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The interplay between non-alcoholic fatty liver disease and innate immunity in hepatitis B virus patients

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) is the most epidemic liver disorder worldwide as a result of rapid lifestyle transformation over the past few decades and is expected to elevate in the next few years as well as it is ranging from plain hepatic steatosis via non-alcoholic steatohepatitis (NASH) to liver cirrhosis and hepatocellular carcinoma (HCC).

Main text: NAFLD can also stimulate the diseases progression as diabetes and cardiovascular. Therefore, understanding the NAFLD pathogenesis is of vital clinical interest additionally is a crucial for disease treatment and prevention. After analyzing NAFLD and liver diseases prevalence, it has been a belief regarding the interaction between NAFLD and chronic hepatitis B (CHB).

Conclusion: The liver is an essential innate immune organ with large numbers of innate immune cells that contribute in NAFLD pathogenesis, additionally play the influential role that control NAFLD progression in the hepatitis B patients. Here, we summarized the recent advances in understanding and managing the NAFLD patients with chronic hepatitis B infection and interplay with innate immunity.

Keywords: HBV, Fatty liver, NAFLD, NASH, Innate immunity

Background

In fact hepatitis B virus (HBV) infection is still a major public health problem that leads to complicated progression of severe liver diseases including cirrhosis and hepatocellular carcinoma [1]. Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in the world with a global prevalence of 25.24%, and popularity is alarmingly expanding in adult, adolescent, and children populations, and it is a condition in which the aberrant lipid is accumulated and stored in the liver. There are many causes hepatic steatosis than consumption of alcohol [2, 3]. NAFLD includes a spectrum of disorders ranging from the simple fatty liver to non-alcoholic steatohepatitis (NASH), with developing fibrosis leading to cirrhosis [4]. NAFLD significantly increases the risk of development of chronic kidney disease in type 2 diabetic patient [5], also patients with NAFLD have a super chance of evolving cardiovascular disease [6]. The increasing rate of NAFLD among HBV-infected patients is alarming; it is estimated that as many as 29.6% of HBV patients worldwide have NAFLD [7]. The reflective cohort study found that fatty liver disease in HBV patients can separately increase HBV-associated HCC progress by 7.3-fold [8]. Also a meta-analysis comprising of 4100 HBV patients reported that body mass index (BMI), obesity; moderate alcohol consumption, diabetes mellitus, elevated serum triglycerides, and HBV viral load were risk factors of NAFLD in HBV patients [9].

A better understanding of the epidemiology of NAFLD among HBV patients is very important for the implementation of efficient preventive strategies with chronic HBV infected patients. The innate immune system is

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initiating the response of the organism to serious stressors, including pathogens, tissue injury, and malignity. The liver is a foremost innate immune organ with enormous numbers of innate immune cells, including natural killer T (NKT), natural killer (NK) cells, and Kupffer cells (KCs) which play crucial roles in the extravagant production of hepatic Th1 cytokines in NAFLD. Moreover, liver innate immune cells share in the pathogenesis of NAFLD [9]. Abundant research data shows that innate immune processes both within and outside the liver is engaged with NAFLD [10].

Toll-like receptor 4 (TLR4) plays a chief role in the innate immune system that activate two specific intracellular signaling pathways via MyD88-independent pathways causing the stimulation of tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), and type 1 interferons (IFNs I) and also play a vital role in NAFLD progress [11]. Many studies gave different conclusions about the correlation between NAFLD and HBV replication. Some of these studies showed increased rate of NAFLD in HBV patients, and showed suppression of viral replication by NAFLD [12]. This review article is aimed to discuss the relationship and interplaying between NAFLD, innate immunity in HBV-infected patients, and valuable recommendations to avoid disease complications.

Main text

Molecular organization of HBV

HBV is a partially double-stranded relaxed circular DNA virus consists of 3.2 kb gnome that translated into four overlapping open reading frames (ORFs). Viral polymerase is the largest one which also has reverse transcriptase (RT) activity. Viral envelope proteins (large, middle, and small surface antigen (HBsAg). Pre-core protein that encode (HBeAg and HBcAg) which made the viral capsid. The smallest ORF is (HBx) protein which plays an important role in HBV replication and regulation in vitro and in vivo models [13–15]. The HBV viral ORFs were encoded in capped and polyadenylated RNAs transcripts that can classified into genomic and sub-genomic which play as a template for HBV proteins translation (0.7 kb) that encodes HBx proteins 2.1 kb and 2.4 kb HBsAg transcripts encoded (M, S, and L), respectively. On the other hand, HBV gnomic transcripts encode precore, core, and polymerase proteins and pregenomic RNA (pgRNA) which consider a template for HBV replication and reverse transcription to build HBV DNA genome [16–18]. HBV is classified into ten genotypes (A-J) due to high degree of genetic heterogeneity, variability, and about 8% complete genome differences. Some genotypes were sub-genotyped into sub-genotypes due to 4% sequence divergence. These genotypes and sub-genotypes can display complex ethnical, geographical distributions, and clinical implications [19–21].

