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REVIEW

Is the kidney a target of SARS-CoV-2?

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Martinez-Rojas MA, Vega-Vega O, Bobadilla NA. Is the kidney a target of SARS-CoV-2? *Am J Physiol Renal Physiol* 318: F1454–F1462, 2020. First published May 15, 2020; doi:10.1152/ajprenal.00160.2020.—The new disease produced by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) represents a major pandemic event nowadays. Since its origin in China in December 2019, there is compelling evidence that novel SARS-CoV-2 is a highly transmissible virus, and it is associated to a broad clinical spectrum going from subclinical presentation to severe respiratory distress and multiorgan failure. Like other coronaviruses, SARS-CoV-2 recognizes human angiotensin-converting enzyme 2 as a cellular receptor that allows it to infect different host cells and likely disrupts renin-angiotensin-aldosterone system homeostasis. Particularly, a considerable incidence of many renal abnormalities associated to COVID-19 has been reported, including proteinuria, hematuria, and acute kidney injury. Moreover, it has been recently demonstrated that SARS-CoV-2 can infect podocytes and tubular epithelial cells, which could contribute to the development of the aforementioned renal abnormalities. In this review, we discuss the biological aspects of SARS-CoV-2 infection, how understanding current knowledge about SARS-CoV-2 infection may partly explain the involvement of the kidneys in the pathophysiology of COVID-19, and what questions have arisen and remain to be explored.

acute kidney injury; angiotensin-converting enzyme 2; COVID-19; proteinuria; renin-angiotensin-aldosterone system

INTRODUCTION

Since 2003, severe acute respiratory syndrome (SARS) caused by different viral agents has been recognized as a clinical entity of great epidemiological concern, because it can be fatal (4, 22). In December of 2019, Zhu et al. (87) reported a cluster of patients with pneumonia of unknown etiology linked to the seafood market in Wuhan, China; since that moment, a novel coronavirus, SARS-coronavirus 2 (SARS-CoV-2) was isolated and identified. The infection spread rapidly in and out of China, and the World Health Organization declared a global emergency on January 31, 2020; 11 days afterward, it announced the name for the new coronavirus disease as coronavirus disease 2019 (COVID-19) because of its appearance last year. On March 11, 2020, the World Health Organization declared that the COVID-19 outbreak was considered a pandemic, as there were already more than 118,000 reported cases, of which 40,000 were diagnosed in 114 countries outside of China, with 4,291 deaths (https://bit.ly/2xiAO2B). As of April 13, 2020, SARS-CoV-2 has spread widely around the world, affecting 213 countries/regions, with more than 1,773,000 confirmed cases and more than 111,000 deaths attributed to this virus (https://bit.ly/34A85Ct).

Here, we review the biological aspects of SARS-CoV-2 infection, how understanding current knowledge about SARS-CoV-2 infection may partly explain the involvement of the kidneys in the pathophysiology of COVID-19, and what questions have arisen and remain to be explored.

COVID- 19 (SARS-COV-2) BIOLOGY

Structural Characteristics

Human coronaviruses are enveloped positive-stranded RNA viruses of the order *Nidovirales*. There are seven different coronaviruses known that possess the ability to infect human cells; some of them cause mild upper respiratory symptoms, and others are potentially fatal. SARS-CoV-2 is a lineage B betacoronavirus known to cause severe respiratory disease (16). It has multiple transmembrane glycoproteins, named Spike (S), which mediate molecular interactions with the host (69). S glycoproteins comprise two functional subunits: S1, which mediates host receptor binding to angiotensin-converting enzyme 2 (ACE2), and S2, which is responsible for viral and cellular membrane fusion (74, 75). The S protein has a

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novel polybasic furin cleavage site at the S1-S2 boundary, which is the target of intense glycosylation in a mucin-like domain and may mediate a wider tropism within the organism (2). The receptor-binding domain (RBD) located in S1 is the most variable part of the coronavirus genome; in SARS-CoV-2, critical amino acids (L455, F486, Q493, S494, N501, and Y505) confer the RBD a high affinity for the extracellular domain of human ACE2 (75), which could have resulted from natural selection directly on a human host or on other mammals with human-like ACE2 (86).

SARS-COV-2 ONTOGENY

The epidemic outbreak of COVID-19 is estimated to have emerged between the end of November and the beginning of December 2019. There are two possible scenarios that could explain the origin of the virus, which have been discussed previously by Andersen et al. (2) and are briefly described below.

