ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2021 July 14; 27(26): 3951-4251

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

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The *WJG* is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2021 edition of Journal Citation Report® cites the 2020 impact factor (IF) for *WJG* as 5.742; Journal Citation Indicator: 0.79; IF without journal self cites: 5.590; 5-year IF: 5.044; Ranking: 28 among 92 journals in gastroenterology and hepatology; and Quartile category: Q2. The *WJG*'s CiteScore for 2020 is 6.9 and Scopus CiteScore rank 2020: Gastroenterology is 19/136.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ji-Hong Liu*; **Production Department Director:** *Yu-Jie Ma*; **Editorial Office Director:** *Ze-Mao Gong*.

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Andrzej S Tarnawski, Subrata Ghosh

EDITORIAL BOARD MEMBERS
http://www.wjgnet.com/1007-9327/editorialboard.htm

PUBLICATION DATE
July 14, 2021

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https://www.wjgnet.com/bpg/GerInfo/287

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https://www.wjgnet.com/bpg/gerinfo/242

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https://www.wjgnet.com/bpg/GerInfo/239

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World J Gastroenterol 2021 July 14; 27(26): 3971-3983

DOI: 10.3748/wjg.v27.i26.3971

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

OPINION REVIEW

Chronic hepatitis B infection with concomitant hepatic steatosis: Current evidence and opinion

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Author contributions: Shi YW, Yang RX and Fan JG contributed to the study concept and design; Shi YW and Fan JG contributed to drafting the manuscript; Fan JG contributed to critical revision of the manuscript for important intellectual content; All authors confirmed critical revision of the manuscript for important intellectual content.

Supported by National Key Research and Development Program of China, No. 2017YFC0908903; and National Natural Science Foundation of China, No. 81873565 and No. 81900507.

Conflict-of-interest statement: The authors declare that theyhaveno competinginterests.

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Abstract

With the increasing incidence of obesity and metabolic syndrome worldwide, concomitant nonalcoholic fatty liver disease (NAFLD) in patients with chronic hepatitis B (CHB) has become highly prevalent. The risk of dual etiologies, outcome, and mechanism of CHB with concomitant NAFLD have not been fully characterized. In this review, we assessed the overlapping prevalence of metabolic disorders and CHB, assessed the risk of advanced fibrosis/hepatocellular carcinoma in CHB patients concomitant with NAFLD, and discussed the remaining clinical issues to be addressed in the outcome of such patients. We also explored the possible roles of hepatitis B virus in the development of steatosis and discussed difficultiesof histological evaluation. For CHB patients, it is important to address concomitant NAFLD through lifestyle management and disease screening to achieve better prognoses. The assessment of progressive changes and novel therapies for CHB patients concomitant with NAFLD deserve further research.

Key Words: Nonalcoholic fatty liver disease; Hepatitis B; Metabolic disorders; Steatosis; Mechanism; Disease burden

Core Tip: The pathophysiology of concomitant hepatitis B and hepatic steatosis remains unclear. This review comprehensively discusses the epidemiology, risk factors, long-term outcomes, histological assessment, potential mechanisms, and therapeutic options in this field. We believe further studies can clarify the interactions of hepatitis B virus and steatosis, and provide novel strategies for the management of hepatitis B patients

Manuscript source: Unsolicited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: China

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B, B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): E

Received: February 6, 2021
Peer-review started: February 6, 2021
First decision: April 19, 2021
Revised: April 28, 2021
Accepted: May 27, 2021
Article in press: May 27, 2021
Published online: July 14, 2021

P-Reviewer: Kishida Y, Lee SW, Moriya K, Tai DI
S-Editor: Ma YJ
L-Editor: Filipodia
P-Editor: Xing YX

with concomitant steatosis.

