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Literature Review

Relationship between non-alcoholic fatty liver disease and hepatocarcinoma: An integrative review

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Abstract

This integrative review explores the connection between Non-Alcoholic Fatty Liver Disease (NAFLD) and Hepatocellular Carcinoma (HCC). NAFLD is characterized by the presence of steatosis in more than 5% of hepatocytes in the absence of excessive alcohol consumption (> 20 g/day in men and > 30 g/day in women) or other chronic liver diseases. On the rise globally, the vast majority is associated with risk factors, mainly obesity and type 2 diabetes mellitus. Advanced NAFLD, including non-alcoholic steatohepatitis, emerges as an important precursor to HCC, in some cases, even before the presence of cirrhosis, due in addition, recent studies highlight NAFLD as a main cause of liver transplantation for HCC. Non-invasive diagnostic methods, such as fibroscan liver elastography, exhibit promise for evaluating hepatic steatosis. Therapeutic interventions aim to slow the progression of NAFLD and mitigate the risks of HCC.

Introduction

There was a recent change in the nomenclature from Nonalcoholic Fatty Liver Disease (NAFLD) to steatotic liver disease associated with Metabolic Dysfunction (MASLD), and it was decided to maintain NAFLD nomenclature so as not to generate conflicts in the literature.

Nonalcoholic Fatty Liver Disease (NAFLD) has emerged as one of the most prevalent liver conditions worldwide, posing a growing public health challenge. Epidemiological studies have documented an increased prevalence of NAFLD in about 25% of the global population. A review by Liu, et al. [1] highlights that MLD can affect up to 60% of the population in some risk groups, especially in obese individuals with type 2 diabetes. Traditional risk factors such as age, male gender, prediabetes, and family history have been associated with MLDMD.

Analysis of data by Kim, et al. (2019) evidences a strong association between NAFLD and the development of hepatocellular carcinoma, being the second cause of

Hepatocellular Carcinoma (HCC) in patients in the liver transplant queue in the United States.

However, NAFLD is not confined to adults alone, as its prevalence in children and adolescents is increasing exponentially. This alarming trend raises concerns about future liver disease burdens and their implications for public health and health systems.

The consequences of NAFLD can be severe and include the development of Nonalcoholic Steatohepatitis (NASH), liver fibrosis, cirrhosis, and hepatocellular carcinoma. NASH is characterized by liver inflammation, which can progress to fibrosis, cirrhosis, and hepatocellular carcinoma, leading to liver dysfunction and the need for transplantation.

An important complication of chronic liver diseases is the development of hepatocellular carcinoma, as it represents the 5th leading cause of mortality in the world and is often associated with patients with cirrhosis.

Hepatocarcinogenesis in patients with Nonalcoholic Fatty

Liver Disease (NAFLD) has been the subject of increasing scientific interest. Studies have investigated the associations between NAFLD and the development of Hepatocellular Carcinoma (HCC), especially in patients without cirrhosis.

The intestinal microbiota has been increasingly recognized as an influential factor in the pathogenesis of NAFLD, interacting with hepatic metabolism and affecting systemic inflammation, as well as a diet rich in processed foods, rich in sugars and saturated fats also generates a state of hepatic inflammation [2].

Regarding NAFLD, Singal, et al. [3] analyzed the current knowledge and implications for the management of this type of cancer in patients with NAFLD, noting that there is a need for studies that address the screening guidelines for HCC surveillance in NASH. Additionally, Liu, et al. [1] reported that there is a case-control study that identified the contribution of NAFLD to hepatocarcinogenesis in non-cirrhotic patients, the etiopathogenesis in these cases is multifactorial, encompassing environmental factors, increased oxidative stress, chronic inflammatory status, and immune response.

A longitudinal investigation was conducted by Kim, et al. (2019) to assess the association between NAFLD and HCC, revealing that NAFLD is associated with the development of HCC. The objective of this study is to conduct an integrative review of the current literature on the relationship between NAFLD and hepatocarcinoma.

The general objective

To demonstrate the relationship between Non-Alcoholic Fatty (NAFLD) and the development of Hepatocarcinoma (HCC), exploring clinical, diagnostic, and therapeutic aspects.