Natural Selection Before Zoonotic Transfer

Early cases in the Huanan seafood wholesale market support the notion of a common animal source. It is expected that bats (*Rhinolophus affinis*) served as a reservoir host for a potential progenitor virus (RaTG13), which has 96% identity with SARS-CoV-2 (86), but it exhibits important differences in the RBD (75). Malayan pangolins (*Manis javanica*) are other possible reservoir or intermediate hosts for the SARS-CoV-2 ancestor, because some pangolin betacoronaviruses have closer similarities within their RBD (2). An important finding against this hypothesis is that both RaTG13 and pangolin coronaviruses lack a polybasic furin cleavage site, while it is found in other less-related coronaviruses. The acquisition of both the polybasic cleavage site and the affinity to its host receptor ACE2 through the RBD may be an example of convergent evolution due to mutations within a high population density of the host involved (18).

Natural Selection in Humans After Zoonotic Transfer

Given the similarity of the RBD of pangolin coronavirus to that of SARS-CoV-2, an alternative hypothesis could be justified, where the first human transmissions were through many zoonotic events and the new acquisition of the polybasic cleavage site in SARS-CoV-2 would support the notion of a mutation just before human-to-human transmission. These short transmission chains were seen in the Middle East respiratory syndrome-coronavirus outbreak (23).

MECHANISMS OF CELLULAR INFECTION BY SARS-COV2

COVID-19 has a broad clinical spectrum; most of the studies published to date have revealed the lungs as the main organs affected in the disease, while a smaller number of studies have reported the involvement of other organs like the gastrointestinal system, bone marrow, liver, heart, and kidney, among others (33, 41, 83). This multiorgan involvement could be linked to the wide distribution of ACE2, which is the molecular receptor that allows host cell infection by SARS-CoV-2 (49, 83).

The presence of ACE2, specifically in type II pneumocytes together with the expression of viral process-related genes in these cells, suggests that the lungs are the primary sites of entry for SARS-CoV-2 in the body (85). However, the presence of ACE2 in enterocytes and the oral mucosa can explain the fecal-oral transmission route (32, 81).

After host exposure to SARS-CoV-2, the virus recognizes the NH_2-terminal peptidase domain of ACE2 at the surface of the cell membrane using S domain B (S^B) (74, 82). To accomplish this, S1 needs to form homotrimers with a partially opened apex conformation, something that is thought to be a pathogenic characteristic of all human coronaviruses. After binding to ACE2, S is cleaved by host furin-like protease, such as plasmin (36), specifically at the named S2′ site; this process activates S2 for membrane fusion by inducing conformational changes that expose the internal fusion heptad repeat peptides (HR1 and HR2), bringing viral and cellular membranes to close proximity. The eventual fusion is shown in Fig. 1 (6, 47). The presence of the furin polybasic cleavage site at the S1/S2 boundary may expand tropism due to the near-ubiquitous distribution of furin-like proteases (74). In addition, endosomal cell entry of SARS-CoV-2 is facilitated by a low pH and pH-dependent endosomal cysteine protease known as cathepsin (89). There is evidence that endosomal acid pH is crucial for the processing and internalization of SARS-CoV. Based on this, it has been proposed that the antimalarial drug chloroquine could increase endosomal pH, since chloroquine is known to protonate quickly and concentrate in endosomes, which prevents the fusion of the virus to the endosome and could exert a successful antiviral effect against SARS-CoV-2 (72). So far, there is only rational evidence to justify chloroquine treatment, backed by consensus expert opinion; however, the evidence is weak and rigorous clinical trials are still needed (17).

After entering to the cytosol, the SARS-CoV-2 RNA begins the translation of its replicase and structural proteins, exploiting the endogenous transcriptional machinery of the infected cell to generate new virions and spread throughout the infected organ. According to a previous study on SARS-CoV, genome replication and virion assembly would occur within double membrane vesicular arrangements of the endoplasmic reticulum (ER) and the Golgi complex just before viral release (Fig. 1) (58).

