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MANAGEMENT OF NON-ALCOHOLIC HEPATIC STEATOSIS: WHAT'S NEW?

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Abstract: **Goal:** review the manifestations and pathophysiology of hepatic steatosis in the scientific literature, focusing on reporting therapeutic methods that can help in the management of this disease and thus try to prevent its progression into steatohepatitis, cirrhosis and hepatocellular carcinoma. Methods: the work was carried out through a bibliographic search in the main academic databases, such as PubMEd, ScienceDirect and Springer Journal; using the descriptors "NASH" and "NAFLD" and "Liver" and "therapy". **Results:** Unhealthy lifestyle habits are directly related to the increasing incidence of NAFLD in the world population. In view of this, NAFLD, as a hepatic manifestation of metabolic syndrome, represents a public health problem that needs to be managed by a multidisciplinary health team. Therapy is carried out through changes in lifestyle, which may include surgical or drug treatment. **Final considerations:** Non-alcoholic hepatic steatosis is considered a manifestation of metabolic syndrome and is an important cause of liver cirrhosis, generating several complications. Therefore, the ideal management of hepatic steatosis includes the treatment of the etiology and also the comorbidities associated with the disease, but further studies are still needed in search of definitive treatment that prevents the complex progression of the pathology.
Keywords: Steatohepatitis; Hepatic steatosis; Metabolic syndrome; Therapy.

INTRODUCTION

Non-alcoholic hepatic steatosis (NAFLD) is a pathology characterized by the accumulation of fat in hepatocytes in patients whose history of alcoholism is excluded (YOUNOSSI et al., 2016). Due to the increase in metabolic diseases today, the worldwide prevalence of NASH is approaching 30%. In its diagnosis, there must be evidence of hepatic

steatosis, either by imaging or histology, and the absence of secondary causes of liver fat accumulation, such as alcoholism, prolonged use of steatogenic medications or hereditary disorders (CHALASANI et al., 2018). A recent Consensus changes the nomenclature of the pathology, which is now called hepatic steatosis related to metabolic dysfunction (MASLD) (RINELLA et al., 2023). In this sense, MASLD is considered a manifestation of metabolic syndrome, associated with phenomena such as obesity, hypertension and insulin resistance (HUTCHISON et al., 2023).

During the course of NAFLD, the liver tends to go through a process of inflammation and non-alcoholic steatohepatitis (NASH), progressing to liver cirrhosis, up to the stage of hepatocellular carcinoma (KLEINER et al., 2019). Furthermore, this term has also undergone changes in nomenclature recently, becoming known as steatohepatitis related to metabolic dysfunction (MASH) (RINELLA et al., 2023). Recent research finds trends that NAFLD will become the main cause of liver cirrhosis in the near future, surpassing those caused by alcoholism, and hepatitis B or C infection (RINELLA et al., 2023).

To date, it is known that 10% weight loss in patients with NAFLD, in order to prevent progression to liver fibrosis, is a widely recommended approach by doctors to their patients (HYDES et al., 2020). However, the existence of treatments that would prevent the complex progression of severity of the pathology is still questioned. We therefore aim to review existing scientific literature, in search of therapeutic methods that can help in the management of hepatic steatosis, in addition to trying to prevent its progression to life-threatening stages.

METHODOLOGY

The present work was prepared based on descriptor searches in the main academic databases, such as PubMed, ScienceDirect and Springer Journal. To this end, the descriptors ((NASH) AND ((liver)) AND ((therapy)) AND ((NAFLD)) were used. The articles must have been written in English.

Table 01 classifies the selected scientific articles based on authors, title, indexing platform, journal, and year of publication. In total, 21 articles were selected, which formed the framework for this literature review.

RESULTS AND DISCUSSIONS

PHYSIOPATHOGENESIS OF HEPATIC STEATOSIS

It is known that a hypercaloric diet tends to cause accumulations of triglycerides in adipose tissue, and, furthermore, in liver tissue (HUTCHISON et al., 2023). As a result, an inflammatory profile is initiated in the patients' liver, with the secretion of adipokines (adiponectin, resistin, leptin and visfatin) and pro-inflammatory cytokines (interleukins and tumor necrosis factor alpha). This profile will generate a process of low-grade chronic inflammation in the body, promoting the onset of NAFLD and NASH (HYDES et al., 2020).

