Involvement of the exocrine pancreas during COVID-19 infection and possible pathogenetic hypothesis: a concise review

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SUMMARY

The gastrointestinal system may be affected by COVID-19 infection with an incidence variable from 3% up to 79%. Several works show that the pancreas, both in its exocrine and endocrine function, can be affected by this viral infection, although this organ has been poorly analyzed in this current epidemic context. This mini-review aims to provide a summary of available studies on exocrine pancreas involvement during COVID-19 infection. A search through MEDLINE/PubMed was conducted on the topic in hand. With regard to exocrine function, some studies highlight the presence of an associated hyperenzymemia (hyperamylasemia, hyperlipasemia), while others describe isolated and rare cases of acute pancreatitis. More attention should be paid to pancreatic impairment in subjects with COVID-19, as this may prove to be one of the elements aggravating its clinical course. Indeed, acute pancreatitis, especially when presenting in severe forms with hyperstimulation of the pro-inflammatory response, may represent a crucial factor in the progression of COVID-19, entailing both an increase in hospitalization days and in mortality rate.

Keywords: Amylase, COVID-19, hyperamylasemia, hyperlipasemia, lipase, pancreas, SARS-CoV-2.

INTRODUCTION

The term COVID-19 defines the disease caused by a new coronavirus named SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2), which has led to the declaration of a pandemic some months ago by the World Health Organization (WHO) [1]. It is mainly characterized by the onset of respiratory symptoms and pneumonia. However, this virus may affect a wide spectrum of organs and may localize also in the digestive tract, inducing gastrointestinal (GI) symptoms. In a recent review, Tian Y et al. have analysed the presence of this specific symptomatology in patients with SARS-CoV-2 related infection and found an incidence ranging from 3% up to 79% according to the available studies. In particular, the following manifestations were found with a variable incidence: vomiting (3.6-66.7%), anorexia (39.-50.2%), diarrhoea (2-49.5%,) nausea (1-29.4%), gastrointestinal bleeding (4-13.7%) and

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abdominal pain (2.2-6.0%) [2]. While a correlation has been recognised between GI manifestations and COVID-19, the possible association between SARS-CoV-2 related infection and pancreatic diseases still remains uncertain and not-well defined [3]. For example, it has been shown that COVID-19 is able to affect pancreatic endocrine tissue, leading to the disregulation in the control of the glucose serum levels [4]. In this respect, the involvement of this pancreatic compartment in patients with COVID-19 and a higher probability of diabetes mellitus development in these individuals has been widely investigated and also reported [4]. According to the available data, it has been suggested that SARS-CoV-2 represents a risk factor for the onset of diabetes in infected patients, with an increased morbidity and mortality [5,6]. On the other hand, the pancreatic exocrine function has been poorly examined in this specific virosis. Nevertheless, some works are pointing out the possible alteration of the pancreatic structure/function in the course of COVID-19, including either tissue injury with pancreatitis or only the increase in pancreatic enzymes (amylase and lipase). It is known that the involvement of the pancreas is not a peculiar prerogative of the SARS-CoV-2. In fact, in a recent systematic review focused on various pathogens, such as the etiological cause of acute pancreatitis, viruses were the main responsible agents in 65.3% of cases [7]. It has been demonstrated that a wide spectrum of viruses, including hepatotropic ones, such as Hepatitis A, B, C and E viruses, Cytomegalovirus, Human Immunodeficiency virus, Coxackie virus, Paramyxovirus, Herpes Simplex virus and Varicella-Zoster virus, infect pancreatic cells and induce clinical pictures with different grades, ranging from mild to severe [8,9]. Even influenza viruses related infection can be associated with the development of acute pancreatitis, although a few cases have been reported [10, 11]. However, since only the infection of the pancreas by SARS-CoV-2 is the topic of this review, the etiopathogenetic events occurring during acute pancreatitis caused by the other viruses will be not further discussed. The aim of this mini-review has been to identify, by a research conducted through MEDLINE/PubMed, the studies which have considered the exocrine pancreatic involvement arising during COVID-19. In particular, the following keywords have been searched: "pancreas", "SARS-CoV-2", "COVID-19", "amylase", "lipase", "hyperamylasemia", "hyperlipasemia" and "pancreatitis".