Citation: Shi YW, Yang RX, Fan JG. Chronic hepatitis B infection with concomitant hepatic steatosis: Current evidence and opinion. *World J Gastroenterol* 2021; 27(26): 3971-3983
URL: https://www.wjgnet.com/1007-9327/full/v27/i26/3971.htm
DOI: https://dx.doi.org/10.3748/wjg.v27.i26.3971

INTRODUCTION

Chronic hepatitis B (CHB) has become highly prevalent worldwide in recent decades, affecting 350 million people, especially in Africa, Latin America and the Asia-Pacific region[1]. Although the incidence of hepatitis B virus (HBV) infection has recently decreased because of the widespread use of vaccines, the number of existing CHB patients remains significant[2]. CHB patients are at risk of severe liver-related adverse events, including decompensation, hepatocellular carcinoma (HCC), and even death. The persistence of covalently closed circular DNA (cccDNA) and incomplete immune tolerance lead to continuing HBV reproduction, resulting in chronic liver inflammation and fibrosis[3]. Despite the availability of potent antiviral treatments, we have not yet been able to eradicate HBV.

Nonalcoholic fatty liver disease (NAFLD) has become epidemic in those with chronic liver disease, with a worldwide annual incidence ranging from 6% to 35%[4]. The constantly increasing prevalence of NAFLD is paralleled by global increases of obesity and insulin resistance[5]. The natural course of NAFLD is asymptomatic and slowly progressive. A considerable proportion of CHB patients have concomitant hepatic steatosis or even steatohepatitis. A number of studies have investigated the relationship between CHB and NAFLD. Current evidence suggests that hepatic steatosis may have a protective effect on CHB by decreasing HBV viral markers, but CHB patients with concomitant NAFLD are faced with increased risks of advanced liver disease and HCC[6]. The management of such patients is challenging. We know little about the mechanisms of the interactions between HBV and steatosis. Therefore, this review was performed to determine the impact of HBV on hepatic steatosis and its underlying mechanisms.

EPIDEMIOLOGY OF STEATOSIS IN CHB

Prevalence and incidence of steatosis in patients with CHB

NAFLD is defined as the presence of steatosis (*i.e.* more than 5% liver fat content) without coexisting etiologies of secondary steatosissuch as alcohol abuse, metabolic dysfunction, and drug-induced liver injury[7]. Of the viral etiologies, hepatitis C virus (HCV) infection is known to influencechanges in insulin resistance and lipid metabolismthat would lead to hepatic steatosis and more severe inflammation in patients with chronic hepatitis C (CHC)[8]. The prevalence of fatty liver in CHC patients has been reported to range from 40% to 80%[9], depending on metabolic status, alcohol abuse and, virus genotypes[10]. Unlike HCV, there is currently no direct evidence that HBV increases the risk of steatosis. Even so, concomitant hepatic steatosis is not uncommon in HBV-infected patients.

NAFLD is reported to account for nearly 25% of the causes of elevated serum alanine aminotransferase (ALT) among CHB persons[11]. The prevalence of biopsy-proven NAFLD in CHB patients has been estimated to range from 14% to 30%[12-17]. Our recent study reported a prevalence of hepatic steatosis in CHB of 17.3%[18].A meta-analysis reported a higher prevalence of 29.6%[19]. Another recent study found a lower prevalence of NAFLD in CHB patients than in controls (13.5% *vs* 28.3%) using proton magnetic resonance spectroscopy, a highly reliable steatosis assay[20]. We performed a meta-analysis that found a lower prevalence of steatosis in CHB than in the general population (Supplementary material). The results of nine studies indicated a negative association with a possible risk for steatosis in CHB (pooled odds ratio (OR)= 0.81, 95%CI: 0.71-0.920, P = 0.001; Figure 1). Furthermore, the incidence of steatosis in a Korean cohort study was significantly lower in CHB patients than in the