HBV infection and epidemiology

The host and viral factors were affecting on HBV infection variations which can be classified into acute infection (presence of HBsAg and HBcAg-IgM). The presence of HBeAg indicting high level of HBV replication and most people during the acute infections have no symptoms. However, some patients developed acute illness with obvious symptoms for several weeks and rare patients can develop liver failure which can lead to death. Chronic HBV infection indicated presence of HBsAg more than 6 months. Persistence of HBsAg for long time is a marker for developing liver cirrhosis and hepatocellular carcinoma (HCC) in 20–30% of adults. In addition, some patients develop occult HBV infection (OHI) which characterized by presence of HBV DNA in the liver tissues and absence of HBsAg in serum [22–24]. Moreover, HBV infection is one of the major global health problems that mainly cause liver cirrhosis and liver cancer with 100-folds more that uninfected populations [25, 26]. WHO statistics were shown that about 337,000 annual deaths [27]. In 2017, 257 million people had chronic HBV infection, which resulted in 887,000 deaths [28, 29]. HBV endemicity is classified into three groups: low (< 2%), low-intermediate (2–4.9%), high-intermediate (5–7.9%), and high (≥ 8%) [30].

Non-alcoholic fatty liver disease (NAFLD) definition and epidemiology

Non-alcoholic fatty liver disease (NAFLD) is defined by accumulation of triglyceride (TG) in hepatocytes (lipid droplets with 5% in hepatocytes cytoplasm) and can lead to non-alcoholic steatohepatitis (NASH), which is characterized by steatosis, inflammatory changes, and hepatocyte cell ballooning associated with varying degrees of liver fibrosis [2, 31]. NAFLD is considering a major cause of liver-related morbidity and mortality worldwide, and most common reason for chronic liver disease in the western world [32]. NAFLD can be classified into two phenotypes: (I) steatosis (fatty liver) and (II) steatohepatitis. About 15–20% of non-alcoholic steatohepatitis (NASH) patients were progressed to liver cirrhosis and also a risk factor for heart disease [33, 34]. Recently, many studies have found development of liver cancer in NAFLD cases even in the absence of cirrhosis [35, 36]. These abnormalities were developed even in absence of extra-alcohol consumption [2]. Globally, 25% of populations suffering from NAFLD, and the incidence were increased in the Middle East and South America rather than in Africa [37]. The progression of NAFLD was different, it's related to high obesity in North America and Europe (~ 83% of patients) and normal body mass index (BMI) in Asia with "lean NASH" [38].

NAFLD usually accompanied by many metabolic syndrome such as obesity, insulin resistance (IR), type 2

diabetes mellitus (T2DM) and dyslipidemia that exhibited an increased overall mortality compared to the general population [30, 39]. Moreover, NASH patients also have a higher risk of liver fibrosis, cirrhosis, and liver cancer that lead to mortality [40, 41]. There are different factors affecting on NAFLD progression and clinical manifestations such as environment, the microbiome, metabolism, comorbidities, and genetic risk factors that have been underscored by studies identifying a higher risk of fibrosis among family members of those diagnosed with NASH [42, 43]. The host genetic factors were affecting on NAFLD subtypes that could be used as sensitive predictive and monitoring markers in NAFLD diagnosis and treatment [44].

Risk factors for NAFLD and NASH

The occurrence of metabolic syndrome (MetS) which consists of obesity, hyperglycemia, dyslipidemia, and systemic hypertension (HTN) is considered high risk factor of NAFLD [45] and the effective treatment of NASH could have the additional benefit of improving the features of MetS. MetS is also an important role in adverse cardiovascular (CV) events and overall mortality in patients with NAFLD [46, 47]. Type 2 diabetes mellitus (T2DM) has the clearest biologic link to the progression of NAFLD (75%) which can be developed to NASH and advanced fibrosis more than non-diabetics patients [48, 49]. Moreover, NAFLD and diabetes were considered risk factor to develop the liver related complications such as liver cirrhosis and hepatocellular carcinoma [50]. Insulin resistance has been affecting on disease progression and integrated with NAFLD pathogenesis [51]. On the other hand, bettering insulin resistance improves NASH. Although, patients with NAFLD are also at increased risk of incident diabetes [52].

