Nutr Hosp. 2017; 34(3):727-730 ISSN 0212-1611 - CODEN NUHOEQ S.V.R. 318

Nutrición Hospitalaria

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

Silvana Neves Ferraz de Assunção[1], Ney Christian Boa Sorte[2], Crésio Dantas Alves[3], Patricia S. Almeida Mendes[2], Carlos Roberto Brites Alves[4] and Luciana Rodrigues Silva[5]

Departments of [1]Anaesthesiology, [2]Pediatry, [3]Endocrinology, [4]Infectious Diseases and [5]Hepatology. Universidade Federal da Bahia. Hospital Universitário Professor Edgar Santos. Salvador de Bahia, Brazil

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.

Received: 07/11/2016
Accepted: 08/01/2017

Assunção SNF, Sorte NCB, Alves CD, Mendes PSA, Alves CRB, Silva LR. Nonalcoholic fatty liver disease (NAFLD) pathophysiology in obese children and adolescents: update. Nutr Hosp 2017;34:727-730

DOI: http://dx.doi.org/10.20960/nh.723

Correspondence:

Silvana Neves Ferraz de Assunção. Universidade Federal da Bahia. Hospital Universitário Professor Edgar Santos. Avenida Santa Luzia, 400, Horto Florestal. Brotas, Salvador de Bahia. Brazil.
CEP: 40.295-050
e-mail: Anest.silvana@gmail.com

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). NAFDL 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 steatotics 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.

OBESITY

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 polimorfirms (PAI-I 6754G/5G and PPAR-γ2 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 α1-antitrypsin deficiency are also implicated in the pathogenesis of NAFLD (40).

REFERENCES

1. Ludwig J, Viggiano TR, McGill DB, Oh BJ. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. Mayo Clin Proc 1980;55:434-8.
2. Lewis JR, Mohanty SR. Nonalcoholic fatty liver disease: A review and update. Dig Dis Sci 2010;55:560-78.
3. Angulo P, Keach JC, Batts KP, Lindor KD. Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. Hepatol 1999;30:1356-62.
4. Kemmer N, Neff GW, Franco E, Osman-Mohammed H, Leone J, Parkinson E, et al. Nonalcoholic fatty liver disease epidemic and its implications for liver transplantation. Transplantation 2013;96(10):860-2.
5. Younossi ZM, Stepanova M, Afendy M, Fang Y, Younossi Y, Mir H, et al. Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. Clin Gastroenterol Hepatol 2011;9(6):524-30.
6. Padilha PC, Rocha HF, Alves N, Peres WA. Prevalence of nonalcoholic fatty liver disease in obese children and adolescents: A systematic review. Rev Paul Pediatr 2010;28:387-93.
7. Bellentani S, Saccoccio G, Masutti F, Crocè LS, Brandi G, Sasso F, et al. Prevalence of and risk factors for hepatic steatosis in Northern Italy. Ann Intern Med 2000;132:112-7.
8. Szczepaniak LS, Nurenberg P, Leonard D, Browning JD, Reingold JS, Grundy S, et al. Magnetic resonance spectroscopy to measure hepatic triglyceride content: Prevalence of hepatic steatosis in the general population. Am J Physiol Endocrinol Metab 2005;288:E462-8.
9. Patton HM, Yates K, Unalp-Arida A, Behling CA, Huang TT, Rosenthal P, et al. Association between metabolic syndrome and liver histology among children with nonalcoholic fatty liver disease. Am J Gastroenterol 2010;105:2093-102.

