Gene Expression **2023** vol. 000(000) | 000–000 Epub
DOI: 10.14218/GE.2022.00007

Review Article

Chronic Infection Considerations in Nonalcoholic Fatty Liver Disease Patients

Xiaoqian Ding[1#], Zhenzhen Zhao[2#], Shousheng Liu[2], Jie Zhang[1], Yong Zhou[3*] and Yongning Xin[2*]

[1]*Department of Infectious Diseases, Qingdao Municipal Hospital, Qingdao University, Qingdao, China;* [2]*Clinical Research Center, Qingdao Municipal Hospital, Qingdao University, Qingdao, China;* [3]*Department of Gastroenterology, Qingdao Sixth People's Hospital, Qingdao, China*

Received: November 21, 2022 | **Revised:** January 07, 2023 | **Accepted:** March 21, 2023 | **Published online:** April 13, 2023

Abstract

Nonalcoholic fatty-liver disease (NAFLD) has become one of the most common and important chronic liver diseases worldwide. Some chronic infectious diseases are associated with the risk of NAFLD. These can induce abnormal glucose and lipid metabolism, insulin resistance, inflammatory activation and other responses, which increase the risk of progression of liver fibrosis. The present study describes the pathogenesis and management of NAFLD with chronic infectious diseases, such as hepatitis B virus, hepatitis C virus, *Helicobacter pylori*, and human immunodeficiency virus infections.

Introduction

In recent years, the global incidence of nonalcoholic fatty-liver disease (NAFLD) has increased (25%),[1] and the incidence of hepatitis B virus (HBV, 25.6%),[2] hepatitis C virus (HCV, 0.94%),[3] *Helicobacter pylori* (HP, 50%)[4] and human immunodeficiency virus (HIV, 0.47%)[5] infections remains high in the population. The risk factors of NAFLD have been extensively studied, such as advanced age, high body mass index (BMI), waist circumference, type-II diabetes, insulin resistance, lipodystrophy syndrome,[6] obesity, male gender, hypertension, metabolic syndrome (MS), and abnormal biochemical indicators.[7] Hepatic steatosis leads to changes in immune function. This may be due to the decrease in vitamin D levels that impairs innate immunity,[8] and the increase in the number of Kupffer cells that induce a pro-inflammatory state.[9] Thus, the interaction between NAFLD and infectious diseases in the occurrence and development of diseases needs to be further understood. The infections above can induce reactions, such as inflammatory activation, insulin resistance, abnormal glycolipid metabolism, and increased risk of hepatic fibrosis progression.[6,7] The present study reviews the role of chronic infections, such as HBV, HCV, HIV and HP, in the occurrence and development of NAFLD, and its treatment options.

Keywords: Nonalcoholic fatty-liver disease; Hepatitis B virus; Hepatitis C virus; Human immunodeficiency virus; Helicobacter pylori..

Abbreviations: ADV, adenovirus; ALT, alanine aminotransferase; ART, antiretroviral therapy; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; CHB, chronic hepatitis B; CMV, cytomegalovirus; DAAs, Direct-acting Antiviral Agents; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; HO-1, Hemohemolytic oxygenase-1; IL-6, interleukin-6; IR, insulin resistance; LDL, low-density lipoprotein; MTP, microsomal triglyceride transfer protein; MS, metabolic syndrome; NAFLD, nonalcoholic fatty-liver disease; NASH, non-alcoholic steatohepatitis; NRTIs, nucleotide reverse transcriptase inhibitors; PPAR, peroxisome proliferator-activated receptor; SOCS, suppressors of cytokine signaling; SVR, sustained virological response; TLR, toll-like receptor; TNF-α, tumor necrosis factor-α; TG, triglyceride; VLDL, very low density lipoprotein; Vpr, Viral protein R.

[*]**Correspondence to:** Yong Zhou, Department of Gastroenterology, Qingdao Sixth People's Hospital, 9 Fushun Road, Sifang District, Qingdao 266033, China. ORCID: https://orcid.org/0000-0003-4615-5879. Tel: 15588994752, Fax: 0532-88905831, E-mail: joana791010@163.com; Yongning Xin, Clinical Research Center, Qingdao Municipal Hospital, Qingdao University, No. 1 Jiaozhou Road, Qingdao 266071, China. ORCID: https://orcid.org/0000-0002-3692-7655. Tel: +8613105121889, Fax: 0532-85968434, E-mail: xinyongning@163.com

[#]These authors contributed equally to this work.

How to cite this article: Ding X, Zhao Z, Liu S, Zhang J, Zhou Y, Xin Y. Chronic Infection Considerations in Nonalcoholic Fatty Liver Disease Patients. *Gene Expr* 2023;000(000):000–000. doi: 10.14218/GE.2022.00007.

Hepatitis B virus

HBV infection causes a wide range of liver diseases, including acute hepatitis, chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). Most adults who are infected with this virus recover, while 5–10% of infected subjects cannot clear the virus, and develop chronic hepatitis B (CHB). CHB infection is one of the most common co-existing liver diseases in NAFLD patients.[10]

Pathogenesis

As the two most common liver diseases, CHB and NAFLD interact with each other. The severity of steatosis is independently associated with the level of HBV DNA in blood.[11] Hu *et al.* established a high-fat diet-induced NAFLD mouse model of HBV sustainable replication.[12] They reported that liver steatosis inhibits HBV DNA replication, and that the replication of HBV does not alter the metabolism of lipids in mice. Compared to HBV mice, the serum hepatitis B e antigen, hepatitis B surface antigen (HBsAg), hepatitis B core antigen (HBcAg), and HBV DNA levels significantly decreased in HBV-infected NAFLD mice.

