An Acad Bras Cienc (2022) 94(Suppl. 3): e20211501 DOI 10.1590/0001-3765202220211501
Anais da Academia Brasileira de Ciências | *Annals of the Brazilian Academy of Sciences*
Printed ISSN 0001-3765 I Online ISSN 1678-2690
www.scielo.br/aabc | www.fb.com/aabcjournal

HEALTH SCIENCES

COVID-19 and Acute Kidney Injury – Direct and Indirect Pathophysiological Mechanisms Underlying Lesion Development

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Abstract: COVID-19 is a pandemic disease caused by the SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) responsible for millions of deaths worldwide. Although the respiratory system is the main target of COVID-19, the disease can affect other organs, including the kidneys. Acute Kidney Injury (AKI), commonly seen in patients infected with COVID-19, has a multifactorial cause. Several studies associate this injury with the direct involvement of the virus in renal cells and the indirect damage stimulated by the infection. The direct cytopathic effects of SARS-CoV-2 are due to the entry and replication of the virus in renal cells, changing several regulatory pathways, especially the renin-angiotensin-aldosterone system (RAAS), with repercussions on the kallikrein-kinin system (KKS). Furthermore, the virus can deregulate the immune system, leading to an exaggerated response of inflammatory cells, characterizing the state of hypercytokinemia. The such exaggerated inflammatory response is commonly associated with hemodynamic changes, reduced renal perfusion, tissue hypoxia, generation of reactive oxygen species (ROS), endothelial damage, and coagulopathies, which can result in severe damage to the renal parenchyma. Thereby, understanding the molecular mechanisms and pathophysiology of kidney injuries induced by SARS-COV-2 is of fundamental importance to obtaining new therapeutic insights for the prevention and management of AKI.

Key words: Acute kidney injury, angiotensin, coronavirus, inflammation, SARS-CoV-2.

INTRODUCTION

In December 2019, the attention of health authorities turned to COVID-19, a disease caused by the SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) responsible for millions of deaths worldwide (Chen et al. 2020). The clinical spectrum of the disease ranges from typical symptoms of upper respiratory tract infection to more severe complications, such as pneumonia and severe acute respiratory syndrome (SARS) (Qi et al. 2021). Although the respiratory system is the main target of COVID-19, the disease can also have repercussions on other organs, including the kidneys (Perico et al. 2020, Adapa et al. 2020, El-Sayed et al. 2021).

Studies investigating renal involvement in the course of COVID-19 disease are still limited. However, growing evidence indicates that renal changes are frequent and can range from mild proteinuria to more severe acute renal injury (AKI) (Li et al. 2020c, Adapa et al. 2020, El-Sayed et al. 2021, Almeida et al. 2021). AKI is a clinical syndrome characterized by a sudden decline in glomerular filtration rate (GFR), which may

result in increased serum levels of nitrogen slag, changes in hydro electrolytic homeostasis, and acid-base imbalance (KDIGO 2012). Recently, several studies have demonstrated the occurrence of AKI in the course of the disease of the new Coronavirus (Zhou et al. 2020, Li et al. 2020a, El-Sayed et al. 2021). AKI is a prevalent complication among patients with COVID-19 and an indicator of disease severity, whose incidence ranges from 30% to 50% in patients hospitalized in the intensive care unit (ICU) (Ahmadian et al. 2020, Cheng et al. 2020b, Cummings et al. 2020). Evidence also points out that chronic kidney disease (CKD) and elevated serum creatinine levels may represent a higher risk for developing more severe forms of COVID-19, with an important impact on the morbidity and mortality of hospitalized patients (Adapa et al. 2020).

The underlying mechanisms of SARS-CoV-2-induced AKI are not yet fully understood. However, several factors may be involved in the pathogenesis of renal damage, including mainly local and systemic inflammatory responses, endothelial dysfunction, hypercoagulation, and imbalance of the renin-angiotensin-aldosterone system (RAAS) (Qu et al. 2014, Li et al. 2020d, Santoriello et al. 2020, Hamming et al. 2004). Although still controversial, evidence suggests that the activation of these pathophysiological mechanisms is due to direct viral infection, due to the renal tropism of the virus, and/or indirect factors widely present in critically ill patients who need ventilatory and hemodynamic support (Ames et al. 2019, Ronco & Reis 2020). Thus, the current literature highlights two main hypotheses to explain AKI: the *hypothesis of direct tissue injury* and the *hypothesis of indirect tissue injury*.

The first hypothesis, or *hypothesis of direct tissue injury,* is based on the ability of the circulating virus to enter the renal tubular cells through the angiotensin-converting enzyme 2 receptor (ACE2) expressed on proximal tubule cells, which is the main portion affected in kidney injury. ACE2 is a zinc metalloprotease, which shares homology with the angiotensin-converting enzyme (ACE) in its catalytic domain and provides different critical functions in the RAAS (Donoghue et al. 2000). Thus, when the virus enters and multiplies in renal cells, several pathophysiological mechanisms are activated, including the main dysregulation of RAAS, kallikrein-kinin system (KKS), and inflammatory pathways which culminate in acute tissue injury (Chu et al. 2005, Bradley et al. 2020). On the other hand, the second hypothesis is based on a series of systemic developments resulting from initial viral infection, including exacerbation of the immune response and circulatory and hemodynamic changes (Santoriello et al. 2020, Qin et al. 2020).

Given the clinical importance of the kidney repercussions associated with COVID-19 in hospitalized patients, as well as its impact on the quality of life of these patients after the hospitalization period, the elucidation of the pathophysiological mechanisms underlying SARS-CoV-2-induced AKI is essential to characterize the spectrum of lesions, as well as to define the appropriate and most effective therapeutic approach for each case. Therefore, the main objective of this article is to discuss current information on the pathophysiological aspects underlying SARS-CoV-2-induced AKI, exploring the direct and indirect molecular mechanisms involved in the development of lesions.

MATERIALS AND METHODS

We performed the bibliographic search in the MedLine/PubMed electronic databases. The initial literature screening was based on the

title and abstract, using the following keywords: COVID-19, SARS-COV-2, acute kidney injury, renal, histopathology, pathophysiological mechanisms, and pathophysiology. Targeted searches were conducted using terms such as inflammation, complement system, RAAS, ACE2, kallikrein-kinin system, and coagulopathy. We made no restrictions on the publication dates of articles. The articles were independently selected by three authors, which included publications from 1998 to 2021.

