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Non-alcoholic fatty liver disease and COVID-19: Harmless companions or disease intensifier?

Abstract

The pandemics of coronavirus disease 2019 (COVID-19) and non-alcoholic fatty liver disease (NAFLD) coexist. Elevated liver function tests are frequent in COVID-19 and may influence liver damage in NAFLD, while preexisting liver damage from NAFLD may influence the course of COVID-19. However, the prognostic relevance of this interaction, though, is unclear. Obesity is a risk factor for the presence of NAFLD as well as a severe course of COVID-19. Cohort studies reveal conflicting results regarding the influence of NAFLD presence on COVID-19 illness severity. Striking molecular similarities of cytokine pathways in both diseases, including postacute sequelae of COVID-19, suggest common pathways for chronic low-activity inflammation. This review will summarize existing data regarding the interaction of both diseases and discuss possible mechanisms of the influence of one disease on the other.

Key Words: COVID-19; Postacute sequelae of COVID-19; Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Inflammation; Fatty liver

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Core Tip: The “colliding” pandemics of coronavirus disease 2019 (COVID-19) and non-alcoholic fatty liver disease (NAFLD) influence each other in several ways. Molecular similarities of cytokine pathways in both diseases including postacute sequelae of COVID-19 (PASC) may be responsible for amplification of chronic low-active inflammation. While there are conflicting data regarding the clinical influence of NAFLD on acute COVID-19 and vice versa, further research is necessary to study the long-term influence of COVID-19 hygienic measures and PASC on NAFLD.

6 INTRODUCTION

The prevalence of non-alcoholic fatty liver disease (NAFLD) has increased rapidly over the past 30 years, particularly in Western countries. This is due to a lifestyle with hypercaloric diets and obesity leading to a concomitant increase in metabolic syndrome^[1]. It is estimated that approximately 30% of people in Western countries have NAFLD, and approximately 5% have non-alcoholic steatohepatitis (NASH), the inflammatory variant of fatty liver^[2]. NAFLD and NASH represent chronic liver diseases with high morbidity and potential mortality.

⁸ The coronavirus disease 2019 (COVID-19) pandemic began in Wuhan, China, in late 2019. From there, the disease spread rapidly throughout the world. To date, over 500 million people have contracted COVID-19 and over 6 million people have died from it^[3]. Despite effective vaccination, it is foreseeable that the coronavirus cannot be eradicated. While vaccination protects against a severe course, it cannot completely prevent infection and minor disease. To that extent, COVID-19 is likely to persist in the world as a disease, its severity depending on the prevailing variants, and to impact the population and preexisting concomitant diseases in an individual. After acute COVID-19 resolves, a proportion of COVID-19 patients suffer from postacute sequelae of COVID-19 (PASC) also named “long COVID” - ³ as a range of new, returning, or ongoing ¹² health problems people can experience four or more weeks following initial severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection^[4,5]. Therefore, in addition to acute COVID-19, postacute sequelae from COVID-19 are an emerging global health crisis, and there are hints that metabolic factors and a chronic inflammatory state (both characteristics of NAFLD) predispose patients to PASC^[6].

While NAFLD is a noninfectious disease whose pandemic spread depends on people's lifestyle, especially dietary habits, COVID-19 has an acute course due to its nature as an infectious disease. This leads to waves of infection that have prompted epidemic hygiene countermeasures to contain the infection, especially in the past 2 years (2020 and 2021). Lockdowns have occurred in numerous countries to restrict the mobility of people and thus prevent the spread of the coronavirus. The harsh isolation and lockdown measures in the past 2 years under the more pathogenic previous

variants had significant sociological and psychological effects. Thus, in addition to the direct viral effects of COVID-19 on the liver, there are also indirect effects on the liver or liver disease, which ¹ may play an important role in the further development of these diseases. As COVID-19 can still cause renewed lockdowns and isolation measures in the future, for example, when more lethal mutations arise again or due to newly emerging infectious diseases, such effects should also be modeled and taken into account in the future.

NAFLD and COVID-19 can be referred to as “syndemic”^[7]. They represent, in a sense, “colliding pandemics”^[8] due to the various possible interactions, which have different dynamics but some molecular and pathogenetic commonalities. These effects are summarized in this review and the current state of the evidence is evaluated. Between August and September 2022, we searched PubMed using the terms coronavirus, COVID-19, SARS-CoV-2, NAFLD, fatty liver, NASH, MAFLD. We analyzed all retrieved abstracts and obtained the full papers, if the study was dedicated to the connection between COVID-19 and NAFLD.

