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Review Article

Non-Alcoholic Steatohepatitis and Intestinal Microbiome

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Abstract

Non-alcoholic steatohepatitis (NASH) is a progressive liver disease characterized by fat accumulation, inflammation, and damage to liver cells, often linked to metabolic dysfunction. It commonly presents with overweight, type 2 diabetes, elevated cholesterol, and high blood pressure, as well as excess fat in the liver. Now, we will examine this frequent and aggressive pathology and its relationship with the gut microbiome. Our aim is to identify processes that can minimize the impact of NASH and, consequently, guide new treatments for its management.

Keywords: *Non-Alcoholic Steatohepatitis (NASH); Intestinal Microbiome (GM); Non-Alcoholic Fatty Liver Disease (NAFLD)*

Introduction

Non-alcoholic steatohepatitis (NASH) is a very common condition associated with metabolic processes, insulin resistance, and necroinflammation, leading to high mortality. It can result in compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, and ultimately, extrahepatic malignancies, cardiovascular disease, chronic kidney disease, or liver transplantation. The highest mortality rates occur in patients with hepatocellular carcinoma, reaching up to 41.85% [1]. It tends to progress more rapidly than non-alcoholic fatty liver disease (NAFLD). Patients with cirrhosis should undergo screening for hepatocellular carcinoma and esophageal varices. A healthy lifestyle and the reduction of obesity and overweight remain crucial for its prevention [2].

Pathophysiology

Non-alcoholic steatohepatitis (NASH) is a complex pathology that can cause morbidity and mortality due to liver involvement. Therefore, it is important to understand its complex pathophysiology, as well as the early recognition of symptoms and its management through lifestyle changes and antifibrotic agents, although these remain insufficient. *Desulfovibrio desulfuricans*, *E. coli, Clostridium, Anaerococcus hydrogenalis*, and *Klebsiella pneumoniae* can convert choline into trimethylamine. NASH is strongly associated with obesity, overweight, and metabolic syndromes. It differs from NASH due to the presence of fibrosis detected in liver biopsies. It has been suggested that it should be termed global metabolic dysfunction rather than just hepatic dysfunction. The lack of predictive biomarkers also limits the management of NASH. Although most patients with fatty liver are asymptomatic, many patients with steatohepatitis report fatigue, malaise, or persistent right upper quadrant abdominal pain when directly questioned [3].

Diagnosis

Non-invasive quantification of liver fat is now possible due to advances in imaging modalities. Emerging data suggest that high levels of liver fat and their temporal change, measured by non-invasive quantitative methods, may be associated with disease progression. Ultrasound-based modalities have moderate diagnostic accuracy for liver fat content and are suitable for screening. However, among non-invasive imaging modalities, MRI-derived proton density fat fraction (MRI-PDFF) has the highest diagnostic accuracy. Patients should be stratified by fibrosis severity to investigate the utility of quantitative liver fat measurements [4]. A healthy liver contains some fat, but when fat represents more than 5 to 10% of its weight, it is called fatty liver or steatosis. A quarter of patients are diagnosed with NAFLD, with histological evidence not only of fat accumulation in hepatocytes, but also of liver cell damage and death due to long-term inflammation. Liver biopsy remains the gold standard for diagnosis. As the disease progresses, ascites and symptoms of liver cirrhosis, such as edema and jaundice, may develop [5].

Intestinal microbiome and its impact on non-alcoholic steatohepatitis

NAFID is the most severe form of hepatic steatosis; currently, the role of intestinal barrier dysfunction and gut microbiota (GM) in its onset and progression is highlighted. The effects of inflammatory factors, TLR4 signaling, and the gut-liver axis (through its influence on liver immune function) are emphasized. The impact of GM on extraintestinal organs, as well as on neurohumoral signaling in the gut, hepatic lipid metabolism, inflammation, and fibrosis, is also noteworthy. Knowing this effect, efforts are underway to improve intestinal permeability and GM (approximately 40 trillion microorganisms) through the impact of biotic factors, lifestyle modifications including exercise, diet, fecal microbiota transplantation (FMT), and fecal phage transplantation. Furthermore, metabolic dysfunctions in adipose and muscle tissue, as well as variations in GM levels, contribute to the progression of fatty liver disease [6]. It poses a threat to public health. Its progressive stage is characterized by hepatic steatosis, inflammation, distension, and fibrosis. Recent scientific research has demonstrated that GM levels and its metabolites have a significant impact on its development. If GM levels are imbalanced, it becomes a source of pathogens and molecules that lead to the disease [7,8]. Pezzino S. and his group [9], referring to NAFLD, point out that it is often asymptomatic and accompanied by other symptoms of metabolic syndrome. The presence of the gut-liver axis is crucial, as it tends to disrupt the intestinal barrier, resulting in endotoxemia and inflammation, with deterioration of the intestinal barrier, increased intestinal permeability, and changes in bile acid profiles and metabolite levels.

Intestinal dysbiosis and non-alcoholic steatohepatitis

Intestinal dysbiosis can lead to decreased synthesis of primary bile acids, reducing the activation of nuclear receptors, which regulate energy and thus contribute to impaired function in the pathogenesis of NASH. Furthermore, intestinal dysbiosis often causes nutritional deficiencies, intestinal permeability, and excessive fermentation. Glutamate has provided further insight into the diverse biological functions of primary bile acids [10]. Glutamate and bile acid metabolism are closely linked and play a crucial role in immune regulation, metabolic processes, and overall health. Glutamate facilitates the conversion of secondary bile acids to primary bile acids through enzymatic modifications, acting as signaling molecules that regulate the immune response via bile acid receptors. Imbalances in GM composition disrupt bile acid metabolism, leading to activation of bile acid receptors, contributing to various disorders, and influencing the structure and function of the microbial community. *Verrucomicrobia, Fusobacteria*, and *Proteobacteria* increased in the presence of dysbiosis [11].

