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Revisión

Nonalcoholic fatty liver disease (NAFLD) pathophysiology in obese children and adolescents: update

Fisiopatología de la enfermedad del hígado graso no alcohólica (EHGNA) en niños y adolescentes obesos: actualización

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Abstract

Objective: Although the nonalcoholic fatty liver disease was first identified in 1980, it presents multifactorial and unclear pathophysiology. In this review, we intend to update the pathophysiological mechanisms of a high morbidity and mortality associated disease that is affecting obese children worldwide.

Data sources: The PubMed and the Cochrane Library databases were used in the search strategy for articles related to nonalcoholic fatty liver disease and published in the last three decades.

Data summary: This review describes the current knowledge on the different mechanisms related to the pathophysiology of nonalcoholic fatty liver disease focused on histological, anatomical and biochemical aspects involved in triggering steatohepatitis and leading to cirrhosis.

Conclusions: The clinical research and advanced technological resources demonstrated several determinants pathophysiological mechanisms of nonalcoholic fatty liver disease trying to assist in their treatment and change its natural course.

Key words:

Non-alcoholic fatty liver disease. Fatty liver. Obesity.

Resumen

Objetivo: aunque la enfermedad de hígado graso no alcohólico se identificó por primera vez en 1980, presenta una fisiopatología multifactorial y mal definida. En esta revisión, tenemos la intención de actualizar los mecanismos fisiopatológicos de esta enfermedad con alta morbilidad y mortalidad asociadas que está afectando a niños obesos en todo el mundo.

Fuentes de datos: las bases de datos PubMed y la Biblioteca Cochrane se utilizaron en la estrategia de búsqueda de los artículos relacionados con la enfermedad de hígado graso no alcohólico publicados en las últimas tres décadas.

Resumen de datos: esta revisión describe el conocimiento actual acerca de los diferentes mecanismos relacionados con la fisiopatología de la enfermedad de hígado graso no alcohólico, con especial énfasis en aspectos histológicos, anatómicos y bioquímicos implicados en el desencadenamiento de la esteatohepatitis y conducentes a la cirrosis.

Conclusiones: la investigación clínica y los recursos tecnológicos avanzados han demostrado diversos mecanismos fisiopatológicos determinantes de la enfermedad de hígado graso no alcohólico, tratando de ayudar en su tratamiento y cambiar su curso.

Palabras clave:

Enfermedad del hígado graso no alcohólico. Hígado graso. Obesidad.

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Continuous scientific medical advances in the last decades provide new insights on the pathophysiology of some intriguing health problems such as nonalcoholic fatty liver disease (NAFLD). First described in 1980 (1), NAFLD is a disease characterized by the accumulation of fat in the cytoplasm of hepatocytes, not related to alcohol, causing the so called fatty liver (2). The presence of at least 5% of affected hepatocytes in biopsies' fragments provides the histopathologic diagnosis of fatty liver (3). This condition is characterized as a spectrum ranging from liver steatosis to steatohepatitis (characterized by inflammation and fibrosis), and finally cirrhosis. It is, therefore, a serious condition that can cause liver failure in a short period of time (4). NAFLD is now the most common form of chronic liver disease and its prevalence is rapidly growing around the world (5). The real prevalence of NAFLD in the pediatric population is still unknown and variable, with a range of prevalence from 3.0 to 60.3% in obese children and adolescents. Its physiopathological mechanisms are not yet fully understood, although it is recognized to be increasing especially among overweight children and adolescents, with at least 50% of them presenting some degree of NAFLD (6). NAFLD prevalence is variable depending on the region, surveyed population and the mode of NAFLD diagnosis. In Europe, the prevalence of NAFLD is estimated to be 25% (7). In the United States it is estimated to be 34% in adults (8) and 10-20% in children (9). In Asia, rates about 30% are reported, despite the lower body mass index (BMI) (10). The available evidence on NAFLD-associated morbidity and mortality demonstrates that children affected by NAFLD are at increased risk of death or undergoing a liver transplant when compared to children of the same age and sex but without the disease (11). The natural history of NAFLD in children reveals a progressive evolution of the disease, leading to the development of liver cirrhosis in an expressive percentage of this population (12). NAFLD is closely related to obesity, environmental/nutritional factors, and genetic predisposition (3). Obesity, a chronic and prevalent nutritional disorder in the world, is often associated with fatty liver, hypertension, insulin resistance and dyslipidemia (13). It affects several age groups, including children and adolescents. In a murine model, obesity-induced steatosis led to an increased oxidative stress, as well as chronic inflammation of the liver (14). Insulin resistance, a frequent condition in obese patients, has a key role in the pathophysiology of NAFLD (15). Similarly, the high food intake common to obesity can cause changes in the intestinal flora, with lipid metabolism injury causing fatty liver (16). Laboratory findings in obese individuals showed increased levels of inflammatory markers, acute phase inflammation proteins, hormones, free radicals and other endothelial activation factors. This fact demonstrates the existence of an underlying inflammatory condition, determining the onset of NAFLD (17). In this review, current and comprehensive data to explain the pathophysiology of NAFLD, especially in obese children and adolescents, are described. In this population the evolution of NAFLD is more insidious than in adults, probably due to the fact that this age group does not present proper mechanisms of adaptation to metabolic changes caused by obesity. On the other hand, this population is supposedly more susceptible to therapeutic interventions, making

them a candidate to new treatment strategies to prevent evolution to end-stage liver disease.

