Consequences of COVID-19 for Pancreas

Subjects: Biochemistry & Molecular Biology | Gastroenterology & Hepatology

Contributor: Urszula Abramczyk

Coronaviruses are enveloped, single- and positive-stranded RNA viruses that infect birds and mammals. In humans, coronaviruses cause respiratory tract infection, usually the common cold, but they can also cause severe respiratory illness including severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), caused by severe acute respiratory syndrome-related coronavirus (SARS-CoV) and Middle East respiratory syndrome-related coronavirus (MERS-CoV), respectively. Although coronavirus disease 2019 (COVID-19)-related major health consequences involve the lungs, a growing body of evidence indicates that COVID-19 is not inert to the pancreas either.

COVID-19 pancreas SARS-CoV-2 diabetes

1. Effects of Severe Acute Respiratory Syndrome-Related Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome-Related Coronavirus (MERS-CoV) on the Pancreas

Coronaviruses are enveloped, single- and positive-stranded RNA viruses that infect birds and mammals. In humans, coronaviruses cause respiratory tract infection, usually the common cold, but they can also cause severe respiratory illness including severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), caused by severe acute respiratory syndrome-related coronavirus (SARS-CoV) and Middle East respiratory syndrome-related coronavirus (MERS-CoV), respectively [1]. Coronaviruses tend to cause epidemics and even pandemics. The first coronavirus pandemic was the SARS outbreak in 2002–2003 [2]. With the experience gained during the SARS pandemic, it was possible to more quickly identify subsequent outbreaks of the MERS epidemic in 2012 [3]. The pathomechanism of both viruses is very similar—they even both use transmembrane protease serine 2 (TMPRSS2), except SARS-CoV uses angiotensin-converting enzyme 2 (ACE2) as its receptor, whereas MERS uses dipeptidyl peptidase-4 (DPP4) [4][5]. Moreover, there is a difference in terms of the severity and frequency of symptoms, which was observed in MERS patients as more frequent hospitalization in the intensive care unit (ICU) compared to SARS patients [2]. Diabetes was one of the significant and independent predictors for developing severe SARS-CoV and MERS-CoV [6][7][8]. In MERS, no viral antigen was detected in any tissue other than pneumocytes [7], despite multiple organ dysfunction syndrome in critically ill patients. In SARS-CoV, the presence of the virus was detected not only in respiratory epithelial cells, but also in small intestinal and colonic epithelial cells, in which it also revealed replication features [9]. It is known that the ACE2 receptor is also present in tissues such as the heart, kidney, and pancreas [8][9].

2. Pancreatic Damage during Diabetes Mellitus and COVID-19

Pancreas tissue damage may cause to the lack of control over normal blood glucose levels in the body. Type 1 diabetes (T1D) is caused by insulin deficiency due to βcell dysfunction of immunologic or idiopathic cause. In contrast, β pancreatic cells in type 2 diabetes (T2D) become depleted over time due to compensatory insulin secretion caused by insulin resistance. There is also type 3 diabetes (T3D), which is described as diabetes associated with the development of Alzheimer's disease [10]. It should not be confused with type 3c (pancreatogenic) diabetes, which relates to the exocrine and digestive functions of the pancreas. The issue concerning the impairing effect of hyperglycemia (glucotoxicity) on the secretory function of the islets of Langerhans has also been increasingly raised. In addition to endocrine dysfunction, some diabetic patients may also develop moderate exocrine pancreatic insufficiency (EPI), in which pancreatic enzyme secretion is impaired. EPI can be observed in almost all patients with type 3c (pancreatogenic) diabetes (secondary to pancreatic pathology), whereas the prevalence of this dysfunction in patients with T1D or T2D is 40% and 27%, respectively [11].

With the ongoing SARS-CoV-2 pandemic, patients with reduced normal pancreatic function are at high risk for COVID-19 requiring hospitalization. In particular, elevated blood glucose levels in patient with and without diabetes makes them at high risk of mortality [12]. Hyperglycemia impairs the immune response (e.g., by reducing the activity of macrophages and polymorphonuclear leukocytes), which in addition influences the excessive cytokine response, and thus has a strong proinflammatory effect.

The receptors for ACE2, which are also present in the pancreas, are a target of SARS-CoV-2 in the body, which may result in acute failure of both the islets of Langerhans and exocrine cells [13]. Infection-induced, transient β cell dysfunction may cause an uncontrolled hyperglycemic state, especially in patients whose pancreas is already affected by diabetes mellitus. Persistent hyperglycemia usually predisposes to severe COVID-19 and to viral infection complicated by secondary infections.

