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Lipotoxicity and Cytokine Storm in Severe Acute Pancreatitis and COVID-19

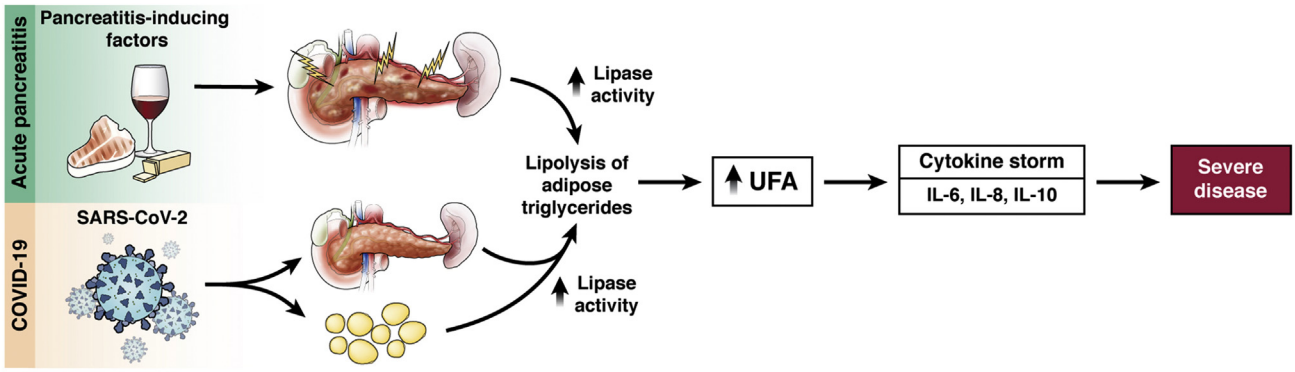
See "Mortality from coronavirus disease 2019 increases with unsaturated fat and may be reduced by early calcium and albumin supplementation," by El-Kurdi B, Khatua B, Rood C, et al, on page 1015.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–induced coronavirus disease-2019 (COVID-19) has become a pandemic affecting >7 million people worldwide so far.[1] The relatively high mortality of COVID-19 (around 10% of closed cases) is often linked to multiorgan failure, which supports the notion that an inappropriate host response to the viral infection might play a role in disease outcomes. In this issue of *Gastroenterology*, the Lipotoxicity in COVID-19 Study Group from the Mayo Clinic reports the enticing observation that progression of COVID-19 to multiorgan failure resembles lipotoxic organ failure during severe acute pancreatitis. Thus, the authors posit that, in both diseases, interstitial leakage of pancreatic lipase may occur resulting in adipose lipolysis and increased levels of unsaturated fatty acids.[2] These toxic fatty acids cause mitochondrial injury and stimulate the excessive production and release of proinflammatory immune mediators (cytokine storm) that can drive disease progression with eventual multiorgan failure, including the acute respiratory distress syndrome, the leading cause of COVID-19 related mortality (Figure 1, *A*).[3] An increasing number of publications have reported that SARS-CoV-2 targets the pancreas resulting in elevation of serum lipase activity or rarely even frank pancreatitis.[4–7] Autopsy data suggest that the incidence of focal pancreatitis in COVID-19 may be higher than diagnosed clinically.[8] However, it is conceivable that the virus targets not only the pancreas, but also adipocytes causing increased lipolysis through the adipose triglyceride lipase (Figure 1, *A*).[2]

Fatty acids bind to calcium and albumin and hypocalcemia and hypoalbuminemia are often present in severe COVID-19. Therefore, the authors propose that early treatment of COVID-19 with albumin and calcium supplementation may improve disease outcomes by complexing unwanted fatty acids.[2] However, once a cytokine storm has been triggered by the toxic effects of unsaturated fatty acids, calcium/albumin supplementation is not expected to be effective any longer as the host immune response drives further organ damage, resulting in high mortality.

