Vol 1| Issue 13| 2020

Enteron

Dear Doctor,

Greetings from Micro Labs limited.

Inside This Issue

Should you require any specific article or medical information, please feel free to contact us at medicalservices@microlabs.in
Looking forward to your valuable feedback

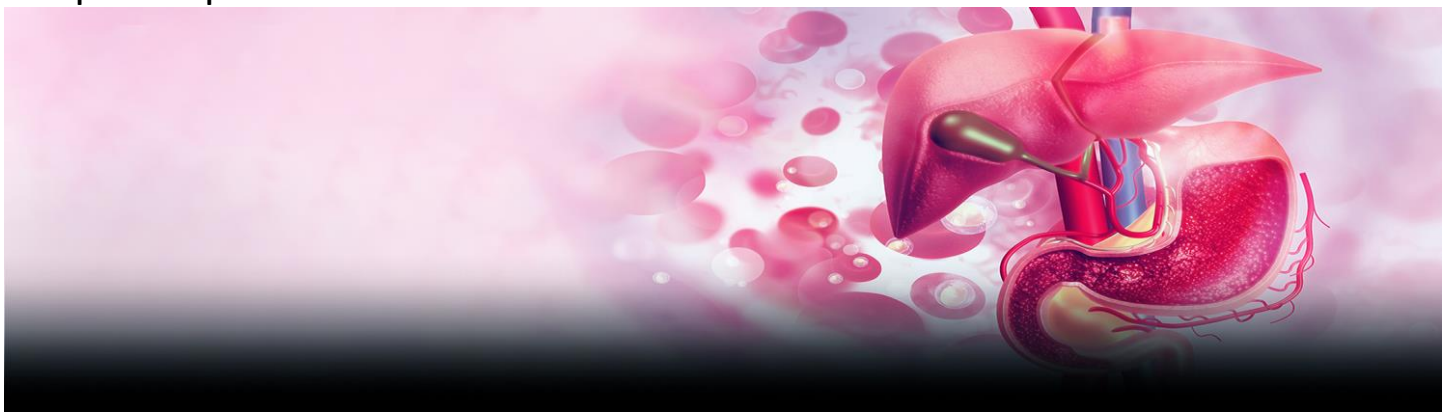
Best Regards,
Medical Team, Micro Labs Ltd

From NAFLD to MAFLD

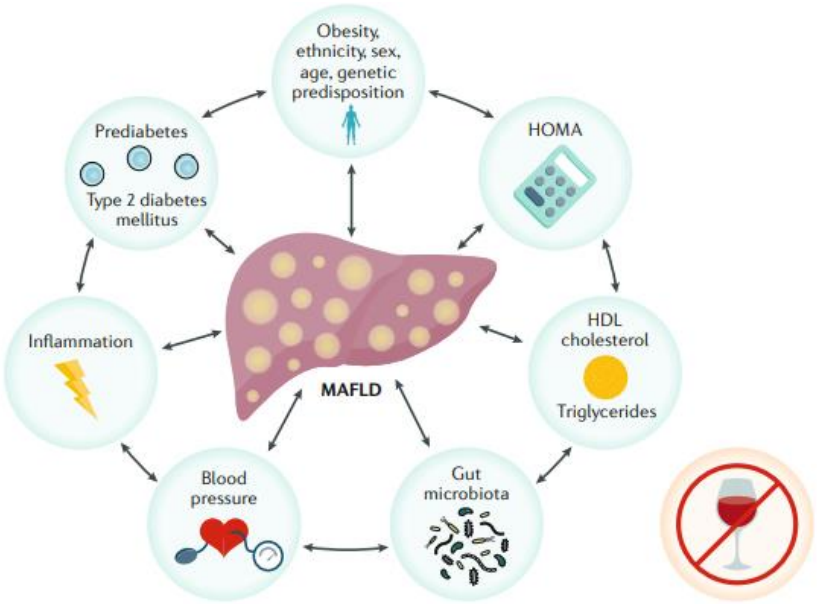
In several cases, NAFLD represents a positive disease, and its frequency mirrors obesity and diabetes rates. Based on Marchesini et al.'s initial findings, several research over the past 20 years have shown specifically that NAFLD is a metabolic condition reflecting the hepatic expression of a systemic metabolic disorder. Two recent perspective papers have taken the initiative, based on observations obtained over the past two decades, to suggest a new term for NAFLD — that is, the metabolic related fatty liver disease (MAFLD).

