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EDITORIAL

Nonalcoholic fatty liver disease, metabolic risk factors, and hepatocellular carcinoma: An open question

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Abstract

Non-alcoholic liver disease (NAFLD) defines liver abnormalities ranging from simple steatosis to nonalcoholic steatohepatitis with or without cirrhosis development, occurring in the absence of significant alcohol consumption, use of teratogenic medication, or hereditary disorders. The association between NAFLD and metabolic syndrome is well documented and widely recognized. Obesity, type 2 diabetes mellitus (T2DM), and dyslipidemia are the most common metabolic risk factors associated with NAFLD. Among the components of metabolic syndrome, current evidence strongly indicates obesity and diabetes as hepatocellular carcinoma (HCC) risk factors. There is also growing evidence that suggests an increased risk of HCC in NAFLD patients, even surpassing other etiologies in some high-income countries. Epidemiologic data demonstrate a parallel rise in prevalence of obesity, diabetes, NAFLD, and HCC. As obesity and its related diseases have steadily afflicted larger populations, HCC incidence is expected to increase in the future. Pathophysiologic mechanisms that underlie NAFLD development and subsequent progression to nonalcoholic steatohepatitis and cirrhosis (insulin resistance and hyperinsulinemia, oxidative stress, hepatic stellate cell activation, cytokine/adipocytokine signaling pathways, and genetic and environmental factors) appear to play a significant role in the development of NAFLD-related HCC. However, a comprehensive view of molecular mechanisms linking obesity, T2DM, and NAFLD-related HCC, as well as the exact sequence of molecular events, is still not understood in its entirety. Good-quality data are still necessary, and efforts should continue towards better understanding the underlying carcinogenic mechanisms of NAFLD-related HCC. In this paper, we aimed to centralize the most important links supporting these relationships, focusing on obesity, T2DM, and NAFLD-

related HCC, as well as point out the major gaps in knowledge regarding the underlying molecular mechanisms behind them.

Key words: Diabetes mellitus; Hepatocellular carcinoma; Metabolic syndrome; Non-alcoholic fatty liver disease; Obesity

Core tip: Nonalcoholic liver disease (NAFLD) comprises both simple steatosis or nonalcoholic fatty liver and nonalcoholic steatohepatitis, with or without cirrhosis. Recent data demonstrate a strong association between most features of metabolic syndrome and NAFLD. Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver, for which current epidemiologic data show an increased incidence in NAFLD patients. Basic research has identified pathways linking obesity, type 2 diabetes, systemic inflammation, NAFLD/nonalcoholic steatohepatitis, and HCC. However, more data are necessary in order to effectively establish these relationships, and perhaps pave the way for possible cures to prevent HCC in certain populations.

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INTRODUCTION

Nonalcoholic liver disease (NAFLD) defines liver abnormalities ranging from simple steatosis or nonalcoholic fatty liver to nonalcoholic steatohepatitis (NASH) with or without cirrhosis development. The current definition of NAFLD does not require secondary hepatic fat accumulation, such as significant alcohol consumption, use of steatogenic medication, or hereditary disorders[1-3]. Several studies have independently demonstrated a strong association between NAFLD and each feature of metabolic syndrome (MetS)[4-7]. Currently, all guidelines agree that NAFLD is strictly associated with metabolic risk factors[3], especially obesity, type 2 diabetes mellitus (T2DM), and dyslipidemia[2]. Although it has been suggested that NAFLD is a MetS hepatic feature[5,8,9], a study based on data analysis from 3846 subjects of the United States third National Health and Nutrition Examination Survey found that NAFLD is not an independent component or manifestation of MetS, but rather a condition strongly associated with MetS features[10].

Although being overweight and obese are preventable and modifiable conditions, their prevalence has increased globally in recent decades[11]. These conditions, as well as their related diseases such as T2DM, coronary heart disease, stroke, some cancer types, NAFLD, and osteoarthritis, have a large economic impact on the health care system[12-14]. There is numerous evidence that obesity is a risk factor for digestive cancers such as esophageal[15], colorectal[16-18], bile duct[13], pancreatic[12,19], and liver[12,18,20,21] cancer.