Similar to COVID-19, a fraction of cases of acute pancreatitis also progresses to severe disease with multiorgan failure as the leading cause of mortality.[9,10] Although fatty acid-induced damage may be involved in the early stages of both diseases, the primary cause of organ failure is more likely the ensuing cytokine storm. To compare the relationship of serum cytokines and severity, we performed a meta-analysis of cytokine patterns in the early stages of the 2 diseases. After careful selection, 12 studies on acute pancreatitis and 9 studies on COVID-19 were eligible for inclusion in the meta-analysis. Details of the systematic search, the selection process, the analysis, the characteristics and quality of the studies are described in the Supplementary Methods, Supplementary Figure 1, and Supplementary Tables 1–3. The results show that the pattern of altered cytokine levels is very similar in severe acute pancreatitis and COVID-19. Thus, IL-6, IL-8, and IL-10 levels were higher in severe versus nonsevere cases of the two diseases (Figure 1, *B*). A similar tendency was observed for tumor necrosis factor-α, whereas interferon-γ levels showed no difference as a function of severity. Lower levels of IL-1β were apparent in severe versus nonsevere acute pancreatitis, but this difference was absent in COVID-19 (Supplementary Figure 2). The remarkable similarity of cytokine elevations in severe acute pancreatitis and severe COVID-19 suggests that therapeutic removal of cytokines may improve outcomes in both diseases. In this

A



B

Study or subgroup	Severe Mean	SD	Total	Non-severe Mean	SD	Total	Weight	Std. mean difference IV, random, 95% CI
Interleukin-6								
Acute pancreatitis								
Deng LH, Hu C	447.4	150.5	20	58.9	22.2	20	12.3%	3.54 [2.51, 4.57]
Jain S, Midha S	216	106.3	14	135.3	14.6	40	13.0%	1.46 [0.78, 2.13]
Kolber W, Dumnicka P	809.6	1728.3	8	89.9	63.9	58	12.8%	1.24 [0.47, 2.01]
Nieminen A, Maksimow M	787.9	1074.9	25	92.4	106.7	138	13.3%	1.62 [1.16, 2.08]
Novotny P, Malina D	114.5	75.9	14	111.8	157.9	70	13.2%	0.02 [-0.56, 0.59]
Qiu L, Zhou Y	49.9	3.1	17	26.9	2.6	46	10.7%	8.29 [6.70, 9.89]
Sharma D, Jakkampudi A	481.7	439.4	18	147.6	25.1	10	12.7%	0.91 [0.10, 1.73]
Zhang R, Shi J	222.7	109.1	9	31.8	13.6	27	12.0%	3.44 [2.31, 4.57]
Subtotal (95% CI)			125			409	100.0%	2.42 [1.29, 3.55]
Heterogeneity: Tau²=2.45; Chi²=124.33; df=7 (*P*<.00001); I²=94%								
Test for overall effect: Z=4.18 (*P*<.0001)								
COVID-19								
Cai Q, Huang D	28.9	15.2	58	9.7	6.1	240	11.7%	2.22 [1.88, 2.56]
He R, Lu Z	11.2	2.2	16	12.2	1.1	12	10.2%	-0.53 [-1.30, 0.23]