A group of experts in those articles convincingly described why a name change is overdue. Indeed, their new definition clearly establishes this disease as a metabolic disorder as criteria now require evidence of hepatic steatosis accompanied by one of three characteristics: that is, either overweight or obesity, T2DM or lean or normal weight with evidence of metabolic dysregulation. A lot of challenges remain for the MAFLD field, as outlined in these two excellent papers. One of such issues is the variability in MAFLD because various subtypes in diseases that occur, so both natural history and the trajectory of inter-individual diseases are highly unpredictable. Another problem is the issue of metabolically balanced obesity (MHO), which theoretically impacts as much as 45 percent of obese individuals.

It is debated if MHO is actually a benign condition as it is linked with adverse cardiovascular consequences and induces fibrosis linked with MAFLD. One of the remaining questions is what is meant by metabolic health and how that could be defined. Could it be sufficient to define metabolic health in the future by excluding hepatic steatosis, as accumulation of liver fat is probably one of the most sensitive parameters indicating metabolic dysfunction? Importantly, in addition to metabolic impairment, numerous other disorders manifest in hepatic steatosis, liver damage caused by alcohol and medications representing the most prominent cases.



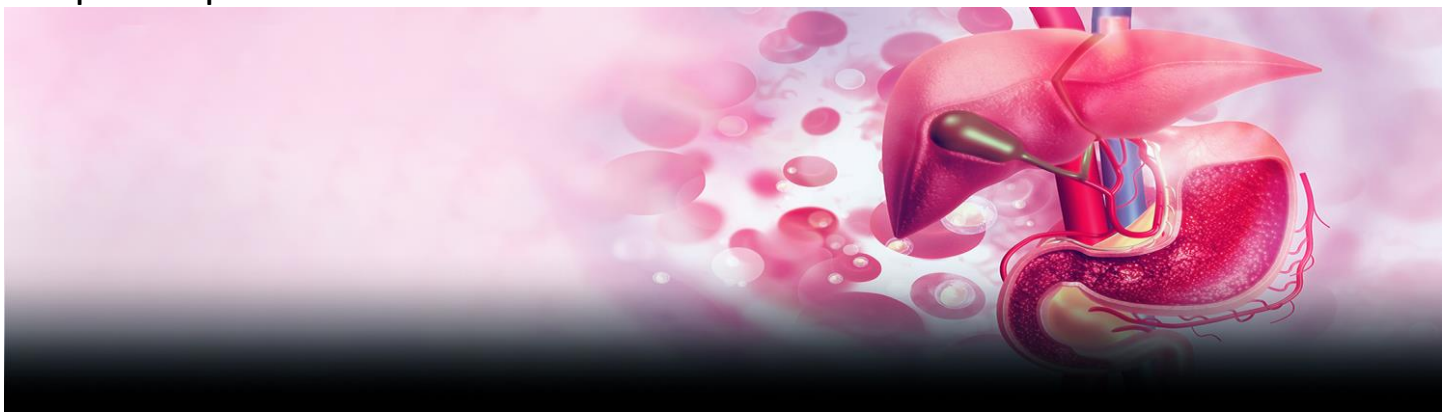
The guidelines identifying metabolic risk factors are what hepatologists already ought to know and become acquainted with: this category involves waist circumference, blood pressure, serum triglycerides, HDL cholesterol, prediabetes, HOMA score and extremely responsive C-reactive protein rates in serum. These two reports have important implications for the entire field of hepatology as this new view of this disease will in future have a major impact on the design of clinical trials. This new concept may also promote the creation of MAFLD clinics jointly operated by hepatologists and diabetologists to enhance patient treatment.



MAFLD: an 'old' new disease

An update on the nomenclature, as discussed by Eslam et al., can only be a first step, and should build the basis for following new directions for research. If we accept 'MAFLD' as the standard terminology, we must also accept what has already been learned in metabolic disorders and one of the most important clinical concepts is the association of metabolic disorders with low-grade inflammation. Obesity-related disorders such as metabolic syndrome and T2DM in many cases are characterized by low-grade systemic inflammation including inflammation of the adipose tissue. Interestingly, Eslam and colleagues have listed high-sensitive C-reactive protein rates as one of the metabolic risk factors as it is well known that this biomarker is commonly important in metabolic disorders. The liver community in MAFLD has somewhat ignored inflammation as the histology outcome studies focused on the correlation of disease with fibrosis. But this link may be precisely because hepatic biopsy is a glimpse taken of a long-lasting recurrent condition at a specific moment.