MOLECULAR SIMILARITIES OF BOTH DISEASES

¹ NAFLD covers a wide spectrum of severity, ranging from bland fatty liver without any inflammation (NAFL) and with little or no tendency to progress all the way to NASH with inflammatory reactions and hepatocyte damage with or without fibrosis. A total of 5% to 20% of patients with NAFLD develop NASH, which undergoes a further transition to higher-grade fibrosis and eventually liver cirrhosis in 10% to 20% of cases^[9]. These clinical features of NAFLD are the background for chronic low inflammatory activity of the disease. Intestinal barrier dysfunction plays a major role in triggering and amplifying these inflammatory processes, leading to translocation of bacteria or bacterial components into the portal circulation and induction of hepatic inflammation^[10]. Obesity induced by an unhealthy lifestyle (insufficient exercise and hypercaloric diet) leads to increased secretion of proinflammatory leptin, interleukin (IL)-6, and tumor necrosis factor (TNF)- α from peripheral adipose tissue, while

secretion of adiponectin, an inhibitor of human stellate cell proliferation, is decreased^[11]. The massive disruption of lipid metabolism due to the disturbed balance between lipolysis, oxidation, secretion, and uptake of lipids between adipose tissue and liver contributes to hepatic steatosis as well as lipotoxicity, affecting key cellular elements such as the endoplasmic reticulum or mitochondrial function^[12]. In terms of a vicious cycle, hepatic metabolic pathways (especially β -oxidation) are dysregulated and further reinforce the imbalance in lipid metabolism^[13] and thus lipotoxicity. Activation of human stellate cells and cytokine production by Kupffer cells follows, with IL-1 β , TNF- α , IL-6, interferon (IFN)- γ , nuclear factor-kappaB, and reactive oxygen species being key extracellular and/or intracellular proinflammatory mediators that maintain chronic low-activity inflammation and induce the development of fibrosis^[14,15].

Interestingly, several of these factors also appear to play important roles in COVID-19 pathogenesis in the context of systemic inflammatory response syndrome. IL-1 β , TNF- α , IL-6, and IFN- γ are elevated during acute COVID-19 disease^[16], and IL-6 in particular may be considered a central cytokine for the hepatic effects of COVID-19 due to its principal role in the negative acute phase response. After acute COVID-19 resolves, chronic systemic inflammatory responses may persist in patients with sequelae after acute disease, although the exact molecular drivers of PASC are largely unknown. Recently, Schultheiß *et al*^[17] showed that PASC is associated with chronic elevation of IL-1 β , TNF- α , and IL-6 levels. Phetsouphanh *et al*^[18] even demonstrated elevation of IFN- γ (and other proinflammatory cytokines) in patients 4 mo after SARS-CoV-2 infection, irrespective of whether they had PASC symptoms.

It is therefore straightforward to speculate that low-activity NAFLD inflammation may be amplified or exacerbated by the acute phase of COVID-19 and chronic systemic inflammatory responses in at least some patients after acute COVID-19, resulting in interactions between the two diseases at the molecular level (see Figure 1).

CLINICAL EFFECTS OF COVID-19 ON THE LIVER AND THEIR MECHANISMS

Because COVID-19 is an aerosol-transmitted disease, clinical symptoms of respiratory disease have always been the primary clinical focus. However, many case series and clinical studies show that COVID-19 also has systemic effects. These include vascular inflammation, thrombosis, and other organ involvement. Liver inflammation is therefore only part of a systemic inflammatory component of SARS-CoV-2 and is almost never the primary clinical symptom.

In a comprehensive review, it was shown that COVID-19 leads to elevations in liver enzymes in approximately 17%-58% of patients^[19]. Elevations of transaminases ("hepatitis") dominate, and cholestatic constellations are much less frequent, suggesting predominantly hepatocytic damage^[19]. Frequently, this concomitant COVID hepatitis is clinically inapparent. In a recent meta-analysis involving over 77000 patients, the prevalence of clinically overt liver damage was shown to be correlated with the severity of COVID-19. In this analysis, liver damage was described in 40%-47% of severe COVID-19 cases, whereas patients with a milder course were affected in only 10% on average^[20]. COVID-19 may trigger acute-on-chronic liver failure in patients with liver cirrhosis due to NAFLD^[21]. In contrast, severe hepatic inflammation with impairment of liver function does not seem to occur in patients without advanced preexisting fibrosis^[22].

Intracellular uptake of SARS-CoV-2 requires ¹⁰ binding of the virus with the spike protein to angiotensin-converting enzyme 2 (ACE2). Further molecular interactions with transmembrane serine protease 2, among others, lead to priming of the S protein and internalization of the virus and its genetic material into the cell^[23].