Methodology

This integrative review was conducted following the guidelines of the interactive literature review protocol. The methodological process was divided into distinct stages, from the formulation of the guiding question to the synthesis and discussion of the results. The guiding question was developed with the objective of directing the integrative review, seeking to understand the relationship between Nonalcoholic Fatty Liver Disease (NAFLD) and the risk of developing hepatocarcinoma. An electronic search was conducted in the PubMed, Scopus, and Web of Science databases. Search terms used included variations of nonalcoholic fatty liver disease”, “NAFLD”, “nonalcoholic steatohepatitis”, “NASH”, “hepatocellular carcinoma”, “hepatocarcinoma”, “liver cancer”, “association” and “relationship”. The Boolean operators “AND” and “OR” was employed to match the search terms appropriately. Scientific articles published in indexed journals, in English and Portuguese, from 2010 to 2024 were included in the review.

Results and discussion

The relationship between Nonalcoholic Metabolic Fatty Liver Disease (NAFLD) and hepatocarcinoma has been the subject of intense investigation, considering the significant

implications for public health. Analysis of the selected studies provides valuable insights into this association.

Liu, et al. [1] conducted a clinical and pathological study that contributes to the understanding of the mechanisms underlying hepatocarcinogenesis in non-cirrhotic patients with NAFLD. They suggest that NAFLD plays a role in the development of hepatocarcinoma even in the absence of cirrhosis, highlighting the need for close monitoring in patients with NAFLD. Kim, et al. (2019), who demonstrate a significant association between NAFLD and hepatocarcinoma, reinforcing the importance of NAFLD as an independent risk factor, observed similar results in the study.

In addition, studies such as the one by Lee, et al. (2013) highlight the interaction between NAFLD and metabolic syndrome in the development of hepatocarcinoma, suggesting a complex interaction between multiple risk factors. Younossi, et al. [4] identified an association between NAFLD and hepatocarcinoma in the United States.

Piscaglia, et al. (2016) contribute insights into the clinical patterns of hepatocarcinoma in patients with NAFLD, highlighting the importance of surveillance in patients with this condition.

Other studies, such as the one by Hassan, et al. (2002) and Wong, et al. (2012), further expand the scope of the discussion, considering other risk factors for hepatocarcinoma, such as diabetes mellitus and chronic hepatitis B infection.

Pathophysiology

The development of hepatocarcinoma involves a complex interaction between several cellular and molecular processes. Obesity, characterized by excessive accumulation of adipose tissue, triggers a cascade of events that contribute to liver carcinogenesis. Insulin resistance, commonly seen in obesity, leads to the exacerbated release of insulin and Insulin-like Growth Factors (IGF), which can promote cell proliferation and inhibit apoptosis in the liver [5].

In addition, obesity induces a chronic low-grade inflammatory state, characterized by an increase in pro-inflammatory cytokines, such as tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6). This chronic inflammation contributes to the progression of fatty liver, which is the accumulation of fat in the liver. Steatosis can progress to Nonalcoholic Steatohepatitis (NASH), characterized by inflammation and cell damage in the liver [6].

Progression of NASH to liver cirrhosis increases the risk of hepatocarcinoma. The fibrosis resulting from the chronic inflammatory response creates an environment conducive to genetic mutation and uncontrolled cell proliferation. In addition, fibrosis alters the architecture of the liver, creating regions of hypoxia and oxidative stress, which further promote carcinogenesis [7].

Obesity is also associated with hormonal imbalance, including elevated levels of circulating estrogen, which can

influence the development of hepatocarcinoma. In addition, obesity is related to the accumulation of lipids in the liver, resulting in lipotoxicity and cell damage [8].

The polymorphism in the PNPLA 3 gene generates a substitution of isoleucine for methionine, causing lipolytic activity on triglycerides. The decrease in the activity of this enzyme will soon lead to the development of macrovascular hepatic steatosis evolving with hepatic inflammation [9].