10. Kojima S, Watanabe N, Numata M, Ogawa T, Matsuzaki S. Increase in the prevalence of fatty liver in Japan over the past 12 years: Analysis of clinical background. J Gastroenterol 2003;38:954-61.
11. Feldstein AE, Charatcharoenwitthaya P, Treeprasertsuk S, Benson JT, Enders FB, Angulo P. The natural history of nonalcoholic fatty liver disease in children: A follow-up study for up to 20-years. Gut 2009;58:1538-44.
12. Schwimmer JB, Deutsch R, Kahen T, Lavine JE, Stanley C, Behling C. Prevalence of fatty liver in children and adolescents. Pediatrics 2006;118:1388-93.
13. Moyer VA, Klein JD, Ockene JK, Teutsch SM, Johnson MS, Allan JD, et al. Screening foroverweight in children and adolescents: Where is the evidence? A commentary by the childhood obesity working group of the US Preventive Services Task Force. Pediatrics 2005;116:235-8.
14. Elariny HA, Baranova A. Comment on: Diet-induced obesity associated with steatosis, oxidative stress and inflammation in liver. Surg Obes Relat Dis 2012;8(1):81-3.
15. Tilg H, Moschen AR. Evolving therapies for non-alcoholic steatohepatitis. Expert Opin Drug Discov 2014;9:687-96.
16. Moschen AR, Kaser S, Tilg H. Non-alcoholic steatohepatitis: A microbiota-driven disease. Trends Endocrinol Metab 2013;24:537-45.
17. De Almeida IT, Cortez-Pinto H, Fidalgo G, Rodreigues D, Camilo ME. Plasma total and free fatty acids composition in human non-alcoholic steatohepatitis. Clin Nutr 2002;21:219-23.
18. Caprio S. Definitions and pathophysiology of the metabolic syndrome in obese children and adolescents. Int J Obes (Lond) 2005;29(Supl) 2):S24-5.
19. Louthan MV, Theriot JA, Zimmerman E, Stutts JT, McClain CJ. Decreased prevalence or nonalcoholic fatty liver disease in black obese children. J Pediatr Gastroenterol Nutr 2005;41:426-9.
20. Angulo P. Nonalcoholic fatty liver disease. N Engl J Med 2002;346:1221-31.
21. Zachary D. Goodman. The impact of obesity on liver histology. Clin Liver Dis 2014;18:33-40.
22. Vajro P, Lenta S, Socha P, Dhawan A, McKiernan P, Baumann U, et al. Diagnosis of nonalcoholic fatty liver disease in children and adolescents: Position paper of the ESPGHAN Hepatology Committee. J Pediatr Gastroenterol Nutr 2012;54:700-13.
23. Falck-Ytter Y, Younossi ZM, Marchesini G, McCullough AJ. Clinical features and natural history of nonalcoholic steatosis syndromes. Sem Liver Dis 2001;21:17-26.
24. Neuschwander-Tetri BA, Caldwell SH. Nonalcoholic steatohepatitis: Summary of an AASLD Single Topic Conference. Hepatol 2003;37:1202-19.
25. Browning JD, Horton JD. Molecular mediators of hepatic steatosis and liver injury. J Clin Invest 2004;114:147-52.
26. Dandona P, Aljada A, BandyopadhyayA. Inflammation: The link between insulin resistance, obesity and diabetes. Trends Immunol 2004;25(1):4-7.
27. Neuschwander-Tetri BA. Hepatic lipotoxicity and the pathogenesis of nonalcoholic steatohepatitis: The central role of nontriglyceride fatty acid metabolites. Hepatol 2010;52:774-88.
28. Westerbacka J, Lammi K, Hakkinen AM, Rissanen A, Salminen I, Aro A, et al. Dietary fat content modifies liver fat in overweight nondiabetic subjects. J Clin Endocrinol Metab 2005;90:2804-9.
29. Louthan MV, Barve S, McClain CJ, Joshi-Barve S. Decreased serum adiponectin: An early event in pediatric nonalcoholic fatty liver disease. J Pediatr 2005;147:835-8.
30. Molnar D, Decsi T, Koletzko B. Reduced antioxidante status in obese children with multimetabolic syndrome. Int J Obes Relat Metab Disord 2004;28:1197-2658.
31. Chassaing B, Etienne-Mesmin L, Gewirtz AT. Microbiota-liver axis in hepatic disease. Hepatol 2014;59(1):328-39.
32. Dawson PA, Karpen SJ. Intestinal transport and metabolism of bile acids. J Lipid Res 2015; 56(6):1085-99.
33. Hylemon PB, Zhou H, Pandak WM, Ren S, Gil G, Dent P. Bile acids as regulatory molecules. J Lipid Res 2009;50(8):1509-20.
34. Clemente JC, Ursell LK, Parfrey LW, Knight R. The impact of the gut microbiota on human health: An integrative view. Cell 2012;148(6):1258-70.
35. Mouzaki M, Comelli EM, Arendt BM, Bonengel J, Fung SK, Fischer SE, et al. Intestinal microbiota in patients with nonalcoholic fatty liver disease. Hepatol 2013;58(1):120-7.
36. Duncan SH, Lobley GE, Holtrop G, Ince J, Johnstone AM, Louis P, et al. Human colonic microbiota associated with diet, obesity and weight loss. Int J Obes (Lond) 2008;32(11):1720-4.
37. Scaglioni S, Verduci E, Salvioni M, Biondi ML, Radaelli G, Agostoni C, et al. PPAR-γPro12Ala variant, insulin resistance and plasma long chain polyunsaturated fatty acids en childhood obesity. Pediatr Res 2006;60:485-9.
38. Ciesck S, Hadem J, Fischer J, Manns MP, Strassburg CP. A rare cause of nonalcoholic fatty liver disease. Ann Intern Med 2006;154-5.
39. Schwimmer JB, McGreal N, Deutsch R, Finegold MJ, Lavine JE. Influence of gender, race, and ethnicity on suspected fatty liver in obese adolescents. Pediatrics 2005;115:e561-5.
40. Nobili V, Manco M. Therapeutic strategies for pediatric non-alcoholic fatty liver disease: A challenge for health care providers. World J Gastroenterol 2007;13(18):2639-41.