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Chapter 6

Metabolic Risk Factors in Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is the most frequent primary malignancy of the liver and it is one of the leading causes of cancer-related deaths worldwide. The global burden of hepatocellular carcinoma is growing nowadays. Most cases of hepatocellular carcinoma develop in the background of chronic hepatitis C and B and liver cirrhosis-well-known risk factor. But despite the reducing incidence of chronic hepatitis infections, an increase in the incidence of hepatocellular carcinoma was observed in the last decades. This could be explained by the increasing prevalence of obesity, type 2 diabetes mellitus, nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH), which are becoming important risk factors in hepatocellular carcinoma. Regular surveillance, as performed for patients with viral hepatitis, is required for patients with metabolic risk factors.

Keywords: hepatocellular carcinoma, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis

1. Introduction

Hepatocellular carcinoma (HCC) is one of the dominant histopathological types of liver cancer, accounting for almost 90% of primary liver cancers worldwide, it is the sixth most common cancer and it is the third cause of cancer-related deaths worldwide [1]. Despite the decreasing incidence of HCC related to viral hepatitis, an increase in the incidence of HCC was observed especially in Europe and America [2]. The global burden of hepatocellular carcinoma in 2012 was of 14 million cases and it is predicted to grow to 22 million over the next two decades.

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The most common and known risk factor for HCC are viral infection, virus B or C, toxic factors - alcohol and aflatoxin and immune diseases like primary biliary cirrhosis. There is an increasing number of HCC developed on liver metabolic diseases, including NAFLD and NASH, based on epidemiological evidence that shows a relationship of these diseases with an incident of HCC, regardless of the common known risk factors like alcohol consumption or chronic viral hepatitis.

It is not surprising the growing interest in the last few years on the mechanisms underlying the transition from liver metabolic disorders to HCC that is involving these new metabolic risk factors that include inflammation, insulin resistance, lipid and bile acids metabolism and the gut microbiota. A better understanding of the impact of these factors on the liver microenvironment may have potential benefit on the management of liver disease [3].

Metabolic syndrome has been associated with an increased risk of HCC and each component of this syndrome may increase cancer risk and also a synergic effect has been described [4, 5]. Overweight and obesity are well recognized independent risk factors for HCC, visceral adiposity showing stronger association with HCC risk than general body weight [6, 7]. Studies demonstrated that obesity may also influence HCC prognosis, Body Mass Index (BMI) seems to be a predictor of microvascular invasion and poor prognosis, while visceral adiposity is associated with HCC recurrence after treatment [8, 9]. Type 2 diabetes mellitus has been recognized in various studies as an important independent risk factor for HCC regardless of alcohol consumption [10]. Hyperlipidemia and hypertension are two additional components of metabolic syndrome that have been studied as risk factors for HCC, and hypertension seems to be related to a higher risk of HCC, whereas the relation between HCC and hyperlipidemia remains controversial [4, 5]. Also, synergism between the new risk factors and traditional risk factors has to be considered, for example, a strong synergic effect of alcohol abuse and type 2 diabetes mellitus has been described, also diabetes and obesity have been reported to enhance the risk of HCC in patients with chronic hepatitis [11, 12].

Non alcoholic fatty liver disease (NAFLD) is one of the most common cause of chronic liver disease and include a large spectrum of chronic liver disorders ranging from simple hepatic steatosis with no evidence of hepatocellular injury to non-alcoholic steatohepatitis (NASH), advanced fibrosis, cirrhosis and liver failure and currently, all guidelines agree that NAFLD is associated with the increasing percentage of obesity, type 2 diabetes mellitus, hypertension and dyslipidemia in our population [13, 14]. Several studies have demonstrated a strong association between NAFLD and each components of metabolic syndrome and there is enough evidence to define NAFLD itself as a liver component of metabolic syndrome [15–19, 46].

