DOI: 10.53469/jcmp.2024.06(08).27

Progress in the Study of Renal Injury Caused by a Novel Coronavirus

Xian Lu[1], Genping Lei[2,*], Dong Yang[1], Jingxue Bai[1]

[1]Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
[2]Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang 712000, Shaanxi, China
Correspondence Author

Abstract: ***Novel Corona Virus Pneumonia (Corona Virus Disease 2019, COVID-19) in December 2019 became an epidemic disease. Chronic kidney disease (CKD) patients are highly sensitive to COVID-19, in-depth study and understanding of the mechanism of action and prevention and treatment strategies of CKD patients infected with novel coronavirus appears to be crucial. This article explored the selected topic by combing the relevant literature, and summarized the susceptibility to COVID-19 and the mechanism of renal involvement in CKD patients; the article shows that COVID-19 mainly enters the cells with ACE2 as the receptor to damage the kidneys directly, but also through cytokine storm, endothelial damage, immune dysregulation and other indirect ways of renal damage.***

Keywords: Corona Virus Disease 2019, Chronic kidney disease, Pathogenesis, Cytokine storms**.**

1. Introduction

COVID-19 is an emerging acute respiratory infectious disease caused by "SARS-CoV-2" (severe acute respiratory syndrome corona virus 2), which is mainly characterized by rapid transmission and universal susceptibility. Patients with COVID-19 present with fever, dry cough, and malaise [1], and the main organ involved is the lungs, although extrapulmonary organ involvement has also been noted in several studies [2]. CKD is chronic renal structural and functional dysfunction (history of renal damage greater than 3 months) of various causes, including glomeruar filtration rate (GFR) normal and abnormal. GFR) normal and abnormal pathological damage, abnormal blood or urine composition and abnormal imaging, or unexplained GFR decline (<60 ml/min-1.73 m2) for more than 3 months [3].

Current studies have found that COVID-19 damages the kidney by various mechanisms, mainly infecting cells with angiotensin converting enzyme 2 (ACE2) as a receptor [4]. Since the kidney is an organ with high expression of ACE2, it is more susceptible to neocoronavirus invasion [5]. Acute kidney injury (AKI) caused by neocoronaviruses has become one of the independent risk factors for patient mortality, and the risk of death during hospitalization for neocoronavirus pneumonia in CKD patients is much higher than usual [6].

2. Literature Search Strategy

We searched PubMed, Web of Science, China Knowledge Network (CNKI) and other databases, and the search time was set as the period from the establishment of the database to May 2023, and the search terms in Chinese included "novel coronavirus", "chronic kidney disease" and "acute kidney injury". "acute kidney injury", English search terms include "Corona Virus Disease 2019" "Chronic kidney disease "" acute kidney injury". Inclusion criteria: Literature related to the susceptibility of CKD patients to COVID-19 and the mechanism of renal involvement. Exclusion criteria: Literature not related to the topic of this article, poor quality, and unavailability of full text. Finally, 28 articles were included in the literature.

3. Susceptibility of CKD patients

The main organ of COVID-19 infection is the lung, but extrapulmonary infections are also prominent in the clinical course. In the case of the kidneys, which are richly vascularized, renal blood flow accounts for 25% of cardiac output, and although this high renal blood flow is effective in balancing electrolytes and acid-base levels, hypersensitivity counteracting hemodynamic changes, systemic, infectious, or immune disorders is unavoidable [2].

COVID-19 is highly contagious and the population is generally susceptible, especially those who are frail and have poor resistance. CKD patients are more susceptible to COVID-19 infection due to the functional defects of innate immune cells and their pro-inflammatory state leading to an increased susceptibility of the organism to infection [7]. Li Juan [8] and others pointed out that CKD patients are mostly an elderly population with multiple comorbidities, which often have an imbalance of CD4+/CD8+ and a decrease in the activity of natural killer cells; and secondly, some CKD patients need to take glucocorticoids and immunosuppressants, which can further compromise their immune system and increase susceptibility to COVID-19; in addition, since blood from the entire body passes through the kidneys several times a day, and certain small arteries and capillaries in the kidneys may be damaged by SARS-CoV-2, viruses and inflammatory cytokines in the bloodstream can damage the kidneys; finally, as a CKD patients, a subgroup of patients, dialysis patients are a more susceptible population, with a higher probability of being exposed to potentially contaminated environments because their routine treatments usually require travel to hospitals.

