



The Proportion of HCC Related to Obesity, Diabetes, And Metabolic Syndrome Will Likely Increase in the Future; Nonalcoholic Steatohepatitis HCC

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Abstract

NAFLD is a wide spectrum disease ranging from simple steatosis, NASH to liver cirrhosis and is the most common type of CLD in the Western world (25% in the general population). Many studies showed an increased incidence of T2 DM in patients with NAFLD independently of ordinary risk factors. This association carries more burdens to CVD, also cancer including HCC, which happens particularly in those with NASH and exacerbated by metabolic syndrome. The pathophysiology of NAFLD involves many factors, and the intestinal microbiota plays an important role in the pathogenesis of both NAFLD and HCC. Although the risk ratios of DM, obesity, and metabolic syndrome do not approach those of HCV or HBV, they are far more prevalent conditions than HCV and HBV in developed countries. Given the increasing prevalence of these conditions, the proportion of HCC related to obesity, DM, and metabolic syndrome will likely increase in the future. Lack of a general consensus due to the paucity of data makes us still do not know if it is Possible to Stop or Cease the NASH to Turn into HCC and increase its incidence. However, Exercise, especially vigorous, Metformin and Statins may be helpful. Obeticholic acid, Elafibranor, Selonsertib and Cenicriviroc, the new drugs for NAFLD/NASH treatment we are waiting for, may carry more hope to decrease HCC.

Abbreviations: CLD: Chronic Liver Disease; NAFLD: Nonalcoholic Fatty Liver Disease- MS: Metabolic Syndrome; T2DM: Type 2 Diabetes Mellitus; NASH: Non Alcoholic Steatohepatitis; HCC: Hepatocellular Cancer; TLR: Toll-Like Receptor.

NAFLD is a wide spectrum disease ranging from simple steatosis, NASH to liver cirrhosis and is the most common type of CLD in the Western world. Many studies showed increased incidence of T2 DM in patients with NAFLD independently of ordinary risk factors. The risk of T2 DM ranged from 33% to 55% in patients with NAFLD [1].

A meta-analysis of 20 observational studies, involving more than 115 000 individuals, demonstrated that NAFLD was associated with an almost two-fold increased risk of T2 DM over a median period of 5 years [2]. The prevalence of NAFLD is estimated to be about 25% in the general population, and even higher in certain parts of the world and in some patient populations, such as among

the obese and patients with diabetes. This high prevalence is closely associated with the rise in the rates of obesity and MS. Components of MS include increased fasting plasma glucose or T2DM, hypertriglyceridemia, low high density lipoprotein level, increased waist circumference, and hypertension [3].

Bidirectional relation between NAFLD and MS component was documented recently, most important is T2DM. This association carries more burdens to CVD, also cancer including HCC [1,4]. Observational studies have shown that older age, too much fibrosis, diabetes, obesity, MetS, high iron, much alcohol consumption, and menopause are further risk factors for HCC development in NAFLD/NASH [3]. HCC is rare among adolescents and accounts for less than 1% of all malignant neoplasms among children younger than 20 years [5].

The progression to HCC in NAFLD happens particularly in those with NASH and exacerbated by metabolic syndrome (Table 1), or PNPLA3 gene polymorphism [6].

Study Type	HCC Cases	Metabolic Syndrome Definition	RR (95% CI)
Case-control	3,649 cases of 195,953 controls	NCEP-ATP III	2.58 (2.40–2.76)
Cohort	266 cases of 578,700	WHO	1.35 (1.12–1.63)
Cohort	1,931 cases of 23,625	NCEP-ATP III	M: 1.89 (1.11–3.22); F: 3.67 (1.78–7.57)
Cohort	1,858 cases of 27,724	AHA	M: 1.73 (1.03–2.91); F: 1.18 (0.55–2.51)

Table 1: Association Between Metabolic Syndrome and HCC: Systemic Review and Meta-Analysis- modified from [7].