ACE2: PHYSIOLOGY AND DISTRIBUTION

ACE2 is a type I transmembrane protein with carboxypeptidase activity that was described in 2000 by two different groups, Tipnis et al. (67) and Donoghue et al. (21). The main targets of ACE2 are angiotensin I and angiotensin II peptides. Although there are other peptides subjected to ACE2 proteolysis, such as neurotensin 1–13, apelin 13, dynorphin 1–13, and some of kinin metabolites, it exhibits the highest affinity for angiotensin II. Angiotensin I (decapeptide) is typically converted to angiotensin II (octapeptide) by ACE1, whereas ACE2 inactivates both peptides by converting them to angiotensin 1–9 and angiotensin 1–7, respectively (21, 67, 71). Full-length ACE2 consists of the NH_2-terminal peptidase domain (PD) and a COOH-terminal collectrin-like domain (CLD) that ends with a single transmembrane helix and a short cytosolic segment.

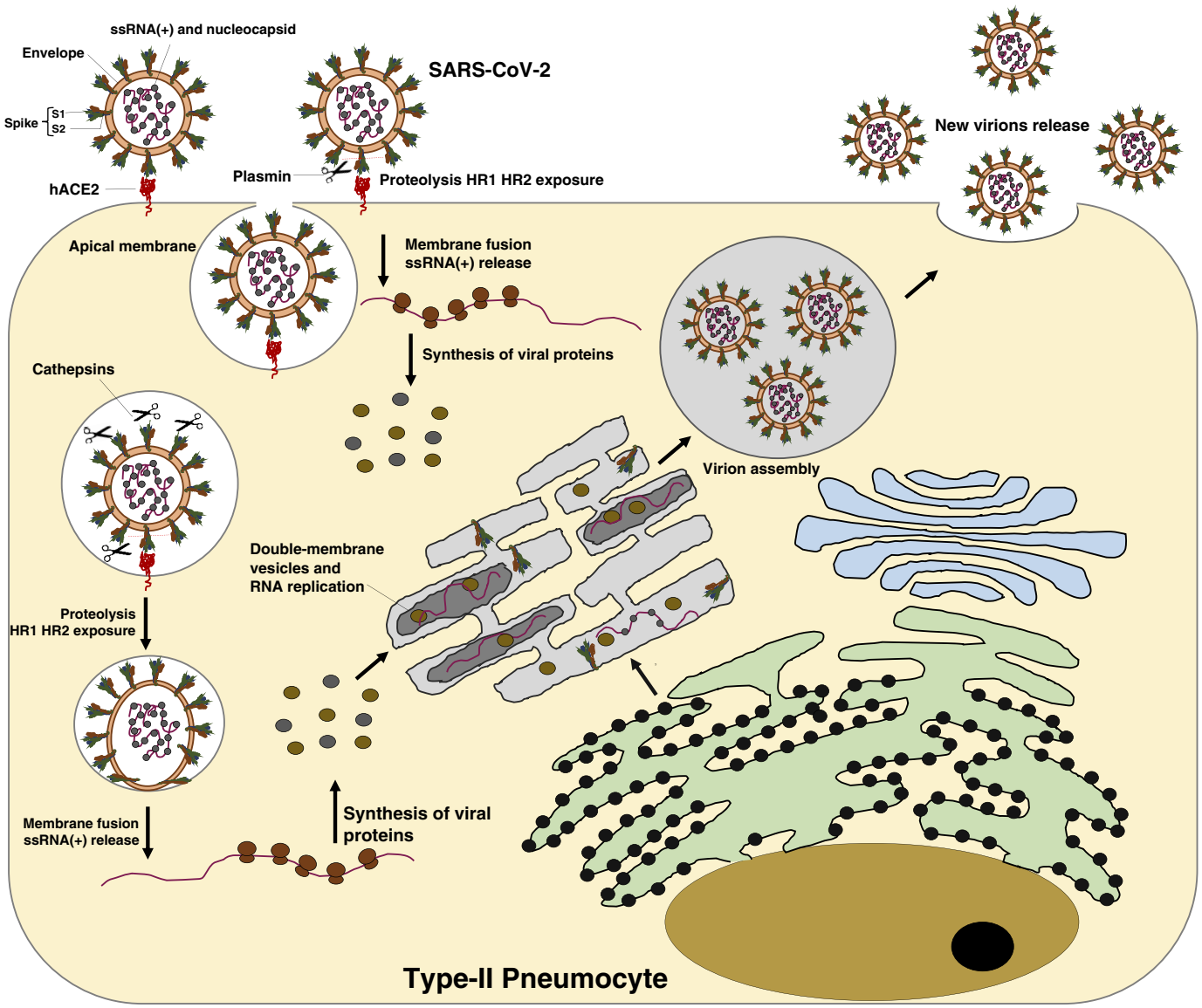

Fig. 1. Cellular infection by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2). The virus recognizes human angiotensin-converting enzyme 2 (hACE2) in the apical membrane of type II pneumocytes with domain B of S1 in the protein Spike (S). It can then take the endocytic pathway or the plasma membrane pathway. In the former, the virion is internalized in a phagosome, where S suffers proteolysis by host proteases, which generates conformational changes that expose the fusion peptides HR1 and HR2 located within S2. In the plasma membrane pathway, proteases with extracellular domain cleave S outside the cell immediately after the binding to ACE2. When HR1 and HR2 are exposed, whether inside the phagosome or in the plasma membrane, they mediate the fusion of host and virion membranes, allowing the release of viral RNA into the cytosol and the early expression of viral genes. Some of these viral proteins are thought to induce the formation of a reticular complex originated from the endoplasmic reticulum. This complex and the double-membrane vesicles inside it constitute the molecular factory of new virions. After assembly of the different components of the newly formed virions, they are secreted outside cell, and the cycle begins once again.

Interestingly, in polarized cells, ACE2 is exclusively located in the apical membrane (32).

Originally, ACE2 was thought to be exclusively expressed in the heart, kidneys, and testes (21). However, studies in humans and mice have demonstrated ACE2 expression in most organs, with the highest activity in the ileum and kidney followed by type I and type II pneumocytes, adipocytes, heart, brain stem, small intestine enterocytes, stomach, liver, vasculature, and nasal and oral mucosa (28, 81, 88). Despite its wide distribution, the physiological significance of ACE2 expression in most of these tissues remains elusive. In general, ACE2 contributes to balance angiotensin II activity in both systemic and local scenarios.