3. Pancreatic Damage in Patients without Pre-Existing Diabetes Infected with SARS-CoV-2

It has been postulated that, either by direct invasion of pancreatic cells by the virus or by indirect mechanisms described below, SARS-CoV-2 has a destructive effect on the pancreas and can lead to insulin deficiency and development of T1D [14].

If the hypothesis that SARS-CoV-2 infection causes hyperglycemia is true, increased statistics of new T1D cases should be observed. Indeed, there are publications that describe such a phenomenon. For instance, Unsworth et al. and Kamrath et al. describe an increase in new-onset T1D in children during the COVID-19 pandemic [15][16]. Although pancreatic β cell damage induced transient hyperglycemia in SARS-CoV, it is still unclear whether β cell damage is transient or permanent in SARS-CoV-2 [17]. This information appears to be of great importance because

COVID-19 in children is frequently considered “harmless”. Therefore, it is reasonable to sensitize parents to the fact that the consequences of COVID-19 may be potentially dangerous for their children.

4. Etiology Associated with ACE2, TMPRSS2, and Na+/H+ Exchanger

As previously mentioned, SARS-CoV infection of host cells is facilitated by ACE2, but also by the transmembrane protease serine 2 (TMPRSS2) and other host cell proteases such as cathepsin L (CTSL) [18].

ACE2 is an enzyme that is expressed to varying degrees in most cells of the human body [19][20][21]. This enzyme catalyzes the conversion of angiotensin II to angiotensin 1–7, taking part in the maintenance of body homeostasis by influencing the regulation of blood pressure and water–electrolyte balance through the renin–angiotensin–aldosterone (RAA) system [22]. Moreover, ACE2/angiotensin (1–7) stimulates insulin secretion, reduces insulin resistance, and increases pancreatic βcell survival [21][22].

In addition to the key role it plays in maintaining body homeostasis, ACE2 is now also the best-studied target for SARS-CoV-2 S glycoprotein, enabling infection of host cells [21][23]. ACE2 in the pancreas is expressed mainly within the pericytes of pancreatic microvessels and to a lesser extent on the surface of the islets of Langerhans, including pancreatic β cells [24]. SARS-CoV-2 shows 10–20 times more activity against ACE2 than SARS-CoV, which significantly increases the infectivity of SARS-CoV-2 [25][26]. Furthermore, studies indicate that SARS-CoV may also downregulate ACE2 expression in cells. This causes an imbalance between ACE and ACE2, consequently leading to blood pressure disorders and systemic inflammation [21][27][28]. Due to the 79% genetic similarity between SARS-CoV and SARS-CoV-2 [29], it is speculated that ACE2 expression may also be downregulated during SARS-CoV-2 infection, causing i.a. MODS observed in COVID-19 [21].

During cell infection by SARS-CoV-2, in addition to the role played by ACE2, it is also appropriate to consider the significant pathogenic role of TMPRSS2 that is necessary for the preparation of S glycoprotein by its cleavage, thereby enabling fusion of the virus with the host cell [30][31]. The S1 and S2 domains can be distinguished in the SARS-CoV-2 S glycoprotein. The S1 domain is involved in binding to the ACE2 receptor and then TMPRSS2 intersects with the S protein, including at the boundary of the S1 and S2 domains and within the S2 domain, which enables the virus–cell fusion [32][33]. According to studies, TMPRSS2 expression is significantly increased in obese patients, which may contribute to the poorer prognosis that is observed during COVID-19 in this patient group [34]. Moreover, obese patients are frequently already burdened with problems such as insulin resistance at baseline, while the presence of ACE2 and TMPRSS2 within the pancreas as a binding site for SARS-CoV-2 may exacerbate insulin resistance causing problems in terms of diabetes management in COVID-19 patients.

There are also other mechanisms by which COVID-19 may affect the development of hyperglycemia. It is reported that the virus may also affect the glucose regulation through the Na+/H+ exchanger and lactate pathways. The mechanism is that angiotensin II, which accumulates during infection, contributes to insulin resistance and—by activating the Na+/H+ exchanger in the pancreas—it leads to hypoxia and extracellular acidification, which, through

the accumulation of calcium and sodium ions in the cells and the production of reactive oxygen species, damages pancreatic tissue [35]. Simultaneously, the concentration of lactate increases, which in COVID-19 infection is intensively released, among other things, from adipose tissue, and then monocarboxylate transporters transport lactate and H+ ion inward in the cell, which increases Na+/H+ exchanger activation, further disrupting pancreatic homeostasis [35].

