ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 14, Issue, 07, pp. 66296-66298, July, 2024
https://doi.org/10.37118/ijdr.28551.07.2024

REVIEW ARTICLE **OPEN ACCESS**

NON-ALCOHOLIC HEPATIC STAEATOSIS: A SYSTEMATIC REVIEW

Luiza Fernandes de Oliveira*[1]; Nathalia Beck Pencinato[1]; Gabrielle Ribeiro Braga[1]; Larissa Rodrigues Mendes[1]; Ana Caroline Lima Faria[1]; Gustavo Roque de Queiroz[1] Ana Letícia Dornelas Moreira[2]; Frederico Luiz Serra da Costa[2]; Paulo Gomes Nascimento Prompto[3] Amanda Leopoldino De Carvalho[4]; Eduardo Moreira Dias Filho[4], Cecilia Borsoi Barros Musso Froz[4] and Bárbara dos Santos Tayt-Sohn[3]

[1]Doctor at Iguaçu University (UNIG), Brazil; [2]Doctor at Estácio de Sá University (UNESA), Brazil; [3]Medical Student at Iguaçu University (UNIG), Brazil; [4]Medical Student at Integrado Center University (INTEGRADO), Brazil; [5]Medical Student at Estácio Vista Carioca University (IDOMED), Brazil

ARTICLE INFO

Article History:
Received 17th April, 2024
Received in revised form
20th May, 2024
Accepted 28th June, 2024
Published online 30th July, 2024

Key Words:
Non alcoholic fatty liver disease;
Diagnosis; Therapy

Corresponding author:
Luiza Fernandes de Oliveira,

ABSTRACT

Non-alcoholic fatty liver disease is a multifactorial pathology with a pathophysiology that has not yet been fully elucidated. It is associated with metabolic syndrome, diabetes mellitus, obesity, systemic arterial hypertension and hyperlipidemia. The prevalence of this pathology is between 10 and 24% of world population. The evolution of this condition can be hepatic steatosis, with accumulation of lipids in hepatocytes, liver cirrhosis and hepatocellular carcinoma. Diagnosis is through abdominal ultrasound. Treatment consists of dietary changes and physical activity, the latter being considered one of the most effective modulating factors in preventing diseases such as hepatic steatosis, and promoting health. Pharmacological treatment is carried out when changing lifestyle habits is ineffective and includes several options, the most studied being vitamin E and pioglitazone, while most other drugs remain with low levels of evidence. Studies conclude that there is still a lack of studies to increase the level of therapeutic recommendations, but that increasing the level of physical activity can contribute to reducing fat in the liver and preventing the appearance of hepatic steatosis.

Citation*: *Luiza Fernandes de Oliveira; Nathalia Beck Pencinato; Gabrielle Ribeiro Braga; Larissa Rodrigues Mendes; Ana Caroline Lima Faria; Gustavo Roque de Queiroz Ana Letícia Dornelas Moreira; Frederico Luiz Serra da Costa; Paulo Gomes Nascimento Prompto, Amanda Leopoldino De Carvalho; Eduardo Moreira Dias Filho, Cecilia Borsoi Barros Musso Froz and Bárbara dos Santos Tayt-Sohn. 2024. *"Non-alcoholic hepatic Staeatosis: A Systematic Review". International Journal of Development Research*, 14, (07), 66296-66298.

INTRODUCTION

The World Health Organization identifies obesity as one of the biggest public health problems in the world. The projection is that, in 2025, around 2.3 billion adults are overweight; and more than 700 million, obese[1]. In Brazil, obesity is growing more and more. The comparison between 2006 – 2016 of data from the Surveillance of Risk and Protection Factors for Chronic Diseases by Telephone Survey (VIGITEL Brazil) shows that the excess weight increased from 42.6% to 53.8%, that is, an increase in 26.3% in 10 years, being more prevalent in men. In obesity, the increase was from 11.8% to 18.9%, that is, an increase of 60% in 10 years[2]. Regarding the prevalence of overweight and obesity in the States, there is significant variation. According to data from the Factor Surveillance of Risk and Protection for Chronic Diseases by 2017 Telephone Survey (VIGITEL Brasil 2017), overweight in males is higher in Cuiabá with 65.8% and lowest in the Federal District with 51.6%. Regarding sex female, the highest percentage of overweight is found in Rio de Janeiro with 55.7% and the smallest Palmas with 42.1%[3].

