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Review article

Kidney diseases and COVID-19 infection: causes and effect, supportive therapeutics and nutritional perspectives

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ABSTRACT

Recently, the novel coronavirus disease 2019 (COVID-19), has attracted the attention of scientists where it has a high mortality rate among older adults and individuals suffering from chronic diseases, such as chronic kidney diseases (CKD). It is important to elucidate molecular mechanisms by which COVID-19 affects the kidneys and accordingly develop proper nutritional and pharmacological strategies. Although numerous studies have recently recommended several approaches for the management of COVID-19 in CKD, its impact on patients with renal diseases remains the biggest challenge worldwide. In this paper, we review the most recent evidence regarding causality, potential nutritional supplements, therapeutic options, and management of COVID-19 infection in vulnerable individuals and patients with CKD. To date, there is no effective treatment for COVID-19-induced kidney dysfunction, and current treatments are yet limited to anti-inflammatory (e.g. ibuprofen) and anti-viral medications (e.g. Remdesivir, and Chloroquine/Hydroxychloroquine) that may increase the chance of treatment. In conclusion, the knowledge about kidney damage in COVID-19 is very limited, and this review improves our ability to introduce novel approaches for future clinical trials for this contiguous disease.

1. Introduction

It has been shown that SARS-CoV-2, the cause of coronavirus disease 19 (COVID-19), attaches to its target cells using angiotensin-converting enzyme 2 (ACE2), which is expressed by epithelial cells of several organs, e.g., lung, intestine, blood vessels and kidney [1]. Although severe acute respiratory syndrome coronavirus (SARS-CoV-2) mainly causes respiratory disease, it might result in renal insufficiency and multi-organ failure (MOF) in serious cases [2]. High ACE2 expression was identified in both renal proximal tubular cells and bladder urothelial cells [3]. On the other hand, CKD patients or renal transplant recipients experience a clinically greater risk of severe COVID-19 infection and acuteness. In addition, researchers have reported frequent renal failure and greater occurrence of acute kidney injury (AKI) with poor clinical outcomes in patients with COVID-19 (Table 1) [4, 5]. Recent studies have shown that the prevalence of renal failure upon admission and the progression of AKI during hospitalization of COVID-19 patients was high and this was associated with increased inpatient mortality [6]. Moreover, male gender

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Table 1. Chronic kidney disease (CKD) and acute kidney injury (AKI) in patient with coronavirus disease 2019 (COVID-19).

Author	Study	Disorder	Number of patient	Country	Median or range age (years)	Sex (M&F)	Number (Percent)
Huang *et al.,* [165]	Retrospective	CKD	41	China	41–58	30M&11F	3 (7.31%)
Chen *et al.,* [166]	Retrospective	CKD	99	China	55.5	67M&32F	3 (3.03%)
Wang *et.al.,* [167]	Retrospective	CKD	138	China	56	78M&63F	56 (40.57%)
Li *et.al.,* [168]	Retrospective	CKD	17	China	22–65	9M&8F	8 (47.05%)
Guan et.al., [169]	Retrospective	CKD	1099	China	35–58	640M&459F	1 (0.09%)
Zhang *et.al.,* [170]	Retrospective	CKD	140	China	57	71M&69F	2 (1.42%)
Wu *et.al.,* [171]	Retrospective	CKD	80	China	46	39M&41F	1 (1.25%)
Liu *et al.,* 2020 [172]	Retrospective	CKD	12	China	62–72	1M&1F	2 (16.66%)
Murillo-Zamora *et al.,* 2020 [173]	Retrospective	CKD	740	Mexico	43.7	424M&316F	13 (1.8%)
Chen *et al.,* 2020 [174]	Retrospective	AKI	113 decreased	China	68	171M&103F	28 (25%)
Zhan et al., 2020 [175]	Case report	AKI	1	China	54	1M	1 (100%)
Yang *et al.,* 2020 [8]	Retrospective	AKI	52	China	59.7	35M&21F	15 (29%)
Zhou *et al.,* 2020 [176]	Case report	AKI	1	Iran	27	1 F	1 (100%)
Cheng *et al.,* 2020 [6]	Prospective cohort study	AKI	701	China	63	367M&334F	36 (5.1%)
Shi *et al.,* 2020 [177]	Cohort study	AKI	416	China	64	205M&211F	8 (1.92%)
Zheng *et al.* 2020 [4]	Retrospective	AKI	555	China	52	269M&286F	29 (6%)
Russo *et al.,* 2020 [178]	Retrospective	AKI	777	Northern Italy	70	59%M&41%F	176 (22.6%)
Zahid *et al.,* 2020 [179]	Retrospective cohort study	AKI	469	USA	66	268M&201F	128 (27.3%)
Richardson *et al.,* 2020 [180]	Case series	AKI	2634	USA	NA	NA	523 (22.2%)
Hong *et al.,* 2020 [181]	Retrospective	AKI	98	South Korea	55.4	38M&60F	9 (9.2%)
Cheruiyot *et al.,* 2020 [5]	Systematic review & meta-analysis	AKI	5832	-	-	-	1730 (29.66%)
Fu *et al.,* 2020 [182]	Systematic review and meta-analysis	AKI	49048	-	-	-	5152 (10.50%)
Robbins-Juarez *et al.,* 2020 [183]	Systematic review and meta-analysis	AKI	13137	-	-	-	2233 (17%)
Lazzeri *et al.,* 2020 [184]	Case series	AKI	336	Turkey	54	192M&144F	98 (29.2%)

AKI: Acute kidney injury; **M**: Male; **F**: Female; **CKD**: Chronic kidney disease; **US**A: United States of America.

and kidney disease independently correlated with higher mortality risk, suggesting renal function must be particularly monitored in order to efficiently control the disease [7, 8, 9].

Several clinical outcomes, such as sepsis, acute respiratory distress syndrome (ARDS), respiratory failure, coagulopathy, septic shock, AKI, and acute myocardial injury have been shown to be higher in non-survivor patients [10]. Moreover, systemic inflammation along with MOF can induce renal injuries through multiple mechanisms, such as the renal hemodynamic modifications, induction of the immune cells, endocrine dysregulation, as well as the massive release of inflammatory cytokines which result in tubular and glomerular cell injuries [11]. Furthermore, a weak immune system caused by patient's poor nutrition may jeopardize the body's ability to fight COVID-19. It seems that nutritional status can influence clinical outcomes in patients with underlying kidney disease. COVID-19 can cause moderate or severe kidney injury with signs including hematuria, proteinuria, elevated urea nitrogen, and creatinine, but the effects may ease over time (REF). The exact impact of COVID-19 on the kidneys is not yet clear but kidney cells have angiotensin-converting enzyme 2 receptors that enable the SARS-CoV-2 to attach, penetrate, invade, replicate, and potentially damage the host tissue. Another possibility is related to pneumonia that is often observed in severe cases of COVID-19 infection and could induce kidney dysfunction in patients via aberrant decreases in blood oxygen level.

The immune response to the SARS-CoV-2 may also be responsible for the observed effects. In this case, the hyper-activation of the immune system during COVID-19 infection in some patients could lead to the so-called cytokine storm and this sudden, large influx of cytokines can cause severe inflammation and destroy kidney tissue. Finally, SARS-CoV-2 can cause the formation of tiny clots in the bloodstream, which can clog the smallest blood vessels in the kidney and consequently impair renal circulation and function. In such conditions recommended nutritional supplements are vitamins (A, C, D, and E), natural ingredients (like Quercetin) trace elements (Zinc, Selenium, Copper, and Magnesium), and probiotics (like *Lactobacillus* and *Bifidobacterium* species). Protocols that minimize the infection risk and increase the overall recovery and survival are critical among all other public healthcare measures. This review is aimed at providing current information on kidney diseases and COVID-19. PubMed, Scopus, Science Direct, and Google Scholar were searched using the following keywords: COVID-19 OR SARS-CoV-2 OR 2019-nCoV, kidney diseases, chronic kidney disease, CKD, acute kidney injury, acute renal injury, AKI, kidney transplantation and nutritional supplements. In this review, we discuss the causes and potential mechanisms of COVID-19-induced kidney disease, some potential therapeutic options including nutritional factors, and suggest a comprehensive approach for COVID-19 management in kidney disease.

2. Chronic kidney disease and COVID-19

The presence of CKD might be viewed as one of the key factors for susceptibility to COVID-19 [12]. Based on the statement of the United States Centers for Disease Control and Prevention (CDC), about 15 percent of the adults in the United States suffer from CKD [13]. In addition, patients with end-stage kidney disease were considered to be a largely susceptible group for COVID-19 with an infection rate of 16% [14]. The prevalence of CKD in COVID-19 patients has been reported to be about 0.09%–47.05% (Table 1). Therefore, it is necessary to advise the CKD patients to take precautionary actions to lower the risk of exposure to SARS-CoV-2. Importantly, it is necessary for physicians to engage in close monitoring of the patients with CKD who are suspected to have COVID-19 for early determination of the symptoms of the disease [12].