In the kidney, ACE2 is present in podocytes, mesangial cells, parietal epithelium of Bowman's capsule, proximal cell brush border, and collecting ducts (3, 32, 40, 84). Several models of nephropathy have shown that ACE2 is implicated in reducing glomerular and tubular damage as well as fibrosis (43, 48, 63, 84). In this regard, male mice developed age-dependent glomerulosclerosis and albuminuria in the absence of the *Ace2* gene, which was effectively reverted with angiotensin II type 1 receptor blockers, supporting the role of ACE2 in angiotensin II equilibrium (51). Noteworthy, pharmacological blockade of the renin-angiotensin-aldosterone system (RAAS) increases both cardiac and renal ACE2 activity (35). ACE2 was first recognized as a viral receptor after the SARS epidemic in 2003 (42).

CLINICAL COURSE OF COVID-19

SARS-CoV-2 is more contagious than previous coronaviruses known, because of its greater binding affinity to ACE2 (79), but produces less severe cases than other SARS-causing viruses (4, 22, 41). The median incubation period is around 4 days, but it can be as long as 12 days according to early reports. Transmission appears to be independent of clinical presentation and is best correlated with viral load, which peaks at 10 days after symptom onset (41).

Early experience from China confirmed male predominance in incidence (58%) compared with female. The most common symptoms were fever (88.7%) and cough (67.8%), and the most common radiological finding on admission were ground glass opacity (56.7%) and bilateral patchy shadowing in the lungs (51.8%) (33). Other common symptoms, especially in deceased patients, included fatigue, dyspnea, chest tightness, and sputum production, whereas less common symptoms included anorexia, diarrhea, and myalgia (12). Between 16% to 20% of cases are severe or critical, and 61.5% of this group died after 4 wk (33, 83). Patients with diabetes, hypertension, coronary heart disease, chronic obstructive pulmonary disease, cerebrovascular disease, and kidney disease exhibited worse clinical outcomes when infected with SARS-CoV-2 (45).

According to the European Centre for Disease Prevention and Control, the evidence from analyses of cases showed that 80% of patients with COVID-19 had mild disease, without pneumonia or with mild pneumonia, most of whom recover spontaneously. In contrast, 14% of infected patients experienced a more severe form of the disease, and 6% became critically ill (31).

