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Journal of Infection and Public Health 14 (2021) 922–926

Contents lists available at ScienceDirect

Journal of Infection and Public Health

journal homepage: http://www.elsevier.com/locate/jiph

Review Article

COVID-19 infection and the kidneys: Learning the lesson

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ARTICLE INFO

Article history:
Received 11 September 2020
Received in revised form 11 March 2021
Accepted 18 May 2021

Keywords:
SARS-CoV-2, pathogenesis
Acute kidney injury
Dialysis
Transplantation
Diagnosis

ABSTRACT

The novel coronavirus 2019 pandemic has become a global health crisis. In an attempt to decipher how kidneys are affected by COVID-19 infection, this review focuses on pathogenic and clinical links between COVID-19 infection and the kidneys. SARS-CoV-2 infected patients are target for kidney affection, renal tropism, among other multiorgan complications. COVID-19 related kidney affection is reported not only in infected chronic kidney disease patients but also in those with no prior history of kidney disease. As nephrologists try to keep up with the rapidly evolving, sometimes hasty, reports on renal affection in COVID-19, kidneys continue to be deleteriously affected particularly in critical care settings. This review aims to briefly portray renal involvement in COVID-19 amid this unprecedented deluge of scientific data. Based on gained knowledge and expertise, it is prudent to develop and regularly update preventive, diagnostic and therapeutic strategies to improve clinical outcome and reduce mortality.

Contents

Introduction

COVID-19 is a newly emerging human infectious disease that marked the beginning of the third decade of the 21st century. The novel coronavirus that causes COVID-19 is designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was first reported in the city of Wuhan, china and rapidly spread across the country causing an epidemic. COVID-19 affected most countries around the globe and has been reported in all ages, including children [1]. On 11th of March 2020, the WHO declared COVID-19 a pandemic that was later described by WHO on 23rd of March as "accelerating pandemic" when cases eclipsed 350,000. To date worldwide cases climb above 116 million and deaths over 2.5 million [2].

Coronaviruses (CoV) are animal and human pathogens that can cause lethal zoonotic infections. CoV possess a distinctive morphology with crown-like spikes on their surface, hence the name "corona". In 2003, CoV gained considerable attention as significant causes of severe lower respiratory disease. Since 2003, SARS-CoV-2 is the third emergence of CoV infection with severe lower respiratory tract disease following severe acute respiratory syndrome

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https://doi.org/10.1016/j.jiph.2021.05.010

coronavirus (SARS-CoV) in 2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 [3–5].

COVID-19 pandemic has profoundly affected everyone, yet its impact on patients continues to unfold. To date the understanding of its epidemiology, pathogenesis and clinical manifestations is still evolving. Scientists and researchers across the globe are extensively studying the disease to expand the currently limited scientific knowledge on this novel virus.

Although COVID-19 primarily involves the lungs manifesting as acute respiratory disease, other organ involvement has been reported including kidney, gastrointestinal tract, liver, heart, and central nervous system. Therefore, the novel coronavirus 2019 pandemic has led to an unprecedented high alert among almost all health care disciplines including nephrology [6–8].

Pathogenesis

SARS-CoV-2 has an identical confining structure to that of SARSCoV-1, hence COVID-19 pathogenesis largely resembles that of SARS-CoV-1. SARS-CoV-2 spike glycoprotein expressed on the viral envelope binds angiotensin-converting enzyme 2 (ACE2) with around 10 fold higher affinity than SARS-CoV1. ACE2 is known to be abundantly expressed on multi-ciliated cells of the airway epithelium that SARS-CoV-2 preferentially infect. After binding, SARS-CoV-2 enters host cells where it encounters the innate immune response. It infects the new host by inhibiting or eluding its innate immune signaling. Nevertheless, how SARS-CoV-2 manages to elude immune response and drive pathogenesis is still largely unclear [9].

SARS-CoV-2 damages the lining epithelial cells of the respiratory airways causing cytopathic effects and ciliary dysfunction [10]. A cytokine storm results in hyper inflammation with severe inflammatory cascade that initially targets macrophage, lymphocyte and pneumocytes. As SARS-CoV-2 enters the cell it takes control of the endogenous transcriptional machinery of alveolar cells to replicate and spread through the entire lung tissue [8,11].