PATHOPHYSIOLOGICAL MECHANISMS BASED ON THE HYPOTHESIS OF DIRECT TISSUE DAMAGE

Evidence of the presence of SARS-Cov2 in the renal cells

The hypothesis of direct tissue injury is based on the ability of SARS-CoV-2 to enter and replicate in the kidney cells, with consequent activation of several signaling pathways capable of deregulating cellular homeostasis, culminating in structural changes and loss of its functions (Ahmadian et al. 2020). This hypothesis has been supported by some studies that have demonstrated evidence of direct viral infection through the detection of SARS-CoV-2 mRNA and proteins in tubular and glomerular recurrent cells (Chu et al. 2005, Ahmadian et al. 2020, Yin & Wunderink 2018).

Histopathological and immunohistochemical analyses of renal tissue in patients with COVID-19 have contributed both to the characterization of lesions and the identification of antigenic particles in different segments of the nephron. In this sense, studies with transmission electron microscopy have identified the presence of virus-like particles in the cytoplasm of the proximal tubular epithelium, podocytes, and to a lesser extent in the distal tubules (Su et al. 2020, Diao et al. 2021, Werion et al. 2020, Bradley et al. 2020). Some studies have also demonstrated the presence of SARS-CoV-2 by immunohistochemical expression of viral nucleocapsid protein (NP) antigen in renal tubules (Diao et al. 2020, Szabolcs et al. 2021). In addition, coronavirus-like particles were observed in vacuoles or cisterns of the rough endoplasmic reticulum (RER) and the smooth endoplasmic reticulum (REL) in cells of the proximal tubule by electron microscopy (Werion et al. 2020). These findings agree with those reported by Diao et al. (2020) who demonstrated that infected renal cells of the proximal tubules were quite swollen, with expansion and structural impairment of RER, REL, mitochondria, and lysosomes.

The presence of viral fragments in the urine is also a strong indication of direct infection of SARS-CoV-2 in the kidneys. In this sense, Caceres et al. (2021) observed that among 52 patients with COVID-19, 20 (39%) SARS-CoV-2 U-viral load, of which 17 developed AKI with an average U-viral load four-times higher than patients with COVID-19 who did not have AKI. The predilection of the virus for the kidneys can be partially explained by the fact that urine is an acidic environment, which allows the activation of the enzyme cysteine cathepsins, a primary protease pointed out to facilitate the entry of the virus into renal cells through endocytosis (Chong & Saha 2021). On the other hand, some studies have not observed the presence of SARS-CoV-2 viral particles or RNA in the kidney of patients with COVID-19 (Bradley et al. 2020, Wu et al. 2020, Sharma et al. 2020, Kudose et al. 2020). However, it is not possible to completely rule out the presence of the virus in renal tissue in these studies due to the possibility that viral particles are in concentrations below the detection limit.

Therefore, collectively all these findings strongly suggest that COVID-19-induced AKI may involve direct infection of SARS-CoV-2 in

the renal cells, triggering several mechanisms that culminate in the development of lesions in several parts of the nephron.

SARS-Cov-2 entry mechanisms in the cells

It is well established that SARS-CoV-2 uses the angiotensin-2-converter enzyme (ACE2) to enter host cells. In 2003 it was described as a receptor for the Severe Acute Respiratory Syndrome (SARS) coronavirus (Li et al. 2003). ACE2 is an insoluble transmembrane metalloprotease homologous to ACE, 42% sequence identity and 61% sequence similarity (Donoghue et al. 2000). Despite this, ACE2 contains a single zinc-binding domain HEXXH, which is homologous to the active sites of ACE, it is not inhibited by ACE inhibitors. This enzyme exists both as a membrane-associated form and as a secreted form, being widely distributed in cells of various body structures, such as the heart, lung, testicles, hypothalamus, and kidneys (Donoghue et al. 2000, Li et al. 2020c). ACE2, in addition to playing a relevant role in the route of direct infection by SARS-CoV-2, is also part of a regulatory system called the renin-angiotensin-aldosterone system (RAAS). This system consists of a complex and elegant cascade of regulatory and counterregulatory vasoactive peptides responsible for controlling blood pressure, acting both systemically and locally in the kidneys to regulate vascular tone, renal sodium reabsorption, and extracellular fluid volume (Ames et al. 2019). Furthermore, the deregulation of this system is widely associated with the progression of lesions, with induction of pro-inflammatory and profibrotic pathways in various types of renal diseases, including COVID-19-induced AKI (Chong & Saha 2021, Xu et al. 2017). Although a broader approach to RAAS is beyond the scope of this article, Figure 1 provides an overview of the operation of the classical axis (vasoconstrictor) and the non-classical axis (vasorelaxant) of this system. Briefly, this system starts with the production of angiotensinogen in the liver, which will be cleaved into angiotensin (Ang) I by renin, an enzyme synthesized and released in the kidneys in response to stimuli related to low blood pressure. From then on, the system is divided into two distinct and antagonistic axes: the classic and non-classic axes (Povlsen et al. 2020). The classic axis is described by the conversion of Ang I into Ang II, through ACE, and the consequent binding of this peptide to the type 1 Ang II receptor (AT1-R), leading mainly to vasoconstriction. On the other hand, the most important active peptide of the non-classical axis is Ang 1-7, which is generated from the hydrolysis of Ang II by the ACE2 action. ACE2 can also convert Ang I to Ang 1-9, which in turn is cleaved by neutral endopeptidase (NEP) or ACE to produce Ang 1-7. Finally, Ang I can also be cleaved to Ang 1-7 by the prolyl carboxypeptidase of Ang II or directly by the action of NEP. Thus, Ang 1-7 binds to its MAS receptor (MAS-R), producing, among other effects, increasing endothelial function, potent vasodilation, anti-cardiac hypertrophy, besides anti-fibrotic, anti-inflammatory, and anti-apoptotic effects (Ferreira & Santos 2005, Jiang et al. 2014, Santos et al. 2003).