Acute kidney injury (AKI) is infrequent in the context of mild to moderate SARS-CoV-2 infection (5%); in these patients, the most common kidney abnormalities are subclinical. Interestingly, a recent prospective study including 701 patients with moderate or severe disease showed that 43.9% exhibited proteinuria and 26.7% hematuria at hospital admission, while around 13% presented elevated levels of either serum creatinine, blood urea nitrogen, or both (13). During hospitalization, AKI occurred just in 5.1% of SARS-CoV-2-infected patients. All these kidney abnormalities had a significantly higher risk of in-hospital death: proteinuria 1+ (1.8, 0.81–4.0), proteinuria 2+ to 3+ (4.84, 2.0–11.7), hematuria 1+ (2.99, 1.39–6.42), and hematuria 2+ to 3+ (5.5, 2.5–12.0) after adjusting for age, sex, disease severity, comorbidity, and leukocyte counts (13).

Recent evidence shows that AKI is more common in critically ill patients with COVID-19. Accordingly, in 52 critically ill patients admitted to the intensive care unit in Wuhan, China, AKI was the most common extrapulmonary complication, present in 15 patients (29%), more common than cardiac injury (23%) and liver dysfunction (23%). Of all patients with AKI, 8 patients (25%) needed continuous renal replacement therapy and 12 patients (80%) died with a median duration from intensive care unit admission to death of 7 days (interquartile range: 3–11) (83).

All together, this suggest that kidney abnormalities are more common than expected and are associated with higher mortality, even when they are present as subclinical manifestations, and when they are clinically relevant, this leads to even greater lethality.

KIDNEY ABNORMALITIES INDUCED BY SARS-COV-2: POTENTIAL INVOLVEMENT OF ACE2 PATHOPHYSIOLOGY

A previous study (56) on SARS-CoV infection showed that the virus RNA is effectively detected in urine 10 days after the onset of symptoms, and the excretion gradually decreased until day 21; unfortunately, it has not been studied in SARS-CoV-2 yet. Autopsies of SARS-CoV-confirmed patients demonstrated the virus presence in tubular epithelial cells by immunohistochemistry and in situ hybridization (20). In addition, 35% of heart specimens from SARS-CoV-infected patients revealed the coexistence of viral RNA and reduced ACE2 protein expression (52). A retrospective study during the SARS-CoV outbreak found that only 6% of SARS-CoV-infected patients exhibited AKI (15). However, AKI was a fatal complication of SARS, given that almost 92% of patients with SARS with AKI died. This study also evaluated whether active replication of SARS-CoV existed in the tubular cells of postmortem patients infected with SARS-CoV by analyzing the presence of viral particles using electron transmission microscopy. The authors found that SARS-CoV was not detectable in any of the analyzed samples and suggested that renal impairment was likely related to multiorgan failure (15). This study suggested that AKI in patients with SARS-CoV could be the result of cytokine release syndrome (CRS) (68) rather than active viral replication in the kidney.

In contrast to the previous studies with SARS-CoV-infected patients, recent studies have reported that the human kidney is a specific target for SARS-CoV-2 infection (19, 25, 53, 66). In fact, Diao et al. (19) examined viral nucleocapsid protein in the kidney of postmortem patients and found that SARS-CoV-2 antigens accumulated in renal epithelial tubules, suggesting that SARS-CoV-2 infects the human kidney directly, which leads to kidney dysfunction and contributes to viral spreading in the body. The difference between the higher renal tropism of SARS-CoV-2 versus SARS-CoV could be explained by the increase affinity of SARS-CoV-2 for ACE2, allowing greater viral load in several organs, and especially into the kidney, which may act as viral reservoir (57). An additional study of 26 autopsies found virus particles characteristic of SARS-CoV-2 in the proximal tubular epithelium and podocytes by electronic microscopy (66). This finding was associated with foot process effacement and occasional vacuolation and detachment of podocytes from the glomerular basement membrane (66).

These findings, along with the consensual physiological role of ACE2 in the kidneys, raise the possibility of a complex multifactorial pathophysiology explaining kidney abnormalities in COVID-19, involving a direct cytopathic effect of the virus, a local disruption in RAAS homeostasis, and a systemic inflammatory response to infection, as shown in Fig. 2.