When most of the ciliated cells in the alveoli are infected, they cease to carry out its normal function of clearing the airways, with progressive accumulation of debris and fluids in the lungs and acute respiratory distress syndrome (ARDS) [12].

Excessive release of plasminogen activators due to inflammation-induced endothelial cell injury might explain the high concentrations of D-dimer and fibrin degradation products in patients with severe COVID-19 [13]. Post-mortem examination reports confirm increased clotting and disseminated intravascular coagulation with microvacular thrombosis and pulmonary infarction [14]. It has been suggested that local impairment of the fine balance between host coagulation and fibrinolytic pathway within the alveolar spaces is presumably the cause which is significantly enhanced by the vasoconstriction and the reduced blood flow induced by the profound hypoxemia in the pulmonary capillaries [13] In some COVID-19 patients, microangiopathy has been confirmed in other organs leading to splenic infarction, renal infarction and myocardial injury possibly due to myocarditis and microangiopathy [15].

Pathogenesis of kidney injury

Although kidney involvement in COVID-19 infection has been reported, the spectrum of kidney injury keeps unfolding and expanding. How kidneys are involved in COVID-19 is still unclear, however the interplay of the below mechanisms has been postulated:

1) Direct cellular injury with devastating metabolic alteration and activation of catabolic pathways leading to severe and uncontrollable electrolyte derangement [16]. ACE2 expressed on renal tubular cells and podocytes was identified as binding partner for SARS-CoV-2 infection. Thus COVID-19 mediated angiotensin II accumulation may promote an imbalanced RAAS activation, leading to inflammation, fibrosis and vasoconstriction [17]. Viral RNA has been previously identified in kidney tissue and urine in SARS-CoV infection [18]. Moreover recent reports of SARS-CoV-2 isolation from the urine sample of an infected patient; and immunohistochemical identification of accumulated SARS-CoV-2 nucleocapsid antigen in kidney tubular cells, render the kidney as possible target of this novel coronavirus [19,20]. Recent human tissue RNA-sequencing data demonstrated kidney enrichment with ACE2, transmembrane serine protease 2 (TMPRSS2), and cathepsin L (CTSL) genes that facilitate SARSCoV-2 infection thus rendering the kidney a particular target for SARS-CoV-2–associated kidney injury [21,22].
2) Inflammatory and immune over-reaction is characterized by an enhanced release of circulating mediators. Critically ill patients have significantly higher plasma levels of TNFα; IFN-γ-induced protein 10 (IP10); macrophage inflammatory proteins1A (MIP1A); granulocyte colony stimulating factor (GCSF) and monocyte chemoattractant protein-1 (MCP1) suggesting the likely role of highly pro-inflammatory condition and cytokine storm in the disease progression and severity [8]. The high levels of circulating harmful mediators appear to interact with kidney-resident cells leading to endothelial dysfunction, microcirculatory derangement, and tubular injury [23].
3) Severe COVID-19 infection results in procoagulant state with evident vascular consequences of SARS-CoV-2 induced coagulopathy as microvascular thrombosis, acute tubular and cortical necrosis with subsequent fibrinoid necrosis and glomerular ischemia and irreversible kidney damage [24] SARS-CoV-2 infection facilitates the induction of endotheliitis in several organs as a direct consequence of viral involvement and the host inflammatory response [25]. This provides a rationale for therapies to stabilize the endothelium whilst tackling viral replication, particularly in patients with preexisting endothelial dysfunction such as diabetes, hypertension and obesity [26].
4) In critically ill patients with prolonged ICU stay, other factors contribute to kidney injury including hemodynamic instability, nephrotoxic drugs, mechanical ventilation and sepsis. Septic AKI in such patients act synergistically with other mechanisms of kidney damage [27].

Lung kidney cross talk

Inflammatory and immune over-reaction with cytokine overproduction is involved in lung–kidney bidirectional damage and plays critical role in disease progression Fig. 1. During COVID-19 infection, injury of renal tubular epithelium promotes the upregulation of IL-6, subsequently leading to higher alveolar-capillary permeability and pulmonary haemorrhage. Nevertheless the mechanism of IL-6 injury to lung epithelial and endothelial cells remains to be elucidated. Also, ARDS may result in renal medullary hypoxia which induces even more insult to tubular cells [27]. The interplay of these mechanisms have considerable therapeutic implications including the extracorporeal removal of inflammatory cytokines.