Li S, Jiang L	29.2	16	26	10	5.8	43	10.9%	1.76 [1.19, 2.33]
Liu T, Zhang J	36.5	44.3	66	2.5	0.9	11	10.6%	0.82 [0.16, 1.47]
Liu X, Li Z	55.6	44.4	25	39.3	71.1	87	11.4%	0.24 [-0.20, 0.69]
Qin C, Zhou L	29.7	21.8	286	19.4	20.8	166	12.0%	0.48 [0.29, 0.67]
Wei YY, Wang RR	37.5	18.4	30	16.5	10.1	137	11.4%	1.74 [1.31, 2.18]
Zheng C, Wang J	142.9	115.1	21	84.7	66.1	34	11.0%	0.65 [0.09, 1.21]
Zhu Z, Cai T	26.54	24.6	16	5.3	4.54	111	10.9%	2.22 [1.62, 2.81]
Subtotal (95% CI)			544			841	100.0%	1.08 [0.48, 1.68]
Heterogeneity: Tau²=0.78; Chi²=139.70; df=8 (*P*<.00001); I²=94%								
Test for overall effect: Z=3.51 (*P*=.0004)								
Interleukin-8								
Acute pancreatitis								
Deng LH, Hu C	51	46.4	20	5	3.8	20	15.0%	1.37 [0.67, 2.07]
Kuuliala K, Penttila AK	339.8	577.3	3	94.2	34.7	6	12.3%	0.70 [-0.75, 2.16]
Nieminen A, Maksimow M	81.5	26.1	25	29.3	11.5	138	15.3%	3.55 [2.97, 4.13]
Penttila AK, Lindstrom O	101.4	40.2	10	45.9	6.3	144	14.6%	4.79 [3.95, 5.63]
Sharma D, Jakkampudi A	181.1	140	18	46.1	21.4	10	14.6%	1.15 [0.31, 1.99]
Yang YZ, Xiang J	58.7	14.1	32	28.3	8.5	42	15.2%	2.67 [2.03, 3.31]
Zhang R, Shi J	52.3	13.9	9	21.7	3.9	27	13.2%	3.96 [2.73, 5.19]
Subtotal (95% CI)			117			387	100.0%	2.63 [1.58, 3.67]
Heterogeneity: Tau²=1.79; Chi²=70.53; df=6 (*P*<.00001); I²=91%								
Test for overall effect: Z=4.91 (*P*<.00001)								
COVID-19								
Li S, Jiang L	13.5	2.2	26	8.2	2	43	47.8%	2.52 [1.87, 3.18]
Qin C, Zhou L	19.4	7.5	286	12.5	5.5	166	52.2%	1.01 [0.81,1.21]
Subtotal (95% CI)			312			209	100.0%	1.73 [0.25, 3.22]
Heterogeneity: Tau²=1.09; Chi²=18.93; df=1 (*P*<.0001); I²=95%								
Test for overall effect: Z=2.29 (*P*=.02)								
Interleukin-10								
Acute pancreatitis								
Deng LH, Hu C	85	82.7	20	4.2	2.5	20	20.7%	1.35 [0.66, 2.05]
Jain S, Midha S	156.7	14	14	157	7.7	40	20.8%	-0.03 [-0.64, 0.58]
Qiu L, Zhou Y	24.9	1.8	17	10.2	1.3	46	17.9%	10.03 [8.14, 11.92]
Sharma D, Jakkampudi A	11	17.6	18	18.3	34.1	10	20.6%	-0.29 [-1.07, 0.49]
Zhang R, Shi J	46.3	14.7	9	20.7	9.8	14	20.0%	2.07 [1.01, 3.14]
Subtotal (95% CI)			78			130	100.0%	2.43 [0.39, 4.47]
Heterogeneity: Tau²=5.11; Chi²=113.66; df=4 (*P*<.00001); I²=96%								
Test for overall effect: Z=2.33 (*P*=.02)								
COVID-19								
He R, Lu Z	7.2	0.7	16	6.3	0.3	12	21.7%	1.54 [0.68, 2.41]
Liu T, Zhang J	5.6	2.4	66	3	0.6	11	24.3%	1.15 [0.48, 1.81]
Qin C, Zhou L	7.6	3.5	286	5.7	1.5	166	28.8%	0.65 [0.45, 0.84]
Zhu Z, Cai T	6.9	3.7	16	3.3	1.1	111	25.2%	2.17 [1.58, 2.77]
Subtotal (95% CI)			384			300	100.0%	1.35 [0.56, 2.14]
Heterogeneity: Tau²=0.55; Chi²=26.67; df=3 (*P*<.00001); I²=89%								
Test for overall effect: Z=3.35 (*P*=.0008)								