PATHOGENETIC HYPOTHESIS

Which could be the pathogenetic events occurring in the pancreas during a viral infection mainly characterised by respiratory symptoms, possibly leading to the damage of the exocrine compart-

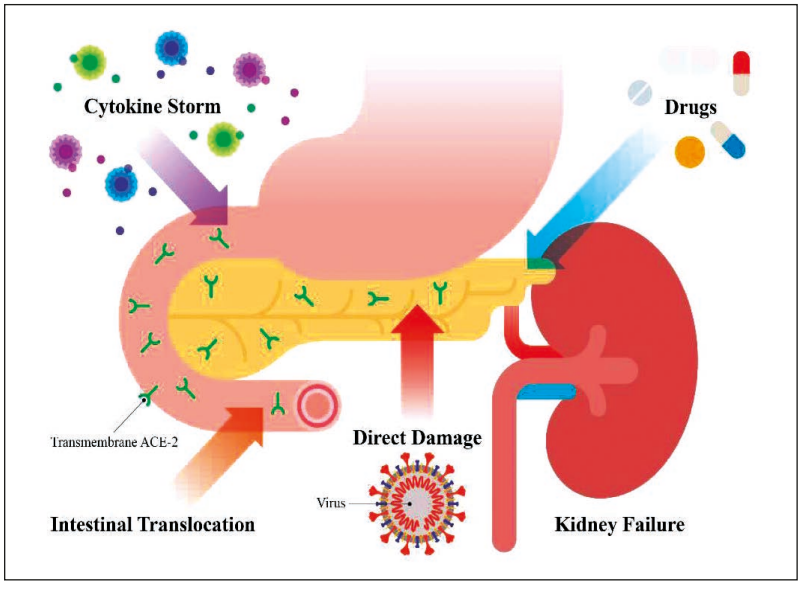

Figure 1 - Possible mechanisms underlying the pancreatic damage.

ment in this organ? Multiple mechanisms may play a role in this process and may be very similar to the ones proposed for the liver, including:

1) Direct damage: the virus is able to bind to the receptors of ACE-2 which are expressed also in the gastrointestinal tract and in the pancreas [12-14]. Generally, these receptors are proposed to counteract acute pancreatic inflammation. It is assumed that inflammatory markers are released as a result of their binding to the SARS-CoV-2.
2) Kidney failure: as the kidneys are fundamental in eliminating amylases and lipases from the circulatory stream, their malfunction, even temporary, can lead to a transient increase in pancreatic enzymes.
3) Intestinal translocation: as observed in a recent review, diarrhoea is present in about 2-49.5% of the COVID-19 cases and, in addition, it is known that the viral RNA can be found in the stool [2, 15-17]. It is also necessary to consider both the presence of ACE-2 receptors in GI lumen and the alteration of the barrier permeability, the latter resulting from intestinal infections which can also facilitate the reabsorption of the pancreatic enzymes themselves [13, 18-20].
4) Drug-induced pancreatic injury: the available therapies used for the COVID-19 treatment may cause tissue injury in this organ. Several drugs have been reported to damage the pancreatic tissue, including:
   A) antiviral drugs, such as lopinavir/ritonavir, when orally administered together,
   B) antipyretics,
   C) tocilizumab and baricitinib, which may induce hypertriglyceridemia.
5) Cytokine storm: this condition refers to the key role of the activated immune system in response to "external agents", with consequent uncontrolled inflammatory systemic response [21-26].

Accordingly, following SARS-CoV-2 infection, especially in severe forms of COVID-19, a release of wide spectrum of cytokines, such as interleukin IL-2, IL-6, IL-8, IL-7, interferon-γ and tumour necrosis factor-α, occurs [26, 27]. As emphasized in a recent review, viruses generally may stimulate the release of these cytokines and inhibit the anti-viral response induced by interferon [28, 29]. Moreover, SARS-CoV-2 promotes the development of cytokine storm, via some of its structural proteins, including spike and nucleocapsid ones [25] (Figure 1).

INCREASE OF PANCREATIC ENZYMES AND ACUTE PANCREATITIS IN COVID-19 PATIENTS

According to the available data in the literature, we have identified five papers describing the increase of pancreatic enzymes (hyperamylasemia

Table 1 - Hyperamylasemia and hyperlipasemia during SARS-CoV-2 infection.