3. Kidney transplant recipients and COVID-19

Infection and development of COVID-19 have been observed in patients with a kidney transplant in Italy [15]. In fact, COVID-19 infection in kidney transplant recipients might be life-threatening and require intensive care unit admission [2]. Akalin and colleagues showed a very high early death amongst the kidney transplant recipients suffering from

COVID-19 (28%) compared to the general population (1–5%) [16]. Compared to the general population, the kidney transplant recipients who contracted with COVID-19 showed similar manifestations (Table 2) [17, 18, 19]. However, they had much serious COVID-19 pneumonia, albeit a majority of the patients recovered following a lengthier virus shedding and clinical course.

Furthermore, physicians are expected to identify and minimize any risks caused by infections. It has been suggested that if the number of clusters of differentiation (CD) 3, CD4 as well as CD8 cell count are very low in the recipients with COVID-19, the dose of immunosuppressive drugs should be reduced. This is particularly the case for those who are taking anti-thymocyte globulin which declines T cell subsets for several weeks [16].

4. Kidney injuries in COVID-19, causes and potential mechanisms

Previously, it was thought that the kidneys are not targeted by viruses. This viewpoint has changed over time. Theoretically, kidney infections by viruses can be caused in a variety of ways. When trapped in glomeruli, viruses accumulate and multiply, and may cause direct damage to the host tissue. Likewise, tissue antigens can indirectly stimulate responses, and as a local stimulant, viruses can make the kidneys susceptible to bacterial invasion. Indeed, any infection in the body can activate viruses present in the kidneys, and thus cause glomerulonephritis and pyelonephritis by a viral infection [20].

Recent findings have suggested that hematuria and proteinuria could result in during COVID-19 disease, whereas some patients might exert signs of AKI. As with previous reports, the viral RNA presence in kidney tissue and urine of this infection, suggesting that the urinary tract is also a major target of SARS-CoV-2, and a direct effect into renal tubules and interstitium is possible [21, 22]. Researchers have been looking into possible mechanisms of renal failure following COVID-19 viral infection and the causes of impaired kidney function. Recent studies have shown that the coronavirus enters the cell through ACE 2 and activates Toll-like receptors (TLRs). TLRs play an important role in innate immunity. These receptors detect molecules that are released from damaged tissues. TLRs potentially activate transcription factors, regulate the expression of pro-inflammatory cytokines/chemokines, and are also involved in the innate immune response. These receptors have been reported to play an important role in the pathogenesis of kidney disease (Figure 1). Excessive activation of these receptors is associated with many kidney diseases including ischemic kidney damage, AKI, end-stage renal failure, acute tubulointerstitial nephritis, acute renal transplant rejection and delayed allograft function [23].

On the other hand, TLRs activate interferon-alpha, cytokines, tumor necrosis factor-alpha (TNF-α), induce secretion of interleukins (IL)-6 and -12 (Figure 1), which in turn result in the production of $CD8^{+}$-specific cytotoxic T-cells and $CD4^{+}$ helper T-cells leading to the production of antigen-specific B-cells and antibody production [24]. If the body is unable to provide a proper immune response to a viral infection, the inflammation can cause a cytokine storm, acute respiratory distress syndrome, and diffuse organ involvement [25]. A new study used single-cell RNA sequencing analysis to find the accurate location of ACE2 and transmembrane protease serine (TMPRSS) expression and distribution in kidney cells. They found that podocytes and proximal straight tubule cells are likely to be targeted by SARS-CoV-2. In addition, AKI is induced as a result of the cell response to the viral infection, highlighting that AKI is strongly associated with high mortality and morbidity in COVID-19 patients. Concomitant pneumonia in renal patients may be accompanied by synergistic attacks of the cytopathic effects of the virus and systemic inflammatory response, especially in acute cases associated

Table 2. Recipients of the kidney transplant, who needed hospitalization for the approved coronavirus disease 2019 (COVID-19).

Author	Study	Patient number	Country	Age	Sex: M&F	The most first clinical symptoms	Result or suggestions to therapy
Zhu *et al.*, 2020 [19]	Case report	1	China	52	1M	Dyspnea, Fatigue, pain and tightness in chest, loss of appetite, nausea, cough, intermittent abdominal pain.	Decreased utilization of the immuno-suppressant and lower dosage of methyl-prednisolone-based treatment.
Zhang *et al.*, 2020 [61]	Case series	5	China	45	4M &1F	Fever, cough, myalgia or fatigue, & sputum production	Lower dosage of the maintenance immuno-suppressive treatment in the course of hospitalization.
Guillen *et al.*, 2020 [185]	Case report	1	Spain	50	1 M	Gastrointestinal viral disease & fever	Immunocompromised patients might present with atypical clinical manifestations.
Gandolfini *et al.*, 2020 [15]	Case report	2	Italy	75 52	1 M 1 F	Fever, cough & myalgia	The patient received colchicine to reduce inflammation.
J Am Soc Nephrol *et al.*, 2020 [17]	Case series	15	USA	51	10M &5F	Fever &/or cough	Immuno-suppression reductions as well as the addition of hydroxy-chloroquine and azithromycin were used to manage the patients.
Zhu *et al.*, 2020 [18]	Retrospective	10	China	45	8M &2F	Cough, fever, fatigue, and shortness of breath.	Transplant recipients experienced more sever COVID-19 pneumonia. Immunosuppressant reduction & low-dose methylprednisolone therapy.
Arpali *et al.*, 2020 [186]	Case report	1	Turkey	28	1 F	Fevers, malaise, sore throat, & rhinorrhea	A kidney transplant patient with a mild form of SARS-CoV-2 infection
Fernández-Ruiz *et al.*, 2020 [187]	Case series	18	Spain	71	14M &4F	Fever & respiratory symptom	CRP levels at various points were higher among recipients, which showed unfavorable outcome.
Banerjee *et al.*, 2020 [2]	Case series	7	UK	54	4M &3F	Fever & respiratory symptom	Supportive care and immunosuppressant reduction.
Fontana *et al.*, 2020 [188]	Case report	1	Italy	61	1M	Persistent fever and shivering	Immunosuppression reduction & use of hydroxychloroquine as well as Tocilizumab.
Akalin *et al.*, 2020 [16]	Case series	36	USA	60	26M&10F	Fever, cough, dyspnea, & myalgia	The decreased fever as one of the early symptoms, the decreased CD3, CD4, and well as CD8 cell count & faster clinical development.
Sharma *et al.*, 2020 [189]	Case-control study	41 SOT	USA	60	34M&7F	Shortness of breath followed by cough, fever.	COVID-19 severity was similar but the use of RRT was higher in SOT COVID-19 patients.

USA: United States of America, **UK**: United Kingdom, **M**: Male, **F**: Female; CRP: C reactive protein; **COVID-19**: Coronavirus disease 2019, **SARS-CoV-2**: Severe acute respiratory syndrome coronavirus 2, **CD**: Cluster of differentiation; **SOT**: Solid organ transplant; **RRT**: Renal replacement therapy.

with severe proteinuria [26]. However, these reports and the proposed mechanism of the pathophysiology of AKI during COVID-19 are just beginning and still needs to be verified in tissues from COVID-19 cases and examination in animals and cells.

A recent clinical study demonstrated a potential correlation between the level of plasma proinflammatory factors (IL-2, IL-7, IL-10, granulocyte-colony stimulating factor (GSCF), interferon gamma-induced protein 10 (IP10), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 alpha (MIP1α) and TNF-α) and severity of COVID-19 infection [27]. Therefore, the cytopathic effects of the virus through the inflammatory response and the direct effect of the virus on kidney cells can be accounted as possible mechanisms of kidney damage (Figure 1) [27]. Thus, COVID-19 by inducing AKI leading to immune activation, rise in the level of inflammatory chemokines, mediators, pro-inflammatory cytokines, and inducible nitric oxide synthetase through M1 subtype of macrophages to form reactive cytotoxic peroxynitrite ($ONOO^-$), all of which mediate renal failure. Furthermore, cytokine storm syndrome has a major role in several infection-mediated multiple organ dysfunction syndromes, such as kidneys [21]. Evidence suggests that IL-6 can be can be used as a marker in cytokine storm situations which is increased in this pandemic disease [28]. Cytokine generation has been noted in cases of invasive mechanical ventilation, continuous kidney replacement therapy (CKRT) and extracorporeal membrane oxygenation (ECMO) [29]. Approximately all the patients with AKI who receive KRT are on mechanical ventilation. These findings indicate that cytokine storm and severe hypoxemia could result in AKI, without the direct invasion on the kidney by the coronavirus [30]. Recent findings based on retrospective study demonstrated alveolar damage associated with the tubular injury which called the lung-kidney axis-in ARDS [31]. IL-6 overproduction due to lung–kidney bidirectional damage positively correlates with higher alveolar-capillary permeability and pulmonary hemorrhage following AKI [32].

