Review Article

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Pathways of Renal Involvement in Covid-19 infection

ABSTRACT:

Introduction: The causative agent of the highly infectious pandemic COVID-19 is SARS-CoV-2. According to WHO, as of August 18th 2020, the number of confirmed cases was and confirmed deaths was 771,635 from 216 countries. The most affected organ system in COVID-19 is the respiratory system. Later studies proved that the virus caused multiorgan infections. Several studies shows that SARS-CoV-2 causes damage to the renal system and; critically ill patients with associated renal damage show a higher mortality rate as compared to those patients with an unaffected renal system .This review article aims at updating the knowledge about associated kidney failure in covid-19 cases and its impact on the morbidity and mortality.

Summary: The virus damages the renal system through two different mechanisms: Direct and Indirect pathway. The direct pathway explains how the virus damages the renal system by directly acting upon the target cells in the kidney.SARS-CoV-2 gains its entry by binding to the ACE2 receptors on the target cell. The SARS-CoV-2 progresses its journey and extensively spread the infection, damaging the kidneys leading to the failure of the renal system. The indirect pathway of damage speaks about the secondary damage caused to the renal system due to cytokine release syndrome caused by SARS-CoV-2.This pathway also points out the formation of microthrombi in the glomerular capillaries and also kidney hypoperfusion. AKI in covid-19 patients can occur secondary to multiorgan failure.

Conclusion: This review aims to build a foundation concerning the direct pathway and indirect pathway by means of which SARS-Cov-2 infects the kidneys by summarizing the numerous researches carried out till date to update the knowledge gained thus far to aid in building better protocols for covid-19 management and decrease morbidity caused due to renal damage.

Keywords: COVID-19, AKI ,SARS-CoV-2 , renal system, CRS .

INTRODUCTION

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The causative agent of the highly infectious pandemic COVID-19 is SARS-CoV-2 (~~Anjum and Islam 2021~~Anjum and Islam 2021).~~..~~ As per the WHO updates on August 18 2020, the number of confirmed cases was 21,756,357 and confirmed deaths was 771,635 in 216 countries. The virus comes under the category was SARS-CoV-2. It causes SARS and the outbreak was in 2002. MERS-coronavirus (MERS-CoV) is another virus which was identified in 2012 in Saudi Arabia. It causes Middle East respiratory syndrome (MERS).

[1][2]Coronaviruses primarily infects the human respiratory system (~~Islam 2021~~ Islam 2021).

The most affected organ system in COVID-19 is the respiratory system. Later studies proved that the virus caused multiorgan infections. Autopsies of several dead COVID-19 patients confirmed its presence in CNS, GIT, CVS, kidney which accelerated the mortality rate.

Several studies shows that SARS-CoV-2 causes damage to the renal system and; critically ill patients with associated renal damage show a higher mortality rate– as compared to those patients with an unaffected renal system. [3]

Incidence of AKI in COVID-19 patients has hiked from 3%- 9% to 15%. It has been reported that 92% of the COVID-19 patients who had AKI died.[4].

This review article aims at updating the knowledge about associated kidney failure in patients of covid-19 and its impact on the morbidity and mortality.

DISCUSSION

1. DIRECT DAMAGE PATHWAY:

SARS-CoV-2 gains entrance to human body via the ACE2 receptors. ACE-2 receptors are massively distributed in the lung, liver, small intestine, and brain, though the presence is much lower as compared to the kidney.[5] With the help of S proteins, the virus identifies ACE2 receptors on the target cell.[6] In the airway epithelial cells,ACE2 works hand in hand with viral S-protein priming serine protease TMPRSS2.The cells of kidney have low TMPRSS2.But these have abundant potential viral S (spike) priming proteases, for example , - cysteine protease cathepsin B/L, serine protease dipeptidyl peptidase 4 (DPP4) and glutamyl aminopeptidase. These work with ACE2 allowing SARS-CoV-2 virus to enter into the proximal tubule cells of the kidney.[3]

