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Latent Acute Kidney Injury in COVID-19

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Summary. Since the outbreak of COVID-19, a bidirectional interaction between kidney disease and the progression of COVID-19 has been demonstrated. Kidney disease is an independent risk factor for mortality in patients with COVID-19, as well as severe acute respiratory syndrome coronavirus infection 2 (SARS-CoV-2), leading to the development of acute kidney injury (AKI) and chronic kidney disease (CKD) in patients with COVID-19. However, detection of kidney damage in patients with COVID-19 may only occur at a late stage based on current clinical blood and urine tests. Some studies point to the development of a subclinical acute kidney injury syndrome (subAKI) with COVID-19. This syndrome is characterized by significant interstitial tubular damage without altering the estimated glomerular filtration rate. Despite the complexity of the mechanism(s) underlying the development of subAKI, changes in the mechanism of protein endocytosis in proximal tubular epithelial cells have been proposed. This article focuses on data regarding subAKP and COVID-19, as well as the role of PTEC and the mechanism of endocytosis of their proteins in its pathogenesis.

Key words: COVID-19; kidney disease; renal protein reabsorption; proximal tubule; megalin; renin-angiotensin system.

Introduction

COVID-19, the syndrome caused by severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2), has had a major global impact since December 2019 [1–3]. Initially described as causing SARS associated with high mortality and morbidity, it is now generally accepted that COVID-19 contributes to multiple organ dysfunction [4,5]. Unprecedented scientific efforts have expanded our understanding of the pathogenesis and progression of the disease, leading to significant improvements in the clinical management of COVID-19, such as treatment with antivirals and monoclonal antibodies, as well as the development of standardized treatment protocols for hospitalized patients, as well as vaccination campaigns [6] . Despite these achievements, knowledge about the pathogenesis of multiple organ dysfunction in COVID-19 is still little known. The kidneys are a key target of SARS-CoV-2 [7–9]. Several reports indicate a high prevalence of acute kidney injury (AKI) in patients with severe COVID-19 [10–12]. Conversely, AKI and chronic kidney disease (CKD) are independent risk factors associated with COVID-19 severity and mortality [13–15]. According to the guidelines for improving kidney disease global outcomes (KDIGO), AKI is characterized by an increase in serum creatinine >0.3 mg/dL at 48 hours, a 1.5-fold increase in serum creatinine from baseline within 7 days and/or urine output <0.5 ml/kg/h for 6 hours [16]. However, an important trap is the threshold for serum creatinine sensitivity, which increases in response to a decrease in the estimated glomerular filtration rate (eGFR) >50% due to renal functional reserve [17]. This process delays the detection of kidney damage, which may be associated with a worse outcome in patients with COVID-19.

The use of biomarkers of tubular injury to determine early kidney injury has created a new concept called subclinical AKI (sub-AKI) [17, 18]. There is still no consensus on a specific definition of subOPP. Based

on recent reports, we suggest that subAKI represents a broad spectrum of parenchymal renal lesions without changes in glomerular function as defined by the KDIGO criteria associated with the presence of biomarkers of renal injury in urine [17-19]. Biomarkers of urinary tubular injury may include b2-microglobulin and kidney injury molecule 1 (KIM-1), markers of proximal injury, and neutrophil gelatinase-associated lipocalin (NGAL), a marker of distal injury [19]. The presence of these biomarkers in urine is usually associated with microalbuminuria [17–19]. Currently, sub-AKI is recognized as a new syndrome and risk factor for the development of AKI and CKD [17,18]. In addition, subAKI predicts adverse outcomes such as dialysis requirements and mortality in patients without established AKI [17,20]. Thus, early detection of subAKI may improve treatment and outcomes in patients with kidney injury. However, clinical data on the development of sub-AKI and its impact on the prognosis of COVID-19 are still poorly known. In this review, we discuss new insights into the possible development of subAKI in patients with COVID-19 and its possible harmful consequences. early detection of subAKI may improve treatment and outcomes in patients with kidney injury. However, clinical data on the development of sub-AKI and its impact on the prognosis of COVID-19 are still poorly known. In this review, we discuss new insights into the possible development of subAKI in patients with COVID-19 and its possible harmful consequences. early detection of subAKI may improve treatment and outcomes in patients with kidney injury. However, clinical data on the development of sub-AKI and its impact on the prognosis of COVID-19 are still poorly known. In this review, we discuss new insights into the possible development of subAKI in patients with COVID-19 and its possible harmful consequences.

