{X}$	128.32	73.95	52.39	133.21	69.85	39.23
	m	18.18	12.90*	7.12***	16.53	8.85**	°°6.65***
GGT (12-64)	$\overline{X}$	214.54	103.02	52.73	197.93	94.05	64.65
	m	39.50	17.83*	°8.90***	39.10	17.53*	14.40**
PLT (150-400)	$\overline{X}$	79.19	97.92	116.81	109.32	128.14	142.85
	m	9.41	8.86	9.46*	13.51	*12.61	15.62

PT % (70-120)	$\overline{X}$	60.18	70.33	77.05	68.77	77.15	85.69
	m	4.01	3.58	4.44**	3.60	2.96	3.12***
INR (0.8-1.2)	$\overline{X}$	1.78	1.39	1.23	1.48	1.316	1.137
	m	0.11	0.08**	0.05**	0.08	0.06	°0.05***

* - statistical significance P<0.05 compared to values recorded before treatment in the same group

** - statistical significance P<0.01 compared to values recorded before treatment in the same group

*** - statistical significance P<0.001 compared to values recorded before treatment in the same group

* - significance on the left side < 0.05 comparing two groups HCV+HCC and HCVnon-HCC in the same timeframe

** - significance on the left side < 0.01 comparing two groups HCV+HCC and HCVnon-HCC in the same timeframe

o - statistical significance P<0.05 compared to week 12 in the same group

oo - statistical significance P<0.01 compared to week 12 in the same group

AFP levels were also high in both groups before the antiviral treatment and had a decrease during the study, but not significant.

In both groups a significant decrease of some liver function tests (Bilirubin Total, Bilirubin Direct, ALP) only 3 months (24 weeks) after finishing the treatment was recorded and in HCVnon-HCC group Bilirubin Direct was significantly (P<0.05) lower compared to HCV+HCC group. Only in week 24 a decrease of AST levels (P<0.001) was recorded in the first group, while in the second this happened after finishing the treatment (P<0.001). The last values of AST in HCVnon-HCC group were significantly lower compared to HCV+HCC group. ALT and GGT levels had the same dynamic in both groups, significantly decreasing (P<0.05) immediately after the end of the treatment, which was reaffirmed during the third phase of testing (P<0.05 - P<0.001). ALB level decrease was most apparent in HCV+HCC group, average levels were significantly increasing in both groups (P<0.001) 24 weeks after starting the treatment and in HCVnon-HCC patients already after the end of the treatment (P<0.05).

As mentioned earlier, PLT count in the overwhelming majority of patients was low before starting the treatment, more so in HCV+HCC group (79.19± 9.41) than in HCVnon-HCC group (109.32± 13.51) as shown in the table. Despite the rising count of PLT in HCV+HCC patients (P<0.05) still in week 24 it was considerably below (116.81± 9.46) the norm. Already after finishing the treatment the PLT count was higher (P<0.05) in HCVnon-HCC group than in HCV+HCC group.

Among coagulation test values PT% and INR were studied. Before starting the treatment prothrombin index was low in majority of patients (86.7%) from the first group, however, after 24 months an increase of PT%(P<0.01) was recorded. In the second group PT% index was low in half of the patients and by the end of the study it was significantly increased (P<0.001). In

regards to INR, both groups showed high scores, considerably higher in HCV+HCC patients, still in both groups it reached the norm after 24 weeks (P<0.01 - P<0.001).

We have also studied the correlational between studied values in different timeframes.

In the first group (HCV+HCC) after the treatment we recorded positive medium and high correlation between PIVKA-II and Bilirubin Total (r=0.61; P<0.05), Bilirubin Direct (r=0.73; P<0.05), ALP (r=0.66; P<0.05), ALT (r=0.84; P<0.05), inverse correlation with ALB (r= - 0.62; P<0.05), no correlation between PIVKA-II and AFP (r=0.32; P<0.05). At the end of the study (week 24), positive high correlation was recorded between AFP and Bilirubin Total (r=0.89; P<0.05), Bilirubin Direct (r=0.73; P<0.05) and, again, no correlation was recordedbetween PIVKA-II and AFP (r=0.15; P<0.05).

