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EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM

Review Article

Non Alcoholic Fatty Liver Disease: Participation of Genetic, Metabolic, Biochemical and Immunologic Factors in the Pathogenesis

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Received: September 20, 2019; **Published:** January 09, 2020

Abstract

Non Alcoholic Fatty Liver Disease (NAFLD) occurs as a result of the accumulation of free fatty acids (FFA) y Triglycerides (TG) in the cytoplasm of hepatocytes. There are a correlation between NAFLD and risk factors as obesity, diabetes, dyslipidemia, high blood pressure (HBP), and other conditions related to lifestyle. It is considered a public health problem and studies have demonstrated that a high percentage (90 to 100%) of the obese patients present some degree of NAFLD. It is estimated that by 2030 around 38% of the world population will have overweight and another 20% will be obese. In the pathogenesis of NAFLD participates metabolic, biochemical and immunologic events with continuous stimulation. The establishment, development and progression of NAFLD is due to the accumulation of reactive oxygen species (ROS) as well as inflammation resulting from the up regulated release of pro-inflammatory cytokines from hepatocytes. Investigations appoint that the augment of proinflammatory/profibrotic cytokines and decrease of anti-inflammatory/anti-fibrotic determine an imbalance which leads to the hepatic injury.

In NAFLD the alteration of lipid and carbohydrate metabolism that leads to the accumulation of liver fat is the initial stimulus; the imbalance of cytokines and oxidant/anti-oxidant factors, ROS accumulation and the mobilization of immune cells, oxidative stress, lipotoxicity, apoptosis and fibrosis are processes lead to imminent tissue damage.

Keywords: *NAFLD; ROS (Reactive Oxygen Species); Imbalance*

Introduction

Non Alcoholic Fatty Liver Disease (NAFLD) occurs as a result of the accumulation of free fatty acids (FFA) y Triglycerides (TG) in the cytoplasm of hepatocytes. The patients can present different process, such as: lesions of Simple Hepatic Steatosis (SHS), steatosis with inflammation (Non Alcoholic Steatohepatitis, NASH), Cirrhosis(C) and Hepatocellular Carcinoma (HCC) [1].

The main factors associated with NAFLD [2] are obesity and Diabetes mellitus type 2 (DM-2). It is estimated that by 2030 around 38% of the world population will have overweight and another 20% will be obese [3]. The prevalence de NAFLD is in the general population of 20-30% affecting children and adults [2].

In a high percentage (90 to 100%) the obese patients present some degree of NAFLD. In patients with DM-2 the prevalence ranges from 10 to 75% and in those with hyperlipidemia between 20 and 92% [2]. In patients with persistent hypertransaminasemia and cryp-

togenic cirrhosis in adults should considerer the diagnosis of NAFLD [4]. Studies have linked the components of the metabolic syndrome with the presence of fat in the liver [5].

We review the participation of determining factors in the establishment, development and progression of NAFLD due to its high prevalence in world population. The existence of pathologies that lead to NAFLD and that can be preventable establish the importance of this issue.

Participation of genetic, metabolic, biochemical and immunologic factors in the pathogenesis of NAFLD

The pathogenesis of NAFLD is complex. Studies have demonstrated the correlation between NAFLD and risk factors as obesity, diabetes, dyslipidemia, high blood pressure (HBP), and other conditions related to lifestyle [6]. The genetic participation have been demonstrated [7,8]. Adiponutrin (PNPLA3) rs738409 polymorphism has been found to be associated with susceptibility to NAFLD. The rs738409 G allele is associated with severity of NASH and occurrence of fibrosis in patients with NAFLD [9].

Studies have permitted analysis the Genome-wide association to identify markers of severity in NAFLD [10]. The existence of the expression of biomarkers in the pathogenesis of NAFLD has been demonstrated and have specific functions related with adipocyte differentiation and lipid storage liver regeneration, inhibition of the adipogenesis, protection of hepatocytes from cell death, activation of lipogenesis, regulation of glucose and fatty acid metabolism among others [11-15].

The pathogenic mechanism of NAFLD, according to some researchers, is explained by the "double impact theory" [16,17]. In the "first impact", there are alterations in the metabolism of fats and this determines the development of hepatic steatosis. The cells have diminished their ability to respond to insulin, therefore, compensatory hyperinsulinemia occurs. Adipose tissue releases free fatty acids (FFA) into the liver. It decreases the absorption of glucose in the musculoskeletal, while in the hepatocyte the hyperinsulinemia increases gluconeogenesis. There are alterations in the transport of triglycerides and reduction of adiponectin levels and liver resistance to leptin [16].

The "second impact" is due to oxygen free radicals (OFR) that favor the synthesis of proinflammatory cytokines and chemokines by Kupffer cells and hepatocytes, which act on fatty acids of cell membranes causing lipid peroxidation or oxidative degradation of lipids. Investigations appoint that the augment of proinflammatory/profibrotic cytokines and decrease of anti-inflammatory/anti-fibrotic determine an imbalance which leads to the hepatic injury. In the first group of cytokines it is include: Interleukin-1 (IL-1), IL-6, IL-17, IL-21, IL-23, tumor necrosis factor-α (TNF-α) and transforming growth factor-βeta (TGF-β). In the second group: IL-4, IL-10, IL-22 and interferon-gamma (IFN- γ) [18,19]. The final products of lipid peroxidation are 4-hydroxynonenal (HNE) and malondialdehyde (MDA) and are involved in the genesis of hepatic lesions. In addition, HNE has neutrophil chemotactic activity [20-24]. Likewise, the alteration of lipid and carbohydrate metabolism leads to the accumulation of liver fat, the mobilization of immune cells such as neutrophils and the presence of regulatory proteins create a proinflammatory environment that triggers cellular lesions in the liver and other tissues. In addition, oxidative stress, lipotoxicity and apoptosis processes lead to imminent tissue damage. All the above, explain the evolution towards phenomena of necrosis, inflammation, fibrosis and liver cirrhosis. As is known the obesity is one of factors associated with NAFLD therefore, "the prevention of obesity with adequate diet, exercise, contention of stress is determinant to avoid consequences adverse organic that limit the time of life" [25,26].

Conclusion

Non Alcoholic Fatty Liver Disease (NAFLD) occurs as a result of the accumulation of FFA and TG in the cytoplasm of the hepatocytes. The accumulation of fat in the hepatic tissue initiates a cascade of biochemical events that includes oxidative stress, mitochondrial dysfunction, lipid peroxidation, extracellular matrix balance dysfunction and inflammatory response. The development and progression to NAFLD is due to the accumulation of reactive oxygen species (ROS) as well as inflammation resulting from the upregulated release of pro-inflammatory cytokines from hepatocytes. Studies appoint that the augment of proinflammatory/profibrotic cytokines and decrease

of anti-inflammatory/anti-fibrotic more biochemical and metabolic events establish an imbalance that is responsible of liver inflammation, hepatocyte necro-apoptosis and fibrosis.

There are many pathologies that are preventable and that lead to NAFLD. However, the statistics reveal a significant increase year by year which is worrying.

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Volume 7 Issue 2 February 2020