COVID-19 and kidney disease

Data from the Acute Disease Quality Initiative workgroup show that approximately 20% of patients hospitalized with COVID-19 develop AKI, and the prevalence increases to approximately 50% in patients admitted to intensive care units [8]. A systematic review including 30,639 patients hospitalized with COVID-19 found similar results [11]. In addition, the use of renal replacement therapy has been observed to range from 9% in hospitalized patients to 20% in patients in the intensive care unit.

Conversely, renal dysfunction is an independent risk factor for poor prognosis in patients with COVID-19 [13-15]. A study using the OpenSAFELY platform, with records of approximately 17 million patients, showed that decline in kidney function, as measured by eGFR, is a key risk factor for COVID-related mortality [15]. Dialysis or kidney failure increases the risk of death from COVID-19 by 3.7 times. Patients with COVID-19 who develop AKI have lower eGFR than patients with AKI that does not depend on COVID-19. These observations support the idea that patients with COVID-19 develop more severe kidney damage [10–12].

An increasing number of reports suggest that patients with acute COVID-19 may experience persistent renal dysfunction after discharge [14,21–23]. Yende and Parikh [21] suggested that subclinical inflammation and damage may persist for many months after the diagnosis of COVID-19, which increases the risk of developing AKI and CKD. According to Al-Aly et al. [22] in a cohort study (followed by a 6-month follow-up) using the US Department of Health Veterans Affairs database observed that patients with COVID-19 have a higher risk of kidney injury even after the first 30 days of diagnosis. In another cohort study of 89,216 patients, COVID-19 survivors were shown to have an increased risk of developing AKI, decreased eGFR, progression to end-stage renal disease and serious kidney disease [23]. Despite evidence suggesting that decreased renal function may be a symptom of post-COVID, future clinical studies should test whether persistent kidney injury after acute COVID-19 is caused by SARS-CoV-2 infection and/or the result of medical restrictions during the pandemic. [24].

In a 6-month follow-up study by Huangiotensin et al. [25] showed that 13% of patients with COVID-19 without clinical AKI had a decrease in eGFR. This observation points to the development of an occult kidney injury, such as subAKP, during acute COVID-19. In a retrospective cohort study, markers of subAKI, such as proteinuria and urinary β2-microglobulin levels, were associated with COVID-19 severity and lower hospital discharge rates despite unchanged eGFR [26]. In a recent review by Legrand et al. [11] pointed to a possible role for subAKP in patients with COVID-19. They noted that late diagnosis based on KDIGO guidelines may contribute to a poor prognosis in patients with COVID-19. Although the development of AKI is usually associated with severe COVID-19, it has been shown that subAKI develops in patients with mild to moderate COVID-19, including children [27,28]. These observations highlight the

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importance of timely detection of subAKI in patients with COVID-19. In a prospective study, the presence of biomarkers in urine was associated with adverse renal outcomes in patients hospitalized with COVID-19 [29].

Proximal tubular epithelial cells are a target for the development of subAKI in patients with COVID-19.

A hallmark of subAKI is damage to the PT associated with a proinflammatory and profibrotic phenotype, resulting in interstitial tubular injury [17–19]. Interestingly, PTECs have been proposed as the main site of SARS-CoV-2 replication in the kidney [10,30]. Rahmani et al. [31] showed using scRNA sequencing that PTECs have a high potential co-expression of SARS-CoV-2 receptors and proteases involved in cell infection, such as ACE2, NPR-1, TMPRSS2, CTSB, and FURIN.

Alternative routes for infecting SARS-CoV-2 cells have also been proposed. Wang et al. [32] showed that CD147 mediates SARS-CoV-2 entry into VeroE6 cells (monkey kidney cells) and BEAS-2B cells (human bronchiolar cells). The authors found that human CD147 (also known as basigin) allows the virus to enter insensitive BHK-21 cells (hamster renal fibroblast cells). CD147 is highly expressed on the basolateral side of the PTEC [33]. Mori et al. [34] showed that LLC-PK1 cells (a porcine PTEC strain) expressed human KIM-1, which supported the uptake of a pseudovirus displaying the SARS-CoV-2 spike protein. Interestingly, KIM-1 is increased in PTEC with the development of sub-AKI and AKI [35,36].