Common pathogenic mechanisms of NAFLD

Hepatic steatosis is a precursor of NAFLD; steatosis can be occurred by several mechanisms such as increased fat supply, decreased fat export in the form of very low-density lipoprotein-triglyceride, decreased free fatty β-oxidation and increased de novo lipogenesis (DNL) [53]. Molecular mechanisms affecting the prevalence of fatty liver due to certain cytokines derived from inflammation sites, especially from extra-hepatic adipose tissues. More importantly, insulin resistance (IR) appeared to play important role in massive metabolic dysregulations of NAFLD that initiate and progress hepatic steatosis. Simple hepatic steatosis, more characteristically, liver cell damage, and accompanying inflammation and/or fibrosis were considered pathological features of NASH. Currently, many pathogenic mechanisms and pathways have been proposed to explain the transition from simple steatosis to NASH, like lipotoxicity, oxidative stress, mitochondrial dysfunction, and endoplasmic reticulum stress [53]. Diacylglycerol (DAG) and ceramides are a lipid derived second messengers that generated by hepatic insulin resistance due to lipid accumulation. Furthermore, lipid accumulation in the liver lead to the progression of endoplasmic reticulum stress (ER stress), mitochondria stress, and impaired autophagy, resulting in the condition known as lipotoxicity. Finally, these events caused the immune response in the Kupffer cells and hepatic stellate cells, which leads to the progression of NASH, hepatic cirrhosis, and in some severe cases, hepatocellular carcinoma as shown in (Fig. 1) [54].

Diagnostic possibilities in non-alcoholic fatty liver disease and non-alcoholic steatohepatitis

From many years ago, more systematic findings have discovered the risk of NAFLD and NASH. These risk factors were T2DM, obesity, hypertension, and dyslipidemia even with normal liver transaminases and enzymes. NAFLD and NASH could be suspected with further measurements like liver stiffness (fibroscan® test), CT-scan (sensitive and specific, but exposes the patient to radiation), or magnetic resonance induction (MRI), which is the gold standard, but most expensive to identify liver steatosis. Currently, the histological liver biopsy evaluation is the only reliable diagnostic tool for NASH with fibrotic stage of the liver to predict the liver cirrhosis [55]. MRI elastography is the best method for fibrosis prediction but often not available or not tolerant by the patients. Many accurate non-invasive tests to examine the hepatic fibrosis were fibrosis-4 index, aminotransferase (AST), and platelet ratio (APRI) [56, 57].

In vitro models to study NAFLD

Human hepatoma cell lines such as HepG2 and immortalized primary human hepatocytes were used as in vitro models for NAFLD. But, it has some challenges such as complications of molecular pathways and some functional aberrations compared to non-immortalized primary human hepatocytes model [58–61]. Godoy et al. has reported that the use of liver biopsy-derived primary human hepatocytes as NAFLD model is applicable but also limited and can only cultivated for a few days and de-differentiation challenge [62]. The application of hepatocytes cells as a robust in vitro model to examine the different aspects of liver functions and metabolic pathways such as cholesterol and glycogen metabolism has evaluated in recent years. But there are some limitations due to limited availability. In addition, PHHs culturing were quickly de-differentiated and lose their liver functions [63].

The most applicable and advanced in vitro model is human-induced pluripotent stem cell (iPSC)-derived hepatocytes that provide a good alternative model to PHHs

