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SARS-CoV-2 infection of the pancreas promotes thrombo-fibrosis and is associated with new-onset diabetes

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Abstract

Evidence suggests an association between severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection and the occurrence of new-onset diabetes. We examined pancreatic expression of angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2), the cell entry factors for SARS-CoV-2, using public single cell RNA sequencing datasets, and pancreas tissue from control male and female non-human primates (NHPs) and humans. We also examined SARS-CoV-2 immunolocalization in pancreas cells of SARS-CoV-2-infected NHPs, and patients deceased from coronavirus disease 2019 (COVID-19). We report expression of ACE2 in pancreatic islet, ductal, and endothelial cells in NHPs and humans. In pancreata from SARS-CoV-2-infected NHPs and COVID-19 patients, SARS-CoV-2 infected ductal, endothelial and islet cells. These pancreata also exhibited generalized fibrosis associated with multiple vascular thrombi. Two out of eight NHPs developed new onset diabetes following SARS-CoV-2 infection. Two out of five COVID-19 patients exhibited new onset diabetes at admission. These results suggest that SARS-CoV-2 infection of the pancreas may promote acute and especially chronic pancreatic dysfunction that could potentially lead to new-onset diabetes.

Keywords: SARS-CoV-2, ACE2, pancreas, islet, endothelial cell, thrombosis, diabetes
Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), affects multiple tissues including the pancreas (1). Evidence suggests that COVID-19 is associated with new onset of ketosis-prone forms of diabetes or the insulinopenic decompensation of preexisting diabetes (2-4). These observations raise the prospect of a diabetogenic effect of SARS-CoV-2, beyond the known stress response associated with acute illness. For example, SARS-CoV-2 infection may produce new mechanisms of pancreatic insulin-producing β failure or aggravate the pathophysiology of β cell dysfunction in preexisting type 2 diabetes (3, 5). In parallel, emerging evidence suggests that COVID-19 produces pancreatic exocrine dysfunction resulting in acute pancreatitis (6). Still, there is very limited epidemiological data supporting new onset of insulin-deficient diabetes with COVID-19.

SARS-CoV-2 cellular entry is mediated via angiotensin converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2), which together anchor and cleave SARS-CoV-2’s spike glycoproteins, allowing for viral internalization (7). Studies on ACE2 expression in pancreatic insulin-producing β cells have shown conflicting results, with some studies reporting ACE2 expression in β cells (8-11) while others showed little or no expression (12, 13). Nevertheless, multiple studies report the expression of ACE2 and TMPRSS2 in pancreatic exocrine ductal cells (8, 9, 12, 13).

SARS-CoV-2 infects and replicates in cells of the human endocrine and exocrine pancreas (9). Increasing evidence also suggests that SARS-CoV-2 infects endothelial cells and, that COVID-19 is a multi-organ endothelial cell disease (14). The evidence of SARS-CoV-2 infection of pancreatic cells, including endothelial cells, and its consequences on pancreas histopathology remains poorly explored.

In this study, we used public single cell RNA sequencing (scRNAseq) datasets, pancreas sections from male and female controls, SARS-CoV-2-infected non-human primates (NHPs), and patients deceased from COVID-19, to assess the expression of ACE2 and TMPRSS2 and localize SARS-
CoV-2 infection across pancreas cells and examine the effect of SARS-CoV-2 infection on pancreas histopathology.
**Results**

ACE2 protein expression in pancreata of non-human primates. We studied ACE2 expression by immunofluorescence using archived pancreas samples from male and female African green monkeys (AGMs) and Rhesus macaques (RMs) infected with SARS-CoV-2 (15) (Supplemental Figure 1A). We observed similar ACE2 immunostaining in rare insulin expressing β cells (INS+) in non-infected controls (Figure 1A and C), and SARS-CoV-2-infected (Figure 1B and C) male and female non-human primates (NHPs). ACE2 immunostaining was more pronounced in glucagon expressing α cells (GCG+) from non-infected control (Figure 1A and D) and SARS-CoV-2-infected (Figure 1B and D) male and female NHPs. In the exocrine pancreas, we observed high ACE2 expression in large ducts (large lumen surrounded by stroma) in male and female non-infected controls (Figure 1E and G), and SARS-CoV-2-infected (Figure 1F and G) NHPs. Similarly, we detected expression of ACE2 in small ducts (small lumen surrounded by parenchyma) of non-infected control (Figure 1F and J) male and female NHPs. Notably, ACE2 expression was dramatically decreased in small ducts of male and female SARS-CoV-2-infected NHPs compared to non-infected controls (Figure 1I and J).