Based on these observations, it is possible that direct infection of the PT epithelial cells (PTEC) with SARS-CoV-2 may be the central mechanism for the development of subAKI in patients with COVID-19. Agreeing with this, Caceres et al. [37] showed that there is a correlation between the presence of SARS-CoV-2 in the urine and the incidence of AKI and mortality in patients with COVID-19. However, there are still no studies showing a direct correlation between SARS-CoV-2 infection in kidney cells and the development of AKI in patients with COVID-19. Multiple organ damage may also be associated with the detrimental effect of SARS-CoV-2 on renal function, manifested by hemodynamic changes and/or exacerbated immune responses such as cytokine storms [1, 2, 4, 38]. PTECs express various cytokine receptors, including IL-6R [39], IL-4R [40], and TNF-_R [41]. There is an association between plasma levels of IL-6 and the development of AKI in patients with COVID-19 [40]. Medeiros et al [4] showed that COVID-19 associated AKI is accompanied by significant changes in circulating levels of immune mediators such as IFN-, IL-2, IL-6, TNF-_, IL-1Ra, IL-10 and VEGF. They hypothesized that this phenomenon may contribute to the onset of AKI. In another study using urine collected from 29 patients with COVID-19 admitted to the intensive care unit, a strong correlation was observed between pro-inflammatory cytokines and AKI [41]. That this phenomenon may contribute to the occurrence of AKI. In another study using urine collected from 29 patients with COVID-19 admitted to the intensive care unit, a strong correlation was observed between pro-inflammatory cytokines and AKI [41]. that this phenomenon may contribute to the occurrence of AKI. In another study using urine collected from 29 patients with COVID-19 admitted to the intensive care unit, a strong correlation was observed between pro-inflammatory cytokines and AKI [41].

Saigili et al. [28] have shown an association between the number of neutrophils and the development of AKI, pointing to the role of inflammation in this process. This hypothesis is supported by the observation in a comparative study that the prevalence of AKI in patients with COVID-19 is similar to that in patients infected with seasonal influenza [45]. Despite a similar prevalence, COVID-19 was associated with a higher risk of developing Int. AKI in initial stage 3 and higher rates of proteinuria than with influenza infection, suggesting that additional mechanisms are involved in COVID-19-associated kidney damage.

The role of albumin reabsorption in the proximal tubules in the development of subAKP.

It has been suggested that megalin-mediated protein reabsorption may initiate the interstitial tubular injury seen in subAKI [40]. Proteinuria is an independent risk factor for the severity of COVID-19, the development of AKI, and the progression of CKD [9-11]. The prevalence of proteinuria has been found to be high among patients with COVID-19, even in those who have not developed AKI [5]. In addition, a correlation has been demonstrated between proteinuria and glucosuria and the severity of COVID-19 disease [5,7]. These data point to the role of PT protein reabsorption in this process. In this context, we focused on the possible role of megalin, a proximal tubular epithelial cell protein receptor, as a sensor and

integrator between the development of tubular proteinuria and subAKI in patients with COVID-19.

Tubular proteinuria is associated with modifications of protein reabsorption in the epithelial cells of the proximal tubules, which occurs through the mechanism of receptor-mediated endocytosis [5,6]. The receptor is formed by the association of three proteins: megalin, cubilin, and amniophilin. Megalin (also known as LDL-related protein 2 [LRP2]) is a member of a family of LDL-like substances highly expressed in the luminal membrane of proximal tubular epithelial cells and plays a critical role in the internalization of the protein-receptor complex [6,7]. Megalin is considered to be a molecular platform that combines extracellular and intracellular signals and works as a sensor for changes in tubular albumin concentration, as well as a target for various signals. It works as a scaffold protein, anchoring various signaling and structural molecules, such as protein kinase B (Akt) [58], disabled homologue 2 (Dab2) [59], and autosomal recessive hypercholesterolemia (ARH) [6]. It is also a target for post-translational modifications such as phosphorylation, O-GlcNAcylation, and proteolysis [1–3].