Considering all of the above reasons, CKD patients are more susceptible to COVID-19 than the general population. The development of COVID-19 may result in rapid deterioration of impaired kidney function and even death.

4. Mechanisms of Renal Involvement

Renal involvement in patients with neocoronary pneumonia is dominated by tubular damage, and their renal symptoms

include proteinuria, hematuria, and AKI, which mostly occur in critically ill patients [9].

4.1 Direct Renal Damage

It is academically recognized that this new coronavirus is similar to the SARS virus (SARS-CoV) that arose in 2003, and both have similar cellular receptor recognition mechanisms [10]. Both SARS-CoV and SARS-CoV-2 are morphologically coronaviruses, with 79.5% homology, and therefore SARS-CoV-2 is regarded as a variant of SARS-CoV [11].

Spiny glycoproteins (S proteins) distributed on the surface of the coronavirus envelope are key determinants of coronavirus host selection and tissue tropism [12], which can facilitate viral entry into target cells and are the main target of action for a variety of antibodies [10]. In 2003, ACE2 was shown to be an important receptor for SARS-CoV. Yu Che [13] et al. proposed that ACE2 is an enzyme in the renin-angiotensin system (RAS) that acts as a receptor to assist the SARS-CoV-2 virus to invade host cells and thus cause infection. ACE2 has several genes related to viral evolution, replication, life cycle and aggregation, and thus promotes viral replication [14]. Similar to SARS-CoV, SARS-CoV-2 also targets the S-protein, but due to viral mutation, the S-protein of SARS-CoV-2 forms a tighter "molecular ridge", which enables SARS-CoV-2 to better attach to the ACE2 receptor and spread at a high rate, which is a key factor in the development of SARS-CoV-2. One of the molecular bases for the high infection rate of SARS-CoV-2 is the activation of S proteins by hydrolysis of various host proteases, among which the role of transmembrane serine protease (TMPRSS2) is the most representative one [15], which plays an assisting role in the infection of SARS-CoV-2.

ACE2 is highly expressed in renal tissues especially at the proximal renal tubules [9]. Based on histopathological analysis that reveals the manifestation of kidney injury caused by neocollagenic infection, the expression of ACE2 and TMPRSS2 in human renal cells was also further confirmed using single-cell transcriptome sequencing (scRNA-seq) [10]. In RAS, ACE2 functions to enzymatically cleave Ang II to form more short peptide Ang (1-7) with protective function, which in turn acts as a vasodilator, anti-inflammatory, anti-oxidative stress, anti-thrombotic, and anti-fibrotic [16]. A previous study found that ACE2 expression decreased after SARS virus infection, leading to the loss of its protective function in tissues [13]. Following viral infection, tubular injury can be induced by deposition of MAC complexes (the final step of the complement cascade) on renal tubules and infiltration of CD68+ macrophages in the tubular interstitium [14]. SARS-CoV-2 also promotes loss of the proximal tubular brush border, non-isometric vacuolization, and necrosis [17]. Renal biopsies of patients with COVID-19 were suggestive of collapsing glomerular (CG) disease, significant acute tubular injury was observed by light microscopy, viral particles were detected in tubular epithelial cells and podocytes by electron microscopy, and immunofluorescence staining of SARS-CoV-2 nucleoprotein in renal tubular cells was positive; these pathologic findings suggested that SARS-CoV-2 infected renal parenchymal cells [9]. These results suggest that the novel coronavirus can directly cause renal tissue damage.

