Review Article

Non-alcoholic Fatty Liver Disease and Hepatocellular Carcinoma; Is there a Real Coorelation?

Ahmed Elsayed Ahmed[1], Naif Khalid Alsayed[2]*, Huda Faisal Alwahbi[3], Abdulelah Shallal Ameq Alanazi[4], Abdulelah Saleh Alaqil[5], Seham Qassim Alhaffaf[6], Sayed Murtadha Abdulla[7], Reem Awad Alnezawi[8], Sara Omran Bin Ali[8], Meshari Abdullatif Aldawood[9], Mohammed Saeed Alshehri[10]

[1]Faculty of Medicine, Al Mouwasat Hospital, Al Khobar, Saudi Arabia. [2]Faculty of Medicine, Shaqra University, Dawadmi, Saudi Arabia. [3]Faculty of Pharmacy, Tadawina Pharmacy, Qassim, Saudi Arabia. [4]Faculty of Medicine, King Saud bin Abdulaziz University, Riyadh, Saudi Arabia. [5]Faculty of Medicine, Almaarefa University, Riyadh, Saudi Arabia. [6]Faculty of Medicine, Prince Mohammed bin Nasser Hospital, Jazan, Saudi Arabia. [7]Faculty of Medicine, Xi'an Jiaotong University, Xi'an, China. [8]Faculty of Medicine, Fakeeh College, Jeddah, Saudi Arabia. [9]Faculty of Medicine, Imam Mohammad Ibn Saud Islamic University, Riyadh, Saudi Arabia. [10]Faculty of Pharmacy, Pharmacist in public security Ministry of health, Riyadh, Saudi Arabia.

Abstract

Hepatocellular carcinoma (HCC) ranks as the sixth most prevalent cancer globally and stands as the third leading cause of cancer-related fatalities. Over the past few decades, non-viral factors contributing to HCC have become increasingly apparent, with non-alcoholic fatty liver disease (NAFLD) emerging as the most significant. NAFLD encompasses a spectrum ranging from simple liver fat accumulation in individuals without excessive alcohol consumption to non-alcoholic steatohepatitis (NASH), which may or may not involve cirrhosis. The Medline, Pubmed, Embase, NCBI, and Cochrane databases were searched for studies of patients with non-alcoholic fatty liver disease. Incidence, etiology, and management options were analyzed. As the field progresses, early indications of potentially reduced responsiveness to immunotherapy for NAFLD-related HCC highlight the need for more frequent and rigorous investigations into non-immune systemic treatments for this patient subgroup. Furthermore, it is crucial to conduct randomized controlled trials specifically assessing the effectiveness of immunotherapy in this population. Several considerations must be addressed in such studies, including the precise definition of NAFLD, metabolic-associated fatty liver disease, or NASH, the diversity within this group encompassing lean NAFLD, metabolic syndrome-related NAFLD, and other subtypes, as well as the influence of concurrent health conditions and medication profiles.

Keywords: Non-alcoholic fatty liver disease, Hepatocellular carcinoma, NASH-HCC, Metabolic syndrome

Introduction

The accumulation of triglycerides in the liver tissue, or steatosis, is the hallmark of non-alcoholic fatty liver disease (NAFLD). Steatogenic medications or chronic viral hepatitis are not present, nor is there excessive alcohol usage. It may develop into non-alcoholic steatohepatitis (NASH), which may or may not include fibrosis and entails steatosis and liver inflammation [1].

NAFLD is recognized as a global health challenge in the 21st century within the realm of liver diseases and is closely linked to the increasing prevalence of obesity. In 2016, the World Health Organization reported that there were more than 1.9 billion overweight or obese adults worldwide [2]. NAFLD is also associated with various metabolic conditions beyond obesity, including type 2 diabetes mellitus (T2DM), hyperlipidemia, and high blood pressure, making it a hepatic manifestation of the metabolic syndrome (MetS).