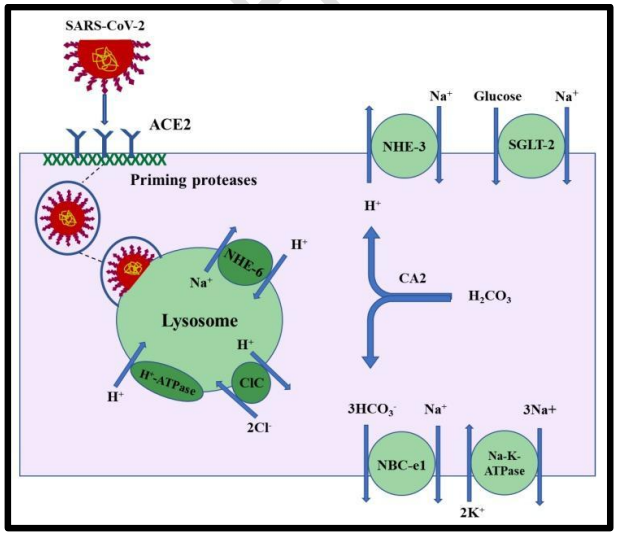

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Figure 1. Spike protein binds to the apical membrane of the PT cells of kidney -> the virus is internalized -> virus enters lysosomes.".[3]

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After entering the target cell through ACE2 receptors, they make way to lysosome through endosome. In lysosome, SARS-CoV-2 attains ability for replication and infection. The acidic pH in lysosomes favors the replication and maturation of the virus. Damage on the renal system in COVID-19 patients have the potential to accelerate the mortality rate thrice the usual.[3]

Several studies conducted all over the world provide clear proofs for direct renal infection in COVID-19 patients. The urine sample of COVID-19 patients in the 2^{nd}-3^{rd} week expressed viral fragments indicating onset of Acute Kidney Injury (AKI).[3]ACE2 receptors are expressed in a large number in the brush border cells, lesser in podocytes and absent in mesangial cells and glomerular endothelial cells. Therefore, proximal tubule is susceptible for major damage like acute tubular necrosis.

Pathogenesis of AKI in covid-19 patients was explained in several studies as follows: Conversion of angiotensin II to angiotensin I-VII is very important as it controls harmful effects like vasoconstriction, inflammation and thrombosis. This conversion is done by ACE2(soluble or insoluble form).As entry of SARS-CoV-2 causes a great depletion in the ACE2 , conversion of Ang II to Ang I-VII does not take place , subsequently increasing AngII level and decreasing Ang I-VII levels in the body of covid-19 patients. The body loses its control over those above-mentioned hazardous effects. The increased AngII binds to angiotensin receptors type 1 which further leads to coagulation ,pulmonary inflammation and finally AKI.[7]

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COVID-19 patients with AKI also exhibit proteinuria and a hematuria. The most common sign of kidney dysfunction in COVID-19 patients is mild to moderate proteinuria. There is increased filtration of plasma proteins in the glomeruli. This is due to the direct damage of podocytes, in the glomerular apparatus, and alterations in RAAS caused by the virus. Increased protein excretion can also be due to tubular injury caused by the virus.

In an autopsy followed by light and electron microscopic examinations of renal tissues of dead COVID-19 patients, conducted by Evan A Farkash, Allecia M Wilson and Jeffrey M Jentzen, 7 from the 26 dead patients expressed the presence of SARS-CoV-2 in renal tubular epithelium. They observed **tubular isometric vacuolization with light microscopy and double-membrane vesicles containing vacuoles with electronic microscopy**. They suggest this to be a histological marker for direct renal infection.[8]

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Diao and colleagues gave another strong proof of direct kidney infection in COVID-19. They could find the accumulation of SARS-CoV-2 antigens in the kidney tubules when they examined the viral nucleoplasm protein in-situ in a kidney post mortem.[9]

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In case of COVID-19 pneumonia , a study was conducted in Tongji hospital ,China. Out of those patients whose urine dipstick analysis was studied,75.4% showed abnormal results.[10]

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2. INDIRECT DAMAGE PATHWAY

A histopathological analysis conducted by Adrian Post and his team, on kidney autopsy of 26 COVID-19 patients, 3 were found to have segmented fibrin thrombus formation in glomerular capillary loops .This points out to a possibility of microthrombus formation in COVID-19 infection.[11].During their study they could also find that the cause of indirect kidney damage is induced cytokinin release and also , the possibilities of hypoperfusion of kidney due to restrictive fluid strategy, endothelial damage, third-space fluid loss and hypotension cannot be ignored.