Regarding obesity, the VIGITEL Brasil 2017 survey shows that in the case of males, the highest prevalence was in Macapá with 28.5% and lowest in the Federal District with 14.2%. For women, it is found in Manaus (24.1%) had the highest percentage of obese women and the lowest in Florianópolis with 14%[3]. In this context, non-alcoholic hepatic steatosis (NASH), which has as a risk factor for obesity, it has an increased incidence, becoming an important cause of chronic liver injury worldwide4,5. This pathology is characterized by the accumulation of fat in the liver, representing more than 5% of the organ's weight, in the absence of consumption excessive alcohol consumption (rated at 20 g/day for women and 30 g/day for men) or other conditions such as hepatitis caused by virus B, virus C or Epstein vírus – Barr, in addition to autoimmune hepatitis, primary biliary cirrhosis, cholangitis sclerosing, hemochromatosis, α1 – antitrypsin deficiency, Wilson's disease and medical hepatitis[4,6]. It is a multifactorial disease. Currently, there is no evidence scientific information about which genes would be involved in this process, but some genes related to abdominal obesity and development of type II diabetes mellitus. Furthermore, genes blocking exit of VLDL (very low density lipoprotein) from hepatocytes, mutations and

polymorphisms of genes associated with oxidative stress or the protection of superoxide dismutase enzyme, in addition to genes related to the inflammation and fibrosis would also have some relationship with the disease[5,6]. The main associations of non-alcoholic hepatic steatosis are with metabolic syndrome, diabetes mellitus, obesity, hypertension and hyperlipidemia (particularly hypertriglycerdemia) as its core the process of insulin resistance. However, EHNA can happen also in thin individuals, constituting a risk fator independent cardiovascular[5,6]. Regarding the pathophysiology, it has not yet been fully elucidated, but Day and James in 1998 defended two possible theories that would be directly linked to liver injury. The first is based on the accumulation of fat in the liver and the second in oxidative stress, resulting in lipid peroxidation, activation of stellate cells and generation of liver tissue fibrosis[7]. In detail, it can be seen that the elucidated mechanism of pathogenicity of non-alcoholic hepatic steatosis is linked to reduced cellular capacity to respond to insulin action, generating hyperinsulinemia compensatory[5]. The action in adipose tissue occurs on hormone-sensitive lipase, increasing the risk of lipolysis with consequent release of fatty acids free in the liver. Glucose absorption decreases by the muscle while there is an increase of gluconeogenesis, decreased glycogen synthesis and increased release of free fatty acids, altering the transport of triglycerides as well as VLDL and inhibiting β-oxidation[5]. Regarding oxidative stress in hepatocytes, initially, it is compensated by endogenous cellular mechanisms. But acid overload free fatty acids, reported above, generates free oxygen radicals in the chain mitochondria and consequently, the peroxidation of membrane lipids cell phones[5].

Therefore, pro-inflammatory cytokines are released, such as TNF α (fator of tumor necrosis α), TGF – β1 (growth factor β1) and IL-8 (interleukin 8), which associated with the end products of 4-hydroxynonenal (HNE) peroxidation and malondialdehyde (MDA) result in toxic damage to the liver, favor formation of Mallory corpuscles and increase collagen synthesis of stellate cells. In this context, there is also the activation of FAS ligands that generate cell death of hepatocytes. All these changes account for the necroinflammatory evolution, liver fibrosis and cirrhosis observed in steatosis non-alcoholic hepatic[5]. Therefore, the evolution of NASH can be complicated by hepatites non-alcoholic, liver cirrhosis with all hypertension commemorative portal and even serve as a risk factor for the development of carcinoma hepatocellular[7]. Patients with NASH are generally asymptomatic and may present hepatomegaly, making identification difficult, especially when by excess abdominal adipose tissue. Initially, patients are diagnosed by increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and/or during an ultrasound (USG) of the abdomen of routine. The latter is more commonly used for initial diagnosis because it is safe, low-cost and easily accessible[8]. Elevation of alkaline phosphatase and gamma GT is seen more in patients with NASH and advanced fibrosis. Additionally, other parameter increases laboratory tests can be seen, such as ferritin and serum iron. And despite these laboratory changes, the distinction between non-alcoholic hepatic steatosis and non-alcoholic hepatitis requires biopsy for histopathological study[8]. Given the increasing prevalence of diagnoses of hepatic steatosis non-alcoholic, the health problems of the affected population and the lack of consensus on regarding possible treatments for this pathology, the search for knowledge in order to understand in the existing literature the possibilities most up-to-date therapies for non-alcoholic fatty liver disease.

DISCUSSION

Ludwing et al described non-alcoholic fatty hepatites almost 40 years ago for the first time[8]. However, they did not demonstrate initially, the multifaceted character that this pathology presents and after thirty years and several studies carried out, currently, there is a better understanding about the epidemiological, etiological, pathophysiological and therapeutic treatment for non-alcoholic hepatic steatosis[17]. Despite advances in understanding this pathology, there is still no a consensus regarding the treatment of non-alcoholic hepatic steatosis. Various therapies and forms of action have been successfully investigated fickle[5,12]. In view of this, there is a need to search for new perspectives of treatment, mainly pharmacological, that will have effective action in this pathology that is increasingly increasing its incidence. Regarding non-pharmacological therapy, Gelli et al. 6 discuss the main strategy with scientific proof, which is changing the style of life, that is, dietary pattern and the practice of physical activity whose main favorable repercussion is weight loss. Published in the World Journal of Gastroenterology, this publication emphasizes that epidemiological evidence suggest a direct relationship between non-alcoholic fatty liver disease and a lifestyle unhealthy[6]. However, a major barrier is imposed on dietary and lifestyle changes. practice of physical activity, which is primarily adherence to changes and subsequent maintenance of these improvements for a long period. The main core of this challenge would be to find the motivation for this lifestyle change, despite knowledge of the importance of a healthy diet and physical activity as essential pillars for a full life without association with illnesses[6].

