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WORD COUNT	2463	TIME SUBMITTED	27-DEC-2022 08:47PM
		PAPER ID	94510867

Name of Journal: *World Journal of Gastroenterology*

Manuscript NO: 79951

Manuscript Type: OPINION REVIEW

COVID-19 and liver injury in individuals with obesity

Lempesis IG *et al*. COVID-19 Liver injury in obesity

Abstract

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that manifests as a variety of clinical manifestations, including liver damage, most commonly hepatocellular pattern as determined by liver function tests (LFTs). Liver injury is associated with a worse prognosis overall. Conditions associated with the severity of the disease include obesity and cardiometabolic comorbidities, which are also associated with non-alcoholic fatty liver disease (NAFLD). The presence of NAFLD, similarly to obesity, is associated with an unfavorable impact on the COVID-19 outcome. Individuals with these conditions could present with liver damage and elevated LFTs due to direct viral cytotoxicity, systemic inflammation, ischemic or hypoxic liver damage, or due to drug side effects. However, liver damage in the setting of NAFLD could also be attributed to a pre-existing chronic low-grade inflammation associated with surplus and dysfunctional adipose tissue in these individuals. Here we investigate the hypothesis that a pre-existing inflammatory status is exacerbated after SARS-CoV-2 infection, which embodies a second hit to the underestimated liver damage.

Key Words: COVID-19; SARS-CoV-2; Non-alcoholic fatty liver disease; Obesity; Inflammation; Liver; Adipose tissue

Lempesis IG, Karlafti E, Papalexis P, Fotakopoulos G, Tarantinos K, Lekakis V, Papadakos SP, Cholongitas E, Georgakopoulou VE. COVID-19 and liver injury in individuals with obesity. *World J Gastroenterol* 2022; In press

Core Tip: The severe acute respiratory syndrome coronavirus 2 that causes coronavirus disease 2019 has a variety of clinical manifestations, including liver damage. Obesity and other dysmetabolic diseases linked to non-alcoholic fatty liver disease are a few of the factors that contribute to the severity of the illness. Due to the direct viral cytotoxicity, people with these illnesses may have liver damage and increased liver

function tests. However, liver injury might also be related to pre-existing inflammation and the detrimental effects of excessive and dysfunctional adipose tissue in these people.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1,2], which was first identified in December, 2019 in Wuhan, China, and has since spread globally, resulting in an ongoing pandemic[2]. COVID-19 represents a systemic disease that can cause a variety of clinical manifestations, which range from asymptomatic individuals to mild respiratory symptoms and severe-critical illness[3-7]. A plethora of underlying pathways drive the pathophysiology, including activation or dysregulation of localized (*e.g.*, vascular) and generalized inflammation, which leads to multi-organ failure and eventually death[2,3,8-12]. Among the clinical manifestations, liver involvement, indicated by abnormal liver function tests (LFT) in patients, was noted early in the pandemic's development[13]. However, major liver damage is not common[14-18]. The liver may be affected by SARS-CoV-2 directly (*i.e.*, translocation of the virus from the intestines to the liver) or *via* indirect ways (*i.e.*, systemic inflammatory response, ischemic and hypoxic liver damage, drug-related liver injury, and impacts on pre-existing liver diseases)[14,16,17]. Co-existing liver disease, including metabolic/obesity related non-alcoholic fatty liver disease (NAFLD), may also negatively impact the course of COVID-19[14,15]. Early observations of COVID-19 have highlighted obesity as one of the most common underlying conditions in patients hospitalized with COVID-19[19,20]. Obesity was further associated with hospital admission and as an independent predictor of severity, intensive medical intervention, and mortality of COVID-19[15,19]. Obesity, determined by increased total fat mass [body mass index (BMI) > 30 kg/m^2], is a chronic multifactorial disease that predisposes to numerous comorbidities, including metabolic [insulin resistance (IR) states, type 2 diabetes mellitus (T2DM), NAFLD], cardiovascular diseases, and various types of cancer[15,22-29]. Patients with poorer clinical

outcomes for COVID-19 are characteristically older (more than 60 years) and have several metabolic syndrome manifestations, and/or obesity, and T2DM, a profile similar to those at increased risk of NAFLD[13,29,30]. Co-existing hepatic diseases like NAFLD and metabolic dysregulations could theoretically impact the manifestations and progression of COVID-19, and the liver injury in that population could represent a combination of the underlying condition exacerbated by the virus and inflammatory responses.