Studies report that the SARS-CoV-2 virus has an envelope of glycoproteins, whose subunit S1 binds to the ACE2 receptor present on the cell surface, allowing its transport through the cytoplasmic membrane (Soleimani 2020, Hoffmann et al. 2020). In the kidney, it was observed that the expression of the ACE2 receptor occurred sharply in the proximal tubules, followed by a smaller extent in the podocytes, and rarely found in the glomeruli (Mizuiri & Ohashi 2015, Perico et al. 2020, Hamming et al. 2004, Pan et al. 2020). In one of the first histopathological analyses of renal tissue in patients with AKI and positive for COVID-19, it was found that the SARS-CoV-2 ACE2 receptor

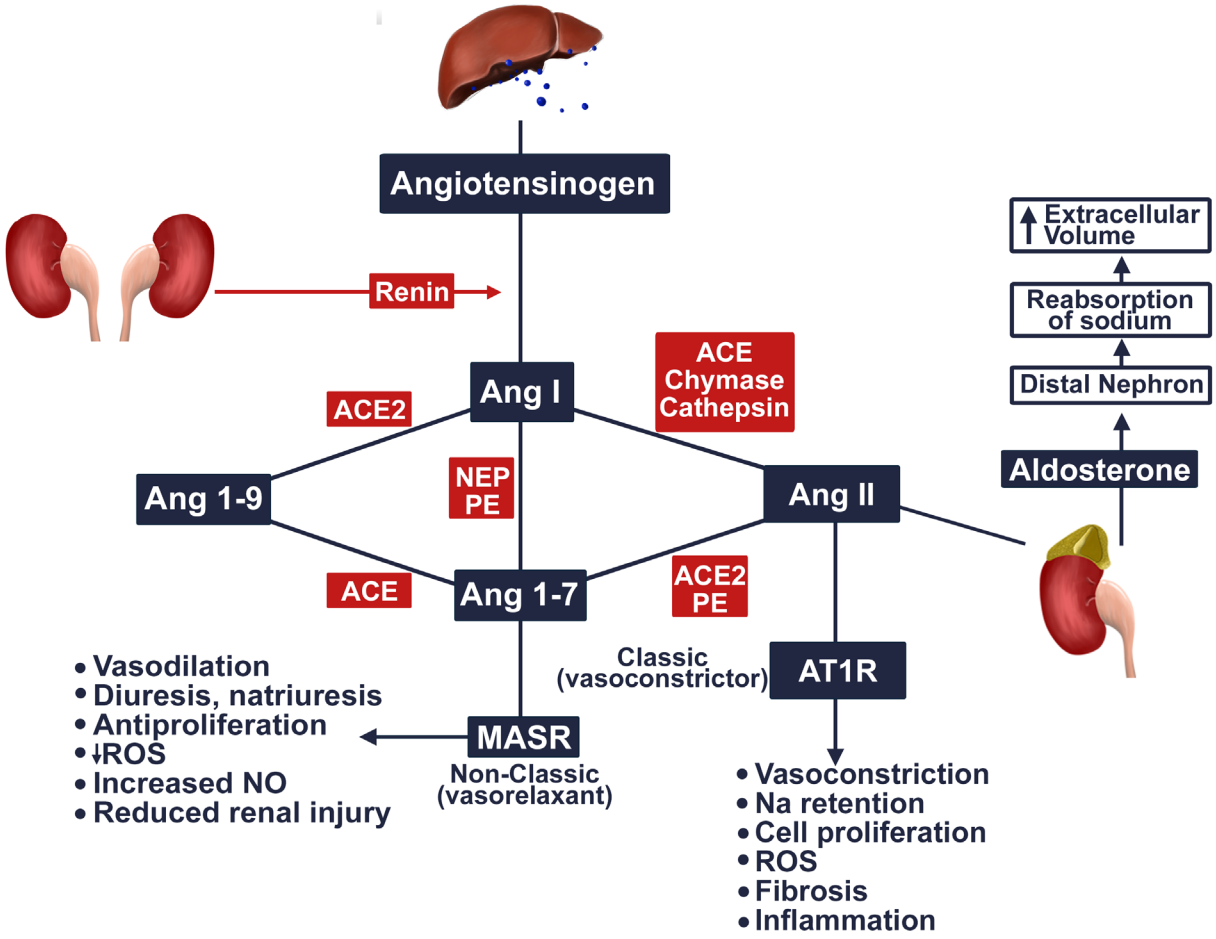

Figure 1. Classical and non-classical axis of the renin angiotensin aldosterone system. Renin, produced in the kidneys, cleaves the angiotensinogen synthesized in the liver to form angiotensin (Ang) I, which will later be converted into Ang II through the action of the Angiotensin-Converting Enzyme (ACE). Other enzymes, including chymase and cathepsin, serve as an alternative pathway for converting Ang I to Ang II. Ang I also serves as a substrate for neprilysin (NEP) and prolyl endopeptidase (PE), which cleaves it to form Ang 1-7. Furthermore, PE is able to cleave Ang II into Ang 1-7. Another important enzyme for the functioning of this system is the ACE2, responsible for the transformation of Ang I into Ang 1-9 and Ang II into Ang 1-7. Ang II, in addition to stimulating the production of aldosterone in the adrenal gland, binds to its AT1 receptor (AT1R) to activate the classic axis of this system. On the other hand, Ang 1-7 binds to its MAS receptor (MASR), activating the non-classical axis, capable of neutralizing the vasoconstrictor axis.

was upregulated in the proximal tubular cells, especially in areas with an acute injury (Su et al. 2020). It is noteworthy to note that this increase was not related to therapeutic measures, since, when necessary, these patients were treated with calcium channel blockers for hypertension, while ACE inhibitors or angiotensin receptor blockers, indicated as supposedly responsible for the overregulation of these receptors, were not used (Su et al. 2020).

In addition to the ACE2 receptor, auxiliary proteins belonging to protease families, such as transmembrane serine protease 2 (TMPRSS2), act as co-receptors in collaboration with ACE2, cleaving the viral S protein and thus facilitating the entry of coronavirus into target cells (Soleimani 2020, Hoffmann et al. 2020, Zhou et

al. 2015). Unlike airway epithelial cells, studies report that tubular cells express very low levels of TMPRSS2 (Soleimani 2020, Vaarala et al. 2001, Lucas et al. 2008). However, these cells express abundant levels of primary protease potentials that can replace TMPRSS2, including cathepsin cysteine protease B/L, glutamyl aminopeptidase, and protease serine dipeptidyl peptidase 4 (DPP4) (Soleimani 2020, Nistala & Savin 2017, Girardi et al. 2001, Qi et al. 2020), thus facilitating the entry of SARS-CoV-2, especially into proximal tubule cells.