5. The Etiology Associated with a Systemic Proinflammatory Environment, Immune System Aggression, and Production of Novel Autoantigens

A broad spectrum of proinflammatory cytokines, such as IL-2, IL-6, IL-7, IL-8, interferon-γ, and Tumor Necrosis Factor α (TNF-α), is released during, in particular severe, COVID-19 infection [36][37][38]. Based on current studies, it is reasonable to suspect that these cytokines are released in response to the binding of the virus to ACE2 receptors that are also located in the pancreas [9][36]. The cause of pancreatic damage during COVID-19 is the cytokine storm that plays a key role in this case, because in both acute pancreatitis (AP) and severe COVID-19, elevated levels of the aforementioned interleukins are associated with the severity of these both disease entities. Particular attention should be paid to IL-6, because it is suspected to play a key role in the pathogenesis of AP as well as acute respiratory distress syndrome (ARDS) that is the most common and most severe clinical manifestation of COVID-19. In COVID-19-induced ARDS, IL-6 levels are correlated with disease-related mortality [39][40][41]. At the same time, high IL-6 levels correlate with an increased risk of developing severe pancreatitis [42][43].

The production of neutralizing antibodies is also an important response of the body in the course of COVID-19 [44][45][46]. It has been observed that early seroconversion and very high antibody titers occur in patients with severe SARS-CoV-2 infection [47][48]. The available literature details a mechanism called antibody-dependent enhancement (ADE), which is associated with a pathological response of the immune system [47]. ADE exploits the existence of FcRS receptors located on various cells of the immune system, for example, macrophages and B lymphocytes [47]. This relationship may lead to a likely bypass of the classical viral infection pathway by ACE2, and virus–antibody complexes may stimulate macrophages to overproduce cytokines including significant IL-6 [47][49].

Molecular mimicry may be also one of potential causes of pancreatic cell damage [50]. There are similarities in the protein structure of the virus and β-pancreatic cells, which may induce cross-reactivity and lead to autoimmunity [50]. Furthermore, viral infection may also lead to increased cytokine secretion by surrounding dendritic cells and activation of naive T cells in genetically predisposed individuals [50].

6. Pancreatitis in COVID-19

Although the impact of the discussed coronavirus-induced disease on exocrine function is not fully understood, available literature is not able to unambiguously determine whether the tissue damage leading to AP occurs as a

result of direct SARS-CoV-2 infection [51] or as a result of systemic MODS with increased levels of amylase and lipase [36]. Liu et al.'s study involving 121 COVID-19 patients with a mean age of 57 years and a variable course of infection proved above-normal levels of amylase and lipase in 1–2% of patients with moderate COVID-19 infection and in 17% of patients with severe COVID-19 infection. This may support the hypothesis that SARS-CoV-2-induced disease has a destructive effect not only on the endocrine portion of this gland, but also on the exocrine one [13].

However, elevated levels of pancreatic enzymes in question do not have to mean the destruction of pancreatic cells—after all, such a situation may occur during kidney failure or diarrhea in the course of COVID-19. Furthermore, there remains the question of the effect of drugs administered during SARS-CoV-2 infection on changes in pancreatic function [36], discussed further in this article.

According to the International Association of Pancreatology (IAP) and the American Pancreatic Association (APA), the diagnosis of AP is based on meeting two out of three of the following criteria: clinical (epigastric pain), laboratory (serum amylase or lipase > 3 × upper limit of normal), and/or imaging criteria (computed tomography, magnetic resonance imaging, ultrasound) [52]. Pancreatic lipase is considered as a potential marker of SARS-CoV-2 severity with concomitant AP. In Hemant Goyal et al.'s study, as many as 11.7% out of 756 COVID-19 patients had hyperlipidemia and they were three times more likely to have severe COVID-19 [53]. Those with higher lipase levels—17% out of 83 patients—required hospitalization [54]. However, it is difficult to distinguish whether these patients required hospitalization for severe systemic COVID-19 infection or for pancreatitis in the course of COVID-19 infection.

AP in the course of COVID-19 was analyzed in different age groups; however, some studies only involve children [55]. Compared to pancreatic islet cells, cells of the exocrine pancreatic ducts are more abundant in ACE2 and TMPRSS2 that are necessary for the virus to penetrate the cell [56]. Infection of these cells may be one of the causes of AP [57]. Infections, both bacterial and viral, are one of the causes of AP. The definitive mechanism of how viral infections affect pancreatic cells is not known; however, a study by Maria K Smatti et al. found that there is infection of pancreatic islet cells and replication of the virus within them, ultimately resulting in autoimmune reactions that eventually affect both diabetes and AP in a negative way [58]. For non-SARS-CoV-2 patients, the etiology of AP is known and confirmed in most cases, although 69% of those undergoing infection do not have definite etiology of AP while meeting the AP-Atlanta criteria for diagnosis [59].

