Vitamin C and Kidney Injury

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Vitamin C is an important micronutrient and antioxidant for the human body. In animal experiments, it can protect the kidneys from injury caused by nephrotoxic drugs. A major feature of COVID-19 and similar viral infection is the cytokine storm, which causes a rise of multiple cytokines in the blood. Those cytokines result in the oxidative stress in cells, which leads to damage to organs and tissues, including the kidneys. Here, we reviewed the current literature on kidney damage in COVID-19 patients and analyzed the possible etiology and mechanisms. In addition, we summarized the potential use of vitamin C in preventing kidney damage in experimental animal models and the underlying mechanisms. Vitamin C appears to protect and facilitate recovery of kidneys from injuries derived from excessive of oxidative stress, a feature of cytokines storm in people with COVID-19. Finally, we would like to argue that vitamin C may be protective of the renal functions in COVID-19 patients with pre-existing kidney diseases.

Keywords: vitamin C ; COVID-19 ; Oxidative stress ; kidney injury ; antioxidant

1. Introduction

Coronaviruses received the name due to their appearance under the electron microscopy. They infect both humans and animals. Their infections in humans lead to clinical symptoms in the respiratory, digestive and central nervous systems. The impact on the respiratory system is the most obvious, which can result in death [1]. Beginning in the end of 2019, a pandemic of a respiratory disease of unknown origin occurred in Wuhan, China. Some patients died of respiratory distresses. The pathogen was finally determined as a novel type of coronavirus after its sequence was revealed in January, 2020. The World Health Organization (WHO) named this coronavirus as the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2) belonging to the β-coronavirus cluster, which also contains members responsible for Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) pandemics [2]. Then, the disease associated with this SARS-COV-2 infection is named as coronavirus disease 2019 (COVID-19). According to the earliest available data, the majority of patients diagnosed with COVID-19 before January 1, 2020, were linked to a seafood wholesale market in Wuhan [3]. Around the world, as of April 15, 2021 according to WHO (https://www.who.int/emergencies/diseases/novel-coronavirus-2019), more than 137,866,311 COVID-19 cases have been reported, and the death toll has exceeded 2,965,707 in 223 countries, areas or territories.

In the initial phase of the SARS-COV-2 infection, the latent period is about 4.5 days, and the infectivity was high with doubling time of the number of infected patients at 7.4 days [3]. Viral particles in the air enter the subjects via the mucous membranes in the respiratory tract, oral cavity or eye conjunctiva, etc. The most common symptoms are fever and dry cough, which can be seen in 80 to 90% of patients with COVID-19 [4]. Additionally, 40% of COVID-19 patients suffer from fatigue and 18.6% experience dyspnea, while nasal congestion, nausea and diarrhea are seldom reported [5]. Clinical data indicate that one out of six patients with COVID-19 will develop respiratory distresses and will need adequate medical care [6]. Before people receive vaccines, the best way to prevent the spread of this virus is to maintain a social distance, wash your hands frequently, avoid close contacts, and do a good job of early screening and isolation of infected people.

Vitamin C (ascorbic acid) is a micronutrient that is water soluble and considered as an antioxidant [7]. It influences various aspects of the immune system, particularly immune cell functions [8][9]. The human body could not synthesize vitamin C due to the lack of the enzyme responsible for the last step of its de novo biosynthesis [10][11]. Vitamin C deficiency leads to scurvy, a disease characterized by unable to form functional collagen, which causes weakening of collagen structures in tissues, poor wound healing, and impaired immunity [12]. Individuals with scurvy are highly susceptible to potentially fatal infections such as pneumonia [13]. In addition, infections can significantly increase vitamin C usage due to inflammation and metabolic requirements. It has been observed that scurvy often followed infectious epidemics in populations and may develop after respiratory infections [14]. This may be apparent for malnourished individuals.

2. The Impacts of the Cytokine Storm in COVID-19

Cytokines are signaling proteins produced by immune cells to regulate the body's immune responses [15][16][17]. Those immune cells include neutrophils, monocytes, macrophages, B and T cells, which synthesize and secrete cytokines to modulate immune responses in animals [18][19].

Cytokine release syndrome (CRS), also known as 'cytokine storm', can occur in various conditions including sepsis , severe systemic infection and chimeric antigen receptor T cell therapy [20]. The extensive and uncontrolled release of proinflammatory cytokines is detrimental to the body. Clinically, the cytokine storm is often associated with the systemic inflammation and multiple organ failures [11]. Patients with COVID-19 in critical conditions have an elevated cytokine profile similar to those in patients with SARS and MERS [21]. The levels of interleukin (IL)-1α, IL-1β, IL-7, IL-8, IL-9, IL-10, granulocyte-macrophage colony stimulating factor, interferon gamma (IFN-γ), fibroblast growth factor, granulocyte-colony stimulating factor (G-CSF), IFN-γ-inducible protein (IP10), macrophage inflammatory protein 1 alpha (MIP1A), platelet-derived growth factor, monocyte chemoattractant protein (MCP1), vascular endothelial growth factor, and TNF-α of inflammatory factors are increased in patients with COVID-19 [22].