The essence of MAFLD inflammation can be persistent – relapse or sporadic, as in many other recurrent inflammatory and liver diseases, and liver biopsy could simply be absent. This concept is familiar in gastroenterology; for example, chronic – relapsing inflammation is typical in Crohn's disease, and long-term sequelae include fibrosis development,



strictures and stenosis. There is no doubt that there is a natural course of disease in many diseases within and outside the gastrointestinal tract and there is a recognition of the timely therapy requirement, there is an urgent need for non-invasive techniques either in the sense of biomarkers or imaging to enable the detection of liver inflammation and fibrosis over the course of the disease. In 'metabolic' medicine the development of these strategies should be of high importance

Source: Tilg H, Effenberger M. From NAFLD to MAFLD: when pathophysiology succeeds. Nat Rev Gastroenterol Hepatol (2020). https://doi.org/10.1038/s41575-020-0316-6

Association of Positive Hepatitis B Core Antibody with Cirrhosis and Hepatocellular Carcinoma in Non-alcoholic Fatty Liver Disease

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) affects at least one quarter of the world's adult population and is a leading cause of cirrhosis and hepatocellular carcinoma (HCC). NAFLD has long been considered a disease of wealthy countries in the West, and is increasingly recognized in other parts of the world. A recent meta-analysis suggests that NAFLD also affects approximately 30 per cent of Asian people. Throughout Asia another famous chronic liver condition is chronic hepatitis B. Although fatty liver is less common in patients with chronic hepatitis B virus (HBV) infection, there is an increased risk of HCC and mortality in patients with both conditions.

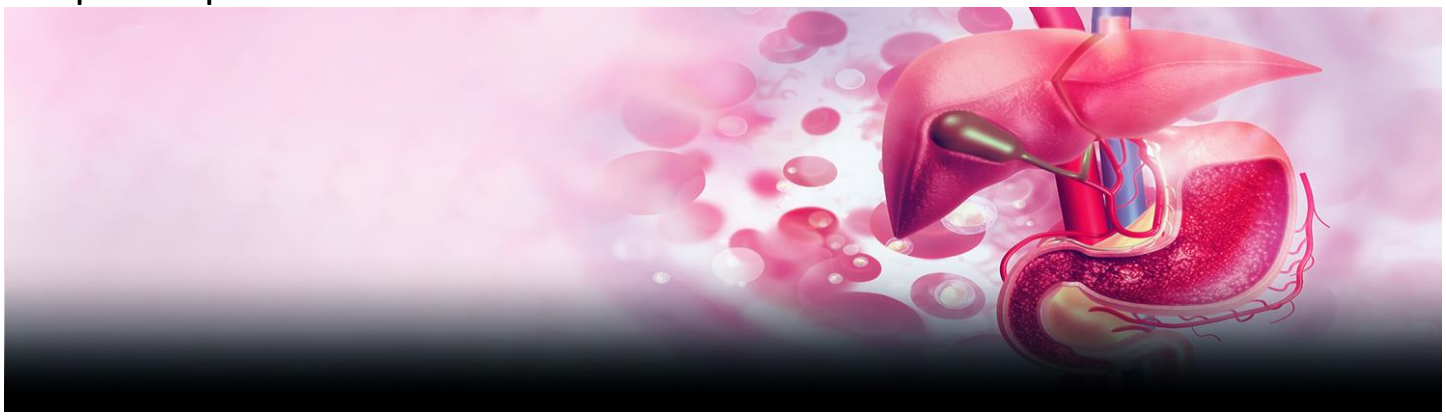
Metabolic illnesses such as diabetes and obesity also increase the risk of cirrhosis and HCC in chronic hepatitis B patients. Even after seroclearance of the hepatitis B surface antigen (HBsAg), diabetes remains associated with an increased risk of HCC. As well as the high prevalence of chronic hepatitis B in Asia, there is evidence of occult or previous HBV infection in many patients. This is defined by the existence, in a patient with negative HBsAg, of positive antihepatitis B core antibody (anti-HBc) with or without antihepatitis B surface antibody (anti-HBs). The existence of HBV DNA is referred to as occult HBV infection in blood, liver, or other tissues. Patients with preceding HBV infection may suffer liver injury during the active HBV infection. Additionally, incorporation of HBV DNA into the host genome can increase the risk of HCC. In most cases, intrahepatic HBV DNA, or covalently closed circular DNA, can be found in patients with cryptogenic HCC. Similarly, several research of patients with persistent hepatitis C showed a correlation between positive anti-HBc and HCC although this was not supported by other researchers. The aim of the study to evaluate whether positive anti- HBc is associated with more severe liver histology and HCC in patients with NAFLD.