Authors	*Number of patients with SARS-CoV-2*	*Amylase (U/L)*	*Lipase (U/L)*
Wang F et al. [22]	9 of 52 (17%)	115±25	71±34
Zhang J et al. [30]	19	64.3 (56.4-94.6) (mg/L)	NA
Bruno G et al. [31]	6 of 70 (8.5%)	Serum amylase peak: 562 223 194 202 730 119 (Mean value=338.3)	Serum lipase peak: 2,430 1,025 812 831 3,445 511 (Mean value= 1641)
McNabb-Baltar J et al. [32]	9 of 71 (12.1%)	NA	151.8 SD±148.4 Only 2 (2.8%) patients developed hyperlipasemia exceeding 3 times the upper limit of normal (>180 U/L)
Barlass U et al. [33]	14 of 83 (16.8%)	NA	Considered only the lipase values greater than 3 times the normal one (>156 U/L)

NA = not available.

and hyperlipasemia) in SARS-CoV-2 patients [22, 30-33]. These results are summarized in Table 1.
According to the revised Atlanta classification, the diagnosis of Acute Pancreatitis (AP) can be made when at least two of the following three characteristics are present:

1) typical abdominal pain of this disease ("pancreatic pain");
2) serum lipase or amylase levels at least three times greater than the upper limit of normal;
3) findings of acute pancreatitis with imaging techniques (contrast-enhanced computed to-

Table 2 - Acute pancreatitis during SARS-CoV-2 infection.

Authors	*Num. of patients*	*Age-Sex*	*Abdominal pain*	*Amylase Lipase (U/L)*	*Imaging*	*Drugs taken in the previous days*
Hadi A et al. [35]	1*	68-F	present	934 NA	NA	losartan, levothyroxine, alendronate, cyanocobalamin
	1*	47-F	assent	<1.500 NA	Abdominal ultrasound: pancreas was diffusely voluminous	antibiotics (non specificated)
Rabice SR et al [36]	1**	36-F	present	88 (normal) 875	Abdominal ultrasound: pancreas not visualized due to bowel gas	acetaminophen, dicloxacillin
Aloysius MM et al. [37]	1	36-F	present	325 627	CT scan: pancreas normal	none
Anand ER et al. [38]	1	59-F	present	NA NA	CT scan: pancreas edematous	vancomycin
Kataria S et al. [39]	1	49-F	present	501 1.541	CT scan: pancreas edematous with diffuse enlargement	ceftriaxone, azithromycin
C Akarsu et al. [40]	40	Median age 55 yr (26-84)	Present in 35 pts (87.5%)	383.9±76.3 663.8±98.7	CT scan: (Balthazar score) [33]: A=19 pts B=14 pts C=3 pts D=1 pts E=3 pts	NA
Cerda-Contreras C et al. [24]	1	72-F	NA (patient sedated)	NA 1.247 U/L	CT scan: pancreatic edema	baricitinib, dexamethasone, enoxaparin
Alves AM et al. [41]	1	56-F	NA (patient sedated)	544 U/L 2.993 U/L	CT scan: tail parenchymal enlargement and surrounding retroperitoneal fat stranding	losartan, hydro-chlorothiazide, antibiotics (non specificated)
Kumaran NK et al. [42]	1	67-F	present	1.483 U/L NA	CT scan: necrotising pancreatitis	NA

NA = not available; *two cases of AP in patients with severe forms of COVID-19, who both needed hemodialysis for acute renal failure; **woman at the 33 weeks of gestation.

mography, magnetic resonance imaging and transabdominal ultrasonography) [34].

To date, forty-nine cases of AP have been reported in literature in patients affected by COVID-19, as shown in Table 2 [24, 35-42].