Another possible input route of SARS-CoV-2 into the cell is via CD147/basigin. CD147 is a transmembrane glycoprotein belonging to the immunoglobulin family, also known as extracellular matrix metalloproteinase inducer (EMMPRIN), which interacts with several other proteins, including caveolin-1, integrins, and cyclophilins, the latter having an important role in the coronavirus replication process (Wang et al. 2020). In normal kidneys, CD147 is highly expressed only on the basolateral side of tubular epithelial cells (Kosugi et al. 2015). However, the expression of CD147 was also observed in interfacial and apical sides and in some podocytes and parietal cells in the kidneys of patients with COVID-19 (Su et al. 2021). Therefore, all this evidence suggests that after causing the lung infection, the virus can enter the bloodstream, accumulate in the kidneys and cause damage to kidney cells. Figure 2 summarizes the possibilities of entry of SARS-CoV-2 into the host cell, as well as the interaction between the receptor and the cell co-receptor with the virus spike protein.

Direct mechanisms of tissue injury by SARS-CoV-2

The pathophysiological mechanisms underlying direct lesions induced by SARS-Cov-2 are not yet fully understood. However, evidence suggests that after the entry of the virus into the kidney cells, the main mechanisms of injury include the deregulation of RAAS and the kallikrein-kinin system (KKS), and the escalation of the inflammatory process, vascular permeability, vasoconstriction, and production of reactive oxygen species (ROS) (Figure 2).

As mentioned, ACE2 is very important for the balance of RAAS axes through the production of Ang (1-7), whose biochemical and functional features promote several cytoprotective effects that counter-regulate the effects of Ang II, including potent vasodilator and antiproliferative effects (Ferreira & Santos 2005). Furthermore, Ang (1-7) confers a renoprotective effect reducing the inflammatory process, vasoconstriction, and thrombotic events (Mizuiri & Ohashi 2015). However, when using the ACE2 receptors to enter the cell, SARS-CoV-2 negatively regulates its expression either by sequestration and internalization or by cleavage of its extracellular domain (Nicolau et al. 2020). Thus, the pathological process mediated by COVID-19 is associated with the deregulation of RAAS due to excessive concentrations of Ang-II in circulation and increased activation of the AT1 receptor, resulting in the exacerbated activation of its classical axis. The Ang-II surplus, in turn, promotes a decrease in renal blood flow through its vasoconstrictive property, besides enabling the increase of the inflammatory process, cell proliferation, and generation of ROS (Mizuiri & Ohashi 2015). Therefore, it is possible that patients diagnosed with COVID-19 may develop AKI due to ischemia secondary to vasoconstriction and decreased renal perfusion (Chong & Saha 2021, Ng et al. 2020).

Additionally, the lower expression of ACE2 receptors in the renal endothelium also generates disorders in the KKS, which further aggravates the scenario of tissue injury. This system is involved in inflammatory processes,