ACE2 and TMPRSS2 expression in human pancreata. We studied ACE2 and TMPRSS2 expression across tissues of the human protein atlas (HPA) (16). In bulk-tissue RNAseq datasets from the HPA, ACE2 mRNA and protein are expressed in both endocrine and ductal cells of the pancreas (Supplemental Figure 1, B and C). This is in agreement with single cell RNA sequencing (scRNAseq) datasets that also show ACE2 mRNA expression in pancreatic endocrine and ductal cells (Supplemental Figure 1, D-F).

To examine the co-expression of ACE2 and TMPRSS2 in human male compared to female pancreatic cells, we constructed a pancreas single cell expression atlas using six scRNAseq datasets (17-22) (Supplemental Figure 2, A and B), stratified by sex (Supplemental Figure 2C). We validated sex stratification across cell types (Supplemental Figure 2D) and datasets...
Supplemental Figure 2E) based on classical X and Y chromosome associated genes XIST and UTY respectively.
We studied ACE2 and TMPRSS2 co-expression in male and female cells expressing at least 1 count of ACE2 and TMPRSS2 mRNA. These data revealed sex-specific differences in co-expression, including co-expression by specific cell populations in males but not females. Cell types where ACE2 and TMPRSS2 co-expression is observed in both sexes include ductal cells (0.69% in males vs 0.51% in females), activated stellate cells (0.44% in males vs 0.05% in females), and acinar cells (0.05% in males vs 0.12% in females). Significant cell types showing co-expression of these two markers in males, but not females, include quiescent stellate cells (0.17%), macrophages (0.25%), endothelial cells (0.15%) and α cells (0.07%) (Supplemental Figure 2, F and G). Notably, using a scRNAseq dataset of chronic pancreatitis (17), we observed the highest ACE2 and TMPRSS2 co-expression in male ductal (8.62%) and β cells (2.06%) (Supplemental Figure 2, H and I).

We studied ACE2 protein expression by immunofluorescence in pancreas sections from five male and three female human donors. We observed ACE2 expression in GCG+ α cells and to a lesser extent INS+ β cells in both male and female islets, without apparent sex difference (Figure 2A-D).
In the exocrine pancreas, cytokeratin-19 expressing (CK19+) ductal cells accounted for the highest expression level of ACE2 across the pancreas in human males and females and without apparent sex difference (Figure 2E-G).

SARS-CoV-2 infects pancreatic cells in NHPs. We examined SARS-CoV-2 nucleocapsid protein (SARS-CoV-2-NP) immunopositivity in NHPs’ pancreas sections. Note that two of eight SARS-CoV-2-infected females NHPs, AGM1 and AGM2, developed severe new onset diabetes requiring euthanasia 21 days and 9 days after infection respectively. One infected male exhibited elevated glucose 24 days after infection. Note that the severity of SARS-CoV-2 infection differs significantly in African green monkeys and Rhesus macaques (15), which could have precipitated the onset of diabetes in the former but not the latter. None of the non-infected primates developed
hyperglycemia (Supplemental Figure 3A-C). We did not detect any localization of SARS-CoV-2-NP in endocrine α or β cells in eight male and female SARS-CoV-2-infected NHPs (Figure 3A). However, SARS-CoV-2-NP co-expressed with platelet endothelial cell adhesion molecule-1 (PECAM1/CD31)-expressing endothelial cells of the islet microcapillaries in one male NHP (Figure 3A). SARS-CoV-2-NP also colocalized with CK19+ ductal cells within large ducts across the pancreas to a similar extent in three male and the two diabetic female SARS-CoV-2-infected NHPs, which we did not observe in non-infected controls (Figure 3, B and C, and Supplemental Figure 3D). Consistent with the disappearance of ACE2 expression in small ducts of SARS-CoV-2-infected NHPs described above (Figure 1, I and J), we observed no immunoreactivity for SARS-CoV-2-NP in small ducts from all SARS-CoV-2-infected NHPs. Notably, among pancreatic cells, we observed the highest SARS-CoV-2-NP immunopositivity in CD31+ endothelial cells from small pancreatic arteries in all eight SARS-CoV-2-infected males and female NPHs, which was not observed in non-infected controls (Figure 3, D and E).

