Opportunities for Research for COVID-19 in the Mission of NIDDK

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The current worldwide pandemic of the coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to cause incredible morbidity and mortality on a global level. Presently, there is no effective pharmacologic therapy nor a vaccine to offer. Given the circumstances and mode of transmission, the coronavirus crisis is expected to remain a significant part of our lives for the foreseeable future, continuing to cause economic hardships, straining our health care system, and changing the way we work and live on a daily basis. From this crisis, we have learned, and will continue to learn, new information almost daily. What we did know prior to the pandemic was that past viral pandemics have clearly demonstrated the association of chronic disease comorbidities with increased risk for morbidity and mortality (1–3). This observation is no different with the current crisis, as a number of chronic diseases appear to be important comorbidities in those with COVID-19 infection (3,4). As recently reported, during 1–30 March 2020, 89.3% of hospitalized adults had one or more underlying conditions. The most commonly reported conditions overall were hypertension (49.7%), obesity (48.3%), chronic lung disease (34.6%), diabetes (28.3%), cardiovascular disease (27.8%), and kidney disease (13.1%) (4), several of which fall within National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) mission areas. It is important from a medical perspective that we fully understand the clinical characteristics of individuals affected, risk factors for mortality and other outcomes, potential underlying health disparities, and other clinical variables in order to be in the best position as a medical community to inform on mitigation strategies and treatment until a vaccine is found.

At present, clinicians managing patients with acute onset of multisystem dysfunction must make urgent decisions with little evidence to guide their practice. Even more difficult, despite the disproportionate impact on patients with preexisting conditions, there is little information on how to manage one or more established chronic diseases in COVID-19 (5,6). It is clear, however, that as with other severe infections, glycemic control in individuals with diabetes will be impaired and, when hospitalized, patients with type 2 diabetes who use oral agents will mostly likely require insulin (3). Thus, immediate efforts are needed to gather data from health care systems, hospitals, and existing clinical networks/trials to better understand metabolic, phenotypic or physiologic, and clinical factors that are involved or predictive of COVID-19 susceptibility and clinical course to better understand the heterogeneity of individual response to COVID-19 infection. In this regard, many of these important topics are covered in other articles in this special section of *Diabetes Care*.

While we have learned a great deal about the mode of entry for COVID-19 and the resulting pathophysiology, we need targeted research to further understand these underlying mechanisms. Specifically, it is known that SARS-CoV-2, like SARS-CoV-1, enters the cells via the angiotensin-converting enzyme 2 (ACE2) receptor (3,7). ACE2 has been well known to be expressed in the alveolar epithelial cells in the lungs and upper respiratory tract, but we also know that it is expressed in other tissues such as heart, small and large intestines, and pancreas (3,7). We also recognize that that ACE2 is highly expressed in proximal tubular cells, distal tubule and collecting duct cells, and less prominently in glomerular visceral and parietal epithelial cells (podocytes) of the kidney (8). The locations of the receptor are not only of interest in understanding the severe pulmonary manifestations of COVID-19, but may be very relevant to understanding how COVID-19 plays a role in contributing to worsening or development of disease in

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other tissues. It would be important to know why those who have both COVID-19 and diseases in the mission of NIDDK have different outcomes based on underlying disease factors or therapies being utilized to treat their condition. Thus, we are very interested in learning how COVID-19 is related to the development or effects of diabetes, obesity, kidney disease, and digestive diseases. Below, we propose several research opportunities to identify novel pathogenic pathways and potential translational targets of the kidney, digestive, and endocrine/metabolism system.

Obesity and diabetes as underlying conditions were present in 48.3% and 28.3% of adults aged ≥18 years with COVID-19–associated hospitalizations and were present in 41% and 31.3% of those aged ≥65 years (4). Many potential mechanisms have been postulated to explain the susceptibility for COVID-19 in patients with diabetes including *1*) higher affinity cellular binding and efficient virus entry, *2*) decreased virus clearance, *3*) diminished T-cell function, *4*) increased susceptibility to hyperinflammation and cytokine storm syndrome, and *5*) presence of cardiovascular disease (9). Chronic inflammation, increased coagulation activity, immune response impairment, and potential direct pancreatic damage by SARS-CoV-2 are also postulated as the underlying mechanisms of the association between diabetes and COVID-19 (5). Even if a patient does not have diabetes, there is a need for heightened awareness for pancreatic inflammation as reported in some individuals with COVID-19 and the contribution to either exacerbation or development of diabetes in acutely ill patients given that ACE2 receptors are expressed in exocrine and endocrine pancreas (7).