RR, Risk Ratio

The pathophysiology of NAFLD involves many factors, and the intestinal microbiota plays an important role in the pathogenesis of both NAFLD and HCC. NAFLD and NASH are associated with alterations in the gut microbial population through various routes, such as alterations in gut epithelial permeability, choline metabolism, endogenous alcohol production, release of inflammatory cytokines, regulation of hepatic TLR, and bile acid metabolism. In addition, altered bile acid metabolism, release of inflammatory cytokines, and TLR-4 expression may promote NAFLD/NASH-associated HCC [8] (Figure 1).

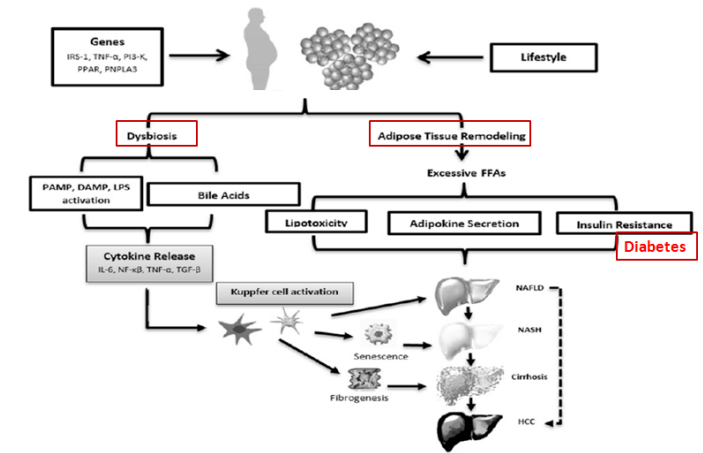


Figure 1: Role of Obesity and MS in HCC Pathogenesis.

Role of Obesity and MS in HCC Pathogenesis

Obesity and metabolic syndrome lead the oncogenesis in the setting of abnormal hepatic morphology, and hepatic steatosis may provide the appropriate microenvironment for the development of cancer. Insulin resistance leads to fat accumulation in the hepatocytes by lipolysis and hyperinsulinemia. Obesity may lead to release of pro-inflammatory cytokines, inhibition of anti-inflammatory cytokines, and lipotoxicity.

Abbreviations: DAMP, damage-associated molecular pattern; LPS, lipopolysaccharide; PAMP, pathogen-associated molecular pattern. Adapted from [9].

Although the RRs of DM, obesity, and metabolic syndrome do not approach those of HCV or HBV (table 2), they are far more prevalent conditions than HCV and HBV in developed countries. Given the increasing prevalence of these conditions, the proportion of HCC related to obesity, DM, and metabolic syndrome will likely increase in the future [10].

Multivariate analysis of variables associated with HCC		
	Odds ratio (95% CI)	P
Diabetes		
Absent	1	0.01
Present	2.2 (1.2-4)	
HBV		
Absent	1	≤ 0.001
Present	252.1 (53.7-1183.9)	
HCV		
Absent	1	≤ 0.001
Present	106.5 (58.2-194.9)	
Alcohol		
Absent	1	≤ 0.001
Present	121.2 (61.9-233.7)	

Table 2: Modified from [11].

HCC in NAFLD Non-cirrhotic

Has usually large measurements, is partially or well differentiated, and generally lacks encapsulation. HCC in NAFLD may arise in the absence of histologically definite or evident inflammation. Dysregulated hepatic and circulating pro-inflammatory cytokines and adipokines, oxidative and endoplasmic reticulum stress, and dysbiosis are likely associated with obesity-related Hepatocarcinogenesis [12].

An interesting possibility is the malignant transformation of hepatocellular adenoma, associated with obesity in non-cirrhotic patients with NAFLD [3]. Currently, there is a lack of recommendations for surveillance of patients with NASH and without cirrhosis, probably because of the difficulty of identifying

patients with NASH without a liver biopsy. However, recent blood-based biomarkers could be an affordable alternative for identification of patients at high risk of NASH and advanced fibrosis [13].

