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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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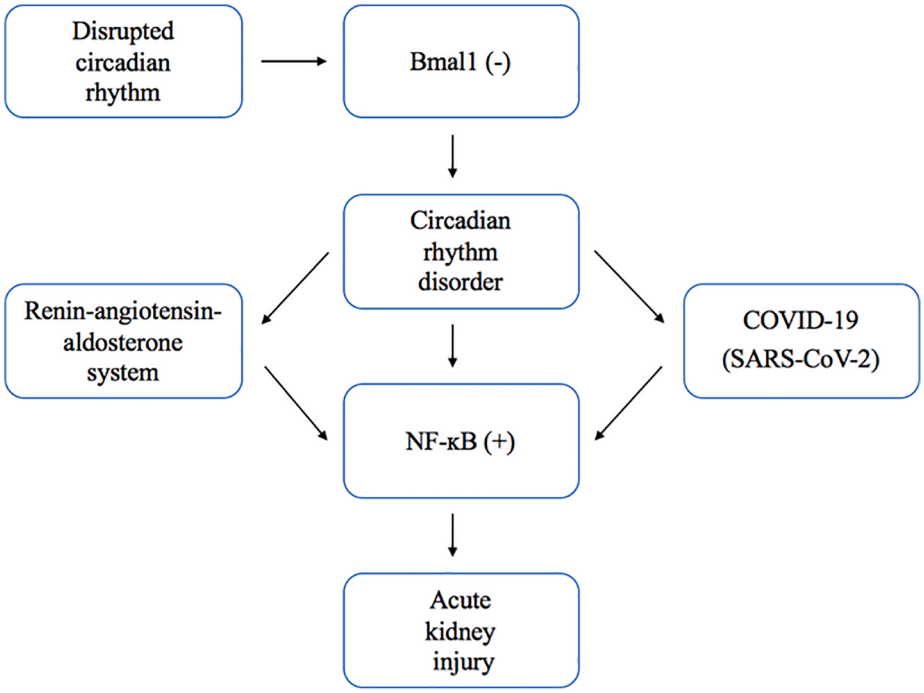

Fig. 1. Disruption of the circadian rhythm results in a decrease in the expression of the *Bmal1* gene which may trigger circadian disorders. Dysregulated renin-angiotensin-aldosterone system (RAAS) and the SARS-CoV-2 increase the level of Angiotensin II— which acts via AT_1 receptor to activate the NF-κB pathway and mediates inflammation in the kidneys by secreting pro-inflammatory cytokines.

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 (AT_1) 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.

References

[1] Zhu N, Zhang D, Wang W, Li X, Yang Bo, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382(8):727–33. https://doi.org/10.1056/NEJMoa2001017.

[2] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 IN Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054–62. https://doi.org/10.1186/s13054-020-03098-9.

[3] Pei G, Zhang Z, Peng J, Liu L, Zhang C, Yu C, Ma Z, Huang Yi, Liu W, Yao Y, Zeng R, Xu G. Renal Involvement and Early Prognosis in Patients with COVID-19 Pneumonia. JASN 2020;31(6):1157–65. https://doi.org/10.1681/ASN.2020030276.

[4] Ragab D, Haitham Salah E, Taeimah M, Khattab R, Salem R. The COVID-19 cytokine storm; what we know so far. Front Immunol 2020;11:1446. https://doi.org/10.3389/fimmu.2020.01446.

[5] Hoffmann M, Kleine-Wever H, Kruger N, Muller M, Drotsten C, Pholhlmann S. The novel coronavirus 2019 (2019-nCoV) uses the SARS coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry in target cells. Cell 2020;181:1–10. https://doi.org/10.1101/2020.01.31.929042.

[6] Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, Huan Yi, Yang P, Zhang Y, Deng W, Bao L, Zhang B, Liu G, Wang Z, Chappell M, Liu Y, Zheng D, Leibbrandt A, Wada T, Slutsky AS, Liu D, Qin C, Jiang C, Penninger JM. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus–induced lung injury. Nat Med 2005;11(8):875–9. https://doi.org/10.1038/nm1267.