Hepatic tropism of SARS-CoV-2 has been shown recently^[24]. However, the exact mechanism of infection of the liver is unclear. Although ACE2 protein expression was observed in the liver, this expression is predominantly located in Kupffer cells (and only at relatively low levels in hepatocytes). In line with that, ⁹ the SARS-CoV-2 spike protein could be detected in Kupffer and parenchymal cells (for example, hepatocytes)^[24,25]. As a potential mechanism of hepatocyte infection, alternative

hepatocyte cell entry facilitators are under discussion, *e.g.*, high-density lipoprotein scavenger receptor class B member 1^[24] and the asialoglycoprotein receptor^[26].

Several mechanisms of liver cell damage are conceivable (see also Figure 1). A direct cytotoxic effect does not appear to be the dominant mechanism of damage in the normal liver. Healthy hepatocytes express almost no ACE2, whereas in liver cirrhosis, ACE2 expression and activity are significantly higher^[27]. These molecular regulatory mechanisms tend to argue against direct cytotoxic effects of SARS-CoV-2 in healthy liver but could explain why cirrhotic patients are more susceptible to (further) liver damage or more severe COVID-19 disease overall.

Inflamed hepatocytes (as well as other somatic cells) may exhibit mitochondrial dysfunction in NAFLD or NASH^[28,29], which in turn favors ACE2 upregulation^[30] and could support viral infection. Conversely, COVID-19 also appears to directly affect mitochondrial function^[31]; thus, these effects may amplify each other and induce a more severe course of both diseases.

Another pathogenetic mechanism is the additional fat storage in hepatocytes triggered by SARS-CoV-2. COVID-19 causes dyslipidemia^[32] and autopsy studies show a high proportion of steatosis in COVID-19 patients^[33-35]. However, it remains unclear in many cases whether steatosis was already preexisting or triggered upon infection. NAFLD patients apparently express ACE2 and various serine proteases at higher levels in the liver^[36]; thus, preexisting steatosis may promote COVID-19-induced damage. In turn, COVID-19 may exacerbate steatosis. Whether these dynamics are quantitatively significant effects must remain open for now and deserves future research.

The most significant hypothesis of hepatocyte injury based on clinical characteristics concerns inflammatory cytokine-mediated pathways^[37], with commonalities between acutely mediated COVID-19 effects and NAFLD-mediated chronic liver inflammation (especially IL-6; see above). ACE2 expression on Kupffer cells^[38] may be the origin of virus-mediated, locally amplified liver inflammation.

Autopsy studies also support possible vascular-associated mechanisms for COVID-19-mediated liver injury^[35,39]. One early ² series of postmortem liver biopsies from

patients with COVID-19 reported portal or sinusoidal vascular thrombosis in at least 50% of patients^[39]. Patients with COVID-19 exhibit coagulopathy and endotheliopathy, characterized by elevated levels of von Willebrand factor and factor VIII^[40]. As factor VIII is produced primarily by liver sinusoidal endothelial cells (LSECs)^[41], hypercoagulable LSECs might play an additional role in COVID-19-related liver injury. Of note, endotheliopathy has been reported to be sustained following COVID-19^[42], suggesting not only acute but also long-term interactions and consequences of endothelial-mediated inflammation with chronic liver diseases such as NAFLD. Another direct link between COVID-19 and NAFLD may be *via* plasminogen activator inhibitor 1 (PAI-1). PAI-1 has been shown to be elevated among COVID-19 patients^[43]. This role of PAI-1 in COVID-19 liver injury is potentially interesting, especially in NAFLD patients, as elevated PAI-1 has been associated with NAFLD and NASH^[44]; therefore, COVID-19-induced PAI-1 elevation may aggravate NAFLD.

The mechanisms described above partly overlap or influence each other, as indicated by the arrows in Figure 1. The pathogenic significance of these molecular associations is not clear in most cases. There are many hints to suggest that the effects of COVID-19 on the liver and especially NAFLD are multifactorial and may also differ individually. Despite these different possible mechanisms, severe liver injury and liver failure are rare even in prediseased liver patients^[22].