Based on the observations that obesity and diabetes are major risk factors for COVID-19 morbidity and mortality, research opportunities abound in this area. What are the specific clinical factors and operative mechanisms at the cellular level in individuals with diabetes that predispose to susceptibility to infection and lead to a higher risk of hospitalization and intensive care unit use and increased mortality? What role does glycemic control play in susceptibility or outcomes, and does current antidiabetes medication play a role? Because of evidence that the mode of entry of COVID-19 is through ACE2 and that treatment with ACE inhibitors or angiotensin receptor blockers—frequently used by people with diabetes—have the potential to cause upregulation of ACE2 (3), research on these processes that might contribute to viral infection or clinical outcomes is greatly needed. Another area that needs to be addressed is the role of COVID-19 in our most vulnerable populations that have a huge burden of diabetes and obesity. Preliminary data show a disturbing pattern of disproportionate risk and worse outcomes of COVID-19 among underrepresented minorities (10). Research to address these marked disparities warrants urgent attention.

Kidney disease remains an important comorbidity for COVID-19, both as a risk factor (chronic kidney disease) for hospitalization and as an important morbid outcome (acute kidney injury [AKI]). This is particularly true for older individuals, as kidney disease was present in 25.4% of individuals hospitalized with COVID-19 infection (4), and a more recent analysis shows chronic kidney disease in hospitalized COVID-19 patients as the third most common comorbidity, 12.7%, that followed hypertension and diabetes (11). Development of AKI increases the mortality rate by two- to sevenfold. The incidence of AKI in hospitalized patients with COVID-19 has been reported to be as high as 34.5%, with up to 5.4% requiring renal replacement therapy (12). AKI appears to be heterogenous, precipitated by hypovolemia, heart failure and cardiogenic shock, cytokine storm, hypoxic respiratory failure, hypercoagulable states, rhabdomyolysis, and direct viral infection of the renal epithelium. Kidney biopsy studies have found SARS-CoV-2 viral particles in tubular epithelium and podocytes, which suggests direct cytotoxicity (13). In patients with severe AKI, hemodialysis or continuous venovenous hemofiltration is required to sustain volume and metabolic homeostasis. Hemodialysis in critically ill, infected patients is associated with significant clotting complications and mortality as well as increased infection risk to staff.

Areas of research opportunity include observational studies to define the incidence and risk factors for the development of AKI in COVID-19–infected patients and to collect biosamples that will inform diagnostic and predictive disease biomarkers. These studies will help describe the natural history of COVID-19–associated AKI and provide investigational and clinical resources for future studies. While difficult to perform, kidney biopsies from patients with early AKI could help us understand the underlying pathophysiologies at the cellular and molecular level and begin to target specific treatments to specific subgroups of patients. Foundational basic science studies include identification of novel kidney-specific COVID-19 receptors (to explain why chronic kidney disease is a risk factor for COVID-19 and perhaps a viral reservoir), cell biologic studies in human kidney tissue (especially that acquired from patients), the development of animal models to identify novel biomarkers and therapeutic targets, and studies that define the long-term sequelae of COVID-19 infection on renal function. The consequences of renin-angiotensin system inhibition are unknown and could be addressed in large observational studies of patients with COVID-19 as well as basic studies. Ultimately, we will need clinical trials to test interventions to prevent or treat COVID-19–induced AKI. This is particularly important, as low glomerular filtration rate is currently an exclusion criterion for many antiviral studies.

Reports of COVID-19 presenting initially in some patients as an acute gastrointestinal syndrome with nausea, vomiting, diarrhea, and sometimes hematochezia further support the idea that the range of cells, tissues, and organs directly involved in the viral infection extends to the exocrine pancreas, gastrointestinal tract, and liver. Diarrhea as a symptom was reported in 26.7% and 28.8%, and nausea and vomiting in 24.4% and 20.5%, for individuals ≥18 and ≥65 years old, respectively (4). There is great concern that transplant patients and patients with immunologically mediated immune and inflammatory disorders such as inflammatory bowel disease, cirrhosis of the liver, or chronic exocrine pancreatic disease may be affected adversely. Further, there is little information to determine whether specific therapeutic agents, particularly anti-inflammatory, immunosuppressive, and specific drugs and biologics targeted at the immune system increase risk or perhaps even are protective. Important research questions include the following: What are the risks in patients with viral hepatitis taking antiviral drugs or who are coinfected with HIV? Are there dietary or

nutritional measures that are beneficial or detrimental? In procedure-oriented specialties such as gastroenterology, invasive procedures such as endoscopy may present high risks to health care workers; when and how should urgent procedures be performed? When elective procedures resume for important unrelated health reasons, such as screening colonoscopy, how will they be conducted safely? As we consider research opportunities in these areas, it is important to note that research questions regarding the endocrine system in diabetes and metabolic diseases and physiological and pathological responses of the digestive system are tightly intertwined.