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There was another suggestion which came up from the studies that AKI might be associated with multiorgan failure which was not due to viral replication in the kidney, but cytokine release syndrome(CRS) or cytokine storm. The role of CRS was confirmed by the elevated levels of TNF-α, interferon-γ, IL-1β ,IL-6 and IL-8 in critically ill covid-19 patients. [4] . From the above mentioned ,IL-6 is the most important pro-inflammatory cytokine. Tocilizumab and sarilumab are the monoclonal antibodies against IL-6 which are used in case of CRS[12]. AKI associated with CRS can have many causes underlying , like increase in vascular permeability, decrease in systemic volume, intrarenal inflammation and cardiomyopathy. This ends in cardiorenal syndrome type 1.This condition is clinically manifested as hypotension, intra-abdominal hypertension, edema and pleural effusion.[13]

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The CRS pathway is one among the three pathways that comes under renal involvement by cytokine damage. The other two pathways are hemophagocytic syndrome and increased cytokine generation. The mechanism of renal damage involved in these pathways is common, which is , direct cytokine lesion.[13]

Another fact which was mentioned in a study was that, severe unexplained fluid loss may occur in covid-19 with hyperpyrexia and GIT manifestations, like diarrhea, may result in decreased volume, which may contribute significantly to AKI in some settings. Mechanical ventilation support given to critically ill patients of covid-19 with pneumonia or ARDS can also develop AKI because they of their treatment with pressure. This kind of treatment can cause increased intrathoracic pressure leading to a rise in renal venous pressure. As the renal venous pressure increases ,renal filtration drops down. [14]. It was documented in a study held in New York that covid-19 patients who were given mechanical ventilation, developed AKI within the time of a day of admission.[15]Activation of RAAS is seen secondary to the increase in sympathetic tone ,which is due to any form of positive pressure ventilation. [14]

The significant relationship between AKI and respiratory failure is illustrated by the following findings from 1993 patients of covid-19 on whom the study was done.

i. AKI developed in patients of covid-19 within a shorter duration of time after they were provided with mechanical ventilation.
ii. 89.7% with mechanical ventilation support developed AKI when compared to those 21.7% without ventilator support.
iii. Stages 2 and 3 of AKI, which are the severe stages of AKI developed in 65.5% of patients with mechanical support for respiration while it did not happen in the 6.7% patients without ventilator support.
iv. Also ,RRT requirement was the most in supported patients – with 96.8%.[16]

KDIGO put forward a criteria for defining and staging AKI following which all the investigations associated with AKI are done.

- **Stage I** : Level of serum creatinine(SCr) increases by 1.5-1.9 times the baseline in 7 days or level of serum creatinine rise by 0.3mg/dl in 48 hrs.
- **Stage II** : Serum Creatinine level increases 2.9 times the baseline in 7 days
- **Stage III** : Level of serum creatinine increases 3 times the baseline in 7 days ;RRT initiated[16].

The definition for baseline of serum creatinine level is that the median of the serum creatinine level in the duration of 8-365 days before admission to the hospital[16] .

AKI associated with multiorgan failure not only results from CRS, but also because of the further mentioned reasons. It might be cardiomyopathy or viral endocarditis which can damage the renal system by cardiorenal syndrome type 1. Damages on the respiratory system, caused by covid-19, like damage to alveoli causes renal medullary hypoxia. High peaking in airway pressure and intra-abdominal hypertension can lead to renal compartment syndrome. Renal compartment syndrome is also caused by positive fluid balance. Another underlying reason can be rhabdomyolysis which causes tubular toxicity. Septic shock secondary to SARS-CoV-2 infection can also cause AKI.[13]

Luca Perico, Ariela Benigni, Giuseppe Remuzzi suggested possibilities of kidney inflammation and edema, based on their study of a CT scan report in which the kidney of the COVID-19 patient showed reduced density.[9].

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The damage caused can be prevented by disabling the replication and maturation of SARS-CoV-2 which is favored by the acidic endosomal pH. Weak bases like chloroquinone,NH_3Cl can increase the pH in the endosomal environment and can provide a successful antiviral effect.[17],[3]Concanamycin A, bafilomycin A are inhibitors of vacuolar H+ ATPases,they can prevent lysosomal acidification and hence prevent transport and replication of SARS-CoV-2.[3]Nephrotic drugs such as aminoglycosides, ACE inhibitors ,NSAIDS can also reduce renal damage in COVID-19.For checking tubular stress in the patients, nephrocheck is also suggested.[18].High intake of dietary sodium can cause down regulation of ACE2 expression in the kidney.[19]

Other risk factors associated with covid-19 AKI mentioned in a study including patients from USA and China were high BMI ,male sex ,DM ,chronic kidney disease, black race, CVS disease and CHF. It is also mentioned in this study that the development of AKI in covid-19 patients in China is less compared to its occurrence in USA.[14]

SYSTEMIC STUDY OF AKI ASSOCIATED WITH COVID-19

In almost 75% of the covid-19 patients (with AKI), AKI developed mostly within the first 72 hours of admission[20].In a study conducted on 193 patients of covid-19 by Li and his team, the observations were as follows :

- Patients with proteinuria – 59%
- Patients with hematuria – 44%
- Patients with increased blood urea nitrogen(BUN) level – 14%
- Patients with increased serum creatinine – 10% [21]