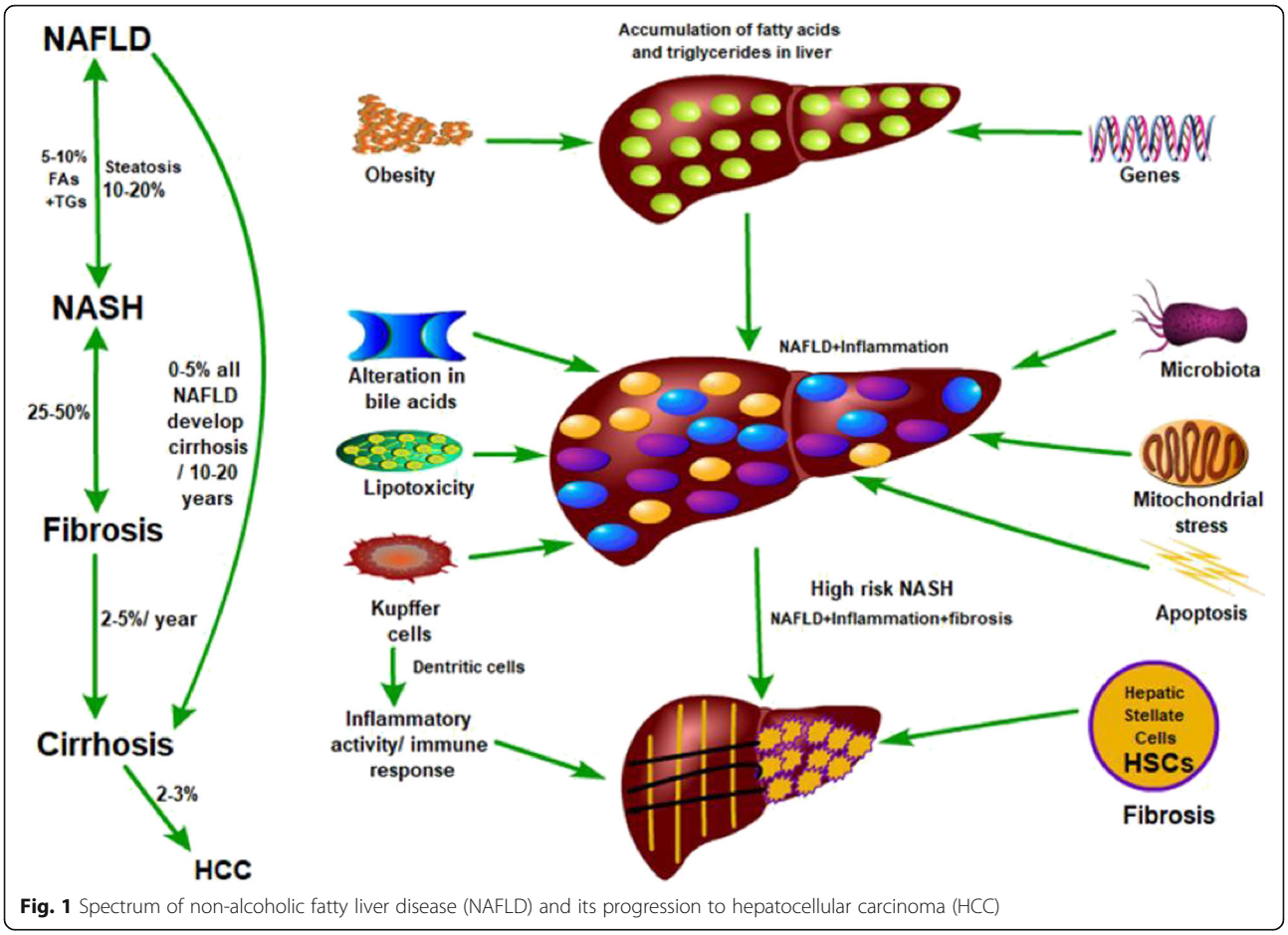

Fig. 1 Spectrum of non-alcoholic fatty liver disease (NAFLD) and its progression to hepatocellular carcinoma (HCC)

due to easy reprogramming from dermal fibroblasts and then differentiated into hepatocyte-like cells (HLCs), which functionally look like PHHs [64]. Many advantages were provided in iPSC-HLCs such as recapitulation of the metabolic variations observed in the population, potency in both short- and long-term drug screening and in investigating hepatotoxicity or developing novel therapeutics actions [65–67]. In addition, iPSC-HLCs have been utilized for fetal liver exposure to toxic substances [68] and identification non-coding micro-RNAs regulating human liver damage [69, 70]. Furthermore, HLCs have been successfully used as applicable in vitro models to study hepatic diseases such as systemic amyloidosis [71], liver-stage malaria and hepatitis C viral infection [72]. IPSC-HLCs could also offer a gold model for examination basic liver metabolic mechanisms, e.g., lipid metabolism as well as its dysregulation is related to different diseases such as fatty liver disease or atherosclerosis.