Primary liver cancer is a major contributor to global cancer incidence and mortality[22]. Worldwide, liver cancer is the fifth most common cancer and the second most frequent cause of cancer death in men, while in women it is the seventh most commonly diagnosed cancer and the sixth leading cause of cancer death[23]. Major risk factors for hepatocellular carcinoma (HCC), the most common histologic type of primary liver cancer, include hepatitis B virus (HBV) and hepatitis C virus (HCV) chronic infections, alcoholic liver disease, and NAFLD[24].

Several population-based studies conducted in various geographic areas have recorded a significantly increased incidence of HCC in patients with diabetes and obesity[12,18,20,21,25]. There is also growing evidence that suggests an increased risk of HCC in NAFLD patients[26-28]. Under these circumstances, NAFLD-related HCC incidence is expected to increase in the future.

Considering that obesity is preventable, and other metabolic features (*i.e.*, diabetes mellitus and dyslipidemia) can be "controlled", a question arises: "Can NAFLD, and consequently NAFLD-related HCC, be prevented in some way?" According to a perhaps overly simplistic interpretation, due to a present lack of a comprehensive view of multiple pathways involved in NAFLD-related HCC pathogenesis, the answer might be "Yes".

METABOLIC RISK FACTORS, NAFLD, AND HCC

Epidemiologic evidence

There is growing evidence that overweight and obesity, defined by the body mass index (BMI)[11], and MetS have reached a pandemic dimension. According to the World Health Organization, more than 1.4 billion adults (35% of adults) worldwide were overweight (BMI $\geqslant$ 25-29.9 kg/m^2), and of these, 500 million (13% of adults) were obese (BMI $\geqslant$ 30 kg/m^2), in 2008[29]. If overweight and obesity rates continue at their current pace, it is estimated that 3.3 billion adults (57.8% of adults) will become overweight or obese by 2030[30]. On the other hand, overweight and obesity are leading risks for overall mortality, accounting for approximately 3.4 million adult deaths each year. Additionally, they are responsible for 44% of the diabetes burden, 23% of the ischemic heart disease burden, and between 7%

and 41% of certain cancer burdens[11].

Although BMI is the most commonly reported index in epidemiologic studies, body fat topography, and especially truncal or central obesity, appear to be more important in pathophysiologic mechanisms that link obesity and cancer. Central obesity, measured by waist circumference or the waist-to-hip or waist-to-height ratios, is the key feature of most MetS definitions, and has also been known to be directly correlated with insulin resistance[31-33].

There is a strong evidence for the association between obesity and T2DM. According to results of a study that analyzed the United States third National Health and Nutrition Examination Survey 1999-2006 data, the prevalences of overweight and obesity among United States adults with diabetes were 80.3% and 49.1%, respectively[34]. Overweight and obesity are responsible for about 80% of cases of T2DM in most European countries[35]. The same parallel between obesity and T2DM rates was not observed in Asian populations, where the risk to develop diabetes begins even at a lower BMI. Despite lower rates of overweight and obesity than the United States or Europe, many Asian countries have similar or higher rates of T2DM. Higher prevalence of central obesity without necessarily developing generalized obesity in Asian populations may explain the increased T2DM predisposition among normal-weight individuals[36].

Current evidence strongly indicates that obesity and diabetes are HCC risk factors[37-40]. A meta-analysis of 11 cohort studies from Europe, the United States, and Asia showed that summary relative risks (SRRs) with 95%CI of HCC were 1.17 (95%CI: 1.02-1.34) for overweight and 1.89 (95%CI: 1.51-2.36) for obese individuals, compared with normal-weight individuals[41]. Similarly, a meta-analysis of 26 prospective observational studies including 25337 HCC cases reported that excess body weight (SRR = 1.48, 95%CI: 1.31-1.67) and obesity (SRR = 1.83, 95%CI: 1.59-2.11) are associated with an increased risk of HCC in both males and females[42]. The positive associations observed in that study were independent of geographic location, alcohol consumption, and history of diabetes or HBV and/or HCV infections. An evaluation based on a systematic review of nine cohort studies in a Japanese population indicates a relative risk of 1.74 (95%CI: 1.33-2.28) for overweight/obese individuals compared with normal/low-weight individuals[43].

The association between general obesity and the risk of HCC has been studied more than the relationship between central obesity and HCC risk. According to the results of a recent multicenter prospective European cohort study, central obesity promotes a high risk for HCC, as waist-to-height ratio showed the strongest association with HCC, independent of general body weight[44].