In a recent prospective study on 367 patients affected by COVID-19, acute pancreatitis was found in 12.6% of patients, that is in 50 of the 316 individuals included in the analysis [40]. The authors classified the COVID-19 patients, according to the severity of the disease: 50 patients (15.8%) in mild, 189 patients (59.8%) in severe and 77 patients (24.3%) in critical status. Acute pancreatitis was not observed in patients with mild grade of SARS-CoV-2 infection, while it was detected in 15 (7.9%) and 25 (32.5%) subjects with severe and critical forms of this infectious disease. The authors underlined that seriousness of acute pancreatic inflammation increases with the degree of severity of the lung involvement ($p<0.0001$). The hospitalization and the mortality rates were also higher in patients with COVID-19 associated with AP ($p=0.0038$ and $p<0.0001$, respectively) [40]. Barlass et al. assessed the relationship between a significant increase of lipase serum levels (greater than 3 times the upper limit of normal) and clinical outcome in a cohort study of patients with COVID-19 between March 12th and April 3rd, 2020. Among 294 patients admitted to hospital with SARS-CoV-2 infection, data about pancreatic lipase levels were available in 83 and 14 of them (7.9%) had high lipase serum levels (>3 ULN). These individuals had more elevated rates of leukocytosis and altered liver enzymes ($p<0.01$). Furthermore, patients with higher lipase levels had more elevated probability of ICU admission and intubation (92.9% vs 32.8%; $p<0.001$) and (78.6% vs 23.5%; $p<0.002$), respectively [33]. In a recent retrospective study, Gubatan J et al. investigated the presence of a previous history of acute or chronic pancreatitis in a cohort of 14.235 individuals tested for SARS-CoV-2 [43]. The authors found out that these diseases were present in 102 cases (0.7%). Among them, an acute pancreatitis was detectable in 85.3% and a chronic pancreatitis in 14.7% [43] The authors also noted a higher prevalence (7.8%) (8/102) of COVID-19 among patients with prior pancreatitis, which is greater if compared to the same population tested for the presence of the virus and proven to be serologically positive (2.8%) in another study [44].

DISCUSSION

Based on the analysis of the available data, this review highlighted how SARS-CoV-2 infection can also affect the exocrine pancreas. Liu L et al. work may contribute to explain the probable mechanisms underlying hyperamylasemia [45]. The authors focused on the virus SARS-CoV responsible for Severe Acute Respiratory Syndrome in 2003, which has been recently shown to exhibit the 79% of its genome in common with this new virus (SARS-CoV-2) in animal models [46]. It was found out that the first infected "target" cells were epithelial ones, expressing ACE-2 receptors, which line the ducts of the salivary glands [45]. Data related to SARS-CoV-2 virus and extra-pancreatic tissues as a source of possible enzymatic increases are currently not available yet. Recently, Fox SE et al. have performed ten autopsies on African American patients, aged 44-78 years. It was shown the presence of thrombosis in lungs and in heart, while these findings were not apparent in other organs, such as pancreas [47]. On the contrary, in a prospective autopsy study, Lax SF et al. found focal pancreatitis in 5 out of 11 patients (mean age: 80.5 years; 8 male and 3 female) died from COVID-19 (45.5%), suggesting that the real incidence of pancreatitis may be underestimated [48]. As previously underlined, during AP the levels of amylase tend to increase after 6-24 hours from the beginning of its development, reaching a peak at 48 hours [49]. Over a period of the next 5-7 days after onset, amylase levels typically tend to normalize and this event could make diagnosis more difficult, as one of the three Atlanta criteria would be missing [34, 49]. The patients with AP described in Table 2, were hospitalized and most of them were under sedation and/or intubated in ICUs, so they were not able to report the abdominal pain. In this condition another criterion of the Atlanta classification ("pancreatic pain") is missing, so the diagnosis of AP is based exclusively on the finding of the increase in pancreatic enzymes associated with imaging. It is known that in the AP the immune system initially tends to release pro-inflammatory cytokines, with consequent Systemic Inflammatory Response Syndrome (SIRS) which is generally followed by a Compensatory Anti-inflammatory Response Syndrome (CARS) [50]. A strong factor influencing the prognosis of AP is represented by

the intensity of these two phases (SIRS, CARS). In fact, the excessive prevalence of the first one leads to the Multi-Organ Dysfunction Syndrome (MODS), especially during the early course of the disease [51]. To date, only a few studies have analysed the clinical course of patients with COVID-19 and suffering from pancreatitis, as well as the possible association between the pancreatic involvement and more severe forms of infection. By using the Mhealth Fairview System, Dirweesh et al. have carried out a retrospective analysis between March 1st and June 30th, 2020, with the aim to assess the outcome and the prognosis of subjects with acute pancreatitis who were enrolled during the development of COVID-19 epidemic. Seventy-five individuals were tested for SARS-CoV-2 by means of PCR and were included in the study. The presence of the virus was proved in 14 of them. Significant higher morbidity and mortality, as well as multiorgan failure and persistent organ failure, were observed in individuals with coexisting acute pancreatitis and positive PCR testing for SARS-CoV-2, according to Bedside Index of Severity in Acute Pancreatitis scores [52].

