


Elevation of pancreatic enzymes during SARS-CoV-2 infection

Oruç Numan Gökçe 

Department of General Surgery, Onsekiz Mart University Faculty of Medicine, Çanakkale, Turkey

ABSTRACT

As the number of SARS-CoV-2 infected patients grew, a global picture of the disease began to emerge, with organ involvement other than the respiratory system, which had been reported as the disease's first manifestation, becoming apparent. The objective of this study was to compile pancreatic enzyme elevations during SARS-CoV-2 infection, about which new information has begun to emerge, along with possible suggested mechanisms.

Keywords: Amylase, COVID-19, lipase, pancreatic enzyme elevations, SARS-CoV-2.

As the number of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected patients increased during the coronavirus disease-2019 (COVID-19) pandemic, it was noticed that the disease did not only cause pulmonary damage, as previously reported but also had a wide range of clinical manifestations. Theories have been proposed on a wide range of topics, including the pathophysiology of the disease, the mechanisms of mortality, which organs are involved, how to prevent the disease, and the treatments to be administered in COVID-19, and research on these topics is ongoing worldwide.^[1-3] The gastrointestinal (GI) tract is also a hotly debated topic, and entry of this enveloped and single-stranded ribonucleic acid (RNA) virus into cells is mediated by the angiotensin-converting enzyme 2 (ACE-2) receptor. It has been reported that ACE-2 receptors in the liver, biliary tract, and hepatic epithelial cells may play a role in GI involvement.^[4] Amylase/lipase levels have also been observed to rise in some patients during the course of the disease.^[5-8]

The aim of this review was to summarize the existing published literature on pancreatic enzyme elevations during COVID-19, along with possible suggested mechanisms.

THE STRUCTURE AND GENERAL CHARACTERISTICS OF THE PANCREATIC GLAND

The human pancreas is an organ with two distinct functions: exocrine and endocrine. The exocrine gland is made up of pancreatic acinar cells and duct cells, which produce digestive enzymes and sodium bicarbonate, respectively. The primary function of the exocrine pancreas is to secrete digestive enzymes that are responsible for normal digestion and absorption of food, as well as to assimilate nutrients. Meanwhile, the endocrine gland, which is made up of five different types of secretory islet cells, secretes peptide hormones to maintain glucose homeostasis. Pancreatic secretory functions are delicately regulated by neurocrine, endocrine, paracrine, and intracrine mechanisms. Inappropriate activation or inactivation of these mechanisms leads to pancreatic diseases.^[9,10]

PANCREATITIS

Pancreatitis is a condition in which digestive enzymes that are normally inactive become

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Correspondence: Oruç Numan Gökçe, MD.
e-mail: orucnumangokce@gmail.com

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active and digest their own tissue and other organs, causing widespread inflammation.^[11] In acute pancreatitis etiology; diseases of the bile ducts, alcohol use, endocrine, and metabolic diseases (primary hyperparathyroidism-hypercalcemia, hyperlipidemia, diabetes coma, uremia, pregnancy), familial/genetic factors, trauma (external, operative, endoscopic retrograde cholangiography), ischemic conditions (hypotension, atheroembolism, cardiopulmonary bypass, vasculitis), pancreatic duct obstruction (tumor, papillary stenosis, pancreatic divisum, *Ascaris* infestation), duodenal obstruction, various viral and bacterial infections (leptospirosis) and hypothermia are the main reasons.^[12,13]

The development of acute necrotizing pancreatitis as a result of leukocyte stimulation and necrosis, as well as the systemic damaging effects of inflammatory mediators tumor necrosis factor (TNF), interleukin (IL)-1, platelet-activating factor (PAF), is the focus of research.^[14]

Diagnosis of acute pancreatitis

The revised Atlanta criteria are used to make the diagnosis of acute pancreatitis.^[15] Acute pancreatitis is diagnosed by the presence of at least two of the three criteria listed below.

