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Mini Review

COVID-19 Infection in the Kidney: Information Thus Far

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Abstract

Coronavirus Disease 2019 (COVID-19) is a worldwide spread pandemic that mostly affects the respiratory system. The viral agent of COVID-19 infection is the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) which results from subclinical infection to multi-organ failure. According to a recent report patients hospitalized with COVID-19 are at high risk of Acute Kidney Injury (AKI). There is currently a discussion regarding how COVID-19 affects kidneys, with contradictory assertions about the method. The current article summarizes the most recent reports and studies on COVID-19 infection in the kidney.

Keywords: Coronavirus Disease 2019; Acute Kidney Injury; Severe Acute Respiratory Syndrome Coronavirus 2

Introduction

It has been reported that COVID-19 affects other organs including the renal system and might be leading to acute kidney injury (AKI) related mortality [1,2]. A study in the USA reported that during the peak of the COVID pandemic in 2020, 56.9% of COVID patients developed AKI, which is twice as the regular patients (25.1%). Another study revealed that in 59 COVID patients, 63% exhibited proteinuria, 19% had elevated plasma creatinine levels, and 27% had elevated urea nitrogen levels. Patients recovered from COVID were also reported to have lower kidney function. However, the etiology of kidney injury in COVID-19 is not completely understood. There are arguments about the possibility of direct viral cytotoxicity and indirect activity through virus-induced cytokines, sepsis, and hypoxia. Both SARS-CoV-2 and SARS-CoV enter cells via two different pathways. One through the Angiotensin-Converting Enzyme 2 (ACE2) receptor [3] and the other through endocytosis. Coronavirus bind to ACE2 which then gets primed by a protease called TMPRSS2 leading to the internalization of the ACE2-viral spike complex [4]. ACE2 is expressed by various organs in the body including the kidney. Single-cell RNA seq (scRNA-seq) data from the urinary system revealed that approximately 4% of kidney Proximal Tubule (PT) cells have high ACE2 expression [5].

On the other side, the indirect mechanism of infection of the kidney by COVID is also reported. Amplification of virus in the body cause release of cytokines and chemokines which will further attract inflammatory cells. This results in a cytokine storm leading to endothelial dysfunction, microangiopathy which all contribute to the damage of the kidney. Both *in vivo* and *in vitro* studies have contradicting results regarding the COVID infection of the kidney.

In Vivo Study

Research before the pandemic discussed the acute renal impairment associated with coronavirus. In a study, the autopsy of SARS subjects revealed that hypertensive nephrosclerosis and autolysis were present in the kidney specimens. Acute tubular necrosis was also detected in the specimens [6]. Other than tubular injury, Collapsing Glomerulopathy (CG) has also been reported in COVID-19 patients [7-9]. Electron microscopy imaging of COVID positive patient kidney samples showed the segmental collapse of the capillary tuft in glomeruli with enlarged podocytes, acute tubular injury with minimal interstitial inflammatory infiltrates [8]. The results also reported mild interstitial fibrosis and tubular atrophy with moderate arteriosclerosis. They suggested the presence of viral-like spherical particles in the podocyte cytoplasm [9]. But the study lacks conclusive results to suggest the direct viral cytotoxicity on glomeruli in the patients.

Meanwhile, some argue that viral-like inclusions in the EM images could be microvesicular bodies containing exosomes that fall within the size range of SARS coronaviruses. Viral RNA was not detected in biopsy samples from patients with COVID-19 with kidney disease. They suggested that viral particles present in renal tissue from previous reports might be from renal blood vessels [10].

In Vitro Study

There have not been many articles published focusing on *in vitro* COVID infections studies in the kidney. Kidney organoids derived from human embryonic stem cells expressed ACE2 and TMPRSS2 supporting the direct infection principle [11]. The same group reported that Kidney Injury Molecule-1 (KIM-1) is an alternative receptor for SARS-CoV-2. Anti-KIM-1 antibodies reduced the endocytosis of SARS-CoV-2 spike protein by human kidney epithelial cells expressing KIM-1. The group also reported the use of an inhibitor of KIM-1, called TW-37 reduced endocytosis [12]. Other than ACE2, the CD147 receptor is reported to support the entry of SARS-COV2. CD147 is a transmembrane glycoprotein that is involved in viral infection. The study reported that a CD147 facilitated the entry of virus in Human Embryonic Kidney (HEK293) cells [13]. The use of CD147-antagonistic peptide-9 inhibited the effect of SARS-CoV in the cells. In another study from the same group the use of Meplazumab, a humanized anti-CD147 antibody inhibited the binding of virus and invasion of virus in Vero E6 cells [14]. The *in vitro* COVID models using kidney cell types may play a crucial role in the development of a potential antiviral drug.

Conclusion

The pathogenesis of acute renal failure in COVID-19 individuals is still not understood. It is important to prevent the AKI associated

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with COVID to reduce the mortality rate. More studies, focusing on COVID-19 infection in kidneys using either *in vivo* or *in vitro* might hopefully find a solution in the future.

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