REVIEW ARTICLE

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Hepatocellular carcinoma *versus* nonalcoholic fatty liver disease: metabolic, environmental, and genetic association? *De facto*?

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary cause of liver cancer and is also considered to be the fourth most frequent cause of cancer and the third most common cause of cancer-related deaths worldwide[1]. The majority of these cases develop due to existing chronic liver conditions such as hepatitis B or C viral infections and alcohol[2]. However, previous shreds of evidence have shown that 15–50% of HCC is presented as idiopathic and could not be explained with any known etiology[3]. However, recent studies suggest that nonalcoholic fatty liver disease (NAFLD) can be a possible risk factor for the development of HCC[4], and it can act through various mechanisms such as insulin resistance, oxidative stress, steatosis, and imbalances in an interplay of adipokine or cytokine. These are propounded as the most important factors responsible for the pathogenesis and progression of NAFLD that could also have a deterministic role in the pathway of liver cancer as it promotes cell growth and DNA damage. Behavioral therapy and several insulin-sensitizing agents have been tried and tested to achieve a better success rate in the management of this condition[5]. This approach was alleged as it could help improve insulin resistance and attenuate the necroinflammation, steatosis, and fibrotic changes in the liver parenchyma. *Unum castigabis centum emendabis* (Rebuke one and correct a hundred). Therefore, an in-depth and detailed understanding of the underlying mechanisms responsible for the mediation of HCC during insulin resistance and identification of its genetic determinants would help in providing actual diagnostic and therapeutic tools of interventions.

METHODS

We have conducted a conventional systematic literature review study to identify the clinical, environmental, and genetic factors responsible for the association between NAFLD and HCC with a special focus on molecular pathogenesis and its application to develop newer diagnostic and therapeutic tools. Search engines such as PubMed, Google Scholar, Scopus, and Science Direct were used to obtain literature regarding e-waste management practices throughout the world. The search strategy included different terms for "Non-Alcoholic Fatty Liver Disease," "Hepatocellular carcinoma," "Genetic Factors," "Environmental factors," "Molecular factors," "Metabolic factors," "Novel Therapy," "Liver cancer," and "Novel diagnostics" as key words.

Inclusion criteria for the case studies, guidelines documents, reports, original and review articles, and other relevant documents retrieved and considered for the review were as follows:

1. Studies prescribing the data in the English language
2. Open access documents and reports available on the journal/websites
3. Studies dealing with a section on clinical, environmental, and genetic factors responsible for the association between NAFLD and HCC or molecular pathogenesis and its implementation to improve newer diagnostic and therapeutic tools.

Pathogenesis of NAFLD

The pathogenesis of NAFLD remains unclear, and understanding the mechanism is arduous. In fact, it is a complex condition

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that is believed to have multifactorial causation. Two hit hypotheses were frequently used to explain this complex mechanism of NAFLD: steatosis and fibrotic changes. Currently, multiple hit hypotheses are used to explain the mechanism as multiple factors act together in predisposing the person to the mentioned condition, such as the combination of environmental, genetic, and metabolic factors responsible for disturbance in lipid homeostasis and accumulation of excessive triglycerides in the liver. In addition to the above-mentioned factors, insulin resistance is responsible for the disease progression as it may lead to endoplasmic reticulum stress, lipotoxicity, and disturbance in autophagy, which ultimately induce hepatocyte injuries, death, hepatic inflammation, and progressive fibrogenesis[5].

Pathogenesis of HCC in association with NAFLD

Similar to the NAFLD, the occurrence of HCC among NAFLD cases is also a complex and multifactorial phenomenon that depends on the mechanisms described for chronic liver injuries, molecular imbalances associated with dysmetabolism and obesity such as the remodeling of adipocytes, lipotoxicity, adipokines secretion, and insulin resistance[4, 5]. Recent evidence suggest that the gut-liver axis plays an important role in the acceleration of the oncogenesis process among patients with NAFLD. Farnesoid X nuclear receptor has been established to possess significant metabolic effects and plays a significant role in producing histopathologic improvement in NASH that occurs through its pharmacological activation by obeticholic acid. Delineation of these mechanisms, hepatic fibrosis, and oncogenesis in NASH can assist in producing enhanced interventional strategies for the prevention, surveillance, diagnosis, and management of cancer among this population[6]. Hence, we purposed to detail and hypothesize the possible risk factors responsible for HCC in NAFLD. Possible risk factors are demographic factors such as age and gender; metabolic factors such as obesity, excessive insulin, and hepatic iron overload; environmental factors; and genetic factors resulting in advanced stages of fibrotic changes and cirrhosis.

Demographic factors

Age and gender

Hepatocellular carcinoma occurs at higher rates among males around the world irrespective of the etiology. Similar differences are seen in the development of NAFLD. Both age and gender differences are seen in their incidence and severity. NAFLD is most commonly observed in males among the younger age groups, whereas it is observed among the elderly females (>50 years)[7].

