Review

Metabolic Dysfunction-Associated Fatty Liver Disease and Chronic Viral Hepatitis: The Interlink

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Metabolic Dysfunction-Associated Fatty Liver Disease and Chronic Viral Hepatitis: The Interlink

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Abstract: Metabolic dysfunction-associated fatty liver disease (MAFLD) has now affected nearly one third of global population and became the number one cause of chronic liver disease in the world because of the obesity pandemic. Chronic hepatitis resulting from hepatitis B virus (HBV) and hepatitis C virus (HCV) also remain significant challenges to liver health even in the 21st century. The coexistence of MAFLD and chronic viral hepatitis can markedly alter the disease course of individual diseases and can complicate the management of each of these disorders. Thorough understanding of the pathobiological interlink and interactions between MAFLD and these two chronic viral hepatitis infections are crucial for appropriate management of patients. We update these interlinks in this comprehensive clinical review.

Keywords: metabolic dysfunction-associated fatty liver disease (MAFLD); chronic viral hepatitis; Hepatitis B virus (HBV); Hepatitis C virus; Hepatic Fibrosis; Cirrhosis; Hepatocellular carcinoma

Introduction

Metabolic dysfunction-associated fatty liver disease (MAFLD) has become the most common cause of chronic liver disease in recent years affecting nearly one-third of the global population because of the obesity pandemic[1]. Although a good proportion of MAFLD cases can remain clinically nonprogressive, some cases can develop severe forms of disease such as hepatic fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). Several factors including environmental, epigenetic, genetic, metabolic, and infective causes can influence the progression of MAFLD to advanced stages of liver disease[2]. In fact, the old terminology nonalcoholic fatty liver disease (NAFLD), was changed in 2020 to MAFLD by the international consensus panel to reflect these associations of the disease[3]. With the new nomenclature, several uncertainties in relation to the pathobiology and consequences of the disease have been resolved[4].

Chronic viral hepatitis resulting from infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) remains an important cause of advanced liver disease in several regions of the world. Hepatic steatosis is a common feature of both chronic HBV[5] and HCV[6] infections. When patients with MAFLD acquire these chronic viral infections or vice versa, the pathobiological characteristics of either disease can be markedly altered, and the risk of progression to advanced liver disease can be perpetuated. Moreover, managing individual disorders can be more complex when they co-exist. Therefore, it is important to understand the pathophysiological interlink between these infections and MAFLD when they co-exist to plan appropriate management which is the aim of this clinical update review.

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MAFLD and chronic HBV infection

Epidemiology

According to the World Health Organization (WHO) report from 2015, more than 250 million people globally were suffering from chronic hepatitis B (CHB) infection[7]. Additionally, 887,000 people died from complications related to CHB including cirrhosis and liver cancer in the same year. This data underscores the immense burden that CHB places on global public health. There is no direct evidence that CHB is associated with an increased risk of hepatic steatosis. Several meta-analyses have examined this phenomenon. In a meta-analysis of 17 studies which included 4,100 HBV-infected patients and 8 of which also included 945 HCV-infected patients, it was reported that approximately 29.6% of patients with HBV developed fatty liver, like that of the general population[8]. The same study observed that 60% of the patients with HCV developed fatty liver. Moreover, the study observed a statistically significant positive association with the male sex (OR 1.74, 95%CI [1.28-2.38], P <0.001) and body mass index (SMD 2.17, 95%CI [1.23, 3.11], P <0.001); and a negative association with HBV-DNA (SMD -74.12, 95%CI [-82.93, -65.31], P <0.001). This strong negative association between HBV-DNA and steatosis may indicate a protective effect of HBV infection on steatosis. Another meta-analysis of 54 studies involving 28,648 CHB patients found a pooled prevalence of hepatic steatosis of up to 32.8%[9]. A more recent meta-analysis, which included 98 studies and 48, 472 patients, demonstrated an even higher global prevalence of hepatic steatosis among CHB patients, reaching 34.93%[10].