Multiple clinical studies have suggested that there is strong crosstalk between the kidneys and heart [33, 34]. For this reason, the reported findings suggest cardiomyopathy and acute viral myocarditis could contribute to AKI through renal vein congestion, hypotension, renal hypoperfusion and reduction in glomerular filtration rate (GFR) in COVID-19 patients. These findings are important in CKD patients who are exposed to the SARS-CoV-2 and such patients should be given appropriate treatment and protection strategies. Previous studies have shown that podocytes and proximal straight tubule cells act as host cells. Podocytes and proximal cells play an important role in urinary filtration, reabsorption, and secretion. Podocytes are significantly susceptible to bacterial and viral attacks, and damage to podocytes easily induces severe proteinuria. According to previous reports regarding other types of coronavirus, namely Middle East respiratory syndrome coronavirus (MERS-CoV), renal failure was induced by kidney cell apoptosis through increasing the fibroblast growth factor-2 (FGF2) and Smad7 expression [35]. Interestingly, inhibiting Smad7 by antisense oligonucleotide targeting Smad7 efficiently decreased MERS-CoV replication and resulted in renal protection against virus assault [35]. Thus, it should be considered that kidney injury in COVID-19 patients might be associated with renal cell apoptosis induced through the higher expression of FGF2 and Smad7. Dehydration may be another possible mechanism by which the SARS-CoV-2 induces AKI. Dehydration is associated with fever in COVID-19 patients who often suffer from increased sweating. Fluid and electrolyte loss subsequently result in the reduction of GFR and AKI in severe cases although in mild cases dehydration can be reversed by increasing fluid intake [36]. Other potential mechanisms of AKI can be due to inappropriate use of nonsteroidal inflammatory drugs, and the presence of underlying diseases such as diabetes and hypertension (Figure 1) [37, 38]. Autopsy examinations revealed that SARS-CoV-2 contaminates renal tubules directly and causes severe kidney injury through cytopathogenic action or by infiltration CD68 + macrophages into interstitial compartment, along with tubular accumulation of complement membrane attack complex (C5b-9) [39, 40]. In addition to the direct virulence of SARS-CoV-2, many factors contributing to AKI include drug-induced rhabdomyolysis, hypoxia, and aberrant coagulation [41].

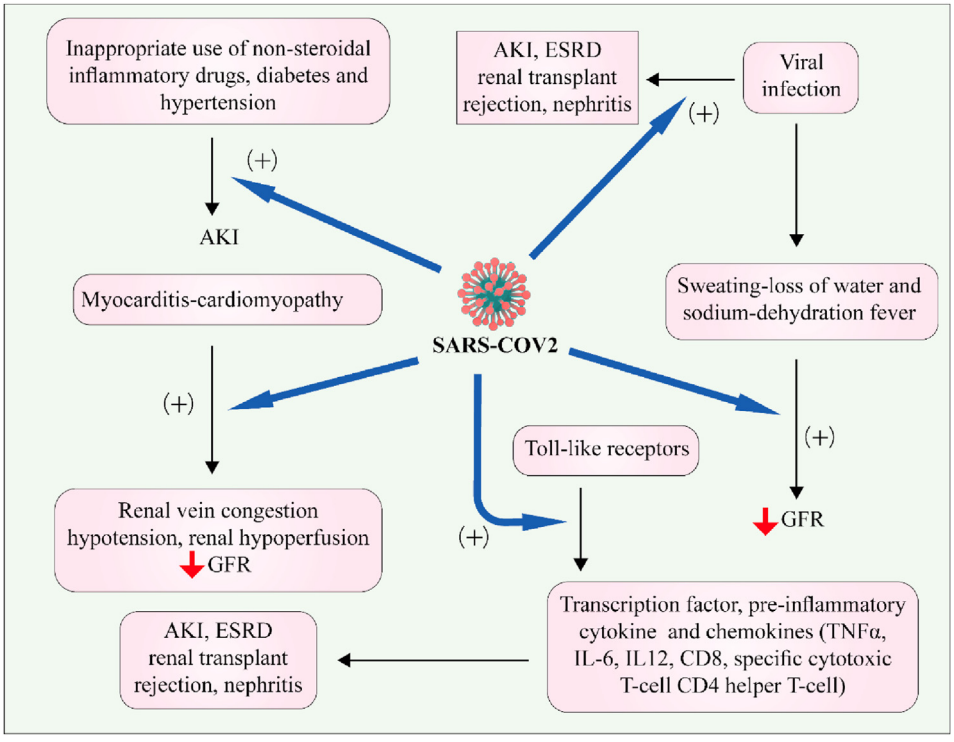

Figure 1. Renal insufficiency following SARS-COV-2 infections, causes and potential mechanisms. Kidney infections by viruses can be caused in a variety of ways. Excessive activation of Toll-like receptors results in renal dysfunction. Abbreviations: SARS-COV-2: Severe acute respiratory syndrome coronavirus 2; GFR: Glomerular filtration rate; ESRD: End-stage renal disease; AKI: Acute kidney injury.

Recently, SARS-CoV-2 was also shown to penetrate target cells through CD147, a receptor on host cells with interaction with diverse components such as cyclophilins, caveolin-1, and integrins. CD147 has also been found to play a key role in various kidney diseases by immune-inflammatory responses and aberrant cell cycle. Apparently, targeting the CD147-cyclophilins axis could be a potentially promising strategy to treat COVID-19 [42, 43].

5. Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) and COVID-19

Recently, ACEIs and ARBs were linked to COVID-19 infection due to the close association between ACE2 and SARS-CoV-2. ACE2 is a type I transmembrane metallocarboxypeptidase which could elicit viral entry response for SARS-CoV-2. ACE2 is broadly expressed in the gastrointestinal system, heart, kidney, and lung. According to the latest report, both ACEIs and ARBs could markedly augment ACE2 mRNA expression. Based on these findings, it is hypothesized that these drugs could deteriorate the condition of COVID-19 cases [44]. No study to date has been conducted to evaluate clinical data, so further studies are needed to investigate the potential undesirable impacts of these medications on COVID-19. The renin-angiotensin system (RAS) is a hormone system that modulates the development of hypertension in kidney diseases, fluid, salt balance, and systemic vascular resistance.

Angiotensin II (Ang-II) is a naturally occurring peptide hormone and the main active substrate of the RAS pathway that has the capacity to bind to type-1 receptors (AT1R), thereby promoting vasoconstriction in both afferent and efferent glomerular arterioles, and an increase in blood pressure, fibrosis, and salt retention in the human body [45, 46, 47]. The most important effect of Ang-II is the maintenance of GFR by rising renal vascular resistance and decreasing renal blood flow [48]. Medications that are commonly used to block the RASs, e.g. ACEIs and ARBs which have been licensed for the treatment of hypertension, heart failure, CKD, and diabetes might be detrimental to patients by facilitating the entry of the virus into cells due to overexpression of ACE2 receptors [49]. There is however a lack of evidence to support the effects of ACEI and ARB treatment on COVID-19 patients. In addition, ACEI and ARB did not increase morbidity or mortality [50]. According to the recent clinical study, treatment with ACEIs or ARBs resulted in cardiovascular and renal protection in COVID-19 cases while discontinuing these medications caused blood pressure destabilization and decompensation in HF patients, leading to a substantial increase in heart attacks and deterioration in renal function by increasing intraglomerular pressure and systemic blood pressure [51]. ACE2 as a SARS-CoV-2 receptor converts Ang II into Ang-(1–7), which acts on the Mas receptor, expressed on a variety of cell lineages including type 2 alveolar epithelial cells, mitigating blood pressure by vasodilation and through increasing renal sodium and water excretion, while decreasing inflammation by nitric oxide signaling pathway. Conversely, activation of ACE–Ang II signaling has been reported as having opposing effects, whereby ACE converts Ang I to Ang II, which increases blood pressure by inducing vasoconstriction, increasing renal tubular sodium and water reabsorption throughout the nephron, and increasing oxidative stress, inflammation and fibrotic markers through AT1R [52, 53, 54]. Another possible mechanism may be attributed to the fact that the SARS-CoV-2 entry into cells is mediated by downregulation of ACE2 expression, resulting in an increase in angiotensin II levels, and by deregulated conversion of Ang II (into Ang 1–7), with a possible loss of its beneficial effects [30]. Especially when AKI develops during hospitalization, severe infected patients often have the highest prevalence of anemia. Anemia is a potential risk factor in clinical course leading to hypoxemia, it eventually exacerbates peripheral tissue ischemia. Accordingly, many patients end up receiving a blood transfusion during the disease course. The pathogenesis and progression of anemia during COVID-19 infection has many reasons including inflammation and iron deficiency. Besides this, recent studies confirm that SARS-CoV-2 suppresses the heme biosynthetic pathway [55].