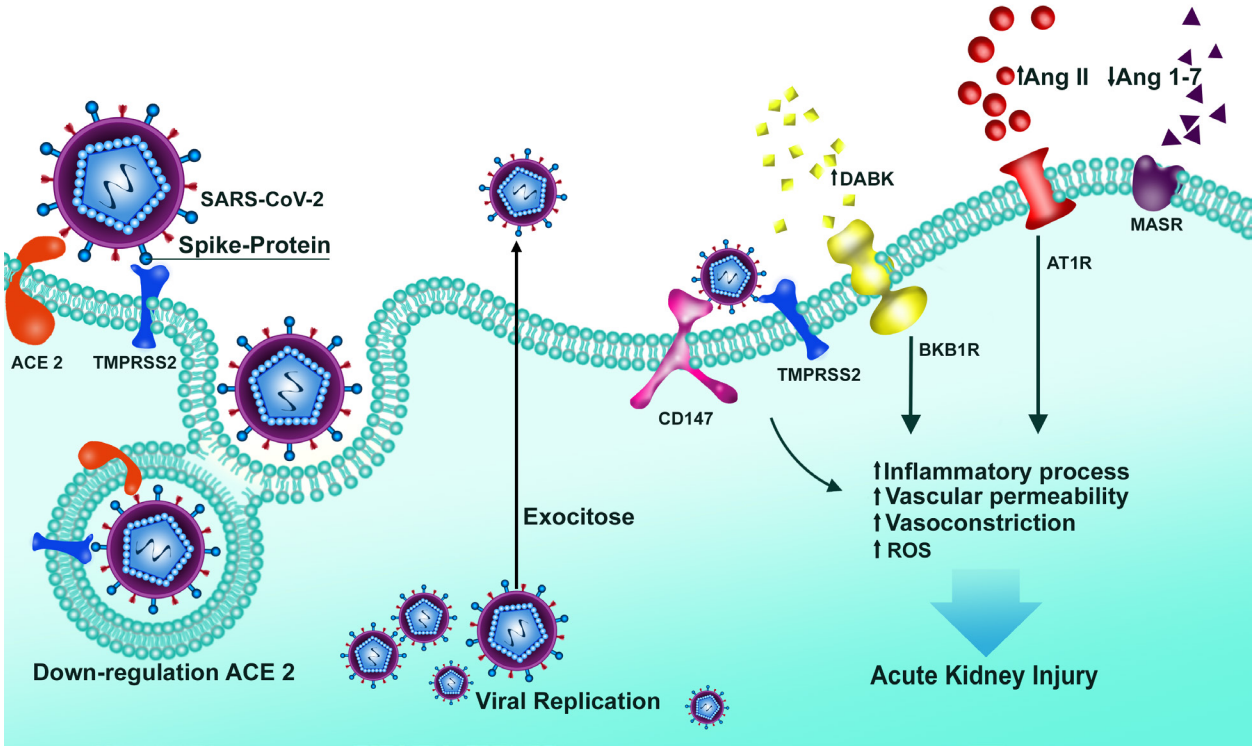

Figure 2. Direct effects of SARS-CoV-2 associated with acute kidney injury. SARS-CoV-2 invades the host cell through interaction with ACE2 present in the cell membrane. For this, the presence of co-receptors that contribute to the spike protein cleavage and subsequent virus internalization is necessary. Among the possible auxiliary proteins, TMPRSS2, cysteine cathepsin B/L, glutamyl aminopeptidase, and serine protease dipeptidyl peptidase 4 (DPP4) stand out. Virus entry can also occur through CD147, a glycoprotein present on the basolateral and apical face of cells from patients with COVID-19. Down-regulation of ACE2 stimulates hyperactivation of the classical RAAS axis, as well as the DABK-BKB1R axis of the kallikrein-kinin system. CD147, in addition to facilitating the entry of the virus, induces the expression of inflammatory cytokines. These events contribute to viral pathogenesis by aggravating kidney damage.

control of vascular tone, electrolyte transport, and cell proliferation (Pesquero & Bader 1998). Normally, kallikrein is activated by the Hageman factor in tissue injury situations and, once active, converts kininogen into kinins, among which stands out bradykinin, a peptide responsible for vasodilation and increased capillary permeability (Ramalho 2000). Bradykinin is rapidly cleaved by ACE in des-arg-bradykinin (DABK), a pro-inflammatory metabolite, which in turn is hydrolyzed by the action of ACE2 (Ramalho 2000, Sodhi et al. 2018). It is assumed that the downregulation of ACE2, induced by SARS-CoV-2 in the process of cell infection, results in the accumulation of DABK in the tissue, activating pro-inflammatory pathways that aggravate the damage of the renal parenchyma, as it occurs in the lungs (Mahmudpour et al. 2020, Nicolau et al. 2020). ACE2 proteolytic activity is inhibited after coronavirus cell infection, which turns it unable to inactivate DABK. As described by Oliveira et al. (2021), under this condition, the lung environment is prone to kinin-dependent local vascular leakage leading to angioedema via B1R and eventually B2R. Also, in that study, it was described that this blockade leads to increased Ang II levels, which stimulates the non-blocked angiotensin II receptor, AT2R, and triggers intracellular acidification by inhibiting the amiloride-sensitive Na+/H+ exchanger (Oliveira

et al. 2021). In addition, stimulation of the AT2R by Ang II causes intracellular acidification that increases kininogenase activity by kallikrein activation, resulting in the kallikrein-kinin system stimulation via BK releasing (Tsutsumi et al. 1999).

The local inflammatory process following the entry of SARS-CoV-2 into the cell can also be mediated through CD147 (Sodhi et al. 2018). As stated earlier, this receptor has interaction with several proteins, such as cyclophilins, caveolin-1, and integrins (Chueh et al. 2020, Qu et al. 2014). Among the proteins that interact with CD147, cyclophilin has been the target of several studies in recent years, especially the A cyclophilin subtype (CyPA) (Liu et al. 2013, Tian et al. 2020, Li et al. 2020b, Liao et al. 2021). Although CyPA is found mainly in the intracellular environment, it can be secreted in the extracellular medium due to inflammatory stimuli. Its extracellular form interacts with the CD147 receptor performing its chemotactic activities for monocytes, neutrophils, and eosinophils (Qu et al. 2014). Thus, from immunostaining of renal tissue samples biopsied from patients with SARS-CoV-2, Su et al. (2021) observed increased CyPA expression in the tubular epithelium, as well as in podocytes and parietal cells, which may partially explain the inflammatory process present in the renal tissue of these patients. On the other hand, it is known that CyPA plays an important suppressive role in the development of TCD4+ cells, so the positive regulation of these primary proteases may be related to the records of lymphocytopenia observed in patients with COVID-19 (Su et al. 2021, Guan et al. 2020).

Finally, CD147 involvement was also demonstrated in inflammatory processes in experimental AKI models. Kato et al. (2009) demonstrated that CD147 was associated with massive recruitment and infiltration of inflammatory cells in the renal tissue of CD147-positive mice with ischemia/reperfusion-induced AKI. However, when the mice CD147 deficient were analyzed, there was a decrease in the recruitment and infiltration of inflammatory cells in the tubular interstitium and greater preservation of renal function of these animals (Kato et al. 2009).

PATHOPHYSIOLOGICAL MECHANISMS BASED ON THE HYPOTHESIS OF INDIRECT TISSUE DAMAGE

In addition to the damage caused by the direct cytopathic effects of SARS-CoV-2 under the host renal cells, the virus can also induce an exaggerated systemic immune response responsible for several pathophysiological changes, including hemodynamic changes, generation of ROS, and coagulopathies, which culminate in renal parenchyma involvement, endothelial damage, and serious repercussions to renal function. The indirect mechanisms of renal injury induced by COVID-19 are represented in Figure 3.

Cytokine storm syndrome

The inflammatory process associated with SARS-CoV-2 initially occurs in the lungs, as it is well known (Brandão et al. 2020). Then, at the systemic level, the immune response is responsible for neutralizing the viral replication process, limiting the spread of the virus, and performing the cleansing of infected cells (Ivashkiv & Donlin 2014, Li et al. 2020a). However, when super-activated, this response can generate a condition of widespread aggressive inflammation called hypercytokinemia or 'cytokine storm' (Noris et al. 2020). This cytokine storm generates especially damage to the pulmonary parenchyma, but also serious hemodynamic and circulatory repercussions capable of promoting extensive renal involvement (Chueh et al. 2020).