The rising incidence of NAFLD/NASH worldwide led to an important rise in HCC incidence related to these chronic liver diseases [3]. Many studies have demonstrated over the years that NAFLD can lead to hepatic fibrosis and cirrhosis, increasing therefore the risk for developing HCC [20, 21]. Among these patients with Non alcoholic fatty liver disease or non-alcoholic steatohepatitis, studies show that the third cause of death is liver disease, and HCC represents the main cause of death in these patients [20–23]. The incidence rate for developing HCC in patients with NASH related hepatic cirrhosis is up to 27% in retrospective studies [24]. Increased incidence of HCC was also been reported in patients with NAFLD in the absence of hepatic cirrhosis, and several risk factors for HCC development have been identified [6, 25–29].

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2. Natural history: Progression from hepatic steatosis to HCC

The term nonalcoholic fatty liver refers to a variety of liver disease that ranges from simple isolated hepatic steatosis, to non-alcoholic steatohepatitis with or without cirrhosis, and progression to HCC.

Although NAFLD diagnosis can be made by imaging (ultrasound or magnetic resonance), biopsy still remain the gold standard for diagnosis. Histology generally displays the accumulation of triglycerides in hepatocytes, usually in mixed macrovesicular or microvesicular droplets, in the absence of alcohol abuse, steatogenic medication or hereditary disorders [30].

The prevalence of NASH is difficult to determine because biopsy is required, with specific criteria such as steatosis, hepatocellular injury, mainly in the form of ballooning, and lobular inflammation, and once cirrhosis is present, NASH may be difficult to evaluate because often the fatty deposition disappear. Liver fibrosis may be present in non-cirrhotic NASH, initially in perisinusoidal acinar zone 3 [31]. Because of the need of histopathologic confirmation, NASH is most likely underdiagnosed and it may be misclassified as cryptogenic cirrhosis, which shares the same risk factors including diabetes and obesity [32, 33, 46]. Therefore, to estimate correctly the prevalence of NASH, a novel NASH category including obese patients with cryptogenic cirrhosis or with unknown HCC etiology has been proposed.

The prevalence of NAFLD and NASH is variable and it is depended on the method of diagnostic used to confirm the disease, and it is usually underreported because of the asymptomatic nature and can be underestimated and poorly treated.

NAFLD is present in more than 25% of adult population and about 10 to 20% of NAFLD patients may progress to NASH, which may progress to cirrhosis in 20–45% of cases, and cirrhosis is a well-known risk factor for HCC, and approximately 7% of patients with NASH-related cirrhosis may progress to HCC within 6 years [31].

Patients with nonalcoholic steatohepatitis are more susceptible to develop progressive advanced liver disease when compared to benign course of simple hepatic steatosis. In a study that included 420 patients with NAFLD/NASH, it was demonstrated a higher mortality in these patients when compared to the general population and also liver-related deaths occurred in 13% compared to 1% in general population, and 3% of patients with NAFLD developed hepatic cirrhosis. [34] Another study showed increased rates of hepatic cirrhosis in patients with non-alcoholic steatohepatitis (25%) compared to patients with fatty liver without non-alcoholic steatohepatitis (3%), and also showed an increased risk of liver disease related death in these patients (11% *vs* 2% in patients with fatty liver without NASH) [35].

Patients with compensated liver cirrhosis related to non-alcoholic steatohepatitis present with better survival outcomes compared to patients with HCV related cirrhosis, but in the presence of uncompensated liver cirrhosis poor prognosis was observed in both populations [36, 37], and currently, both, the American and European Associations for the Study of Liver Diseases, recommend screening for HCC in all patients with non-alcoholic steatohepatitis related cirrhosis [38].

Evidence from studies suggests that an important proportion of patients with NAFLD-associated HCC, do not have histologic evidence of liver cirrhosis. In one study from 1168

patients that underwent hepatic surgery for HCC, 6 out of 8 patients with NASH-related HCC did not had any histopathological evidence of liver cirrhosis and also the study suggested that the presence of hepatic cirrhosis in NASH-related HCC patients is lower compared to HCV-related HCC [29].

In another study that analyzed 128 patients with HCC recruited over a period of 12 years, it was reported that a significant number of patients with NASH developed HCC in the absence of fibrosis when compared to HCC of other etiology [39]. To explain this phenomenon in non-cirrhotic NAFLD patients, one proposed hypothesis is the malignant transformation of liver cell adenoma, and there are some published reports that have suggested that in the presence of metabolic syndrome features, liver cell adenoma may incur a malignant transformation [40, 41].