It has been shown that megalin is involved in the survival and death of proximal tubular epithelial cells, regulation of the immune response, and their metabolism [8]. Long et al. [6] showed that megalin knockout (KO) modulates the expression of PI3K/Akt, genes associated with metabolism, pro-inflammatory response, and signaling pathways. An association between interstitial tubular injury and megalinum has been observed in lrp2 -/- mice [40,41], which exhibit some characteristics of proximal tubular epithelial cell dysfunction such as Fanconi syndromes, albuminuria, phosphaturia, glycosuria, and markers of tubular injury such as KIM- 1. [44]. Similar characteristics are observed in patients with Donne-Barrow/Facio-Oculo-Acoustico-Renal (DB/FOAR) syndrome caused by megalin loss-of-function mutations [67,68]. Megalin is also an antigenic target for anti-brush border antibody human kidney disease (ABBA disease), which causes primary interstitial renal tubular disease [9]. Megalin deficiency progresses to glomerular dysfunction, suggesting that tubular damage may precede glomerular dysfunction [18].

Kormann et al. [7] showed a high prevalence of Fanconi syndrome in a retrospective cohort of 42 patients with laboratory-confirmed COVID-19 without a history of kidney disease. The authors observed at least two PT anomalies (incomplete Fanconi syndrome) in 75% of patients. The main disorders were proteinuria (88% of patients), renal phosphaturia (55% of patients), hyperuricosuria (43% of patients) and normoglycemic glucosuria (30% of patients). Verion et al. [21] showed that patients with COVID-19 have low molecular weight proteinuria and increased urinary excretion of b2-microglobulin associated with decreased megalin expression and focal proximal tubular necrosis. Accordingly, proteomic analysis of urine samples from patients with COVID-19 revealed a decrease in megalin excretion. The authors suggested a possible correlation with a decrease in PT protein reabsorption, observed in patients with COVID-19 [22]. In addition, in a recent work, our group showed that the spike protein reduces megalin expression and albumin endocytosis in a PTEC model [23]. Importantly, these effects were not associated with changes in aquaporin 1, indicating a specific mechanism for albumin endocytosis.

Megalin and the renin-angiotensin system: a possible link between kidney damage and severe COVID-19.

The renin-angiotensin system (RAS) is formed by a complex network of peptides and proteases that play an important role in the control of the internal environment [36-38]. Two distinct types of RAS have been described: systemic and tissue. Despite the same structure, they are activated by different signals and play different roles in physiological and pathophysiological conditions [36–39]. The RAS includes two major axes: (1) angiotensin II receptor (Angiotensin II)/AT1 (AT1R) and (2) angiotensin-(1-7) (Angiotensin-(1-7) receptor/Mas (MASR) and Angiotensin II/ AT2 receptor (AT2R). Activation of the Angiotensin II/AT1R axis causes vasoconstriction, as well as pro-inflammatory and profibrotic effects [76,80-82], while activation of Angiotensin-(1-7)/MASR and/or Angiotensin II/AT2R compensates for these effects [35]. In this regard, angiotensin-converting enzyme type 2 (ACE2),

One attractive hypothesis is that SARS-CoV-2 cells promote overactivation of the Angiotensin II/(AT1R) axis due to ACE2 inhibition [19–21]. This inhibition includes spike-mediated SARS-CoV-2 binding to ACE2, leading to its cleavage and internalization [1]. Liu et al. [22] showed an increase in plasma angiotensin II levels in Chinese patients with COVID-19 in 2019, which was associated with viral load and lung damage. In addition, Zoufaly et al. [23] showed in a case report that treatment of a 45-year-old woman

