

## Hepatocellular carcinoma and metabolic syndrome: The times are changing and so should we

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### Abstract

Although hepatocellular carcinoma (HCC) is as prevalent as ever as a cancer-related mortality, and some would even argue that it is increasing, the pattern of its etiologies has been changing. Specifically, the domination of viral hepatitis C virus is being overcome, partly because of the emergence of the antiviral treatments, and partly because of the significant increase, especially in developed countries, of the combination of obesity, diabetes, metabolic syndrome, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. This editorial will explore the interconnection of this group of diseases and how they are linked to HCC. More importantly, it will argue that this shift in HCC etiology essentially means that we have to change how we approach the treatment of HCC, by changing our focus (and resources) to earlier stages of the disease development in order to prevent the appearance and progression of HCC.

**Key words:** Hepatocellular carcinoma; Diabetes; Obesity; Steatosis; Non-alcoholic fatty liver disease; Body-mass index; Non-alcoholic steatohepatitis

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**Core tip:** There is a changing landscape whereby metabolic syndrome and non-alcoholic fatty liver disease and non-alcoholic steatohepatitis have replaced hepatitis viral infections and alcohol as the predominant causes of cirrhosis and hepatocellular carcinoma (HCC) on the global scale. As such, we need to change the treatment focus and address metabolic syndrome and its elements in an effort to intervene more timely in the development of cirrhosis and HCC.

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver, whereas among all types of cancers HCC is the fifth most common with an aggressive nature that had it ranking second in 2012 in terms of causes of cancer-related death in the world<sup>[1,2]</sup>. The prevalence and aggressiveness of HCC have led to a world-wide interest and an increasingly multidisciplinary approach with the use of new technologies and molecular analysis with the hope of achieving a more patient-targeted approach. From a surgical standpoint, the armamentarium available has been increasing with examples such as hepatic resection, microwave or radiofrequency ablation, transarterial chemoembolization, irreversible electroporation, and of course liver transplantation (LT). The latter is especially important as HCC frequently coexists with cirrhosis and LT represents a treatment for both. Unfortunately, the lack of donors has led to efforts to expand the donor pool with the use of Donors after Cardiac Death, split grafts, living related and expanded criteria grafts, all of which necessitate careful donor and recipient selection and matching. Despite all these efforts, HCC remains a formidable opponent and the only significant victory that we have been able to enjoy in this last decade is the advent of the latest all oral, ribavirin- and interferon-free regimens of direct acting antivirals against the hepatitis C virus (HCV) which have achieved 90% sustained virological response, which is essentially a cure<sup>[3]</sup>. The fact that this is for all genotypes, has led to LT actually providing a cure for HCV, rather than a short interlude from an aggressive recurrence; at the same time, it is part of a big change in the landscape of HCC etiology and management.

## CHANGING LANDSCAPE OF HCC

Specifically, the progress having to do with the HCV epidemic and the persistent increase in obesity, diabetes, non-alcoholic steatohepatitis (NASH), and non-alcoholic fatty liver disease (NAFLD) have allowed metabolic syndrome (MetS) to take the reins regarding factors and diseases affecting the liver and eventually leading to HCC<sup>[4]</sup>.

### *Defining NAFLD and NASH*

Before proceeding any further it is important to present some of the definitions of the terms used. The reason is that very frequently the term NAFLD is associated and may be used interchangeably with the other terms such as NASH or "hepatic steatosis", which is not correct as there are significant differences with clinical implications. The term "hepatic steatosis" refers to the presence of micro- or macro- or mixed vesicular fat in the cytoplasm of the hepatocytes<sup>[5]</sup>. Using the American Association for the Study of Liver Diseases guidelines for the definition of NAFLD we need to establish primary hepatic steatosis (confirmed either by imaging or biopsy), while at the same time exclude any secondary causes of hepatic steatosis (medications, alcohol, hereditary)<sup>[6]</sup>. NASH represents an extension of NAFLD, whereby the presence of primary hepatic steatosis (need more than 5%) leads to inflammation and hepatocellular injury (ballooning), and is the form that can actually progress to fibrosis, cirrhosis and HCC<sup>[7]</sup>. Today, NAFLD represents the most common chronic liver disease worldwide. It constitutes an epidemic with prevalence in adults in developed countries somewhere between 30%-50%, with the main obstacle in finding a more concise measurement being the difficulties in the diagnostic methods between the different studies<sup>[8-10]</sup>. NAFLD is frequently associated with obesity, type II diabetes mellitus (T2DM), and dyslipidemia, all of which are components of the MetS<sup>[11,12]</sup>. The definition of MetS developed over time and through different medical associations, such as the International Diabetes Federation (IDF), World Health Organization and the United States National Cholesterol Education program Adult Treatment Panel. Eventually this led to the Harmonized (consensus) definition in 2009 incorporating those of the IDF and the American Heart Association, which includes any three of the following: (1) Waist circumference: According to population and country-specific definitions; (2) Triglycerides:  $\geq 150$  mg/dL (1.7 mmol/L); (3) High density lipoprotein cholesterol:  $< 40$  mg/dL (1.03 mmol/L) in men and  $< 50$  mg/dL (1.29 mmol/L) in women; (d) Blood pressure:  $\geq 130$  mmHg systolic;  $\geq 85$  mmHg diastolic; and (5)

Fasting glucose:  $\geq 100$  mg/dL (5.6 mmol/L) or use of medication<sup>[13]</sup>.