The association between hepatitis B virus infection and non-alcoholic fatty liver disease (NAFLD)

An inverse association between HBV and some metabolic syndrome has been reported in recent studies [73]. Furthermore, few studies have investigated the effect of HBV infection on the risk of NAFLD but still in debate. Liu et al. have reported that HBV patients have a lower level of triglycerides that may be affect NAFLD development [74]. Moreover, some previous studies reported that HBX protein inhibits the secretion of apolipoprotein B, which play an important role in very low-density lipoprotein and low-density lipoprotein (VLDL) [75, 76]. In addition, other studies have showed the link between HBV seropositivity and low serum cholesterol levels [77, 78]. In human studies, HBV infection affecting the secretion of various adipokines and may decrease the lipid profile levels [79, 80]. On the other hand, Ramcharran et al. have reported that lipid metabolism has been implicated in hepatitis C viral entry, replication, and response to treatment and may be lipid metabolism affected by HBV replication [81]. In depth understanding of mechanism between HBV replication and NAFLD may discover new treatment targets on NAFLD [82].

Limitations to study the relationship between NAFLD and HBV

Several limitations should be considered to study the association between HBV and NAFLD such as (1) Xiong's

meta-analysis study used different methods to diagnose the NAFLD outcomes, including ultrasound and proton-magnetic resonance spectroscopy (H-MRS) [83]. But, their results with different diagnostic measures were combined that leads to heterogeneity regarding aspects in the meta-analysis process. In addition, the methodological differences may limit the comparability of studies and influence the impact identified on NAFLD risk. (2) Their results have been explained as a relationship between HBV and NAFLD only that may be confounding bias. Because, a number of adjusted factors should be considered and discussed such as physical activity and other dietary factors. For example, Zelber-Sagi et al. and Hallsworth et al. have showed that HBV patients have active physical activity and good dietary habits, which affect NAFLD incidence. (3) Failure to get information about HBV-infected patients under antiviral treatment may affect the development of NAFLD. (4) All included studies in their meta-analysis were carried out in Asia, and it is thus difficult to generalize their findings to the general population [84, 85].

Chinese studies confirmed the link between NAFLD and HBV

NAFLD was found in 23.3% of the studied group and linked to higher liver enzymes, TGs, and fasting blood sugar (FBS) in Chinese-based study [86]. However, the accurate correlation between NAFLD and HBV infection has not been fully understood [7, 12, 82, 87, 88]. On the other hand, HBX protein affects lipogenic genes such as sterol regulatory element-binding protein1c (SREBP1C), fatty acid synthase, and peroxisome proliferator-activated receptor (PPAR) [89]. On the contrary, many studies reported that HBV infection was not associated with hepatic steatosis and insulin resistance that may relate to metabolic factors but not viral factors [90–92].

In addition, HBV infection was related to lower prevalence of fatty liver, especially in overweight or obese subjects or were older than 50 years. However, the association between HBV and fatty liver was less obvious if patients were normal-weight or younger than 50 years. On the contrary, in subjects with fatty liver disease regardless of their age and BMI were correlated with HBV positivity [76], although many previous studies have tried to clarify the link between HBV infection and fatty liver disease [7, 12, 76, 82, 87, 88]. In China, a great difference in HBV-related fatty liver. In Beijing, the frequency of fatty liver in HBV patients is higher than that for the general population, but lower than that in HCV patients [91, 93]. On the contrary, in Shanghai, the prevalence of NAFLD in HBV patients was less than that for the general population [76, 94]. Moreover, Wang et al. 2008 showed that chronic HBV infection presented with no significant impact in the prevalence of fatty liver in patients younger than 50 years [95].

The association between NAFLD, innate immunity in HBV patients

NAFLD is becoming common in both general population and HBV patients that reflect the incidence of obesity in both western and eastern countries with broad spectrum ranging from simple hepatic steatosis through non-alcoholic steatohepatitis (NASH) to liver cirrhosis [7]. Nowadays, many Asian patients are suffering from both NAFLD and chronic HBV infection. However, the mechanism of NAFLD and its effects on HBV infection have not yet been adequately clarified in patients with CHB [96, 97].

Some previous studies reported that hepatic steatosis in CHB patients is mainly associated with metabolic disorders, such as obesity, type 2 diabetes mellitus (T2DM), and dyslipidemia; it is not associated with HBV viral load or genotype [7, 82, 98, 99]. This is proved by the strongly expressive results indicating a negative association of hepatic steatosis with viral load. Thus, hepatic steatosis may enhance viral clearance and inhibit HBV DNA replication. However, we have not been successful in elucidating the mechanism underlying the association between steatosis and HBV [82, 98]. Some evidences indicate that toll-like receptor 4 (TLR4) signals the pathway associated with the pathogenesis of NAFLD in patients with HBV infection. TLRs are a family of pattern recognition receptors that play a critical role in the innate immune system as ten different types of TLRs are expressed in human beings. Toll-like receptor 4 is a cell surface receptor that is crucial for the activation of innate immune responses [100].