Hegyi et al. show the mechanism of MODS formation during COVID-19 infection and AP [60]. This is lipotoxicity, involving an interstitial increase in pancreatic lipase levels, which leads to the breakdown of triacylglycerols contained in adipose tissue cells and the release of unsaturated fatty acids. These in turn exert a toxic effect on mitochondria causing the release of cytokines, which results in a cytokine storm.

There is also a hypothesis, which claims that AP can develop because of blood circulatory centralization resulting from uncontrolled cytokine storm created by SARS-CoV-2 infection [61]. There exist reports that say that pancreatic ischemia may be the cause of different degrees of acute pancreatitis [62][63]. This statement can be supported by

the reports that state that pancreatic blood reperfusion inhibits the development of AP and accelerate pancreas recovery [64].

Another mechanism of developing AP during COVID-19 may be a coagulation cascade activation caused by active inflammatory process due to SARS-CoV-2 infection [65]. The ongoing inflammatory process causes not only hemostasis imbalance for blood clotting, but it also leads to intensification of coagulation by removing epithelial cell protein C receptor (EPCR) from epithelial by the means of inflammatory mediators and thrombin [65]. This means that both processes intensify each other. Simultaneously, it was proved that COVID-19 predisposes patients to venous thromboembolism resulting from excessive inflammation, platelet activation, and endothelial dysfunction [66]. It is also important to notice that AP is inherently connected with a coagulation cascade activation, increased fibrinolysis and, hence, higher level of D-dimers [67]. Acute pancreatitis severity may depend on hemostasis imbalance; local coagulation results in mild AP whereas, in more severe AP cases, the imbalance may lead to development of disseminated intravascular coagulation (DIC) [68]. These observations have been supported by the results of experimental studies showing that the inhibition of coagulation reduces the development of AP [69][70][71] and exhibits therapeutic effect in this disease [72][73]. Additionally it is worth noticing that infection-related hyperglycemia has powerful inflammation-promoting effects on the organism (especially when organism is under stress), thus increasing the number of inflammatory mediators [68]. Unfortunately, it is impossible to decide which process is dominant in causing AP in COVID-19 patients: local inflammation caused by SARS-CoV-2 or systemic hemostasis imbalance.

References

1. Zhang, S.F.; Tuo, J.L.; Huang, X.B.; Zhu, X.; Zhang, D.M.; Zhou, K.; Yuan, L.; Luo, H.J.; Zheng, B.J.; Yuen, K.Y.; et al. Epidemiology characteristics of human coronaviruses in patients with respiratory infection symptoms and phylogenetic analysis of HCoV-OC43 during 2010–2015 in Guangzhou. PLoS ONE 2018, 13, e0191789.
2. De Wit, E.; Van Doremalen, N.; Falzarano, D.; Munster, V.J. SARS and MERS: Recent insights into emerging coronaviruses. Nat. Rev. Microbiol. 2016, 14, 523–534.
3. Zaki, A.M.; van Boheemen, S.; Bestebroer, T.M.; Osterhaus, A.D.M.E.; Fouchier, R.A.M. Isolation of a Novel Coronavirus from a Man with Pneumonia in Saudi Arabia. N. Engl. J. Med. 2012, 367, 1814–1820.
4. Song, Z.; Xu, Y.; Bao, L.; Zhang, L.; Yu, P.; Qu, Y.; Zhu, H.; Zhao, W.; Han, Y.; Qin, C. From SARS to MERS, thrusting coronaviruses into the spotlight. Viruses 2019, 11, 59.
5. Shirato, K.; Kawase, M.; Matsuyama, S. Middle East Respiratory Syndrome Coronavirus Infection Mediated by the Transmembrane Serine Protease TMPRSS2. J. Virol. 2013, 87, 12552.