### **Epidemiology of NAFLD and NASH**

The relation between NAFLD, and as an extension NASH, and MetS is a complex one. In the past, NAFLD was viewed as the hepatic component of MetS given its relationship with obesity and insulin resistance. Over time we have essentially seen that this is a two-way street, as on the one hand NAFLD can lead to T2DM and its relation to obesity and the lipid abnormalities combined with the hepatic inflammation can lead to MetS. On the other hand, the various manifestations of MetS can lead to a deterioration of NAFLD and move towards NASH, fibrosis, cirrhosis and eventually HCC<sup>[13,14]</sup>. As complex as the relationship between NAFLD/NASH and MetS may seem, that of NAFLD/NASH to HCC is a much more straightforward one. Currently, NAFLD-related cirrhosis or NAFLD-related HCC are the second cause of LT in the United States, whereas NAFLD is responsible for somewhere between 5%-20% of HCC cases in the Western world<sup>[15,16]</sup>. This is depicted in an excellent study by Younossi *et al*<sup>[17]</sup> who aim to identify the global prevalence of NAFLD and NASH, while at the same time describing their natural history and progression. By looking at reports between the years 1989 and 2015, they arrive at three main conclusions: (1) There is a significant global burden of NASH and a global prevalence of NAFLD of 25% with a geographical variation. This last point could have to do with genetic and cultural differences which can certainly play a role in shaping body mass; (2) The progression of fibrosis that can be seen in NAFLD and NASH is very slow with these patients having a  $> 50\%$  chance of non-liver related mortality<sup>[17]</sup>. The incidence of HCC among NAFLD patients is very low at a frequency of 0.44/1000 person-years; however, the prevalence of NAFLD in the population makes up for that, and as a result NAFLD by affecting over 1 billion adults world-wide remains a basic cause of LT<sup>[18]</sup>; and (3) Despite the fact that liver-related events may be responsible for only a small fraction of deaths in NAFLD and NASH patients, NASH is rapidly becoming the most common etiology of liver-related death globally.

The above findings present an association between a metabolic disease predominantly and a type of cancer. This is quite intriguing, especially if we consider that the mechanism is not completely clear. Alterations in gene expressions may play a significant role, as a high number of them were observed during the progression from steatosis to NASH, with special emphasis on the fibrosis and inflammation aspects<sup>[19]</sup>. As part of this progression towards cirrhosis and, eventually, HCC, extracellular matrix and angiogenesis genes are up regulated, whereas others that affect iron homeostasis are down regulated<sup>[20]</sup>. A central part of the evolution of NASH, at the molecular level, is the down regulation of the Wnt signaling pathway, as Wnt inhibitors are up regulated<sup>[21]</sup>. This is directly related to HCC, as dysregulated activation of Wnt signaling has been linked to HCC subclasses<sup>[21]</sup>.

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## **OBESITY**

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Obesity represents a common denominator between NAFLD/NASH and MetS, and as such deserves special mention. At first its role seems quite straightforward as the association of obesity with T2DM and cardiovascular disease are expected to present a risk to a person's health. This may lead us to believe that the mere presence of obesity should lead to higher morbidity and mortality; yet, there have been several studies using data from the National Surgical Quality Improvement Program of the American College of Surgeons which have failed to find a correlation between obesity and mortality in surgical patients<sup>[22,23]</sup>. This has also been the case with studies in general or colorectal surgery, leading to the term "obesity paradox", in order to describe the unexpected protective effect of obesity<sup>[24,25]</sup>. Part of the explanation for this may be the existence of different definitions for obesity and corpulence, as well as the different distributions of fat in either adipose subcutaneous tissue or visceral obesity<sup>[26,27]</sup>. Either way, the above should not distract from the fact that abdominal obesity is directly linked to MetS, with its variables including visceral obesity, insulin resistance, dyslipidemia and systemic hypertension<sup>[28]</sup>. Furthermore, obesity is linked to NASH, which is also closely associated with MetS, thus bringing everything to a full circle. The relation between MetS and NASH with obesity as the "go-between" has led to NASH becoming the fastest growing indication for LT in the US, with a prediction that by 2025 approximately 25 million Americans will have developed NASH, a fifth of whom may need to undergo transplantation<sup>[29,30]</sup>. If that were not enough, in those patients undergoing LT, the prevalence of NASH after 6 months is around 50%-60%, as opposed to 23% in the general population<sup>[31,32]</sup>. The main explanation for this is the immunosuppressive medications and their side-effects. However, what is significant

is the fact that the presence of MetS post-transplantation is predictive of NASH recurrence, which can jeopardize the graft and the patient's life<sup>[33,34]</sup>.