Viral glycoproteins binds to specific porphyrin ligands to produce a complex, whereas others consistently attack heme to detach the ferrous iron (Fe2+) forming porphyrin [55]. It should be noted that one mediator for virus entry, the glucose regulated protein 78 (GRP78), derived from bone marrow cells [56], suggesting that this may presumably affecting the erythropoiesis process [56]. Additionally, increased RBC distribution width (RDW) reported as a potential marker of slower erythropoiesis and turnover, has been correlated with enhanced

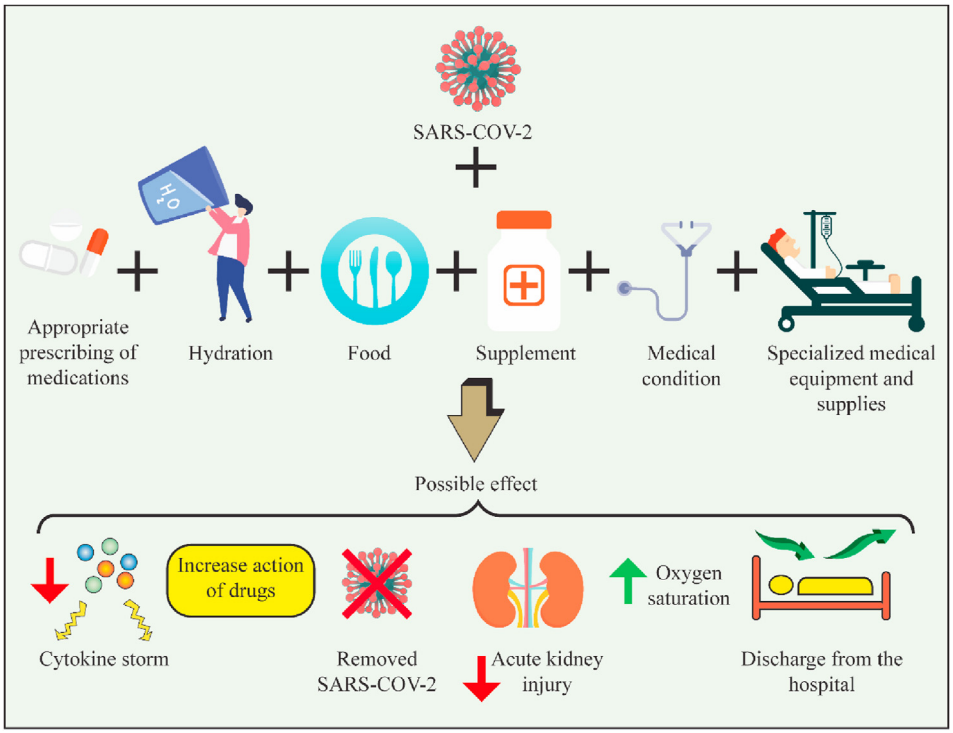

Figure 2. Patients with COVID-19 outcomes as well as underlying disorders can lead to an elevated risk of acute kidney injury and its consequences. Recommendations on the management of the COVID-19 with acute kidney injury are suggested at the bottom of the figure. Abbreviations: COVID-19: Coronavirus disease 2019; CRRT: Continuous renal replacement therapy; hrsACE2: Human recombinant soluble angiotensin-converting enzyme 2; SARS-COV-2: Severe acute respiratory syndrome coronavirus 2.

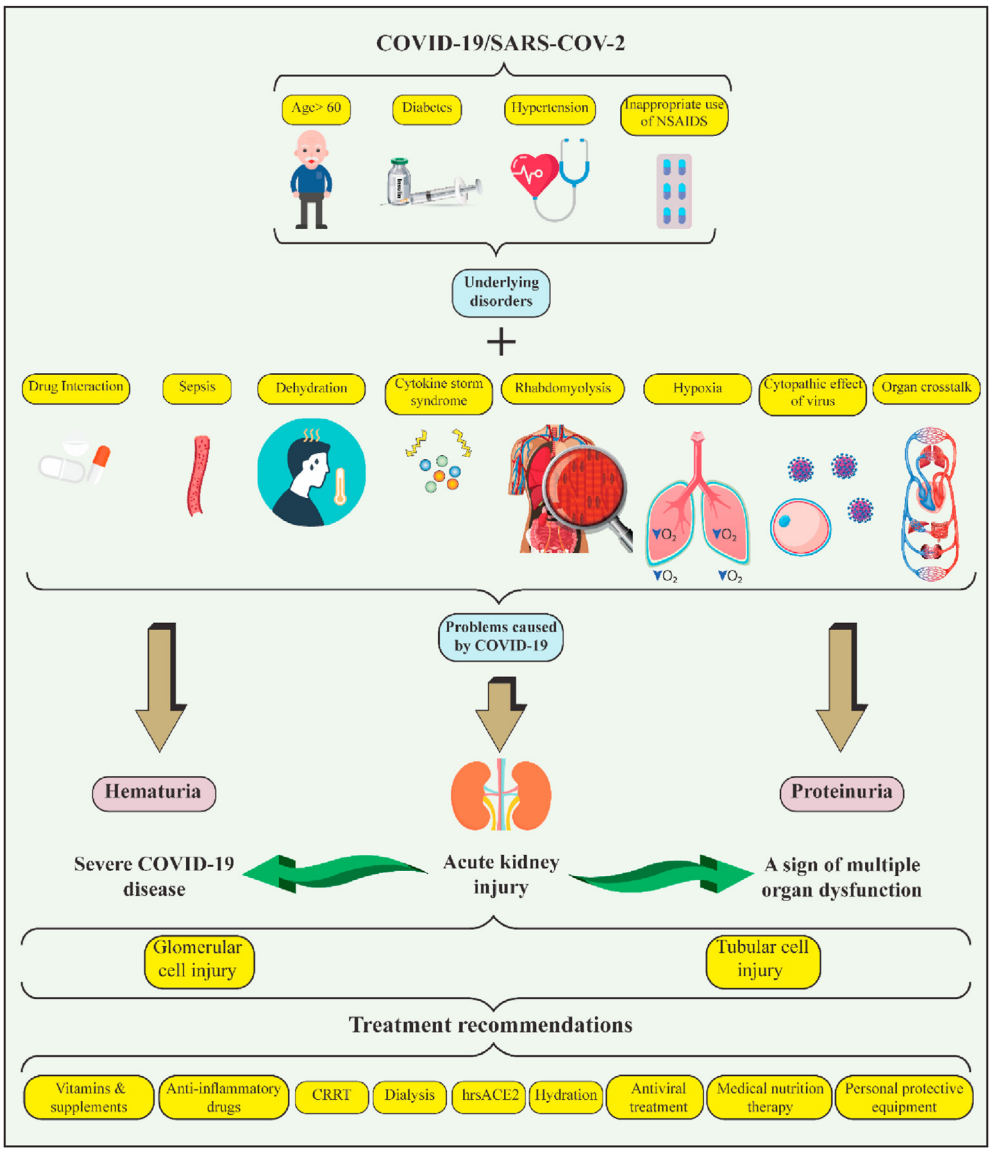

Figure 3. The possible effect of interaction between medications, food, supplement, medical condition, specialized medical equipment and supplies in the care of coronavirus disease 2019 (COVID-19) patients with acute kidney injury. Abbreviation: SARS-COV-2: Severe acute respiratory syndrome coronavirus 2.

COVID-19 mortality [57]. In addition, as reported by Ehsani [58], there exist a similarity between the cytoplasmic tail of the SARS-CoV-2 virus spike glycoprotein and the hepcidin binding protein, potentially contributing to disorder of iron metabolism and homeostasis. SARS-CoV-2 by its hepcidin-like function may describe the extremely elevated ferritin levels found in COVID-19 patients [30].