6. Azhar, E.I.; Hui, D.S.C.; Memish, Z.A.; Drosten, C.; Zumla, A. The Middle East Respiratory Syndrome (MERS). Infect. Dis. Clin. N. Am. 2020, 33, 891–905.
7. Arabi, Y.M.; Balkhy, H.H.; Hayden, F.G.; Bouchama, A.; Luke, T.; Baillie, J.K.; Al-Omari, A.; Hajeer, A.H.; Senga, M.; Denison, M.R.; et al. Middle East Respiratory Syndrome. N. Engl. J. Med. 2017, 376, 584–594.
8. Yang, J.K.; Lin, S.S.; Ji, X.J.; Guo, L.M. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol. 2010, 47, 193–199.
9. Leung, W.K.; To, K.; Chan, P.K.; Chan, H.L.; Wu, A.K.; Lee, N.; Yuen, K.Y.; Sung, J.J. Enteric involvement of severe acute respiratory syndrome-associated coronavirus infection. Gastroenterology 2003, 125, 1011–1017.
10. Nguyen, T.T.; Ta, Q.T.H.; Nguyen, T.K.O.; Nguyen, T.T.D.; Giau, V. Van Type 3 Diabetes and Its Role Implications in Alzheimer's Disease. Int. J. Mol. Sci. 2020, 21, 3165.
11. Pezzilli, R.; Andriulli, A.; Bassi, C.; Balzano, G.; Cantore, M.; Fave, G.D.; Falconi, M.; Group, L.F. the E.P.I. collaborative (EPIc) Exocrine pancreatic insufficiency in adults: A shared position statement of the Italian association for the study of the pancreas. World J. Gastroenterol. 2013, 19, 7930–7946.
12. Abramczyk, U.; Kuzan, A. What Every Diabetologist Should Know about SARS-CoV-2: State of Knowledge at the Beginning of 2021. J. Clin. Med. 2021, 10, 1022.
13. Liu, F.; Long, X.; Zhang, B.; Zhang, W.; Chen, X.; Zhang, Z. ACE2 Expression in Pancreas May Cause Pancreatic Damage after SARS-CoV-2 Infection. Clin. Gastroenterol. Hepatol. 2020, 18, 2128–2130.
14. Hayden, M.R. An Immediate and Long-Term Complication of COVID-19 May Be Type 2 Diabetes Mellitus: The Central Role of β-Cell Dysfunction, Apoptosis and Exploration of Possible Mechanisms. Cells 2020, 9, 2475.
15. Unsworth, R.; Wallace, S.; Oliver, N.S.; Yeung, S.; Kshirsagar, A.; Naidu, H.; Kwong, R.M.W.; Kumar, P.; Logan, K.M. New-Onset Type 1 Diabetes in Children During COVID-19: Multicenter Regional Findings in the U.K. Diabetes Care 2020, 43, e170–e171.
16. Kamrath, C.; Mönkemöller, K.; Biester, T.; Rohrer, T.R.; Warncke, K.; Hammersen, J.; Holl, R.W. Ketoacidosis in Children and Adolescents with Newly Diagnosed Type 1 Diabetes During the COVID-19 Pandemic in Germany. JAMA 2020, 324, 801–804.
17. Boddu, S.K.; Aurangabadkar, G.; Kuchay, M.S. New onset diabetes, type 1 diabetes and COVID-19. Diabetes Metab. Syndr. 2020, 14, 2211–2217.
18. Katopodis, P.; Anikin, V.; Randeva, H.S.; Spandidos, D.A.; Chatha, K.; Kyrou, I.; Karteris, E. Pan-cancer analysis of transmembrane protease serine 2 and cathepsin L that mediate cellular

SARS-CoV-2 infection leading to COVID-19. Int. J. Oncol. 2020, 57, 533–539.

19. Zou, X.; Chen, K.; Zou, J.; Han, P.; Hao, J.; Han, Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front. Med. 2020, 14, 185–192.
20. Hamming, I.; Timens, W.; Bulthuis, M.; Lely, A.; Navis, G.; Goor, H. van Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J. Pathol. 2004, 203, 631–637.
21. Ni, W.; Yang, X.; Yang, D.; Bao, J.; Li, R.; Xiao, Y.; Hou, C.; Wang, H.; Liu, J.; Yang, D.; et al. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. Crit. Care 2020, 24, 422.
22. Santos, R.A.S.; Sampaio, W.O.; Alzamora, A.C.; Motta-Santos, D.; Alenina, N.; Bader, M.; Campagnole-Santos, M.J. The ACE2/Angiotensin-(1–7)/MAS Axis of the Renin-Angiotensin System: Focus on Angiotensin-(1–7). Physiol. Rev. 2018, 98, 505–553.
23. Li, W.; Moore, M.J.; Vasilieva, N.; Sui, J.; Wong, S.K.; Berne, M.A.; Somasundaran, M.; Sullivan, J.L.; Luzuriaga, K.; Greenough, T.C.; et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003, 426, 450–454.
24. Fignani, D.; Licata, G.; Brusco, N.; Nigi, L.; Grieco, G.E.; Marselli, L.; Overbergh, L.; Gysemans, C.; Colli, M.L.; Marchetti, P.; et al. SARS-CoV-2 Receptor Angiotensin I-Converting Enzyme Type 2 (ACE2) Is Expressed in Human Pancreatic β-Cells and in the Human Pancreas Microvasculature. Front. Endocrinol. 2020, 11, 596898.
25. Wrapp, D.; Wang, N.; Corbett, K.S.; Goldsmith, J.A.; Hsieh, C.-L.; Abiona, O.; Graham, B.S.; McLellan, J.S. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 2020, 367, 1260–1263.
26. Glowacka, I.; Bertram, S.; Herzog, P.; Pfefferle, S.; Steffen, I.; Muench, M.O.; Simmons, G.; Hofmann, H.; Kuri, T.; Weber, F.; et al. Differential Downregulation of ACE2 by the Spike Proteins of Severe Acute Respiratory Syndrome Coronavirus and Human Coronavirus NL63. J. Virol. 2010, 84, 1198–1205.
27. Haga, S.; Yamamoto, N.; Nakai-Murakami, C.; Osawa, Y.; Tokunaga, K.; Sata, T.; Yamamoto, N.; Sasazuki, T.; Ishizaka, Y. Modulation of TNF-α-converting enzyme by the spike protein of SARS-CoV and ACE2 induces TNF-α production and facilitates viral entry. Proc. Natl. Acad. Sci. USA 2008, 105, 7809–7814.
28. Oudit, G.Y.; Kassiri, Z.; Jiang, C.; Liu, P.P.; Poutanen, S.M.; Penninger, J.M.; Butany, J. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. Eur. J. Clin. Investig. 2009, 39, 618–625.
29. Muniangi-Muhitu, H.; Akalestou, E.; Salem, V.; Misra, S.; Oliver, N.S.; Rutter, G.A. COVID-19 and Diabetes: A Complex Bidirectional Relationship. Front. Endocrinol. 2020, 11, 758.