1. Abdominal pain compatible with acute pancreatitis,
2. Serum amylase & lipase levels greater than three times the upper limit of normal,
3. Detection of pancreatitis-related findings in radiological imaging (ultrasonography, magnetic resonance imaging, or computed tomography [CT]).^[15-18]

A REVIEW OF THE LITERATURE ON THE POSSIBLE MECHANISMS OF SARS-CoV-2-ASSOCIATED PANCREATITIS

ACE-2 messenger RNA levels are expressed more strongly in the pancreatic exocrine glands and islet cells than in lung alveolar epithelial cells, the pancreas may be a potential target for SARS-CoV-2 infection.^[7,8] However, the mechanism of pancreatic damage caused by the SARS-CoV-2 virus is unknown.^[7] Pancreatitis or pancreatic enzyme abnormalities occur as a result of the cytopathic effect of inflammation

and edema directly destroying pancreatic acinar cells, or the systemic immune response caused by SARS-CoV-2 replication or indirectly by SARS-CoV-2.^[19-21] Pancreatic enzyme activation, complement system activation, microcirculation disorder, leukocyte overactivation, and pancreatic acinar cell apoptosis and necrosis may all play a role. Another viewpoint is that the endothelial location of ACE-2 receptors and the immune response to SARS-CoV-2 infection may cause acute pancreatitis (AP) in COVID-19 patients by causing vascular thrombosis in pancreatic venous.^[19-23]

Drug-induced pancreatitis may develop secondary to the drugs used in the treatment. Pancreatic damage can be seen clinically in these conditions. One of the agents found particularly guilty is antipyretics.^[13] Because lopinavir & ritonavir are p450 enzyme system substrates, they can cause a variety of drug-drug interactions. Hepatitis or pancreatitis can develop as a result of the patient's drug combination or as a result of the drug's effect alone.^[22-24]

However, no studies have been conducted to determine whether SARS-CoV-2 can cause pancreatic cell damage, resulting in acute pancreatitis.^[21]

There are also opposing views in the literature regarding COVID-19-related pancreatic involvement.^[6,25-28] Some authors emphasize that pancreatic enzyme elevations are due to the current clinical picture rather than pancreatitis.^[6,27] According to Goyal et al.,^[26] lipase, one of the pancreatic enzymes, is nonspecific and can be elevated in a variety of conditions, including infections, renal dysfunction, drug-induced, GI, and hepatobiliary disease. Given this, it was emphasized that assessing the prevalence of hyperlipidemia and predicting clinical outcomes in COVID-19 is critical.^[26] Pezzilli et al.^[27] evaluated 110 patients in their study and reported that none of the patients developed clinical signs or morphological changes consistent with acute pancreatitis, but amylase values in 24.5% of the patients and lipase values in 16.4% were found to be above the upper limits. It was also reported in this study that both amylase and lipase levels exceeded three times the upper normal limit in only 0.9% of patients who did not have clinical signs of pancreatitis. According to Pribadi and

Simadibrata,^[28] increased amylase & lipase values in COVID-19 patients do not always indicate pancreatic damage, and that elevated enzyme levels can be found in other clinical conditions.

Liu et al.^[21] investigated the amylase & lipase levels in 121 COVID-19 infected patients. According to this study, 1.85% of patients with mild clinical course had both amylase and lipase elevations, 17.91% of patients with severe clinical course had elevated amylase, and 16.41% had high lipase. They reported five (7.46%) patients with severe COVID-19 changes in the pancreas & pancreatic duct as focal enlargement without acute necrosis. Since two of the patients had a history of nonsteroidal anti-inflammatory drugs and four of the patients had a history of glucocorticoid treatment, the possibility of drug-induced pancreatitis was also emphasized in these patients. It has been reported that five patients with pancreatic damage died, while eight others were discharged. This study also noted that, while COVID-19 patients do not exhibit symptoms of necrotizing pancreatitis, the consequences of pancreatic damage can be severe (for example, exacerbating systemic inflammation, accelerating the onset of acute respiratory distress syndrome, or even transforming into chronic pancreatitis, which can have a serious effect).^[21]

Some authors argue that in pediatric patients infected with COVID-19, elevated amylase & lipase levels and possible pancreatitis may develop. According to Suchman et al.,^[29] 112 (1.37%) of 8,159 pediatric patients hospitalized with pancreatitis were diagnosed with COVID-19, and 13 (0.16%) were diagnosed with pancreatitis. According to this study, pancreatitis can also occur in pediatric COVID-19 patients and may be more common in the COVID-19 population.^[29]