Effect of MAFLD on CHB infection and chronic liver disease progression:

MAFLD is associated with increased Th17 cell-related gene expression, increased IL-21 levels, activation of T as well as B cells, production of inflammatory cytokines, and elimination of HBV proliferation with resultant immune clearance of HBV DNA, and HbeAg[11]. NASH stage of MAFLD is associated with increased expression of Toll-like receptors (TLRs) in hepatocytes, kupffer cells (KCs), hepatic stellate cells (HSCs), sinusoidal endothelial cells, and hepatic dendritic cells (DCs)[12]. Lipopolysaccharide (LPA) induces activation of the TLR4 and the myeloid differentiation factor 88 (MyD88)-mediated pathways in obese individuals[13]. Activation of the TLR4/Myd88 pathway contributes to the activation of HSCs, and the production of chemokines which in turn recruits further KCs[14]. TLR4 activation in KCs induces the secretion of pro-inflammatory cytokines (IL-1, IL-6, IL-8, TNF-α, and chemokines) and profibrogenic factors (TGF-β) to activate the inflammation-fibrosis-carcinoma sequence[14]. The TLR4/MyD88 signaling also induces the production of IFN-β, IL-6, and TNF-α to inhibit HBV replication[13]. Thus, activation of innate immunity through TLR signaling is associated with the inhibition of HBV replication and the retardation of the progression of MAFLD to NASH, fibrosis, and HCC[15].

MAFLD-associated metabolic stress could reduce peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1α) which in turn could inhibit HBV replication and induce Fas-mediated apoptosis of HBV-infected cells resulting in HBV-clearance and reduction of HBV-related liver disease progression[16]. CHB is associated with a decreased risk of hyperlipidemia[17,18] and raised serum adiponectin levels[19], both of which could contribute to a lower risk of hepatic steatosis.

On the other hand, the production of saturated fatty acid - palmitic acid as a metabolic component of MAFLD could be associated with impaired function of hepatic DCs, and impaired HBsAg processing/presentation leading to inadequate immune response/HBV-clearance, and thereby development of severe HBV-related liver disease progression[20]. Neutrophil-derived reactive oxygen species (ROS) induced by MAFLD could result in the activation of p38 mitogen-activated protein kinase (MAPK), which in turn could augment HBV replication and result in the progression of MAFLD to NASH[21].

Effects of CHB infection on the MAFLD and chronic liver disease progression

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Some of the transcription factors (including CEBP[22], CREB[23], HNF3[24], HNF4[25], FXR[26], RXR[27], and PPAR[28]) involved in the transcription of HBV DNA are involved in the hepatic glucose, lipids, bile acid, and xenobiotic metabolism[28] may either inhibit or induce regeneration, inflammation, fibrosis, and malignant transformation of hepatic cells. Differential expressions of IL-13, G-CSF, CCL11, IL-6, and IL-4 are thought to play a role in developing steatosis and fibrosis in patients with CHB infection. IL-13 facilitates hepatic steatosis and fibrosis, the latter through mechanisms including the stimulation of TGF-β1 gene expression[29] and through activation of the JAK-STAT-6 pathway that in turn results in the production of CCL11, an eosinophil chemotactic protein[30]. The CCL11-mediated hepatic eosinophilic infiltration and activation results in hepatic steatosis and fibrosis[31]. G-CSF ameliorates hepatic steatosis by reducing the expression of SREBP-1c[32]. IL-4 and IL-6 protect against hepatic fibrosis[33], IL-4 through secretion of matrix metalloproteinase-12 (MMP-12)[34], and IL-6 through the promotion of proliferation/survival of HSCs[35].

In patients with CHB infection, Hepatitis B protein X (HBx) – a 17 kDa soluble protein coded by the HBV DNA induces expression of various genes related to lipid accumulation including *PPAR*[36], *SREBP*[36], *FABP1*[37], *LXR*[38], *and FATP2*[39], thereby promoting lipogenesis. HBx also stimulates various transcription factors including STAT3, NF-κβ, PI3K/AKT, and Src[40], which in turn promote hepatocyte proliferation[40], inhibit apoptosis[40], and stimulate inflammation[41], thereby leading to the development of HCC. Moreover, the pre-S1 domain of the HBV envelope binds to Sodium Taurocholate Cotransporting Polypeptide (NCTP), limiting the function of NCTP, thereby promoting compensatory bile acid synthesis, cholesterol provision, and hepatic steatosis[42].