METHODS

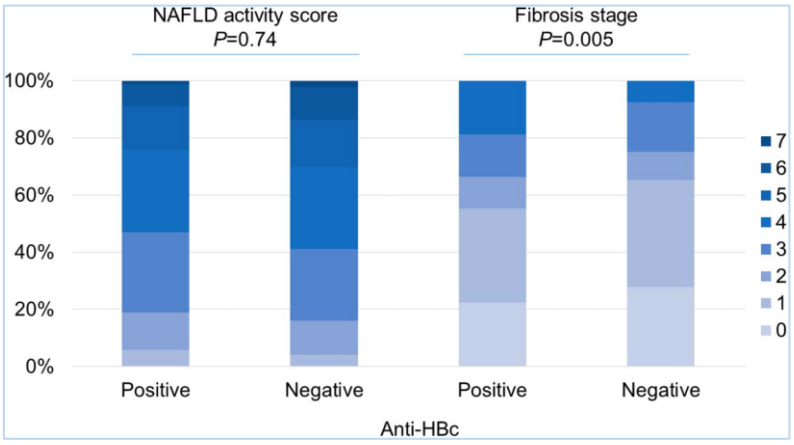
This was a multicentre study of 489 patients with biopsy-proven NAFLD and 69 patients with NAFLD related or cryptogenic HCC. Antihepatitis B core antibody (anti-HBc) was used to detect the previous HBV infection.

RESULTS

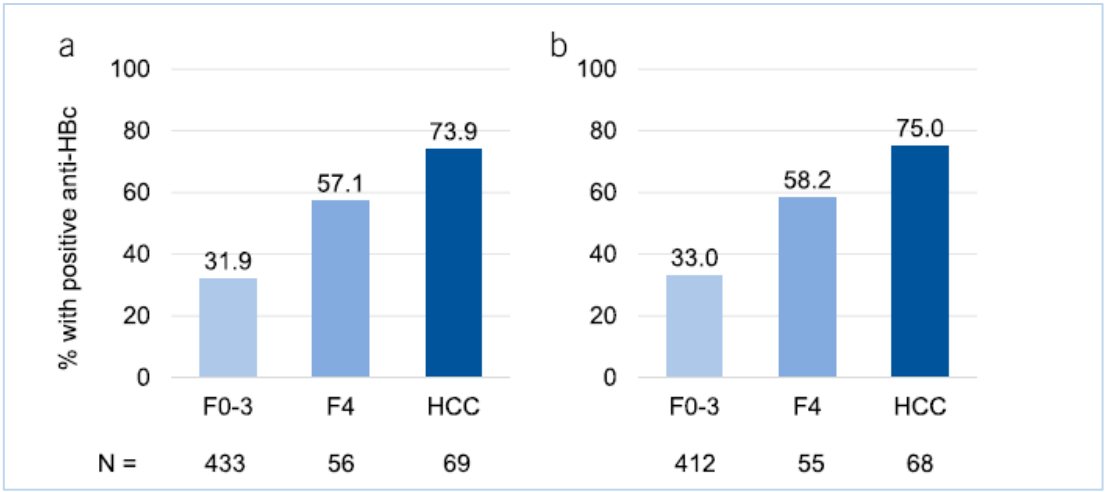
In the biopsy cohort, positive anti-HBc was associated with lower steatosis grade but higher fibrosis stage. 18.8% and 7.5% of patients with positive and negative anti-HBc had cirrhosis, respectively ($P < 0.001$). The association between anti-HBc and cirrhosis remained significant after adjusting for age and metabolic factors (adjusted odds ratio 2.232; 95% confidence interval, 1.202–4.147). At a mean follow-up of 6.2 years, patients with positive anti-HBc had a higher incidence of HCC or cirrhotic complications (6.5% vs 2.2%; P 5 0.039). Among patients with NAFLD-related or cryptogenic HCC, 73.9% had