Furthermore, Toll-like receptor (TLR) plays a significant role in the pathogenesis and progression of various chronic liver diseases (CLDs), including NAFLD, HCV, HBV, fibrosis and HCC.[13] In HBV-transgenic mice, the TLR4/myeloid differentiation factor 88 (MyD88) pathway was stimulated in NAFLD, and this was induced by stearic acid steatosis. This activated the innate immune system, and released numerous proinflammatory cytokines (such as tumor necrosis factor [TNF]-α and interleukin [IL]6),[14] inhibiting the HBV replication in CHB/NAFLD patients.

The effects of HBV on steatosis can be reflected at the mouse level, cellular level, and molecular level.[12,14,15] HBV-infected HepG2 cells can stimulate the expression of genes related to cholesterol metabolism, and increase the hepatic cholesterol level through TLR2.[15] A recent case-control study revealed that HBsAg seropositivity is associated with lower risk of developing NAFLD.[16] Furthermore, the risk of HCC was higher in CHB patients with NAFLD, when compared to that in CHB patients without NAFLD.[17] A study conducted in South Korea followed up 321 CHB patients for an average of 5.3 years to track the impact of NAFLD on HCC in CHB patients. It was found that the superimposed NAFLD (8.2%) was associated to CHB patients with a higher HCC risk, when compared to CHB patients without NAFLD (1.9%).[17] In addition, NAFLD has effects on liver fibrosis and cirrhosis in HBV patients. A cohort study suggested that for CHB patients with virologically stationary CHB, persistent severe steatosis promotes the rapid progression of liver fibrosis, and that this is an independent risk factor for liver fibrosis.[18] However, anti-HBs-Ab was not found to be associated with histological severity, while anti-HBC positivity was associated with cirrhosis in NAFLD patients, which in turn, may be associated with HCC and cirrhosis complications.[19]

Metabolic factors (obesity and type-II diabetes) are predisposing factors for CHB patients to develop NAFLD.[16]

Management

The diagnosis of HBV infection is based on the HBV DNA serum levels, and other serological markers, such as HBsAg, and antibodies to HBsAg (anti-HBs) and HBcAg (anti-HBc).[20]

Dietary adjustments combined with an appropriate increase in physical activity, including lifestyle adjustments, are recommended as the initial treatment for all HBV-positive NAFLD patients.[21] Ceylan *et al.* reported that viral replication decreases in NAFLD patients with chronic HBV infection. However, NAFLD does not have an effect on the virologic response to entecavir and tenofovir treatment after six and 12 months of treatment.[22] For patients with NAFLD, the virological responses were lower after 24, 48 and 96 weeks of entecavir treatment. It was hypothesized that this might be due to the reduced bioavailability of entecavir in fatty hepatocytes, and the reduced levels of cytochrome enzymes involved in drug metabolism.[23] More studies need to be carried out to determine whether and how antiviral therapy has an impact on the development of NAFLD.

By the end of 2014, the HBV vaccine was introduced nationwide in 184 countries. The global coverage of three doses of HBV vaccine was estimated at 82% (vs. 1% in 1990).[2] HBV is mainly transmitted vertically or horizontally, and neonatal immunoprophylaxis at birth is the most important and effective method to prevent it.[24] HBV vaccines are used in at least 184 countries, with a three-dose coverage rate of 82%.[2]

In conclusion, HBV infection may reduce the risk of NAFLD. However, for NAFLD, in addition to common risk factors, the effect of other risk factors, and the use of entecavir and tenofovir on the disease course of NAFLD remains unclear, and requires further studies.

Hepatitis C virus

The worldwide prevalence of HCV infection approximates to 1.6%, affecting approximately 115 million individuals.[25] Globally, genotype 1 (G1) is the most common, and accounts for roughly one in two of all HCV infections in adults, followed by the G3, G2, G4, G6 and G5 genotypes.[25] The average prevalence of NAFLD in HCV-infected individuals is approximately 55% (40–86%). The prevalence of NAFLD is significantly higher in HCV-infected individuals, when compared to that in non-HCV-infected individuals.[26] Furthermore, the incidence of NAFLD is higher in patients infected with other genotypes of HCV, when compared to patients infected with non-genotype 3 HCV.[27]

Pathogenesis

Recent data has suggested that NAFLD is associated with fibrosis progression, which results from chronic HCV infection, and appears to be induced by insulin resistance and liver fat degeneration. HCV infection induces liver fatty degeneration and insulin resistance, liver fatty degeneration promotes the production of liver inflammation, and insulin resistance and liver inflammation leads to liver stellate cell activation, leading to liver fibrosis.[27] Both steatosis and insulin resistance are independently associated with advanced liver fibrosis.[28]