Environmental factors concerning metabolic factors

Obesity and type 2 diabetes mellitus

Obesity is one of the most common risk factors for NAFLD and type 2 diabetes mellitus (DM) due to insulin resistance. Asians have an increased risk of developing type 2 DM even with normal or low body mass index (BMI) as retaining a higher rate of central obesity in the absence of generalized obesity. This predisposes them to develop type 2 DM[8]. Association between obesity and NAFLD is depicted through the studies conducted among the patients who had undergone gastric bypass or bariatric surgery with a prevalence of NAFLD ranging from 85% to 98%[9]. A systematic review conducted in Asia, the United States, and Europe showed that the overweight and obese individuals had a significantly higher risk of developing HCC compared to the ones with normal or low BMI[10]. Also, the prevalence of NAFLD among type 2 DM cases is significantly higher, and they are at more risk of developing carcinomas[11].

Underlying pathophysiology

Potential mediators responsible for obesity-linked HCC include dysregulation of anti-inflammatory or pro-inflammatory cytokines, particularly the increased leptin or reduced adiponectin, lipotoxicity, and hyperinsulinemia, which stimulates insulin-like growth factor-1 (IGF-1). First of all, we would like to emphasize the adipocyte remodeling and secretion of cytokines. Obesity is usually characterized by the expansion and remodeling of adipose tissues that lead to a state of chronic inflammation, which is characterized by a different cytokine secretion pattern by the adipocytes. These cytokines include adiponectin and leptin. Other cytokines implicated are tumor necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-β), interleukin-6 (IL-6), and interleukin-1beta (IL-1β). TNF-α can induce many pro-oncogenic pathways and obesity by increasing its levels in both malignant and non-malignant tissues[12]. TNF-α and IL-6 were demonstrated to promote diethylnitrosamine-induced HCC in an experimental model of dietary-induced obesity that could be due to the upregulation of extracellular signal-regulated kinases (ERK) and STAT3 pathways[13].

Reduced adiponectin in obesity is responsible for suppressing the angiogenesis of the tumors and inhibits the growth and metastasis of HCC, whereas adiponectin acts through the activation of a tumor suppressor called 5′-adenosine monophosphate-activated protein kinase. It increases apoptosis of cells by regulating mammalian target of rapamycin pathway and c-Jun N-terminal kinase or caspase-3 pathway[14]. Leptin is known to

have potent pro-inflammatory and pro-fibrogenic activities. Its growth-promoting effects act through ERK, STAT3, Janus kinase (JAK), phosphatidylinositol 3-kinase (PI3K), or protein kinase-B (Akt) signaling pathways[13]. This counterpoise between the contrasting effects of adiponectin and leptin plays an important role in the oncogenesis associated with steatosis of the liver.

The liver is at risk of ectopic accumulation of lipids due to various factors, particularly the excess dietary lipids transported through portal veins among obese individuals. Inhibition of phosphatase and tensin homolog (PTEN) expression occurs due to excess collection of unsaturated fatty acids in hepatic cells. PTEN acts as a tumor suppressor and regulates PI3K signaling pathway that is either deleted or mutated in HCC[15].

Obesity causes both systemic and hepatic insulin resistance, which is further worsened by the accumulation of hepatic lipids. Excess insulin for a prolonged period promotes the IGF-binding protein production and increases the IGF-1&2 bioavailability[16]. This stimulates the development of cancer through activation of oncogenic pathways by involving mitogen-activated protein kinase (MAPK), PI3K/Akt, and vascular endothelial growth factor[17]. In addition, sterol regulatory element-binding proteins (an essential component in regulating lipogenesis) within the liver get activated by lipid accumulation in that crucial organ. Of note, in patients with cancer, this protein markedly induces lipogenesis and is linked to poor prognosis[18].

Iron overload

Excessive load of iron in the liver can cause serious insult and augment the risk of developing HCC. It occurs in patients with alcoholic liver disease, hereditary hemochromatosis, post-transplant cases, and HCC patients with a non-cirrhotic liver. Oxidative stress or genetic mutation can lead to necrotic inflammation and carcinogenesis of the liver. Finally, these patients are found to have a more than 200-fold risk of developing HCC[19].

CONCLUSIONS

In-depth understanding about the potential role of genetic predisposition, diet type, gut microbiota, and other environmental and metabolic factors linking the NAFLD and HCC has become crucial. Mostly genetic factors play a significant role in the NAFLD development and progression. The future studies focus on genetic epidemiology requires replication, expression studies, and animal models to understand the molecular role of the genetic variants. The understanding of genetic determinants may lead us to newer diagnostic and therapeutic approaches or interventions, which can prevent or control the progression of NAFLD to liver cancer.

AUTHORS' CONTRIBUTIONS

DT: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft. **IS**: Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **AP**: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft. **DS**: Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **PV**: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft. **PI**: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft. **JR**: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft. **CK**: Validation, Visualization, Writing – review & editing.