Here, we present the current evidence for hepatic involvement in COVID-19 in obese individuals and the impact of fatty liver disease. Then, we test the idea that liver damage in people with obesity and/or NAFLD could be caused by a "second hit" from the virus on top of hepatic dysfunction that was already there. This is likely caused by metabolic dysregulation and a chronic inflammatory state that is linked to obesity.

CURRENT EVIDENCE OF HEPATIC INVOLVEMENT IN COVID-19

Patients with COVID-19 have experienced varying degrees of liver damage, ranging from self-limited hepatitis to significant liver injury and liver failure[31,32]. Impaired LFT without other hepatic manifestations was shown to be present in almost 50% of the patients with COVID-19 in various studies[31-33]. The spectrum of pathological LFT includes elevated liver enzyme concentrations of transaminases [aspartate transaminase (AST), alanine transaminase (ALT)]; cholestatic enzymes including alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT), and lactate dehydrogenase, elevated bilirubin, and finally impaired synthetic activity as seen with prothrombin time (PT) prolongation, and decreased albumin concentrations[31,34]. Based on the pattern of the affected LFT, liver damage is categorized as parenchymal (AST, ALT), cholestatic (ALP, GGT), or mixed. The most common type of liver damage, in up to 75% of cases, is parenchymal, indicating hepatocellular damage as a major part of physiopathology[31,34,35].

Several studies have shown elevated AST or ALT during acute COVID-19 illness[4-7,31,36-39]. A higher proportion of patients with severe cases (46.2% *vs* 12.7% in mild cases)

had elevated AST and ALT[36,40-42]. AST appeared to be elevated first, followed by ALT in patients with severe disease[33,34]. Accordingly, AST was found to be correlated with mortality and liver dysfunction[5], showing an increased odds ratio (OR) in severe cases in other studies[42,43]. Elevated LFT was also recorded in subclinical cases (AST in 8.7% and ALT in 8.9%)[39].

The cholestatic pattern of elevated LFT was typically accompanied by elevated parenchymal enzymes[31]. In both mild and severe cases, ALP and bilirubin levels were found to be moderately elevated[37]. In a systematic review and meta-analysis of 64 studies, it was shown that the prevalence of elevated total bilirubin (9.7%), GGT (15%), and ALP (4.0%) were lower as compared to elevated levels of aminotransferases (AST 23.2% and ALT 21.1%)[44]. Interestingly, in a retrospective study where ALP and GGT concentration levels were usually within normal values, pathological levels of GGT were found in 37.6% of patients with NAFLD[45].

Further to these observations, a meta-analysis of 24 studies showed that a significantly longer PT in patients with severe COVID-19 was associated with higher morbidity rates. In addition, Elshazli *et al*[46] also concluded in their systematic review that prolonged PT was associated with a higher risk of disease progression to severe COVID-19 and even admission to an intensive care unit (ICU). Impaired synthetic liver function, as also assessed by hypoalbuminemia, was present and associated with an increased risk in patients with COVID-19[47]. Similarly, hypoalbuminemia was correlated with the severity of the disease and morbidity[31]. Overall, irrespectively of which LFT was affected, once hepatic damage was involved, patients had an increased risk of mortality and severe disease, as was shown in a systematic review of 107 studies and 20874 patients[48]. Acute liver injury is an important predictor for disease development[49]. In patients with chronic liver disease (CLD), including NAFLD, liver damage may occur more often. CLD from any cause was discovered to be a risk factor for extended hospitalization and the fatal course of COVID-19[31].