In the last years, many studies tried to establish the relationship between NAFLD and NASH, cryptogenic cirrhosis and HCC. The true prevalence of NASH and NASH-related HCC is probably underestimated due to the asymptomatic nature of the disease, and in up to 29% of HCC cases, the underlying etiology of liver disease remains unknown or are considered as cryptogenic cirrhosis [40]. Histopathological features that are suggestive for non-alcoholic steatohepatitis are more frequently observed in patients with HCC of unknown etiology than in patients with HCC related to chronic viral hepatitis or alcoholic etiology [32]. Even if the true prevalence of NAFLD/NASH-related HCC is not yet well defined, the increasing incidence of obesity and diabetes, suggests that the incidence NAFLD/NASH-related HCC will continue to grow in the next years, and there are already numerous studies that are investigated the relation between these diseases [46].

3. Metabolic risk factors, NAFLD and HCC

It is established that HCC and NAFLD share many risk factors and the development of HCC in NAFLD/NASH patients is probably multifactorial and involves low grade chronic systemic inflammatory response, excessive fat accumulation and insulin resistance [40, 46].

3.1. Obesity

There is more evidence that overweight and obesity and metabolic syndrome have reached a epidemic proportion over the last decades, and there are evident data that show that 80% of NAFLD patients are overweight or obese [42]. According to the World Health Organization, in 2008, more than 35% of adults worldwide are overweight, and of these, 13% are obese [29] and if overweight and obesity rates continue at their current ascending trend, it is estimated that more than 3.3 billion adults will become overweight or obese by year 2030 [43].

Overweight and obesity are leading risk factors for overall mortality, accounting for more than 3.4 million adult deaths every year, and are considered risk factors for 44% of the diabetes, 23% of the ischemic heart disease, and between 7 and 40% of certain cancer [42].

Body Mass Index is the most commonly used index in epidemiologic studies, but body fat topography, and especially central obesity, seems to be more important in pathophysiologic mechanisms that connect obesity to cancer. Central obesity, is the key feature in most metabolic syndrome definitions, and has also been directly correlated with insulin resistance [44, 46].

Obesity have been associated with disproportion between visceral and subcutaneous adipose tissue and with chronic inflammatory state due to adipokine imbalance that is defined as increased levels of leptin and decreased levels of adiponectin. Furthermore, obesity has been associated with other risk factors including insulin resistance, increased hepatic lipid storage and alteration of intestinal flora [46].

Adipokine imbalance as mentioned before occurs with simultaneous increased leptin and decreased adiponectin levels resulting in a pro-inflammatory and pro-oncogenic state. Both leptin and adiponectin are hallmarks of obesity, and have been extensively studied and both have been related to NAFLD and progression to liver cancer.

Leptin is secreted by adipose tissue and acts as a hormone and it is involved in the process of satiety. High levels of leptin and resistance to its action are observed in obese persons. Leptin has been demonstrated to be implicated in NAFLD progression, liver fibrosis, NASH and eventually in the carcinogenesis process of HCC through multiple molecular mechanisms. And these mechanisms are the activation of JAK2/STAT3, PI-3 K/Akt, ERK pathways and the inhibition of the TGFβ1-induced apoptotic pathway [24]. For example, the activation of Akt pathway was observed in about 40% of HCC patients. Leptin's role is to have growth factor-like activities on hepatic cells and HCC cells, and also have proinflammatory, profibrogenic and proangiogenic role on liver microenvironment and also it is implicated in the process of cell growth, angiogenesis and metastasis [31].

Adiponectin is the most abundant hormone of adipose tissue and has well known metabolic functions, having anti-inflammatory, antifibrotic, antiangiogenic, and antiproliferative activities on the liver microenvironment. Adiponectin exerts antifibrotic effects on hepatic cells through activation of the signaling AMPK axis and inhibition of TGFβ-mediated profibrogenic gene expression, and in addition, adiponectin may also induce apoptosis of hepatic cells. The anti-inflammatory activity of adiponectin is mostly related to inhibition of NFkB signaling axis [31]. A direct effect of adiponectin on HCC cells has also been described, induces apoptosis and inhibits HCC cell proliferation and migration. In addition, adiponectin prevents HCC development by activation of the AMPK signaling pathway and consequent modulation of mTOR and JNK/caspase 3 axis, resulting in growth cell inhibition and enhanced apoptosis [4]. A number of observations support the reduced adiponectin levels observed in obese patients and were associated to increased incidence of hepatic steatosis, fibrosis and accelerated progression to HCC [45].