Recently, the lipotoxicity in COVID-19 Study Group of the Mayo Clinic published a study focused on unsaturated fat intake which seems to be associated with an increase in mortality due to COVID-19. The Members observed how this kind of fat are able to induce organ failure and how early administration of albumin and calcium, nutrients binding unsaturated fatty acids, can reduce this injury. The sudden progression of COVID-19 to MODS resembles the lipotoxic organ failure occurring during severe acute pancreatitis. The authors argued that in both of these pathologies (COVID-19 infection and AP), fatty lipolysis from pancreatic inflammation leads to an increase in the levels of fatty acids [53]. These last ones, directly damaging the mitochondria, are able to determine an increase in the production of pro-inflammatory cytokines (cytokine storm), with consequent facilitation of progression in a MODS and in an Acute Respiratory Distress Syndrome (ARDS), well-known causes of mortality related to COVID-19 [54]. It may be also hypothesized that the virus does not affect only the cells of the exocrine pancreatic parenchyma, but also the adipocytes, with consequent fat lipolysis [53].

Furthermore, another possibility is that the virus can directly replicate inside the cells of the pancreas as it has been reported for other viruses (Hepatitis A, B, C and E viruses, Cytomegalovirus, Human Immunodeficiency virus, Coxsackie virus, Paramyxovirus, Herpes Simplex virus and Varicella-Zoster virus) [55-58]. It has to be underlined that the antigens and/or the genome of some viruses have been detected inside pancreatic acinar cells (HBV, HCV, HIV, Cytomegalovirus, Coxsackievirus etc.) [59, 60]. However, to date, no studies have investigated whether the antigens and/or genome of SARS-CoV-2 are identifiable in the exocrine or endocrine cells of pancreas. If this hypothesis was confirmed, new scenarios in our diagnostic and prognostic abilities could emerge.

CONCLUSIONS

In conclusion, to date, the pancreatic involvement during SARS-CoV-2 infection is not yet well defined and, above all, little investigated. Analyzing the available data, it would seem that acute pancreatitis, especially when observed in severe forms with hyperstimulation of the pro-inflammatory response, may represent a crucial factor in the progression of COVID-19. However, this review has an important limit, as most of the data collected mainly derive from case histories on hospitalized patients. These individuals generally are affected by severe forms of COVID-19 infection and the association with acute pancreatitis could be considered as kind of bias, also considering other confounding factors previously mentioned. Further studies are needed on this topic to better clarify the real impact of SARS-CoV-2 in pancreatic damage and its role in human pathogenesis.

Conclusive remarks

1) SARS-CoV-2, as several other viruses including hepatotropic viruses (Hepatitis A, B, C and E viruses), Cytomegalovirus, Human Immunodeficiency virus, Coxsackie virus, Paramyxovirus, Herpes Simplex virus and Varicella-Zoster virus, have been recognized as a cause of pancreatic involvement.
2) It is still unclear whether in patients affected by COVID-19, SARS-CoV-2 causes a direct pancreatic damage, by infecting its acinar cells, or an indirect one, by stimulating an excessive and sudden systemic inflammatory response with the release of a large amount

of pro-inflammatory cytokines. However, it has to be considered that antigens and viral genome of some viruses, such as HBV, HCV, HIV, Coxsackie virus, Cytomegalovirus have been detected in pancreatic acinar cells. According to these observations, it may be hypothesized that SARS-CoV-2 also may have a similar behavior. Therefore, the increase in serum amylase and lipase levels, reported by some articles, might be due to pancreatic infection or multiorgan interest, or both of these factors together. However, further studies are needed to clarify all these points.

3) The possibility of pancreatic involvement should always be considered in patients with SARS-CoV-2 related infection. Therefore, serum levels of amylase and lipase enzymes should be tested in all patients with COVID-19, even in asymptomatic subjects. On the basis of the above mentioned pathogenetic mechanisms, it should be investigated whether more elevated amylase and lipase levels are associated or not with a more severe course of this specific virosis. More data concerning to this topic are requested.
4) A better knowledge of the mechanisms involved in the development of acute pancreatitis, during the course of COVID-19, may represent a paradigm to understand the pathogenesis and the outcome of SARS-CoV-2 related infection and may provide useful insights for the possible introduction of effective treatments against this disease.

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Conflict of interest
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