It's noteworthy that over the past decade, the prevalence of NAFLD has consistently risen, increasing from 15% in 2005 to 25% in 2010 [3]. From our perspective, given the rapidly increasing global prevalence of NAFLD, HCC in individuals with NAFLD will soon become a major public health concern and emerge as a leading reason for liver transplantation [4].

Epidemiology of HCC Associated with NAFLD

The epidemiology of hepatocellular carcinoma (HCC) associated with non-alcoholic fatty liver disease (NAFLD) reveals a strong connection between obesity, diabetes, and the risk of HCC. Obesity and high body mass index (BMI) increase the risk of HCC significantly, with obese individuals being up to 189% more likely to develop liver cancer than

Address for correspondence: Naif Khalid Alsayed, Faculty of Medicine, Shaqra University, Dawadmi, Saudi Arabia.
Purenaif@outlook.com

How to cite this article: Ahmed AE, Alsayed NK, Alwahbi HF, Alanazi ASA, Alaqil AS, Alhaffaf SQ, et al. Non-alcoholic Fatty Liver Disease and Hepatocellular Carcinoma; Is there a Real Coorelation?. Arch Pharm Pract. 2023;14(S):A06231530.

those with a normal BMI [4]. Type 2 diabetes, often linked to obesity, is also a major risk factor for HCC. Studies have shown that diabetes can triple the risk of HCC, and there are synergistic interactions between diabetes and other HCC risk factors [5].

NAFLD, a liver condition often associated with obesity and diabetes, has become increasingly common, affecting up to 30% of the general adult population and 90% of morbidly obese individuals. It is also closely related to insulin resistance and hyperinsulinemia [6]. In advanced NAFLD, around 20% of cases progress to steatohepatitis, which carries a risk of cirrhosis and subsequently, HCC. The prevalence of HCC in cirrhotic NAFLD remains uncertain, but recent reports suggest that it may become a leading cause of liver cancer, especially in developed countries [7]. HCC can also develop in cases of cryptogenic cirrhosis, where no clear underlying cause is identified. Recent research suggests that NAFLD and metabolic syndrome may contribute to these cases, but they often go unnoticed unless detailed medical histories are considered.

Thus, the rising prevalence of obesity, diabetes, and NAFLD is closely linked to an increased risk of HCC, which may become a leading cause of liver cancer in developed countries, potentially surpassing other causes like hepatitis C. Understanding these connections is crucial for early detection and prevention efforts [8].

Pathogenesis of HCC Associated with NAFLD

The development of hepatocellular carcinoma (HCC) in cirrhosis is a complex and gradual process that can take several decades in chronic liver disease. It involves various molecular mechanisms:

- Chronic Liver Damage: In response to metabolic and oxidative stress, inflammation, immune responses, and fibrosis, the liver experiences cycles of damage and repair, creating an environment favorable for cancer development.
- Genomic Aberrations: Over time, genetic abnormalities accumulate as chronic hepatitis progresses to cirrhosis and eventually to HCC. Initially, epigenetic changes can lead to abnormal DNA methylation and alterations in chromatin structure. This can then result in structural genomic changes such as point mutations, allelic deletions, chromosomal gains, telomere shortening, and reactivation of telomerase [9].
- Selection of Pre-Malignant Cells: A crucial step in this process is the selection of specific pre-malignant hepatocytes or progenitor cells from which HCC eventually arises.
- Heterogeneity: HCC displays remarkable genomic heterogeneity, suggesting that multiple regulatory pathways are disrupted during its development. This includes the reactivation of developmental pathways, upregulation of growth factors, and activation of proliferative signaling cascades. Additionally, inhibition of cell cycle regulators and disruption of tumor suppressors contribute to uncontrolled cell proliferation.
- Functional Redundancy: The complexity of hepatocarcinogenesis leads to functional redundancy and robustness, which contribute to the poor overall prognosis. This means that multiple pathways can drive cancer development, making it difficult to target with therapies [10].
- Heterogeneous Phenotypes: Malignant hepatocytes can exhibit diverse characteristics based on different disease mechanisms, etiologies, and clinical courses. Molecular analyses of genomics, microRNAs, and proteins can identify distinct patterns of alterations associated with HCC in liver diseases of various origins.
- Potential for Targeted Therapies: The molecular signature of HCC in specific contexts, such as non-alcoholic fatty liver disease (NAFLD), may provide insights into potential targets for prevention, diagnosis, and treatment, particularly in cases associated with obesity and diabetes [9].