Machado et al. and Michelson et al. have explained the mechanism linked between TLR4 and NAFLD via MyD88-dependent and MyD88-independent pathways that activated with binding TLR4 to induce proinflammatory cytokine genes, such as tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), and type 1 Interferon (IFNsI) [11, 101]. On the other hand, bacterial endotoxin lipopolysaccharide (LPS) is a well-known as TLR4 ligand [102, 103], and, non-bacterial substances such as free fatty acids (FFAs) may also function as TLR4 ligands. Palmitic acid (PA) and oleic acid (OA) are the most common FFAs that bind with TLR4 to activate the expression of proinflammatory cytokines in macrophages, adipocytes, and liver cells [100, 104, 105]. TLR4/MyD88 signaling pathways played an important role in NAFLD incidence. In addition, downstream proinflammatory cytokines (TNFα, IL-6) promoted the progression of NAFLD. However, the interaction between chronic HBV infection and TLR4 is complex; some studies have

indicated that HBV replication is inhibited when LPS signals TLR4 to upregulate IFN-β expression levels through MyD88 independent pathway [106, 107]. On the other hand, some direct and indirect mediators inhibit viral replication such as IFNα/β, TNFα, IL-1, and nitric oxide [107, 108] as shown in (Fig. 2).

The relationship between serum HBV DNA level and NAFLD was investigated in previous studies that showed that HBV DNA levels were lower in NAFLD patients [7]. In HBV transgenic rat model, when NAFLD developed, serum HBV DNA, HBsAg, and HBeAg levels were decreased, i.e., NAFLD was thought to suppress HBV replication [76]. In another study, HBsAg-positive signals staining in liver biopsy samples was reported to be decreased in NAFLD compared with non-NAFLD patients [109]. Chu et al. 2013 have reported that HBV infection patients who were HBsAg seroconversed in short time with NAFLD patients [110]. Furthermore, NAFLD prevalence was found to be higher in patients with HBsAg seroconversion [111]. Fas receptors increasing on the surface of hepatocytes has been thought to facilitate cell apoptosis, which resulted in increased viral clearance in patients with NAFLD [112].

On the contrary, there are also same studies that reported an increased rate of NAFLD with HBV patients [111, 113, 114]. Especially, HBX proteins that enhance the transcription of sterol regulatory element-binding protein-1c (SREBP-1c) and peroxisome proliferator-activated receptor (PPAR) that promote NAFLD by means of stimulating the synthesis of acetyl-CoA carboxylase1 and fatty acid synthase and detection of gene expression of the enzymes responsible for lipid degradation such as cyp4A [113, 114]. In another study, Jiang et al. 2011 have showed that, an increasing serum HBV DNA levels has been reported in increased SREBP-1c levels and NAFLD [115]. Regarding to all these studies, one may consider that HBV infection increased the potential of NAFLD; however, this potential has been less than that of host factors such as metabolic syndrome. Moreover, NAFLD itself appears to suppress HBV viral replication. NAFLD was affected on virologic response to entecavir treatment in the literature and showed that