Epidemiologic studies estimate that diabetes is associated with a 2-4-fold greater risk of HCC compared with nondiabetics, independently of other major HCC risk factors[39]. In a large longitudinal study (173643 patients with diabetes and 650620 patients without) with a follow-up of 10-15 years, NAFLD incidence was significantly higher among patients with diabetes (incidence rate 18.13 *vs* 9.55 per 10000 person-years, respectively, $P < 0.0001$). Similarly, a significantly higher incidence of HCC among patients with diabetes was obtained (incidence rate: 2.39 *vs* 0.87 per 10000 person-years, respectively, $P < 0.0001$)[45]. A systematic review and meta-analysis of 26 studies (13 case-control and 13 cohort) published in 2006 by El-Serag *et al*[46] revealed a 2.5-fold greater risk of HCC among patients with diabetes compared with nondiabetic controls. This significant association was independent of alcohol use or viral hepatitis in studies that examined these factors. Another systematic review and meta-analysis, published in 2012 by Wang *et al*[47], showed slightly lower SRRs. Based on 25 cohort studies, this meta-analysis revealed that individuals with diabetes have a 2.0-fold increased risk of HCC, compared with nondiabetics (SRR = 2.01, 95%CI: 1.61-2.51).

Epidemiologic data demonstrate that both obesity and T2DM increases the HCC risk. NAFLD, which is present in up to 90% of all obese persons and up to 70% of T2DM patients[24], appears to play a key role in HCC development. In a large United States healthcare database study between 2002 and 2008, NAFLD was the most common underlying HCC risk factor (59%), followed by diabetes (36%) and HCV infection (22%)[48]. Similar results were obtained in a study performed in Germany, which identified NAFLD as the most common etiology for HCC, exceeding HBV and HCV chronic infection, as well as alcoholic liver disease[49]. These results could be explained by effective measures to reduce HCV infection incidence, the major source of HCC in the United States and other developed countries, together with increasing NAFLD prevalence in these geographic areas[50].

The majority of patients with NAFLD have fatty livers, and their liver-related death rate is significantly lower, while approximately 20% of NAFLD cases have NASH that may progress to cirrhosis (20%-45%), a well-recognized HCC risk factor[51,52]. On the other hand, most cases of HCC (80%-90%) occur in liver cirrhosis of various etiologies[24], and NAFLD seems to be no exception[22]. HCC development in cirrhotic NAFLD is well documented. Results of a recent meta-analysis showed an increased HCC risk for cohorts with NASH and cirrhosis (cumulative incidence between 2.4% over 7 years to 12.8% over 3 years)[28]. However, the HCC risk in NASH cohorts was substantially lower than in HCV-related cirrhosis cohorts according to this study. Recent epidemiologic evidence also suggests an association between noncirrhotic NAFLD and HCC risk[53-58]. Yet, several gaps were identified in current understanding of the epidemiologic evidence that support the occurrence of HCC in noncirrhotic and cirrhotic NAFLD: there were few large cohorts with

long-term follow-up, most studies were underpowered to perform multivariate analysis[28], few studies on ethnicity-dependent differences[59], and few studies to assess the quality of epidemiologic evidence.

In summary, epidemiologic data demonstrate a parallel increase in the prevalences of obesity, T2DM, and NAFLD-related HCC. Cumulatively, the epidemiologic evidence suggests an association between the main components of MetS (obesity and T2DM) together with NAFLD, and an increased HCC risk, which is better documented in NASH-cirrhosis cohorts.

Animal models

Findings from animal models are necessary for a better understanding of the complex inter-relationships between NAFLD, metabolic risk factors and HCC. Using a novel mouse model of NASH-HCC on a diabetic background *via* a combination of streptozotocin and high-fat diet (the STAM model), Fujii *et al*[60] demonstrated the inter-relationships between NAFLD/NASH, T2DM, and HCC development. This study provided strong evidence that NASH-related fibrosis is an essential histologic process for HCC development in diabetic populations.

In a recent study, Dowman *et al*[61] evaluated the liver-related consequences of long-term diet-induced obesity in a murine model of NASH, using the American Lifestyle-Induced Obesity Syndrome (ALIOS) based on high-fat/fructose diet and sedentary lifestyle. This study indicates that, in the absence of toxins or genetic variation, ALIOS mice developed NASH, stem cell mediated-regeneration, and HCC. Park *et al*[62] demonstrated in an experimental mouse model the key role of dietary or genetic obesity in HCC development, as well as the pathophysiologic mechanisms linking obesity, inflammation, and HCC.