3. The Effects of COVID-19 on the Kidneys and Treatment Strategies

The occurrence of CRS has been observed in COVID-19 since it was reported [23]. In patients with COVID-19, the coronavirus infection triggers the inflammatory cytokine storm. The significant elevations of cytokines in the circulation will cause not only serious inflammatory reactions, but also different degrees of organ damages, resulting in the corresponding symptoms [24]. After reaching to the kidneys, inflammatory cytokines cause renal tubular damages, affect the filtration of the kidneys, lead to the accumulation of metabolites in the body, and further aggravate the clinical symptoms and threaten life [25].

Cytokines mainly damage the renal tubules and cells. The damages alter renal tubular permeability, which leads to impaired renal filtration function and renal injuries. When CRS occurs, a large number of cytokines circulate in the blood and damage the vascular permeability. For example, the levels of IL-2, IL-6, IL-7, IL-10, IP10, G-CSF, MCP1, MIP1A, and TNF-α are higher in critically ill patients with COVID-19 than those in the mild group [23][26]. Intravascular fluids infiltrate into the interstitial space, which causes a relative lack of blood volume and systemic edema. The reduced blood volume will drop blood pressure and cause insufficient renal blood supply. The filtration rate of the kidneys decreases, which will further cause accumulation of harmful substances in tissues, intensify systemic symptoms, and cause a vicious cycle to aggravate the conditions. If renal damage is not corrected, further development will lead to acute renal failure in patients especially the elderly or those with basic diseases.

The prevalence of acute kidney injury (AKI) among patients with COVID-19 was thought to be low initially. For example, in a Chinese cohort of 1,099 patients with COVID-19, 93.6% were hospitalized, 91.1% had pneumonia, 5.3% were admitted to the ICU, 3.4% had acute respiratory distress syndrome and only 0.5% had AKI [4]. However, a recent study indicates that the incidence of AKI in 85 cases of COVID-19 patients was reported to be about 27.6% [27]. Elder patients are easier to develop acute renal failure. Severe acute tubular necrosis and lymphocytic infection were found in the autopsy of six subjects with AKI after the death, but cortical necrosis was not known [27]. The human kidneys may be a target for the coronavirus infection [28]. The autopsy report of a patient who died of COVID-19 also revealed acute proximal tubule injury herniation, renal tubular endodermal injuries and peripheral erythrocyte aggregation, glomerular fibrin embolism and inflammation [29]. Some of these patients did not show evidence of AKI detected by routine tests (creatinine and/or urea nitrogen), which indirectly suggests that early renal injuries may be overlooked clinically.

So far, the incidence of renal injuries in patients with coronavirus infection has not been reported clinically. This may be due to the fact that the disease progresses rapidly after a patient is infected with the virus, and impacts the lungs, brain and heart first. Early effects on the kidney did not appear. Probably, only microscopic changes occur in the early stage of kidney injury [25]. However, after the infection of SARS-CoV-2, the disease progresses rapidly in the respiratory system, which becomes difficult to detect damages to the renal functions in time [30]. Therefore, the changes in the kidneys tend to be ignored due to the dramatic changes in other organs. We would like to argue that it is probably too late to correct and protect the kidney functions when the damages occur. As the kidneys play a critical role in the regulation of whole-body metabolism and homeostasis, the damages of renal functions will affect the whole-body metabolism and aggravate the patient's condition. Early detection and protection of renal functions in patients with COVID-19 should be planned ahead of time and considered seriously during the treatment of COVID-19.

For COVID-19 patients with kidney conditions, additional treatments probably have to be used. Extracorporeal “blood purification,” mainly in the form of hemodialysis, has been a main clinical practice of many nephrologists for the past 5 decades [25]. Another possibly older procedure, therapeutic plasma exchange, separates and then removes potential detrimental materials from the plasma of the patients [31][32][33]. In contrast to hemodialysis, therapeutic plasma exchange preferentially removes biologic substances of high molecular weight such as autoantibodies or alloantibodies, antigen-antibody complexes, and paraproteins. These molecules may be cleared through two alternative procedures: centrifugal separation and membrane separation [34]. Extracorporeal therapies hemodialysis and therapeutic plasma exchange have been considered to remove cytokines in patients with sepsis and may be used in critically ill patients with COVID-19 [35]. The removal of cytokines may avoid damages to other tissues and organs. This can be achieved through four types of approaches: direct hemoperfusions using a neutro-macroporous sorbent; plasma adsorption using a resin after plasma is separated from whole blood; continuous kidney replacement therapy (CKRT) with hollow fiber filters of adsorptive properties; and high-dose CKRT with medium cut-off or high cut-off membranes [32].

