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Acute kidney injury due to COVID-19 and the circadian rhythm

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ABSTRACT

The COVID-19 pandemic caused by the novel coronavirus (SARS-CoV-2) affects several organs including the kidneys. When examining patients with acute kidney injury (AKI) due to COVID-19, it is important to consider the circadian rhythm because in addition to its biological clock function, disruption of the circadian rhythm has been reported to be associated with the pathogenesis of several disorders, including AKI. Angiotensin-converting enzyme 2 (ACE2), an important component of the renin-angiotensin-aldosterone system (RAAS), displays circadian rhythmicity. Studies have shown that over-expression of human ACE2 increases the replication of SARS-CoV-2, which may lead to disruptions and tissue damage due to the suppression of the brain and muscle ARNT-like protein-1 (Bmal1) gene and high pro-inflammatory cytokines expressions in the tissues. Therefore, understanding and regulating the circadian rhythm and expression pattern of the key components of RAAS can prevent or reduce the severity of acute kidney injury that may occur with COVID-19 infection.

Introduction

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a huge global health challenge [1]. The kidney is one of several organs affected by COVID-19 and there are several records of patients who have had abnormalities in proteinuria and hematuria upon admission to hospital [2,3]. COVID-19 related deaths have been linked to cytokine storm induced by the virus. Excessive production of inflammatory cytokines causes serious acute respiratory distress, which may result in multi-organ failure and death; hence, targeting the cytokines when managing patients with COVID-19 may improve survival [4]. Viruses usually invade the host cellular machinery where they replicate and cause infections. SARS-CoV-2 and SARS-CoV-1 have been shown to invade the host cells bound to angiotensin-converting enzyme 2 (ACE2) receptor, which is found in different tissues including the kidneys and lungs [5,6]. There is paucity of data on the circadian pattern of ACE2 expression in the lung tissue; however, its role in COVID-19 and the renin-angiotensin-aldosterone system (RAAS) cannot be overemphasized [7,8]. Therefore, identifying the impact of COVID-19 on the kidney at an early stage and subsequent use of therapeutic and preventive measures may reduce the severity of damage and mortality.

Hypothesis

Acute kidney injury (AKI) is one of the various manifestations of COVID-19, mostly in patients with a history of kidney disease [9–11]. We hypothesized that regulating the circadian rhythm and expression pattern of the key components of RAAS, especially ACE2, would optimize the evaluation and management of acute kidney injury due to COVID-19 infection.

COVID-19 and the circadian rhythm

The circadian clock system, which regulates and maintains the physiological processes, has been linked with various disorders [12–15]. Central clocks generate oscillations using regulators like clock-controlled genes in a negative feedback loop. Positive gene regulators like the brain and muscle ARNT-like protein-1 (Bmal1) and circadian locomotor output cycles kaput (CLOCK), produce a heterodimer which activates the gene transcription of the negative gene regulators [16]. The Bmal1 is an important circadian regulatory gene that has been shown to play a role in the regulation of infections caused by herpes simplex virus-1 (HSV-1) and influenza A. Studies have shown that HSV-1 and the influenza A virus can disrupt circadian regulation by suppressing Bmal1 expression in order to enhance replication [17,18]. These findings show

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the survival instinct of viruses in the host physiology to promote proliferation [19].

Any disruptions in the sleep-wake cycle, as seen in the current COVID-19 pandemic, may influence the ability of the body’s circadian clock to maintain regular biological rhythms and homeostasis. In particular, diminished levels of Bmal1 are associated with increased cytokine expression via nuclear factor kappa B (NF-κB) and NADPH oxidase activity [4,15]. The clinical manifestations of oxidative stress and inflammation have improved following the restoration of the circadian clock via organized lifestyle modifications, sleep and stress management [20].

Acute kidney injury and the circadian rhythm

Bmal1 deficiency due to disruption of the circadian rhythm increases the susceptibility to various disorders including kidney and cardiovascular diseases. However, methods for estimating the phase of human circadian rhythm have been designed to optimize therapeutic outcomes in clinical settings [21]. The circadian rhythmicity of RAAS is well known [22,23] and it has been reported that the activation of RAAS stimulates tubular reabsorption of sodium, which may trigger an imbalance in the circadian blood pressure pattern [24]. Angiotensinogen (AGT) is primarily synthesized in the proximal tubules of the kidney [25] and then released into the tubule lumen from where it can reach the distal tubule to encounter other components of RAAS to produce angiotensin II (Ang-II). A dysregulated RAAS due to ACE2 interaction with SARS-CoV-2 increases the level of Ang-II which acts via angiotensin-1 (AT1) receptor to propagate severe inflammation by activating the NF-κB pathway (see Fig. 1). This may explain why activation of intrarenal RAAS as well as an increase in blood pressure and proteinuria occur simultaneously in patients with AKI and in the chronic progressive nephritis model [26,27].

Acute kidney injury in COVID-19

Acute kidney injury is the sudden loss of kidney function resulting in the buildup of serum creatinine and decrease in urine output [28]. Reports from the USA and Europe revealed that COVID-19 patients in intensive care units developed AKI [29,30]. AKI is an important clinical outcome that may occur as a complication of another illness like COVID-19 infection. The link between kidney status and severity of COVID-19, especially in patients who developed AKI, has been established [11,31]. Several factors may contribute to AKI, some of which include ventricular dysfunction due to COVID-19 pneumonia, renal endothelia cell damage, rhabdomyolysis, activation of RAAS and cytokine storm following SARS-CoV-2 replication [2,32–34] (see Fig. 1). Sun et al. recently examined and isolated SARS-CoV-2 from the urine sample of a COVID-19 patient, and their findings suggested that the novel coronavirus also targets the kidney [35]. A recent study reported a high mortality and incidence rate in COVID-19 patients with renal complications including AKI [3]. Nogueira et al. concluded that proteinuria, hematuria and AKI frequently occur amongst patients with severe COVID-19 infection [36]. Aside from supportive and kidney replacement therapy, there is no antiviral agent available for the treatment of COVID-19 related acute kidney injury.

Conclusion

Understanding how viruses influence the circadian rhythm of their hosts would impact the clinical management of viral infections. Regulatory Bmal1 deficiency and activation of RAAS play important roles in acute kidney injury due to COVID-19. This condition may cause further complications that may arise with kidney damage and COVID-19. Therefore, this study suggests that understanding and regulating the circadian rhythm and expression pattern of the key components of RAAS can prevent or reduce the severity of acute kidney injury that may occur with COVID-19.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence...
the work reported in this paper.

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