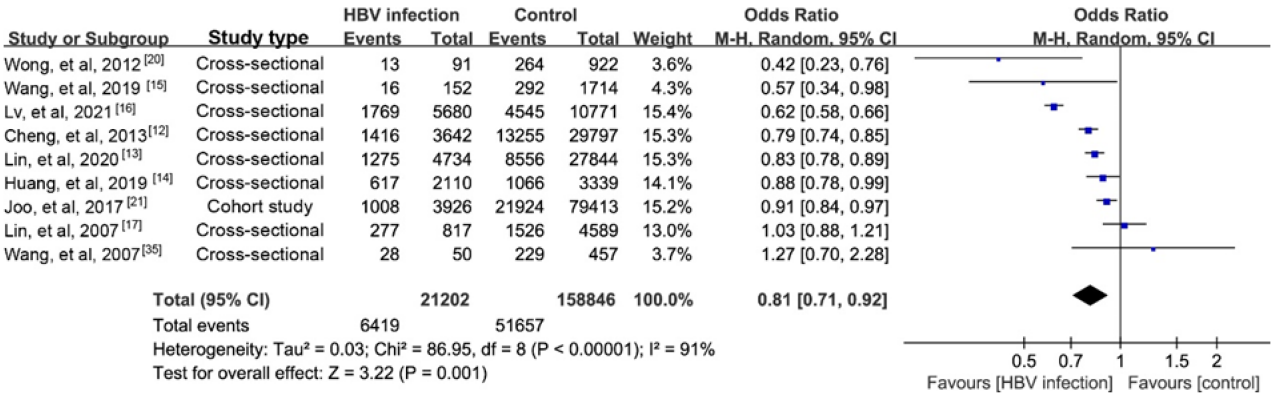

Figure 1 Meta-analysis of the prevalence of hepatic steatosis in patients with hepatitis B virus infection*vs* control.

controls (40.6 *vs* 43.5 per 1000 person-years)[21], and that was lower than an estimate of 52.34 per 1000 person-years in the general population reported by another meta-analysis[22].

Various factors may have contributed to the low prevalence of steatosis in patients with CHB. A study with propensity score analyses reported that a concurrent HBV infection was associated a lower risk of NAFLD than that in subjects who were only hepatitis B core antibody (anti-HBc) positive[23]. Other viral factors, including HBV genotypes, serum HBV DNA level, and hepatitis B e-antigen (HBeAg)positivity, were reported not to be associated with the prevalence of steatosis[20]. Our previous study reported that subclinical hypothyroidism had a role the development of steatosis in CHB patients, and that elevated thyroid stimulating hormone levels, even at normal ranges, were associated with an increased odds ratio of steatosis (OR = 1.54)[24]. Host metabolism has a role the development of steatosis. It was reported that overweight (OR = 5.99), hypertriglyceridemia (OR = 2.95), and type 2 diabetes (OR = 1.88) were risk factors for hepatic steatosis in CHB patients[25,26]. CHB patients with NAFLD presented with altered metabolic profiles and unhealthy lifestyle habits[27,28]. We speculate that differences in the estimated prevalence of NAFLD reported in these studies may be partly explainedby the modified metabolic status in CHB.

Metabolic dysfunctions in CHB

Metabolic dysfunctions have been considered as key factors for incident steatosis in CHB,with oxidative stress, insulin resistance, and hyperglycemia as contributors to hepatic steatosis. Insulin resistance increases fatty acid synthesis, delivery of free fatty acids to the liver, and accumulation of triglycerides in hepatocytes. Chronic inflammatory processes are activated in obesity, type 2 diabetes mellitus (T2DM),and other insulin-resistant states. In this context, activated macrophages release tumor necrosis factor-α and interleukin-6, which promote low-grade inflammation of adipose tissue and even the progression of hepatic damage[29,30]. Proinflammatory cytokines play a crucial role in liver inflammatory responses by promoting hepatocyte apoptosis, hepatic stellate cell proliferation, and angiogenesis[31]. In chronic liver disease, inflammation, fibrosis, and liver function decompensation disrupt liver synthesis functions. Decreased lipoprotein biosynthesis results in lower serum triglyceride and cholesterol levels[32]. Several large studies have described the associations between HBsAg positivity and disorders of lipid metabolism. HBsAg-positive patients had decreased serum cholesterol and triglyceride levels and a decreased prevalence of hyperlipemia [27,33,34]. Our study revealed a lower levels of hepatoxic lipids in serum from NAFLD-HBV patients than in those with only NAFLD[35]. The natural course of HBV infection may play a role in changes in lipid metabolism, especially in elderly patients [36]. This inverse relationship between HBV infection and serum lipid profile may also contribute to reducing the prevalence of metabolic syndrome[37,38].

