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COVID-19 nephropathy; probable mechanisms of kidney failure

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The mechanistic understanding of signaling pathways that contributes to the kidney involvement by coronavirus disease 2019 (COVID-19) is an extremely critical point for improving therapeutic options. These pathways consist of the production of pro-inflammatory factors, the infiltration of pro-inflammatory cells into the renal interstitium, the activation of C5b-9 complexes, and receptor-angiotensin converting enzyme 2 (ACE2). Cytopathogenic effects and invasion into renal tubular cells have been confirmed.

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Coronavirus disease 2019 (COVID-19) is a recent viral epidemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This virus as a member of the β -coronavirus subgroup, is a positive RNA retrovirus. This infectious disease was found first in China and emerged around the world. Nowadays, it is a real epidemic which has affected all countries with several infected cases and numerous human deaths (1,2). This virus was originally transmitted to humans via animals such as bats. However, it continues its transmission among humans (3,4). COVID-19 has several clinical signs and symptoms such as dry cough, high fever, vomiting, myalgia, sputum production, headache, haemoptysis and diarrhea (5-7). Molecular diagnosis of COVID-19 requires molecular analysis using RT-PCR (reverse transcription polymerase chain reaction). However, other tests based on serological methods of viral antigens such as ELISA (enzyme-linked immunosorbent assay) technique are also begun to be efficiently used (8). There is neither vaccine available nor therapeutic treatment which aimed specifically at biochemical mechanisms of SARS-CoV-2 such as its penetration, retro-transcription, replication and assembly (9). In this situation, only alternative strategy such as prevention and reducing the risks of the transmission of this virus is lockdown.

COVID-19 may lead to death, especially in severe cases and this mortality is significantly high in elderly patients and/or in patients with chronic diseases (10). Recently an association of COVID-19 with acute kidney injury was documented. During infection, the virus circulates in the blood to reach kidney and cause damage to renal resident cells which are manifested by proteinuria, hematuria, and elevated levels of blood urea nitrogen, serum creatinine, uric acid as well as D-dimer (10-12). COVID-19 causes kidney involvement in about 3-9% of the patients and several studies reported that in-hospital mortality of COVID-19 patients who developed AKI is significantly higher (5.3 times higher in AKI than 1.5 times in chronic illnesses) (10,13-15). Currently, studies have begun to investigate influence of COVID-19 on kidney function while several mechanisms have been identified (Figure 1).

Firstly, COVID-19 exploits the ACE II as a receptor to entry the cells which is present much higher in kidney than lungs, as reported previously (16). Hence, lungs contamination with SARS-CoV-2 may be paralleled in kidneys. Consistent with this possibility, recent studies informed the presence of virus in kidney tissues. Using immunohistochemistry of SARS-CoV-2 nucleocapsid protein antigen in kidney specimens of six death cases, authors revealed that SARS-CoV-2 can be detected in

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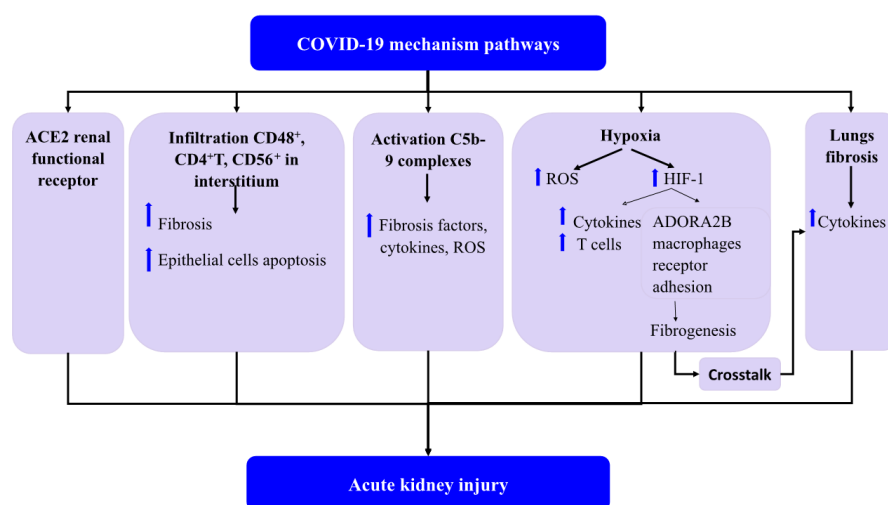