Clinical consequences of COVID-19 on the kidneys

Kidney involvement is a major complication of COVID-19 infection and a significant risk factor of death. COVID-19 impact on healthy and diseased kidneys continues to unfold.

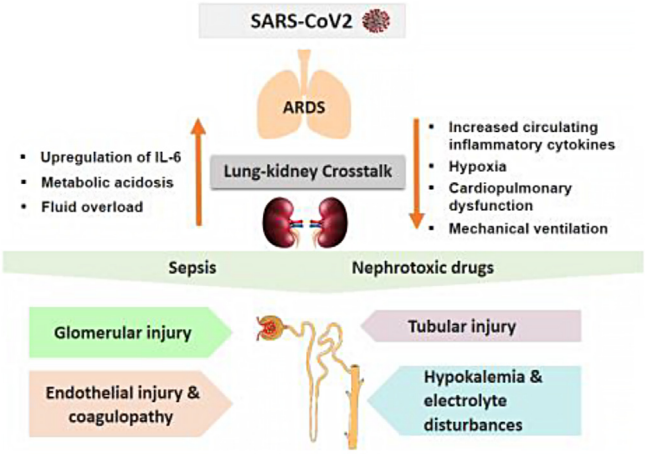

Fig. 1. Lung kidney crosstalk and mechanisms of kidney injury in COVID-19.

Acute kidney injury (AKI)

Data on AKI in COVID-19 is increasing with variable incidence of this severe complication. This seems understandable given the accelerated pace of the pandemic particularly with the overwhelming impact of lower respiratory involvement and respiratory failure. AKI is a commonly reported complication of COVID-19 that has been linked to increased morbidity and mortality. Recently, SARS-CoV-2 RNA was detected in the kidneys of 23 (72%) of 32 patients with AKI, compared to lower frequency of SARS-CoV-2 renal tropism in patients without AKI with viral RNA only found in three (43%) of seven patients [28].

In a large cohort of 1099 patients with COVID-19, 93.6% were hospitalized, 91.1% had pneumonia, 5.3% were admitted to the ICU, 3.4% had acute respiratory distress syndrome (ARDS) yet only 0.5% had AKI [29].

In another single-center case series of 138 hospitalized patients with confirmed COVID-19 pneumonia in Wuhan, China, AKI was reported in 3.6% of all patients. Unsurprisingly when calculated among the subset of study ICU admitted patients ICU, AKI increased to 8.3% [7].

Moreover researchers reported an association between kidney disease and mortality in hospitalized patients. More than 40% had evidence of abnormal kidney function and 5.1% had AKI during their hospital stay. The incidence of AKI was significantly higher in patients with elevated baseline serum creatinine (11.9%) compared to patients with normal baseline values (4.0%), Also, proteinuria, hematuria, and AKI over stage 2 were associated with increased risk of mortality. Excess risk of mortality by at least 4 times had been reported among those with stage 3 AKI with seemingly critical role of lung-kidney crosstalk [30].

A pooled analysis including five studies with a total sample size of 1415 COVID-19 patients to analyze electrolytes in COVID-19 patients with and without severe form confirmed that COVID-19 severity is associated with lower serum concentrations of sodium, potassium and calcium [31]. Recently, a case–control study in three hospitals in France, included 594 adult emergency department (ED) COVID-19 patients who were matched to 594 non-COVID-19 ED patients (age and sex controls) from the same period demonstrated that hyponatremia and hypokalemia were independently associated with COVID-19 infection in adults visiting the ED [32].

Electrolyte disturbances not only have clinical implications on patient management, but also aid in exploring the underlying pathogenetic mechanisms in COVID-19. Increased release of antidiuretic hormone in response to a volume depletion presumably contributes to hyponatremia in COVID-19 patients. As SARS-CoV-2 binds to its ACE2 host receptor, it reduces ACE2 expression, resulting in increased urinary potassium in response to high angiotensin II. Hypokalaemia further exacerbates ARDS and acute cardiac injury, particularly in patients with lung or heart comorbidities [31,32].