The most frequent finding of kidney dysfunction in patients with COVID-19 is mild to moderate proteinuria (13). Just a little fraction of plasma proteins is filtered in the renal glomeruli, and most of them are effectively reabsorbed in the proximal tubule, so that basically no proteins appear in normal urine. The glomerular filtration barrier depends on adequate function of its three components: endothelial cells, the glomerular basement membrane, and podocytes (9). Podocytes are known to be particularly sensitive to RAAS homeostasis, with angiotensin-1–7 being the most abundant product, probably due to the specific expression of ACE2 in this region (70). If a

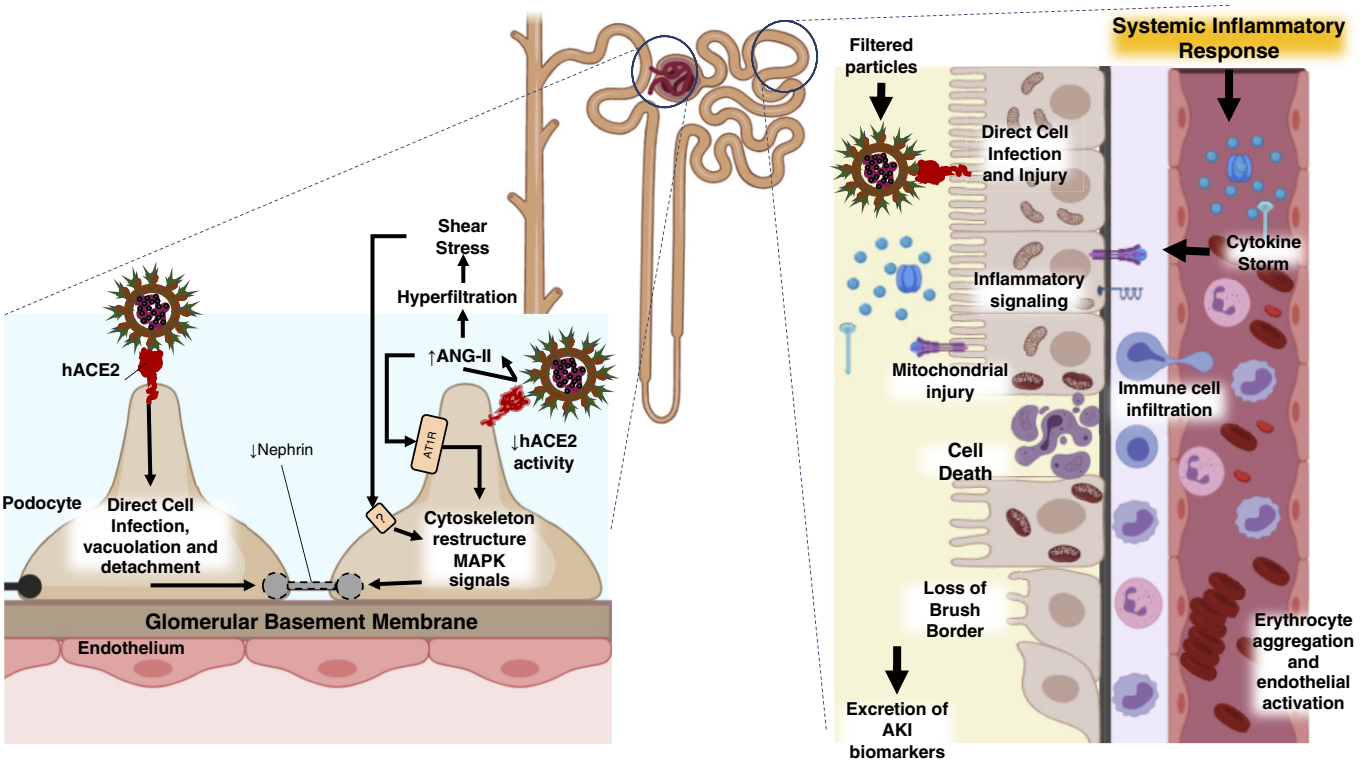

Fig. 2. Possible mechanisms of kidney damage by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2). Angiotensin-converting enzyme 2 (ACE2) expression in podocytes makes the glomerulus a direct target of SARS-CoV2 infection, leading to podocyte vacuolation, foot process effacement, and cell detachment. In addition, the occupation of ACE2 by SARS-CoV-2 could prevent angiotensin II clearance, which could contribute even more to podocyte dysfunction. ACE2 in proximal epithelial cells also makes them a direct target of SARS-CoV-2 infection and virus-related injury. This process could be aggravated by an uncontrolled systemic inflammatory response involving a cytokine storm and local inflammation. (This image was created with Biorender.) hACE2, human ACE2; AT1R, angiotensin II type 1 receptor; AKI, acute kidney injury.