Therefore, the pathophysiology of obesity-related hepatocarcinoma is multifaceted. Insulin resistance, chronic inflammation, steatosis, fibrosis, and hormonal imbalances are key components in this complex interaction. Understanding these mechanisms is essential for the development of targeted preventive and therapeutic strategies aimed at halting the progression of hepatocarcinoma in patients with obesity and reducing its incidence and impact on public health [4].

Epidemiology

Hepatocarcinoma (HCC) is the most common form of primary liver cancer, it is the 5th most common cancer in the world, corresponding to 90% of all cases of liver neoplasms and its relationship with Non-Alcoholic Fatty Liver Disease (NAFLD) has gained prominence due to the increasing prevalence of these two conditions worldwide [10].

The prevalence of NAFLD-related HCC varies geographically, reflecting the global distribution. In regions where NAFLD is more prevalent, such as North America, Western Europe, and parts of Asia, a higher incidence of NAFLD related to this condition is also observed. It is estimated that about 25% of the global population has NAFLD, and it is more common in high-income countries with diets high in fat and carbohydrates [11,12] (ADAMS, 2020). It is estimated that up to 70% of NAFLD cases are related to the 2 main risk factors type 2 diabetes and obesity [13].

However, it is important to note that the relationship between NAFLD and HCC is complex, especially when associated with factors such as obesity, type 2 diabetes, and insulin resistance [14].

The prevalence and incidence of Hepatocarcinoma (HCC) vary widely worldwide, one review showed a prevalence of HCC in cirrhotic patients of 38%, and in non-cirrhotic patients with NAFLD of 14%. In another study, the overall incidence of HCC was shown to be 0.44 per 1000 person-years, in patients with NAFLD this rate increased to 5.29 per 1000 person-years (PINYOPORNPANISH K, 2021)

Obesity contributes to the progression of hepatic steatosis to Nonalcoholic Steatohepatitis (NASH), which is a significant precursor to liver cirrhosis and, consequently, hepatocarcinoma. Studies, such as the one by Singal, et al. [3], show that NASH is an independent risk factor for the development of hepatocarcinoma, even before the presence of cirrhosis. Hepatic steatosis and NASH can cause chronic inflammation, oxidative stress, and fibrosis in the liver, creating an environment conducive to the emergence of cancer.

Non-invasive diagnostic methods

The evaluation of Nonalcoholic Fatty Liver Disease (NAFLD) has benefited significantly from advances in imaging techniques, such as elastography and abdominal ultrasound, which recommends screening for advanced fibrosis in high-risk populations, which includes people with prediabetes or T2DM [15] (LIMA, 2021). These tools play a key role in early detection, monitoring of disease progression, and making more informed clinical decisions [16,17].

Abdominal ultrasound plays a crucial role in the screening and initial diagnosis of NAFLD [18]. It is a non-invasive technique, widely available and relatively accessible [19]. Ultrasound can detect hepatic steatosis, which is the accumulation of fat in the liver, and assist in the evaluation of associated complications such as hepatocellular carcinoma, detects steatosis rates when greater than 12.5%, limited in cases lower than this rate [20].

Liver biopsy is still the gold standard for diagnosis, however, it is an invasive test and can have serious complications [20].

ALT is not an ideal indicator for diagnosing these conditions. Recent evidence also points to the need to revise the reference values, especially the upper limit, of ALT in certain populations. In morbidly obese patients, lowering the transaminase cut-off point has been suggested to improve the detection of cases with NASH while maintaining an acceptable sensitivity, although this proposal still lacks validation (MA. X, 2021)

Mofrad, et al. [21] found that the prevalence of advanced fibrosis was similar in groups with and without ALT elevation (5 of 15 versus 13 of 36, respectively), indicating that the entire histological spectrum of NAFLD can be observed in individuals with normal ALT values. In addition, the histological spectrum does not differ significantly in these individuals compared to those with elevated ALT levels, and a normal ALT level does not ensure the absence of underlying steatohepatitis with advanced fibrosis. These results were corroborated in 2019 by Ulasoglu and colleagues, who also suggested that ALT levels may indicate a more severe metabolic profile in individuals with NAFLD.