30. Baughn, L.B.; Sharma, N.; Elhaik, E.; Sekulic, A.; Bryce, A.H.; Fonseca, R. Targeting TMPRSS2 in SARS-CoV-2 Infection. Mayo Clin. Proc. 2020, 95, 1989–1999.
31. Matsuyama, S.; Nao, N.; Shirato, K.; Kawase, M.; Saito, S.; Takayama, I.; Nagata, N.; Sekizuka, T.; Katoh, H.; Kato, F.; et al. Enhanced isolation of SARS-CoV-2 by TMPRSS2-expressing cells. Proc. Natl. Acad. Sci. USA 2020, 117, 7001–7003.
32. Thunders, M.; Delahunt, B. Gene of the month: TMPRSS2 (transmembrane serine protease 2). J. Clin. Pathol. 2020, 73, 773–776.
33. Shen, L.W.; Mao, H.J.; Wu, Y.L.; Tanaka, Y.; Zhang, W. TMPRSS2: A potential target for treatment of influenza virus and coronavirus infections. Biochimie 2017, 142, 1–10.
34. Taneera, J.; El-Huneidi, W.; Hamad, M.; Mohammed, A.K.; Elaraby, E.; Hachim, M.Y. Expression Profile of SARS-CoV-2 Host Receptors in Human Pancreatic Islets Revealed Upregulation of ACE2 in Diabetic Donors. Biology 2020, 9, 215.
35. Cure, E.; Cure, M.C. COVID-19 may affect the endocrine pancreas by activating Na+/H+ exchanger 2 and increasing lactate levels. J. Endocrinol. Investig. 2020, 43, 1167–1168.
36. Zippi, M.; Fiorino, S.; Occhigrossi, G.; Hong, W. Hypertransaminasemia in the course of infection with SARS-CoV-2: Incidence and pathogenetic hypothesis. World J. Clin. Cases 2020, 8, 1385–1390.
37. Tisoncik, J.R.; Korth, M.J.; Simmons, C.P.; Farrar, J.; Martin, T.T.; Katze, M.G. Into the eye of the cytokine storm. Microbiol. Mol. Biol. Rev. 2012, 76, 16–32.
38. Mehta, P.; McAuley, D.F.; Brown, M.; Sanchez, E.; Tattersall, R.S.; Manson, J.J. COVID-19: Consider cytokine storm syndromes and immunosuppression. Lancet 2020, 395, 1033–1034.
39. Zhou, F.; Yu, T.; Du, R.; Fan, G.; Liu, Y.; Liu, Z.; Xiang, J.; Wang, Y.; Song, B.; Gu, X.; et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet 2020, 395, 1054–1062.
40. Hojyo, S.; Uchida, M.; Tanaka, K.; Hasebe, R.; Tanaka, Y.; Murakami, M.; Hirano, T. How COVID-19 induces cytokine storm with high mortality. Inflamm. Regen. 2020, 40, 37.
41. Liu, B.; Li, M.; Zhou, Z.; Guan, X.; Xiang, Y. Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? J. Autoimmun. 2020, 111, 102452.
42. Rao, S.A.; Kunte, A.R. Interleukin-6: An Early Predictive Marker for Severity of Acute Pancreatitis. Indian J. Crit. Care Med. 2017, 21, 424–428.
43. Sathyanarayan, G.; Garg, P.K.; Prasad, H.; Tandon, R.K. Elevated level of interleukin-6 predicts organ failure and severe disease in patients with acute pancreatitis. J. Gastroenterol. Hepatol. 2007, 22, 550–554.