Prevention

To slow the progression of the disease, follow a Mediterranean diet rich in fruits, whole grains, vegetables, and healthy fats; reducing your intake of alcohol, simple sugars, and portion sizes. Therefore, you should minimize your consumption of soft drinks, juices, sweetened tea, and sports drinks to achieve a healthy weight. Exercise regularly, staying active every day of the week. Don't forget to manage type 2 diabetes mellitus and monitor your liver condition [12].

Treatment

Currently, there is no FDA-approved drug that can cure NASH. Given the importance of GM in NASH, a compound derived from dietary fiber has been identified. In summary, in addition to what has already been considered for prevention, we can include the following therapies: biotics, antifibrotics, gut microbiota transplantation, and fecal bacteriophage transplantation [13].

A compound derived from dietary fiber to treat NAFLD

NASH is the severe form of NAFLD and is characterized by liver inflammation and fat accumulation. The use of inulin fiber has been shown to alleviate this metabolic disorder in mice through GM. Inulin, *P. distasonis*, or pentadecanoic acid restored intestinal barrier function in NAFLD models, reducing serum expression of lipopolysaccharides and hepatic pro-inflammatory cytokines. This generates beneficial metabolites that could suppress metabolic diseases [14].

Biotics in NAFLD

In recent years, the use of probiotics, prebiotics, and synbiotics has become an important therapy for numerous gastrointestinal diseases by modifying the metabolic pathway. Some probiotics improve liver parameters and phenotype. They are live microorganisms that produce health benefits in the host. These include *Lactobacillus, Bifidobacterium*, and *Streptococcus*. Their oral intake could become an effective management tool for prevention and treatment. They reduce inflammation, liver triglycerides, and body weight, as well as visceral adipose tissue, and improve insulin resistance [15]. Prebiotics, like their relatives probiotics and synbiotics, are significant therapies in gastrointestinal processes. They can generate mild side effects due to their osmotic properties. The most commonly used are fructooligosaccharides, galactooligosaccharides, lactulose, and inulin [16]. Synbiotics also have specific applications in the treatment of NAFLD. For example, Fadhilah J and his team [17] have shown that they significantly reduce the liver enzymes ALT and AST. They also have a favorable impact on lipid profiles (total cholesterol and LDL cholesterol) and blood glucose levels.

Antifibrotics in NASH

The severity of fibrosis is the only histological predictor, and this is where antifibrotics come into play, despite their numerous controversies. Antifibrotics authorized for pulmonary fibrosis (nintedanib and pirfenidone) have been suggested as potentially effective in NASH. However, the framework for *in vitro* trials has limitations that need to be overcome [17].

Fecal microbiota transplantation (FMT)

This is considered an effective method for correcting bacterial imbalance, although its impact on NAFLD and its molecular mechanisms have not been fully determined. However, it is known that disease progression tends to worsen, and some of the functions of microorganisms in the liver, via the gut-liver axis, are also known. This can aid in the comprehensive evaluation of FMT [18]. Since there are currently no medications that correct fatty liver disease, the disease will continue to progress. FMT is considered to replenish the bacterial environment and restore physiological colonization, recovering bacterial diversity and abundance. Meanwhile, transplantation will remain relevant due to its minimal side effects and long-term tolerability. The liver receives 70% of its blood supply through the portal vein, which transports all metabolic products derived from GM, a concept inherent to the gut-liver axis [19].

Fecal bacteriophage transplantation

Understanding that bacteriophages are involved in fecal microbiota transplantation, we can determine the actual effects of transplanting only the phages. The difference lies in the fact that when only the phages are transplanted, the response is more intense, as is the duration of microbial presence. However, the results remain uncertain. Xue L, Y, and associates [20] conducted a randomized, controlled clinical trial of fecal microbiota transplantation (FMT), using oral probiotics, diet, and physical exercise, and administering the phages via colonoscopy. They reviewed the cases one month later, obtaining significant differences in both clinical outcomes and gastrointestinal (GI) levels. The impact was more pronounced in lean patients than in obese patients. They concluded that FMT can improve the disease by balancing GM imbalance.

Complications

These include extrahepatic malignancies, chronic kidney disease, psychological dysfunction, gastroesophageal reflux disease, obstructive sleep apnea syndrome, periodontitis, hypothyroidism, growth hormone deficiency, and polycystic ovary syndrome. Their management requires close interaction between patients and their various healthcare professionals [21]. Guidelines and/or recommendations exist, among which those of Francque SM and her group stand out [22].

Mortality

NASH is the leading cause of liver-related mortality worldwide due to its tendency to progress to cirrhosis and hepatocellular carcinoma. Any progression of the disease carries a mortality rate twice that of those without progression. Risk factors include age, congestive heart failure, coagulopathy, electrolyte imbalances, and unexplained weight loss [23].

Conclusion

- Non-alcoholic fatty liver disease (NAFLD) will continue to grow, as there are no approved medications for its treatment.
- Existing findings diverge regarding the effects of fecal microbiota transplantation (FMT).
- It appears that fecal bacteriophage transplantation (FBT) has a better response.
- Sequencing and metagenomic studies of 16S ribosomal RNA (rRNA) are needed.
- A better understanding of the specific mechanisms of intestinal dysbiosis is required.
- More clinical evidence or results obtained from non-human primates are needed to validate the results of experiments performed in rodent models.

Conflicts of Interest

The authors declare that do not have affiliation or participation in organizations with financial interests.

Ethical Approval

This report does not contain any study with human or animal subjects carried out by the authors.

Informed Consent

The authors obtained informed written consent from the patients, in order to develop this article.

Declaration on the Use of Artificial Intelligence

The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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