Performing a liver biopsy is mandatory in order to predict the risk of progression of patients with NAFLD to the stages of liver fibrosis and NASH (NAVARRO-MASIP et al., 2024). Furthermore, despite the possible associated complications, the procedure is considered the gold standard for diagnosing NASH and staging liver fibrosis (LEONI et al., 2018). In this sense, studies with NAFLD prevalence data were categorized by biopsy indication criteria, such as: elevation of liver enzymes; clinical signs of liver disease; or retrospective biopsy evaluation (YOUNOSSI et al., 2016).

Authors	Database	Magazine	Tile	Year of release
AITHAL, G. P. et al.	PubMed	Gastroenterology	Randomized, Placebo-Controlled Trial of Pioglitazone in Nondiabetic Subjects With Nonalcoholic Steatohepatitis.	2008
BRUNNER, K. T. et al.	Springer Journal	Current Obesity Reports	Nonalcoholic Fatty Liver Disease and Obesity Treatment.	2019
CHALASANI, N. et al.	PubMed	Hepatology	The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases.	2018
CIGROVSKI BERKOVIC, M. et al.	PubMed	Frontiers in Nutrition	NAFLD and Physical Exercise: Ready, Steady, Go!	2021
HARNOIS, D. M.	PubMed	New England Journal of Medicine Current	Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis.	2010
HARRISON, S. A. et al.	PubMed	New England Journal of Medicine Current	A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis.	2024
HUTCHISO, A. L. et al.	Science Direct	Journal of Hepatology	Endocrine aspects of metabolic dysfunction-associated steatotic liver disease (MASLD): Beyond insulin resistance.	2023
HYDES, T. J. et al.	PubMed	Clinical and Molecular Hepatology	Evidence-based clinical advice for nutrition and dietary weight loss strategies for the management of nafld and nash.	2020
KLEINER, D. E. et al.	PubMed	JAMA Network Open.	Association of Histologic Disease Activity w ith Progression of Nonalcoholic Fatty Liver Disease.	2019
KOUTOUKIDIS, D. A. et al.	Science Direct	Metabolism: Clinical and Experimental	The effect of the magnitude of weight loss on non-alcoholic fatty liver disease: A systematic review and meta-analysis.	2021
LEONI, S. et al.	PubMed	World Journal of Gastroenterology	Current guidelines for the management of non-alcoholic fatty liver disease: A systematic review with comparative analysis.	2018
LOEFFELHOLZ, C. V. et al.	Springer Journal	Biomedicines	he Role of Physical Activity in Nonalcoholic and Metabolic Dysfunction Associated Fatty Liver Disease.	2021
LOOMBA, R. et al.	Springer Journal	The Lancet Gastroenterology and Hepatology	Semaglutide 2·4 mg once weekly in patients with non-alcoholic steatohepatitis-related cirrhosis: a randomised, placebo-controlled phase 2 trial.	2023
MAHAPATRA, M. K.; KARUPPASAMY, M.; SAHOO, B. M.	Springer Journal	Reviews in Endocrine and Metabolic Disorders	Semaglutide, a glucagon like peptide-1 receptor agonist with cardiovascular benefits for management of type 2 diabetes.	2022
NAVARRO-MASIP, È. et al.	Springer Journal	Obesity Surgery	Obesity Surgery Mid-term Effects of Bariatric Surgery on Metabolic Dysfunction-Associated Fatty Liver Disease Remission and Predictive Factors: A Prospective Study with a Focus on Non-invasive Diagnosis.	2024
NEVOLA, R. et al.	PubMed	International Journal of Molecular Sciences	GLP-1 Receptor Agonists in Non-Alcoholic Fatty Liver Disease: Current Evidence and Future Perspectives.	2023
POUWELS, S. et al.	PubMed	BMC Endocrine Disorders	Non-alcoholic fatty liver disease (NAFLD): a review of pathophysiology, clinical management and effects of weight loss.	2022
RINELLA, M. E. et al.	Science Direct	Journal of Hepatology	A multisociety Delphi consensus statement on new fatty liver disease nomenclature.	2023
UCHIDA, D. et al.	PubMed	Nutrients	Beneficial and paradoxical roles of anti-oxidative nutritional support for non-alcoholic fatty liver disease.	2018
VILAR-GOMEZ, E. et al.	Science Direct	Gastroenterology	Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis.	2015
YOUNOSSI, Z. M. et al.	PubMed	Hepatology	Global epidemiology of nonalcoholic fatty liver disease—Meta-analytic assessment of prevalence, incidence, and outcomes.	2016

