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Mini Review

Fatty Liver Disease, a New Pandemic?

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Received: March 23, 2021; **Published:** April 14, 2021

Abstract

Nonalcoholic fatty liver disease represents a major health problem worldwide, as it is the most common cause of chronic liver disease with a high prevalence in childhood, adolescence and adults and is associated with obesity. Multiple hits have been postulated in the pathogenesis. Reference is made to the intestine-liver axis among the mechanisms involved as well as the role of dysbiosis of the intestinal microbiome and alterations of the barrier and in the permeability of the intestine. The value of diet and exercises together with therapeutic management is discussed. Mention is made to new emerging drugs subject of clinical trials in the preclinical and clinical phase related to the pathogenesis stage of nonalcoholic steatohepatitis, while emphasizing the investment and development projects for 2020-2029 by the global pharmaceutical industry. The potential use of gut microbiota manipulations is mentioned as a target in new next generation probiotic adjuvant therapy in association with diet and exercise as promising future treatments.

Keywords: *Fatty Liver; Nonalcoholic Fatty Liver Disease; Steatohepatitis, Treatment: Medications; Intestinal Microbiota Modulation; Probiotics*

Introduction

Nonalcoholic fatty liver disease (NAFLD) is currently a relevant global public health problem, comprising a spectrum of liver diseases. It is associated with obesity, insulin resistance, type 2 diabetes mellitus (T2DM), and cardiovascular risk factors with high blood pressure, hyperlipidemia and metabolic syndrome. The histological study of the liver establishes categories, represented by simple steatosis, which can progress to nonalcoholic steatohepatitis (NASH) subtype, with a potential evolution in its advanced forms to liver fibrosis, cirrhosis and eventually hepatocellular carcinoma, while most of them only exhibit simple steatosis [1].

NAFLD has become the most frequent among liver diseases in the last 30 years with a total worldwide prevalence of fatty liver disease of 25% and nonalcoholic steatohepatitis. NAFLD represents the leading cause of liver disease in developed countries, but its diffusion is currently also emerging in Asian countries, South America and other developing countries. It is progressively becoming one of the main diseases responsible for hepatic insufficiency, hepatocarcinoma and the need for orthotopic liver transplantation. It varies between 1,5 to 6,45% while in T2DM it is 37,3%. The highest percentage corresponds to the population of South America (31%), Middle East (32%), Asia (27%), EE. UU. (24%), Europe (23%), and lowest in Africa (14%). Epidemiology and the prevalence of the disease vary in different groups, particularly according to sex, age, body mass index, type 2 diabetes and dyslipidemia [2]. Epidemiological studies in NAFLD and NASH have been shown to have a two-fold higher risk of mortality related to cardiovascular diseases and non-liver cancers, compared to those without NAGLD [3].

The intestine-liver axis plays a major role in the possible pathogenesis of NAFLD and NASH: damage to the intestinal barrier resulting from dysbiosis and increased intestinal permeability, as factors that allow the passage to portal circulation of molecular patterns associated with pathogens including lipopolysaccharides and bacterial metabolites [4].

Sufficient experimental studies in mice and humans have now accumulated supporting evidence on the role of the gut microbiota and the gut-liver axis in the pathogenesis of NAFLD. The dysbiosis events of the microbiota represented by a decrease in the microbial population and deterioration of the intestinal mucosa, due to the rupture of the tight and occlusive epithelial cell junctions, cause damages in the intestinal epithelium and the mucosal barrier with low degree of chronic local inflammation, as well as alterations of intestinal permeability that predispose to immune dysfunction of the intestinal mucosa and hepatotoxic effects. NASH is aggravated by the persistence of inflammation of the intestinal mucosa, an expression of the pathogenesis mechanism of liver damage with pro-inflammatory activity provoked in metabolic states by dysbiosis [5]. However, to date the mechanisms of the intestinal ecosystem described in the pathogenesis of NAFLD have not been definitively clarified [6].

In recent years the hypothesis of "multiple-hi" has been postulated, expression of multiple aggressions that simultaneously intervene in the progress of NAFLD/NASH, which includes insulin resistance, genetic, epigenetic and nutritional factors, due to excessive calories, with association to intestinal microbiota, valued as one of the main factors of pathogenesis, which has prioritized the attention of researchers [7,8].

In humans, NAFLD is closely linked to decisive events that occur-barrier alterations in the composition of the intestinal microbiota and in the permeability of the intestine, changing levels of bile acids or metabolites ethanol, choline and others - associated to changes in bacterial species [9]. Moreover, the progression of the fatty liver disease may be currently explained as consequence of endotoxins released in dysbiosis that participate together with the immune system in the hepatic inflammatory process and thus perpetuate the development of organ infiltration [5].

