Krzewicka-Romaniuk Ewa, Siedlecka Dagna, Makuch Marcelina, Pradiuch Anna, Wójcicka Grażyna. Patophysiology of nonalcoholic fatty liver disease. Journal of Education, Health and Sport. 2019;9(9):987-991. eISNN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.3462889
http://ojs.ukw.edu.pl/index.php/johs/article/view/7539

The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8. 2) and § 12. 1. 2) 22.02.2019.

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 25.08.2019. Revised: 31.08.2019. Accepted: 22.09.2019.

PATOPHYSIOLOGY OF NONALCOHOLIC FATTY LIVER DISEASE

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KEY WORDS: NAFLD; liver disease; fatty liver

Abstract Clinically, NAFLD is the most common cause of asymptomatic increases in transaminases. NAFLD is also currently the most common liver disorder in developed countries, affecting 24% of the world's population. The prevalence of NAFLD in European societies is estimated in the range of 17-46% and shows an upward trend with the increasing incidence of obesity and type II diabetes.
NAFLD occurs in about 7% of people without excess weight, however, they are usually people with impaired insulin sensitivity, leading a sedentary lifestyle, having an increased cardiovascular risk, with higher levels of hepatic lipids as a result of reduced fat accumulation and reduced mitochondrial activity in adipose tissue and increased de novo hepatic lipogenesis.

INTRODUCTION

The definition of nonalcoholic fatty liver disease (NAFLD) includes:
1) fatty liver in imaging or histological examination, i.e. the presence of lipid vacuoles in more than 5% of hepatocytes or the presence of triglycerides occupying> 5.6% of liver volume in magnetic resonance spectroscopy with simultaneous:
2) the absence of causes of secondary fat accumulation in the liver, such as the consumption of significant amounts of alcohol, taking medications that cause steatosis or hereditary diseases.

Clinically, NAFLD is the most common cause of asymptomatic increases in transaminases. NAFLD is also currently the most common liver disorder in developed countries, affecting 24% of the world's population[1]. The prevalence of NAFLD in European societies is estimated in the range of 17-46% and shows an upward trend with the increasing incidence of obesity and type II diabetes.
NAFLD occurs in about 7% of people without excess weight[2], however, they are usually people with impaired insulin sensitivity, leading a sedentary lifestyle, having an increased cardiovascular risk, with higher levels of hepatic lipids as a result of reduced fat accumulation and reduced mitochondrial activity in adipose tissue and increased de novo hepatic lipogenesis.[1]

RISK FACTORS

In most patients, NAFLD is associated with metabolic risk factors such as obesity, diabetes and dyslipidemia, and is therefore considered as a manifestation of the metabolic syndrome.[3] Obesity is a common and well documented risk factor for NAFLD. This applies to both increased BMI and abdominal obesity. In people with severe obesity undergoing bariatric surgery, the incidence of NAFLD may exceed 90%, and up to 5% of patients may have previously unsuspected cirrhosis.[4]

In addition, NAFLD is very common in patients with type 2 diabetes - hepatic steatosis was found in ultrasound in 60–70% of patients. NAFLD very often coexists with hypertriglyceridemia and low HDL cholesterol. Both the frequency of NAFLD and the risk of liver fibrosis and death increase with age. According to recent studies, another risk factor for fatty liver is male sex. Some data suggest the co-occurrence of hypothyroidism, hypopituitarism, hypogonadism, sleep apnea and polycystic ovary syndrome with NAFLD.[4]

Diet rich in cholesterol, highly saturated fatty acids and fructose, also known as "bar" or "fast food" type, contribute to the development of NAFLD.[5] "Normal" high-fat diet contributes to the development of obesity, insulin resistance and fatty liver with minimal inflammation and without fibrosis, while a "fast-food" diet causes over-expression of the genes responsible for increased liver fibrosis, inflammation, excessive load of endoplasmic reticulum and lipoapoptosis.[6]

PATHOGENESIS

INSULIN RESISTANCE

Insulin resistance seems to play an important role in the pathogenesis of NAFLD. The consequence of insulin resistance in visceral adipose tissue is increased lipolysis, which causes the release of excessive amounts of FFA into the blood of the portal vein. FFA are esterified to triglycerides in the liver.[2] In addition, the liver, in which excessive triglyceride deposition and inflammatory processes occur, become a source of proinflammatory cytokines and adipokines ("hepatokines"), C-reactive protein and type 2 plasminogen activator inhibitor. These substances are responsible for maintaining chronic subclinical inflammation in the body , peripheral insulin resistance, hypercoagulability and endothelial damage.[4]

MICROBIOTA

Apart from visceral adipose tissue, intestinal bacterial flora plays a key pathophysiological role in the pathogenesis of NAFLD. Quantitative and qualitative changes in the intestinal microbiome contribute to the loss of mucosal integrity and increase its permeability to endotoxins and other bacterial products. Hepatic effects for endotoxins by their effect on type 9 (hepatocytes, Borowicz-Kupffer cells) and type 1 (stellate cells) Toll-like receptors are cellular apoptosis, inflammation and fibrosis.