Another aspect of steatosis in CHB is that impaired glucose and lipid metabolism make intrahepatic lipid content more sensitive to changes in energy intake. Liver inflammation and elevated ALT have been reported to be related to insulin resistance [39,40]. Evidence suggests that the prevalence of insulin resistance is higher in patients with CHB concomitant with NAFLD than in patients with HBV or NAFLD alone[41]. Numerous studies have reported a negative association of CHB and steatosis without aparallel risk associated with insulin resistance[40]. First, decreased liver functional reserve was found to promote insulin resistance, and because it is involved in glucose

metabolism, liver damage from hepatitis causeddisorders of glucose metabolism. The risk of developing diabetes was decreased in CHB after excluding patients with cirrhosis. Second, the association of insulin resistance and steatosis was attenuated by multiple host factors other than viruses, andage and obesity were both confounders of the risk of diabetes in CHB patients[42].

In CHB patients, steatosis resultsfrom a combination of metabolic abnormalities and the status of HBV infection. Thataccounts for the reported differences in the prevalence of steatosis in CHB patients and explains why previous HBV infection does not affect the prevalence of NAFLD[23]. The design of early studies failed to comprehensively evaluate metabolic status, calorie intake, and physical activity of CHB patients. Therefore, it was not possible to adjust for all confounding factors. Causes associated with those factors deserve investigation.

PROGRESSION AND OUTCOMES OF CHB WITH NAFLD

Disease severity of CHB with NAFLD

Chronic HBV infectionand NAFLD are the leading causes of chronic liver disease worldwide. Previous studies have considered steatosis to be an irrelevant or even a protective factor of CHB[25,43],but few focused on the effect of HBV on the severity and long-term outcome of NAFLD. The meta-analysis mentioned above revealed a strong negative association between serum viral load (*e.g.*, HBV DNA level and HBsAg positivity) and hepatic steatosis[19]. Similarly, a Korean cohort with non-CHB controls found an association between HBsAg positivity and a reduced risk of NAFLD [21]. After adjusting for metabolic factors, including insulin resistance, the association was attenuated[21], which indicated that metabolic and viral factors should both be taken into consideration.

Nonalcoholic steatohepatitis (NASH) is a severe form of NAFLD, that is prevalent in CHB patients. In a North American and European cohort, the prevalence of biopsy-proven NASH was approximately 17%[44]. NASH is characterized by necroinflammation and hepatocyte ballooning and is the major cause of advanced liver fibrosis, cirrhosis, and HCC in NAFLD[45]. Compared with bland steatosis, NASH has a more rapid progression in fibrosis[46], and it has been associated with anincreasedincidence of HCC, of up to 5.29 per 1000 person-years[47]. There is no doubt that CHB patients with NASH have a higher risk of developing advanced fibrosis, HCC,or even death than patients without steatohepatitis[44,48]. Concomitant NASH should thus be taken seriously in CHB patients. Hepatic inflammationis key fordisease progression. Although it would be difficult to differentiate the cause of inflammation from steatohepatitis in CHB patients, the risk of disease progression would be decreased if HBV replication could be suppressed before age 40. Therefore, the outcome of CHB patients with NASH would be improved in patients with early-stage NAFLD and low HBV replication phase. Comprehensive assessment and close monitoring are required in the management of CHB patients, irrespective of their viral load.