HCV infection is associated with a variety of metabolic disorders, which are known as, hepatitis C-related metabolic disorder syndrome. This metabolic disorder is characterized by insulin resistance, hypocholesterolemia, hyperuricemia, and altered body fat distribution.[29] HCV affects the development of NAFLD in various ways, in which insulin resistance and fat degeneration play an irreplaceable role. Furthermore, various factors can lead to insulin resistance, such as obesity, high BMI,[30] and HCV.[28] In addition, some inflammatory factors can cause insulin resistance, such as TNF-α and IL6.[31] For obese subjects with viral genotype 1, the TNF-α and IL6 inflammation markers increase, and the insulin signaling pathway is reduced by increasing the expression of the suppressors of cytokine signaling (SOCS)-3 gene.[31] For cases of chronic hepatitis C (CHC) infection, the incidence of insulin resistance was reported to be high (up to 80%).[32] HCV infection with the G3 genotype is generally recognized as an independent risk factor for steatosis.[33] The severity of hepatic steatosis correlates with the viral load, and the G3 genotype-associated steatosis is relieved after sustained virological response (SVR) with the antiviral treatment.[33] HCV G3 genotype infection is associated with specific lipid accumulation. Hourioux *et al.* used an *in vitro* cell model to compare the lipid area of cell sections that produced the genotype G3 HCV core protein with the genotype 1a HCV core protein.[34] It was found that the cumulative lipid droplet area was significantly greater in HCV G3 genotype cells, when compared to 1a genotype cells ($p < 0.001$).[34] This may be attributed to the fact that phenylalanine residues have a higher affinity for lipids, when compared to tyrosine, and that these are specific to the G3 genotype.[34] Furthermore, compared to the core protein of HCV-1b, the core protein of HCV-3a significantly upregulates fatty acid synthetase, which is an important enzyme for the synthesis of lipids.[34] The HCV-1b core protein has previously been shown to inhibit both MTP and very low density lipoprotein (VLDL) secretion.[35] This effect is more pronounced in the G3 genotype, and a recent study revealed that the MTP activity in the liver is significantly reduced

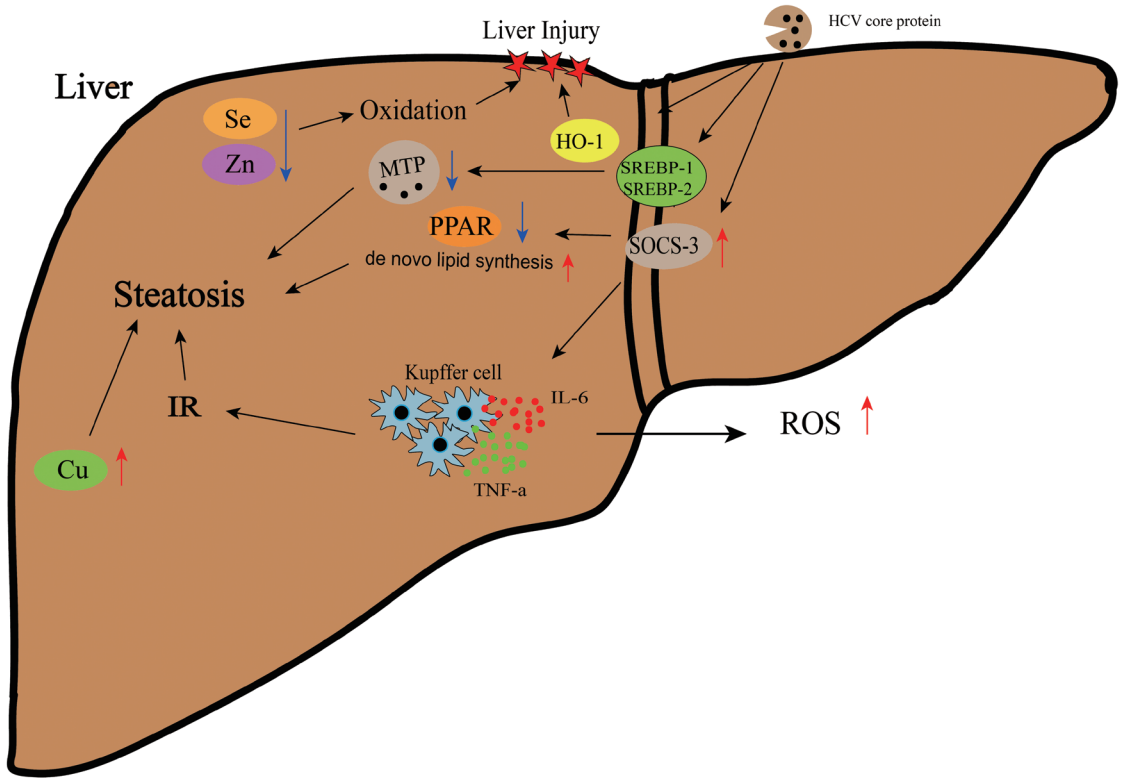

Fig. 1. Mechanism of HCV infection affecting the occurrence and development of NAFLD. The red arrow indicates that the index level went up, and the blue arrow indicates that the index level went down. HO-1, Hemohemolytic oxygenase-1; IL-6, interleukin-6; IR, insulin resistance; MTP, microsomal triglyceride transfer protein; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; TNF-α, tumor necrosis factor; SOCS-3, suppressor of cytokine signalling 3; SREBP, Sterol regulatory element binding protein.

in patients infected with the CHC G3 genotype, when compared to other genotypes ($p = 0.004$).[36] CHC G3 genotype infection can reduce hepatic lipoprotein synthesis and release, and aggravate the degree of hepatic steatosis.[37] In HCV cirrhosis patients, G3 genotype HCV has been independently associated with increased risk of HCC.[37]