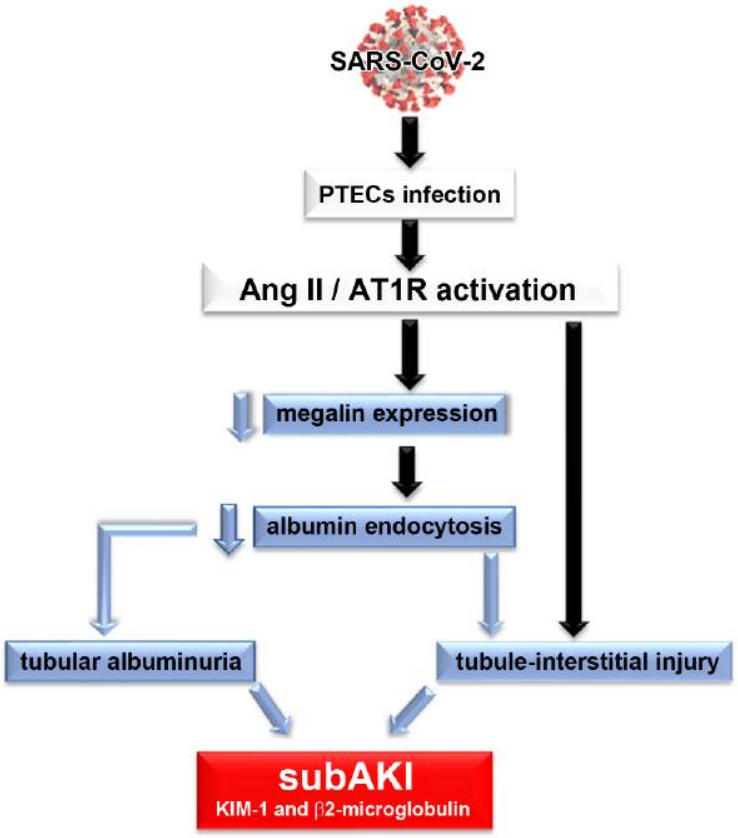
diagnosed with severe COVID-19 with human recombinant soluble ACE2 (hrsACE2) for 9 days reduced levels of Angiotensin II, pro-inflammatory interleukins such as IL-6 and IL- 8, inflammatory marker ferritin and C-reactive protein. These effects were followed by the recovery of the patient. The general consensus is that the severity of COVID-19 has been associated with elevated plasma levels of Angiotensin II [14].

On the other hand, some studies have found no change or even a decrease in plasma Angiotensin II levels in patients with COVID-19 [15,16]. However, the level of Angiotensin II in specific tissues was not assessed. Recently, Ensor et al. [17] observed that injection of spike protein into male mice increased lung angiotensin II levels and inhibited ACE2 activity in adipocytes. These results suggest that tissue RAS may play an important role in the development of kidney injury in patients with COVID-19, rather than systemic RAS. However, the question of how renal RAS correlates with the development of kidney damage in patients with COVID-19 remains open.

Conclusions and perspectives

The current literature shows a clear correlation between kidney injury and COVID-19 severity with PTEC as a target in this process [7-9]. The mechanism underlying the development of tubular injury likely involves a complex network leading to a proinflammatory and profibrotic phenotype. We postulate that megalin, a component of the albumin endocytosis mechanism, functions as a sensor in the development of renal tubular injury and tubular proteinuria observed in patients with COVID-19.

We hypothesized that the damage to the PT epithelium observed in patients with COVID-19 includes a decrease in ACE2 activity, leading to an increase in Ang II levels and subsequent activation of the Ang II/AT1R axis (Fig. 1). Once activated, the Ang II/AT1R axis promotes decreased megalin expression and albumin endocytosis, leading to tubular albuminuria, as seen in patients with COVID-19 [71]. Interstitial tubular injury, characterized by a proinflammatory and profibrotic phenotype, may result from modifications in the mechanism of albumin endocytosis and/or from direct modulation of the Ang II/AT1R axis-mediated immune response. Together, these factors contribute to the occurrence of subAKI in acute COVID-19.



Picture 1.A proposed model for the genesis of subclinical acute kidney injury in patients with COVID-19.

We hypothesized that SARS-CoV-2 PTEC infection promotes overactivation of the Ang II/AT1R axis, resulting in decreased megalin expression, decreased albumin endocytosis, and hence tubular albuminuria. The development of interstitial tubular damage may be caused by changes in the mechanism of albumin endocytosis as such and/or by a direct effect of overactivation of the Ang II/AT1R axis. All these conditions characterize the development of subOPP. In this case, tubular injury biomarkers such as KIM-1 and b2-microglobulins and albuminuria can be observed in patients' urine.

If the repair mechanism works and the damage stops, there is no progression of sub-AKI to AKI (Fig. 2A, B, blue dotted line). At the same time, a "fingerprint" is established, which increases the sensitivity of the epithelium to a new renal stroke. This process correlates with a higher risk of developing AKI and/or CKD in patients with COVID-19 (Fig. 2A, B, blue dotted line). On the other hand, if recovery mechanisms fail, AKI associated with decreased eGFR may develop, as seen in patients with severe COVID-19 (Fig. 2A, B, solid blue line). In patients with comorbidities, such as hypertension and diabetes, who already have kidney damage and activation of the renal Ang II/AT1R axis, an increase in the sensitivity of the system can be observed (Fig. 2A, B, solid red line). Thus,