Pathophysiologic link

Although there is a great amount of progress in understanding the carcinogenesis, the exact mechanism of HCC development in NAFLD has not yet been fully elucidated. However, several lines of evidence demonstrate a strong association between chronic inflammation and cancer, including HCC[63].

Dysregulation of both hormonal axes and cytokines pathways during obesity, diabetes, and NAFLD promotes a vicious cycle between metabolic and immune responses, inducing a chronic active inflammatory state that may lead to hepatocarcinogenesis. Thus, pathophysiologic mechanisms that underlay nonalcoholic fatty liver development and subsequent progression to NASH and cirrhosis (insulin resistance and hyperinsulinemia, oxidative stress, hepatic stellate cells activation, cytokine/adipocytokine signaling pathways, genetic and environmental factors)[64] have also been shown to promote the development of NAFLD-related HCC[38,40,55,57,65].

Insulin resistance and subsequent compensatory hyperinsulinemia have been shown to have a key role in the pathogenesis of NAFLD-related HCC[66]. The insulin-like growth factor (IGF) axis, closely linked to insulin resistance and hyperinsulinemia, plays an important role in HCC pathogenesis[67], particularly in NAFLD-related HCC[68].

The IGF axis includes three ligands (insulin, IGF-1, and IGF-2), three receptors (insulin receptor, IGF-1R, and IGF-2R), substrates [insulin receptor substrate (IRS) and Shc proteins], and ligand binding proteins[69,70]. Insulin resistance and hyperinsulinemia have been shown to upregulate IGFs and IRS-1 production[71], thus contributing to HCC pathogenesis[66]. IGF-1 is produced by several tissues such as liver, bone, muscle, and brain[70]. However, the liver is the main source of circulating IGF-1 during the postnatal period. IGF-1 synthesized in the liver acts as an endocrine growth factor, while IGF-1 synthesized by other tissues acts locally, in a paracrine and/or autocrine manner[72]. Yet, during hepatocarcinogenesis, IGF-1 secretion by adjacent hepatocytes may lead to paracrine stimulation of HCC and more aggressive tumor behavior[68].

IGF-1 can act on various receptors, but has a higher affinity for IGF-1R[70]. IGF-1R, a tyrosine kinase receptor, is overexpressed *in vitro* and in animal models of HCC, and is also involved in the degeneration of preneoplastic lesions[40]. However, insulin receptors and IGF-1R share almost the same signaling pathway[70]. Binding of insulin and IGF-1 to insulin receptors and IGF-1R, respectively, promotes liver carcinomatosis and tumor development by stimulating cell proliferation and inhibiting apoptosis. IGF-1 also promotes angiogenesis through increased vascular endothelial growth factor production[58,73,74].

IGF-2 is highly expressed in fetal liver, but its level decreases after birth. However, IGF-2 expression is increased in viral hepatitis and cirrhosis, as well as in HCC[69]. During hepatocarcinogenesis, IGF-2 has multiple protumorigenic functions such as inhibiting apoptosis, promoting cellular proliferation, and activating angiogenesis[74].

Another key component of the IGF axis and hepatocarcinogenesis is IRS-1, the main substrate of IGF-IR activation. IRS-1 is overexpressed in HCC and is also shown to be involved in cytokine signaling pathways[75].

Oxidative stress and cytokine/adipocytokine pathways are two other important links in NAFLD-related HCC pathogenesis. The development and progression of NAFLD is also associated with oxidative stress and release of reactive oxygen species (ROS), which likely contribute to the development of HCC[38]. Existence of preneoplastic changes such as increased hepatocyte proliferation and decreased apoptosis have been documented in the steatotic liver of *ob/ob* mice, before fibrosis or cirrhosis occurs. Because hepatic mitochondrial production of ROS is significantly

increased in *ob/ob* mice, it has been suggested that oxidative stress is one of the mechanisms driving hepatocyte proliferation in nonalcoholic fatty livers[76].