[7] Ferrario CM, Jessup J, Gallagher PE, Averill DB, Brosnihan KB, Smith R, et al. Effect of renin-angiotensin system blockade on renal Angiotensin-(1–7)- forming enzymes, ACE-2 and receptors. Kidney Int 2005;68:2189–96. https://doi.org/10.1111/j.1523-1755.2005.00675.x.

[8] Wang G, Lai FM, Lai KB, Chow KM, Kwan CH, Li KT, Szeto CC. Discrepancy between intrarenal messenger RNA and protein expression of ACE and ACE2 in human diabetic nephropathy. Am J Nephrol 2009;29:524–31. doi: 10.1159/000185629.

[9] Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, et al. Acute kidney injury in patients hospitalized with COVID-19. Kidney Int 2020;98:209–18. https://doi.org/10.1016/j.kint.2020.05.006.

[10] Mohamed MMB, Lukitsch I, Torres-Ortiz AE, Walker JB, Varghese V, Hernandez-Arroyo CF, Alqudsi M, LeDoux JR, Velez JCQ. Acute kidney injury associated with coronavirus disease 2019 in urban New Orleans. Kidney360 2020;1(7):614–22. https://doi.org/10.34067/KID.0002652020.

[11] Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, Li J, Yao Y, Ge S, Xu G. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int 2020;97(5):829–38. https://doi.org/10.1016/j.kint.2020.03.005.

[12] Andreani TS, Itoh TQ, Yildirim E, Hwangbo D-S, Allada R. Genetics of circadian rhythms. Sleep Med Clinics 2015;10(4):413–21. https://doi.org/10.1016/j.jsmc.2015.08.007.

[13] Mills J, Minors D, Waterhouse J. The circadian rhythms of human subjects without timepieces or indication of the alternation of day and night. J Physiol 1974;240(3):567–94. https://doi.org/10.1113/jphysiol.1974.sp010623.

[14] Shimba S, Ishii N, Ohta Y, Ohno T, Watabe Y, Hayashi M, Wada T, Aoyagi T, Tezuka M. Brain and muscle Arnt-like protein-1 (BMAL1), a component of the molecular clock, regulates adipogenesis. Proc Natl Acad Sci 2005;102(34):12071–6. https://doi.org/10.1073/pnas.0502383102.

[15] Wang S, Lin Y, Yuan X, Li F, Guo L, Wu B. REV-ERBα integrates colon clock with experimental colitis through regulation of NF-κB/NLRP3 axis. Nat Commun 2018;9(1):4246. https://doi.org/10.1038/s41467-018-06568-5.

[16] Shearman LP, Sriram S, Weaver DR, Maywood ES, Chaves I, Zheng B, et al. Interacting molecular loops in the mammalian circadian clock. Science 2000;288(5468):1013–9. https://doi.org/10.1126/science.288.5468.1013.

[17] Sengupta S, Tang SY, Devine JC, Anderson ST, Nayak S, Zhang SL, Valenzuela A, Fisher DG, Grant GR, López CB, FitzGerald GA. Circadian control of lung inflammation in influenza infection. Nat Commun 2019;10(1). https://doi.org/10.1038/s41467-019-11400-9.

[18] Edgar RS, Stangherlin A, Nagy AD, Nicoll MP, Efstathiou S, O'Neill JS, Reddy AB. Cell autonomous regulation of herpes and influenza virus infection by the circadian clock. Proc Natl Acad Sci USA 2016;113(36):10085–90. https://doi.org/10.1073/pnas.1601895113.

[19] Zhang Z, Hunter L, Wu G, Maidstone R, Mizoro Y, Vonslow R, Fife M, Hopwood T, Begley N, Saer B, Wang P, Cunningham P, Baxter M, Durrington H, Blaikley JF, Hussell T, Rattray M, Hogenesch JB, Gibbs J, Ray DW, Loudon ASI. Genome-wide effect of pulmonary airway epithelial cell–specific Bmal1 deletion. FASEB J 2019;33(5):6226–38. https://doi.org/10.1096/fj.201801682R.

[20] Zhuang X, Rambhatla SB, Lai AG, McKeating JA. Interplay between circadian clock and viral infection. J Mol Med 2017;95(12):1283–9. https://doi.org/10.1007/s00109-017-1592-7.