3.2. Insulin resistance

Insulin resistance it is another important component of the metabolic syndrome, and along with obesity, is involved in the chronic inflammatory state directly linked to NAFLD. Insulin

resistance is also related to oxidative stress, which has the most important role in carcinogenesis in the presence of NAFLD and NASH.

Epidemiologic studies show that diabetes is associated with an increased risk of developing HCC compared with non-diabetics patients, regardless of other HCC risk factors and also seems to be independent of obesity [47]. In a large study conducted on patients with and without diabetes, with a follow-up period of 10–15 years, NAFLD incidence was significantly higher among patients with diabetes and a significantly higher incidence of HCC among patients with diabetes was observed [7]. Meta-analysis published over the years, revealed a 2 to 3-fold greater risk of HCC in patients with diabetes compared with non-diabetic patients, and this significant association was reported independent of alcohol abuse or chronic viral hepatitis in studies that examined these factors [48, 49].

Epidemiologic data demonstrate that both obesity and type 2 diabetes mellitus have increases the risk for HCC, and NAFLD, which is present in up to 90% of obese persons and up to 70% of type 2 diabetes mellitus patients [24], appears to play an important role in HCC development. NAFLD is nowadays considered the most common risk factor for HCC, followed by type 2 diabetes and it is exceeding the incidence of chronic viral infections and alcoholic liver disease [48, 50]. These can be explained by effective measures to reduce HCV infection incidence, which was the major cause of HCC in the United States and in other developed countries, and also can be explained by the increasing prevalence of NAFLD in these areas [51].

The strong relationship between visceral obesity and insulin resistance (IR) is well known, but insulin resistance is not related only to adipose tissue, in fact, liver accumulation of fatty acid metabolites can induce hepatic insulin resistance. One of the main fatty acid metabolite involved in hepatic insulin resistance is diacylglycerol (DAG) and it has been proposed as a predictor for hepatic insulin resistance [52]. The consequent hyperinsulinemia downregulates s expression of IRS2 in the hepatic cells increasing hepatic insulin resistance and in addition, insulin stimulates lipogenesis through activation of SREBP-1c, inducing, in a vicious circle with further fat accumulation and insulin resistance [31]. The liver microenvironment may induce insulin resistance also in other tissues, in fact, an increase in liver fat content may be considered a very strong predictor of insulin resistance in skeletal muscles, hepatic and adipose tissue, regardless of adiposity. In conclusion, liver fat content may predict the development of metabolic syndrome or diabetes, and the underlying mechanism may be the altered gene expression and protein synthesis and secretion also observed in NAFLD [53]. It is known that hyperinsulinemia occurs as a response to insulin resistance, and that is considered a risk factor for liver fibrosis and HCC development by activation of hepatic stellate cells, by dysregulation in the proliferation-apoptosis balance in hepatic cells, and by stimulation of angiogenesis. The most studied mechanism involved in NAFLD-related HCC is the IGF signaling axis that has a growth factor-like activity on hepatic cells and also a pro-angiogenic activity on the hepatic vascular system. Dysregulation of the IGF signaling axis has an important role in hepatic carcinogenesis and it is represented by the low levels of IGF1 in serum and overexpression of IGF-II. Insulin receptors (IRS) bind to insulin or IGF and share the same pro-oncogenic pathways with IGF1 receptor (IGF1R), including the activation of P13K/Akt and MAPK [54, 55].

3.3. Lipotoxicity

Increased lipid accumulation in the liver arises from lipolysis within peripheral adipose tissue, dietary sources and de novo hepatic lipogenesis, and this increased lipid accumulation causes hepatic lipotoxicity resulting in the excessive production of saturated and monounsaturated free fatty acids (FFAs) [40, 46, 56]. These FFAs undergo β-oxidation leading to formation of reactive oxygen species that will further induce mitochondrial damage, endothelial reticulum stress, and gene transcription promoting inflammatory cell signaling pathways.