Steatosis associated with MAFLD, and the resultant oxidative stress might generate an intra-hepatic pro-fibrotic and pro-cancerous environment[43]. Additionally, CHB-associated deficiency of PML (promyelocytic leukemia protein) results in altered lipid metabolism and steatosis-associated carcinogenesis[44]. Finally, reduced levels of global DNA methylation in patients with concurrent MAFLD and CHB lead to chromosomal abnormality, instability, fragility, and HCC development[45].

Complications

Hepatic steatosis was observed in nearly 18% of patients with biopsy-proven CHB infection[46]. Steatosis had an independent association with body mass index and fasting blood glucose levels, and it has no correlation with the degree of hepatic fibrosis[46]. There is a possible genetic susceptibility to develop steatosis in CHB infection, with the rs1010023 polymorphism in *PNPLA3* gene and rs58542926 polymorphism in *TM6SF2* gene increasing the tendency to develop MAFLD among patients with CHB infection[43]. HBx could play an important role in increasing the risk of HBV-induced steatosis. On the other hand, the reduced risk of hyperlipidemia and the increased adiponectin levels could reduce the risk of HBV-induced steatosis. Although MAFLD is associated with lower HBV viral load and with an increased rate of HBsAg clearance, both CHB and MAFLD could act synergistically to promote the progression of liver disease causing hepatocyte injury, inflammation, fibrosis, and HCC. A co-occurrence of CHB and MAFLD poses a significant risk of the above-mentioned complications.

A retrospective study involving 1076 CHB patients with a median follow-up period of 9.8 years evaluated the importance of MAFLD in patients with CHB[47]. The study observed that MAFLD is associated with reduced event-free (aHR 2.00, 95% CI 1.26-3.19), HCC-free (aHR 1.93, 95% CI 1.17-3.21), and transplant-free survival (aHR 1.80, 95% CI 0.98-3.29) implying higher risk for liver-related events and death. A prospective study of 10,546 CHB patients observed that after a median follow-up period of 5.1 years, MAFLD is associated with a 58% reduced risk of HCC (adjusted hazard ratio or aHR 0.42, 95% CI 0.25-0.68, p <0.001)[48]. The steatosis and metabolic dysfunction had distinctive effects on the risk for HCC. While steatosis was protective against HCC (aHR 0.45, 95% CI 0.30-0.67, p <0.001), a greater burden of metabolic dysfunction increased the HCC risk (aHR 1.40 per dysfunction increase, 95% CI 1.19-1.66, p <0.001)[48]. MAFLD can have both metabolic and non-metabolic complications in patients with co-existing CHB as given in Table 1.

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Table 1. Metabolic and non-metabolic complications of MAFLD co-existing with CHB[49-54].

Metabolic complications
Insulin Resistance
Dyslipidemia – elevated triglyceride and LDL cholesterol levels
Obesity
Hypertension
Cardiovascular disease
Non-metabolic Complications
Hepatic fibrosis
Hepatocellular Carcinoma (HCC)
Chronic liver disease-related complications - ascites, encephalopathy, and variceal bleeding
Increased risk of infection
Quality of life - fatigue, discomfort, and the need for ongoing medical care

