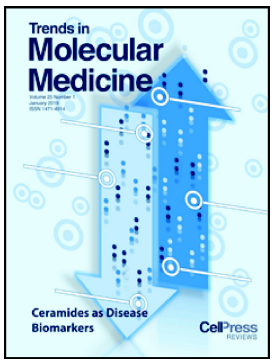

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SARS-CoV-2 targets the liver and manipulates glucose metabolism

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Abstract

A recent publication by Barreto and colleagues showed that SARS-CoV-2 directly triggers hyperglycemia by infecting hepatocytes and inducing PEPCK-dependent gluconeogenesis. We discuss the biological importance of these findings, including the hepatic tropism of SARS-CoV-2. Likewise, we comment on the clinical implications of the bidirectional connection between COVID-19 and non-communicable diseases.

Keywords: SARS-CoV-2, liver, glucose metabolism

Modern societies are suffering from chronic, highly prevalent, endemic diseases, known as non-communicable diseases, which include cardiovascular diseases, cancers, chronic respiratory diseases, and diabetes. Likewise, the twenty-first century is witnessing significant health challenges, including emerging infectious diseases, zoonosis, and new contagious diseases.

The COVID-19 pandemic has unmasked a new paradigm: the crosstalk between epidemics worsens the clinical scenario. We have learned that host risk factors impact the COVID-19 course, including lifestyle, obesity/overweight and other comorbidities, genetic predisposition, underlying immune-related conditions, and even demographic differences among the affected individuals. Nevertheless, we still do not know the underlying molecular mechanisms and potential causative links between infections (viral) and non-communicable diseases. That includes the connection between COVID-19 and non-communicable diseases onsets and the impact of COVID-19 on exacerbating existing non-communicable diseases.

A recent publication by Barreto and colleagues showed that SARS-CoV-2 directly triggers hyperglycemia by infecting hepatocytes [1]. The authors used retrospective clinical and laboratory data to assess the pattern of blood glucose changes since patients' admission and through the disease course, including surrogate markers of endocrine pancreas indemnity. The authors also used postmortem liver biopsies to assess the presence of SARS-CoV-2 and its host receptors in hepatocytes. Finally, the authors exposed human hepatocytes to the ancestral SARS-CoV-2 strain and variants of concern. They found that liver cells are susceptible to the virus infection by detecting the presence of the spike protein within the hepatocytes. Most importantly, the authors provided data showing that infection of hepatocytes is a crucial cause of hyperglycemia in COVID-19 patients by inducing PEPCK-dependent gluconeogenesis.

Is SARS-CoV-2 on the list of hepatotropic viruses?

The lung and the respiratory tract are the main target sites of SARS-CoV-2 replication. However, there is robust evidence indicating SARS-CoV-2 hepatic tropism.

For example, single-cell transcriptomic analysis reveals that hepatocytes express the receptors commonly used by SARS-CoV-2 to enter human cells, including ACE-2 and TMPRS22 [2]. More recently, the assessment of autopsy specimens of patients who died from COVID-19 shed light on the concept that SARS-CoV-2 can efficiently replicate in the liver [3].

Barreto and coworkers provided evidence that SARS-CoV-2 can infect, replicate, and produce infectious viral particles in primary human hepatocytes. Nevertheless, the authors could not find proof of cytopathic changes in the liver [1], which is consistent with autopsy findings in patients with fatal COVID-19 [4]. Although Barreto et al. provided robust evidence that SARS-CoV-2 hepatocyte entry depends on ACE2 and GRP78, an intriguing aspect is that the simultaneous inhibition of both targets diminished the effects of individual receptor blockades [1]. It seems plausible to hypothesize that there are other players co-operating to internalize the virus. Likewise, SARS-CoV-2 may use diverse cell-entry mechanisms, including other liver cell types, for instance cholangiocytes [2].

The hepatic tropism of SARS-CoV-2 may have other clinical consequences, for example, the possibility of chronic liver infection. In connection with this, the mice coronavirus (MHV), which presents ~ 1000 nucleotide divergence from the first SARS-CoV-2, causes chronic hepatitis in mice.

Glucometabolic control by SARS-CoV-2 in the liver: why gluconeogenesis instead of glycolysis?

Hepatic glucose production is regulated by gluconeogenesis and glycolysis. The strategies of viruses for deriving energy from the host cells vary according to the virus and the tissue or

the cell types. For example, SARS-CoV-2 induces glycolysis in monocytes [5], which might explain the increased lactate dehydrogenase (LDH) levels observed in patients with severe COVID-19 outcomes. Hepatotropic viruses, for instance, hepatitis C virus, do not present consistent mechanisms, as both gluconeogenesis and glycolysis have been reported. Gluconeogenesis, which enables glucose synthesis from lactate and amino acids such as alanine, is restricted to the liver and kidney cells. This process involves a series of transamination reactions and the activity of critical enzymes, including phosphoenolpyruvate carboxykinase (PEPCK) and the catalytic subunit glucose-6-phosphatase (G-6-Pase). Intriguingly, Barreto et al. found that infected hepatocytes increase glucose production via the stimulation of PEPCK activity without changes in the gene transcription.

Molecular signatures explaining gluconeogenesis modulation by SARS-CoV-2: Is there a single truth?

Other potential molecular mechanisms may explain glucose metabolic reprogramming by SARS-CoV-2 (**Figure**). For example, Mercado-Gomez reported that the binding of the SARS-CoV-2 spike alters mitochondrial activity and glucose homeostasis in human primary hepatocytes [6].