METHODS

We reviewed the literature related to the topic of obesity and nonalcoholic fatty liver disease (NAFLD) available in the PubMed database, published in Portuguese and English by 2016, using the following descriptors: "non-alcoholic fatty liver disease; "fatty liver"; "obesity". The articles included involved children and adolescents of both sexes, exogenous obesity carriers and some of its comorbidities. Coincident articles and those who did not contribute methodologically to the scope of this research were excluded. The search strategy in SciELO and Medline databases using the same descriptors did not result in articles of interest for review. Thus, the search resulted in 53 articles, and after reading them, 40 were selected because they were closer to the scope of this article, which focused on two important pediatric metabolic disorders, NAFLD and obesity.

NONALCOHOLIC FATTY LIVER DISEASE (NAFLD) PATHOPHYSIOLOGICAL ASPECTS RELATED TO OBESITY IN CHILDREN AND ADOLESCENTS

The exact mechanism that determines NAFLD remains unknown, although evidence shows that this disorder develops from primary metabolic abnormalities determined by inflammatory cytokines, insulin resistance and oxidative stress commonly found in obese patients (18). In a broader approach, obesity alters hepatic metabolism triggering one histopathological sequence of events characterized by the death of steatotic liver cells and release of enzymes that culminate in focal and non-specific inflammation (19). Additionally, in NAFLD, an accumulation of lipids in the cytoplasm of hepatocytes in the form of vacuoles which are organized by determining the fatty infiltration of the liver known as steatosis occurs, which in turn progresses to an inflammatory frame (steatohepatitis), with resulting fibrosis and liver cirrhosis (20). In the long run, NAFLD may progress to hepatocellular carcinoma (21).

According to the consensus published by the European Society of Paediatric Gastroenterology, Hepatology and Nutrition 2012 (22), NAFLD is defined as follows:

- *NAFLD*: the simplest form of steatosis, with moderate levels of inflammation.
- *Nonalcoholic steatohepatitis (NASH)*: accumulation of macrovacuolar intra hepatocyte with periportal inflammation, hepatocellular ballooning and perisinusoidal fibrosis.
- *Cirrhosis*: fibrosis in advanced stage with loss of liver structure.

The natural history of NAFLD shows that different mechanisms contribute in parallel to the development of NAFLD and its evolution to inflammation and fibrosis (23). Basically, the disease is the

result of the imbalance between supply and use of triglycerides and free fatty acids (FFA) in the liver and impairment of beta-oxidation of free fatty acids, which causes lipid deposits in the cytoplasm of hepatocytes (24).

Below, we summarize some of these mechanisms.

OBESEITY

Obesity, especially central obesity, often progresses to hepatic steatosis. In obese individuals we see a chronic, low grade, inflammatory condition mediated by inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α), as well as leptin and adiponectin, which add a significant contribution (25). Fatty liver impairment disrupts homeostasis by increasing in release of inflammatory and non-inflammatory cytokines (26). This triggers a cascade of hepatocyte injury, with production of more inflammatory mediators that leads to an impairment of liver metabolic capacity.

INSULIN RESISTANCE

Insulin resistance is a key mechanism for the development of NAFLD in both adults and children. It is observed that in children, insulin resistance is associated with compensatory hyperinsulinemia. The association of hepatic insulin resistance with hyperinsulinemia impairs the mitochondrial oxidation process of free fatty acids and lipid peroxidation, and results in the formation and accumulation of toxic lipid metabolites such as reactive oxygen species (ROS), which causes oxidative stress and hepatocellular injury (27). Dietary factors such as high glycemic index intake and high intake of fatty meals that would jeopardize the metabolism of carbohydrates are theories proposed to explain the complex mechanism by which insulin resistance could cause the appearance of fatty liver in obesity. This diet elicits insulin release, resulting in increased plasma and hepatocellular concentrations of free fatty acids (FFA) (28). NAFLD in children would be aggravated by decreased plasma adiponectin. Adiponectin attenuates insulin action on insulin receptors through its anti-inflammatory action, preventing hepatocellular damage by free fatty acids. On the other hand, the high TNF- α leads to increased insulin resistance and mitochondrial production of reactive oxygen species (ROS), as well as decreased plasma levels of antioxidants such as glutathione peroxidase (29).

GUT MICROBIOTA (INTESTINAL FLORA)

The normal intestinal flora is made up of a multitude of bacteria living in balance, performing important functions, including the immune defense. Disruption of this balance (*dysbiosis*) would increase the passage of toxins into the portal circulation, causing local inflammation, with release of inflammatory markers (30). The intestinal microbiota also influences the secretion of biliary acids,

which have a regulatory function in the digestion and metabolism of nutrients such as carbohydrates and lipids (31,32). Some available evidence suggests that alterations in the intestinal flora can lead to the development of NAFLD, and that the expression of the disease would be influenced by biliary acids (33). Studies indicate that *dysbiosis* secondary to obesity could act as a determinant of the pathophysiology of NAFLD in children and adults (34-36).

GENETIC FACTORS

The influence of genetic factors determining NAFLD is not well elucidated, although the role of interaction between genes and environment on the onset of metabolic diseases is recognized. Genetic polymorphisms (PAI-I 6754G/5G and PPAR- γ 2 Pro12Ala, among others) indicate a potential association with insulin resistance and obesity in children (37). Genetics plays a key role in Wilson's disease, an inherited disorder of copper metabolism in which children present predominantly hepatic manifestations (38). Ethnic background explains the variable predisposition to the development of NAFLD, which has a clearly greater frequency among Hispanics and Asians while it is lower among children of African origin (39).

OTHER NAFLD MECHANISMS

Hereditary hemochromatosis, autoimmune hepatitis, and α 1-antitrypsin deficiency are also implicated in the pathogenesis of NAFLD (40).

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