In summary, the development of HCC in cirrhosis is a complex and multifaceted process involving genetic, epigenetic, and molecular changes, leading to a highly heterogeneous cancer with multiple potential pathways for intervention and therapy. Understanding these mechanisms is crucial for improving the prevention and treatment of HCC in different clinical contexts [10].

Treatment

While there are no approved medications to reverse fibrosis in patients with non-alcoholic steatohepatitis (NASH), some treatments show promise. These include drugs like Obeticholic acid (OCA), metabolic drugs such as semaglutide, and similar medications. Lifestyle modifications, like diet and exercise, play a crucial role in improving hepatic fibrosis and long-term outcomes for NASH patients [11]. The Mediterranean-style diet, to reduce body weight by 5% to 10%, is often recommended. Bariatric surgery is effective for very obese patients who meet the criteria, but it should be carefully considered in cirrhosis patients due to potential complications. Managing risk factors like smoking, alcohol consumption, hypercholesteremia, and type 2 diabetes is essential, and some medications like statins and metformin may offer benefits.

For those with early-stage hepatocellular carcinoma (HCC), curative treatments like radiofrequency ablation, surgical resection, and liver transplantation are options. Palliative therapies, including interventional radiology procedures, can also be considered. For advanced HCC, tyrosine kinase inhibitors like sorafenib, lenvatinib, and regorafenib are used, but their effects on NAFLD/NASH-related HCC need more study [12]. The combination of atezolizumab plus bevacizumab has shown promising results for non-resectable HCC. Liver transplantation, while offering the best odds of survival, poses challenges for NASH-associated HCC

patients due to comorbidities and post-transplant complications [13, 14].

Results and Discussion

In recent years, there has been a rising occurrence of liver cancer (HCC) in patients with non-alcoholic fatty liver disease (NAFLD) due to the lack of effective treatments. Identifying high-risk NAFLD patients for HCC is crucial, but traditional risk factors for liver cancer don't fully apply in this context. Metabolic issues are common in NAFLD and are linked to the severity of liver damage [15].

A systematic review found that diabetes (DM) and being overweight or obese are associated with an increased risk of HCC in NAFLD patients. DM, in particular, poses a significant risk, especially when advanced liver damage is present, increasing the risk fourfold. Elevated blood glucose levels may be a key factor in NAFLD-related HCC [16]. Altered glucose metabolism is critical for tumor growth, including HCC, and insufficient glucose can lead to hypoxia, which activates cancer-related genes and behaviors.

Obesity is another risk factor for NAFLD-related HCC [17]. Obesity is associated with more severe liver damage in NAFLD patients. Adipose tissue expansion and inflammation in obesity can promote tumor growth by interacting with cancer cells. This suggests that obesity contributes to the development of NAFLD-related HCC, although its impact is milder compared to DM. Body mass index (BMI) is commonly used to assess overweight/obesity but has limitations. It cannot differentiate between fat and muscle mass. Skeletal muscle loss is associated with an increased HCC risk, as skeletal muscles secrete substances that inhibit cancer development. Therefore, a more comprehensive assessment of body composition is needed to understand the relationship between obesity and NAFLD-related HCC [18].

