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**COVID-19, liver dysfunction and pathophysiology: A conceptual discussion**

Gonçalves Júnior J. COVID-19, liver dysfunction and pathophysiology

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**Abstract**

The intra and extracellular pathways of hepatic injury by coronavirus disease 2019 (COVID-19) are still being studied. Understanding them is important to treat this viral disease and other liver and biliary tract disorders. Thus, this paper aims to present three hypotheses about liver injury caused by COVID-19: (1) The interactions between severe acute respiratory syndrome coronavirus 2 spike protein and membrane receptors in the hepatocyte; (2) The dysbiosis and “gut-liver axis” disruption in patients with serious clinical presentations of COVID-19; and (3) The inflammatory response exacerbated through the production of interleukins such as interleukin-6. However, despite these new perspectives, the pathophysiological process of liver injury caused by COVID-19 is still complex and multifactorial. Thus, understanding all these variables is a challenge to science but also the key to propose individualized and effective patient therapies.

**Key Words:** COVID-19; Intracellular signaling peptides and proteins; Immunopathology; Liver diseases; Liver injury; SARS-CoV-2

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**Core Tip:** This paper aimed to present new hypotheses on the pathophysiology of liver injury caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Interactions between SARS-CoV-2 spike protein and other membrane receptors in the liver; “gut-liver axis” disruption and dysbiosis; and increased inflammatory process mediated by interleukin-6 and AT1R-metalloprotease 17 seem to be factors that contribute to such injury.

**TO THE EDITOR**

I have read the work of Prof. Gracia-Ramos *et al*[1] about the clinical aspects of the relationship between liver dysfunction and coronavirus disease 2019 (COVID-19). The author aimed to summarize the pathophysiology, clinical importance, and management of COVID-19 in patients with or without preexisting liver disease.

I would like to highlight some hypotheses for the pathophysiological impairment of the liver in COVID-19. To facilitate visualization, I have summarized the findings in Figure 1. I believe the information provided will enrich the current discussion and may enhance the results of the aforementioned paper[1].

The first theory states that liver cells have two receptors that have an affinity with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein. The first receptor is the Cluster of Differentiation 147 (CD147) or basigin (BSG) or Extracellular Matrix Metalloproteinase Inducer (EMMPRIN)[2], and the second receptor is the Liver/Lymph node-specific intercellular adhesion molecule-3-grabbing non-integrin (L-SIGN)[3].

CD147 is a transmembrane glycoprotein of the immunoglobulin superfamily overexpressed in an inflammatory process triggered by viral infections (*e.g.,* Severe Acute Respiratory Syndrome in 2002), bacterial infections, and parasitic infections (*e.g.,* Plasmodium falciparum)[2] (Figure 1). Evidence of CD147 protein expression in the liver tissue was found in 1999[4]. Recently, a United States publication in Nature journal highlighted the possibility that a chimeric anti-CD147 receptor would be a possible treatment for hepatocellular carcinoma[5]. Experimental research has shown affinity between CD147 and SARS-CoV-2 spike protein. A Chinese study published in Nature journal evaluating the *in vitro* association between the CD147 receptor and the SARS-CoV-2 spike protein by enzyme-linked immunosorbent assay and plasmon resonance demonstrated an affinity of 1.85 × 10–7 Michaelis between them. In parallel, the authors demonstrated that in cell cultures, when the CD147 protein is blocked by specific autoantibodies (*e.g.,* meplazumab), SARS-CoV-2 amplification is inhibited. Additionally, the virus was able to enter into naturally non-susceptible cells (*e.g.,* cells of baby hamster lineage) more easily when CD147 expression was induced in this population[6]. Moreover, increased expression of CD147 in tissues outside the lung has also been shown as an alternative pathway for SARS-CoV-2 infection in bioinformatics studies[7] and systematic reviews[8]. Therefore, an interesting hypothesis would be that the affinity between the CD147 receptor and the SARS-CoV-2 spike protein represents another way for the virus to infect liver cells.

L-SIGN is a liver-specific membrane receptor related to viral capture[3]. L-SIGN is already widely studied in diseases that affect the liver, such as diseases caused by the hepatitis C virus, the human immunodeficiency virus, the Rift Valley fever virus, the Uukuniemi virus, and the Toscana virus[9]. A recent study supports this hypothesis by suggesting that L-SIGN may provide a new way for SARS-CoV-2 to enter human cells[10]. In COVID-19, autopsy studies showed that SARS-CoV-2-infected hepatic sinusoid cells expressed more L-SIGN receptors compared to control groups[11]. Besides that, the literature has shown *in vitro* interactions between L-SIGN and the spike protein[12,13], in which this receptor binds to angiotensin II (ACE2), increasing the capacity of SARS-CoV-2 to infect liver cells[8,14] (Figure 1).