regard, extracorporeal cytokine adsorption has been beneficial in septic shock.[11,12] Furthermore, it was recently suggested that hemoadsorption with CytoSorb may decrease 28-day all-cause mortality in patients treated in intensive care units.[13] Huber et al[14] have initiated the PACIFIC trial in which the investigators will evaluate the effectiveness of 2 consecutive 24-hour treatments with CytoSorb on the hemodynamics of patients with early severe acute pancreatitis. The recently registered CYTOAID-COVID-19 (NCT04422626) international, multicenter clinical trial aims to collect systematic, high-quality data on COVID-19 patients admitted to the intensive care unit with acute respiratory failure and treated with CytoSorb. Taken together, the new observations from the Lipotoxicity in COVID-19 Study Group and the ongoing clinical trials suggest a convincing pathophysiologic rationale for a 2-pronged strategy to prevent progression of acute pancreatitis and COVID-19 to severe, potentially fatal disease. Early supplementation with calcium and albumin to decrease fatty acid toxicity and subsequent quelling of the cytokine storm by extracorporeal cytokine adsorption may prevent dismal disease outcomes.

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Supplementary Material and Video

Note: To access the supplementary material accompanying this article and watch this article's video, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2020.05.057.

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Figure 1. *A*, Role of fatty acid toxicity and cytokine storm in acute pancreatitis and coronavirus disease-19 (COVID-19). Factors inducing pancreatitis and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection damage the pancreas and cause lipase leakage resulting in increased lipolysis in visceral adipocytes in both conditions. SARS-CoV-2 may directly affect adipocytes as well. Lipolysis increases levels of unsaturated fatty acids (UFA), causing organ damage and inducing the cytokine storm, which drives disease progression and determines the ultimate severity. *B*, Early IL-6, -8, and -10 levels are strongly associated with severity in acute pancreatitis and COVID-19. Standardized mean differences (squares) with 95% confidence intervals (CI; horizontal lines) were calculated for each study in this meta-analysis. The "Total" column gives the number of patients in the analysis. Results of individual studies were pooled with the random effects model; the pooled point estimates with CI is represented by diamonds in the figure. If the CI does not cross the line of no effect (vertical black line at the 0 value on the horizontal axis), the difference should be considered statistically significant. Studies including patients with acute pancreatitis and those with COVID-19 were pooled separately (top and bottom panels for each cytokine, respectively). Severity of acute pancreatitis was defined as per the 2012 Atlanta Classification in all studies, the nonsevere group consists of cases without persistent organ failure including mild and moderately severe cases. The severity of COVID-19 was defined as per the definitions used in the individual studies: all but one adhered to the Guidelines for the Diagnosis and Treatment of New Coronavirus Pneumonia by the National Health Commission of the People's Republic of China. Further technical details are provided in the Supplementary Methods. The meta-analysis shows that IL-6, -8, and -10 levels were significantly higher in severe versus nonsevere disease in both acute pancreatitis and COVID-19, with considerable statistical heterogeneity across the studies. SD, standard deviation.

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Cell Signaling of Pancreatic Duct Pressure and Its Role in the Onset of Pancreatitis

See "The protective effects of calcineurin on pancreatitis in mice depend on the cellular source," by Wen L, Javed TA, Dobbs AK, et al, on page 1036.

Acute pancreatitis is one of the most common conditions leading to emergency hospital admission.[1] Its variable etiologies include vascular events,[2] drugs,[3] and genetic factors,[4] but the ultimate clinical manifestation is fairly uniform.[5] It involves edema of the gland, the development of pancreatic and extrapancreatic necrosis and systemic complications leading to (multi)organ failure. Although most patients recover from acute pancreatitis, a significant number will progress to chronic pancreatitis.[6] By far the most common risk factors for acute pancreatitis are immoderate alcohol use[7] or gallstone disease.[8] How gallstones induce pancreatitis has long been a matter of debate. Two initial hypotheses that attempted to explain the underlying mechanism are more than a century old. The first proposed that the offending gallstone becomes impacted at the duodenal papilla and creates a communication between the common bile duct and the pancreatic duct, through which bile would flow into the pancreas and initiate pancreatitis. The second hypothesis, published in the same year,[9] proposed that the offending gallstone obstructs outflow from the pancreatic duct and the triggering events are increased hydrostatic pressure and impaired secretion. Clinical studies[10,11] and experimental investigations[12,13] suggest that increased pancreatic duct pressure explains the onset of gallstone-induced pancreatitis much better than a direct action of bile on pancreatic duct or acinar cells.[14] The recognition that iatrogenic pancreatitis induced by endoscopic retrograde pancreatography (ERCP) nowadays contributes significantly to the overall incidence of the disease[15] further supports the assumption that bile reflux, unlike intraductal pressure, is not a likely contributing factor for pancreatitis—be it gallstone or ERCP induced. Regarding the latter, discussions have essentially focused on the question of whether pressure increases alone, or properties of the contrast agent used, contribute more to the risk of developing pancreatitis after ERCP.[16]

Experimental animal models as well as human genetic studies have revealed a number of cellular mechanisms involved in the disease onset. For one, a premature and intracellular activation of digestive proteases, most prominently trypsin, seem to determine the initial degree of pancreatic injury.[17,18] Whether this sustained intracellular protease activity is due to increased activation[19] or impaired degradation[20] depends on experimental circumstances and underlying genetic changes.[21] The extracellular signals that induce premature protease activation can be highly variable,[22] but general agreement exists that they all involve either a rapid release of calcium from intracellular stores[23] or an impaired clearance of high cytosolic calcium concentrations via plasma membrane calcium pumps.[24] Although these conditions have been extensively characterized in models based on pathologic agonist stimulation,[25] it remained largely unknown whether they also apply to gallstone-induced pancreatitis and its associated pressure increases in the pancreatic duct.

A number of studies have shed light on this question: The first were the observations that duct obstruction-induced pancreatitis begins in acinar cells,[5] involves a profound impairment of intracellular vesicle trafficking[26] and acinar cell calcium signals that are shifted from physiologic oscillations to increased peak–plateau patterns when duct pressure is increased,[27] not unlike the response to pathologic secretagogue signals. These studies could, however,