Hepatocyte steatosis is the result of the combination of virus and host factors. The induction effects of different genotypes on steatosis are genotype specific, and the HCV genotype 3 virus has the strongest effect. Viral factors and HCV genotype 3 viral-induced steatosis are the most notable.[38] For patients with non-genotype 3 HCV infections, NAFLD is mainly associated with host factors, such as BMI, obesity (especially visceral obesity),[39] insulin resistance and type-II diabetes, which is known as, "metabolic steatosis". For HCV-infected individuals, the prevalence and severity of fatty degeneration in patients with genotype 3 is much higher.[40]

HCV infection can affect liver steatosis through a variety of mechanisms (Fig. 1). Hemohemolytic oxygenase-1 (HO-1) is an important protective antioxidant defense enzyme. This is induced in some liver injury reactions, such as autoimmune hepatitis, CHB infection,[41] and non-alcoholic steatohepatitis (NASH).[42] It was reported that the HO-1 level decreases in the liver of HCV-infected subjects, and that this was considered to be part of the cause of HCV-induced liver damage.[43] Furthermore, this may directly or indirectly interact with certain HCV proteins in the HO-1 induction pathway.[44] Some studies have revealed that HCV core proteins promote lipid accumulation by activating sterol regulatory element binding protein-1 and -2,[45] inhibiting the microsomal triglyceride transfer protein (MTP) activity[35] and peroxisome proliferator-activated receptor (PPAR) expression, and promoting *de novo* lipid synthesis,[46] depending on the specific genotype. Thus, the assembly, excretion and uptake of VLDL are impaired. The HCV core protein induces oxidative stress by upregulating SOCS-3, activating Kupffer cells, increasing proinflammatory cytokines (*e.g.*, TNF-α), and increasing the reactive oxygen species, thereby promoting insulin resistance and liver fat degeneration, and further inhibiting the secretion of VLDL.[47] Fat degeneration, which is common in CHC, plays an important role in the disease progression. Therefore, treating the liver fat degeneration is particularly important for HCV-infected patients with NAFLD. The presence of HCV infection and NAFLD can cause more severe interference with the steady state of essential minerals (zinc, selenium and copper) in the human body, thereby amplifying the oxidative stress and inflammation.[48]

There are various risk-related factors associated with HCV infection in NAFLD patients, such as leptin, adiponectin, HO-1, some serological indicators (alanine aminotransferase [ALT]/aspartate aminotransferase [AST] ratio, fasting glucose, and triglyceride), and trace minerals (zinc, selenium and copper). Leptin is a protein secreted by fat cells, and is associated with insulin resistance and fat degeneration by increasing proinflammatory cytokines.[49] Elena reported that adiponectin levels were higher in CHC patients, when compared to non-chronic hepatitis C patients.[50] However, these lipid levels declined in patients with obesity, diabetes, CHC and NASH.[51] Furthermore, recent studies have confirmed the significant correlation between liver fat degenera-

tion and insulin resistance, and the decrease in lipid levels.[52] As previously mentioned, HO-1 is involved in the pathogenesis, and its serological level may indicate HCV infection. Lin conducted a study in Taiwan, and tested 1,354 CHC patients. The results revealed that participants with NAFLD had higher levels of fasting glucose, ALT/AST, blood pressure and triglyceride, when compared to non-NAFLD participants.[53] This suggests that for CHC patients, the increase in the serological indicators above may be a sign of NAFLD.

Management

The gold standard to diagnose HCV infection is the HCV RNA test and HCV genotype test.[54] In addition, the total HCV antibodies in serum or plasma can be detected to help diagnose the HCV infection.[55]

For patients with HCV infection, there are various novel treatment plans for certain patients to improve SVR. The data revealed that the combination of IFN-α and ribavirin treatment in CHC patients, especially for patients with fatty degeneration greater than 30%, decreased the SVR rate.[56] Furthermore, some *in vitro* studies have revealed that the use of statins reduce HCV replication.[57] A recent prospective study evaluated the use of rosuvastatin in a joint IFN-α and ribavirin treatment, and revealed that the use of these drugs is associated with improved SVR rates, and reduced fat degeneration and fibros.[58] Therefore, statins, as an auxiliary treatment for patients with fat degeneration and CHC, may appear as a viable option. However, more larger, prospective and randomized studies are needed to evaluate the treatment responses. When patients received the combined treatment that included vitamin E and IFN-α, the viral load significantly decreased.[59] The use of antioxidant d-α-tocopherol has been shown to reduce the rate of fibrosis progression via the inhibition of stellate cell activation, thereby limiting the stellate cell-induced fibrogenesis in CHC patients.[60] Gyanranjan *et al.* reported that after the treatment of Direct-acting Antiviral Agents (DAAs), the liver stiffness measurement (LSM) values decreased, and the controlled attenuation parameter (CAP) values (suggestive of hepatis steatosis) increased in CHC patients.[61] Although the HCV was cured after the treatment with DAAs, follow-ups for the liver disease are still required, because CHC patients have a high risk of NAFLD.[62]

In summary, HCV infection increases the risk of NAFLD. Based on the above studies, in addition to conventional antiviral therapy for NAFLD patients infected with HCV, there are various new therapeutic drugs related to HCV infection in patients with NAFLD, but the actual efficacy of these drugs remain to be further studied.

Human immunodeficiency virus

Liver disease is the leading cause of morbidity and mortality in patients who live with HIV,[63] while NASH, as a progressive stage of NAFLD, is a common disease with abnormal liver function.[7] In a multicenter cohort conducted from 1999 to 2011, the liver disease mortality was 13%, making it the second leading non-AIDS-related cause of death in the study.[64] According to Vodkin *et al.*, HIV-associated NAFLD patients have a higher rate of steatohepatitis, and more significant liver damage.[65] In view of this, the analysis of the association between NAFLD and HIV infection is particularly important for guidance in clinical practice.