There are provocative, although poorly explored strategies, including virus-regulated micro-RNA enhancing of metabolic enzymes. First, SARS-CoV-2-miRNAs may mimic host miRNAs by sharing their seeds [7]. Then, the virus alters specific metabolic enzymes of the Krebs Cycle (*ACO1*, aconitase) or branched amino-acids degradation (*BCAT1*, branched-chain amino acid transaminase 1) [8]. Finally, all these metabolic processes are favored by a milieu of virus-induced lysosomal and proteasomal protein degradation [7].

Other epigenetic mechanisms involving methyltransferases and histone deacetylases, which are target-promiscuous, may also explain virus-mediated glucose production by host-infected cells. Furthermore, a central regulation of PEPCK activity is acetylation/deacetylation [9].

The post-acute sequelae clinical implications.

The manipulation of hepatic metabolism by SARS-CoV-2 may have severe clinical implications in patients suffering from long COVID-19. For instance, there is evidence of patients developing T2D in the post-acute sequelae state of COVID-19. A meta-analysis of nine studies showed that the incidence of diabetes after COVID-19 was 15.53 (7.91–25.64) per 1000 person-years with a significant relative risk (RR) of 1.62 compared to the control group [10]. The factors predisposing to this condition are not entirely clear. However, it is presumed that patients with severe COVID-19 are more prone to develop T2D compared with patients with mild disease [10].

Why do patients develop T2D 4-6 months after acute infection with SARS-CoV-2?

One potential explanation for the post-acute sequela conditions is the presence of viral persistence and chronic infection by SARS-CoV-2. In this regard, the liver and the gut might be tissues associated with the SARS-CoV-2-persistent infection target. The liver is immune-tolerant to hepatotropic viruses, including hepatitis B and C, that cause chronic infection. On the other hand, the gut may be considered an immune-privileged site for SARS-CoV-2, where the virus may evade immune system surveillance.

Another putative explanation is that SARS-CoV2-induced long-lasting epigenetics alterations of the metabolism, and T2D develops in those individuals with scarce pancreatic reserve to manage glucose overload.

In conclusion, the bi-directional association between non-communicable and viral diseases, including COVID-19, offers multiple perspectives on unanswered questions (**Figure**).

Declaration of interests

No interests are declared.

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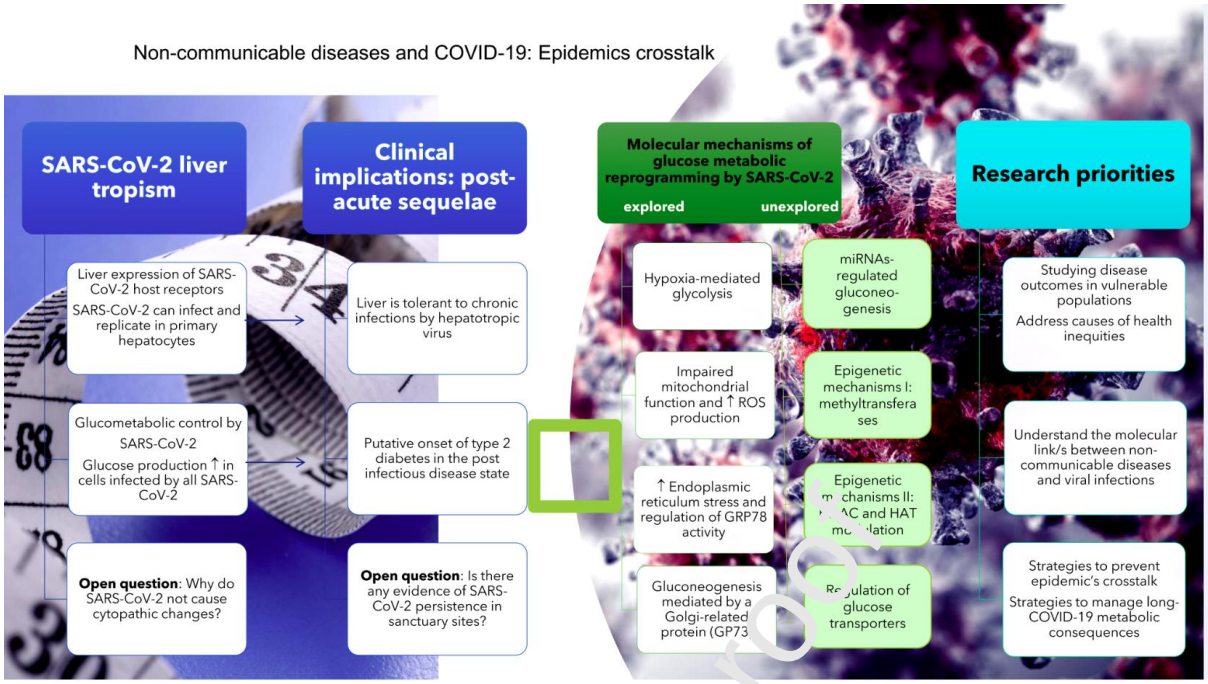

Figure: Non-communicable diseases and COVID-19: Epidemics crosstalk

The figure illustrates the intricate relationship between non-communicable diseases and COVID-19. It summarizes key messages including the hepatic tropism of SARS-CoV2 and glucometabolic control and how these aspects may impact the COVID-19 post-acute sequelae. In addition, the figure lists novel explanations of the glucose metabolic reprogramming by SARS-CoV2 and provides potential research priorities. GRP78: Heat Shock Protein Family A (Hsp70) Member 5. GP73: Golgi Membrane Protein 1.