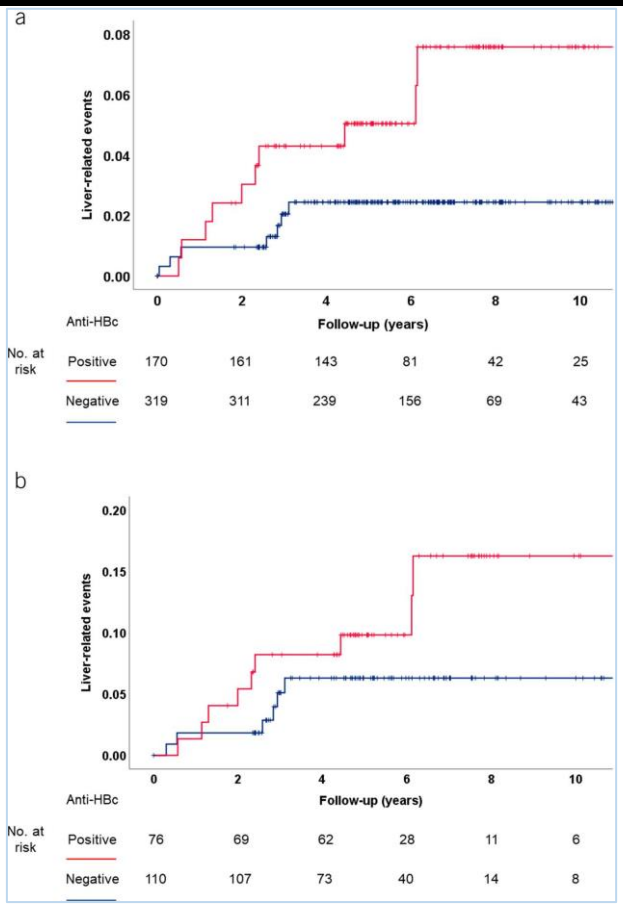
positive anti-HBc. None of the patients had positive serum HBV DNA. By contrast, antihepatitis B surface antibody did not correlate with histological severity.



NAFLD activity score and fibrosis stage of patients with NAFLD with positive and negative anti-HBc. The comparisons were by X^2 test. Anti-HBc, antihepatitis B core antibody; NAFLD, non-alcoholic fatty liver disease.



Proportion with positive anti-HBc among patients with NAFLD with F0-3, F4 and HCC. (a) Entire cohort, (b) subgroup of patients aged older than 30 years. P,0.001 for both comparisons by x2 test. Anti-HBc, anti-hepatitis B core antibody; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease.



Liver-related events in patients with positive and negative anti-HBc (a) entire cohort (P=0.039 by logrank test), (b)subgroup of patients with F2-4 fibrosis (P =0.14 by logrank test). Anti-HBc, anti-hepatitis B core antibody.

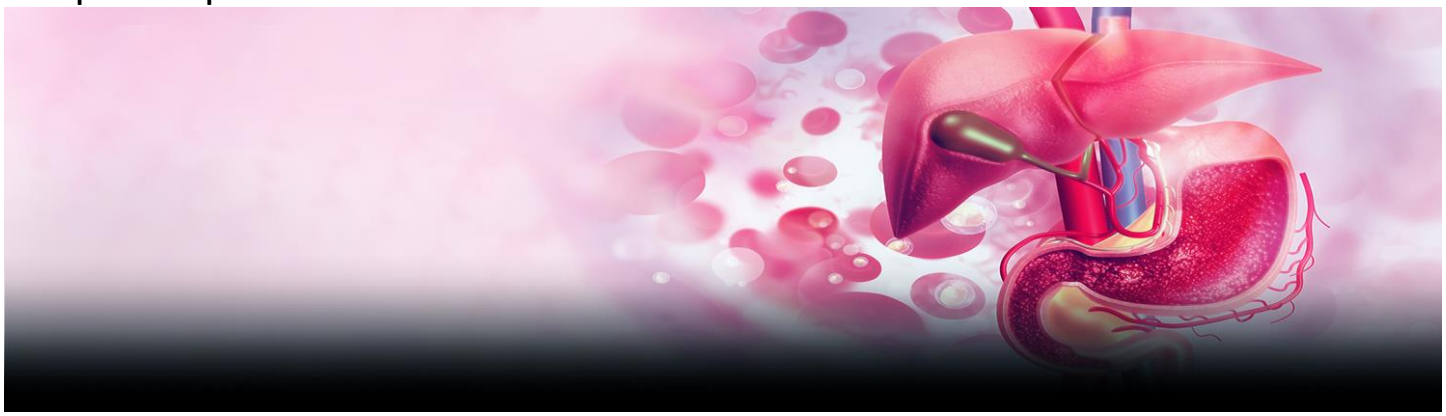
- *NAFLD patients with positive anti-HBc were more likely to have significant fibrosis and cirrhosis than those with negative anti-HBc.*
- *The association between anti-HBc and cirrhosis remained significant after adjusting for age, sex, and metabolic conditions.*
- *Positive anti-HBc was found in 32% of NAFLD patients with F0-3 fibrosis, 57% of patients with NAFLD-related cirrhosis, and 74% of those with NAFLD-related or cryptogenic HCC.*
- *Anti-HBs did not correlate with histological severity of NAFLD.*