Figure 1. COVID-19 mechanism pathways inducing AKI.

distal convoluted renal tubules and proximal straight tubular cells (17). Furthermore, the strong presence of viral RNA in urine samples confirmed that kidneys are also a target of this virus (18). These results explain that renal cells are targeted and infected by SARS-CoV-2. Organ involvement by this virus is an important way to elaborate a new strategy for the prevention and the treatment of this disease.

Secondary, the patient’s immune system response to this virus consists of an exaggerated and often uncontrolled surge of plasma pro-inflammatory factors (IL2, IL7, IL-10, GSCF, IP-10, MCP-1, MIP1A and TNF-α) known as “cytokines storm” (19). The cytokines storm might cause damage to lungs and multi-organs failure including kidneys. Indeed, a recent study reported a reduced density of kidney and showed inflammation and edema of the renal parenchyma using computerized a tomography scan (10). The precise mechanism of cytokines storm leading to AKI is not well understood.

Additionally, SARS-CoV-2 might cause tubular damage through infiltrating renal parenchyma by pro-inflammatory cells. It has been revealed that inflammatory cells like CD68+ macrophages, CD4+ T cells, and CD56+ natural killer cells can be present in tubulointerstitium of affected patients (17). The hyperactivation of these immune cells may eventually promote fibrosis, induce epithelial cell apoptosis, and cause microvasculature change (20).

Moreover, C5b-9 expression, known also as membrane attack complex, is absent in normal kidney. However, C5b-9 complexes activation has been shown to induce renal parenchymal cells to release pro-inflammatory cytokines, ROS (reactive oxygen species) and profibrotic factors leading to kidney damage (21). Developing AKI due to SARS-CoV-2 can also act through triggering

C5b-9 expression. In this context, Diao et al proved a strong C5b-9 deposition on tubular cells compared to glomeruli and capillaries (17). This deposition causes renal interstitial damage.

Summary, cytokines release might exert indirect effects on renal tissue, such as hypoxia, shock, and rhabdomyolysis (12). As we know, kidney is the most sensitive organ to hypoxia (22). Insufficient blood flow from afferent arterioles may lead to AKI (ischemic ATN) and ischemia can induce HIF-1 (hypoxia-inducible factor 1) and then ROS generation of mitochondrial dysfunction (23,24). HIF-1 activates genes that promote the synthesis of fibrous connective tissue which interferes with the kidney’s normal function and enhances effector T cell function, including promotion of cytolytic activity and inflammatory cytokine production while ROS destroys the molecular components of nephron inducing a cells damage and/or death (12,23,25). In addition, HIF-1 up-regulates the ADORA2B receptor on alternatively activated macrophages which contribute to the development and progression of pulmonary fibrosis (10,23). This crosstalk between lungs and kidneys may complicate COVID-19 patients.

The increased incidence of AKI in COVID-19 patients could be due to the synergistic effect of all of these factors and also by state of dehydration, toxic tubular damage, and drug-induced nephrotoxicity (10,26). From this brief commentary, many perspectives can be suggested. Several studies showed the influence of SARS-CoV-2 in urine analysis. Therefore, it would be very interesting to introduce urine tests as a diagnostic guideline for COVID-19 and also predict disease severity, especially for developing countries where resources are limited. Moreover, kidney injury was associated with an increased risk of death in patients. This important issue should

alert medical staff to pay attention to kidney function of COVID-19 patients by avoiding nephrotoxic drugs and precisely observe and monitor kidneys function of affected patients and prevent additional nephrotoxic insult to them. Even if these circumstances are difficult, efforts must be made by contribution of pathologists to better understand the mechanism of action, thus identifying new strategies to improve the therapeutic treatment of COVID-19.

Authors' contribution

KA and BA wrote the paper. All the authors reviewed the manuscript and approved it for publication.

Conflicts of interest

The authors declare no conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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