SARS-CoV-2 infection results in thrombo-fibrosis of the pancreas in NHPs. Examination of the entire pancreas sections stained with hematoxylin and eosin (H&E), revealed multiple microthrombi in small veins across the parenchyma (Figure 4A). The thrombi areas were higher in SARS-CoV-2-infected male and female NHPs than in non-infected controls (Figure 4B). We next stained pancreas sections with picrosirius red (PSR), a classical marker of collagen and ECM deposition (23), to assess inflammation-induced fibrosis. SARS-CoV-2-infected male NHPs exhibited a higher fibrotic area in comparison to non-infected controls, which did not reach significance in female NHPs (Figure 4, C and D). We also quantified pancreatic lipase, a marker of acute pancreatitis, in serum isolated from infected NHPs. Male and female NHPs exhibited elevated serum lipase in comparison to published normal levels (24) (Supplemental Figure 3E).

SARS-CoV-2 infects endocrine, exocrine, and endothelial cells in humans. We finally conducted SARS-CoV-2-NP immunostaining and histological analysis of autopsy pancreas sections acquired from patients deceased from COVID-19 (Supplemental Table 1). We observed co-
localization of SARS-CoV-2-NP with multiple INS+ β cells and non-insulin producing islet cells in one male subject (COVID19-1), who was admitted with new onset diabetes (non-fasting glucose > 300mg/dl), demonstrating SARS-CoV-2 infection of β cells and other islet cells in this patient (Figure 5A). Similar to our observations in SARS-CoV-2-infected NHPs, we observed co-localization of SARS-CoV-2-NP with CK19+ (ductal cells) in the male subject with new onset diabetes, and in one female subject with a history of type 2 diabetes deceased from COVID-19 (COVID19-3). This was not observed in pancreata from non-infected control subjects, demonstrating that SARS-CoV-2 infected the exocrine pancreatic ducts (Figure 5, B and C). In addition, we observed co-localization for SARS-CoV-2-NP with CD31+ endothelial cells in all five male and female subjects deceased from COVID-19 including one normoglycemic individual (COVID19-4), which we did not observe in pancreata from non-infected controls (Figure 5, D and E). Additional analysis of pancreas sections by electron microscopy, revealed the presence of SARS-CoV-2 viral particles in the endothelium and ductal architecture of a female COVID-19 individual (COVID19-3) (Figure 6, A and B).

*SARS-CoV-2 infection produces thrombo-fibrosis and endotheliitis in humans.* In all male and female subjects deceased from COVID-19, analysis of whole pancreas sections stained with H&E revealed multiple microthrombi of pancreatic venules (Figure 7, A and B) and PSR staining exposed significantly increased fibrosis (Figure 7, C and D) compared to controls. Pancreatic and islet expression of intercellular adhesion molecule 1 (ICAM1), a marker of endothelial dysfunction and inflammation (25) was increased in COVID-19 individuals compared to controls suggesting the presence of endotheliitis of the entire pancreas vasculature (Figure 7, E and F) and the islet microvasculature (Figure 7G).
Discussion

Several reports have suggested that COVID-19 is associated with the occurrence of insulin-deficient forms of diabetes, raising the possibility that SARS-CoV-2 produces acute β cell dysfunction (2-4). Here, two out of eight NHPs developed new onset hyperglycemia following SARS-CoV-2 infection, and two out of five COVID-19 patients exhibited new onset hyperglycemia at hospital admission. After assembling a pancreas single cell expression atlas from six public scRNA-seq datasets, we provide novel information on ACE2 and TMPRSS2 co-expression in the same human islet cells in males, extending results obtained by others without sex stratification, and without co-expression at the same single cell level (9, 12), and demonstrating that SARS-CoV-2 can directly infect islet cells. Accordingly, two studies reported the presence of SARS-CoV-2 in islets cells, including individual β cells, in males and females subjects deceased from COVID-19 (9, 12). Here, we provide additional evidence that SARS-CoV-2 infected β cells in a male COVID-19 patient who exhibited new onset diabetes at hospital admission. We also report that SARS-CoV-2 infected the islet microvasculature in a female NHP.

Evidence suggest that COVID-19 produces pancreatic exocrine cell injury, resulting in pancreatitis (6, 26-31). We observe that among pancreatic cells, ductal cells exhibit the highest levels of ACE2 and TMPRSS2 co-expression in the same cells and in both sexes. Accordingly, we show that SARS-CoV-2 infected ductal cells in male and female NHPs, and humans deceased from COVID-19. Further, we observe elevated pancreatic fibrosis in male and female NHPs and humans deceased from COVID-19. During pancreatic inflammation, activated pancreatic stellate cells (PSCs) release inflammatory cytokines and chemokines, produce ECM deposition, altogether resulting in pancreatic fibrosis (32). Consequently, SARS-CoV-2 infection and inflammation of pancreatic cells may activate PSCs, resulting in fibrosis as observed in the infected NHP and human pancreata.