44. Cao, Y.; Liu, X.; Xiong, L.; Cai, K. Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2: A systematic review and meta-analysis. J. Med. Virol. 2020, 92, 1449–1459.
45. Assis, R.R.; de Jain, A.; Nakajima, R.; Jasinskas, A.; Felgner, J.; Obiero, J.M.; Norris, P.J.; Stone, M.; Simmons, G.; Bagri, A.; et al. Analysis of SARS-CoV-2 antibodies in COVID-19 convalescent blood using a coronavirus antigen microarray. Nat. Commun. 2021, 12, 6.
46. Zhao, J.; Yuan, Q.; Wang, H.; Liu, W.; Liao, X.; Su, Y.; Wang, X.; Yuan, J.; Li, T.; Li, J.; et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. Clin. Infect. Dis. 2020, 71, 2027–2034.
47. Iwasaki, A.; Yang, Y. The potential danger of suboptimal antibody responses in COVID-19. Nat. Rev. Immunol. 2020, 20, 339–341.
48. Lee, N.; Chan, P.K.S.; Ip, M.; Wong, E.; Ho, J.; Ho, C.; Cockram, C.S.; Hui, D.S. Anti-SARS-CoV IgG response in relation to disease severity of severe acute respiratory syndrome. J. Clin. Virol. 2006, 35, 179–184.
49. Yasui, F.; Kai, C.; Kitabatake, M.; Inoue, S.; Yoneda, M.; Yokochi, S.; Kase, R.; Sekiguchi, S.; Morita, K.; Hishima, T.; et al. Prior Immunization with Severe Acute Respiratory Syndrome (SARS)-Associated Coronavirus (SARS-CoV) Nucleocapsid Protein Causes Severe Pneumonia in Mice Infected with SARS-CoV. J. Immunol. 2008, 181, 6337–6348.
50. Caruso, P.; Longo, M.; Esposito, K.; Maiorino, M.I. Type 1 diabetes triggered by COVID19 pandemic: A potential outbreak? Diabetes Res. Clin. Pract. 2020, 164, 108219.
51. de-Madaria, E.; Capurso, G. COVID-19 and acute pancreatitis: Examining the causality. Nat. Rev. Gastroenterol. Hepatol. 2021, 18, 3–4.
52. Group, W.; Apa, I.A.P.; Pancreatitis, A. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology 2013, 13, e1–e15.
53. Goyal, H.; Sachdeva, S.; Perisetti, A.; Mann, R.; Inamdar, S.; Tharian, B. Hyperlipasemia and Potential Pancreatic Injury Patterns in COVID-19: A Marker of Severity or Innocent Bystander? Gastroenterology 2021, 160, 946–948.
54. Barlass, U.; Wiliams, B.; Dhana, K.; Adnan, D.; Khan, S.R.; Mahdavinia, M.; Bishehsari, F. Marked elevation of lipase in COVID-19 Disease: A cohort study. Clin. Transl. Gastroenterol. 2020, 11, e00215.
55. Suchman, K.; Raphael, K.L.; Liu, Y.; Wee, D.; Trindade, A.J. Acute pancreatitis in children hospitalized with COVID-19. Pancreatology 2021, 21, 31–33.
56. Müller, J.A.; Groß, R.; Conzelmann, C.; Krüger, J.; Merle, U.; Steinhart, J.; Weil, T.; Koepke, L.; Bozzo, C.P.; Read, C.; et al. SARS-CoV-2 infects and replicates in cells of the human endocrine

and exocrine pancreas. Nat. Metab. 2021, 3, 149–165.