Risk of fibrosis in CHB patients with NAFLD

In patients with NAFLD, fibrosis is the characteristic that is most closely related to long-term adverse events compared with other histological features[49]. In the development of fibrosis in NASH, sustained lipotoxicity and endoplasmic reticulum stress induce cell death in steatotic hepatocytes. Developmental pathways including Notch, Hedgehog and YAP–TAZ are persistently activated to cope with the chronic insult. As a result, crosstalk of hepatocytes-macrophages-hepatic stellate cells and activation of resident Kupffer cells lead to inflammatory and fibrogenic responses[50].

Accumulating evidence suggests an increased risk of advanced fibrosis and long-term adverse prognosis in CHB patients with NAFLD. Our cross-sectional study found that CHB patients with steatosis had less severe fibrosis than those without steatosis [51]; but in prospective cohort studies, the baseline severity of steatosis was associated with more progressive fibrosis[52-54]. Furthermore, Charatcharoenwitthaya *et al*[25] reported that steatohepatitis but not simple steatosis was an independent predictor of significant, advanced fibrosis.The additive effect of steatosis has also been reported in the progression of fibrosis. Persistent severe steatosis led to a 2-fold increased risk of fibrosis progression over a 3-year follow-up[43]. A retrospective cohort study with biopsy-confirmed cirrhosis progression found that CHB patients with concomitant steatosishad a higher proportion of incident cirrhosis (36%) than those without steatosis (22%)[55]. There is little direct evidence of the effect of steatosis on fibrosis regression. It has been reported that low body mass index (BMI) and steatosis

resolution during tenofovir antiviral treatment were associated with fibrosis regression in CHB patients[43,56], suggesting that management of metabolic disorders and concomitant steatosis were key considerations of anti-fibrotic treatment.

Risk of HCC in CHB patients with NAFLD

Previously, more than 70% of HCC morbidity was attributed to chronic viral hepatitis. NAFLD has been predicted to replace viral etiologies in contributing to the HCC burden. NAFLD could account for more than 30% of HCC cases, especially in developed countries[57]. The progression of HCC in CHB patients with NAFLD is complicated, with direct evidence remaining elusive. As previously discussed, liver fibrosis and cirrhosis are recognized as key drivers of HCC[47]. Evidence suggests that metabolic factors are also responsible for disease progression. CHB patients with high BMI values were reported to have increased incidences of cirrhosis and HCC[58],and long-term follow-up has indicatedthat the incidence of HCC and the risks of liver-related mortality increase with the number of associated metabolic factors[59]. Two retrospective liver biopsy-proven cohort studies reported a 2-7-fold increase in the risks of HCC in CHB patients with NAFLD[48,55]. Recent studies reported similar results, but they found the association was reduced after adjusting for metabolic factors and age[6,60]. We speculate that metabolic factors, especially T2DM, play an important role in the development of HCC.

HCC remains the second leading cause of death related to malignancy worldwide [61].Screening and management of metabolic disorders in CHB patients are crucial for the prevention of HCC, andcoexisting factors should be taken into consideration. In the above-mentioned study, the association of hepatic steatosis and HCC development was observed only in patients receiving antiviral treatment, not in the overall population. That is because confounding factors including significant alcohol drinking were not considered[48]. In addition, the prevalence of NAFLD andthe HBsAg seroclearance rate both increase with age[62]. Therefore, patient age may be a confounding factor in the association of HBV infection with the long-term outcome of NAFLD. Noninvasive methods have often been used to identify steatosis in population-based studies, considering the injury risk of liver biopsy and the infeasibility of large numbers of patients,and using different measurements leads to bias in the definition of steatosis. Trial-based studies have carefully selected homogeneous patient samples that were matched for the presence of confounders. If patients with significant metabolic dysfunctions such asT2DM and cardiovascular disease were excluded, then the study results might not be representative of all types of real-world situations.