The incidence and prevalence of HCC in NAFLD depend on the stage of underlying fatty liver disease. While the epidemiological data in relation to HCC in viral hepatitis and alcoholic hepatitis are consistent, there is a lack of strong epidemiological data concerning the incidence and prevalence of HCC in NAFLD. A few longitudinal outcome studies explored the prevalence of HCC in NASH, reporting a prevalence varying from 0 to 3% on a follow-up period between 5.6 and 21 years. The percentage was increased if the incidence of HCC in NAFLD cirrhosis was considered, with a cumulative HCC incidence ranging between 2.4% with a median follow-up of 7.2 years and 12.8% with a 3.2-year median follow-up [14].

Is That Possible to Stop or Cease the NASH to Turn into HCC and increase its incidence?

We do not exactly know this because the etiopathogenesis of NASH is not completely known. Primary prevention, which is our aim focuses on risk factors for HCC and their treatment, secondary prevention concentrates on the treatment of underlying liver diseases in patients with HCC aiming at a prevention of disease progression, and tertiary prevention aims at a reduction of recurrence after successful curative treatment of HCC [15].

A few chemo preventive agents have shown promise in the prevention and treatment of steatohepatitis and fibrosis (small individual studies); thus there is a lack of a general consensus due to paucity of data. Exceptions include nucleoside analogues used to reduce hepatitis B viral replication, and DAAs for HCV which have very high cure rates [16].

Preventions and Treatment in NAFLD-Related HCC

Lifestyle changes

Considering the pathogenesis of HCC in NAFLD, one has to face the burden of **obesity and diabetes**, lifestyle changes is the cornerstone for primary prevention and has been shown to reduce incident NAFLD and the related metabolic disorders and also may reverse NASH and liver fibrosis. It has been reported to have a preventive effect on the development of HCC. A protective effect in the development of HCC has been attributed in general to the Mediterranean diet. Bariatric surgery could be recommended for patients with morbid obesity, it may reduce Liver fibrosis but carries

a risk of decompensation in advanced cirrhotics. Observational studies and animal work suggest that exercise can prevent HCC development (inhibition of mTOR and the activation of AMPK, which are both involved in cell growth and proliferation). In a prospective cohort Study on 507,897 subjects followed up for 10 years: a RR of 0.56 for HCC was found in vigorously active (≥ 5 days/week) compared to sedentary subjects (independent of BMI) [3,10].

Dietary Supplements, Role and Mechanism: Tables 3,4 and Figure 2

Dietary supplement	Mechanism of action	Prevent hepatocarcinogenesis <small>should include improvement in liver fibrosis</small>
Dietary antioxidants coenzyme Q12, vitamin C and E, selenium	vE: A general cytotoxic ROS scavenger erases oxidative stress.	+ (short period studies).
Silymarin <small>is said to be an antioxidative agent</small>	Restored nicotinamide adenine dinucleotide (NAD+) levels, and played a protective role against NAFLD. Ameliorated liver fibrosis in NASH	Potential HCC chemoprevention. Supporting clinical evidence is lacking
Regular coffee (>2 cups/day)	Reduced hepatocellular injury measured by IL6, ALT, AST,& GGT.	Meta analysis (RR 0.71) case-control studies, (RR .53). Tea intake , less
Green tea	Reduction of DNA damage biomarkers	Undetermined
liquorice root		(HR 0.39)
Higher vitamin D , levels		(RR 0.51).
Patients with NASH have a deficiency of vitamin E and D. Vitamin D deficiency probably plays a role in hepatocarcinogenesis.		

Table 3: Adapted from [3,12,17,18].

Dietary supplement	Mechanism of action	Prevent hepatocarcinogenesis
-Unsaturated fat *PUFAs	It inhibit HCC growth through inhibition of COX2 and GSK-3b-mediated b-catenin degradation.	- (HR 0.71) * (HR 0.64)
white meat (chicken, turkey, and fish)		(HR 0.52) red meat (beef and pork) (HR 1.74)
Excessive dietary iron and/or genetic polymorphisms	Induce oxidative DNA damage and inflammation	increase HCC risk independently or alongside other aetiologies.
BCAA	Reduces liver fibrosis	(RR 0.45)
L-carnitine	Controls the oxidative balance to aid the mitochondrial function, a fat-burning supplement. Long-chain fatty acids taken up by mitochondria as complexes with L-carnitine	anti-cancer agent

Table 4: Adapted from [12,19].