A meta-analysis that evaluated the proportion of patients with NAFLD and NASH who had normal transaminase levels found that 25% of patients with NAFLD and 19% of those with NASH had normal ALT values. This study, which included 4,094 patients diagnosed with steatohepatitis, concluded that the relevance of ALT level in the clinical diagnosis of NAFLD and NASH has yet to be confirmed [22].

Clinical laboratory scores, which include FIB-4 scores, are useful for risk stratification of advanced fibrosis [23]. In a meta-analysis of 37 studies (n = 5,735; BMI \geq 30 kg/m²) evaluating the diagnostic performance of Vibration-Controlled Transient Elastography (VCTE), FIB-4, and liver biopsy (NAFLD Fibrosis Score) to estimate advanced fibrosis, the AUROCs for each were 0.85, 0.76, and 0.73, respectively. If the FIB-4 value is less than 1.3, the risk of advanced fibrosis is ruled out, with a negative

predictive value of approximately 91%. If the FIB-4 is greater than 1.3, the patient should be evaluated with another method for the evaluation of fibrosis. Ultimately, the FIB-4 is easy to calculate, making it a suitable scoring system for primary care settings [22].

Elastography in the evaluation of the patient with NAFLD

Elastography is a non-invasive technique that allows the evaluation of liver stiffness, a direct indicator of liver fibrosis [24]. Transient elastography (FibroScan) and magnetic resonance elastography (MR-Elastography) are widely used methods (MARTINS; OLIVEIRA, 2021). For patients with NAFLD, elastography offers the advantages of diagnosis, monitoring of the degree of fibrosis, recognizing it earlier, and reducing the need for an indication of a more invasive test [16] (SILVEIRA, 2021).

Types of elastography: Transient elastography by FibroScan: most used, most validated method at the present time. It uses shear waves, expressed in Kilopascal (kPa) which is proportional to the stiffness of the tissue, so the more hardened the tissue is, the faster the propagations, the more fibrosis it will have (SANDRIN 2003).

MRI elastography (MRI): requires specific equipment and program. High cost and low availability [11].

Main recommendations for clinical follow-up

Ulasoglu and colleagues, Brazilian Society of Endocrinology and Metabolism (SBEM) guideline, Brazilian Society of, carried this integrative review out following guidelines from the 2019 interactive literature review protocol

Hepatology (SBH) and Brazilian Association for the Study of Obesity and Metabolic Syndrome (Abeso):

Patients with NAFLD without advanced fibrosis should be evaluated by a hepatologist every 2 - 3 years. (I, C)

Overweight/obese patients with NAFLD with stage 2-3 fibrosis every 12 months, be evaluated for disease progression and response to treatment (I, C).

Patients with overweight/obesity, NAFLD, and cirrhosis should be evaluated every 6 months to assess progression, response to treatment, and screening for HCC – this with ultrasound of the abdomen and measurement of serum alpha-fetoprotein. (I, C)

Treatment

The treatment of Non-Alcoholic Fatty Liver Disease (NAFLD) encompasses a multidisciplinary approach that aims to reduce liver fat, improve inflammation, and control metabolic risk factors. Therapeutic options range from lifestyle changes to pharmacological interventions [17].

Lifestyle changes form the mainstay of NAFLD treatment. Weight loss is a central objective, since obesity is one of the main risk factors, considered as a primary strategy, and is

recommended for all overweight or obese patients. For every 6 kg of weight lost, there was a reduction of more than 6% in the steatosis evaluated. A greater than 7% reduction in body weight should be considered to improve steatohepatitis without worsening fibrosis. Being a strategy to slow the development and progression of NAFLD [22].

The adoption of a Mediterranean diet should be considered for the improvement of fatty liver, regardless of weight loss. Balanced, rich in fiber, vegetables, fruits, and low in saturated fats and sugars, foods rich in omega-3 and not using ultra-processed foods contribute to the reduction of liver fat, improved insulin sensitivity, and decreased inflammation [22].