The overall long-term outcome of patients with CHB concomitant with steatosis is subject to avariety of risk factors. Liver conditionsincluding NASH and advanced fibrosis were found to have additive effects on event-free survival (HCC, decompensation and transplantation)[44]. Wong *et al*[52] reported that steatosis had no direct predictive effect on these events including cardiovascular events, liver-related complications, malignancy and mortality.

Important issues in clinical management

The effects of steatosis on the progression and remission of CHB have been widely investigated but few studies have focused on the outcome of NAFLD in the natural course of CHB or during antiviral treatment. Issues that should be addressed are: (1) The incidence of NAFLD in CHB and decreased risk of NAFLD in CHB[21] and diabetes[26]. Metabolic factors including weight change and lifestyle habits have not been comprehensively evaluated but a negative association may not reflect the etiology; (2) The progression of fibrosis in NAFLD needs study because the findings of cross-sectional studies are inconsistent. Concurrent HBV infection has been associated with advanced fibrosis[63], but anti-HBc-positive NAFLD patients are reported to have increased risks of cirrhosis, HCC, and liver-related complications[64]. The role of HBV infection status requires investigation; (3) The regression of fibrosis in NAFLD needs study. Steatosis resolution has been reported to be associated with fibrosis regression in CHB[43]; but whether HBV cures or antiviral treatment responses affect fibrosis regression in NAFLD remains unknown; and (4) The resolution of NASH. Given the interaction of steatosis resolution and fibrosis regression, the impact of fibrosis improvement after antiviral treatment of steatosis-related inflammation remains unknown.To address these issues, the interaction between HBV and metabolic homeostasis in the progression of liver disease requires further study.

EFFECT OF ANTIVIRAL TREATMENT ON NAFLD

Few studies have investigated the incidence of hepatic steatosis during antiviral treatment with pegylated interferon and nucleos(t)ide analogs (NAs). NA therapy reduces HBV replication, suppresses inflammation, and improves fibrosis in CHB[56]. Most studies have shown that NAFLD has no impact on viral suppression and biochemical responses during NAs antiviral treatment[65,66]. Whereas, decreased virological responses were also observed in CHB patients concomitant with steatosis in several studies[43,67,68]. In those cases, the authors speculated that the elevated ALT caused by NAFLD could lead to premature antiviral treatment and a poor response.

A recent study reported that lamivudine, entecavir, or adefovir dipivoxil increased the BMI and increased the visceral fat area in CHB patients[69]. It is worth noting that tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) were found toimprove the lipid metabolic profile of CHB patients. Compared with patients treated with entecavir, greater declines in serum lipid components were observed in patients treated with TDF[70]. An *in vitro* study reported that TDF modulated lipid metabolism by upregulating hepatic CD36 by activating PPAR-α[71]. Overexpression of hepatic CD36 improved hepatic steatosis and insulin resistance by reducing hepatic lipids, which might explain the findings above. In a study of CHB patients, switching to TAF improved metabolic dysfunction, reduced serum ALT levels, and improved ALT normalization in patients with or without diabetes despite significant increases in body weight and BMI[72].

Myrcludex B is a novel agent for CHB treatment that inhibits hepatic bile acid uptake transporter Na^+ taurocholate cotransporting polypeptide (NTCP). It has been shown to be safe and welltolerated and is currently in phase 2b clinical trials for the treatment of HBV infection. Recently, a study showed that Myrcludex B induced weight loss and decreased hepatic adiposity by inhibiting the hepatic clearance of bile acids from portal and systemic blood, stimulating glucagon-like peptide-1 (GLP-1) secretion[73].Because these agents potentially improve dyslipidemia and metabolic dysfunctions, TDF, TAF and Myrcludex B could be used to treat metabolic diseases, including NAFLD. They may be the best choice for CHB patients with concomitant NAFLD.