Increased oxidative stress induced by hepatic mitochondrial, peroxisomal, and microsomal ROS[77,78] results in apoptosis, necrosis, inflammation, hepatic stellate cell activation and fibrogenesis, proinflammatory cytokine expression, and cell proliferation[26,79]. Direct effects of ROS, generally attributed to high concentrations at the damage site, include DNA alteration that leads to genomic instability and mutations in proto-oncogenes and tumor suppressor genes, thus fostering neoplastic transformation[80]. An eloquent example is the product of lipid peroxidation, trans-4-hydroxy-2-nonenal, which has been shown to be responsible for mutations of the *p53* tumor suppressor gene, the most frequent abnormality identified in human tumors, including HCC[81]. In addition, ROS can stimulate signal transduction pathways and lead to activation of key transcription factors such as nuclear respiratory factor (Nrf) and nuclear factor (NF)-κB. Nrf1-deficient hepatocytes in an animal model showed increased susceptibility to oxidative stress and damage, resulting in NAFLD and HCC[82]. Inhibition of NF-κB in mouse livers induces NASH and HCC by sensitizing hepatocytes to spontaneous apoptosis[38]. In the setting of hyperinsulinemia, ROS plays an important role in the activation of c-Jun amino-terminal kinase 1 (JNK1). JNK1 appears to be the most important kinase that is upregulated in NAFLD-related HCC[83]. On the other hand, ROS trigger the release of proinflammatory cytokines, which in turn enhance ROS production and cellular injury[84].

The role of proinflammatory cytokines including tumor necrosis factor (TNF)-α, interleukin (IL)-6, leptin, and resistin, as well as the role of decreased amounts of adiponectin in NAFLD development and progression, is well documented[4,5,85-87]. TNF-α activates pro-oncogenic pathways, including JNK, NF-κB, mammalian target of rapamycin, and the extracellular signal-regulated kinases, thus enhancing the production of IL-6[40,87]. IL-6 intracellular signaling involves a complex network of various pathways, including phosphoinositide 3-kinase/protein kinase B, mitogen activated protein kinase, and signal transducer and activator of transcription 3, which lead to cell proliferation, protection from apoptosis, and increased metastatic potential[88]. Adiponectin has been shown to have hepatic cytoprotective properties, improving both hepatic and peripheral insulin sensitivity, and preventing steatosis, inflammation, necrosis, and fibrosis[64]. Animal model studies have shown that hypoadiponectinemia is involved in HCC development[89].

Genetic and environmental factors, as well as the interaction between them, may be responsible for both the individual susceptibility and the clinical course of NAFLD. Recent studies emphasize the role of specific genetic variation in NAFLD susceptibility and NAFLD-related hepatocarcinogenesis. To date, several genetic variants that contribute to NAFLD susceptibility and its progression were identified by genome-wide association studies. Additionally, genetic risk factors for NAFLD were evaluated and validated in large multicenter studies[90,91]. In 2008, two genome-wide association studies independently identified several single nucleotide polymorphisms that are associated with increased hepatic fat content[92] and elevated plasma liver enzyme levels[93]. Romeo *et al*[92] identified a non-synonymous coding single nucleotide polymorphism (rs738409 C/G) that results in an isoleucine to methionine substitution at residue 148 (I148M) in human patatin-like phospholipase domain-containing 3 (*PNPLA3*), which is strongly associated with increased hepatic fat levels. This study also demonstrated that variation in *PNPLA3* contributes to inter-individual differences in hepatic fat content and NAFLD susceptibility. Moreover, it has been shown that the *PNPLA3* I148M polymorphism favors NAFLD progression and liver fibrosis[94], is associated with an increased risk of HCC in severely obese individuals[95], and confers an increased risk of NAFLD-related HCC[96].

In summary, the interplay, interaction and overlapping of all pathogenic pathways creates a vicious circle that leads to NAFLD-related HCC development.

CONCLUSION

Although significant progress has been made in NAFLD-related HCC, many issues remain to be resolved. A unified and comprehensive view of multiple pathways involved in NAFLD-related HCC pathogenesis is currently lacking.

Uncovering the intricate molecular pathways facilitating HCC development will pave the way for developing molecular therapeutic agents aimed at the receptors and specific signaling agents involved. Additionally, preventing obesity, diabetes, MeTs, and NAFLD through efficient measures might lead to a decreased rate of NAFLD-related HCC.

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