4. Vitamin C and Its Potential in the Protection of Renal Injury in COVID-19

Vitamin C acts as an antioxidant to clear reactive oxygen and nitrogen species [36]. For example, it protects lung cells from oxidative damage [37]. Therefore, one important activity of vitamin C is to block oxidative stresses, reduce or prevent productions of reactive oxygen and nitrogen species derived from cellular activities in response to bacterial and viral infections. The viral infections may trigger cytokine storms and lead to increased oxidative stresses in cells and tissues [38].

Table 1 Vitamin C’s protection function in the kidney injuries.

Animals	Reagents used	Ascorbate acid dose	Test time	Effective	Reference
Male albino rabbits (25;5 groups)	Gentamicin, 80mg/kg,im qd	250mg/kg qd	26 days	Yes (P<0.05)	[39]
Male Wistar rats (56;7 groups)	Diazinon, 20mg/kg Ceftriaxone, 100mg/kg	100mg/kg qd	28 days	Yes (P<0.05)	[40]
Male Sprague-Dawley rats (25;5 groups)	Colistin	200mg/kg, bid	7 days	Yes (P<0.05)	[41]
Male Sprague-Dawley rats (48;6 groups)	Nevirapine, 200mg/kg	250mg/kg qd	28 days	Yes (P<0.05)	[42]

Table 1 summarizes studies of using vitamin C to intervene AKI in animal models, which include rabbits and rats. These reports retrieved in the literature search demonstrated the uses of vitamin C to prevent and treat AKI before and after the establishment of renal injury model, respectively. Blood creatinine, urea, malondialdehyde and reduced glutathione levels, the makers of renal functions and oxidative stresses, were measured in these studies [39][40][41][42]. The results showed that vitamin C not only protects the kidney from injuries caused by external factors, but also facilitates the repairments after damages occurred. Vitamin C treatment shortens the repair time needed for the kidneys. At the same time, data of malondialdehyde and reduced glutathione have shown that vitamin C treatment can effectively increase antioxidant capacity in the blood and thus protect against renal injury [42]. Vitamin C probably acts to remove reactive oxygen free radicals and prevent the accumulation of oxidation products, which cause damages to the kidneys. In some studies, pre-treatment with vitamin C resulted in marked improvement in renal functions, manifested by significant decreases in plasma urea and creatinine levels and kidney tissue malondialdehyde levels [43].

Figure 1. Ascorbic acid has been experimentally proven to ameliorate comorbid conditions in SARS-CoV-2-infected patients. Vitamin C appears to promote immune function and reduce inflammation and oxidative stress, and in turn, protect multiple organs in patients with COVID-19. As an antioxidant, vitamin C prevents acute necrosis mediated by immune cells in the kidney. For the lung, cardiac, liver; vitamin C reduces the expression levels of angiotensin converting enzyme 2 (ACE2) expression levels, which limits the binding of the viral particles to the cells. For the kidneys, it prevents the development of acute kidney injury. For the immune system, its autophagy-inducing mechanism impedes the severity of COVID-19 by producing interferons and decreasing the levels of inflammatory interleukins.

The benefits of vitamin C may not be limited to the kidneys. As shown in Figure 1, vitamin C acts as an antioxidant in the body to exert its effects on multiple organs and tissues of the body [44][45][46][47][48][49][50]. The angiotensin-converting enzyme 2 (ACE2) is a functional receptor for SARS-CoV-2 to enter host target cells [51]. ACE2 is widely found in human liver, lung, kidney, intestinal tract and other organs [52]. For the lung, cardiac, liver; vitamin C reduces the expression levels of ACE2 expression levels, which limits the binding of the viral particles to the cells, and protects these organs directly from the viral damages.

