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The etiology and pathophysiology of COVID-19 associated acute kidney injury

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ABSTRACT

Hospitalized COVID-19 patients often develop acute kidney injury (AKI), leading to increased mortality. In order to improve patients' survival rate, it is important to understand the pathophysiology mechanism of AKI. In this brief review, we highlight the most important elements of the etiology and pathophysiology of COVID-19 associated AKI. Acute tubular injury seems to be more frequent than prerenal azotemia in COVID-19 patients and collapsing glomerulopathy is the most encountered form of glomerular disease. Another important role in acute kidney injury seems to play immune cell infiltration, inflammation, endothelial injury and microvascular thrombi. Renin-angiotensin-aldosterone system is also important in the pathophysiology of COVID-19 associated AKI.

Keywords: COVID-19, AKI, etiology and pathophysiology, acute tubular injury, thrombotic microangiopathy, collapsing glomerulopathy

INTRODUCTION

The new coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is affecting the entire global population and the disease caused by it was named coronavirus disease 2019, or COVID-19 [1,2]. COVID-19 clinical presentations varied from asymptomatic / mild symptoms to critical illness and mortality. Common symptoms include headache, myalgia, taste and/or smell abnormalities, sore throat, diarrhea, shortness of breath, and cough. The most encountered significant manifestation of infection is pneumonia. SARS-CoV-2 pneumonia is clinically characterized by fever, cough, dyspnea, and imagistically by chest bilateral infiltrates [3-7].

In addition to lung damage, in COVID-19 patients, other organs may be affected, including the kidneys [4, 7]. AKI is a frequently encountered complication in hospitalized patients with COVID-19, with the incidence varying from 5% to 29%, causing increased length of hospital stay and mortality [8-12].

THE ETIOLOGY AND PATHOPHYSIOLOGY OF AKI IN COVID-19 PATIENTS

Various AKI etiologies have been identified in patients with COVID-19: complications caused by treatment, glomerulopathy, thrombotic microangiopathy, prerenal azotemia and acute tubular injury (Figure 1) [9,13-15].

Prerenal azotemia and acute tubular injury

Patients with COVID-19 may present at least one symptom that could cause hypovolemia (i.e. vomiting, fever, diarrhea). A study conducted by Mo-

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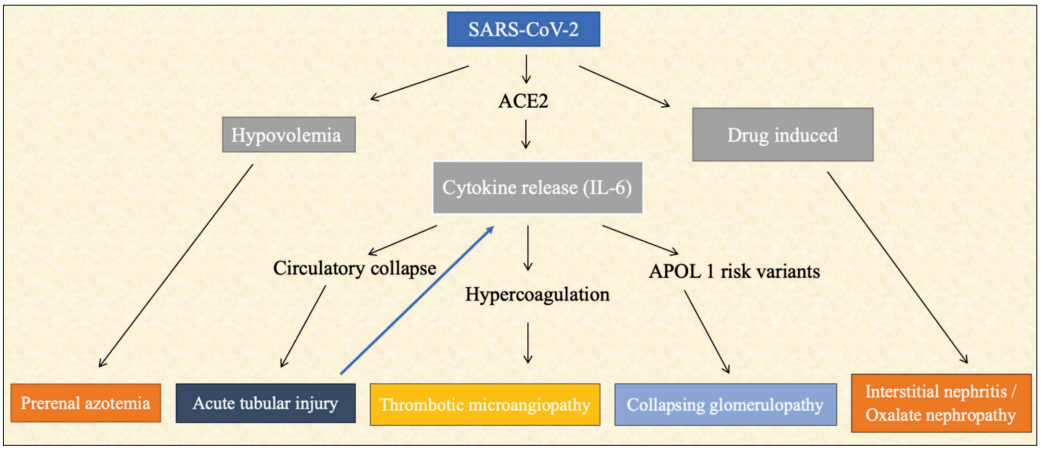

FIGURE 1. The etiology and pathophysiology of COVID-19 related to AKI [15].
SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2;
ACE2 = angiotensin converting enzyme 2; IL-6 = interleukin 6; APOL 1 = apolipoprotein L1

hamed et al. revealed that almost 10% of patients with COVID-19 diagnosed with AKI have prerenal azotemia [9,13,16]. In comparison with the general population, in COVID-19 patients, the etiology of the vast majority of AKI patients (almost 60%) is represented by acute tubular injury (from toxic or ischemic causes). These findings were emphasized by several studies based on kidneys histopathological examination [9,17-19].

It is demonstrated that hyperinflammation is an important factor in the pathogenesis of COVID-19. The main cytokine that propels hyperinflammation in COVD-19 patients is interleukin 6 (IL-6). It seems hyperinflammation associated with COVID-19 could cause acute tubular injury. It is also proven that in patients with AKI, an increased level of IL-6 could produce lung damage [18,20-23].