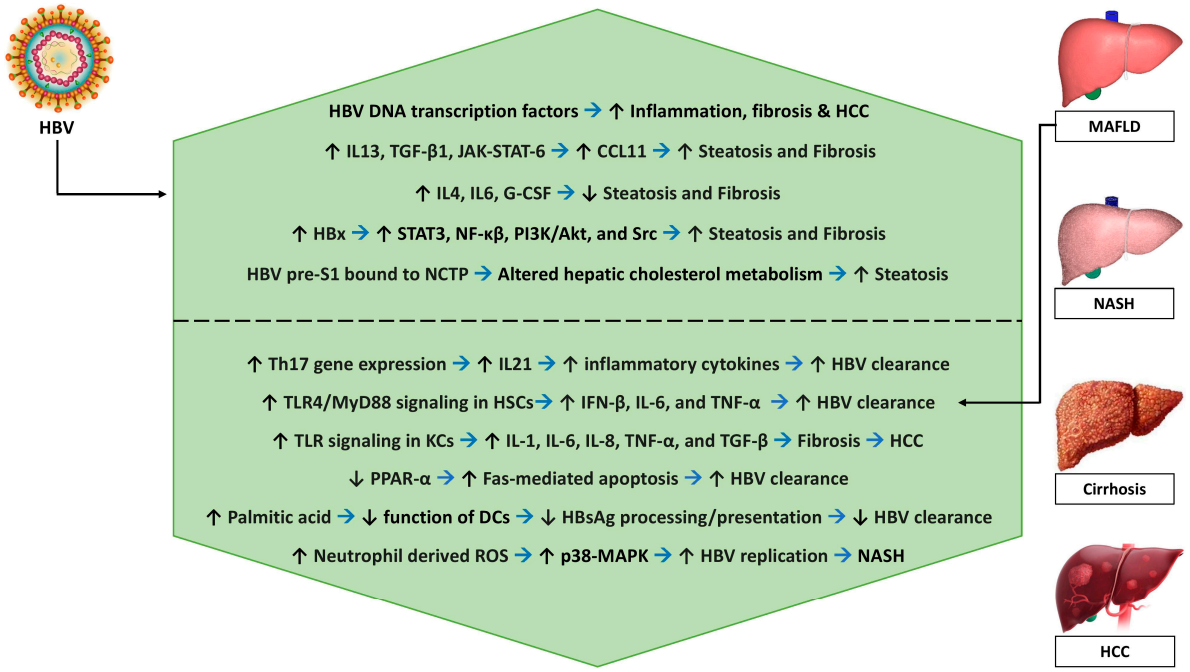

Figure 1. shows the pathobiological interlink between chronic HBV infection and the stages of MAFLD.

Management

The management of MAFLD in patients with CHB involves a multifaceted approach. Traditional liver biopsy, considered the gold standard for diagnosis of hepatic steatosis, is associated with a high risk of internal bleeding[55], making non–invasive methods a more appropriate approach. One such method is the controlled attenuation parameter (CAP) by fibro-scan[56,57], which measures attenuation during ultrasonography to estimate the degree of steatosis. CAP offers a relatively low cost and is suitable for most first-line clinical settings[58]. In CHB patients CAP demonstrated a high degree of accuracy for steatosis assessment compared to other noninvasive methods[59,60]. It has been used in predicting the presence and severity of MAFLD in CHB patients[61].

CHB management requires antiviral treatments such as nucleotide analogs like tenofovir alafenamide, or entecavir to suppress viral replication[62], although cure is often difficult. Patients with concurrent MAFLD may experience variations in viral activity and liver enzymes due to the presence of NASH[63]. Conflicting evidence exists in the response to treatment in patients with coexistent MAFLD and CHB. While some studies indicate lower treatment response in CHB patients with

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hepatic steatosis, others show comparable responses. Monitoring serum ALT and HBV DNA levels and timely intervention for poor responders are crucial for managing CHB in the presence of MAFLD[64,65].

Acute intervention for concurrent MAFLD is crucial, given its adverse impact on overall health. Lifestyle modifications, including strict diet control aiming at weight loss, adherence to certain dietary practices such as a hypocaloric diet, and avoidance of food with high saturated fats or ultra-processed foods coupled with regular exercise, form the cornerstones of therapy[66,67]. Several pharmacological treatment options for steatohepatitis are currently being developed, such as Semaglutide[68], Lanifibranor (pan-peroxisome proliferator-activated receptor agonist)[69], Resmetirom (selective thyroid hormone receptor-β agonist)[70,71] and Obeticholic acid (selective farnesoid X receptor agonist)[72,73], with some promising results, but their routine use in CHB patient with concurrent MAFLD requires further evaluation.