FATTY LIVER DISEASE AND COVID-19

The occurrence of NAFLD in patients with SARS-CoV-2 infection is substantial[4,31,50]. This is the case as specific cardiometabolic chronic conditions intrinsically linked to NAFLD (hypertension, diabetes, obesity, coronary artery disease, and cerebrovascular disease) have been noted as important risk factors associated with an increased risk of severe COVID-19[4,45,51]. In a recent meta-analysis and systematic review of 16 studies, Hayat *et al*[29] examined the NAFLD prevalence, COVID-19, and the outcomes among patients with NAFLD *vs* those without. The study findings show that individuals with NAFLD, as compared to those without, had a higher probability of severe COVID-19 and ICU admission[29]. Furthermore, NAFLD patients tended to have higher COVID-19-related mortality than non-NAFLD patients[6,29].

Assessment of LFT and clinical outcomes in patients with or without NAFLD showed that in the vast majority of patients, liver damage was minor and hepatocellular in type[13,45]. A higher probability of abnormal LFT from admission to discharge was recorded for patients with NAFLD[13,45]. A Chinese analysis found that patients with NAFLD had a higher incidence of severe COVID-19 than those who did not have NAFLD, but only those under 60 years old, and even after adjusting for potentially confounding factors like obesity, diabetes, and hypertension[13,52]. In contrast to that age group, there was no association between for those of age 60 years and older and NAFLD and the severity of COVID-19[13,52]. It was suggested that NAFLD-induced hepatic and systemic immune responses may worsen the severity of the cytokine storm in COVID-19 patients who are younger. Aside from that, older people often have other cardiometabolic comorbidities, which may change any link to NAFLD[13,52].

NAFLD AND OBESITY

Dysfunctional adipose tissue (AT), an organ critical for whole-body homeostasis, is a hallmark of obesity and obesity-related chronic cardiometabolic diseases[28,53-55]. Dysfunctional AT is distinguished by, among other things, hormonal/adipocytokine dysregulation, a state of chronic low-grade inflammation associated with adipocyte hypertrophy and lipid metabolism impairments (reduced capacity to buffer the daily

influx of dietary lipids), resulting in ectopic fat accumulation[28,56-58]. Additionally, decreased AT blood flow, mitochondrial dysfunction, and altered oxygenation are also frequently present in obesity[28,59]. Several pro-inflammatory molecules are increased in obesity and are related to aspects of the metabolic syndrome and other metabolic dysfunctions, including tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), plasminogen activator inhibitor-1, dipeptidyl peptidase 4, and monocyte chemoattractant protein-1[53,54,60-62]. IL-6 can activate macrophages and contribute to the cytokine storm seen in COVID-19[13,63]. The loss of muscle mass and its anti-inflammatory properties, which are common in sarcopenic obesity, may have a negative impact on the chronic inflammatory status, various comorbidities, and COVID-19 outcomes[64].

Liver dysfunction associated with obesity and metabolic diseases, including the spectrum of NAFLD, is characterized by a multifactorial pathophysiological mechanism still under investigation involving multiple pathways[65]. It has been suggested that, in part, the inability to sufficiently increase subcutaneous AT triglyceride stores in response to excessive energy intake and weight gain causes lipids to be diverted to other organs, such as the liver and skeletal muscle, where they accumulate ectopically and cause cellular lipotoxicity, which in turn results in IR and inflammation in these tissues[66-70].

COVID-19: AN ADDITIONAL CAUSE OF LIVER DAMAGE IN PREEXISTING NAFLD AND OBESITY?

COVID-19 systemic inflammatory state is linked with the angiotensin converting enzyme 2 (ACE2) receptors, expressed in a variety of tissues[2,9,11]. Many organ systems, including the lungs, liver, heart, kidney, and blood vessels, contain ACE2 receptors[31]. AT of patients with obesity is estimated to exhibit higher amounts of ACE2, perhaps acting as a SARS-CoV-2 reservoir with delayed viral shedding time[13,63]. The structural spike (S) protein, characteristic of the SARS-CoV-2, predominantly promotes the host's

immunological reaction[9]. The S protein attaches to ACE2 receptor sites on the cell membrane, facilitating cell penetration[9].