Table 01 – Choice of scientific articles to prepare the work

Currently, it is known that lifestyle habits such as a sedentary lifestyle and inadequate diet are directly related to the increasing incidence of NAFLD in the world population (LOEFFELHOLZ et al., 2021). Given this, it is also proven that metabolic dysfunctions would be related to the pathophysiology of NASH, with subsequent progression to NAFLD and other mechanisms of liver injury. In this sense, the pathophysiology of NASH is associated with pathologies such as obesity, dyslipidemia, type 2 diabetes mellitus (DM2), systemic arterial hypertension, making it essential to treat it as a public health problem, suggesting a multidisciplinary approach between endocrinology, gastroenterology and nutrition (HUTCHISON et al., 2023).

BEHAVIORAL MEASURES

Initially, general measures are applied to all patients, which consist of treating metabolic comorbidities associated with lifestyle changes. In this sense, the main pillars of clinical measures aimed at reducing NASH, in addition to weight loss, include dietary re-education and increased frequency of physical activities, as demonstrated in studies of moderate quality scientific evidence (LEONI et al., 2018).

Patients who are overweight or obese must be advised to lose 5 to 7% of their body weight through diet and exercise, and between 7 and 10% when NAFLD is biopsy proven. Studies suggest that this loss of 5% or more of body weight resulted in improvements in liver biochemical tests, liver histology, insulin levels and quality of life. Thus, weight reduction is the main therapy for most patients (KOUTOUKIDIS et al., 2021).

To adapt dietary measures, it is suggested to reduce caloric intake and foods with a high glycemic index, and increase the consumption of monounsaturated fatty acids, omega-3 fatty acids, fiber in addition to specific sources of proteins, such as fish and poultry (POUWELS et al., 2022). It is also recommended to adopt regular physical activity practices, lasting 20 to 60 minutes per session, when at moderate intensity, with a frequency of 4 to 7 days a week (CIGROVSKI BERKOVIC et al., 2021). An example of this was a study consisting of 293 patients, whose NASH was confirmed by biopsy. After applying a low-calorie diet and 200 minutes of walking per week, ¼ of the patients showed complete resolution of steatohepatitis (VILAR-GOMEZ et al., 2015).

Many studies also link caffeine consumption with the improvement of liver enzymes in a dose-dependent manner in individuals with risk factors, in order to reduce oxidative stress and hepatic inflammation, ensuring a hepatoprotective effect. In addition to caffeine, polyphenols are a heterogeneous class of plant-derived compounds that include several water-soluble antioxidants proposed in the treatment of different metabolic disorders, but without major evidence in scientific studies (POUWELS et al., 2022).

DRUG THERAPY

Currently, pharmacological measures that prevent the natural progression of NASH are an important focus in scientific research. To date, there are few pharmacological options available with proven remission of hepatic steatosis or fibrosis.

With a view to improving NASH as a response to weight loss, once the pathology is proven by biopsy, in an off-label manner, glucagon-like peptide-1 receptor agonist (GLP-1 agonists) have been used, such as semaglutide or liraglutide (MAHAPATRA; KARUPPASAMY; SAHOO, 2022). It is also suggested that GLP-1 agonists can modulate the insulin signaling pathway, reducing the storage of triglycerides in hepatocytes and, consequently, improving hepatic steatosis. Furthermore, these drugs have shown a

potential protective effect against liver fibrosis (NEVOLA et al., 2023).