In the second group (HCVnon-HCC) positive medium correlation between PIVKA-II and AFP was detected at the end of the treatment (r=0.58; P<0.05) as well as after 24 weeks (r=0.56; P<0.05).

We decided to compare PIVKA-II and AFP values only in F4 stage patients. Interestingly, in the first group (HCV+HCC) (n=12) a high interconnectedness between PIVKA-II and AFP (r=0.79; P<0.05) was recorded after the treatment and in the last phase of tests the correlation was even more apparent (r=0.94; P<0.05). In the second group (HCVnon-HCC) (n=13) the analysis of values showed a positive medium correlation between PIVKA-II and AFP levels after the treatment (r=0.60; P<0.05), however it became weaker in the last phase (r=0.54; P<0.05).

Discussion

The revolution in treating chronic HCV patients continues to this day and relies on active development of DAAs, many of which are either in clinical trials or are already successfully used in practical medicine, even being used in cases with decompensated LC [28]. LC remains the main risk factor for HCC development [29], and in patients with cirrhosis and active HCV infection the yearly risk of HCC development constitutes 3% [30], the latter being considered the fifth most common and the second deadliest cancer worldwide [31].

However, as noted earlier, there is information about malignization risk even after a successful DAA therapy [26, 27]. Even in the case of sustained virologic response 5.8% of the patients will be diagnosed with liver tumors [32].

The results of our research showthat all the participating patients had a virologic response after the antiviral treatment. Along with that the ALT levels, which are considered the traditional measure of a successful treatment, were decreased and the normalization of liver cell cytolysis values was recorded in half of the patients from both groups. Despite ALT levels remaining above the norm, a statistically significant decrease was recorded in both groups.

3 months after the antiviral treatment HCV RNA was again not detected in any of the patients, however a full biochemical and virologic response was recorded only in 2/3 of HCC and chronic HCV patients and in 85% of patients with chronic HCV only.

As mentioned, PIVKA-II levels were high in all patients before the treatment. At the end of the treatment in the group with HCV without HCC normal values were detected only in 1/5 of the cases and in 60.0% after 3 months. While in the group with HCC and chronic HCV patients PIVKA-II levels were normal only in 13.3% of subjects after 3 months. We also recorded an increase in AFP, but the rate of its decrease was considerably quicker than that of PIVKA-II.

In patients with chronic HCV and HCC, significant statistical differences between serological markers for the latter (PIVKA-II and AFP) were not recorded before the treatment as well as after its end. They are independent diagnostic biomarkers and this matches the information in some international publications [25, 33]. However, a high correlation was recorded between PIVKA-II and AFP in HCV+HCC group when comparing data from F4 stage patients after the

treatment as well as after 3 months. So PIVKA-II and AFP levels showed high correlation only in patients with cirrhosis in HCV+HCC group, and medium correlation in HCVnon-HCC group.

So, the successful treatment of chronic HCV infection with DAAs reduces but doesnot eliminate the risk of HCC, since even 3 months after the treatment with sustained virologic response our data show that in 40% of the patients PIVKA-II levels remain above the norm. Therefore, even in the case of acquiring a sustained virologic response, continuous monitoring is required not only for patients with cirrhosis (F4) but also in cases of severe fibrosis (F3) [34, 35]. It is important to correctly assess HCC development risk factors after DAA therapy, although the strongest factor is, of course, the absence of sustained virologic response.

It has been reported that the age over 50, male gender, diabetes mellitus, esophageal varices [38, 39] and metabolic syndrome [34, 40, 41] can also be risk factors for the development of HCC. It has also been shown that albumin levels <3.5 mg/dl and thrombocyte count <120000/ml, as well as the absence of sustained virologic response, are independently tied to a higher risk of HCC development [42].

Thus, since chronic inflammation can stimulate hepatocyte neoplasm and malignant clone propagation [43], we find appropriate the continued monitoring of HCV patients with cirrhosis (F4) and severe fibrosis (F3) but without HCC, whose PIVKA-II and AFP levels and/or ALT activity remains high despite acquiring sustained virologic response 3 months after treatment with DAAs and who also have hypoalbuminemia, thrombocytopenia, hyperbilirubinemia, and coagulopathy. It should also be noted that the data have been obtainedfrom a small number of subjects, and a larger study and continuous supervision are neede to confirm the results.

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