As a result of the hepatic insulin resistance an increase in the liver of free fatty acids (FFAs) is observed, mainly due to dysregulation of the lipolysis and lipogenesis balance, resulting lipotoxicity that will determine chronic damage to hepatic tissue [51]. But, lipotoxicity is not due only as consequence of the excessive accumulation of FFAs in the liver, and the modification of lipid composition is another contributor to lipotoxicity, and recent studies are aimed at searching for specific metabolic changes as potential signatures of development of HCC in patients with NAFLD [57]. For example, some studies show that, during natural history of progression from normal liver to NAFLD or NASH, the ratio of polyunsaturated fatty acids (PUFAs) is increased in NASH, and phosphatidylcholine (PC) levels are reduced in both NAFLD and NASH, and based on these observations, it has been suggested that the LPA signaling axis may be one of the mechanism that is connecting hepatic steatosis to HCC [58–61].

3.4. Microbiota: Intestinal flora dysregulation

The basis for the ongoing interest on the role of gut microbiota in progression of NAFLD was the observation of fatal NASH that occurred in patients undergoing jejunoileal bypass in bariatric surgery and the reversal after metronidazol therapy [62]. There are several evidences that demonstrate a high prevalence of small intestinal bacterial overgrowth in patients with NAFLD/NASH and that also demonstrate the role of microbiota modifications in the development of NAFLD and NASH [45]. Specific microflora changes may play an important role in progression of hepatic steatosis, especially in obese patients. In patients with NAFLD and NASH was observed a difference in microbiota composition compared with healthy population [63, 64]. The mechanisms implicated in the progression of gut microbiota-related NAFLD and NASH and HCC are: alteration of intestine permeability, persistent activation of innate immune system with consequent chronic inflammation, changes in bile acid metabolism [65].

Patients with NAFLD or NASH show increased levels of lipopolysaccharides (LPS), a known innate immune system activator, on serum confirming the inflammatory state associated with this conditions and alteration in gut permeability with disruption of intercellular tight junctions observed in patients with NAFLD can contribute directly to lipopolysaccharides action to the liver [65, 66].

All these findings were confirmed in human study wherein increased LPS-binding protein (LBP) levels were observed in obese patients with NAFLD and even more in obese patients with NASH, correlating with liver TNFα increased expression [67].

All these mechanisms show how changes in the microbiota, in combination with loss of innate immune sensors, may induce metabolic liver disorders.

Gut microbiota also influences bile acid metabolisms mainly through the stimulation of the bile-acid-activated nuclear receptor and also by interacting with farnesoid X receptor (FXR) which induce excretion of bile acids from the liver and production of antimicrobial peptides [65].

4. Conclusions

Although significant progress has been made in NAFLD/NASH related HCC, many issues still remain to be resolved. With the prevalence of HCV declining in the last years, the incidence of NAFLD/NASH is expected to account for a greater proportion of HCC incidence in the near future due to the growing epidemic of obesity, diabetes and metabolic syndrome, known as independent metabolic risk factors for development of HCC. The annual incidence rate of HCC developed in patients with NASH-related cirrhosis is not yet clearly established and recent evidence show that a significant number of patients with NAFLD or NASH progress to HCC in the absence of hepatic cirrhosis. NAFLD/NASH-related cirrhotic patients receive significantly less surveillance for HCC than those with HCV-related cirrhosis, in contrast to epidemiological data and this represents an important public health problem. Also dysbiosis play an important role in progression of liver disease via changes in bile acids metabolism and dysregulation of intestinal barrier.

In conclusion, metabolic syndrome comprising of obesity, type 2 diabetes, dyslipidemia, hypertension, is related with an increased risk for development of HCC. NAFLD considered the liver manifestation of metabolic syndrome is an important factor implicated in progression to HCC. Also alteration in gut microbiota seems to be connected with HCC occurrence but many questions still remain to be answered.

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Conflict of interest

The authors declare no conflict of interest regarding this review.

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