Additionally, there are other elements that can contribute to the development of acute tubular injury and/or prerenal azotemia (Table 1) [24,25].

TABLE 1. Elements that can contribute to the development of AKI in COVID-19 patients [24,25]

• Direct viral infection (controversial)
• Rhabdomyolysis
• Hypoxia
• Hypotension
• Nephrotoxic drugs (i.e. antivirals, antibiotics)
• Low cardiac output

Glomerulopathy

The most frequent form of glomerular disease associated with COVID-19 is collapsing glomerulopathy. This type of glomerular disease is common in patients with viral infections like Epstein-Barr, cytomegalovirus or HIV. Some studies have shown that this glomerulopathy is associated with non-severe COVID-19, more common in Afro-American patients frequently associating APOL1 risk genotypes [14,26-29]. Different types of glomerular diseases have also been reported in patients with COVID-19 (i.e. immunoglobulin A nephritis, ANCA-vasculitis, minimal change disease, anti-glomerular basement membrane disease, membranous nephropathy), which may show that there is no link between them and COVID-19, and they could be incidental [14,30-32].

Thrombotic microangiopathy

Studies have demonstrated that patients with COVID-19 present a higher incidence of lung macrovascular and microvascular thrombosis. In this type of patients, the presence of kidney thrombosis was also reported. It was documented that COVID-19 patients have endothelial injury (vascular endotheliitis) which increases vascular permeability, and, in association with platelet activation, represents a pro-thrombotic condition that leads to a poor prognosis [33-38]. It was observed in COVID-19 patients (particularly in the severe cases) a high level of circulating complement components (C5a, C5b-9) and kidney and lung tissue depositions of C4d and C5b-9 (activation of the complement cascade in different organs), which promote inflammation and coagulation pathways. Platelet activation that promotes immunothrombosis is a result of SARS-CoV-2 binding platelets via ACE2 (angiotensin converting enzyme 2). Several small studies have highlighted thrombotic microangiopathy within glomeruli, acute glomerular endothelial cell injury and thrombi in the kidney. A marker that could demonstrate that inflammation has a role in the development of intravascular thrombi is the presence of neutrophils and neutrophils extracellular traps, released by activated neutrophils, aggregating with platelets in the kidneys and other organs [39-46].

Angiotensin converting enzyme 2 (ACE2)

SARS-CoV-2 enters into cells using ACE2 as a receptor. ACE2 converts angiotensin II to angiotensin 1-7 (Ang 1-7) that, in comparison with angiotensin II which has pro-inflammatory (pro-inflammatory cytokine release), pro-fibrotic, vasoconstrictor effect, has natriuretic, vasodilatatory, anti-inflammatory and anti-fibrotic activity (Table 2). SARS-CoV-2 infection induces ACE2 membranal degradation which will imbalance renin-angiotensin-aldosterone system, with the reduction of angiotensin 1-7 and increase levels of angiotensin II, leads to fibrosis, hyperinflammation, microcirculatory dysfunction and hypercoagulability. In comparison with lungs, where the production of Ang 1-7 is independent of ACE2, in the kidneys it is majorly mediated by ACE2 that is prevalent in the proximal tubules [25,47,48].

TABLE 2. Effects of angiotensin 1-7 and angiotensin II [25,47,48]

Angiotensin 1-7	Angiotensin II
• Vasodilatation • Anti-fibrotic activity • Anti-inflammatory activity • Natriuretic activity	• Activation of endothelium • Vasoconstriction • Activation of platelets • Pro-inflammatory cytokines release • Pro-fibrotic activity

Treatment related to AKI

A lot of drugs with nephrotoxic potential are used to treat patients with COVID-19, especially those with severe forms. There have been reported some cases of vitamin C related oxalate nephropathy and tubulointerstitial nephritis secondary to the use of antiviral drugs [49, 50]. In patients with COVID-19 associated AKI, we need to consider the drugs we use for treatment as potential etiology of AKI.

CONCLUSIONS

COVID-19 mainly affects the lungs, but also other organs, including the kidneys. Acute tubular injury seems to be more common than prerenal azotemia in COVID-19 patients. Complement activation, inflammation with cytokine release, endothelial injury resulting in hypercoagulation and thrombotic microangiopathy have been often encountered in COVID-19 associated AKI. Different types of glomerular diseases have been reported in patients with COVID-19, but the most frequent form of glomerular disease associated with COVID-19 is collapsing glomerulopathy, more common in Afro-American patients frequently associating APOL1 risk genotypes. The drugs we use to treat COVID-19 must be also considered a cause of AKI. The etiology and pathophysiology of COVID-19 associated AKI seems to be complex, therefore, further studies to validate these findings are required.

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