In a study carried out in patients with cirrhosis related to NASH, where semaglutide was used compared to placebo, improvements were demonstrated in cardiometabolic parameters, such as weight loss, glycemic control and lipid profile. Despite the absence of histological changes with the drug, improvements in non-invasive markers of disease activity were observed, as well as a clinically significant reduction in liver fat using MRI (LOOMBA et al., 2023).

To date, the American Association for the Study of Liver Diseases (AASLD) drug recommendations for NAFLD include pioglitazone for patients with DM2 and vitamin E for non-diabetic patients, with histological proof of NAFLD (CHALASANI et al., 2018). The use of pioglitazone, even in non-diabetic patients, has also been shown to be beneficial in the treatment of NAFLD. This was proven by a study using pioglitazone 30 mg/day or placebo for 12 months, applied to 74 patients with NALFD. As a result, although there were no significant changes in steatosis, these were present in hepatocellular lesions and liver fibrosis (AITHAL et al., 2008).

Another study, with daily vitamin E supplementation in doses of 800 IU, demonstrated a 43% improvement rate in the disease compared to placebo, in addition to improvement in steatosis, inflammation and fibrosis in diabetic patients (HARNOIS, 2010). Oxigen-reactive species are generated during the metabolism of free fatty acids in microsomes, peroxisomes and mitochondria, and constitute an established source of oxidative stress, being increased in NAFLD. In this sense, vitamin E, rich in powerful antioxidant and anti-inflammatory properties, acts to reduce oxidative processes by deactivating reactive oxygen species, minimizing pathophysiological mechanisms involved in NASH (UCHIDA et al., 2018).

Finally, a recent phase 3 study brings a new possibility of drug treatment for NASH, with the use of resmetirom. This is a selective thyroid hormone receptor type b (THR-b) agonist, with direct hepatic action, which has been tested in the treatment of NASH associated with liver fibrosis. During the study, to date, resolution of NASH without worsening of fibrosis has been observed in around 30% of patients using the drug, compared to 9.7% of those using placebo. Improvement of fibrosis by at least one stage, without worsening of NASH activity, was obtained in about ¼ of patients using resmetirom, compared to 14.2% of patients in the placebo group (HARRISON et al., 2024).

SURGERY FOR OBESITY

Bariatric surgery is currently indicated for patients with a BMI of 35, with related comorbidities, such as DM2, closely related to NAFLD (NAVARRO-MASIP et al., 2024). The effects of bariatric surgery, including sleeve gastrectomy, Roux-en-Y gastric bypass (RYGB) and adjustable gastric banding, are beneficial in the medium and long term in improving NAFLD, with younger age, female gender and absence of DM2 associated with disease remission (NAVARRO-MASIP et al., 2024). In a study, patients undergoing sleeve gastrectomy achieved improvement in liver enzymes, in addition to a reduction in liver fat in ultrasound findings before and one year after the intervention. Individuals who underwent RYGB achieved a 26% decrease compared to 21% in those who underwent adjustable gastric banding, in addition to a higher rate of improvement in NAFLD, even with more severe disease and higher BMI (BRUNNER et al., 2019).

CONCLUSION

Non-alcoholic hepatic steatosis affects a significant portion of the world's population today, being considered a manifestation of metabolic syndrome and the main cause of liver cirrhosis, which leads to serious complications, and makes adequate management of the pathology essential, both in diagnosis and in treatment, in order to better prognoses and less progression of the disease. Thus, numerous therapeutic managements stand out in current literature, from lifestyle changes to medication and surgical management.

In summary, it is concluded that the ideal management of hepatic steatosis mainly includes the control of comorbidities associated with the etiology of the disease. More studies are still needed in search of definitive treatment that prevents the complex evolution and severity of the pathology, approaching the disease in a multidisciplinary way between endocrinology, gastroenterology and nutrition, in search of better prognoses and health promotion.

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