Improvement of hepatic steatosis may affect HBV replication, necessitating careful monitoring during metabolic correction. Factors like diabetes mellitus, obesity, and dyslipidemia contribute to the progression of both MAFLD and CHB infection[74], making their aggressive management of both conditions essential. These metabolic risk factors are independently associated with liver disease progression, hepatocarcinogenesis, and overall mortality in CHB patients[75,76]. Therefore, addressing metabolic dysfunction is the key to improving coexistent CHB in patients with MAFLD.

MAFLD and chronic HCV infection

Epidemiology

According to global estimates, approximately 71.1 million people have chronic hepatitis C virus infection, with a global prevalence of 1% in 2015.[77] Globally, the most common HCV genotype is genotype 1 (nearly 50% of all adults with HCV infection), followed by genotypes 3, 2, 4, 6, and 5 respectively[78]. HCV infection, especially genotype 3, is well known to be associated with hepatic steatosis. Genotype 3 is highly steatogenic[79] and it exhibits a steatosis prevalence of up to 86% while other phenotypes possess a steatosis prevalence of around 50%[80]. The mean prevalence of steatosis in chronic HCV is around 55% across all HCV genotypes.[80] HCV genotype 3 is reported to exert a direct cytopathic effect on the liver in direct proportion to the viral load, even in the absence of other metabolic risk factors like visceral obesity and/or diabetes mellitus.[7] The term 'viral steatosis' is used for this entity.[80]

With the change in nomenclature from NAFLD to MAFLD, those patients with HCV infection who are also meeting the criteria for the diagnosis of MAFLD are classified as hepatitis C with MAFLD. Thus, there are now two types of HCV: hepatitis C with MAFLD and hepatitis C without MAFLD. The term 'metabolic steatosis' is used for the entity seen in patients with hepatitis C and MAFLD.[80] Contrary to metabolic steatosis, 'viral steatosis' is associated with reduced LDL cholesterol and triglyceride levels[81]. Genotypes 1, 2, and 4 essentially promote insulin resistance associated with host metabolic risk factors including visceral obesity[79]. MAFLD patients with hepatitis C have a higher risk for advanced hepatic fibrosis but with a similar atherosclerotic CVD risk in comparison to those with MAFLD alone without CHC infection (CHC)[82].

A recent Australian study[83] observed a 43.1% prevalence of MAFLD in patients with CHC infection in contrast to the global prevalence of MAFLD of 25% in the general population[84]. This dual etiology group is associated with an increased risk for hepatic injury, inflammation, and fibrosis (all $P < 0.001$). This study observed that those with CHC and lean MAFLD have a similar rate of advanced fibrosis (31.6%) in comparison to those who have obesity and/or diabetes mellitus (31.8% and 46.2% respectively with $P=0.325$). However, those with dual etiology are at a greater risk of developing advanced fibrosis and HCC even after HCV clearance, implying that managing MAFLD is equally important as HCV clearance to prevent the progression of hepatic disease and death from HCC or cardiovascular disease[84].

Disease characteristics

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Table 2. shows the differences between HCV genotype 3 and other genotypes of HCV in their pathobiological characteristics, response to treatment and disease outcomes on long-term follow up.

Table 2. Comparison of disease characteristics between various genotypes of hepatitis C with regards to the cause of hepatic steatosis and responsiveness to the antiviral therapy[85].