Conclusion

The growing population of individuals with NAFLD/NASH underscores the increasing significance of these liver conditions in the future. While the risk of HCC in NAFLD/NASH patients is lower than that in individuals with HCV-related chronic liver diseases, the sheer number of NAFLD/NASH cases is substantial. Consequently, the proportion of NASH-related HCC cases among all HCC patients is likely to rise. Regrettably, there are presently no efficient diagnostic tools for the swift and precise identification of HCC associated with NAFLD/NASH. Additionally, HCC surveillance for NAFLD patients is conducted less frequently compared to those with HCV-related chronic liver disease and alcoholic liver disease. This underscores the urgent need for the development of accurate blood and imaging tests for HCC surveillance in NAFLD/NASH patients.

ACKNOWLEDGMENTS: None
CONFLICT OF INTEREST: None
FINANCIAL SUPPORT: None
ETHICS STATEMENT: None

References

1. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018;67(1):328-57.
2. Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol. 2018;15(1):11-20.
3. Cholongitas E, Pavlopoulou I, Papatheodoridi M, Markakis GE, Bouras E, Haidich AB, et al. Epidemiology of nonalcoholic fatty liver disease in Europe: a systematic review and meta-analysis. Ann Gastroenterol. 2021;34(3):404-14.
4. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1):73-84.
5. El-Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. Gastroenterology. 2004;126(2):460-8.
6. Veldt BJ, Chen W, Heathcote EJ, Wedemeyer H, Reichen J, Hofmann WP, et al. Increased risk of hepatocellular carcinoma among patients with hepatitis C cirrhosis and diabetes mellitus. Hepatology. 2008;47(6):1856-62.
7. Abdelmalek MF, Diehl AM. Nonalcoholic fatty liver disease as a complication of insulin resistance. Med Clin North Am. 2007;91(6):1125-49.
8. Byrne CD, Olufadi R, Bruce KD, Cagampang FR, Ahmed MH. Metabolic disturbances in non-alcoholic fatty liver disease. Clin Sci (Lond). 2009;116(7):539-64.
9. Rafiq N, Bai C, Fang Y, Srishord M, McCullough A, Gramlich T, et al. Long-term follow-up of patients with nonalcoholic fatty liver. Clin Gastroenterol Hepatol. 2009;7(2):234-8.
10. Regimbeau JM, Colombat M, Mognol P, Durand F, Abdalla E, Degott C, et al. Obesity and diabetes as a risk factor for hepatocellular carcinoma. Liver Transpl. 2004;10(2 Suppl 1):S69-73.
11. Nathani P, Singal AG. Imaging and Biomarker Approaches to HCC Surveillance. Clin Liver Dis (Hoboken). 2021;17(6):401-4.
12. Quezada N, Maturana G, Irarrázaval MJ, Muñoz R, Morales S, Achurra P, et al. Bariatric Surgery in Cirrhotic Patients: a Matched Case-Control Study. Obes Surg. 2020;30(12):4724-31.
13. Cusi K, Orsak B, Lomonaco R, Bril F, Ortiz-Lopez C, Hecht J, et al. Extended treatment with pioglitazone improves liver histology in patients with pre-diabetes or type 2 diabetes mellitus and NASH. Hepatology. 2013;58(supp 1):248a.
14. Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, et al. A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. N Engl J Med. 2021;384(12):1113-24.
15. Sookoian S, Pirola CJ. Systematic review with meta-analysis: the significance of histological disease severity in lean patients with nonalcoholic fatty liver disease. Aliment Pharmacol Ther. 2018;47(1):16-25.
16. Li Z, Zhang H. Reprogramming of glucose, fatty acid and amino acid metabolism for cancer progression. Cell Mol Life Sci. 2016;73(2):377-92.
17. Karstoft K, Pedersen BK. Skeletal muscle as a gene regulatory endocrine organ. Curr Opin Clin Nutr Metab Care. 2016;19(4):270-5.
18. Mittal S, Sada YH, El-Serag HB, Kanwal F, Duan Z, Temple S, et al. Temporal trends of nonalcoholic fatty liver disease-related hepatocellular carcinoma in the veteran affairs population. Clin Gastroenterol Hepatol. 2015;13(3):594-601.