The main criteria for defining AKI was increased serum creatinine level (>0.3 mg/dl) in the patients. Increase in creatinine levels was seen within the first 20 days of admission. BUN increase was seen within 16 days of admission. D-dimer and uric acid levels increased within 20 days of admission. In CT scan analysis, they observed that the patients of covid-19 had a lower mean CT value (17.0-36.0 HU) ,compared to that of normal healthy individuals .[21]

KRT/RRT IN COVID-19 ASSOCIATED AKI

In a study conducted in 2020 by the Turkish society of nephrology, it was mentioned that among the 578 covid-19 patients on whom the study was conducted,13.3-35.7% patients were in need of kidney replacement therapy(KRT). 70.5% of the 578 patients had hypertension,43.8% had diabetes mellitus and 37.6% had chronic kidney disease as comorbidities.[22] The covid-19 Treatment Guideline Panel has recommended continuous renal replacement therapy for those adult covid-19 patients who are critically ill and are in need of KRT. PIRRT is advised in case if CRRT is unavailable. These above-mentioned renal therapies ,CRRT and PIRRT, are more preferred than intermittent hemodialysis .The requirement of continuous monitoring by nursing staff is not necessary in case of CRRT and PIRRT. Other than this, the panel also suggests peritoneal dialysis in case of any emergency in severely ill covid-19 cases.[23]In a study of Rupesh Raina et. al. ,they mentioned many advantages of CRRT viz, reduction in fluid overload. Building up immune stability, reduction of ventilation pressure, acid-base balance maintenance.[24]

ROLE OF *APOL1* GENE

APOL1 gene had been under study recently, considering that this gene has its contribution in FSGS associated with covid-19.APOL1 gene is found in 10-15% of the Afro-American race which encodes for a protein, apolipoprotein L1. Studies point out this gene as “high-risk gene” in this season of covid-19 pandemic. Several biopsy studies of kidneys which suffered from collapsing glomerulonephritis, now being called COVAN, had APOL1 gene [25] Collapsing Glomerulonephritis was not documented in any of the SARS-CoV-2 outbreaks that happened in the European and Chinese population probably because these population lack APOL1 genotype[26] . APOL1 gene is also a risk factor for end-stage kidney disease associated with hypertension[27].Two high risk alleles of the gene was documented in a 65-year-old Afro-American male patient of covid-19 in a study,viz.,APOL1 G1 and APOL1 G2.Another allele of the gene is G_{0} which is a low-risk allele. The genotypes of the gene that stands out to be a risk factor are G1/G1, G1/G2, or G2/G2.Though actual knowledge about the role of this gene is not much explained, the study specifies a few like alterations in the endosome , alterations in the ion channels in the cell membrane, dysfunction of mitochondria etc.[25] _APOL1 gene causes depletion in podocytes and also scarring in the glomerulus. In podocytes ,the gene mediates the activation of viral activity. This dysregulates the functions of the cell organelles causing great damages to the podocytes.[27-35]

CONCLUSION

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It can be concluded that damage on the renal system can result in increased morbidity among COVID-19 patients. SARS-CoV-2 can cause renal damage directly and indirectly. Entry mechanism of SARS-CoV-2 is same regardless of the system it attacks. ACE2 receptors with the help of viral spike protein(S-protein) help the virus enter the human body cells. Acidic pH in the endosomes and lysosomes favor the multiplication of the virus. Since renal damage is exhibited from the second week of covid-19, early monitoring of the renal system and initiating the required and appropriate treatment on the renal system can help prevent the entry of SARS-CoV-2 into the renal system and reduce fatality of COVID-19 due to AKI or indirect renal damage.

Increasing the availability and resources for conducting therapies like CRRT and PIRRT must be enhanced so that the mortality rate of covid-19 sufferers with AKI can be brought down.

As there are studies mentioning about APOL1 gene as a “high-risk gene”, patients presenting with collapsing glomerulonephritis should be tested for the inheritance of the gene, if the patient is an African descendant.

More comparative studies and researches based on evidences must to done to expand the knowledge about the mechanisms of renal damage, development of AKI and role of APOL1 gene. Journals on renal involvement in SARS-CoV-2 infected children are very few until now, which should be considered an important topic to be researched on ,as it would be of great help in future incidences .

Since December, a paramount of research has been done to find ways to bring down the morbidity and mortality associated with this viral infection. The wait for a vaccine forces the world to find alternative methods to decrease this morbidity. Research has proven that if renal damage can be prevented or managed at the right time, it can prove to save lives and reduce deaths caused by this vicious virus.

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