	Genotype 3 HCV	Non-Genotype 3 HCV
Mechanism of steatosis	Viral steatosis	Metabolic steatosis
Location	Periportal zone (acinar 1)	Centrilobular (acinar 3)
HCV RNA viral load	Co-relate with MAFLD severity	No relation with MAFLD severity
Response to Antiviral	MAFLD reversible with SVR	Reduced response to therapy
Consequence	High rate of steatosis, more rapid progression to advanced fibrosis, and increased HCC risk	Lower rates of steatosis, slower progression to advanced fibrosis, and lower HCC risk

Effect of MAFLD on CHC infection and chronic liver disease progression:

Lipid droplets are involved in the replication and virion assembly of the HCV and stimulation of *de novo* lipogenesis (DNL) by MAFLD (and CHC) facilitates entry of virus into the hepatocytes[86]. Moreover, on release from hepatocytes, the mature HCVs in circulation are complexed with lipoproteins[87]. A complex metabolic network exists in the fatty liver to regulate HCV replication. While saturated and monounsaturated fatty acids are required for replication, polyunsaturated fatty acids inhibit HCV RNA replication[88]. Lipid peroxidation – a feature of NASH, inhibits HCV replication[89]. HCV-infected cells have phosphatidylcholines and triglycerides with longer fatty acyl chains[90]. Knocking down fatty acid elongases[90], fatty acid desaturases[90], or phosphatidyl ethanolamine transferase[91] (PEMT) can inhibit HCV RNA replication.

Effect of CHC infection on the MAFLD and chronic liver disease progression:

Development of MAFLD in patients with CHC depends on the host's genetic background including the rs738409 polymorphism in the *PNPLA3 gene* and the rs58542926 polymorphism in *TM6SF2* gene[92]. The CHC infection appears to downregulate the intrahepatic expression of PPAR-α, and its target known as carnitine palmitoyl acyl-CoA transferase 1A (CPT1A), thereby reducing the fatty acid β-oxidation[93]. The presence of HCV core protein results in mitochondrial dysfunction, oxidative stress, and disruption of fatty acid metabolism leading to steatosis[94]. MAFLD from genotypes 1 and 4 are associated with insulin resistance mediated by reduced expression of insulin receptor substrate (IRS1 and IRS2), thereby reducing signaling through phosphoinositide 3-kinase (PI3K) and Akt[95]. Insulin resistance is also mediated by an increased hepatic expression of fatty acid transporter (CD36), which is involved in increasing fatty acid uptake[96].

The MAFLD from genotype 3 is associated with the inhibition of microsomal triglyceride transfer protein (MTTP) resulting in the impaired assembly of ApoB and lipids to form VLDL, thereby impairing triglyceride secretion and thus intracellular triglyceride accumulation in hepatocytes[97]. Another pathophysiological mechanism for MAFLD from genotype 3 is that HCV-3a core protein induces the PI3K-Akt pathway, increases the Sterol Regulatory Element-binding Protein-1c (SREBP-1c) activity which in turn increases the expression of the fatty acid synthase (FAS)[98]. The HCV-3a core protein results in the downregulation of phosphatase and tensin (PTEN) homologs inside the hepatocytes triggering the formation of large lipid droplets[99]. The HCV-3a core protein acts as an inhibitor of PPAR-α activity resulting in lowered triglyceride breakdown and intrahepatic accumulation of fatty acids[100].

The inhibition of PPAR-α activity that accompanies CHC infection increases the nuclear factor kappa B (NF-κB) and activator protein 1 (AP-1) levels leading to the progression of MAFLD to NASH[101]. Similarly, the increased levels of soluble TNF-α receptors that develop in CHC infection

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also can cause progression to NASH[102]. The Kupffer cells exposed to HCV secrete CCL5, which in turn triggers NF-κB and ERK signaling in hepatic stellate cells. The resultant pro-inflammatory (NLRP3, IL1B, IL-6, and CCL5) and pro-fibrotic (TGF-β1, COL4A1, MMP2, and α-SMA) products promote the progression of MAFLD to fibrosis in patients with CHC infection[103].

Complications

CHC patients could develop insulin resistance, hyperinsulinemia, and hyperglycemia. This could occur independently from obesity but is associated with higher HCV replication rate and an enhanced risk of progression to fibrosis. Host factors including obesity, insulin resistance due to obesity, and coexistent MAFLD in patients with CHC infection are associated with a higher degree of hepatic fibrosis, increased risk of HCC, a reduced response to interferon alpha-based therapy, and accelerated atherosclerosis in comparison to CHC infection without MAFLD[104-107]. However, results from the German hepatitis C registry do not observe a significant fibrotic progression in patients with co-existent MAFLD and CHC infection[108]. Figure 2 shows the pathobiological interlink between chronic HCV infection and the stages of MAFLD.