CONCLUSION

In addition, in chinese patients with NAFLD, positive anti-HBc is consistent with cirrhosis and likely HCC and cirrhotic complications. Because NAFLD-related HCC may develop in noncirrhotic patients, future studies should define the role of anti-HBc in the selection for HCC surveillance of noncirrhotic NAFLD patients.

REFERENCE

Chan TT, Chan WK, Wong GL, et al. Positive Hepatitis B Core Antibody Is Associated with Cirrhosis and Hepatocellular Carcinoma in Nonalcoholic Fatty Liver Disease. Am J Gastroenterol. 2020;115(6):867-875.



Increased Risk of Type 2 Diabetes in Individuals with Non-alcoholic Fatty Liver Disease who consume Light-to-Moderate amount of Alcohol

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is one of the most prevalent chronic liver disorders globally, with a incidence of 25.2 percent and 29.2 percent in China. NAFLD 's range covers basic steatosis and steatohepatitis, fibrosis, and in some cases hepatocellular carcinoma. NAFLD is intimately linked to obesity and related metabolic disorders. The health and economic costs of NAFLD are important in terms of the hepatic and extrahepatic complications. NAFLD frequently precedes the type 2 diabetes mellitus (T2DM), and T2DM is one of NAFLD's most prevalent extrahepatic complications. In an early study of 129 patients, Ekstedt et al. found that during a mean follow-up of 13.7 years, most biopsy-proven patients with NAFLD developed diabetes or prediabetes. Another research showed that occurrence of T2DM was predicted positively by the NAFLD category. A newly revised meta-analysis found that NAFLD diagnosed with imaging was correlated with an elevated probability of T2DM incidence more than two fold. Considering NAFLD's high prevalence globally and its major relation to T2DM, rising the incidence of T2DM in patients with NAFLD is a serious problem. Alcohol was postulated as a hazard to certain health problems. However, since awareness of sophisticated quantification of drinking appears, a definition of light to moderate alcohol consumption (LMAC) has arisen and increasing research has focused on its effects on metabolic diseases. Interestingly, strong empirical data shows that LMAC, relative to non-alcohol or severe alcohol consumption, decreased the chances of components of metabolic syndrome, minimized disease development, avoided harmful effects, and also improved longevity.

In T2DM in particular, many studies have held the view that LMAC is associated with lower odds of T2DM and the American Diabetes Association has recommended that adults with diabetes be advised to take moderate alcohol consumption (# 1 drink per day for women, #2 drinks per day for men), similar to the general population. However, alcohol can exert a metabolic liver burden, causing multiple metabolic turbulence and hepatic injury. This raises a challenging question as to whether the same rule applies that LMAC can also prevent T2DM in NAFLD patients from developing as well. In this study they evaluated the effect of LMAC on the risk of developing T2DM in NAFLD individuals. The results may enhance our understanding of the role of LMAC in NAFLD patients, and provide guidance on how best to advise NAFLD patients on alcohol use.

METHODS

A 9-year cohort study was performed among Chinese men who underwent their annual health checkups between 2009 and 2018. NAFLD was diagnosed based on abdominal ultrasound with exclusion of excess alcohol intake and other causes of liver disease. Logistic regression and Cox proportional regression analyses were applied to identify the risk of prevalent and incident T2DM.