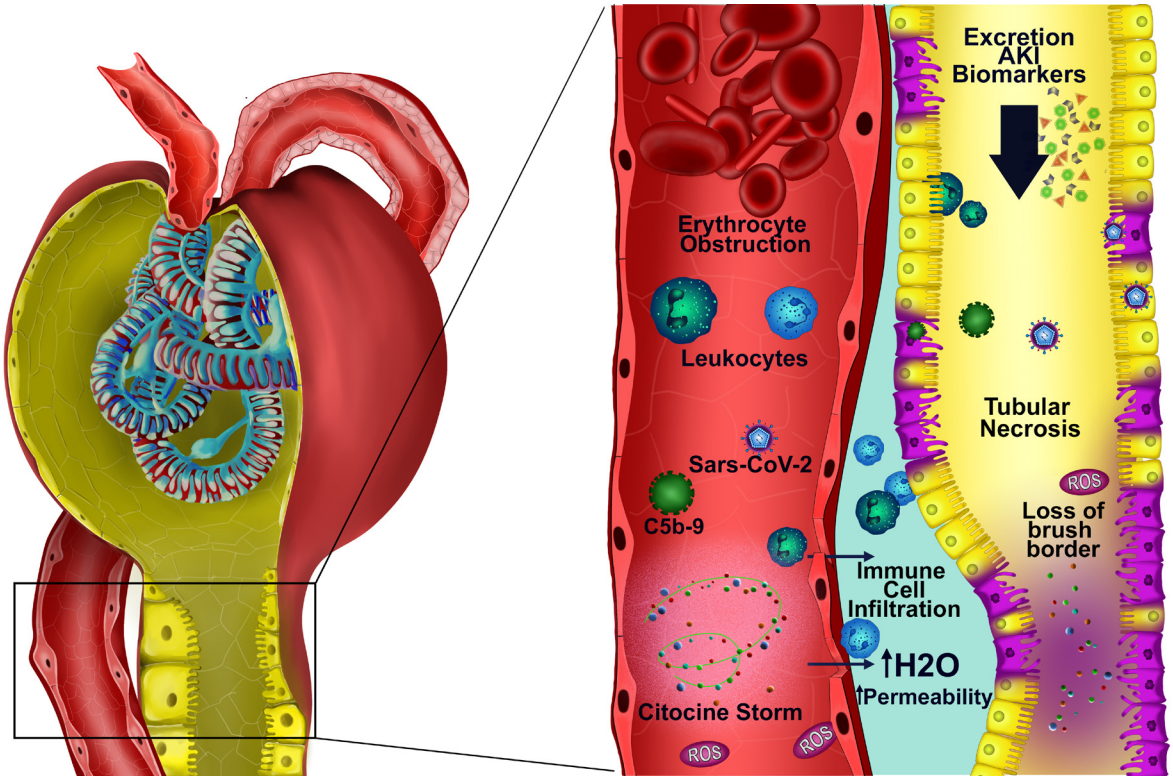

Figure 3. Indirect effects of SARS-CoV-2 associated with acute kidney injury. The hypercytokinemia contributes to the dysregulation of the coagulation pathways, complement system, increased endothelial permeability, and generation of reactive oxygen species (ROS). An erythrocyte aggregation can be noted, obstructing the capillary lumen, contributing to renal hypoperfusion. Furthermore, sites with low oxygen concentrations can contribute to the generation of ROS, further enhancing the reduction in arteriolar blood flow. Increased vascular permeability is associated with the inflammatory response, facilitating the passage of immune cells and water to the interstitial space, with the consequent formation of edema. SARS-CoV-2, ROS, leukocytes, and the deposition of the complement system (C5b-9) can potentiate damage to kidney cells. The reduction in renal perfusion, together with direct damage to the cells of the proximal tubule, allows for acute tubular necrosis (ATN) and loss of the brush border, progressing to AKI.

The exact mechanisms related to the outbreak of hypercytokinemia are not yet fully understood. However, it is known that some infections caused by viruses of the coronavirus family use mechanisms that control the host's immune response, delaying the initial response against infection (Totura & Baric 2012, Channappanavar et al. 2019). Such regulation can be observed with interferon (IFN), one of those responsible for the first line of defense against viral infections, through which the coronavirus induces a late response, making it difficult to clear viral in the body (Totura & Baric 2012, Channappanavar et al. 2019). This late signaling of type I interferon (IFN-I) promotes the accumulation of macrophage-monocytes, resulting in high levels of pro-inflammatory cytokines and chemokines, which characterize the subsequent exacerbated immune response (Channappanavar et al. 2016). Evidence indicates that this cytokine storm may be related to the severity, morbidity and mortality of coronavirus. In this sense, Chen et al. (2020) evaluated the plasma levels of cytokines in patients infected with the new coronavirus, finding that the levels of interleukin 2R (IL-2R), IL-6, IL-10, and

tumor necrosis factor α (TNF-α) were markedly higher in severe cases than in moderate cases. Overall, pro-inflammatory cytokines related to macrophages, particularly IL-6, IL-10, and TNF-α, were found to have increased significantly in most severe cases (Chen et al. 2020).

Another possible factor contributing to SARS-CoV-2-induced hypercytokinemia is lymphopenia. In this sense, it was demonstrated that patients with severe COVID-19 had a deeper reduction in the absolute number of total T lymphocytes, CD4, and CD8 T cells (Chen et al. 2020). Other observational studies have also reported lymphopenia as an important marker of immune system disorder, being present in most patients with COVID-19 during hospital admission (Qin et al. 2020, Huang et al. 2020, Guan et al. 2020). The mechanism underlying lymphocyte depletion is still poorly understood, but some studies attribute an important role to cytokines, claiming that pro-inflammatory cytokines derived from IFN-α/β or mononuclear macrophages induce T-cell apoptosis, which further hinders viral clearance and contributes to the extent of the inflammatory process (Ye et al. 2020). Another possible explanation would be direct infection of SARS-CoV-2 in lymphocytes since these cells express ACE2, which would allow the entry of the virus leading to activation and consequent cell death (Batlle et al. 2020).

Once installed, the storm of cytokines can trigger manifestations in different organs, including the kidneys. Studies have shown that hypercytokinemia may have contributed to the appearance of structural damage and changes in renal function through coagulation pathway disorders, complement system performance and dysregulation, and exaggerated recruitment of pro-inflammatory cells (Gómez-Escobar et al. 2021, Diao et al. 2020). Such alterations, in turn, are often associated with increased vascular permeability and the establishment of hemodynamic changes, triggering the reduction of renal perfusion and consequent acute tubular necrosis (ATN). Thus, ATN has been the main pathological change observed in patients with COVID-19 who developed AKI (Santoriello et al. 2020, Golmai et al. 2020, Volbeda et al. 2021, Ahmadian et al. 2020).