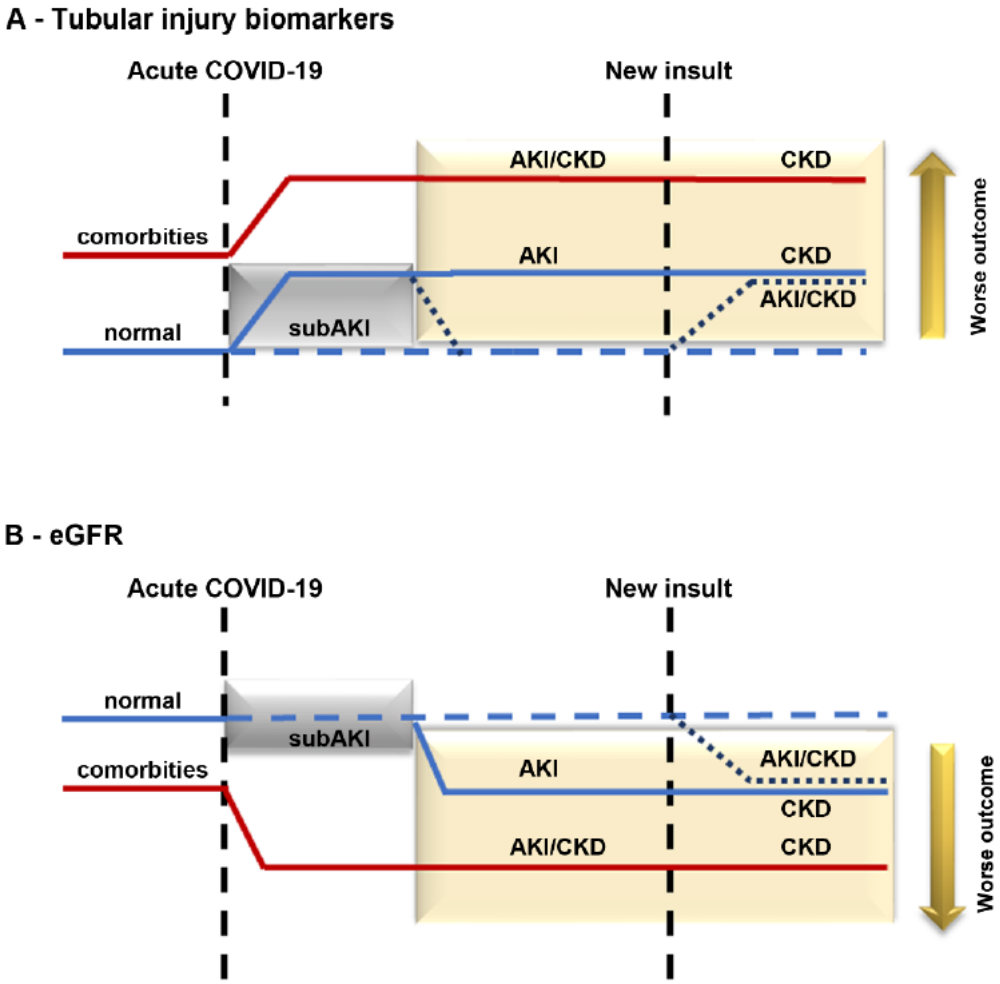


Figure 2.A proposed model for the progression of kidney disease in patients with COVID-19. Kidney injury in patients with COVID-19 without comorbidities (blue line) or with comorbidities (red line). In the acute phase, patients with COVID-19 develop sub-AKI (gray box) characterized by an increase in tubular injury biomarkers (A) without changes in eGFR (B). If the repair mechanism is working, the biomarker levels of tubular damage return to normal (dashed blue line). On the other hand, a subOPP can transition to an OPP if the recovery mechanism is insufficient (solid blue line inside the yellow box). In the case of patients with already established comorbidities such as hypertension and diabetes (solid red line), there may be an increase in tubular injury biomarkers and a decrease in eGFR. If these patients are infected with COVID-19, their kidney damage worsens, leading to more rapid progression of kidney damage. Patients with COVID-19 who develop any kidney injury, including sub-AKI (new stroke), are at higher risk of developing kidney disease after COVID-19.

