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Diabetic kidney disease, a potentially serious issue resulting from collision of the coronavirus disease 2019 and diabetes global pandemics

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Diabetic kidney disease (DKD) is a progressive chronic kidney condition that occurs in the context of both type 1 and type 2 diabetes. DKD is a leading cause of end-stage renal disease (ESRD), a devastating condition that requires either kidney transplantation or life-long regular dialysis for the affected person to survive. Approximately 30%–50% of subjects with diabetes develop DKD. Diabetes is estimated to have affected 463 million people in 2019 globally [1], arguably one of the greatest pandemics in human history.

In late 2019, coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), was initially diagnosed in Wuhan, China [2–4]. This disease rapidly became a global pandemic. At the time that this article was written, >67 million confirmed COVID-19 cases have been recorded globally. The pandemic is still widely prevalent in many countries including both developing and developed nations with >500,000 new cases per day being diagnosed in December 2020 [5].

In COVID-19 patients, particularly those hospitalized with severe COVID-19, diabetes has been a major comorbidity and is associated with a deleterious outcome [6, 7]. It has also been observed that Covid-19 is associated with increased severity of preexisting diabetes manifesting in some individuals as diabetic ketoacidosis [8–11]. Specific recommendations have been proposed to guide the management of diabetes in COVID-19 patients in the early stage of the COVID-19 pandemic [12].

The consequence of the collision of these two great pandemics and the long-term effects on the affected subjects are largely unknown. Whether COVID-19 associated severe complications of preexisting diabetes and new-onset diabetes (see below) make them more prone to DKD, or whether this could lead to a new form of kidney injury is currently unknown. DKD was already a leading cause of death in people with diabetes in the pre-COVID-19 era. Therefore, understanding whether COVID-19 influences the onset and progression of DKD in people with both COVID-19 and diabetes would be important and may require more specific guidelines for monitoring and managing the individuals affected.

Indeed, COVID-19 can cause multi-organ injury leading to severe complications and death [13–16]. SARS-Cov-2, the virus causing COVID-19, and SARS-Cov-1 responsible for the SARS outbreak in 2003, both being coronaviruses, use the same cell surface enzyme protein, angiotensin-converting enzyme 2 (ACE2) as their receptor to enter host cells [17–19]. ACE2 was initially found to be expressed mainly in the heart, kidney, and testis [20], and subsequently confirmed to also be expressed in other tissues such as the nasal airway, lung, gastrointestinal tract, liver, and pancreas [19, 21–30] .Therefore, these ACE2 expressing organs can be the targets of SARS-Cov-2 infection and their physiological functions could potentially be impaired as a result of virus infection, due to viral protein interactions with host cellular proteins as well as due to the anti-viral response including inflammation.

Some of these vulnerable organs such as the pancreas and liver may be involved in and thus could affect glucose metabolism. Thus, impairment of the function of such organs could lead to a deterioration of preexisting diabetes, or cause new-onset diabetes. In some subjects with COVID-19, it has been noted that they develop features of diabetes, such as hyperglycemia, even when they had no prior history of diabetes. This would imply that new-onset diabetes can be caused as a result of SARS-Cov-2 infection. The extent and pathophysiology of this phenomenon are currently being investigated by an international team of experts through the global COVIDIAB Registry led by Monash University and King's College, London [31]. Indeed, SARS-Cov-2 has been demonstrated to infect pancreatic endocrine cells, including insulin-producing beta cells in pancreatic organoids, leading to robust chemokine induction and increased cellular apoptosis [32]. The relevance of this finding in humans is further supported by the presence of ACE2, the receptor for SARS-Cov-2, in the human pancreas including in the insulin-producing pancreatic beta

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cells [27]. This is consistent with the finding reported >15 years ago that ACE2 is expressed in rat pancreatic islets [30]. It is highly likely that SARS-Cov-2, when it reaches the pancreas, would be able to infect pancreatic beta cells and other cells within the islets, either triggering an anti-viral inflammatory response within the pancreas or directly injuring these pancreatic endocrine cells. The virus-induced impairment of beta cell functions such as insulin synthesis and secretion or loss of insulin-producing cells would ultimately lead to acute new-onset diabetes manifested by severe hyperglycaemia.

Virus-induced new-onset diabetes or increased severity of preexisting diabetes in people with COVID-19 would presumably harm the kidney, an organ that is sensitive to increased ambient glucose levels. This would increase the risk of onset of DKD or increase the severity of existing chronic kidney disease in affected subjects. COVID-19 per se is also considered to be a direct causal factor for acute renal injury [33–39]. The kidney, with a high level of ACE2 expression, can be directly infected by SARS-Cov-2 and directly impacted as a result of virus infection and/or the anti-viral inflammatory response, such as cytokine storm as has been observed in COVID-19, particularly in those with severe COVID-19 [40, 41]. Proteomics analysis of urinary proteins from people with COVID-19 has recently confirmed that the cytokine storm occurs in a later stage of COVID-19 with increased severity following an initial stage of immunosuppression [42].

Hypoxia is considered to be a key final common pathway for chronic kidney disease to progress to end-stage renal disease [43, 44]. With pneumonia being a major condition seen in severe COVID-19, often with associated systemic hypoxia, it could promote a renal hypoxic response. Thrombosis is another major complication seen in severe COVID-19 patients [45] and the clots in the circulation can block the small blood vessels and capillaries in the kidney. Furthermore, the renin-angiotensin system (RAS) plays a pivotal role in injuring the kidney due to increased activity of the Angiotensin II/AT1 receptor axis, including in DKD [46]. ACE2 plays a protective role by specifically cleaving Angiotensin II into Angiotensin 1–7, leading to inactivation of Angiotensin II, the major effector hormone of the RAS. Furthermore, the newly formed Angiotensin 1–7 has anti-inflammatory and antifibrotic effects via its receptor Mas [46, 47]. SARS-Cov-1 and other similar coronaviruses, such as SARS-Cov-2, bind to ACE2 to enter cells, leading to increased shedding of ACE2 and downregulation of cell surface ACE2 levels [48, 49]. When this occurs in the kidney, increased renal RAS activity due to ACE2 downregulation would presumably promote renal injury. All these factors together would significantly increase the risk of kidney injury, either increasing the severity of existing chronic kidney disease such as DKD or promoting a new form of kidney injury.

Taken together, diabetes worsens the outcome of COVID-19 and vice versa COVID-19 can further worsen preexisting diabetes or cause new-onset diabetes, leading to fatal multi-organ injury including renal damage. DKD is already a leading cause of death in people with diabetes, with diabetes arguably the greatest non-communicable disease pandemic in human history.

The current collision between diabetes and COVID-19 has generated major new challenges for affected individuals and health providers, including potentially serious and as yet unknown adverse consequences for those with COVID-19. Therefore, more research needs to be carried out to understand the pathophysiology and mechanisms of the interactions among these diseases. This can provide the direction for an optimized management strategy, including evidence-based guidelines for managing COVID-19 patients already affected by or at risk of diabetes and/or renal disease.

Acknowledgment

Nil.

Conflict of Interest

Mark E. Cooper is a Co-Editor-in-Chief of the journal, and Zhonglin Chai is an Editorial Board Member of the journal. The article was subject to the journal's standard procedures, with peer review handled independently of this editor and his research groups.

Author Contribution

Chai Z developed the concept and drafted the manuscript. Zimmet PZ and Cooper ME edited the manuscript. All the authors checked and approved the final version to be published.

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