Pathogenesis

Compared to non-HIV patients, excessive lipid accumulation in the liver in HIV patients is an extremely complex process with no single pathophysiological mechanism. HIV RNA levels are independently associated with multiple lipid markers, such as low-density lipoprotein, VLDL and triglyceride.[66] Thus, HIV RNA levels are significantly correlated to blood lipid indicators, suggesting that HIV replication affects lipid metabolism.[66]

HIV infection can affect lipid metabolism through a variety of mechanisms (Fig. 2). Viral protein R (Vpr) is a 14-kDa protein encoded by all living primate lentiviruses, and plays a role in the viral life cycle.[67] The pathogenesis of NAFLD with HIV infection may be gut microbial action, and the potentially induced pathogenesis of Vpr. The mechanisms of the gut microbiome in the pathogenesis of NAFLD possibly include the impairment of the gut barrier, which causes endotoxemia and the activation of TLRs, increase in short-chain fatty acids in obese adults, altered bile acid metabolism, reduced choline bioavailability, and subsequent changes in farnesoid X receptor (FXR) signaling.[68] Importantly, HIV-1 infection can cause damage to the intestinal epithelium and dysregulation of the microbiota, and the microorganisms and its products can be transplanted from the lumen into systemic circulation.[69]

Neeti *et al.* reported that Vpr genetically modified mice were more likely to have elevated liver triglyceride levels, and increased levels of ALT, choline, and alkaline phosphatase.[70] Four pathways involved in hepatic lipid metabolism were disrupted in this mouse model that led to steatosis: (a) coactivation of the glucocorticoid receptor and co-inhibition of the PPARα to break down fat; (b) coactivation of hepatic X receptor α, which led to the increase in hepatic *de novo* neoadipogenesis (DNL); (c) the PPARα co-inhibition attenuated the hepatic fatty acid oxidation; (d) the PPARα co-inhibition or accumulation of long-chain fatty acids (derived from the DNL) in the microbody.[71] Regardless of whether HIV-1 Vpr is produced or taken up by hepatocytes, this may disrupt hepatic lipid metabolism pathways, including lipid production and fatty acid oxidation, since Vpr replicates the HIV from host immune cells into the extracellular space. Due to the effects of Vpr on other tissues (for example, hyperlipidemia can lead to hepatic steatosis), and since Vpr can regulate a large number of liver genes involved in lipid and sterol metabolism, it was suggested that Vpr may play an important role in the development of other metabolic abnormalities.[70]

HIV infection has an important effect on the development of NAFLD, promoting fibrosis. The HIV enters cells through two co-receptors, CC chemokine receptor 5 (CCR5) and cysteine-X-cysteine receptor 4 (CXCR4). CCR5 and CXCR4 are expressed on activated hepatic stellate cells (HSCs), which are the central mediators of liver fibrosis.[72] HIV can affect the activation of hepatic stellate cells, thereby causing collagen deposition and liver fibrosis.[72] Furthermore, HIV infection and viral proteins promote the expression of type I collagen, and the secretion of proinflammatory collagen, while its envelope glycoprotein gp120 can affect both parenchymal and nonparenchymal cells, leading to inflammation and fibrosis.[72,73] Moreover, the expression of gp120 can be increased by the migration of astrocytes mediated by CCR5, which in turn increases the secretion of monocyte chemoattractant protein-1 and the expression of IL6, resulting in an inflammatory state, and leading to chronic inflammation and damage of the surrounding liver cells. For individuals with HIV/HCV co-infection, gp120 can induce hepatocellular apoptosis by interacting with HCV proteins, such as core, E2, NS3/4A and NS5A.[73] *In vitro* models have revealed the enhanced activation and phosphorylation of signal transduction and transcription factor 1 (STAT1) after the co-stimulation of HCV-E2 and HIV-GP120.[74] Considering the role