pathological process increases glomerular levels of angiotensin II, podocytes acquire a dysfunctional phenotype mediated by cellular responses to this octapeptide due to shear stress and resulting in single nephron hyperfiltration. This phenotype involves Ca^{2+} signaling, cytoskeleton restructure, and nephrin internalization, which finally is manifested by proteinuria (38, 65). The actual tropism of SARS-CoV-2 to podocytes has been recently determined, and it is reasonable to hypothesize that proteinuria is a partial consequence of direct podocyte infection with potential RAAS alterations, which together would affect the glomerular filtration barrier and result in increased filtration of plasmatic proteins.

Tubular injury can also increase renal protein excretion, usually in a mild intensity. Interestingly, patients with COVID-19 with elevated serum creatinine at admission exhibited a higher incidence of moderate proteinuria compared with those with normal serum creatinine (30.2% vs. 7.5%) (13). However, there is no evidence that this depends on a disturbed RAAS and actually relies on the proximal tubule cell response to injury, including the transient loss of polarity and cell death (7, 54).

The incidence of AKI in SARS-CoV-2-infected patients has been variable, and it has been found predominantly in critically ill patients (77, 83). This rises important considerations to take into account for COVID-19-associated AKI pathogenesis. It has been reported that patients in the intensive care unit have higher levels of IL-1β, IL-8, interferon-γ, and TNF-α, among other cytokines, compared with noncritically ill patients (33). This suggest a potential role of CRS, also named as "cytokine storm," comparable with sepsis-associated AKI, where the uncontrolled systemic inflammatory response leads to kidney dysfunction. The occurrence of CRS in COVID-19 has been documented since the first reports of the disease (33, 80). In patients with CRS, AKI might occur as a result of intrarenal inflammation, increased vascular permeability, and volume depletion, which is translated in the findings of autopsies of erythrocyte aggregates obstructing the lumen of capillaries without platelet or fibrinoid material. Proinflammatory IL-6 is considered to be the most important causative cytokine in CRS. Among patients with COVID-19, the plasma concentration of IL-6 is increased in those with acute respiratory distress syndrome (80). The anti-IL-6 monoclonal antibody tocilizumab is widely used to treat CRS in patients who have undergone chimeric antigen receptor T cell therapy, and it is now also being used empirically in patients with severe COVID-19 (50). However, there is no consensual recommendation for or against tocilizumab treatment, and ongoing clinical trials will determine the utility of this treatment (1). Extracorporeal therapies have also been proposed as approaches to remove cytokines in patients with sepsis and could potentially be beneficial in critically ill patients with COVID-19 (29). The rational use for these therapies is that cytokine removal could prevent CRS-induced organ damage (61, 62).

Moreover, studies on SARS-CoV confirmed tropism to monocytes and lymphocytes, where the virus induces proinflammatory responses and cell death, and all of them could

potentially take place during COVID-19 (26, 30). In addition, it is well known that an imbalance in components of the RAAS can contribute to kidney injury by changing renal hemodynamics, altering tubular handling of electrolytes with a higher metabolic demand, and inducing proinflammatory phenotypes in both epithelial and immune cells. It is highly probable that this imbalance could contribute to the renal dysfunction observed in severe patients with COVID-19, which could also be accompanied by a decrease in ACE2 activity (8, 46, 60). It has become clearer that sepsis-associated AKI is multifactorial, involving the kidney inflammatory response, microcirculatory dysfunction, and metabolic reprogramming with mitochondrial injury (55). These mechanisms are compatible with our current understanding of SARS-CoV-2 infection and biology, supporting the prevailing hypothesis that COVID-19-associated AKI takes place in a severe disease scenario with a complex pathophysiological network, but, in contrast to other SARS-related viruses (14), SARS-CoV-2 direct infection of the proximal epithelium could importantly support a causal relationship in AKI development (66).