Evidence also suggests that SARS-CoV-2 infects endothelial cells and that COVID-19 is an endothelial cell disease (14, 33). In severe cases, massive endothelial dysfunction, disseminated
coagulopathy and complement-induced thrombosis produce systemic microangiopathy and thromboembolism (34). Consistent with this concept, we observe expression of ACE2 and TMPRSS2 in pancreatic endothelial cells. Surprisingly, as in the case of islet cells, we observe co-expression of ACE2 and TMPRSS2 in the same cells in males only. The absence of ACE2 and TMPRSS2 co-expression in the same female islet and endothelial cells from the scRNA-seq datasets should be interpreted with caution, as it could be an artifact derived from the lack of sufficient sequencing depth of the scRNA-seq. Nevertheless, we observe SARS-CoV-2 infection of islet microvasculature in a female SARS-CoV-2-infected NHPs. We did not observe SARS-CoV-2 presence in human islet capillaries, but SARS-CoV-2 infected the microvasculature of the exocrine pancreas in all male and female NHPs and humans deceased from COVID-19. Notably, in NHPs and humans, SARS-CoV-2 infection was associated with multiple thrombi of microvessels and to markers of endotheliitis in humans. To what extent endotheliitis and thrombosis are a direct effect of viral endothelial cell infection and dysfunction, or the consequence of immune-induced thrombosis requires further studies. Together, the infection of ductal and endothelial cells could produce indirect β cell insult and dysfunction via proximal inflammation. Indeed, one female COVID-19 patients exhibited new onset diabetes at admission, and two female NHP developed new onset diabetes days after SARS-CoV-2 infection, without SARS-CoV-2 infection of islets.

In summary, SARS-CoV-2 infects pancreatic islet, ductal and endothelial cells in male and female NHPs and humans with COVID-19. In both species, SARS-CoV-2 infection is associated with disseminated pancreatic endotheliitis, microthrombi, fibrosis and the new onset of hyperglycemia, suggesting that COVID-19 produces new onset diabetes. Most importantly, the long-term consequences of a fibro-thrombotic pancreas, such as chronic pancreatic exocrine dysfunction and late-onset diabetes, should be investigated as a post-acute sequelae of COVID-19 (PASC).
Methods

More information is available in the supplemental methods. Immunofluorescence staining. Tissue sections were stained as previously described in (35). Study approval. All studies were approved by the Institutional Animal Care and Use Committee and Institutional Biosafety Committee of Tulane University. The Tulane National Primate Research Center is fully accredited by the American Association for Accreditation of Laboratory Animal Care.

Author contributions

MMFQ and FMJ designed the study. MMFQ, MB, IB, DG performed experiments, analyzed data, and performed statistics. LADM, TF, RVB, RB and JR developed NHP models and provided NHP archived pancreas sections. MMFQ and FMJ wrote the manuscript. RSVH, TF, LADM, JR, EL, JKK and XB reviewed the manuscript. All authors approved the final manuscript. FMJ accepts responsibility for the overall content of this work and ensures all statements in the manuscript are true to his knowledge.

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Conflict of interest statement

The authors declare no conflict of interest.