MECHANISMS OF INTERACTION BETWEEN HEPATITIS B AND STEATOSIS

Currently, the majority of CHB patients are on antiviral treatments that provide potent virological suppression. Viral factors are attenuated, and the relative influence of metabolic factors are increased in the course of NAFLD[74], which was verified in a study in HBsAg transgenic (HBs-Tg) mice. High-fat methionine-choline-deficient diet (MCD)-fed HBs-Tg mice had more liver fat accumulation and macrovesicular fat droplets than wild-type C57BL/6 mice. HBsAg increased susceptibility to steatohepatitis in those mice[75]. The evidence indicates that CHB patients should manage their lifestyle to prevent the incidence of NASH.

Accumulating evidence on single nucleotide polymorphisms (SNPs) and NAFLD severity and progression has helped to elucidate the genetic basis of NAFLD. SNPs of patatin-like phospholipase domain-containing protein 3 (PNPLA3) and transmembrane 6 superfamily member 2 (TM6SF2) are two common genetic determinants of NAFLD[76,77]. In cohort studies of biopsy-proven CHB patients, several SNPs of PNPLA3 were independently associated with steatosis, lobular inflammation, and steatohepatitis andwere similar to the findings of NAFLD studies[48,78,79], in which patients with SNPs of the T allele of rs1010023 in PNPLA3 were more susceptible to hepatic steatosis[78]. The T allele of rs58542926 in TM6SF2 has been associated with altered lipids and hepatic steatosis in CHB patients; this substitution was associated with increased HBV DNA[80]. As the T allele has a low prevalence of 7% worldwide, it may play a role in steatosis in a minority of the population. The evidence suggests the possibilityof genetic susceptibility to fatty liver in CHB.

Clinical studies that describe macroscopic results are often limited by the heterogenous characteristics of enrolled patients. Basic science studies would better balance confounding factors, and provide clues for elucidating the mechanism of interactions between HBV infection and fatty liver. Hepatitis B protein X (HBx), one of the four HBV proteins, has an important role in HBV infection. Previous studies in HepG2-HBx stable cells and in HBx-transgenic mice confirmed that overexpression of HBx induces

hepatic lipid accumulation, and that HBx is a risk factor for steatosis[15]. HBx is mediated by sterol regulatory element binding protein 1 (SREBP-1) and peroxisome proliferator-activated receptor gamma (PPAR-γ)[81]. HBx has been reported to upregulate fatty acid binding protein 1 (FABP1) to promote hepatic lipid accumulation in the development of steatosis in HBV-induced cells[82]. During treatment, the expression of HBx and downstream factors were downregulated by antiviral agents [83], which might be helpful for the improvement of steatosis during antiviral treatments in clinical studies.

As a regulator of adipocyte differentiation, CCAAT/enhancer-binding protein α (C/EBPα) triggers adipocyte differentiation by inducing complex cascades of transcription. In HBx-transfected hepatocytes, HBx stimulates the expression and transcriptional activation of C/EBPα and PPAR-γ[81]. Endoplasmic reticulum stress is associated with liver injury and fibrosis. C/EBPα is also the effector of endoplasmic reticulum stress, but whether HBV-induced endoplasmic reticulum stress plays a role in the development of concomitant steatosis requires further research. The involvement of adiponectin in adipogenic conversion in CHB has been extensively studied. Adiponectin improves hepatic insulin sensitivity and decreases lipid accumulation in macrophages. CHB patients have been reported to have higher serum adiponectin levels[27,84], which could account for the low prevalence of steatosis in HBV-infected subjects. The metabolic changes related to HBV infection at the cellular level could help explain the clinical,but phenotypic differences related to NAFLD at the individual level require further study.