6. Management of COVID-19 in kidney injury

Managing COVID-19 complications in the cases suffering from kidney diseases would have higher difficulties, particularly, in immunosuppressed patients or cases with severe comorbidity (Figures 2 and 3) [59]. It is notable that in the high-risk population, the protocol to screen for SARS-CoV2 might be necessary for re-assessment [60]. Genetic insertion/deletion (I/D) polymorphism in intron 16 of ACE2 is related with changes in tissue and circulating concentrations of ACE. The D allele is highly related with a decreased ACE2 expression. I/D polymorphism reveals substantial geographical discrepancy, with low D allele frequencies in population highest rate of COVID-19 cases and mortality. ACE polymorphism and susceptibility to SARS-CoV-2 might illuminate how the African American community develop more serious types of COVID-19 compare with Western people [39]. Thus, a therapeutic protocol is suggested on the basis of the patients features, the disease stage as well as its seriousness by antiviral, immunomodulatory, as well as immunosuppressive factors [59]. Zhang and colleagues indicated that a mild COVID-19 infection in the kidney transplant recipient could be handled with the symptomatic supportive treatments in combination with the adjusted maintenance immunosuppressive therapies [61].

7. Nutritional immunity in viral infections with particular attention to COVID-19

As one of the leading causes of morbidity and mortality, viral acute respiratory infections (ARI) are a major global health problem. The most common viral pathogens causing acute respiratory infections include orthomyxoviruses (influenza A, influenza B and influenza C), paramyxoviruses (including the parainfluenza viruses (PIV) 1–4, respiratory syncytial virus (RSV) and human metapneumovirus (hMPV)), picornaviruses (including the species rhinovirus (RV) A, RVB, RVC and the enteroviruses A-D), coronaviruses, adenoviruses, and human bocavirus

(HBoV) [62, 63]. The influenza vaccine is the only routinely administered vaccine for a viral respiratory pathogen, which is not fully effective/protective in different seasons and different age groups. Effective antiviral drugs are available only for a limited number of viruses including infections caused by HIV, herpes viruses, hepatitis B and C viruses, and influenza A and B viruses [64, 65, 66, 67]. Therefore, the treatment of viral respiratory infections by new agents is needed wherein developing new pharmacological interventions to prevent and treat respiratory viruses has been recently started by the WHO initiative battle against respiratory viruses [10].

In this regard, the correlation of the risk and course of infections with nutritional status have recently attracted great attention. The metabolic changes in the course of host-pathogen interaction have been highlighted in several experimental and pre-clinical studies. The impact of these alterations on the antimicrobial function of host immune and resistance to infection as well as on pathogen proliferation and pathogenicity have also been elucidated [68, 69].

The dormant or virulent behavior of the pathogen could be influenced by the nutrient content of their environment [70]. The availability and concentrations of different metabolites in the cell and the environment are two significant factors that are believed to impact the immune responses, stimulation or inhibition of antimicrobial immune effector mechanism or establishment of disease tolerance to infection [71, 72]. Nutritional deficiencies and metabolic imbalances have been found to be associated with the risk and outcome of specific infections. Therefore, metabolic interventions and nutrient concentrations can impact the risk of infection in primary care settings or on disease outcomes in critically ill patients. In addition, clinical studies have found associations of nutritional deficiencies and metabolic imbalances with the risk and outcome of specific infections [73, 74].

An intact immune system is the most effective weapon against viral infections. There are several vitamins and trace elements that are essential for the normal function of the immune system [75]. In addition, vitamin supplementation has shown a promising effect on increasing immunity in viral infections. Vitamin A and D supplementation have increased the humoral immunity of pediatric patients following influenza vaccination [76]. A high dose of zinc supplementation has been shown to enhance the immunity of patients with Torque Teno virus (TTV) [77]. Similarly, supplementation with selenium has shown a positive response following an influenza vaccination challenge [78]. Supplementation with micronutrients in addition to several herbals and probiotics was found to be also effective for the treatment and management of viral infections [79]. Moreover, several nutraceuticals and probiotics have also been shown to possess a supportive role in enhancing immune responses [80, 81]. Recent researchers have emphasized the importance of optimal nutritional status for the proper function of the immune system against viral infection and nutrition researchers have provided nutritional advice to prevent damages to the lungs caused by a coronavirus and other lung infections [82, 83].

8. Nutrients and bioactive compounds

The following nutrients and compounds have immune-modulating properties and many have been shown to have general anti-viral properties. Whether these nutrients and bioactive compounds are potentially effective for COVID-19 is still to be clarified, however, these are typically protective and can effectively help to support patients overall health. Worldwide, ~2 billion people are affected by micronutrient deficiencies, including vitamins A, C, and E and the minerals zinc, iron, and iodine. Impaired intellect, poor growth, and increased mortality and susceptibility to infection are considered as the common immunological effects of nutritional deficiency. These effects might be due to their correlation with the development of the immune system and antibody formation. Therefore, supplementation, food fortification, and dietary modifications could help prevention of disease comorbidities. Of particular importance is the fact that the Copenhagen Consensus on Hunger and Malnutrition has proposed that efforts to provide vitamin A, iron, iodine and zinc generates would be more cost-effective than trade liberalization or malaria, water and sanitation programs [84].

8.1. Vitamin A

Maintaining vision, promoting epithelial barrier integrity, growth and development are crucially dependent on vitamins. This fat-soluble vitamin is known to have a regulatory role in cellular and humoral immune responses, accordingly it has a pivotal role in enhancing immune function [85]. In infants, vitamin A supplementation has been shown to improve antibody responses following several vaccines and anti-rabies vaccination [85, 86]. Similarly, children (2–8 years) deficient in vitamin A and D have been found with an enhanced immunity to influenza through vaccination following supplementation with vitamin A and D [76]. Retinoic acid, a metabolite of vitamin A, also helps regulate the immune system via the gut microbiome [87]. Animal studies suggest that the ACE2 receptor which is the cellular receptor for SARS-CoV-2 may be upregulated by all-trans retinoic acid (ATRA), a vitamin A derivative [88, 89]. The query is whether there is nutritional advice to support individuals with renal insufficiency including patients who are ESRD or have AKI to protect against the ravages of COVID-19? Data suggest that inability to biologically access critical micronutrients may play a role in the development and progression of these comorbid conditions in patients with CKD. However, available literature has shown that circulating concentrations of vitamin A seem to be altered in patients with CKD which might simply be due to decreased kidney function, and not the presence of other medical conditions [90]. Nonetheless, the possible link between the vitamin A-COVID-19-kidney disease axis is required to be more clarified.

8.2. Vitamin C

Immune health is significantly dependent on Vitamin C as an important nutrient, specifically for white blood cells to fight infections. Adequate iron is required to protect against vulnerability to infection. This vitamin also enhances iron absorption and could conceivably contribute to its immune-modulating effects [91]. Vitamin C has an essential antioxidant activity due to its ability to readily donate electrons and is an enzymatic cofactor for a family of biosynthetic and gene regulatory monooxygenase and dioxygenase enzymes involved in many physiological reactions in the body, especially immune potentiation [92]. Vitamin C supplementation protects epithelial barrier function homeostasis and enhances the free radical scavenging activity of the skin, thus significantly protecting against oxidative stress [91]. Vitamin C contributes to immune defense by supporting various cellular functions of both the innate and adaptive immune system, modulating inflammatory mediators, and influencing epithelial barriers [91]. Impaired immunity and higher susceptibility to infections have been shown to be associated with vitamin C deficiency [93]. It is extremely beneficial to quench harmful reactive oxygen species (ROS) used by immune cells to deactivate viruses, yet can cause inflammation and damage human cells. ROS are especially critical in patients with the respiratory disease since they cause damage to the lungs. This might participate in the inflammatory storm that affects COVID-19 patients. Having a powerful antioxidant system to clear such excess ROS would be helpful in symptomatic COVID-19 patients [94]. Accordingly, supplementation with vitamin C has been found effective in both preventing and treating respiratory and systemic infections [91]. Although there is no randomized controlled trial (RCTs) investigating vitamin C to prevent or treat of specific viral infections, previous animal studies confirm that it is a substantial factor for antiviral immune responses against the influenza A virus infection by elevated IFN-α/β production [92]. In contrast, in a systematic review and meta-analysis, no conclusive evidence has been found to indicate that there is preventing and treating efficiency in using vitamin C [32]. Kidney disease has been reported as a complication of vitamin C

insufficiency. It is believed that a higher intake of vitamin C, is an effective way to prevent and treat the common cold. Meta-analyses suggest a consistent and statistically significant benefit of vitamin C to prevent the common cold or to reduce its duration and severity and support respiratory defense mechanisms [95]. However, oxalosis which is the accumulation of the metabolic by-product of ascorbic acid must be inhibited in CKD patients, therefore intakes greater than 100–200 mg/day should be avoided [96]. In addition, due to the lack of effective therapy for COVID-19 and the low cost and safety of healthful rich vitamin C foods, it may be worthwhile to be diligent regarding the adequate but non-toxic amount of vitamin C in our daily foods during the COVID-19 pandemic.