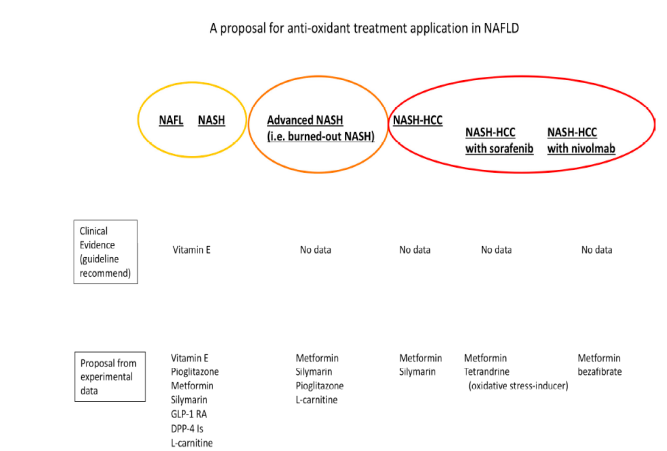


Figure 2: showed [19].

Chemoprevention, Role and Mechanism: Tables 5 and Table 6

Therapy	Mechanism of action	Steatohepatitis and fibrosis	Hepatocarcinogenesis	NB
Metformin (Early use is advised) Anti-oxidant	weight loss and reduction of endogenous ROS as well as the hyperinsulinemia. AMPK-activating agent.	Favorable effects on the NAFLD, do not improve the liver histology	Reduced incidence 50% in diabetics via suppression of mTOR pathway. sulfonylurea and insulin increased incidence of HCC by 62% and 161% respectively. Increase survival of HCC patients who have cirrhosis	have multiple other metabolic benefits SAFE
Statins	anti-inflammatory properties mediated through the inhibition of JAK	Protective effect, do not improve the liver histology	in observational studies decreased incidence of HCC in diabetics, OR 0.88. > In NAFLD without cirrhosis (HR 0.29).	have multiple other metabolic benefits SAFE
Pioglitazone Anti-oxidant		Histological improvement of liver fibrosis after 18 months tt	Usful in inhibiting NAFL progression to NASH and hepatocarcinogenesis	
SAMe	A ubiquitous major methyl donor		Suppresses HCC development.	
GLP-1 RAs and DPP-4Is		Favorable effects on the NAFLD		

Table 5: Adapted from [3,6,12,17,19].

Therapy	Mechanism of action	histological features of NASH	Hepatocarcinogenesis	NB
NSAIDs , including aspirin			A pooled analysis of 10 cohorts suggested a protective effect of aspirin use	
Phytochemicals: Silymarin-carotenoids - curcumin	Activate cytoprotective mechanisms such as the Keap1/Nrf2 pathway		Potential HCC chemoprevention.	Supporting clinical evidence is lacking.
Molecular targeted Therapy ACEs & ARBs	Inhibit AGII mediated NF-kB activation which promotes fibrogenic myofibroblast survival		Inhibit NASH fibrosis and HCC	
-Obeticholic acid, *Elafibranor, Selonsertib, Cenicriviroc	-FXR agonist *A dual PPARa/d agonist	Improved with all		Long-term benefits, safety, & its antihepatocarcinogenesis need further evaluation
Probiotic, Prebiotic, or synbiotic, or antibiotic treatment	Ameliorate IR- limit oxidative& inflammatory liver damage - Reduce body fat& improve glucose metabolism	Improved NASH activity index		Transplantation

Table 6: Adapted from [12,15].

So, lack of a general consensus due to paucity of data makes us still do not know if it is Possible to Stop or Cease the NASH to Turn into HCC and increase its incidence. However, Exercise, especially vigorous (RR of 0.56), Metformin (Reduced incidence 50% in diabetics) and Statins (In NAFLD without cirrhosis HR 0.29) may be helpful. Obeticholic acid, Elafibranor, Selonsertib and Cenicriviroc, the new drugs for NAFLD/NASH treatment we are waiting for, may carry more hope to decrease HCC.

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