During cytokine storms, IL-6 plays an important role in the establishment of lesions due to its ability to induce the recruitment of other pro-inflammatory cytokines and chemokines (Machado et al. 2004, Brandão et al. 2020). Many studies have demonstrated the presence of elevated inflammatory markers, such as C-reactive protein (CRP), in patients with SARS-CoV-2 (Tarragón et al. 2021, Taha et al. 2021, Cheng et al. 2020a). This protein is synthesized by the liver in response to IL-6, which is a biomarker of inflammation widely associated with AKI (Smilowitz et al. 2021, Tarragón et al. 2021, Taha et al. 2021, Wang et al. 2021). The excessive number of inflammatory cells is capable of disrupting the homeostasis of the body, even interfering with the integrity of endothelial cells (Libby & Lüscher 2020). Desai et al. (2002) demonstrated that the increase in IL-6 concentrations was associated with endothelial barrier dysfunction, followed by an increase in renal vascular permeability. Increased vascular permeability is associated with facilitation in the entry of leukocytes and proteins, with consequent formation of edema in the renal interstitium, to increase the distance by which oxygen should diffuse and reach tubular tissue (Kinsey et al. 2008). In addition, cytokines and viral particles activate endothelial cells, which positively regulate the expression of adhesion molecules and monocyte chemoattractants. This leads to the recruitment of activated monocytes to the endothelial cells, as well as increased adherence of leukocytes and leukocyte-endothelium interactions, which allows the passage of leukocytes toward

the renal interstitium. Leukocytes coming out of peritubular capillaries are close to tubular epithelial cells and can directly induce the injury of these cells (Ostermann & Liu 2017) (Figure 3).

Hemodynamic instability

In addition to the tissue lesions themselves, cytokine storms can cause hemodynamic instability, with reduced renal perfusion and consequent damage associated with hypoxia and tissue ischemia (Chong & Saha 2021, Chueh et al. 2020). Sites with low oxygen concentrations may coexist with oxygenated regions of preserved tissue. Interactions between these areas are associated with increased generation of reactive oxygen species (ROS), which may further impair arteriolar blood flow, inducing damage to endothelial cells (Ostermann & Liu 2017, Legrand et al. 2008). It is also possible that hyperactivation of the classic axis of RAAS contributes to the depletion of renal perfusion. As illustrated in Figure 2, the downregulation of ACE-2 from the entry of SARS-CoV-2 in the intracellular medium favors the accumulation of circulating Ang II, which has vasoconstrictor, profibrotic, and pro-inflammatory effects, further reducing renal blood flow and enabling ischemia (Ames et al. 2019, Mizuiri & Ohashi 2015).

In a single-center study in the United States (USA), more than 60% of AKI cases were attributed to acute tubular injury due to ischemia or toxicity (Mohamed et al. 2020). In this sense, it is possible that the AKI observed in patients with COVID-19 may have one of its etiologies based on impaired perfusion of the kidneys. Thus, renal tissue biopsies revealed a diffuse lesion of the proximal tubule with ATN as the most common pathological alteration observed in patients with COVID-19 who developed AKI (Su et al. 2020, Chueh et al. 2020).

Dysregulation of complement

During COVID-19 infection, in addition to the inflammatory response mediated by cytokines and chemokines, there is also the participation of an integral component of the innate immune response, the complement system. This system consists of 3 main routes: classical route, alternative route, and lectin pathway. All these pathways converge in the cleavage of C3 in C3a (inflammation) and C3b (phagocytosis and opsonization). The C3b recruits the C5, cleaving it in C5a, which is a potent anaphylatoxin, as well as in C5b that is responsible for the formation of the membrane attack complex (MAC)/C5b-9 (Sim & Tsiftsoglou 2004). The activation of this system at the physiological level may favor the elimination of pathogens. However, when hyperactivated results in acute and chronic inflammation, tissue injury, and coagulation activation (Noris et al. 2020, Wang et al. 2015). High levels of C5a have been produced as a result of excessive complement activation and are involved in the recruitment of inflammatory cells such as neutrophils, eosinophils, monocytes, and T lymphocytes, activation of phagocytic cells, the release of enzymes based on granules, and generation of pro-oxidant agents (Guo & Ward 2005).

Currently, experimental models are lacking that explain the mechanisms by which the complement system is associated with the damage caused in the course of SARS-CoV-2. For this, some studies suggest mechanisms of injury based on previous analyses in the context of SARS and MERS infection. In an experimental study with C3 deficient mice infected with SARS-CoV, a less severe form of the disease was noted, where this group presented lower weight loss, respiratory dysfunction, and cytokine and chemokine levels compared to the group of wild mice (Gralinski et al. 2018). Jiang et al. (2018) evaluated complement cell levels in

MERS-CoV-infected mice, the results showed that circulating C5a concentrations increased, as well as the expression of their receptor (C5aR), associated with strong deposition of C5b-9 in bronchiolar epithelial cells, pneumocytes, and infiltrating leukocytes. Although the reported studies are related to SARS and MERS, as well as the observed elements are restricted to the respiratory system, these data together may provide additional information about COVID-19, even suggesting that the complement may affect other organs, including the kidneys. In line with this possibility, Diao et al. (2020) noticed through strong immunohistochemistry C5b-9 deposition in renal tissues of patients with AKI, when compared to patients without kidney injury, suggesting that SARS-CoV-2 infection induces NTA through the deposition of C5b-9.

Rhabdomyolysis

Rhabdomyolysis is a clinical syndrome in which skeletal muscle damage arising from direct traumatic injury, drugs, toxins, muscle ischemia, electrolyte, metabolic disorders, and infections results in the release of muscle contents into the circulatory system. This released intracellular content includes creatine kinase (CK), aldolase, lactate dehydrogenase (LDH), and myoglobin, a potentially nephrotoxic protein, leading to renal dysfunction (Souza et al. 2020, Torres et al. 2015). Viral infections can also cause muscle disorders, but influenza is the most common virus associated with rhabdomyolysis (Singh & Scheid 1996, Suwanwongse & Shabarek 2020). Recently, the presence of rhabdomyolysis has been reported in patients with COVID-19. Rhabdomyolysis may be the initial presentation of SARS-CoV-2 or occur at any time during the disease course (Suwanwongse & Shabarek 2020). A single-center retrospective observational study compared laboratory alterations found in patients infected with COVID-19 with and without AKI. Compared to patients without AKI, AKI patients had higher CK and LDH counts (Guanhua et al. 2021). Although this study did not evaluate the appearance of rhabdomyolysis preceding AKI, the alterations found are consistent with those induced by rhabdomyolysis.