[21] Matsumura R, Node K, Akashi M. Estimation methods for human circadian phase by use of peripheral tissues. Hypertens Res 2016;39(9):623–7. https://doi.org/10.1038/hr.2016.68.

[22] Hilfenhaus M. Circadian rhythm of the renin-angiotensin-aldosterone system in the rat. Arch Toxicol 1976;36(3-4):305–16. https://doi.org/10.1007/BF00340536.

[23] Kala R, Fyhrquist F, Eisalo A. Diurnal Variation of Plasma Angiotensin II in Man. Scand J Clin Lab Invest 1973;31(4):363–5. https://doi.org/10.3109/00365517309084318.

[24] Fukuda M, Urushihara M, Wakamatsu T, Oikawa T, Kobori H. Proximal tubular angiotensinogen in renal biopsy suggests nondipper BP rhythm accompanied by enhanced tubular sodium reabsorption. J Hypertens 2012;30(7):1453–9. https://doi.org/10.1097/HJH.0b013e328353e807.

[25] Kobori H, Nangaku M, Navar LG, Nishiyama A. The intrarenal renin-angiotensin system: from physiology to the pathobiology of hypertension and kidney disease. Pharmacol Rev 2007;59(3):251–87. https://doi.org/10.1124/pr.59.3.3.

[26] Coffman TM, Crowley SD. Kidney in hypertension: guyton redux. Hypertension 2008;51(4):811–6. https://doi.org/10.1161/HYPERTENSIONAHA.105.063636.

[27] Navar LG, Prieto MC, Satou R, Kobori H. Intrarenal angiotensin II and its contribution to the genesis of chronic hypertension. Curr Opin Pharmacol 2011;11(2):180–6. https://doi.org/10.1016/j.coph.2011.01.009.

[28] Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the second international consensus conference of the Acute Dialysis Quality Initiative Group. Crit Care 2004;8(4):R204–12. https://doi.org/10.1186/cc2872.

[29] Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA 2020;323(20):2052. https://doi.org/10.1001/jama.2020.6775.

[30] Acute kidney injury in COVID-19 patients. ESICMtv Webinar. Posted April 17, 2020. https://www.esicm.org/blog/?p=2789 [accessed November 22, 2020].

[31] Zhang G, Hu C, Luo L, Fang F, Chen Y, Li J, Peng Z, Pan H. Clinical features and short-term outcomes of 221 patients with COVID-19 in Wuhan, China. J Clin Virol 2020;127:104364. https://doi.org/10.1016/j.jcv.2020.104364.

[32] Ronco C, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. LancetRespir Med 2020;8:738–42. https://doi.org/10.1136/bmj.m3026.

[33] Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F, Moch H. Endothelial cell infection and endotheliitis in COVID-19. The Lancet 2020;395(10234):1417–8. https://doi.org/10.1016/S0140-6736(20)30937-5.

[34] Ronco C, Reis T. Kidney involvement in COVID-19 and rationale for extracorporeal therapies. Nat Rev Nephrol 2020;16(6):308–10. https://doi.org/10.1038/s41581-020-0284-7.

[35] Sun J, Zhu A, Li H, Zheng K, Zhuang Z, Chen Z, Shi Y, Zhang Z, Chen S-B, Liu X, Dai J, Li X, Huang S, Huang X, Luo L, Wen L, Zhuo J, Li Y, Wang Y, Zhang Lu, Zhang Y, Li F, Feng L, Chen X, Zhong N, Yang Z, Huang J, Zhao J, Li Y-M. Isolation of infectious SARS-CoV-2 from urine of a COVID-19 patient. Emerging Microbes Infect 2020;9(1):991–3. https://doi.org/10.1080/22221751.2020.1760144.

[36] Nogueira SÁ, Oliveira SC, Carvalho AF, Neves JM, Silva LS, Silva Junior GB, Nobre ME. Renal changes and acute kidney injury in covid-19: a systematic review. Rev Assoc Med 2020;66:112–7. doi: 10.1590/1806-9282.66.s2.112.