During the study, the authors specifically discuss one type of diet, the Mediterranean, given its low relationship with diseases cardiovascular diseases, for example, and also the greater ease of adherence that some studies have shown. This feeding option was associated with daily physical activities, in addition to the counseling and monitoring in a short period of time, enabling adjustments that favored the achievement of long-term beneficial effects[6]. In relation to the food process, Stachowska et al[10] emphasize the nutritional strategies for calculations about the individualized needs of amounts of micro and macronutrients in order to prevent the progression of non-alcoholic hepatic steatosis through the choice of nutrients that do not worsen the process of insulin resistance intrinsic to the contexto steatotic[10]. The authors Honda et al[4] and the authors Tang et al16 discuss, in their respective publications, on the possibility of using specimens antioxidants, glutathione and tiopronin, in order to act in the process of oxidant stress caused to the liver after the accumulation of fat in the liver according to the theory of Day and James[4,7,16]. In line with this proposal to use herbal medicines as adjuvants in the treatment of steatosis, there is discussion about the administration of curcumin and omega [3]. In relation to curcumin, a natural polyphenol from turmeric, several studies prove its action on molecular targets, having an antioxidant, anti-inflammatory, antidiabetic and antilipidemic action. Rahmani[11] is able to demonstrate a beneficial effect with supplementation of curcumin, specifically, in relation to the attenuation of glycemia and lipid profile, in addition to hepatic steatosis in the context of pathology of non-alcoholic etiology[11].

Omega 3 in high doses appears as a protective factor for cardiovascular diseases, metabolic syndrome, dyslipidemia and steatosis hepatic. However, the current Western diet is increasingly based on the intake of industrialized foods, rich in omega 6, which has a pro- inflammatory, differing from the action of omega 3 which is anti-inflammatory[5,14,15.] Thus, an association was sought with improvements in clinical parameters and laboratory tests in patients with non-alcoholic fatty liver disease, but still more studies are needed to confirm the therapeutic role of omega 3 in this group of patients[14,15]. Finally, there is an approach to the use of hypoglycemic medications, such as ipraglifozin and metformin, and the hormone melatonin and its precursor, the tryptophan[7,12,13,18]. Ipraglifozin is a medication whose action is on the co-transporter of glucose and sodium type 2. This medication class is used in patients diagnosed with type 2 diabetes mellitus for glycemic control. And in the study, proved to be a therapeutic possibility, as there was an improvement in the standard liver inflammation, in addition to glycemic control, weight loss and normalization of ALT levels. Apart from these benefits, its administration route is oral, or In this sense, it is superior to other treatments undertaken patients with a combination of type 2 diabetes mellitus and hepatic steatosis do not alcoholic which is administered by injectable[12]. Regarding metformin, Sofer et al[13] discussed issues specific. The use of metformin proved to be favorable in reducing osteoprotegerin, a marker of the tumor necrosis factor family and associated with vascular disease. Furthermore, this same medicine, possibly associated with improved bone formation in

patients with non-alcoholic hepatic steatosis, but requiring further studies that corroborate this result[13]. The use of melatonin and tryptophan, which is its precursor, was analyzed by Celinski et al[7], proving to be a promising agent in reducing pro-inflammatory cytokines resulting from the oxidative stress of the disease and, also, in improving the parameters of fat metabolism since. These patients have metabolic syndrome and insulin resistance in association with liver fat[7]. Considering the treatment of non-alcoholic hepatic steatosis, it is concluded that Several therapeutic possibilities have already been suggested with various objectives. To reduce body weight, a calorie-restricted diet was used, physical activity, bariatric surgery, among others; for insulin sensitization, agents such as incretin, lipid-lowering drugs, antioxidants and vitamins. Despite this, the main pillar of treatment for hepatic steatosis continues to be a lifestyle change based on healthy eating and physical activity. Finally, there is still a lack of further studies that could expand new treatment possibilities in association with a healthy or unhealthy lifestyle, having an increasingly greater impact on a disease whose incidence is increasing given the current socioeconomic and cultural context.

CONCLUSION

This study demonstrated the relationship between the prevalence of HE and other metabolic diseases, especially weight gain and low levels of physical activity. Studies suggest that the diagnosis of HE often occurs occasionally, but it would be possible to infer that prevention occurs in a similar way to other chronic diseases. It is also indicated that increasing the level of physical activity can help reduce fat in the liver and prevent the onset of HE at any stage of life. It is important to emphasize that other habits in daily life could be associated with HE, in this case, the consumption of alcoholic beverages.

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