Finally, the finding of hematuria in at least 20% of infected patients raises a clinical concern. There are several causes of hematuria, including both kidney damage and extrarenal abnormalities, and to address them it is necessary to evaluate carefully urine sediment (78). Unfortunately, to our knowledge, hematuria has only been reported as a general finding, without exploring its characteristics (2a, 13). There are many possible explanations of hematuria in COVID-19, including coagulopathy, kidney inflammation, and glomerular barrier disruption (as previously discussed) (83). However, the information available makes it very difficult to propose an acceptable hypothesis.

IMPACT OF COVID-19 IN PATIENTS WITH PREEXISTING CHRONIC KIDNEY DISEASE

Patients with chronic kidney disease (CKD) require special attention and even more so in the course of this pandemic. In fact, there was a worldwide concern around the use of renin-angiotensin system inhibitors because they could upregulate ACE2 expression in patients with type 2 diabetes and hypertension, both conditions commonly found in patients with CKD (24, 64). Fortunately, recent studies have provided enough evidence showing that in patients treated with renin-angiotensin system inhibitors, there is not greater risk of SARS-CoV-2 (44, 59). However, patients with CKD, and especially those with end-stage renal disease and with renal replacement therapy, are known to have impaired immune function, and this could contribute to greater SARS-CoV-2 infection susceptibility (34). Additionally, kidney transplant recipients, who receive immunosuppressant therapy, may have a particular risk of acquiring COVID-19 (15a).

Early reports in China described preexisting CKD in only 0.7% of all patients with COVID-19, while the prevalence was of 1.7% in patients with severe pneumonia (31). However, several dialysis centers have reported COVID-19 outbreaks affecting more than 10% of patient with end-stage renal disease and 6% of the medical staff (27, 37, 76). Since then, there have been specific protocols proposed to mitigate the transmission of SARS-CoV-2 in these medical units (39). Interestingly, patients with end-stage renal disease and COVID-19 are more likely to die of cardiovascular complications than of pneumonia (76). Finally, in addition to the possible contributors of kidney dysfunction during active COVID-19 previously discussed, preexistent CKD is a known independent risk factor to develop AKI; this could worsen the expected outcomes of these patients and may involve many pathophysiological mechanisms dependent on comorbidities (10).

Perspectives

Today, we are facing what could represent the greatest pandemic event in human history; fortunately, we are living in a new era of communication, where every character of the scientific community can access the latest data regarding this novel disease and contribute by actively exploring possible solutions against SARS-CoV-2. As we discussed before, COVID-19 has a broad clinical spectrum involving many vital organs, including the kidney, representing a significant threat to survival. Intense research in ACE2 involvement in SARS-CoV-2 infection is critical to understand better COVID-19, not only because of its actual role as viral receptor but also because of its physiological contribution to RAAS homeostasis. Battle et al. (5) have proposed the potential benefit of using soluble recombinant ACE2 to trap SARS-CoV-2 and thereby reduce or prevent infection of cells that express ACE2 on their membrane. This hypothesis has attracted the attention of several scientists, and, now, a clinical trial is underway in China (NCT04287686). Other topics that are mandatory to address are *1*) whether SARS-CoV-2 infection modifies tissue ACE2 expression; *2*) if this were the case, a reduction in ACE2 expression could result from cellular death induced by SARS-CoV-2 infection by itself or an altered transcriptional mechanism; *3*) whether treatment with converting enzyme inhibitors or angiotenin receptor blockers during active COVID-19 modifies the expression of ACE2; *4*) whether patients with chronic diseases have higher expression of ACE2 and plasminogen and therefore have greater susceptibility to infection; and *5*) finally find out whether the course of SARS-CoV-2 infection is modified in patients with chronic diseases who have higher levels of circulating soluble ACE2.

The recent demonstration of SARS-CoV-2 infection in podocytes and proximal epithelial cells provides new insights that allow us to better understand the pathophysiology of kidney damage by COVID-19 and, therefore, guide a rational approach to possible therapeutic strategies. However, several lines of research in other organs (11) provide evidence suggesting that the kidneys contribute partially in the complex pathophysiological network involved in COVID-19, and we still need to explore how other cell types, like pericytes, endothelium, and interstitial cells, are involved in the establishment and maintenance of kidney dysfunction during COVID-19.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

M.A.M.-R. and N.A.B. prepared figures; M.A.M.-R., O.V.-V., and N.A.B. drafted manuscript; M.A.M.-R., O.V.-V., and N.A.B. edited and revised manuscript; M.A.M.-R., O.V.-V., and N.A.B. approved final version of manuscript.

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