REFERENCES

1. European Association for the Study of the Liver; European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2012;56(4):908-43. https://doi.org/10.1016/j.jhep.2011.12.001
2. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55(2):74-108. https://doi.org/10.3322/canjclin.55.2.74
3. Fracanzani AL, Fargion S, Stazi MA, Valenti L, Amoroso P, Cariani E, et al. Association between heterozygosity for HFE gene mutations and hepatitis viruses in hepatocellular carcinoma. Blood Cells Mol Dis. 2005;35(1):27-32. https://doi.org/10.1016/j.bcmd.2005.03.007
4. Dongiovanni P, Romeo S, Valenti L. Hepatocellular carcinoma in nonalcoholic fatty liver: role of environmental and genetic factors. World J Gastroenterol. 2014;20(36):12945-55. https://doi.org/10.3748/wjg.v20.i36.12945
5. Arab JP, Arrese M, Trauner M. Recent insights into the pathogenesis of nonalcoholic fatty liver disease. Annu Rev Pathol Mech Dis. 2018;13:321-50. https://doi.org/10.1146/annurev-pathol-020117-043617
6. Arab JP, Karpen SJ, Dawson PA, Arrese M, Trauner M. Bile acids and nonalcoholic fatty liver disease: molecular insights and therapeutic perspectives. Hepatology. 2017;65(1):350-62. https://doi.org/10.1002/hep.28709

7. Hashimoto E, Yatsuji S, Tobari M, Taniani M, Torii N, Tokushige K, et al. Hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. J Gastroenterol. 2009;44(Suppl 19):89-95. https://doi.org/ 10.1007/s00535-008-2262-x
8. Hu FB. Globalization of diabetes: the role of diet, lifestyle, and genes. Diabetes Care. 2011;34(6):1249-57. https://doi.org/10.2337/dc11-0442
9. Feijó SG, Lima JM, Oliveira MA, Patrocínio RMV, Moura-Junior LG, Campos AB, et al. The spectrum of non alcoholic fatty liver disease in morbidly obese patients: prevalence and associate risk factors. Acta Cir Bras. 2013;28(11):788-93. https://doi.org/10.1590/s0102-86502013001100008
10. Larsson SC, Wolk A. Overweight, obesity and risk of liver cancer: a meta-analysis of cohort studies. Br J Cancer. 2007;97(7):1005-8. https://doi.org/10.1038/sj.bjc.6603932
11. Ahmed MH, Husain NE, Almobarak AO. Nonalcoholic fatty liver disease and risk of diabetes and cardiovascular disease: what is important for primary care physicians? J Family Med Prim Care. 2015;4(1):45-52. https://doi.org/10.4103/2249-4863.152252
12. Shetty K, Chen J, Shin JH, Jogunoori W, Mishra L. Pathogenesis of hepatocellular carcinoma development in non alcoholic fatty liver disease. Curr Hepatol Rep. 2015;14(2):119-27. https://doi.org/10.1007/s11901-015-0260-z
13. Park EJ, Lee JH, Yu GY, He G, Ali SY, Holzer RG, et al. Dietary and genetic obesity promote liver inflammation and tumorigenesis by enhancing IL-6 and TNF expression. Cell. 2010;140(2):197-208. https://doi.org/10.1016/j.cell.2009.12.052
14. Dalamaga M, Diakopoulos KN, Mantzoros CS. The role of adiponectin in cancer: a review of current evidence. Endocr Rev. 2012;33(4):547-94. https://doi.org/10.1210/er.2011-1015
15. Vinciguerra M, Carrozzino F, Peyrou M, Carlone S, Montesano R, Benelli R, et al. Unsaturated fatty acids promote hepatoma proliferation and progression through downregulation of the tumor suppressor PTEN. J Hepatol. 2009;5(6):1132-41.https://doi.org/10.1016/j.jhep.2009.01.027
16. Khandekar MJ, Cohen P, Spiegelman BM. Molecular mechanisms of cancer development in obesity. Nat Rev Cancer. 2011;1112:886-95. https://doi.org/10.1038/nrc3174
17. Alexia C, Fallot G, Lasfer M, Schweizer-Groyer G, Groyer A. An evaluation of the role of insulin-like growth factors (IGF) and of type-I IGF receptor signaling in hepatocarcinogenesis and in the resistance of hepatocarcinoma cells against drug-induced apoptosis. Biochem Pharmacol. 2004;68(6):1003-15. https://doi.org/10.1016/j.bcp.2004.05.029
18. Li C, Yang W, Zhang J, Zheng X, Yaho Y, Tu K, Liu Q. SREBP-1 has a prognostic role and contributes to invasion and metastasis in human hepatocellular carcinoma. Int J Mol Sci. 2014;15(5):7124-38. https://doi.org/10.3390/ijms15057124
19. Fargion S, Valenti L, Fracanzani AL. Role of iron in hepatocellular carcinoma. Clin Liver Dis (Hoboken). 2014;3(5):108-10. https://doi.org/10.1002/cld.350