Overall, we are seeing a paradigm shift where NAFLD/NASH and MetS are steadily replacing hepatitis viral infections (usually HCV) as the main cause of HCC and the second most frequent one for LT. Although the underlying mechanism of the progression from MetS and NAFLD/NASH to HCC is not fully understood, possibilities include the generation of reactive oxygen species, the presence of leptin (a proinflammatory cytokine with angiogenic abilities), the mild yet persistent inflammation state seen in obesity, which may all affect cellular transcription and signaling, thus leading to the appearance of HCC<sup>[35,36]</sup>.

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## TREATMENT

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This paradigm shift that we have seen, which essentially signifies that MetS, through NAFLD/NASH, now represents the main pathway to HCC and cirrhosis, has several connotations for treatment. Specifically, it means that a significant part of our efforts should be towards preventing HCC and cirrhosis, rather than waiting for them to happen and then have to deal with complicated and costly treatments. Efforts should start focusing at dealing with MetS, which mean addressing its main components such as DM, hypertension, dyslipidemia, obesity and through those the effects of NASH and NAFLD. The following are some important parts of this treatment plan and include:

### ***Lifestyle changes***

Weight loss is key in managing all the different elements of MetS, such as obesity, hypertension, dyslipidemia and T2DM, as well as in helping to control NAFLD and its progression to NASH<sup>[37-39]</sup>. This implies a combination of decreased caloric intake, as well as increased physical activity, especially walking. Although there is no consensus as to the specifics of the weight loss, there is agreement that it should be steady.

### ***Pharmacologic therapy***

The intimate causal relationship (possibly in all directions) between MetS, NAFLD/NASH and T2DM has caused a lot of interest in medications, such as metformin and pioglitazone. Metformin, together with the lifestyle changes, is believed to be especially appropriate for patients with T2DM and NAFLD or early NASH, although it has not been shown to have a beneficial effect on liver histology<sup>[40,41]</sup>. Pioglitazone, belonging in the thiazolidinediones category of medications that cause an upregulation of the genes involved in glucose metabolism, resulting in decreased hepatic lipogenesis, thus leading to improved glucose tolerance and decreased hepatic inflammation and avoidance of NASH<sup>[42,43]</sup>. The main limitations have been the need for long-term treatment and the side-effects which include congestive heart failure and stroke among others<sup>[44]</sup>. Well-established medical treatments currently exist also for hypertension and dyslipidemia, which in certain instances, such as the use of statins, have been shown to affect in a positive manner the prevention and progression of cirrhosis and HCC<sup>[45]</sup>.

### ***Nutrition therapy***

Although the question of whether NAFLD and the progression to NASH is a matter of overnutrition or simply the result of a "different" nutritional pattern with different responses from the metabolic system, there is no good data on what the proper diet specifically for NAFLD/NASH patients should be. The closest to a recommendation are those originating from the American Diabetes Association and the American Heart Association, given the prevalence and importance in the whole process of T2DM and cardiovascular disease<sup>[46]</sup>.

### ***Bariatric surgery***

There have been significant advances in bariatric surgery, especially pertaining to identifying the best type of surgery for the specific patient. The recognition of MetS, as well as the effect that we have witnessed bariatric surgery having on T2DM and hypertension, have led to bariatric surgery taking a central role in the management of MetS. There are several procedures such as the adjustable gastric banding, the sleeve gastrectomy, the Roux-en-Y gastric bypass, the duodenal switch or biliopancreatic diversion with all of them having different amounts of restrictive and malabsorptive elements<sup>[47]</sup>. The advances in minimally invasive surgery have also made these procedures more physiologically "attractive" for these patients. As potentially useful as bariatric surgery can be, it needs to be stressed that it is not enough by itself to

avoid the combined ill effects of MetS and especially those pertaining to NAFLD/NASH and the HCC progression; the reason is that the main therapy for MetS remains more a matter of lifestyle adjustments/change, rather than surgical treatment.

## CONCLUSION

The goal of this editorial is to hopefully change the mindset of how we approach cirrhosis and HCC. Specifically, by recognizing the importance of MetS, NAFLD and NASH and the combined role that they play in the progression to fibrosis, cirrhosis and eventually HCC, can help us shift the focus from the management of HCC once it has appeared with challenging and costly procedures and interventions, to the avoidance or management of MetS and its elements with the methods previously described. Additionally, we need to change the way that we have been approaching obesity as the result of bad lifestyle choices and realize that it is a multidimensional disease affecting several organ systems and where successful management requires a spectrum of interventions ranging from public education and preventive care to medications and bariatric surgery. In summary, MetS and NAFLD and their association with NASH, T2DM, hypertension, obesity and cardiovascular disease are all part of an equation which explains today (more than any other cause) the progression of chronic liver disease to cirrhosis and, eventually, to HCC. Once we understand this, we can start changing or adjusting the focus of our interventions for cirrhosis and HCC by placing emphasis on an earlier part of the disease spectrum where all these factors are at play; ultimately, the goal is to prevent than to have to treat.

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