CHALLENGES IN HISTOLOGICAL EVALUATION

NAFLD and CHB use different scoring systems for histological assessment. The fatty liver inhibition of progression algorithm and steatosis, activity, and fibrosis (FLIP-SAF) score[85] and NAFLD activity score (NAS)[86] are used to evaluate histological activity.The criteria include steatosis, lobular inflammation, hepatocyte ballooning, and fibrosis. In the assessment of CHB, Ishaket al[87] and The METAVIR study group [88]have described two major scoring systems to evaluate necroinflammation and fibrosis. Because the pathogeneses of CHB and NAFLD are complex, the coexistence of HBV and steatosis-induced injury may affect each other. The steatosis distribution patterns in CHB patients with concomitant NAFLD and in those with NAFLD alone. In CHB, SHG/TPEF scores of the steatosis distribution and in the peripheral region and that in lobule region were similar.In NAFLD, the steatosis percentage was significantly lower in the peripheral region than in the lobule region[89]. Whether CHB concomitant with NAFLD has novel pathophysiological characteristics remains unclear.

The inflammation of CHB and NAFLD has been differentially evaluated by hepatocyte injury. The modified Knodell necroinflammatory score of the Ishak scoring system is used to assess CHB activity and is based on four variables, periportal or periseptal interface hepatitis, confluent necrosis, focal apoptosis and portal inflammation[87]. The NAS and SAF activity scoresare used to quantify inflammation in NAFLD. Ballooning is the most specific inflammatory characteristic of NAFLD, andin CHB concomitant with NAFLD, ballooning is predictive for clinical outcomes[44]. A cross-sectional studyreported that CHB with steatosis had less necroinflammation and fibrosis than CHB without steatosis[19], but CHB activity has not been associated with the degree of steatosis[90]. Although both algorithms score fibrosis on a scale of from 0 to 4, they are based on different zones and severities. In contrast to viral hepatitis, fibrosis characteristic of NASH is predominantly seen with lobular inflammation. Thus, zone-3 perisinusoidal fibrosis has been the primary focus during evaluations [86].

The dynamic assessment of inflammation and fibrosis are major problems faced in evaluating CHB concomitant with NAFLD. During antiviral treatment, viral suppression attenuates necroinflammation in CHB, inducing fibrosis improvement. Although the pathogenesis of HBV infection and NASH differ, they share a common pathway to fibrogenesis because of necroinflammation. Histological improvement in CHB is defined as a more than 2-point reduction in the Knodell necroinflammatory score with no worsening of fibrosis.Resolution of NASH is defined an inflammation score of 0 to 1 and a ballooning score of 0[91,92]. It is difficult to determine whether changes in CHB inflammation severity influence the NAFLD inflammation score orwhether fibrosis regression in CHB induces improvement of NAFLD. These problems have complicated the assessment of CHB regressionconcomitant with

NAFLD.Currently, with the new nomenclature of metabolic-associated fatty liver disease[93], it is no longer a diagnosis of exclusion. Based on the presence of steatosis and metabolic dysfunction, the diagnosis of NAFLD coexisting with CHB might be more feasible[94]. Thus, new definitions are needed to correctly classify patients during histopathological evaluation in clinical practice.

CONCLUSION

The decreased prevalence and incidence of steatosis in CHB patients are mainly due to altered metabolic profiles. However, concomitant steatosis increases the occurrence of adverse liver-related events, including cirrhosis and HCC. Lifestyle management and screening of metabolic changes associated with steatosis are recommended in CHB patients regardless of viral load. Traditional antiviral therapy has no impact on the incidence of steatosis, but tenofovir and NTCP inhibitors have strong metabolic effects, which could be promising in the treatment of CHB patients concomitant with NAFLD. Further study is necessary to determine whether these associations cause macro changes. As the mechanisms of interactions between steatosis and HBV infection become more clear, future studies will provide novel strategies for the clinical management and treatment of CHB concomitant with NAFLD.

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