4.2 Indirect Renal Damage

4.2.1 Cytokine storm

Cytokine storm, also known as cytokine release syndrome (CRS), is a rapid, massive release of multiple cytokines in the body [18]. Hyperactivation of the immune system during COVID-19 infection may trigger CRS, causing severe inflammation and destroying kidney tissue. Virus-induced CRS causes the body to release large amounts of granulocyte colony-stimulating factor, various interleukins and IFN, which can directly or indirectly damage the kidneys by affecting other organs such as the heart and skeletal muscle [19].

4.2.2 Endothelial damage

Endothelial cells are a class of organs with paracrine, endocrine and autocrine functions, which play a key role in regulating vascular contraction and homeostasis [20].ACE2 is widely distributed on vascular endothelial cells in several tissues, so neocoronaviruses are able to invade into blood vessels through ACE2, causing damage to the endothelium of the blood vessels, which induces thrombosis and local inflammation generation [21]. Endothelial damage and inflammation caused by viral infection are present in several organs of patients with neocoronavirus pneumonia, leading to excessive thrombin production, inhibition of fibrinolysis, and activation of the complement pathway, which causes a thrombotic-inflammatory response, and ultimately leads to microthrombus deposition and microvascular dysfunction [22]. Hypercoagulability caused by endothelial cell injury and other factors will cause acute tubular necrosis and further progress to cortical necrosis, finally causing irreversible renal failure [23].

4.2.3 Immune system dysregulation

In addition to producing direct damage to host cells through, COVID-19 can also affect innate immunity, thus producing indirect cytotoxic effects on the kidney [24].

Innate immunity: Toll-like receptors (TLRs) detect molecules released from damaged tissues and activate transcription factors that regulate the expression of pro-inflammatory cytokines/chemokines involved in the innate immune response [25].TLRs receptors play an important role in the pathogenesis of renal diseases, and their over-activation by coronaviruses can lead to a number of renal disorders such as ischemic kidney injury, AKI, end-stage renal failure, acute tubulointerstitial nephritis, and acute kidney transplant rejection.

Acquired immunity: In the early stage of SARS-CoV-2 infection, the body produces an acquired immune response, and an appropriate immune response is favorable for viral clearance. SARS-CoV-2 often triggers an uncontrollable inflammatory response and causes CRS, which ultimately leads to T-cell apoptosis. One study showed that lymphocytes were significantly lower in COVID-19 patients compared to

non-COVID-19 patients [26]. In turn, dysregulation of the acquired immune response can lead to abnormal activation of macrophages, neutrophils, etc., which in turn hinders viral clearance. In addition, after SARS-CoV-2 infection, due to the dysfunction of the complement system, C5b-9 will accumulate in the lumen of renal tubules, which will cause corresponding renal injury [24].

4.2.4 Others

ACE2 is highly expressed in the small intestine, especially in proximal and distal intestinal epithelial cells. Interaction between SARS-CoV-2 and ACE2 may disrupt ACE2 function and lead to diarrhea, severe diarrhea leading to dehydration that may affect renal function [9]. In addition, patients rarely undergo fluid resuscitation prior to admission, which is highly likely to result in hypovolemic shock, which causes ischemic and hypoxic changes in the kidneys; infectious shock similarly causes renal ischemia and hypoxia, leading to prerenal kidney injury [24]. RhabdomyolysisDirect damage to skeletal muscle cell membranes by SARS-CoV-2 and the cytokine storm caused by the infection result in overactivation of the immune system, potentially leading to rhabdomyolysis, Rhabdomyolysis is a potential pathogenetic mechanism causing AKI [27]. Renal histopathologic studies have found that in patients with neococcal pneumonia, those containing the high risk allele for ApoL1 have a relatively increased risk of collapsing glomerulopathy [28]. In addition to this, there is organ crosstalk between the lungs, heart and kidneys, which also plays a role in the progression of the lesion [10]. Complement activation, sepsis and the use of nephrotoxic drugs can also lead to kidney injury [24].

Acknowledgements

Shaanxi Provincial Administration of Traditional Chinese Medicine Scientific Research Project on Prevention and Treatment of COVID-19 in Chinese Medicine (ZYJXG-L23004).

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