8.3. Vitamin D

Once vitamin D is produced either in the skin from 7-DHC or absorbed from the diet, it must be activated first to 25OHD and then to its active form 1,25(OH)2D in a multistage liver and kidney metabolisms. The production of vitamin D is not enzymatic but depends on UVB [97]. Vitamin D is a fat-soluble essential vitamin that has a substantial role in promoting innate immune responses and suppressing adaptive immune responses (Figure 4) [98]. Multiple cross-sectional studies have shown that vitamin D deficiency is associated with increased susceptibility to serious viral respiratory tract infections [98]. The beneficial effects of vitamin D on protective immunity are partly due to crosstalk between vitamin D metabolism, VDR signaling, and innate immunity, where TLR binding leads to increased expression of both 1-α-hydroxylase and VDR. This results in the binding of the 1,25 D-VDR-RXR heterodimer to the VDREs of the genes for cathelicidin and beta-defensin 4 and subsequent transcription of these proteins [99]. Immune responses may be enhanced by cathelicidin and some β-defensins that not only act against microbes, but also have chemoattractant capabilities, leading to recruitment of neutrophils, monocytes, and other immune cell molecules to the site of infection (Figure 4). Vitamin D substantially exerts a modulatory role in the adaptive immune system. Recently, studies evaluating 157 potential mechanisms showed that vitamin D plays a pivotal inhibitory role in the innate immune sensing of respiratory viral infections, e.g., influenza A and B, parainfluenza 1 and 2, and respiratory syncytial virus (RSV). A systematic review which that included 39 studies on the function of vitamin D in the prevention of respiratory tract infections showed a statistically significant association between low vitamin D status and increased risk of either upper and lower respiratory tract infections [100]. However, several RCTs revealed conflicting findings regarding this association, possibly due to regimens heterogeneity and baseline serum vitamin D level [100]. An RCT evaluating the effect of high-dose (2000 IU) each day versus standard-dose (400 IU) each day vitamin D supplementation showed no significant difference between the two groups on viral upper respiratory tract infections [101]. However, a recent report on the effect of vitamin D supplements on influenza vaccine response among vitamin D deficient elderly individuals exert a lymphocyte polarization into a tolerogenic immune response, where it promoted a higher TGFβ plasma level without ameliorating antibody production [102]. Furthermore, researchers suggest that, a monthly supplementation with high-dose (100,000 IU) per month versus standard-dose group (12,000 IU) per month vitamin D reduced the incidence of acute respiratory infections [103]. It has been shown that the protective effect of vitamin D on antiviral immunity against respiratory infections is presumably dependent on the vitamin D level of the subject in which vitamin D-deficient individuals would benefit more. Given the higher mortality rate from COVID-19 in some countries compared to others, comparing data across nations is complicated. Vitamin D status of populations is one mostly overlooked factor that could be related to the outcome of COVID-19. A growing body of circumstantial evidence has now specifically linked outcomes of COVID-19 with vitamin D status [104]. The role of vitamin D in the response to COVID-19 infection could be two-fold. First, antimicrobial peptides (AMPs) production in the respiratory epithelium is supported with vitamin D, making infection with the virus and progression of COVID-19 signs less likely. Second, vitamin D might help to reduce the inflammatory response to infection with SARS-CoV-2 [98]. Cytokine storm, organ system interaction, and systemic effects are the possible mechanisms of renal injury in patients with Covid-19. The main function of the kidneys is to remove wastes and excess water from the body. It is reported that patients with kidney disease often have low levels of vitamin D in their blood [105, 106]. Furthermore, people with reduced kidney function develop alterations levels of phosphorus and calcium in the blood. Gradual loss of kidney function leading to the inability to get rid of phosphorus into tubules and inactivation of vitamin D, to maintain normal levels of calcium. These changes are sensed by the parathyroid gland and calcium is increased through the elevating production and release of parathyroid hormone. Accordingly, bone metabolism is altered by these metabolic changes to release calcium and accordingly lead to bone abnormalities and, therefore bone deformation, bone pain, and altered risks of fracture may occur [107]. A recent report indicated that even short-term acute vitamin D deficiency could directly lead to hypertension and impacts on renin-angiotensin system components that result in kidney injury. In cases with CKD, vitamin D deficiency has frequently been associated with proteinuria, albuminuria, progression to

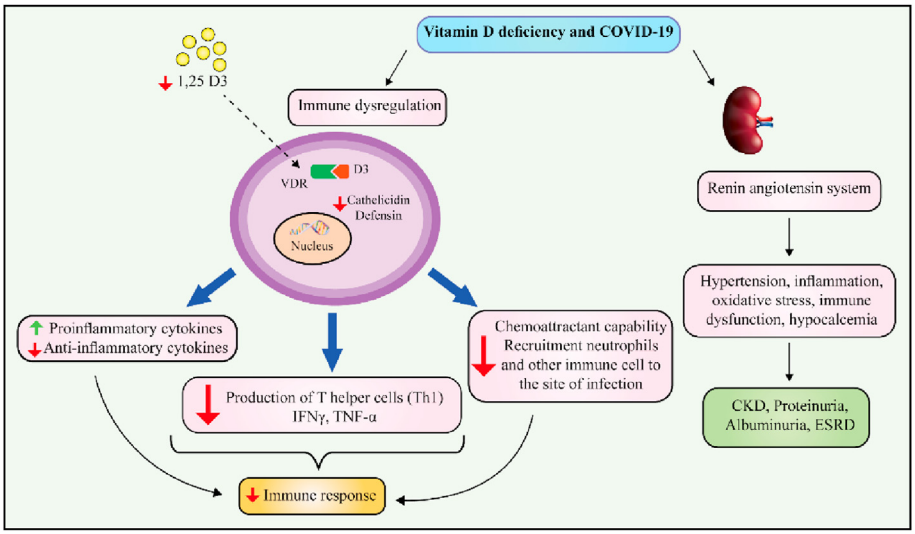

Figure 4. Immune dysregulation and renal insufficiency following SARS-COV-2 infections in Vit D deficiency cases. Immune responses may be decreased due to cathelicidin and some β-defensins reduction which lead to proteinuria, albuminuria, and progression to end-stage renal disease (ESRD) by renin-angiotensin system activation and inducing the oxidative stress and secretion of inflammatory cytokines. Abbreviations: COVID-19: Coronavirus disease 2019; CKD: Chronic kidney disease; ESRD: End-stage renal disease; IFNγ: Interferon Gamma; VDR: Vitamin D Receptor.

end-stage renal disease (ESRD) and increased risk for all-cause mortality (Figure 4) [109].

8.4. Vitamin E

Vitamin E, is a fat-soluble antioxidant vitamin and has the ability to regulate host immune functions [110]. Vitamin E is thought to have benefits for protecting cell membrane polyunsaturated fatty acids (PUFAs) against oxidation, modulates generation of ROS and reactive nitrogen species (RNS) [110]. Although impairment of both humoral and cellular immunity has been associated with vitamin E deficiency [110], the increased risk of pneumonia among 50–69 years old adult smokers have been shown to may be developed by vitamin E supplementation [111]. In a small pilot RCT protective effects of vitamin E have been reported by treatment of chronic hepatitis B [112]. Similar study in the pediatric population showed that vitamin E supplementation led to a higher anti-HBe seroconversion and viral response [113]. Suggested contributing mechanisms were the improvement of effective immune synapse formation in naive T cells and the initiation of T cell activation signals, the reduction of prostaglandin E_2 (PGE2) production by the inhibition of COX2 activity mediated through decreasing NO production, and the modulation of Th1/Th2 balance [114]. There are reports that demonstrate oxidative stress (OS) that is present at the early stages of CKD, augments progressively with renal function deterioration, and is further exacerbated by renal replacement therapy. Supplementation with several exogenous antioxidants such as vitamin E and C to suppress OS and inflammation has been suggested in these patients. The data showed that vitamin E (a-tocopherol) seems to have the most promising results in dialysis patients. However, none of these compounds are recommended by PD or HD guidelines [115]. Further studies are required to establish causality between antioxidant supplementation with vitamin E and CKD and the associated clinical hard end-points of CVD and all-cause mortality.