Some hypotheses have been postulated to report the pathogenesis of rhabdomyolysis during a viral infection. First, direct invasion of the virus can lead to rhabdomyolysis. Secondly, the cytokine storm can cause muscle damage. Finally, circulating toxins can directly destroy muscle cell membranes (Suwanwongse & Shabarek 2020). However, the exact mechanism of COVID-19-induced rhabdomyolysis has not yet been proposed, but direct invasion and hypercytokinemia during SARS-CoV-2 resemble the mechanisms reported for other viral infections.

Endothelial dysfunction and hypercoagulation

The inflammatory response generated by SARS-CoV-2 is strongly related to the increase in coagulatory processes. This increased state of coagulation is almost always mediated by the tissue factor (TF) pathway. Usually, TF is not expressed in monocytes and endothelial cells. However, due to endothelial injury or specific stimuli from endotoxins and cytokines, these cells begin to express the TF (Merad & Martin 2020). The TF forms a complex with factor VII, stimulating the conversion of factor X into Xa. The latter factor plays a crucial role in the coagulation cascade, converting prothrombin into thrombin along with its cofactor Va. Large amounts of thrombin are formed, causing additional platelet activation, intensified fibrin formation from hepatic fibrinogen, and thrombus deposition at the injured site (Witkowski et al. 2016). Tissue factor inhibitor (TFPI), the main anticoagulant pathway, is almost always impaired in an inflammatory process, further accentuating the procoagulant state in the body (Merad & Martin

2020). Thrombosis plays a central role in COVID-19-related AKI since SARS-CoV-2 infection can trigger the activation of the coagulation cascade leading to renal vascular injury, with the development of ischemic glomeruli and fibrinoid necrosis (Cheng et al. 2020b). COVID-19 may predispose to venous and arterial thromboembolic disease due to excessive inflammation, hypoxia, immobilization, and diffuse intravascular coagulation (Klok et al. 2020).

Abnormalities involved in coagulation are associated with a poor prognosis and may represent the main cause of organ failure and death in patients with COVID-19 (Merad & Martin 2020). Tang et al. (2020) revealed that 21 of the 183 patients with COVID-19 died, and this group had higher levels of D dimer and fibrin degradation product (DDP), longer prothrombin time, and part-time thromboplastin activated compared to survivors on admission. In a study with 701 patients, 81.6% had high levels of erythrocyte sedimentation (Cheng et al. 2020a). Nevertheless, coagulation pathway abnormalities, including prolonged activation in Partial Thromboplastin Time and increased D-dimer, were more common in patients with elevated creatinine (Cheng et al. 2020a). Postmortem findings by Su et al. (2020) in patients with SARS-CoV-2 revealed a diffuse lesion of the proximal tubule with loss of brush edge, vacuolar degeneration, and frank necrosis on light microscopy, as well as aggregates of erythrocytes obstructing the lumen of the capillaries without the presence of platelet material (Figure 3). These findings favor ischemic injury and hypoxia of the kidneys by hypoperfusion and show the recurrence of coagulopathies in patients with COVID-19, as well as its important contribution to the onset of AKI (Cheng et al. 2020, Su et al. 2020a).

Finally, both the damage caused by infiltration of the virus into the renal parenchyma and the damage caused by indirect mechanisms are related to the findings of proteinuria and other biomarkers of kidney injury in infected patients, including elevation of serum creatinine and blood urea nitrogen (Rapkiewicz et al. 2020, Cao et al. 2020). In addition, tubular damage itself may be associated with a decrease in glomerular filtration rate (GFR), despite the lack of damage to the glomeruli itself. In the case of damage or dysfunction of tubular cells, sodium reabsorption in the proximal tubule is impaired by increasing the concentrations of sodium chloride arriving in the dense macula. This triggers tubuloglomerular feedback and leads to preglomerular vasoconstriction of the afferent arteriole, resulting in a decline in GFR (Ostermann & Liu 2017).

CONCLUSION

Acute kidney injury is a common complication in patients with COVID-19, with a high impact on morbidity and mortality, primarily characterized by acute tubular necrosis and renal dysfunctions. To date, the available studies suggest the involvement of a series of pathophysiological pathways in the development of lesions, which can be activated by the direct action of the virus in the cells, leading to hyperactivation of the classic axis of RAAS and repercussions in KKS, and by indirect mechanisms resulting from the repercussions of systemic viral infection that trigger an exaggerated inflammatory response, hemodynamic changes, tissue hypoxia, generation of ROS, endothelial damage and coagulopathies.

As perspectives, the elucidation of molecular pathways with the identification of key molecules involved in tissue damage is extremely important for the prevention and treatment of AKI, since it can contribute to the advancement of other research intended at the development of new drugs aimed at blocking

the entry of the virus into the cell, as well as in the control of immune responses.

Acknowledgments

This work was supported by the Institutional Program of Scientific Initiation Scholarship (PIBIC) from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Fundação de Amparo à Pesquisa do Estado da Bahia (FAPESB).

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How to cite

SILVA AVB, CAMPANATI JAG, BARCELOS IS, SANTOS ACL, DE DEUS UP, SOARES JC & AMARAL LSB. 2022. COVID-19 and Acute Kidney Injury – Direct and Indirect Pathophysiological Mechanisms Underlying Lesion Development. An Acad Bras Cienc 94: e20211501. DOI: 10.1590/0001-3765202220211501.

Manuscript received on November 29, 2021;
accepted for publication March 8, 2022

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LSBA conceived the idea and contributed to the review of the partial versions and the final version of the manuscript. AVBS, ACLS, ISB, and JAGC contributed to the research, data interpretation, and manuscript writing. UPD contributed to the production of the images. ISB and JAGC contributed to the translation of the manuscript. TJS, AVBS, ACLS, ISB, JAGC, and LSBA contributed to the revision of the final version of the manuscript. Each author made an important contribution during the writing of this review. All authors have given their final approval and agree with all aspects involved in the writing without any conflicts.