In the liver, ACE2 receptor expression is significantly higher in cholangiocytes than in hepatocytes[31,41]. Direct virus cytopathogenic effects, inflammatory responses, and intrahepatic immune cells stimulation, (micro)vascular thrombosis, hepatic obstruction, destabilized gut-liver axis, drug-induced toxicity and interfaces all play a part in liver damage during COVID-19 infection[31,35,71]. Interestingly, as demonstrated in a diet-induced non-alcoholic steatohepatitis (NASH) model in rodents, ACE2 hepatic expression was shown to be dramatically elevated, potentially enhancing hepatic vulnerability towards SARS-CoV-2 infection in individuals with NAFLD and/or NASH[13,72]. Though, the link between NAFLD and liver-induced production of SARS-CoV-2 vital entry proteins, essentially ACE2, is still debatable[13]. A direct viral cytotoxic effect on hepatocytes appeared to induce mitochondrial and endoplasmic reticulum damages (swelling and distention accordingly), decreased glycogen granules, and malfunction of the cell membrane in hepatocytes[31,33,34,42]. As in dysmetabolic conditions, the liver's homeostasis and metabolic parameters are already impaired. This could have an additional effect on the scene of NAFLD. Finally, moderate micro-vesicular steatosis, along with other histopathological findings in deceased COVID-19 patients, may indicate additional pathways of metabolic derangement and liver damage[73].

In addition, the hyperinflammatory status in COVID-19 may act as a "second hit" to an inflamed fatty liver, causing "acute-on-chronic" steatohepatitis with increased aminotransferases[13,74]. The immune-mediated liver injury is caused by pro-inflammatory cytokines, chemokines, and inflammatory cells produced against the SARS-CoV-2, which are also increased in obesity (IL-6, TNF)[13,28,31,32,34,75]. This may explain the finding that the C-reactive protein to albumin ratio was an independent risk factor for mortality in NAFLD patients with COVID-19 in one study[6]. Another significant immunological mediator of damage is viral-induced T cells (CD8)[31,32].

Another major cause of liver injury in COVID-19 appears to be coagulation disruption and endothelial damage[31,73]. Obesity is associated with hypercoagulation/thrombotic status dysregulation due to increased circulating concentrations of factors VII, and von Willebrand and fibrinogen[13]. Ischemia-induced hypoxic liver injury most likely promotes the establishment of microvascular thrombosis[13,63]. Hypoxia caused by pneumonia is another major cause of liver damage[31]. This could be made worse in the case of COVID-19 and obesity, which is linked to obstructive sleep apnea and lower oxygen levels[28].

Ultimately, other factors may contribute to liver damage. It could be the end result of antivirals, anti-inflammatory medications, anticoagulants, antibiotics, and other treatments used to treat underlying cardiometabolic chronic conditions and utilized during the COVID-19 infection, leading to liver injury[31]. Finally, dysbiosis and gut microbiota changes that usually occur in obesity could be exacerbated during COVID-19 and due to various medications[31,76]. A summary of the mechanisms can be found in Figure 1.

FUTURE PERSPECTIVES

Future studies should focus on elucidating and comparing a variety of populations with various BMIs (including those with normal weight, overweight, and various degrees of obesity), as to date few studies have examined the presence of liver steatosis in patients with overweight or obesity[77]. Furthermore, it should be tested in people who have pre-existing NAFLD to determine the extent of underlying liver damage (NASH, liver fibrosis, or even liver cancer) and to monitor the severity of the COVID-19 infection outcomes. Finally, it would be of great interest to examine the potential differential impact of COVID-19 infection due to different viral variants on individuals with NAFLD and other liver manifestations, as these studies are sparse and focus on cirrhosis of various etiologies[78].

CONCLUSION

In conclusion, the poor clinical outcomes of COVID-19 and the greater risk of pathological LFTs seen in people with obesity and/or NAFLD are likely caused by immune activation and a tendency toward a pro-inflammatory state during obesity, as well as by metabolic and immune-mediated parameters that place the liver at risk. Thus, obesity should be prevented, especially in the context of the COVID-19 pandemic.

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