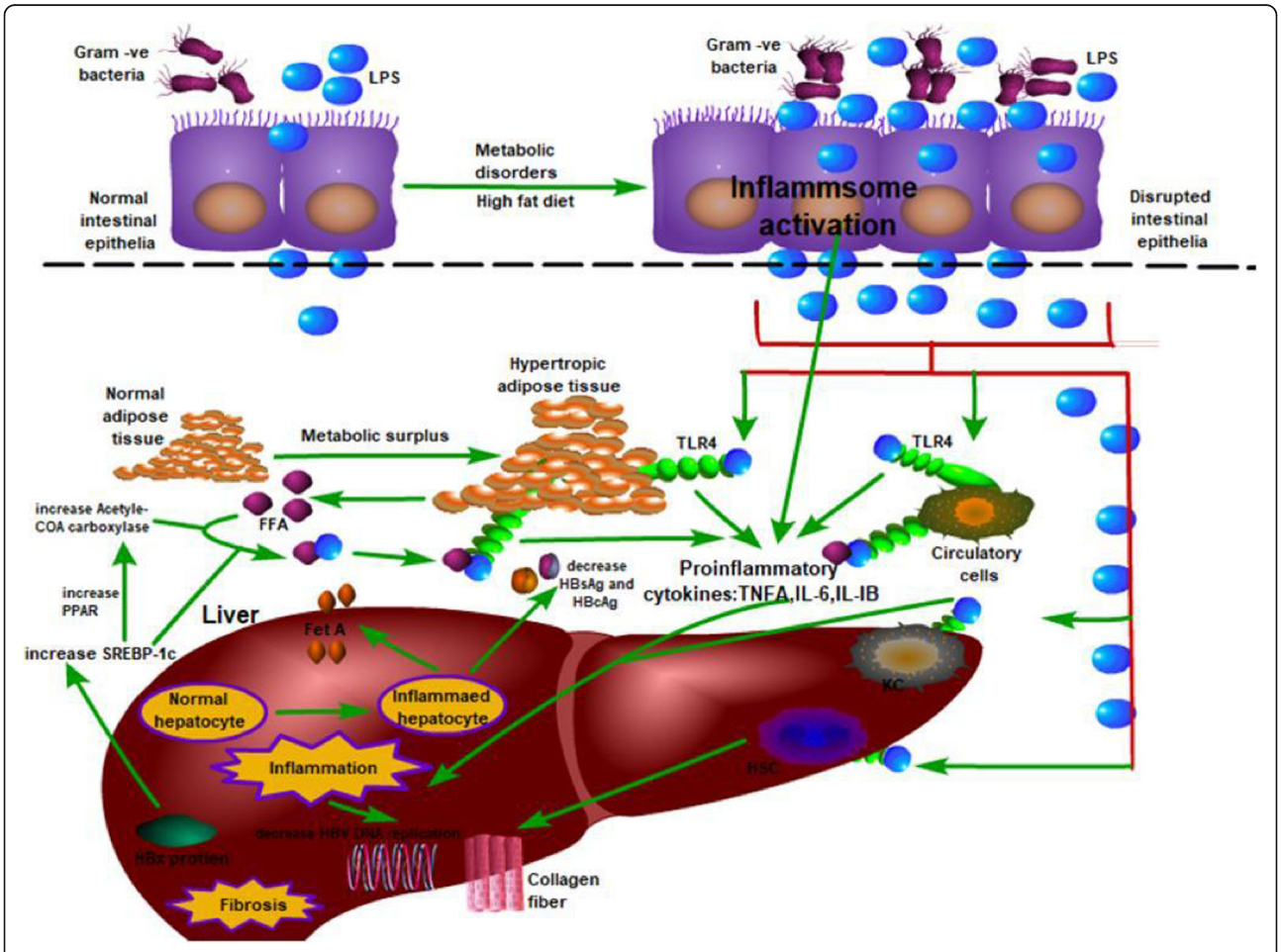

Fig. 2 The interplay between HBV, NAFLD, and innate immunity

virologic response at 24, 48, and 96 weeks of entecavir treatment was less in patients with NAFLD [116] and explained the role of decreased bioavailability of entecavir in fatty hepatocyte and cytochrome enzyme levels on drug metabolism [117, 118].

On the other hand, it has been proved that the HBV DNA levels decreased in animal models of liver steatosis [111]. However, as indicated in epidemiological trials, the effect of host factors such as age and obesity on liver steatosis is more than the effect of HBV replication [119] and FAS receptors levels on the surface of hepatocytes causes more hepatocyte apoptosis [112]. Also, in another study, serum HBV DNA levels were low in patients with liver steatosis [120]. When they consider the previously conducted studies, they have thought that, instead of interpreting this situation as low HBV replication causes liver steatosis, saying that liver steatosis suppresses HBV replication would be more rational [120].

Conclusion

Both chronic hepatitis B and non-alcoholic fatty liver disease establish abnormalities of liver's histopathology and enzymes that potentiate end-stage cirrhosis together along with HCC, consequently threatening the patient's health. Toll-like receptor 4 (TLR4) plays a very critical role in innate immunity activation that essential to NAFLD pathogenesis in patients with HBV infection. Healthy lifestyle maybe needed to stop the progression of steatosis in chronic HBV infection. Since both hepatitis B and NAFLD are liver diseases, it is a vital to protect this organ, so changing patients' lifestyle plays relevant role in the disease treatment, especially nutrition and physical exercise. Overweight persons respond more poorly to hepatitis B treatment so dietary modification as limiting and balanced nutritional scheme permits weight loss and subsequently improve diseases clinical picture, but rapid and uncontrolled weight loss are not recommended as it can be mischievous for patients and may even aggravate NAFLD clinical symptoms, additionally very low calorie diets (388 kcal/day) must be avoided as they can lead to serum bilirubin elevation and overall inflammation activation [121].