57. Correia de Sá, T.; Soares, C.; Rocha, M. Acute pancreatitis and COVID-19: A literature review. World J. Gastrointest. Surg. 2021, 13, 574–584.
58. Smatti, M.K.; Cyprian, F.S.; Nasrallah, G.K.; Al Thani, A.A.; Almishal, R.O.; Yassine, H.M. Viruses and Autoimmunity: A Review on the Potential Interaction and Molecular Mechanisms. Viruses 2019, 11, 762.
59. Inamdar, S.; Benias, P.C.; Liu, Y.; Sejpal, D.V.; Satapathy, S.K.; Trindade, A.J.; Northwell COVID-19 Research Consortium. Prevalence, Risk Factors, and Outcomes of Hospitalized Patients with Coronavirus Disease 2019 Presenting as Acute Pancreatitis. Gastroenterology 2020, 159, 2226–2228.e2.
60. Hegyi, P.; Szakács, Z.; Sahin-Tóth, M. Lipotoxicity and Cytokine Storm in Severe Acute Pancreatitis and COVID-19. Gastroenterology 2020, 159, 824–827.
61. Hu, B.; Huang, S.; Lianghong, Y. Lianghong The cytokine storm and COVID-19. J. Med. Virol. 2021, 93, 250–256.
62. Gullo, L.; Cavicchi, L.; Tomassetti, P.; Spagnolo, C.; Freyrie, A.; D'addato, M. Effects of Ischemia on the Human Pancreas. Gastroenterology 1996, 111, 1033–1038.
63. Lonardo, A.; Grisendi, A.; Bonilauri, S.; Rambaldi, M.; Selmi, I.; Tondelli, E. Ischaemic necrotizing pancreatitis after cardiac surgery. A case report and review of the literature. Ital. J. Gastroenterol. Hepatol. 1999, 31, 872–875.
64. Warzecha, Z.; Dembiński, A.; Ceranowicz, P.; Konturek, P.C.; Stachura, J.; Konturek, S.J.; Niemiec, J. Protective effect of calcitonin gene-related peptide against caerulein-induced pancreatitis in rats. J. Physiol. Pharmacol. 1997, 48, 775–787.
65. Esmon, C.T. Crosstalk between inflammation and thrombosis. Maturitas 2008, 61, 122–131.
66. Wang, D.; Hu, B.; Hu, C.; Zhu, F.; Liu, X.; Zhang, J.; Wang, B.; Xiang, H.; Cheng, Z.; Xiong, Y.; et al. Clinical Characteristics of 138 Hospitalized Patients with 2019 NovelCoronavirus–Infected Pneumonia in Wuhan, China. JAMA 2020, 323, 1061–1069.
67. Lasson, Å.; Ohlsson, K. Consumptive coagulopathy, fibrinolysis and protease-antiprotease interactions during acute human pancreatitis. Thromb. Res. 1986, 41, 167–183.
68. Du, J.D.; Zheng, X.; Huang, Z.Q.; Cai, S.W.; Tan, J.W.; Li, Z.L.; Yao, Y.M.; Jiao, H.B.; Yin, H.N.; Zhu, Z.M. Effects of intensive insulin therapy combined with low molecular weight heparin anticoagulant therapy on severe pancreatitis. Exp. Ther. Med. 2014, 8, 141–146.
69. Maduzia, D.; Ceranowicz, P.; Cieszkowski, J.; Gałazka, K.; Kusnierz-Cabala, B.; Warzecha, Z. Pretreatment with Warfarin Attenuates the Development of Ischemia/Reperfusion-Induced Acute Pancreatitis in Rats. Molecules 2020, 25, 2493.

70. Warzecha, Z.; Sendur, P.; Ceranowicz, P.; Dembinski, M.; Cieszkowski, J.; Kusnierz-Cabala, B.; Tomaszewska, R.; Dembinski, A. Pretreatment with low doses of acenocoumarol inhibits the development of acute ischemia/reperfusion-induced pancreatitis. J. Physiol. Pharmacol. 2015, 66, 731–740.
71. Warzecha, Z.; Sendur, P.; Ceranowicz, P.; Dembiński, M.; Cieszkowski, J.; Kuśnierz-Cabala, B.; Olszanecki, R.; Tomaszewska, R.; Ambroży, T.; Dembiński, A. Protective Effect of Pretreatment with Acenocoumarol in Cerulein-Induced Acute Pancreatitis. Int. J. Mol. Sci. 2016, 7, 1709.
72. Maduzia, D.; Ceranowicz, P.; Cieszkowski, J.; Chmura, A.; Galazka, K.; Kusnierz-Cabala, B.; Warzecha, Z. Administration of warfarin accelerates the recovery in ischemia/reperfusion-induced acute pancreatitis. J. Physiol. Pharmacol. 2020, 71, 417–427.
73. Ceranowicz, P.; Dembinski, A.; Warzecha, Z.; Dembinski, M.; Cieszkowski, J.; Rembiasz, K.; Konturek, S.J.; Kusnierz-Cabala, B.; Tomaszewska, R.; Pawlik, W.W. Protective and therapeutic effect of heparin in acute pancreatitis. J. Physiol. Pharmacol. 2008, 59, 103–125.