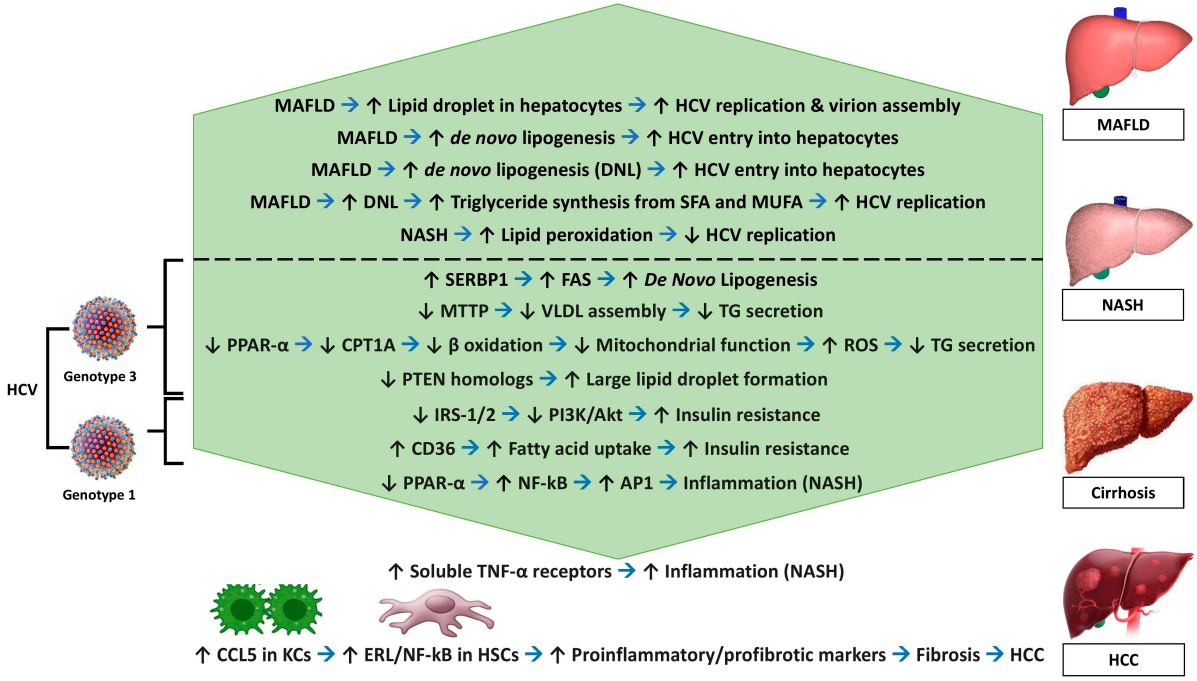

Figure 2.

Management.

Obesity is well known to trigger the development of MAFLD and the progression of CHC infection. Though in the interferon era of CHC treatment obesity was a hindrance to achieving SVR[106], in the era of direct-acting antiviral (DAA) therapy this is no longer the case[109]. In a prospective study comprising 11,469 patients with CHC infection, up to 78% of patients were either overweight or obese at the treatment initiation[110]. After a follow-up of 2 years, patients who managed to achieve SVR gained 0.56 ± 12.8 lbs compared to 3.43 ± 14.6 lbs weight loss in those who failed to achieve SVR ($p < 0.0001$). Moreover, 22% of CHC patients with BMI ≤25 at DAA therapy onset, became overweight during follow-up[110].