Vitamin C has a variety of pharmacological properties, antiviral, antioxidant, anti-inflammatory and immunomodulatory effects, and is a potential treatment option for COVID-19 [53][54]. During the acute phase of infection, vitamin C levels in the plasma and white blood cells decrease due to increased metabolic demands. High-dose vitamin C supplementation helps restore the plasma and white blood cell vitamin C levels. It appears to work by enhancing the function of immune cells and by its antioxidant properties [7]. Vitamin C can support a variety of cellular functions of the immune system, helping to maintain immunity. It supports epithelial barrier function against pathogens and promotes oxidative scavenging activity in the skin, thereby potentially protecting against oxidative stress from the environment [55][56][57]. Moreover, it can enhance the function and chemotaxis of phagocytes and neutrophils, phagocyte bacteria, produce reactive oxygen species, and eventually kill microorganisms [7]. In the early stage of COVID-19 infection, the early manifestations of cardiovascular disease are often accompanied by vascular endothelial dysfunction and organic lesions while oxidative stress and blood pressure can damage vascular endothelium [58]. The anti-oxidative stress characteristics of vitamin C may prevent and slow the onset of heart risk in patients at an early stage [59]. Elderly patients hospitalized with pneumonia or bronchitis who took vitamin C were at least 80% less likely to develop pneumonia, according to the data of a randomized trial [60]. Therefore, vitamin C protects multiple organs in patients with coronavirus infection.

In animal studies, vitamin C has been shown to protect and shorten the duration of treatment after kidney damage caused by harmful substances [42]. The virus directly acts on vascular endothelial cells, leading to endothelial inflammation, which affects several important organs and causes multiple organ failures. The antioxidant and anti-inflammatory effects of vitamin C may protect endothelial cells and thus reduce the incidence of multiple organ failures [61]. In animal studies, the infection of H3N2 can kill mice that are deficient in vitamin C [38]. Here, vitamin C has been thought to be needed for anti influenza virus responses in the early phase of infection, which involves the production of IFN-α/β. IFNs may promote virus clearance, lowing numbers of virus-specific CD8+ and CD4+ T-cells [62].

Figure 2. The positive role of vitamin C in the acute kidney injury induced by chemical toxicity or COVID-19. Renal toxic chemicals and development of COVID-19 can cause acute kidney injury. SARS-CoV-2 viral particles enter cells via its interacting protein Angiotensin Converting Enzyme 2 (ACE2). Viral infections lead to cytokine storm, and cause hemodynamic changes through the high expression of ACE2. Vitamin C acts to reduce oxidative stresses and repair damages, in turn, attenuate the acute kidney injury. Vitamin C can reduce the expression of ACE2, which hinders the entry of virus into cells, and stabilizes blood pressure.

Recently, it has been shown that AKI has a high incidence in patients with severe COVID-19 [63]. Kidney involvement is associated with poor prognosis. As shown in Figure 2, the potential mechanisms involved in renal injury during COVID-19 may include infection, direct invasion of renal parenchyma and hemodynamic instability secondary to renal injury, the inflammatory cytokine storm and the use of nephrotoxic drugs. Renal toxic chemicals and development of COVID-19 can cause AKI. Vitamin C protects against the AKI induced by chemical toxicity or COVID-19. SARS-CoV-2 viral particles enter cells via its interacting protein ACE2. Viral infections lead to cytokine storm, and cause hemodynamic changes through the high expression level of ACE2 [51]. Vitamin C acts to reduce oxidative stress and repair damages, in turn, attenuate AKI. Vitamin C can reduce the expression of ACE2, which hinders the entry of virus into cells, and stabilizes blood pressure.

Coronavirus can cause dysfunction of ACE2, leading to the activation of the renin-angiotensin system, and ultimately to change blood pressure and aggravate excessive inflammatory responses [64]. One important autopsy report of a COVID-19 death showed acute protrusion of proximal tubule injury, but also peritubular erythrocyte aggregation and glomerular fibrin thrombosis with ischemic collapse [65]. This report also describes endothelial injury, hemosiderin deposition,

pigment-tube pattern and inflammation associated with rhabdomyolysis. It is important to note that some of these patients have early evidence of AKI that cannot be detected by routine tests (creatinine and/or urea nitrogen), making it easily overlook the possibility of subclinical renal injury [28]. Viral infections lead to CRS, and cause hemodynamic changes through the high expression of ACE2. Vitamin C can reduce the expression of ACE2, which hinders the entry of virus into cells, and stabilizes blood pressure. It reduces oxidative stresses, repairs damages, and in turn, attenuates the AKI.

5. Summary and Future Perspectives

As a micronutrient, vitamin C takes part in the body's metabolism, and its antioxidant activity plays an important role in protecting the kidneys, lungs and other organs. Patients with coronavirus infection in critical conditions have poor nutrition, indicating that adequate vitamin C uptake or supplementation should be considered for them, especially the elderly and patients with a variety of basic diseases. Adequate vitamin C provides protection to the kidneys and vital organs in the body against inflammation and oxidative stresses. At the same time, it contributes to the stability of the body's metabolism and maintains a healthy state of the internal environment. Future studies probably can be focused on the roles of vitamin C in the regulation of renal cell functions, which have diverse structures and functions. In addition, vitamin C’s functions in the infections of other viruses should be studied in the clinical settings.

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