NASH

Based on the histopathological examination of the liver, NAFLD distinguishes between simple steatosis and non-alcoholic steatohepatitis (NASH), occurring in approximately 10% of NAFLD cases. In this form of the disease, apart from fatty vacuoles, hepatocytes reveal features of damage such as apoptosis or balloon degeneration, and within the lobes or portal spaces an inflammatory infiltrate, which includes, among others neutrophils, can be observed. The NASH fibrosis spectrum extends from its initial forms in the form of pericellular fibrosis (barbed wire type) up to cirrhosis[2], with all its complications such as hepatocellular carcinoma.[7] NASH's natural history studies show that 10-20% of patients develop liver cirrhosis after several years. The factors that determine disease progression are only partially understood. Among them, the most common are polymorphisms of patatin-like phospholipase containing protein 3 (PNPLA3, adiponutrine) and polymorphisms of single nucleotides in the genes of apolipoprotein C3 (APOC3).[2] Considering genetic factors, NAFLD patients should be asked about deaths due to cirrhosis among their closest relatives. The metabolic syndrome is a predictor of fatty inflammation in patients with NAFLD, and therefore may be a criterion for liver biopsy qualification.

The pathogenesis of NASH itself is not fully understood, but one of the main hypotheses assumes "the theory of two strokes".
According to this theory, the first "strike contributing to the development of NASH is lipid accumulation in hepatocytes, mainly in the form of triglycerides, resulting from imbalance between metabolic pathways promoting the uptake and synthesis of WKT by hepatocytes and promoting oxidation and export FFA. Insulin resistance associated with obesity and type II diabetes is considered an extremely important factor in the development of fatty liver. Insulin resistance contributes to peripheral lipolysis and hyperinsulinemia. Lipolysis increases the

amount of circulating WKT and their uptake by the liver. Hyperinsulinemia enhances hepatic fatty acid synthesis by increasing glycolysis and promotes the accumulation of triglycerides inside hepatocytes by reducing the liver's ability to reesterify and pack triglycerides into lipoproteins and send them to the periphery.[3]

Following hepatic steatosis, hepatocytes develop a susceptibility to oxidative stress, which may largely be responsible for the progression of NAFLD from simple steatosis to steatosis associated with necrotic-inflammatory activity and fibrosis. Therefore, oxidative stress has been reported as a "second hit". Mitochondria play a major role in the oxidation of fatty acids. Since the oxidation of mitochondrial fatty acids produces free radicals, mitochondria are the main cellular source of reactive oxygen species (ROS), mainly in the form of hydrogen peroxide. Oxidative stress has been described as a factor that disturbs the balance of ROS generation and the cellular antioxidant defense system. In fatty liver disease, the imbalance between endogenous antioxidant reserves and increased mitochondrial free radical production causes oxidative damage to lipids, protein and DNA with subsequent cell death.[3]

TREATMENT

The basis of NAFLD treatment is combating obesity and correcting disorders that are part of the metabolic syndrome. Weight reduction usually reduces the severity of fatty liver, regardless of whether it was achieved only by a low-calorie diet or by increased physical activity. To reduce fatty liver, a weight reduction of 3-5% appears necessary, while a larger reduction (up to 10%) may be needed to improve necrotic-inflammatory lesions. It is worth remembering that physical activity alone in adults with NAFLD may reduce the severity of liver steatosis, although its effect on other histopathological changes remains unknown.[4]

There is no conclusive evidence of the effectiveness of pharmacotherapy; drugs are proposed to improve insulin resistance e.g. metformin, thiazolidinedione derivatives, reduce liver fibrosis, reduce the level of fatty liver e.g. statins, metformin, and incretin drugs; hepatoprotective and oxidative stress reducing drugs (e.g. ursodesoxycholic acid, vitamin E, betaine) and symptomatic treatment of liver cirrhosis.[8] Hepatoprotective treatment, however, only applies to patients with NASH, because the remaining patients with NAFLD have a very good prognosis for liver disease. Vitamin E (α-tocopherol) at a dose of 800 IU / d should be considered as the first-choice drug in adults with NASH confirmed by biopsy, because it improves the histopathological picture of the liver in this population, although due to reports of the possibility of causing vitamin E to increase stroke incidence brain or prostate cancer, it should be used with some caution. It should also be remembered that despite the widespread use of metformin or ursodesoxycholic acid in the treatment of NAFLD, the data on their effectiveness are inconclusive. For example, according to the AASLD or NICE guidelines, the use of metformin in the treatment of NAFLD is not recommended.
Currently, the best form of therapy remains weight reduction combined with increased physical activity. Liver spectroscopic studies have shown that a weight loss of 5-20% reduces liver fat by 40-80%. It is difficult to imagine a better effect of NAFLD treatment.[4]
ACKNOWLEDGEMENT: None

DISCLOSURE STATEMENT: The authors have no conflicts of interest to declare.

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