In this context, close monitoring of kidney function and electrolytes in hospitalized COVID-19 patients, particularly those in critical setting, and use of sensitive AKI biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL) and/or kidney injury molecule 1 (KIM-1) are warranted to risk-stratify patients and direct resources towards prevention or early detection of AKI and timely intervention to reduce AKI progression and mortality risk.

Dialysis and transplantation in the times of COVID-19

Medical care of dialysis patients during COVID-19 pandemic is quite challenging as patients have depressed immune system let alone associated comorbidities as diabetes and cardiovascular disease. Many strategies for managing dialysis and providing dialysis support for patients during this COVID-19 outbreak had been developed. In a recent report, authors shared the key considerations in planning dialysis services to ensure adequate resources for the provision of uninterrupted dialysis to end stage kidney disease patients, while minimizing risk of transmission of COVID-19 between individual patients, the community and healthcare workers [33].

Recommendations for the prevention and management of COVID-19 patients in hemodialysis, peritoneal dialysis and continuous renal replacement therapy (CRRT) in ICU had been published. It is imperative to do so in a multidisciplinary approach to ensure safe, effective and uninterrupted dialysis while minimizing the risk of infection [33,34].

In an early report from Wuhan, China; COVID-19 infection was confirmed in 37 of 230 hemodialysis patients (16.1%) and 4 of 33 staff members (12.1%) were diagnosed with COVID-19. Of note, hemodialysis patients with COVID-19 had less lymphopenia, lower serum levels of inflammatory cytokines, and milder clinical disease than other patients with COVID-19 infection [35].

Kidney transplant recipients require lifelong maintenance immunosuppression regimen designed to balance efficacy (prevention of rejection) and safety (minimizing risk of infection) at different points of times post-transplantation.

Of 1073 patients with COVID-19 and kidney failure from 26 countries that had been entered in ERACODA, the ERA–EDTA COVID-19 database, 21% of kidney transplant patients and 25% of dialysis patients had died at 28-day follow-up [36].

During this pandemic the main concern, is therefore, immunosuppression rendering kidney allograft recipients more prone to infections including COVID-19. This pandemic not only affected how we care for kidney transplanted patients, but also had its impact on limiting kidney transplantation to lifesaving conditions and putting live kidney transplantation on hold where deceased kidney transplant is feasible. Moreover it serves as a reminder to constantly acknowledge balancing the risk of infections against disease control not only in renal transplant patients but also in other immunosuppressed nephrotic syndrome and renal vasculitis patients.

In the absence of specific therapy for SARS-CoV-2 infections, most nephrology societies have issued recommendations to reduce immunosuppression to levels that are considered safe, while acknowledging that balancing their risks versus benefits can be quite complex [37]. The significant strain and resource constraints in the midst of this outbreak call for modeling prediction, contingency planning and resource management to face the evolving COVID-19 pandemic [38].

Conclusion

The novel coronavirus 2019 pandemic has become the worst public-health crisis in a century presenting numerous unparalleled challenges to global health systems. As COVID-19 impact on kidneys keeps evolving, nephrologists have become increasingly on high alert with mounting reports of kidney involvement. Moreover the pandemic is taking its toll on chronic kidney disease patients disrupting their conservative follow up management, yet smart medical solutions are to be increasingly relied on. Recently issued recommendations are useful to ameliorate the untoward effect of the COVID-19 infection on dialysis and transplantation patients. That being said, the full impact of COVID-19 infection on chronic kidney disease patients remains to be elucidated. Comprehensive strategies including contingency plans, resource management and infection control measures should be developed and regularly updated in dialysis and transplantation units. Moreover close monitoring of kidney function and early urinary testing for urinary sediment as well as urinary biomarkers in COVID-19 patients are highly recommended to optimize early diagnosis and timely therapeutic intervention.

Regular updating of preventive, diagnostic and therapeutic strategies is crucial to improve clinical outcome and reduce morbidity/mortality risks.

Conflict of interest

None declared.

Funding

No funding sources.

Ethical approval

Not required.

Human and animal rights

This article does not contain any studies with human participants or animals performed by the author.

Informed consent

Not applicable.

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