A recommended diet for NAFLD and hepatitis B patients must be rich in fibers, low in calories, and monounsaturated fatty acids. White meat is highly recommended as it is low in fat, and occasionally red meat is accepted. The diet should be rich in vegetables and fruits, which are good sources of antioxidative vitamins (β-carotene, vitamins C, and E). Good sources of vitamin C include red pepper, parsley leaves, and horseradish, while food products rich in β-carotene are carrot, parsley leaves, and onion leaves, and finally vitamin E can be found in wheat germ, sunflower oil, and fortified margarines [122]. The antioxidants in foods help decrease inflammation by combating unstable free radicals, which play role in cell inflammation, and cancers. Walnuts are rich in α-linolenic fatty acid, and consumption of 30 g daily causes a decline in total cholesterol and LDL levels so it is highly recommended [123]. Frying, soft drinks rich in a high-fructose corn syrup, and processed foods, in particular fast food, should be prevented [124]. Oligofructose- prebiotics are highly recommended as a nutritional therapy as it reduce the triglycerides and glucose serum levels, also increase free fatty acid concentrations in the large intestine, moreover reduce the amount of food consumption increases concentration of serum glucagon-like peptide 1 (GLP-1), and finally its supplementation for 6 months regulates glycemia, decreases the risk of insulin resistance, also attenuates the inflammation within hepatocytes [125].

Sugar limitation is a vital part of an immune-boosting diet, as a high-sugar diet (HSD) induces type 2 diabetes (T2D) and obesity, also HSD induced the aberrant activation of the innate immune system, including inflammation, so patients should strive to limit the sugar intake to less than 5% of the daily calories [126]. Patients must stay hydrated as dehydration can lead to complications that can elevate susceptibility to the illness. Sleep and immunity are closely tied, so patients should be sleep adequately at least 7 h at night that may strengthen the natural immunity. Keeping physically fit by regular exercise even walking can aid your liver in many ways, as it helps in burning of more calories and boosts the immune function plus the energy and mood. Moreover management and relieving of stress and anxiety are crucial for immune health [127, 128].

Abbreviations

ALT: Alanine aminotransferase; APRI: Activated platelet ratio I; AST: Aspartate aminotransferase; BMI: Body mass index; CHB: Chronic hepatitis B; CV: Cardiovascular; DAG: Diacyleglycerol; ER: Endoplasmic reticulum; FBS: Fasting blood sugar; FFAs: Free fatty acids; GLP-1: Glucan-like protein 1; HBcAg: Hepatitis B core antigen; HBcAg-IgM: IgM antibody for hepatitis B core antigen; HBeAg: Hepatitis B envelope antigen; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; HBxAg: Hepatitis B x antigen; HCC: Hepatocellular carcinoma; HLCs: Hepaocyte-like cells; H-MRs: Proton magnetic resonance spectroscopy; HSD: High sugar diet; HTN: Systemic hypertension; IFNs I: Type I interferon; IL-6: Interleukin 6; iPSCs: Induced pleuropotent stem cells; IR: Insulin resistance; KCs: Kuppfer cells; LPs: Lipopolysaccharides; MetS: Metabolic syndrome; MRI: Magnetic resonance induction; MyD88: *MYD88* Innate Immune Signal Transduction Adaptor; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; NKCs: Natural killer cells; OA: Oleic acid; OHI: Occult hepatitis infection; ORFs: Open reading frames; PA: Palmitic acid; pgRNA: Pregenomic RNA; PPAR: Peroxisome proliferative activating receptor; RT: Reverse transcriptase; SREBP1C: Sterol regulatory element binding protein 1C; T2DM: Diabetes mellitus type 2; Th1: T helper cells; TLR4: Toll-like receptor 4; TLRs: Toll-like receptors; TNF-α: Tumor necrosis factor alpha; VLDL: Very low density lipoprotein

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Authors' contributions
All authors have read and approved the manuscript. FAKM and MME have written the manuscript and provided review/editing. XZ and PS have participated in devising the idea, the discussions, and the revision. All authors have contributed equally in this manuscript.

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Declarations

Ethics approval and consent to participate
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Competing interests
The authors declare that they have no competing interests.

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