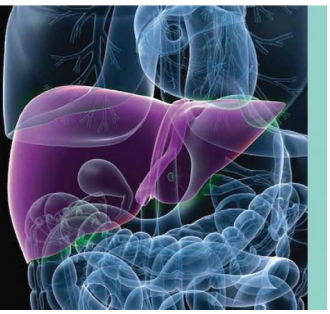

The Impact of Nonalcoholic Fatty Liver Disease on the Outcomes of Coronavirus Disease 2019 Infection

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The novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) responsible for coronavirus disease 2019 (COVID-19) is a major global health threat, causing disease of pandemic proportions. Since it was first reported in Wuhan in December 2019, there have been 168,741,527 confirmed cases and 3,506,180 deaths globally, including 33,213,320 reported cases and 593,156 deaths in the United States as of May 27, 2021.[1]

Although SARS-CoV-2 infection may predominantly result in respiratory illness, such as severe acute respiratory distress syndrome, it also affects other organs. In particular, its effect on the gastrointestinal system continues to emerge as a significant number of patients report gastrointestinal symptoms. Early reports from research investigating the effects of SARS-CoV-2 infection on the gastrointestinal system show a strong association between nonalcoholic fatty liver disease (NAFLD) and COVID-19 progression. This review aims to discuss the association between preexisting NAFLD and SARS-CoV-2 infection. It elucidates on the association between NAFLD and increased risk for SARS-CoV-2 infection, higher risk for severe COVID-19, and poorer outcomes.

METHODS

An Internet-based PubMed search was performed with the aid of a medical librarian. The search was limited to articles published in English as of May 25, 2021. A review of all relevant articles was conducted, and their bibliographies were hand-searched to identify more relevant articles.

DISCUSSION

NAFLD, also known as MAFLD (metabolic-associated fatty liver disease), represents the hepatic manifestation of metabolic syndrome.[2] It is an increasingly common problem

Abbreviations: ACE2, angiotensin-converting enzyme-2; BMI, body mass index; COVID-19, coronavirus disease 2019; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; S, spike; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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in high-income populations and an important cause of chronic liver disease. It is associated with a variety of factors, such as obesity, diabetes mellitus, and other components of the metabolic syndrome that are known to aggravate the severity of COVID-19.[3] Reports from some studies show that individuals with NAFLD have odds of testing positive for COVID-19 of 1.85, as well as an increased risk for having symptomatic COVID-19 infection.[4] They also describe a 6.4 higher odds of COVID-19 progression and longer viral shedding time in patients with NAFLD.[5]

A significant proportion (ranging from 37% to 76%) of hospitalized patients with COVID-19 have been shown to have abnormalities in hepatic function tests, with derangements in hepatocellular enzymes often showing a myriad of hepatocellular, cholestatic, and mixed injury patterns.[6,7] In particular, patients with derangements in transaminases have been shown to have higher mortality and overall worse outcomes.[8] Although the exact mechanism(s) for the gastrohepatic effects seen in SARS-CoV-2 infection remains unclear, it is postulated that the link between SARS-CoV-2 and hepatic injury may relate to viral biology and tropism.[9]

SARS-CoV-2 is an enveloped positive-sense single-stranded RNA virus that shares about 80% of its genome sequence with SARS-CoV, the viral strain responsible for the 2003 SARS outbreak.[10] Similar to the SARS-CoV, it encodes and expresses the spike (S) glycoprotein, which is capable of using the angiotensin-converting enzyme-2 (ACE2) receptor, a membrane-bound aminopeptidase, as a functional receptor for cellular entry.[8] There is a high expression of ACE2 on the apical surface of polarized epithelial cells, and this correlates strongly with the differentiation state of the epithelia (i.e., increased expression in more differentiated epithelia).[11] Although the type II alveolar cells in the lungs have an abundance of ACE2 receptors, this receptor is also present within the gastrointestinal tract. In the hepatobiliary system, the ACE2 receptor is predominantly expressed in cholangiocytes (60% of cells) and endothelial cells, with minimal expression on hepatocytes (3% of cells).[12,13] Its expression has been shown to further increase in conditions of steatosis using experimental models of diet-induced NAFLD and chronic liver injury.[14] Thus, through the upregulated ACE2 receptors in patients with NAFLD, SARS-CoV-2 is thought to enter cells in cholangiocytes and cause direct viral damage with resulting hepatic function test abnormalities, including derangements in albumin, gamma-glutamyl transferase, and transaminases, as has been noted in a significant proportion (56%) of hospitalized patients.[15]

It is also postulated that a disordered immune response to the virus with immunological damage from excessive inflammatory responses (cytokine storm) contributes to the hepatic injury.[16] Proinflammatory cytokines such as TNF-α produced by adipose cells and Kupffer cells cause a dysregulated hepatic innate immunity in patients with NAFLD. This dysregulation results in the decreased activity of proinflammatory M1 macrophages and increased expression of inflammation-suppressing M2 macrophages, thus allowing the progression of COVID-19.[17]

Notably, early research identified obesity and increased body mass index (BMI) as being risk factors for severe COVID-19 infection. More recent research has further teased out these nuanced associations. Liver fat in excess of 10% significantly increased the risk for testing positive for COVID-19 and having severe disease (odds ratio [OR]: 2.96).[4] Obesity in the absence of increased liver fat was not shown to be associated with increased risk for testing positive for COVID-19 or having symptomatic disease. However, a metanalytic review of available data shows that among patients with NAFLD with SARS-CoV-2 infection, obesity increases the risk for having severe COVID-19, with an adjusted OR of 6.32.[18] These findings buttress the specific role of liver fat in modulating the susceptibility to SARS-CoV-2 infection and progression.

Given the importance of liver fat in the modulation of COVID-19 infection and progression, it stands to reason that in addition to current therapeutic options, management plans should include targeted options that address reductions in liver fat. Lifestyle interventions and investigational therapies, such as fibroblast growth factor 19 analogues and selective thyroid hormone receptor-β agonists, are potential adjunctive therapies that may specifically benefit patients with NAFLD in the fight against COVID-19.

LIMITATIONS OF CURRENT RESEARCH

The current research is, however, far from being conclusive because some authors suggest no direct association between NAFLD and COVID-19 severity/outcomes.[19] However, these studies are somewhat limited by their sample size and coverage, potentially limiting their generalizability. They are also unable to adequately account for potential confounders, including treatment and other severity markers of early-stage COVID-19 infections. In contrast, many clinical studies link NAFLD with poor clinical outcomes, most of which use serological measures (i.e., hepatic steatosis index

and Fibrosis-4 score) that already contain independent predictors (BMI and age, for example) of COVID-19 severity, which introduces confounding that likely exaggerates any association between NAFLD and COVID-19 severity/outcomes. It is therefore imperative for future studies evaluating the true association between NAFLD and COVID-19 severity/outcomes to consider using an independent definition of NAFLD, such as gold standard liver biopsy.

CONCLUSION

In summary, the current scientific evidence strongly suggests that NAFLD significantly increases the risk for acquiring SARS-CoV-2 infection, as well as the risk for severe and progressive infection. In lieu of current knowledge, prevention and management strategies should incorporate interventions that reduce hepatic fat content. More prospective studies that use independent measures of NAFLD are, however, needed to validate currently reported associations.

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