RESULTS

Of the 7,079 participants enrolled, 243 had T2DM at baseline and 630 developed T2DM during the 45,456 person-years follow-up. Both at the baseline and by the end of the follow-up, LMAC was associated with a decreased risk of prevalent T2DM in NAFLD-free participants but with a significantly increased risk in patients with NAFLD. LMAC was also associated with a decreased risk of incident T2DM in NAFLD-free participants. The adjusted hazard ratios (95% confidence interval) of incident T2DM were 0.224 (0.115–0.437) and 0.464 (0.303–0.710) for NAFLD-free light drinkers and NAFLD-free moderate drinkers, respectively. Nondrinking, light-drinking, and moderate-drinking patients with NAFLD all showed significantly increased risks of incident T2DM. Compared with NAFLD free non-drinkers, the adjusted hazard ratios (95% confidence interval) of incident T2DM were 1.672 (1.336–2.092), 2.642 (1.958–3.565), and 2.687 (2.106–3.427) for nondrinking, light-drinking, and moderate-drinking patients with NAFLD, respectively.

Variables	Univariate model		Multivariate model	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Subgroup				
NAFLD-free nondrinkers	Reference		Reference	
NAFLD-free light drinkers	0.257 (0.132—0.501)	<0.001	0.224 (0.115—0.437)	<0.001
NAFLD-free moderate drinkers	0.705 (0.463—1.073)	0.103	0.464 (0.303—0.710)	<0.001
NAFLD nondrinkers	2.658 (2.173—3.251)	<0.001	1.672 (1.336—2.092)	<0.001
NAFLD light drinkers	4.857 (3.679—6.411)	<0.001	2.642 (1.958—3.565)	<0.001
NAFLD moderate drinkers	9.215 (7.476—11.360)	<0.001	2.687 (2.106—3.427)	<0.001
Current smoking	3.997 (3.409—4.687)	<0.001	3.415 (2.869—4.065)	<0.001
Age	1.049 (1.044—1.054)	<0.001	1.045 (1.038—1.051)	<0.001
Body mass index ≥ 23 kg/m²	3.173 (2.610—3.857)	<0.001	1.188 (0.948—1.489)	0.134
Waist circumference ≥ 90 cm	3.352 (2.866—3.920)	<0.001	1.279 (1.068—1.531)	0.007
Triglyceride ≥ 150 mg/dL	2.187 (1.869—2.559)	<0.001	1.211 (1.019—1.438)	0.030
SBP ≥ 130 mmHg, DBP ≥ 85 mmHg	2.372 (2.013—2.795)	<0.001	1.158 (0.973—1.377)	0.098
HDL-cholesterol < 40 mg/dL	1.438 (1.145—1.805)	0.002	1.245 (0.987—1.570)	0.064
Fasting plasma glucose ≥ 100 mg/dL	11.129 (9.462—13.089)	<0.001	6.499 (5.463—7.733)	<0.001
Serum uric acid > 7.00 mg/dL	1.621 (1.365—1.924)	<0.001	1.166 (0.975—1.396)	0.092

Association between light-to-moderate alcohol consumption and the risk of incident type 2 diabetes mellitus. The hazard ratio (95% CI) for incident type 2 diabetes mellitus according to alcohol consumption categories. Non-drinker refers to no alcohol consumption in the past 12 months; light drinker refers to,70 g per week; moderate drinker refers to 70–210 g per week

- *LMAC was associated with a decreased risk of T2DM in NAFLD-free participants but with an increased risk of T2DM in participants with NAFLD.*
- *These findings suggested that patients with NAFLD should not intake light-to-moderate alcohol for the purpose of lowering risk of T2DM.*
- *These results may help to understand the role of LMAC in NAFLD and provide guidance on how best to counsel patients with NAFLD regarding alcohol use.*

CONCLUSION

This large cohort study confirmed LMAC in NAFLD-free participants had a protective effect on T2DM. Additionally, they found that LMAC was associated with an increased risk of T2DM in NAFLD patients. These findings suggested that patients with NAFLD should not ingest light to moderate alcohol with a view to reducing the risk of T2DM.

REFERENCE

Xu L, Xie J, Chen S, et al. Light-to-Moderate Alcohol Consumption Is Associated with Increased Risk of Type 2 Diabetes in Individuals with Nonalcoholic Fatty Liver Disease: A Nine-Year Cohort Study. Am J Gastroenterol. 2020;115(6):876-884.