Given the observations reported above, it is important that NIDDK respond with research opportunities to address COVID-19. In this regard, as part of a coordinated National Institutes of Health (NIH) effort, NIH is providing funding to support many available research opportunities related to addressing the COVID-19 crisis (14). As part of this effort, NIDDK has published a funding opportunity, "Notice of Special Interest (NOSI): Availability of Urgent Competitive Revision Supplements on Coronavirus Disease 2019 (COVID-19) within the Mission of NIDDK" (see NOT-DK-20-018 in [14]). The purpose of this NOSI is to highlight the urgent need for research on COVID-19 for diseases in the mission of NIDDK. NIDDK is particularly interested in projects focusing on the direct action of the virus on kidney, gastrointestinal tract function, and the endocrine/metabolic system as well as the collection of biosamples that will inform the understanding of renal, gastrointestinal, and endocrine/metabolic sequelae of viral infection. Pilot clinical studies (observational and interventional) that support the understanding or treatment of COVID-19–related diseases within the mission of the NIDDK are also of interest.

As outlined for the NOSI, the following are areas of research interest for NIDDK:

- Collection of biosamples that could inform the pathogenesis of COVID-19–associated kidney, gastrointestinal, or endocrine/metabolic diseases.
- Studies to gather data from health care systems and ongoing clinical trials to better understand whether patients with COVID-19 and diseases in the mission of NIDDK have different outcomes based on underlying disease factors or therapies for their condition.
- Studies to identify risk factors that could lead to modification of therapy in high-risk individuals such as patients with AKI, organ transplantation, diabetes, inflammatory bowel disease, and other diseases within the mission of NIDDK that are treated with immunomodulators or biologic pathway inhibitors.
- Studies to identify novel pathogenic pathways and potential translational targets for the development of kidney, gastrointestinal, and endocrine/metabolic diseases associated with COVID-19 infection using relevant in vitro and in vivo studies of the kidney, gastrointestinal, or endocrine/metabolism system.
- Pilot clinical studies designed to understand the natural history of COVID-19–related AKI and gastrointestinal or endocrine/metabolic diseases or to evaluate interventions to prevent or treat COVID-19–induced AKI and digestive or endocrine/metabolic disorders.

As the research community emerges from the crisis situation, there should be renewed efforts for multidisciplinary research to conduct integrated basic, translational, and clinical studies aimed at greatly increasing the knowledge base to understand how both the current COVID-19 threat and future health threats affect both healthy people and people with chronic diseases and conditions. We are hopeful that funding research in the above targeted areas will contribute greatly to addressing the paucity of data that currently exists for COVID-19 and to increase the understanding of mechanisms operable for diseases in the mission of NIDDK that may modulate viral pathogenesis. Evidence generated at this time point will be critical when informing on future preventive and therapeutic measures.

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References

1. Yang JK, Feng Y, Yuan MY, et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. Diabet Med 2006;23:623–628
2. Allard R, Leclerc P, Tremblay C, Tannenbaum TN. Diabetes and the severity of pandemic influenza A (H1N1) infection. Diabetes Care 2010; 33:1491–1493
3. Singh AK, Gupta R, Ghosh A, Misra A. Diabetes in COVID-19: prevalence, pathophysiology, prognosis and practical considerations. Diabetes Metab Syndr 2020;14: 303–310
4. Garg S, Kim L, Whitaker M, et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019 — COVID-NET, 14 states, March 1–30, 2020. MMWR Morb Mortal Wkly Rep 2020;69:458–464
5. Hussain A, Bhowmik B, do Vale Moreira NC. COVID-19 and diabetes: knowledge in progress. Diabetes Res Clin Pract 9 April 2020 [Epub ahead of print]. DOI: 10.1016/j.diabres.2020.108142
6. Ceriello A, Stoian AP, Rizzo M. COVID-19 and diabetes management: what should be considered? Diabetes Res Clin Pract 17 April 2020 [Epub ahead of print]. DOI: 10.1016/j.diabres.2020.108151
7. Drucker DJ. Coronavirus infections and type 2 diabetes—shared pathways with therapeutic implications. Endocr Rev 15 April 2020 [Epub ahead of print]. DOI: 10.1210/endrev/bnaa011
8. Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol 2004;203:631–637
9. Muniyappa R, Gubbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. Am J Physiol Endocrinol Metab 2020;318:E736–E741
10. Yancy CW. COVID-19 and African Americans. JAMA 15 April 2020 [Epub ahead of print]. DOI: 10.1001/jama.2020.6548
11. Myers LC, Parodi SM, Escobar GJ, Liu VX. Characteristics of hospitalized adults with COVID-19 in an integrated health care system in California. JAMA 24 April 2020 [Epub ahead of print]. DOI: 10.1001/jama.2020.7202
12. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA 22 April 2020 [Epub ahead of print]. DOI: 10.1001/jama.2020.6775
13. Su H, Yang M, Wang C, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int 9 April 2020 [Epub ahead of print]. DOI: 10.1016/j.kint.2020.04.003
14. NIH Central Resource for Grants and Funding Information. Coronavirus disease 2019 (COVID-19): information for NIH applicants and recipients for NIH funding. Accessed 25 April 2020. Available from https://grants.nih.gov/policy/natural-disasters/corona-virus.htm