INFLUENCE OF NAFLD ON COVID-19

Numerous studies of varying quality have addressed the risk for morbidity and mortality of COVID-19 in subjects with NAFLD (Table 1). The studies are extraordinarily heterogeneous, making reliable conclusions difficult. Numerous studies were published only as letters to the editor, not as full articles. Almost all studies are retrospective and include low numbers of patients. Definitions of NAFLD/metabolic syndrome-associated fatty liver disease (MAFLD) vary considerably; in some cases, only blood-based surrogate scores for steatosis and liver fibrosis (such as the hepatic steatosis index, NAFLD fibrosis score, or Dallas steatosis index) were applied. Imaging

with ultrasound or computed tomography (CT) is mostly used as the criterion for the presence of fatty liver. Biopsy-proven NAFLD is a rare exception. Importantly, data on alcohol consumption are lacking in many studies. No statements are found on inflammatory activity of fatty liver (*i.e.*, on the presence of NASH). Definitions of severe COVID progression are also inconsistent. Studies that define NAFLD only by scores or by imaging (ultrasound, CT) during the course of hospitalization for COVID-19 cannot provide information about the presence of fatty liver before COVID-19 emergence. Control groups almost invariably contain fewer patients with classic metabolic factors, such as diabetes mellitus and obesity, than the respective NAFLD groups; this metabolic imbalance of study groups cannot easily be controlled by multivariate analysis.

These conditions do not allow confident conclusions to be drawn at this time. Presently, the data suggest that NAFLD alone is not a relevant risk factor for severe COVID-19 progression or mortality. In particular, registry studies from large liver collectives with different etiologies tend not to support a special role for NAFLD^[54,63,64,66]. However, available studies also show that the presence of liver fibrosis or cirrhosis is associated with a higher risk of severe COVID-19 disease^[61,69]. In this respect, the increase in risk for a more severe course of COVID-19 may not be attributed to NAFLD per se but rather to advanced liver disease irrespective of the underlying etiology in general.

INFLUENCE OF EPIDEMIC HYGIENIC COVID-19 MEASURES ON NAFLD

Disease hygiene measures in the context of the infectious waves probably represent an important factor in the influence of the COVID-19 pandemic on NAFLD. The psychosocial impact of the COVID-19 pandemic resulted in measurable exacerbations of metabolic comorbidities of NAFLD. A United States cohort study examined 111 NAFLD patients and found decreases in physical activity in 51%, weight increase in 34%, and increases in alcohol consumption in 5% during the COVID-19 pandemic^[72]. A Spanish study screened over 6000 workers for metabolic factors and found significant

increases in body mass index, insulin resistance, and low-density lipoprotein during the pandemic. The average fatty liver index (FLI) as a surrogate for NAFLD increased from 25.2 to 33 in this study^[73]. Another Spanish study showed a decrease in physical activity during lockdown with a consecutive increase in FLI and worsening of metabolic status^[74]. In an Italian cohort study, 48% of 357 NAFLD patients gained weight during lockdown, and this weight gain was associated with abandonment of a Mediterranean diet and decreased physical activity in univariate analysis and various multivariate models. Interestingly, in PNPLA3-GG polymorphism patients, this genotype represented the only favoring factor for weight gain^[75]. A Japanese study examined 973 patients with health checks in 2018 and 2020. In this study, the absolute number of MAFLD patients increased from 261 to 305; however, as the authors identified predominantly higher alcohol consumption as a risk factor for this development, there is actually a definition problem of MAFLD in the strict sense^[76]. Overall, these studies show a decrease in physical activity and an increase in weight in the general population. It can be assumed, though not yet clearly shown, that this favors the *de novo* development or exacerbation of steatosis and inflammation in NAFLD, that fibrosis in turn may be further advanced and that the prognosis of the liver disease overall is thus worsened at the end. Long-term studies into these effects of pandemic-associated lifestyle changes are necessary.

CONCLUSION

NAFLD and COVID-19 have both taken a pandemic course in their own ways. Whereas infectious disease essentially causes short-term disease, NAFLD represents a chronic pandemic. Interestingly, the molecular mechanisms of inflammation are similar, although NAFLD is more of a chronic low-activity inflammation while COVID-19 is an acute inflammatory condition. However, in NAFLD patients with ongoing PASC both conditions may chronically interact with unknown mutual effects.

Obesity certainly represents an important unifying clinical factor of both diseases, as obesity is an important risk factor for the development of NAFLD and the severe course

of COVID-19. In contrast, the presence of NAFLD per se ¹¹ does not appear to be a relevant risk factor for particularly severe COVID-19. The effects of COVID-19 on liver disease are more complex and still poorly understood. While the direct viral effect on NAFLD may be limited, probably because of the short duration of the acute viral infection, the individual effects associated with lockdowns and isolation are potential risk factors for disease progression due to a reported decrease in physical activity together with an increase in obesity. European Association for the study of the liver position papers provide valuable recommendations for liver patients after the outbreak of the pandemic, including specific recommendations for NAFLD patients^[77,78].

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