In 1991 the FDA approved IFN-α as the first antiviral medication for HCV and seven years later ribavirin was introduced[111]. A few years later, three different combinations of DAAs including NS3 protease inhibitors, NS5B polymerase inhibitors, and NS5A inhibitors were approved[112]. The combination of IFN-α and ribavirin decreased the SVR in patients with CHC infection[113]. Adding rosuvastatin to this combination could improve the SVR rates with a reduction in steatosis and fibrosis[114]. Though statins are a viable option, further randomized controlled trials are needed. A

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combination of IFN-α and vitamin E could achieve a significant reduction in the viral load[115]. In CHC patients who are refractory to IFN-α therapy, the addition of an antioxidant d-α-tocopherol reduced the rate of progression of fibrosis through inhibition of stellate cell activation[116].

DAAs (which are currently the first line agents with improved tolerability and superior efficacy for HCV clearance) achieved a median decrease of liver stiffness measurement (LSM) by 0.9 (-0.6-3.2) kPa, P <0.001, but with a median increase of CAP values by 25 (-12.5-61.5) dB/m, P <0.001, indicating that DAAs could increase the hepatic steatosis[117]. Though DAAs could achieve HCV clearance, the co-existing MAFLD can persist, particularly in patients with obesity, thereby increasing the risk of progression of hepatic disease. Hence, co-existing MAFLD should be treated with therapeutic lifestyle changes. However, DAAs have added beneficial effect on the cardiovascular risk factors – with increase in the triglyceride-to-cholesterol ratio in the VLDL molecules[118], improvement in glycemic control[119], and significant reduction in the risk of cardiovascular events[120]. Due to potential drug-drug interactions, DAAs should be carefully selected with statins or antihypertensive drugs[121].

Areas of uncertainty/emerging concepts

Co-existing CHB infection and MAFLD are becoming increasingly common, and it is important to identify the etiology when hepatitis develops. A novel non-invasive diagnostic model is developed using various parameters including CAP, LSM, HBV DNA, and AST in predicting HBV-related inflammation in CHB with concurrent MAFLD to identify patients who need anti-HBV therapy[122]. Uncertainty and challenges exist in the management of patients with co-existing CHB and MAFLD in the absence of long-term follow up data. Though there are inconsistent results on the impact of hepatic steatosis on the efficacy of antiviral therapy for CHB (with some showing reduced and others showing comparable therapy response) and there are insufficient data to confirm a direct link between nucleoside analogues and hepatic steatosis, the onset/progression of MAFLD should be monitored as a potential adverse effect[123]. Antiviral drugs may have effects on the metabolism. For example, tenofovir disoproxil fumarate could significantly reduce the lipoprotein levels in patients CHB[124]. Statins could retard the decompensation of HBV-associated cirrhosis[125] and HCC[126]. As PPAR-α could promote HBV replication[127], they should be cautioned when CHB coexist with MAFLD. The following table (Table 3) summarizes some of the answered and unanswered topics related to co-existent chronic viral hepatitis and MAFLD.

Table 3. Summary of the interactions between chronic viral hepatitis and MAFLD[128].

	HBV	HCV
CHB/CHC promoting fatty liver	No	Yes
CHB/CHC predisposing to diabetes	Unknown	Yes
CHB/CHC worsening lipid profile	No	No
MAFLD promoting CHB/CHC related fibrosis	Yes	Yes
MAFLD promoting CHB/CHC related HCC	Yes	Yes
MAFLD promoting viral replication	No	Yes
MAFLD reducing the antiviral response	Unknown	IFN-α: Yes DAAs: unknown
Drugs for diabetes, hypertension and dyslipidemia reducing the antiviral response	Unknown	IFN-α: unknown Some DAAs: Yes

Conclusion

MAFLD and chronic viral hepatitis from HBV and HCV remain significant challenges to liver health across the globe. Disease progression occurs when MAFLD coexists with HBV or HCV in the same individual resulting in higher complication rates, and the management of either disease becomes more complex. Timely clinical suspicion and appropriate therapeutic interventions might modify the disease outcomes in relation to this dangerous co-existence. More research is needed to

improve our understanding regarding the pathobiology and interactions between these diseases when they coexist and the therapeutic strategies to improve the clinical outcomes.

Conflicts of Interest: None Declared.

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