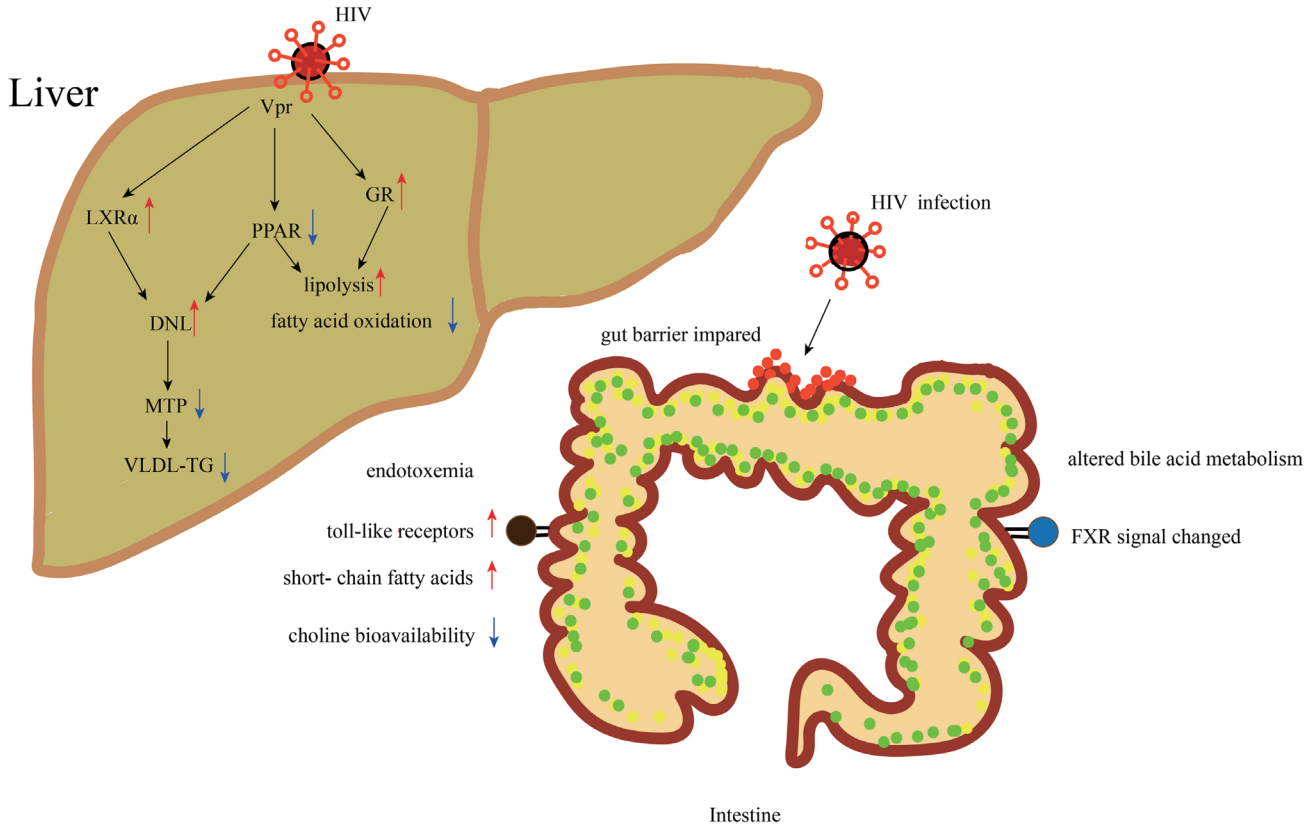

Fig. 2. Mechanism of HIV infection affecting the occurrence and development of NAFLD. The red arrow indicates that the index level went up, and the blue arrow indicates that the index level went down. DNL, de novo lipogenesis; FXR, farnesoid X receptor; GR, glucocorticoid receptor; LXR-α, liver X receptor-α; MTP, microsomal triglyceride transfer protein; PPAR, peroxisome proliferator-activated receptor; VLDL-TG, very low density lipoprotein-triglyceride; Vpr, HIV-assisted protein.

of GP120 in hepatocyte steatosis and fibrosis, this injury pathway can be further investigated as a diagnostic and therapeutic target.

Patients may be at particularly high risk due to the aging population, severe presentation of common NAFLD risk factors, disturbances in the gut-liver axis, and additional effects of mechanisms related to HIV infection and antiretroviral therapy (ART).[63] The secondary causes of fat degeneration are, as follows: ART, HCV, and alcohol.[63]

Management

Liver biopsy is rarely used for the diagnosis and evaluation of NAFLD in HIV carriers, while non-invasive fibrosis tests have been increasingly used.[75,76] For HIV patients, transient elastography (TE) has an advantage over serum markers, because this is not affected by the HIV course or medication.[77] The diagnostic value for liver fibrosis and steatosis was LSM ≥8.0 kPa[78] and CAP ≥248 dB/m,[79] respectively.

As mentioned above, for HIV-infected patients with NAFLD, the basic treatment is general treatment, such as nucleotide reverse transcriptase inhibitors (NRTIs).[66] Studies have been conducted on the drug treatment of different pathways of fat accumulation, such as aramchol,[80] tesamorelin,[81] statins,[82] and cenicriviroc.[83] In a phase II clinical trial, aramchol has been shown to significantly reduce the hepatic fatty liver disease in the general population.[80] However, more clinical trials are needed for tesamorelin, statins and cenicriviroc. Furthermore, most of the HIV-infected patients received combined antiretroviral therapy (cART), which achieved the basic inhibition of viral and immunoactivation of HIV, and the effects of HIV replication on lipid metabolism were eliminated.[66]

Different HIV drugs have different effects on liver steatosis. A number of early ART regimens, particularly NRTIs, have been associated with mitochondrial toxicity through multiple possible mechanisms. This results in mitochondrial toxicity and impaired fatty acid oxidation, which play an important role in the development of ectopic fat deposition and lipid dystrophy in tissues and organs,[84] and contribute to the development of NAFLD through multiple pathways.[85] Early NRTIs were usually associated with mitochondrial dysfunction, particularly stavudine, didanosine and zalcitabine, and to a lesser extent, zidovudine.[86] Modern NRTs, such as tenofovir, have been rarely associated with significant mitochondrial dysfunction in clinical practice, and no relevant studies have reported that these promote the occurrence and development of NAFLD.[86] Both stavudine and didanosine can cause liver damage through mitochondrial damage, oxidative stress, and microfouling fatty degeneration, and should be avoided in NAFLD.[87] The chemokine receptor CCR2/CCR5 antagonist cenicriviroc, which has recently been shown to be effective in HIV treatment by inhibiting the entry of the virus, has also been shown to be effective in early trials for the treatment of NAFLD.[83] Cenicriviroc may be a novel approach to treat or prevent HIV and NAFLD in patients with multiple NASH risk factors.[83]