Two types have been described: hepatic steatosis/nonalcoholic fatty liver (NADL) and nonalcoholic steatohepatitis (NASH), both are histologically categorized under the umbrella of non-alcoholic fatty liver disease (NAFLD). NADL is characterized by the presence of fat in the hepatocytes, no evidence of hepatocellular injury or fibrosis; it is asymptomatic and reversible, while in NASH there are fatty liver and inflammation with cellular damage, it is not reversible and can evolve with or without fibrosis. Also, it is associated with progression to more advanced stages of liver disease: development of cirrhosis (approximately 20% of cases), liver failure and, in rare cases, liver cancer. NASH is little recognized in clinical practice [10,11].

The basis of treatment are hygienic-dietary measures to modify the evolution of the disease and the association with other comorbidities that occur with metabolic syndrome (obesity, T2DM, dyslipidemia, among others) [12]. The changes in the diet with caloric restriction to reduce the weight together with the practice of exercises are fundamental, together with education to modify the lifestyle [13,14].

If current trends continue, the global target for physical activity by 2025 (a relative reduction of 10% in insufficient physical activity) will not be met. Policies to increase the physical activity levels of the population must be prioritized and expanded urgently.

It is of interest to highlight there are multiple pharmacological medications that are used for NAFLD however, none in itself has achieved its effectiveness recognized. Four directions for treatment have been described: metabolic pathways, inflammation, oxidative stress, and fibrosis. Only ursodeoxycholic acid, probiotics and fecal microbiota transplantation have action on two conditions: metabolic pathways and inflammation [12]. The American Association for the Study of the Liver (AASLD) has recommended Vitamin E and pioglitazone only in patients with NASH although there is a possibility for the appearance of adverse effects that require individualization of therapy due to the risk-benefit before treatment [15]. Importantly, metformin, ursodeoxycholic acid, fibrates, omega-3 fatty acids, and the monoclonal antibody simtuzumab have not been shown to be useful, despite their possible similar actions in the NASH mechanism. In recent years, different new clinical trials with novel drugs have been reported [16,17].

Solution to the challenge?

The worldwide epidemic of NAFLD is thought to mainly be driven by an unhealthy lifestyle with little physical activity and a diet high in saturated fats, sugar and fructose [13,14]. In these overweight and obese patients, weight loss brought about by lifestyle modification is considered most effective and safe treat NASH and reduce the risk of advanced forms of liver diseases such as cirrhosis, type 2 diabetes and cardiovascular diseases [12].

Now numerous emerging new drugs that are being tested in large number of preclinical and clinical trials (phase 2-phase 4) and understanding NASH pathogenesis has a crucial role. These drugs target almost all stages to improve insulin sensitivity, glucose and lipid metabolism to inhibit *de novo* lipogenesis and delivery of lipids into the liver what influence apoptosis, inflammation and fibrogenesis. On the other hand, the effect of treatments to regulate the intestinal microbiome and the effects of lipopolysaccharides, bacterial metabolites and bile acids is being investigated. On the other hand, the effect of treatments to regulate the intestinal microbiome and the effects of lipopolysaccharides, bacterial metabolites and bile acids are being investigated [18,19].

There are prepared for the decade 2020 - 2029 for the NASH. Sales for the market will grow from $ 144.4 million in 2019 to $ 27.2 billion in 2029 with an attractive annual growth rate. By the end of 2029, the US will contribute around 94.3% of global sales, while other five European countries (United Kingdom, France, Germany, Italy, Spain) and Japan will account for around 4.5% and 1.2% approximately [19].

Challenges of intestinal modulation. New adjuvant treatment with probiotics?

In this regard, it has been considered the specific microbial communities of each species could outline the stages of NAFLD [20]. During the course of the disease, it has been determined that the abundance of *Bacteroides* was higher in patients with NASH and fibrosis, while the majority of *Ruminococcus* was found in patients with fibrosis, although in multivariate analysis it was specified that *Bacteroides* are independently associated with NASH, while *Ruminococcus* are associated with fibrosis [21].

The so-called Next Generation Probiotics (NGP) [22,23] it has been postulated may be promising candidates to act as definite adjuvants in the manipulation of the intestinal microbiota and the hepatic protector effect in the selective treatment of metabolic conditions due to their high specificity, based on the results of research, using omic techniques, such as metagenomics (composition of the microbiota), metabolomics (functionality), among others [24], although to date only studies have been carried out in animals and very limited in humans [25,26].

Conclusion

In the context of new research, it is necessary to carry out new randomized controlled clinical trials with a sufficient number of cases and unifying the dose criteria in the selected species and strains in view of the therapeutic challenges for NAFLD and especially NASH [18,27]. The challenge will be decisive.

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Volume 8 Issue 5 May 2021