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Figure 1. ACE2 protein expression in NHP pancreata. (A) Representative confocal Immunofluorescence (IF) images of pancreatic islets from uninfected male and female NHPs. Insets show colocalization of insulin/ACE2 (green arrows) and glucagon/ACE2 (yellow arrows). (B) Representative IF images of a pancreatic islet from SARS-CoV-2 infected male and female NHPs. Insets show colocalization of insulin/ACE2 (green arrows), and glucagon/ACE2 (yellow arrows). (C) Quantification of β cells expressing ACE2 and (D) α-cells expressing ACE2 across NHPs. (E) Representative IF images of ACE2 expression in large ducts of control NHP and (F) SARS-CoV-2 infected pancreas (inset, yellow arrows). (G) Quantification of large duct-derived ductal cells expressing ACE2. (H) Representative IF images of ACE2 expression in small ducts in control and (I) SARS-CoV-2 infected NHP pancreas. (J) Quantification of small pancreatic duct derived ductal cells expressing ACE2. Experiments represent n=3-5 biological replicates. Bar graphs are mean +/- SD. Scale bars are 25μm. Statistical test used was a one-way ANOVA with a post-hoc Tukey’s multiple comparison test (C, D, G and J), ****p < 0.0001.
Figure 2. ACE2 protein expression in human pancreata. (A) Representative IF images of pancreatic islets from 2 human female and (B) male donors, showing ACE2 expression in α and β cells. Insets show colocalization between insulin/ACE2 (green arrows) and glucagon/ACE2 (yellow arrows). (C) Quantification of β cells and (D) α cells expressing ACE2. (E) Representative IF images of pancreatic ducts from 2 human female and (F) male donors showing ACE2 expression in ductal cells (CK19). Insets show colocalization CK19/ACE2 (yellow arrows). (G) Quantification of pancreatic ductal cells expressing ACE2. Experiments represent n=3 biological replicates. Bar graphs are mean +/- SD. Scale bars are 25μm. Statistical test used was an unpaired T-test (C, D and G).
Figure 3. SARS-CoV-2 infects pancreatic ductal and endothelial cells in NHPs (A) Representative IF images of a SARS-CoV-2 infected NHP islet, showing SARS-CoV-2-NP colocalization in endothelial cells (CD31). (B) Representative IF images of NHP pancreas showing SARS-CoV-2-NP presence in ductal cells. Insets show CK19/SARS-CoV-2-NP colocalization (yellow arrows). (C) Quantification of SARS-CoV-2 infected ductal cells. (D) Representative IF image of SARS-CoV-2 infected NHP pancreas showing SARS-CoV-2-NP in CD31 expressing endothelial cells. Insets show CK19/SARS-CoV-2-NP colocalization (yellow arrows). (E) Quantification of SARS-CoV-2 infected NHP pancreatic endothelium. Experiments represent n=3-5 biological replicates. Bar graphs are mean +/- SD. Scale bars 25μm. Statistical test used was a one-way ANOVA with a post-hoc Tukey’s multiple comparison test (C and E), *p < 0.05, **p < 0.01.
Figure 4. SARS-CoV-2 infection is associated with pancreatic thrombo-fibrosis in NHPs. (A) Representative pancreas histological sections stained with H&E, showing blood vessels. Images show thrombi in venous compartments of SARS-CoV-2 infected NHP compared to control pancreas. (B) Quantification of thrombi area over pancreas area, across NHP pancreata. (C) Representative pancreatic sections stained with picrosirius red (PSR). (D) Quantification showing fibrosis area over pancreas area. Experiments represent n=3-5 biological replicates. Bar graphs are mean +/- SD. Scale bars 25μm. Statistical test used was a one-way ANOVA with a post-hoc Tukey’s multiple comparison test (B and D), *p < 0.05.
Figure 5. SARS-CoV-2 infect pancreatic endocrine, exocrine and endothelial cells in humans. (A) Representative IF image of a pancreatic islet from a deceased COVID-19 patient showing SARS-CoV-2-NP in β cells (yellow arrows). (B) Representative IF images showing SARS-CoV-2 infected ductal cells (yellow arrows) in deceased COVID-19 subjects. (C) Quantification showing the number of SARS-CoV-2 infected ductal cells. (D) Representative IF images showing SARS-CoV-2 infected endothelium (yellow arrows). (E) Quantification showing the percentage area of infected endothelium, across pancreata. All experiments represent n=3-5 biological replicates. Bar graphs are mean +/- SD. Scale bars 25μm. Statistical test used was an unpaired T-test (C and E). **p < 0.01.
Figure 6. Transmission electron microscopy of SARS-CoV-2 viral particles in the pancreas of COVID-19 patients. (A) Representative transmission electron micrographs (TEM) images of fixed pancreatic tissue. Ductal cells are shown containing SARS-CoV-2 viral particles (insets). Yellow arrows show SARS-CoV-2 viral particles while red arrows show spike protein. (B) Representative TEM images of endothelial cells in fixed COVID-19 patient pancreas. Endothelial cells show presence of SARS-CoV-2 viral particles (inset). Yellow arrows show SARS-CoV-2 viral particles while red arrows show spike protein. All experiments represent n=3-5 biological replicates. Bars 500nm, insets: 100nm.
Figure 7. SARS-CoV-2 infection is associated with thrombo-fibrosis in humans. (A) Representative pancreatic sections stained with H&E, showing blood vessels. Images show thrombi in venous compartments in COVID-19 patients (red arrows) compared to normal pancreas blood vessels (black arrows). (B) Quantification of thrombi area over total tissue area. (C) Representative pancreatic histological sections stained with PSR. (D) Quantification of fibrosis area over total tissue area. (E) Representative IF images showing the distribution of ICAM1 expression in the endothelium of the exocrine and endocrine pancreas (insets) in both COVID-19 patients (left) and uninfected controls (right). All experiments represent n=3-5 biological replicates. Bar graphs are mean +/- SD. Scale bars 25μm. Statistical test used was an unpaired T-test (B, D and F), *p < 0.05, ***p < 0.001.