Aramchol is a fatty acid-bile binder, which can reduce fatty acid synthesis, and increase fatty acid oxidation and liver cholesterol outflow. In a phase II trial, this has been shown to significantly re-

duce fatty liver in the general population.[80] Tesamorelin is a growth hormone-releasing hormone that reduces visceral fat accumulation in HIV-infected individuals.[88–90] In contrast to the GH itself, tesamorelin stimulates lipolysis by increasing endogenous GH, while maintaining negative feedback inhibition.[88] Stanley *et al.* reported that tesamorelin can reduce the liver fat content in HIV-infected NAFLD patients, and it was further revealed that this can slow the progression of fibrosis, and improve liver inflammation.[80,81] However, tesamorelin can reduce insulin sensitivity, leading to hyperglycaemia.[91] Therefore, the security of using this in the long term remains uncertain, and this requires a lot of data to illustrate. A meta-analysis confirmed the fat-lowering effect of statins on HIV-infected patients treated with cART, showing that statins can significantly reduce total plasma cholesterol, triglyceride, and low-density lipoprotein cholesterol levels,[92] and reduce adverse event rates.[93] In addition, studies have revealed that HIV-infected patients treated with intensive statins have a lower cardiovascular disease risk.[82]

In conclusion, HIV infection can increase the risk of NAFLD. Furthermore, HIV infection can accelerate the progression of simple fat degeneration to NASH. Moreover, HIV treatment drugs may induce abnormal blood lipids, insulin resistance, and mitochondrial dysfunction, thereby promoting the development of NAFLD. Researchers and clinicians need to conduct extensive scientific and clinical studies to improve the efficiency of the non-invasive diagnosis and treatment of NAFLD in HIV patients.

HIV/HCV coinfection

Patients with HIV/HCV co-infection have a faster progression of liver fibrosis, and a higher rate of liver decompensation, when compared to HCV patients.[94] HIV/HCV infection is associated with increased risk of hepatic depensation,[95] high HCV viral load,[96] elevated ALT levels,[97] increased possibility of drug interactions,[98] and changes in antiviral drug absorption.[99]

Helicobacter pylori

As it is known, approximately 50% of the global population is estimated to be infected by HP.[100] HP is a Gram-negative and microaerophilic bacterium,[101] which mainly causes gastrointestinal diseases in adults, including chronic gastritis, peptic ulcer, gastric muco-associated lymphoid tissue lymphoma, gastric cancer,[102] *etc.* HP-related samples have been detected in various liver disease biopsy samples, and studies have revealed that HP is associated with liver disease, such as hepatitis and hepatocarcinoma.[103] Furthermore, the HP 16S rDNA was found in liver biopsies of NAFLD patients in 2008,[104] and studies have confirmed that HP infection is significantly associated with NAFLD.[105] Tian *et al.* reported that 47.82% of HP-infected individuals have NAFLD, and that HP infection is significantly correlated to NAFLD (OR = 1.2).[105] Furthermore, the HP infection in individuals with dyslipidemia is significantly correlated with NAFLD (OR = 1.44). Although other studies have arrived to different conclusions,[106] it is more likely that HP infection contributes to the progression of NAFLD.

Pathogenesis

HP infection can significantly increase the degree of steatosis in NAFLD mice, which is induced by high-fat diet.[107] Furthermore, HP infection may be associated with iron deficiency.[108] That is, the liver iron content was lower in HP-infected patients, when compared to uninfected patients.[109] Although the mechanism of iron deposition in the liver of NASH patients has not been determined, iron may play an important role in at least part of the pathogenesis of NAFLD.[110] The formation of hepcidin in NAFLD patients increases the iron load, leading to iron-induced oxidative damage to the intestinal mucosa,[111] and this in turn increases the acid load.[112] Studies have revealed that the increase in acid load can precipitate bile acid, and reduce the inhibition of HP in the bile, thereby increasing the risk of HP infection.[112]

HP has been considered to cause the pathogenesis of NAFLD by increasing insulin resistance, stimulating the release of inflammatory cytokines, and increasing intestinal permeability.[113] Therefore, some scholars have speculated that the mechanism of HP that leads to NAFLD by inducing intestinal microbiota disorder is, as follows: HP invades the intestinal mucosa, leads to intestinal dysfunction, destroys the intestinal villi, increases intestinal permeability, promotes the secretion of bacterial endotoxin (specially lipopolysaccharide) through the hepatic portal vein, and promotes inflammatory reactions.[109] In addition, HP can colonize both the stomach and duodenal epithelium, and the biliary epithelium.[114]

For patients infected with HP, the risk factors for NAFLD are adiponectin,[115] leptin,[116] diet structure, and infected strains.[107] Circulating adiponectin levels are negatively correlated with HP infection.[115] When adiponectin is reduced, the control of oxidation of free fatty acids into the mitochondria weakens, leading to free fatty acid accumulation in the cytoplasm.[117] Leptin can reduce fat deposition in liver tissues by inhibiting the desaturation of liver stearoyl-CoA,[118] and interfering with the insulin signaling.[119] A study that involved 153 patients with dyspepsia revealed a significant negative association between HP infection and serum leptin levels ($p < 0.001$).[116] Furthermore, the cytotoxin-associated gene A (CagA) negative population was significantly associated with the occurrence of NAFLD (OR = 1.30).[120]

Management

HP can be diagnosed through invasive tests, such as urease and molecular tests, and non-invasive methods, such as urea breath tests and fecal antigen tests.[121]