8.5. Quercetin

Quercetin, a plant pigment (flavonoid), is found in many plants and foods. It has special biological impacts that could promote psychomotor performance and decrease infection risk [116]. Quercetin exerts several positive benefits including anti-inflammatory, antioxidant, anti-cancer, antiviral, and psychostimulant activities. It also provides the ability to inhibit platelet aggregation, capillary permeability, and lipid peroxidation, as well as to stimulate mitochondrial biogenesis [117]. Various viruses, including SARS-CoV-2 have been shown to be inhibited by quercetin in laboratory and animal studies [118, 119]. Quercetin treatment was shown to restore reduced activity of many antioxidant enzymes in the respiratory tract including catalase, reduced glutathione, and superoxide dismutase in mice injected with influenza [120]. It is suggested that due to the effect of quercetin on the restoration of the many antioxidant enzymes, it may be beneficial as a supplement in protecting lungs from the deleterious effects of oxygen-derived free radicals released during influenza virus infection [120]. Clinical studies that have looked into quercetin and viral load in clinical settings are limited. Some people suffering from severe COVID-19 have shown signs of kidney damage, even in subjects with no underlying kidney problems before infection with the coronavirus. Early studies have reported that up to 30% of cases hospitalized with COVID-19 in China and New York developed acute or moderate kidney injury [121]. In the animal model of adenine-induced CKD, treatment with quercetin improved renal function, decreased oxidative stress markers, reduced serum FGF23, and lowered renal inflammation and renal tubular injury [122].

8.6. Zinc

Activities of more than 300 enzymes involved in protein synthesis and degradation, carbohydrate and energy metabolism, heme biosynthesis, nucleic acid production, and carbon dioxide transport are dependent on zinc as an essential trace mineral. Zinc is a cofactor of many enzymes and plays a critical role in the structure of cell membranes and in the function of immune cells [123]. Multiple aspects of the immune system are affected by zinc. Due to its crucial role for normal development and function of cells mediating innate immunity, neutrophils, and natural killer (NK) cells, zinc deficiency might cause reducing nonspecific immunity. The growth and function of T and B cells could adversely be influenced by zinc deficiency. Zinc has also been shown to act as an antioxidant and to stabilize membranes that might highlight its role in the prevention of free radical-induced injury during inflammatory processes. One study conducted on 103 children (1 month–5 years old) with pneumonia showed clinical improvement and an increase in the cytokine response in Th1 pattern (IL-2 and INF-γ) in the zinc supplemented group compared to placebo [124]. Enhanced thymic function and the output of new CD4+ naïve T cells have also been reported in another RCT with oral supplementation of high-dose zinc (150 mg/day) following stem cell transplantation [77]. However, in another study the authors did not observe the effectiveness of prolonged supplementation with zinc in inducing or ameliorating the antibody response or number of CD3, CD4 or CD8 lymphocytes after influenza vaccination [125]. Increased IL-2 production and decreased number of infections and hospitalizations have been reported following zinc supplementation in patients with sickle cell disease. A weekly dose of 70 mg zinc not only reduced the incidence of death from pneumonia but also lowered the incidence of diarrhea, with overall mortality reduced by 85% [73, 126]. Protection against infection and improved appetite were reported with balanced potassium and magnesium, and consumption of zinc supplements [73]. Zinc has rather low toxicity and intoxication with zinc is relatively rare. Zinc deficiency caused by malnutrition and foods with low bioavailability, aging, certain diseases, or deregulated homeostasis is a far more common risk to human health than intoxication. Hypozincemia is typical in CKD patients. Zinc deficiency has been proven to deteriorate the symptoms associated with renal insufficiency. Zinc protects against oxidative stress and plays an essential role in microtubule formation and function [127]. Although zinc requirements have not been established in COVID-19 associated AKI, it should be recommended that patients receive the dietary reference intakes (DRI) for this mineral.

8.7. Selenium

Selenium (Se) is a natural trace element that has pleiotropic effects, from antioxidant activity to anti-inflammatory responses [39]. It carries out biological effects through its incorporation into selenoproteins, where selenoproteins play an important role in regulating oxidative stress and other crucial cellular processes in nearly all tissues and cell types. Therefore, it is not surprising that dietary Se strongly influences inflammation and immune responses including those involved in innate and adaptive immune responses [128]. Overall, there is considerable evidence supporting the effects of Se on different types of immune responses in different ways as an “immunity booster”. Increased blood levels of selenium have been demonstrated to be associated with enhanced immune response. On the other hand, Se deficiency has been shown to impair immune cell function and may lead to a slower immune response [128]. Several pieces of literature have also reported that Se deficiency is associated with an increased risk of death and disease progression in people with HIV, while fewer hospitalizations and an improvement in symptoms for these patients were observed in the supplement group [129]. Furthermore, a stronger immune system has been found in supplemented people with influenza, tuberculosis, and hepatitis C [130]. Low serum selenium concentrations has been associated with a greater risk of death, weak immune system, and cognitive impairment, whereas an increased selenium level with selenium treatment exert antiviral effects [131]. In a report, an increase in selenium intake (50–100 μg/day) has been shown to improve immune function in adults with marginal selenium concentration [132]. This report demonstrated

an increased IFN-γ and other cytokines, with an earlier peak T-cell proliferation, and an increase in T-helper cells, indicating a boosted cellular immune response. However, humoral immune responses were unaffected [132].

A 12-week lasting RCT showed that supplementation with daily capsules (50–200 μg/day) of yeast enriched with selenium had both beneficial and detrimental effects. In this study selenium supplementation resulted in a dose-dependent increase in T-cell proliferation, IL-8, and IL-10 in the flu vaccinated group (immune challenge) compared to control groups [78]. Taken together, there is growing evidence suggesting that increasing Se levels in those with fairly low baseline Se levels might have more immune-boosting effects than supplementation in cases with adequate selenium levels. Data obtained from provinces and municipalities with more than 200 cases and cities with more than 40 cases have revealed that patients residing in areas with high levels of selenium were more likely to recover from the COVID-19 versus those residing in areas with the lowest selenium intake. In Heilongjiang province, the lowest selenium intake area in the world, the death rate from COVID-19 was almost five-times as high as the average of all the other provinces outside of Hubei [133]. Selenium is a component within the active site of glutathione peroxidase, which acts as an antioxidant enzyme. Therefore, its function is crucial to decrease the risk of oxidative damage to tissues, including the kidneys and its vascular components by preventing the generation of free radicals. On the other side, given the association of dietary selenium with protein, low-selenium intake and status is of concern during chronic renal failure, when dietary protein restrictions are necessary. Accordingly, oral and intravenous selenium supplementation has proven to be effective in improving the selenium status and immune function of renal patients, while simultaneously decreasing the production of oxidative stress [134, 135]. In addition to the AKI condition that might occur in patients with COVID-19, it seems beneficial to monitor selenium status in patients with renal disease and correct less-than-optimal selenium status with careful selenium supplementation.

8.8. Copper

Several important functions in the body are mediated by copper including metabolism, enzyme function, and reproductive performance. Most notably, copper is an important element for normal activity of antioxidant enzymes, antibody formation, phagocytic activity and exerts a substantial role in immunity by participating in the development and differentiation of immune cells [136, 137]. *In-vitro* studies have shown that copper possesses antiviral properties, where thujaplicin-copper chelates have been shown to inhibit replication of human influenza viruses [138], however, the influenza virus life cycle has been shown to regulate intracellular copper [139]. Another study showed that the percentage of circulating neutrophils, serum IL-2R and the antibody titer against the Beijing strain of influenza were significantly reduced in individuals with the higher copper intake (7.8 mg/day) [140]. Some researchers have shown that the status of copper is apparently not influenced by CKD and no significant differences in the copper levels have been observed between the four stages of CKD [141, 142]. However, the increased level of copper in erythrocytes was correlated with increasing the severity of the renal failure. In another study, 37–39% of patients with acute copper sulfate poisoning developed acute renal failure. Intravascular hemolysis seems to be the key factor responsible for kidney injury in these patients. They concluded that the release of copper from hemolyzed red cells during acute hemolytic episodes may initiate or contribute to the development of renal damage [143]. Given the ability of copper in fighting various infectious viruses including bronchitis virus, poliovirus, human immunodeficiency virus type 1 (HIV-1), and DNA and RNA viruses, it may have the potential of contact killing of SARS-CoV-2 [144]. Therefore, supplementation with copper may act as a preventive and therapeutic regime against COVID-19 by boosting both the innate and adaptive immunity.

8.9. Magnesium

Magnesium is the second-most abundant cation in cellular systems, which mediates a large variety of biological roles including modulating cell proliferation, cell cycle progression and differentiation, enzyme activation or inhibition, and complexing negatively charged groups such as phosphates in nucleic acids [145]. Although some experimental studies indicate that magnesium is likely to play a role in the immunity against viral pathogens [48], different studies have assessed the role of magnesium in different aspects of the immune response, both in animal models and in human systems. The findings of these studies have demonstrated that magnesium is involved in asthma, the immune system in athletes, aging processes and apoptosis in humans, as well as in inflammation, apoptosis, thymocyte gene expression and even in histological and cytological effects in animal models [146]. CKD affects approximately 13% of the general population and is associated with an increased risk of cardiovascular disease (CVD) because of both traditional and nontraditional CVD risk factors. Epidemiological reports have shown an interaction between the higher concentration of serum magnesium and promoted survival among patients suffering from renal insufficiency and a higher concentration of serum magnesium was associated with reduced progression of CKD [147]. Therefore, magnesium deficiency might not only lead to weakness of immune response against viral infection such as COVID-19, but also could adversely affect the risk of AKI.