Based on the discussion, we propose that biomarkers of proximal tubular injury be introduced into the clinical routine for patients with symptoms of COVID-19, especially those who require hospitalization or have comorbidities such as hypertension and diabetes. This process can be assessed by monitoring urinary excretion of b2-microglobulin and KIM-1 associated with microalbuminuria. These biomarkers are currently being tracked in specific clinical assays [22, 23]. This approach can detect the early stage of sub-AKI, allowing timely treatment and avoiding progression of kidney damage. Angiotensin II receptor blockers (ARBs) are used as first-line therapy to halt the progression of renal failure associated with decreased proteinuria independent of blood pressure in patients who do not have COVID-19 [24,25]. In an open randomized trial of 158 patients, Duarte et al. [26] showed that treatment with telmisartan (80 mg/2 times a day) for 14 days reduced C-reactive protein levels, time to discharge, and 30-day mortality. On the other hand, in a double-blind, randomized trial of 117 patients with symptoms of COVID-19, Puskarich et al. [27] did not observe any change in hospitalization for 15 days and viral load when treated with losartan (25 mg/2 times a day) for 10 days. To our knowledge, there are no studies reporting the effect of ARBs on kidney damage seen in patients with COVID-19 symptoms, and this hypothesis should be tested to confirm a possible beneficial effect. In an open randomized trial of 158 patients, Duarte et al. [26] showed that treatment with telmisartan (80 mg/2 times a day) for 14 days reduced C-reactive protein levels, time to discharge, and 30-day mortality. On the other hand, in a double-blind, randomized trial of 117 patients with symptoms of COVID-19, Puskarich et al. [27] did not observe any change in hospitalization for 15 days and viral load when treated with losartan (25 mg/2 times a day) for 10 days. To our knowledge, there are no studies reporting the effect of ARBs on kidney damage seen in patients with COVID-19 symptoms, and this hypothesis should be tested to confirm a possible beneficial effect. In an open randomized trial of 158 patients, Duarte et al. [26] showed that treatment with telmisartan (80 mg/2 times a day) for 14 days reduced C-reactive protein levels, time to discharge, and 30-day mortality. On the other hand, in a double-blind, randomized trial of 117 patients with symptoms of COVID-19, Puskarich et al. [27] did not observe any change in hospitalization for 15 days and viral load when treated with losartan (25 mg/2 times a day) for 10 days. To our knowledge, there are no studies reporting the effect of ARBs on kidney damage seen in patients with COVID-19 symptoms, and this hypothesis should be tested to confirm a possible beneficial effect. that treatment with telmisartan (80 mg/2 times a day) for 14 days reduced C-reactive protein levels, time to discharge, and 30-day mortality. On the other hand, in a double-blind, randomized trial of 117 patients with symptoms of COVID-19, Puskarich et al. [27] did not observe any change in hospitalization for 15 days and viral load when treated with losartan (25 mg/2 times a day) for 10 days. To our knowledge, there are no studies reporting the effect of ARBs on kidney damage seen in patients with COVID-19 symptoms, and this hypothesis should be tested to confirm a possible beneficial effect. that treatment with telmisartan (80 mg/2 times a day) for 14 days reduced C-reactive protein levels, time to discharge, and 30-day mortality. On the other hand, in a double-blind, randomized trial of 117 patients with symptoms of COVID-19, Puskarich et al. [27] did not observe any change in hospitalization for 15 days and viral load when treated with losartan (25 mg/2 times a day) for 10 days. To our knowledge, there are no studies reporting the effect of ARBs on kidney damage seen in patients with COVID-19 symptoms, and this hypothesis should be tested to confirm a possible beneficial effect. in a double-blind, randomized study of 117 patients with symptoms of COVID-19, Puskarich et al. [27] did not observe any change in hospitalization for 15 days and viral load when treated with losartan (25 mg/2 times a day) for 10 days. To our knowledge, there are no studies reporting the effect of ARBs on kidney damage seen in patients with COVID-19 symptoms, and this hypothesis should be tested to confirm a possible beneficial effect. in a double-blind, randomized study of 117 patients with symptoms of COVID-19, Puskarich et al. [27] did not observe any change in hospitalization for 15 days and viral load when treated with losartan (25 mg/2 times a day) for 10 days. To our knowledge, there are no studies reporting the effect of ARBs on kidney damage seen in patients with COVID-19 symptoms, and this hypothesis should be tested to confirm a possible beneficial effect.

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