As far as pharmacological interventions are concerned, drugs are being studied to treat different aspects of NAFLD. The use of GLP-1 analogues (liraglutide, semaglutide, or dulaglutide), GLP-1 receptor agonites (exenatide), SGLT-2 inhibitors, pioglitazone, and vitamin E is recommended. In relation to those who used ISGT2, who were overweight and obese, there was a reduction in ALT and GGT levels, as well as a reduction in liver fat. The use of pyoglatozone improved steatosis, steatohepatitis, and fibrosis. A study, by Vilar-Gomes, showed that the use of vitamin E (800IU/Day) significantly reduced overall mortality and survival without liver transplantation in patients with DM [22].

In more advanced cases of NAFLD, when Nonalcoholic Steatohepatitis (NASH) and significant fibrosis are present, it is important to consider specific interventions to prevent progression to cirrhosis. Bariatric surgery has shown benefits in obese patients with NAFLD, promoting weight loss and improving metabolic conditions [20].

It is important to highlight that the treatment of NAFLD also requires close monitoring and periodic evaluations to monitor the effectiveness of the interventions adopted [25] (SILVA; 2022).

In advanced cases of NAFLD with complications such as cirrhosis or hepatocellular carcinoma, the therapeutic approach may involve specific treatments for these conditions, such as liver transplantation or targeted therapy for liver cancer (OLIVEIRA; PEREIRA, 2020).

Furthermore, it is important to highlight that the therapeutic approach to NAFLD must be personalized, taking into account the clinical and metabolic characteristics of each patient [26-33].

A multidisciplinary approach is fundamental in the treatment of NAFLD. In addition to hepatologists or gastroenterologists, the care team may include endocrinologists, nutritionists, psychologists, and physical education professionals. Collaboration between these specialists is essential to provide comprehensive guidance to patients, addressing not only medical aspects but also behavioral and psychosocial aspects (OLIVEIRA; PEREIRA, 2020).

It is important to highlight that prevention plays a crucial role in the treatment of NAFLD. Encouraging healthy lifestyle



changes from childhood and promoting awareness about the risks associated with obesity and a sedentary lifestyle are fundamental strategies to reduce the incidence of the disease. The dissemination of information about the harmful effects of NAFLD and the promotion of public policies that encourage healthy habits are crucial steps to face this growing public health challenge (SILVA; ALMEIDA; 2022).

Conclusion

This review comprehensively addressed the relationship between Metabolic Fatty Liver Disease (GMHD) and hepatocellular carcinoma, highlighting their complex interconnection and significant clinical implications. GMHD, characterized by excessive fat accumulation in the liver, has emerged as a global public health problem, driven primarily by modern living standards and poor eating styles.

Through this review, it was possible to verify that NAFLD plays a central role in the pathogenesis of hepatocellular carcinoma in non-cirrhotic patients, although the underlying mechanisms are not yet completely elucidated. Inflammation, steatosis, liver fibrosis, and hormonal imbalances emerge as important contributing factors.

Furthermore, assessment using advanced techniques, such as elastography and abdominal ultrasound, has proven crucial in the early identification of liver lesions associated with NAFLD, allowing timely interventions. NAFLD patient with cirrhosis poses an increased risk of HCC. Among non-cirrhotic NAFLD patients, as already mentioned, risk factors such as type 2 diabetes, obesity, genetic factors such as the PNPLA3 gene mutation, and smoking increase additional risk for HCC.

The treatment strategies discussed, from lifestyle changes, and medication use to bariatric surgery, highlight the need for personalized and multidisciplinary approaches, taking into account the severity of NAFLD, the presence of comorbidities, and the individual characteristics of patients. Continued research is critical to deepen our understanding of the molecular pathways involved and develop targeted therapies.

Ultimately, this review highlights the importance of a holistic approach to NAFLD, which goes beyond the purely hepatic approach and encompasses metabolic, nutritional, and genetic factors. The impact of NAFLD on global health and its implications for hepatocellular carcinoma requires collaboration among healthcare professionals, researchers, and policymakers to develop effective prevention and treatment strategies. Awareness, public education, and the promotion of healthy lifestyle habits are essential to reversing the upward trajectory of this condition and improving outcomes for affected individuals.

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