8.10. Melatonin

It has been demonstrated that patients with CKD and those undergoing dialysis display disturbances in circadian rhythms due to altered melatonin levels, and the production of melatonin is reduced with the progression of CKD to ESRD [148]. Melatonin has been widely found in nature, different plants, animals, foods, fungi to eggs, and fish whereas the highest content of melatonin exists in plant foods and nuts [149, 150, 151]. Melatonin exerts protective effects against acute lung injury (ALI)/ARDS caused by viral and other pathogens through its anti-inflammatory and anti-oxidative properties. Melatonin could be beneficial in critical care patients by decreasing vascular disruption, anxiety, sedative use, and improving sleep disruption, which might also be valuable for efficient clinical outcomes for COVID-19 patients. Specifically, melatonin could be a promising potential therapeutic treatment to improve sepsis-induced renal injury (Figure 5) [152]. Recently, researchers demonstrated the potential role of melatonin using network proximity analyses of drug targets in several human coronaviruses (HCoVs) cellular targets, including ACE2, BCL2 Like 1, and nuclear factor-kappa B kinase subunit beta (IKBKB). Melatonin indirectly regulates ACE2 expression, a pivotal receptor that is implicated in virus entry into cells and involved in the infectious viral entry of HCoVs, including 2019-nCoV/SARS-CoV-2. In addition, melatonin has been considered prohibiting calmodulin reciprocal effects with ACE2 by inhibiting shedding of its ectodomain, an important infectious process of SARS-CoV [153, 154, 155].

8.11. Probiotic supplements

As live micro-organisms, probiotics confer a health benefit to the host, including on the gastrointestinal tract, when consumed in adequate amounts as part of the food [156]. Probiotics mediate immunoregulatory effects and studies have shown that functions of systemic and mucosal immune cells and intestinal epithelial cells could be improved through the biological consequences of probiotics in host immunity [156]. They also stimulate an immune response by increasing antibody production [157]. The results of a meta-analysis by Kang et al. demonstrated that the common cold was moderately improved after probiotics consumption [7]. In several studies, *Lactobacillus* and *Bifidobacterium* as probiotics have been used as treatments, in which either less severity of infection or

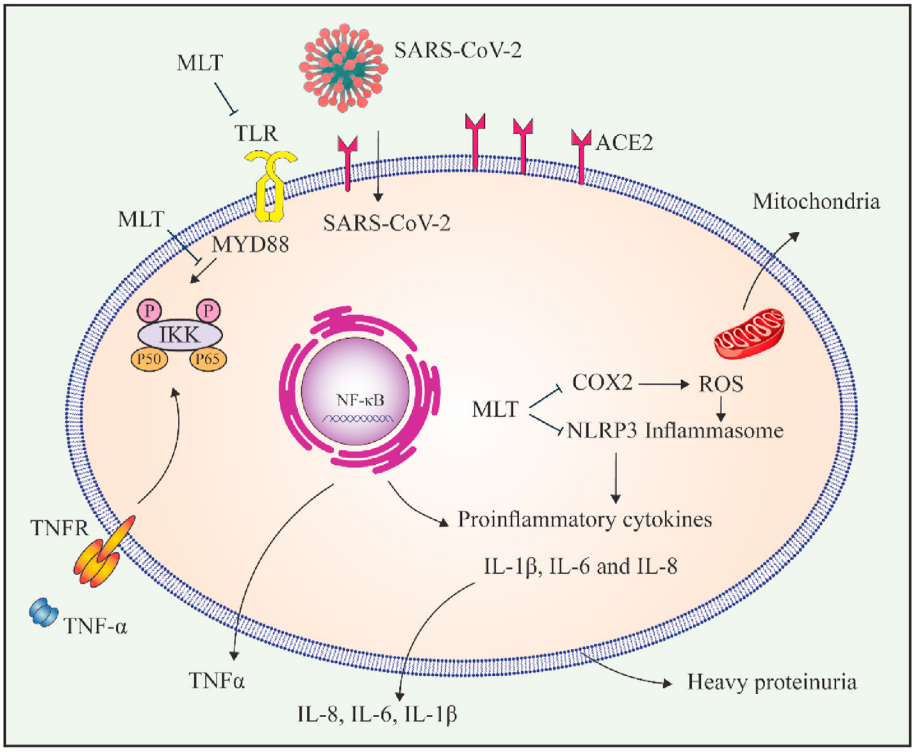

Figure 5. Protective effect of melatonin against kidney injury induced by SARS-COV-2. Melatonin could be improved sepsis-induced renal injury by suppressing Toll-Like Receptors, proinflammatory cytokines. Abbreviation: SARS-COV-2: Severe acute respiratory syndrome coronavirus 2. MLT: Melatonin; ACE2: Angiotensin-converting enzyme 2; NLRP3: NOD-, LRR- and pyrin domain-containing protein 3; TLR: Toll-Like Receptors; MYD88: Myeloid differentiation primary response protein; TNFR: Tumor Necrosis Factor Receptor; ROS: Reactive oxygen species; IKK: IkappaB Kinase; NF-κB: Nuclear factor kappa B.

shortened disease duration with probiotic supplementation have been observed. The effectiveness of *Lactobacillus* for the treatment of respiratory tract infection of viral origin has been shown in several studies [158, 159, 160]. A significant association between *Bifidobacterium* and increased immune function and intestinal microbiota in elderly individuals was observed [161]. There is no scientific evidence yet for using probiotics to protect, prevent or treat COVID-19 infection despite the fact that probiotics might help to reinforce the immune system. Dysbiosis is a pervasive disorder among renal insufficiency patients and may play an important role in CKD complications. According to the currently available evidence in a meta-analysis, there is no conclusive rationale for recommending biotic supplements for improving outcomes in renal patients [162]. Recent studies showed promising effects of probiotics in renal function and reduced levels of urea, blood urea nitrogen, and indoxyl sulfate in CKD patients [163]. Immunological, biochemical, and hemodynamic mechanisms are involved in the pathogenesis of AKI. Studies on animal models have shown that the process and outcome of AKI are affected by the intestinal microbiota, highlighting the promise for treatment with prebiotics and probiotics [164]. Therefore, targeted modulation of the intestinal microbiome can be considered as a potential therapeutic tool for AKI that is also an organ involvement in COVID-19 and should be investigated in future studies.

9. Concluding remarks

The challenging journey of exploring the potential mechanism of COVID-19 in kidney patients has recently begun. SARS-CoV-2 has been shown to target multiple organs e.g. kidney, heart and lungs that subsequently result in multiple organ failure. It enters the cells and induces multiple immune and inflammatory pathways by mediating ACE2 receptors, leading to increasing severe proteinuria in podocytes and proximal straight tubule cells. Moreover, supportive treatments such as nutritional supplements and vitamins could show protective effects by down-regulating inflammatory cytokines such as TNF, IL-6, NF-κB, IL-2, IL-7, IL-10, GSCF, IP10, MCP1, and MIP1A. Taken together, current evidence suggests the therapeutic potential of supportive treatments such as nutritional supplements and vitamins against COVID-19 in kidney patients. Supplementation of Vitamin A, D, E, and several trace elements including zinc, selenium, copper, magnesium, flavonoid quercetin, and probiotics may be beneficial for both prevention and treatment of viral infections including COVID-19, and can enhance immunity against viral infection. Therefore, patients with malnutrition, diabetes and obesity might require personalized nutrition advice to improve their health during this pandemic of COVID-19. Since there are no pharmacological strategies yet for the prevention or treatment of a viral disease like COVID-19, enhancing immunity by nutritional strategies could be a beneficial and low-cost approach that needs to be explored. Achieving a balanced and diverse diet in the current global context with limited movements and, therefore, meeting recommended amounts of calories and micronutrients will be a challenge. However, supplementation with selective micronutrients may be beneficial especially for vulnerable populations such as the elderly. In addition to the survival and patient's outcome, injury to the kidneys can impair metabolism, excretion, dosing and expected concentrations of the medications. As a result, frequent and careful monitoring of kidney function in patients with COVID-19 can lead to early diagnosis of kidney disorders, achieving the optimal therapeutic concentrations, and better management of the disease. However, given the lack of experimental and clinical data, the precise therapeutic relevance of supportive treatments and nutritional supplements remains obscure. Future studies employing clinical cases are required to confirm the observed protective effects of more nutritional supplements.

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