Standard triple therapy (PPI+ clarithromycin and amoxicillin/metronidazole) has been widely used as the first-line regimen. After the eradication of HP, the fasting plasma insulin level ($p < 0.01$) and homeostasis model assessment of insulin resistance (HOMA-IR) ($p < 0.01$) were significantly lower, when compared to those before treatment. This indicates that the HP eradication improved the insulin resistance, and that this might prevent the occurrence of MS and NAFLD.[122,123] In the study conducted by Maharshi *et al.*, after 24 weeks of treatment for HP positive patients, the liver CAP value exhibited a downward trend, but the difference was not statistically significant. Furthermore, the HP eradication had no significant effect on the changes in blood lipid indexes in NAFLD patients,[124] which might due to the small sample size. Further clinical studies are needed to explore the effect of HP eradication on NAFLD.

In conclusion, HP infection increases the risk of NAFLD. Furthermore, HP infection may induce the occurrence of NAFLD by changing the intestinal microecology, and choline, amino acid, and sugar metabolism. The relief and treatment effects of HP clearance in NAFLD needs to be further verified.

Others

Hepatitis A virus (HAV), hepatitis D virus (HDV), and hepatitis E virus (HEV)

Compared to HBV and HCV, there is little evidence that HAV,

HDV and HEV are involved in the development and progression of NAFLD.[125]

Human cytomegalovirus

Cytomegalovirus (CMV) is a beta-herpesvirus, which can infect a wide range of cell types. This can infect monocytes, adipocytes and endothelial cells, and is never completely cleared by the immune system, leading to lifelong infections.[126] CMV infection in NAFLD patients is associated with gender and BMI.[125] In patients with seropositive CMV, the incidence of MS was higher in normal-weight women, when compared to extremely obese women. Furthermore, a study revealed that the triglyceride and insulin levels were lower, and the HDL-cholesterol was higher in CMV-positive obese patients, when compared to CMV-negative patients.[125] Moreover, studies have revealed that CMV can promote the development of NAFLD through *de novo* adipogenesis and oxidative stress.[127,128] The treatment of NAFLD combined with CMV remains mainly as a symptomatic supportive treatment.[129]

In conclusion, it was suggested that CMV infection may increase the risk of NAFLD. However, more studies are needed to confirm this.

Adenovirus (ADV)

ADV belongs to the family of double-stranded DNA viruses, which are icosahedral in structure, have no envelope, and have diameters that range within 65–80 nanometers.[130] There is evidence that human lipogenic adenovirus ADV36/ADV37 infection is associated with obesity, and that this is a causative factor for obesity in humans and animals.[131] There are still a lot of speculations on the mechanisms involved.

First, studies have revealed that obese patients are more susceptible to ADV-36 infection, and that leptin levels are reduced in patients with ADV-36 infection.[132,133] Furthermore, the seropositivity of ADV-36 is associated with better lipid and blood glucose control.[134] Thus, it was speculated that ADV-36 may contribute to chronic inflammation, and the changes in lipid metabolism by reducing the leptin gene expression (as a feedback mechanism) and insulin sensitivity, increasing the glucose uptake, activating the lipogenesis and pro-inflammatory pathways in adipose tissues, and increasing the chemoattractor protein-1 levels in macrophages.[135] Second, several molecular mechanisms that may be responsible for the "metabolic" effects of ADV-36 have been demonstrated. ADV-36 induces the upregulation of the cAMP, phosphatidylinositol 3-kinase (PI3K), and p38 signaling pathways, and the downregulation of Wnt10b, and increases the expression of CCAAT/enhancer binding protein-β and PPAR gam2, leading to lipid accumulation.[136] Furthermore, the E4 Open Reading Frame (orf)-1 (E4ORF1) gene of the virus is required for ADV-36 to induce adipogenesis.[136] At present, there are no approved treatments for ADV infection, and standard treatment relies on drugs approved to fight other viral infections.[137]

In conclusion, the possible mechanism of the involvement ADV-36 in NAFLD is to reduce the leptin gene expression and insulin sensitivity, increase the glucose uptake, and activate the lipogenesis and proinflammatory pathways in adipose tissues, leading to chronic inflammation, and affecting the lipid metabolism. However, these are only some of the assumptions based on previous studies, which needs to be confirmed through a large number of population studies and basic studies.

Conclusion

Most chronic infections are significantly associated with the risk of NAFLD. With the exception of HBV, other chronic infections (HCV, HIV, HIV, CMV and ADV) are associated with increased risk of NAFLD. Chronic infection can induce reactions, such as abnormal glucose and lipid metabolism, insulin resistance, and inflammation activation, which increases the risk of liver fibrosis progression. At present, the molecular mechanism of chronic viral infections, such as CMV, and the risk of NAFLD needs further studies, in order to provide guidance in clinical drug use and treatment. In carrying out antiviral and bacterial treatments, attention should be given to the changes in the condition of NAFLD, in order to achieve the best antiviral and antibacterial treatment effects, and minimize the adverse effects of drug treatments for NAFLD.

Acknowledgments

None to declare.

Funding

The study was supported by a grant from the National Natural Science Foundation of China (No. 32171277).

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Contributed to study concept and design (XYN and LSS), acquisition of the data (DXQ and ZZZ), assay performance and data analysis (ZY and ZJ), drafting of the manuscript (DXQ and ZZZ), critical revision of the manuscript (DXQ and ZZZ), supervision (DXQ).

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