The incidence of acute pancreatitis was 0.07% in a retrospective study involving 50 hospitals and 63,000 COVID-19 infected patients in Spain.^[30] A total of 11,883 COVID-19 infected patients were studied in the United States, and acute pancreatitis was found in 32 (0.27%) of them.^[31] According to a prospective study from our country,^[32] AP alone is a clinical condition that can lead to mortality and maybe one of the causes of the exaggerated immune

response that develops during the progression of COVID-19. Acute pancreatitis was found in 12.6% of the 316 patients in the study. Mild patients did not have AP, but 7.9% of severe patients (n=15) and 32.5% of critically ill patients (n=25) did. C-reactive protein and ferritin levels were found to be significantly higher in those with pancreatitis ($p < 0.0001$). According to the findings of this study, the presence of pancreatic damage caused by SARS-CoV-2 could worsen the clinical condition of the patients and increase the mortality rate in these patients.^[32]

In another study conducted in Italy,^[33] pancreatic enzymes (amylase & lipase) were found to be elevated in 254 of 282 COVID-19 infected patients, with mild pancreatic enzyme (PE) elevation in 66 (26%) and severe elevations (>3 times the upper limit of normal) in 11 (4.3%). Only two patients met the AP diagnostic criteria, and an increase in PE was found in patients with hepatic and renal involvement. Multivariate analysis revealed that mild and severe pancreatic enzyme elevations were significantly associated with intensive care unit admission.^[33]

In a study of 52 COVID-19 infected patients,^[6] only 17% of amylase & lipase elevation was detected without pancreatitis. Another study found that isolated serum lipase levels were higher in COVID-19 patients who did not have AP symptoms.^[34] According to Wang et al.,^[6] SARS-CoV-2 infection could theoretically cause islet damage, resulting in acute diabetes, and hyperglycemia was found in six of nine patients with pancreatic damage.^[6]

Acute pancreatitis is a clinical condition that can be fatal on its own and maybe one of the causes of the exaggerated immune response in COVID-19 progression. It suggests that the presence of pancreatic damage caused by SARS-CoV-2 may worsen the clinical condition of the patients and increase the mortality rate in these patients. In reported cases of COVID-19-related AP, abdominal CT is also within normal limits.^[6,34,35]

Pancreatic damage is more severe in severe COVID-19 infection due to a cytokine storm accompanied by elevated IL-6, IL-8, and IL-10. Similarly, infection causes a cytokine storm with high levels of IL-6, IL-8, and IL-10 in severe acute pancreatitis.^[6,7]

Another important issue is the scarcity of data on the prevalence and course of COVID-19 in patients with underlying pancreatic or biliary diseases.^[8] Ullah et al.^[36] argued that those with pre-existing pancreatic and liver disease are at a higher risk of COVID-19 infection and that decreased pancreatic function may disrupt the intestinal flora, making patients more susceptible to pathogens via the enteric route.

There are also differing viewpoints on the treatment. Although some argue that the treatments for the “pancreatitis-like clinical syndrome” associated with COVID-19 are the treatment of the underlying disease or symptomatic treatment, alternative treatments are also recommended.^[8,37] Tocilizumab is a monoclonal antibody that inhibits the binding of IL-6 to its receptor in a competitive manner, and it has been reported that it may be a novel method. However, scientific data is currently scarce.^[8] Zielecki et al.^[37] reported a 38-year-old patient with hepatosteatosis, hepatosplenomegaly, and alcohol dependence, as well as severe COVID-19 pneumonia and moderately edematous pancreatitis, who was successfully treated with tocilizumab. In studies conducted in 2016 and 2017, tocilizumab was shown to be significantly effective in severe acute pancreatitis and acute lung injury in experimental rat models.^[38,39]

In conclusion, diagnosing COVID-19-related acute pancreatitis, which is diagnosed using the diagnostic criteria, may be difficult. Existing data can be difficult to interpret. The majority of the current cases are case reports and retrospective studies. It is also unknown what the patients’ long-term outcomes will be. Based on current literature, the mechanisms of pancreatic involvement, amylase, and lipase elevation during SARS-CoV-2 infection are not well understood. There are inconsistent results between studies. Therefore, experimental studies on this subject should be prioritized.

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