The second hypothesis (Figure 1) highlights the apparent “gut–liver axis disruption”[15] caused by COVID-19. More than half (60%) of the patients infected with SARS-CoV-2 developed liver injury[16], and some studies have already shown that the hepatic clearance of toxins is negatively impacted by COVID-19[17]. This shows there are varying degrees of dysfunction. Past infections by H1N1[15] and SARS-like viruses[18] led to severe cytopathic alterations in the gastrointestinal tract within 48 h of the beginning of the infectious process[19]. Thus, the disruption of this cross-talk would lead to two consequences: (1) Bacterial translocation stimulating septic shock; and (2) Perpetuation of the septic shock that would lead to a worsened ischemic state[15,20].

The literature has shown a decrease in commensal bacteria and pathogenic microorganisms in patients with COVID-19. This situation persists even after the absence of symptoms and an undetectable viral load by reverse transcription-polymerase chain reaction. Increased colony-forming units of opportunistic bacteria, such as Veillonella spp., Rothia spp., Actinomyces spp.[20], Faecalibacterium prausnitzii, Clostridium ramosum, and Clostridium hathewayi, in the fecal sample of patients with COVID-19, have been associated with more severe illness by SARS-CoV-2[19]. Furthermore, subspecies of Bacteroides sp. (which decrease ACE2 expression in murine intestine models), when present in human fecal samples, have been correlated with a lower viral load of SARS-CoV-2[21,22]. Besides that, epidemiological studies[23] and meta-analyses[24] have shown that COVID-19 can cause cellular dysfunction in enterocytes. More than half (54%) of the patients infected with COVID-19 had SARS-CoV-2 RNA in their fecal samples in a Chinese study[25]. A paper published by Mazza *et al*[26] demonstrated the presence of fecal calprotectin in a patient infected with COVID-19 showing direct damage to the gastric mucosa. Thus, the disruption of the gastric mucosa feeds back the “cytokine storm” caused by COVID-19 and can lead to hepatic tissue injury[27].

Parohan *et al*[28], when analyzing 3428 patients with COVID-19, demonstrated a significant increase in serum aspartate aminotransferase, alanine aminotransferase, and total bilirubin levels with lower levels of albumin in critically ill patients. An epidemiological survey showed that 62% of the patients admitted to intensive care units (ICUs) had increased liver enzymes. Furthermore, in these ICUs, patients had higher values of pro-inflammatory cytokines such as interleukins (IL) 10, 7, 2; monocyte chemoattractant protein-1 (MCP1); gamma induced protein 10 (IP-10); granulocyte colony-stimulating factor (GCSF); and tumor necrosis factor α (TNF-α) when compared to their controls not admitted to ICUs[29]. Indeed, autopsy studies of patients with severe acute respiratory syndrome caused by COVID-19 showed centrilobular sinusoidal dilation and lobular infiltration by small lymphocytes[30]. Percutaneous liver biopsy of patients infected with coronavirus showed histopathological findings suggestive of liver injury, such as acidophilic bodies, hepatocyte ballooning, and lobular activity without fibrin deposition or fibrosis[16].

The third theory is that SARS-CoV-2 endocytosis by immune system cells is caused by AT1R-metalloprotease 17 (ADAM17), which is also involved in the genesis of liver injury (Figure 1). The mechanism by which ADAM17 facilitates viral entry is not yet known. However, it is known that the increase in its activity can lead to the cleavage of pro-inflammatory molecules (*e.g.,* IL-6; TNF-α), reinforcing the inflammatory process and injury to various organs, including the liver, during SARS-CoV-2 infection[31,32]. Additionally, ADAM17 breaks down several proteins that are responsible for liver regeneration/protection. Among ADAM17 substrates are the epidermal growth factor receptor (EGFR) ligand amphiregulin (AR), the heparin-binding-EGF-like growth factor (HB-EGF), and the hepatocyte growth factor (HGF). ADAM17 deletion in cell cultures of hepatocytes led to a decrease in EGFR and HB-EGF (responsible for preventing liver injury). These molecules increased the apoptosis of hepatocytes and decreased their proliferation[33].

Interestingly, studies have shown increased serum levels of ADAMS17 in comorbidities known to be risk factors for severe cases of COVID-19, such as heart failure[34], COPD[35], diabetes mellitus[36], kidney disease[37], and increasing age[34]. On the other hand, decreased ADAM17 activity is correlated with decreased ACE2 receptors, thus having a protective effect against SARS-CoV-2 infections[38].

Therefore, the pathophysiological process of liver injury caused by COVID-19 is complex, multifactorial, and extensive. There are many (intra and extracellular) inflammatory pathways we are not yet aware of, in addition to local and systemic environmental factors that interfere. Understanding all these variables is a challenge to science. Additionally, only with this understanding, we will be able to propose individualized and effective therapies.

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**Footnotes**

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**Figure Legends**



**Figure 1** **Pathophysiological hypotheses explaining liver injury by severe acute respiratory syndrome coronavirus-2.** ACE2: Angiotensin II; ADAM17: AT1R-metalloprotease 17; CD147: Cluster of Differentiation 147; L-SIGN: Liver/Lymph node-specific intercellular adhesion molecule-3-grabbing non-integrin.