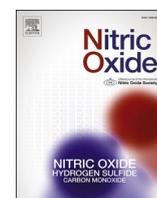Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Renal consequences of the novel coronavirus disease 2019 (COVID-19) and hydrogen sulfide as a potential therapy

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ARTICLE INFO

ABSTRACT

The novel coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, is a global pandemic which is primarily considered a respiratory illness. However, emerging reports show that the virus exhibits both pulmonary and extra-pulmonary manifestations in humans, with the kidney as a major extra-pulmonary target due to its abundant expression of angiotensin-converting enzyme 2 and transmembrane protease serine 2, which facilitate entry of the virus into cells. Acute kidney injury has become prevalent in COVID-19 patients without prior any history of kidney dysfunction. In addition, the virus also worsens kidney conditions and increases mortality of COVID-19 patients with pre-existing chronic kidney disease, renal cancer, diabetic nephropathy, end-stage kidney disease as well as dialysis and kidney transplant patients. In the search for antiviral agents for the treatment of COVID-19, hydrogen sulfide (H_2S), the third established member of gasotransmitter family, is emerging as a potential candidate, possessing important therapeutic properties including antiviral, anti-inflammatory, anti-thrombotic and antioxidant properties. A recent clinical study revealed higher serum H_2S levels in survivors of COVID-19 pneumonia with reduced interleukin-6 levels compared to fatal cases. In this review, we summarize the global impact of COVID-19 on kidney conditions and discuss the emerging role of H_2S as a potential COVID-19 therapy.

1. Introduction

The global outbreak of the novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) has rapidly evolved into a global pandemic with enormous consequences. It has caused significant mortality and loss of capital, with a struggling global economy to contain the pandemic [1]. This virus, which is the third zoonotic virus next to SARS-CoV and Middle East Respiratory Syndrome (MERS-CoV), was first identified in Wuhan, Hubei Province in China in December 2019, from where it has spread to all countries and territories of the globe [2]. The initial signs of SARS-CoV-2 infection such as pneumonia, multiple organ failure and acute respiratory distress syndrome are elicited through the actions of the immune system [1,2]. Various immunopathological changes in patients with SARS-CoV-2 infection have been documented in which lymphopenia, abnormalities in granulocytes and monocytes in serum as well as increase in cytokine production have been reported. These pathological changes seen in the upper respiratory tract is due to uncontrollable viral replication, leading to influx of neutrophils, macrophages and monocytes and elevated production of pro-inflammatory cytokines, the so-called cytokine storm syndrome [1,2].

Current studies have shown that the kidneys are badly affected during SARS-CoV-2 infection, leading to kidney injury especially in patients with comorbidities, and worsening kidney conditions with increased mortality of COVID-19 patients with pre-existing chronic kidney disease, renal cancer, diabetic nephropathy, end-stage kidney

disease as well as dialysis and kidney transplant patients [3–6]. In the search for antiviral agents for the treatment of COVID-19, hydrogen sulfide (H₂S), a gas known for its distinct "rotten-egg" smell and established as the third member of a family of gaseous signaling molecules, is emerging as a potential candidate. In this review, we summarize the global impact of COVID-19 on pathological conditions involving the kidney and discuss the emerging role of H₂S as a potential COVID-19 therapy.

2. Impact of COVID-19 on kidney conditions

The global spread of COVID-19 has left nephrologists and their patients with challenging decisions in the treatment and management of kidney conditions such as acute kidney injury, chronic kidney disease, diabetic nephropathy, renal cancer, kidney infarction, end-stage kidney disease, nephrotic syndrome, dialysis and kidney transplantation. It has been widely reported that SARS-CoV-2 enters its host cell by binding to angiotensin-converting enzyme 2 (ACE2), a cell-surface protein found in a host of tissues and organs including the kidney [7,8]. In the kidney, ACE2 is mainly expressed in epithelial cells of proximal tubule and glomerular parietal epithelial cells [9]. In addition to ACE2, transmembrane protease serine 2 (TMPRSS2), which is also expressed in the kidney, facilitates the fusion of the virus and cellular membranes by cleaving the spike (S) protein of the virus [10]. In the kidney, colocalization of ACE2 and TMPRSS were found in the podocytes and the proximal straight tubule cells as the host cells for COVID-19 infection due to their increased expression of these proteins [10,11]. Interestingly, RNA-sequencing data revealed that ACE2 expression in the kidneys was almost 100-fold greater than in the lungs, suggesting that COVID-19-related kidney injury is significantly through ACE2-dependent pathways [12]. ACE2 is an enzyme of the renin-angiotensin-aldosterone-system that converts angiotensin II to angiotensin 1-7 and angiotensin 1-9. The latter binds to Mas receptor and suppresses the action of angiotensin II/AT1R system [13–15]. As illustrated in Fig. 1, the attachment and proliferation of the virus in the kidneys lead to an increase in kidney function parameters such as creatinine, along with hematuria, proteinuria and other urine abnormalities. Furthermore, kidney structures such as the glomeruli are also inflamed and destroyed. These changes in the kidneys progressively may

lead to renal failure, needing kidney replacement therapy such as dialysis and transplantation in patients with renal manifestations of COVID-19 infection.

2.1. COVID-19 infection and acute kidney injury

Progressive acute kidney injury (AKI) is common among hospitalized COVID-19 patients, and is an independent risk factor for mortality. It has been reported that AKI was one of the complications observed in hospitalized COVID-19 patients with its occurrence ranging between 0.5% and 80% [16]. The mechanisms underlying COVID-19–associated AKI are unknown. However, proposed mechanisms of kidney injury range from direct viral infection to effects on the renin-angiotensin-aldosterone system, hemodynamic instability, coagulopathy, and cytokine storm. In a systematic review and meta-analysis of outcomes for patients with COVID-19 and AKI among 20 cohorts covering 13,137 hospitalized COVID-19 patients, prevalence of AKI was found to be 17%, out of which 77% experienced severe COVID-19 infection and 52% died [17]. AKI was associated with increased odds of death among COVID-19 patients (pooled odds ratio 15.27, 95% CI 4.82–48.36), although there was considerable heterogeneity across studies and among different regions in the world. About 5% of all patients in the study required the use of kidney replacement therapy. The study concluded that kidney dysfunction was common among patients with COVID-19, and patients who develop AKI have inferior outcomes [17]. A recent multinational observational study of hospitalized COVID-19 patients with AKI also showed significantly high plasma levels of soluble urokinase plasminogen activator receptor (suPAR; an immunological risk factor for AKI and predictive of the need for dialysis) compared to AKI patients without COVID-19 infection [18]. This observation suggests that suPAR may play an important role in the pathophysiology of COVID-19-associated AKI.

Proteinuria and hematuria were common features observed in about 40% of COVID-19 patients on hospital admission [19]. In one observational study of 5449 hospitalized patients, the incidence of AKI was 36.6% with 14.3% of patients requiring dialysis and this was even higher in patients admitted at the intensive care unit [20]. Autopsy reports from kidneys of COVID-19 deceased patients revealed acute tubular injury and collapsing glomerulopathy as the most prominent

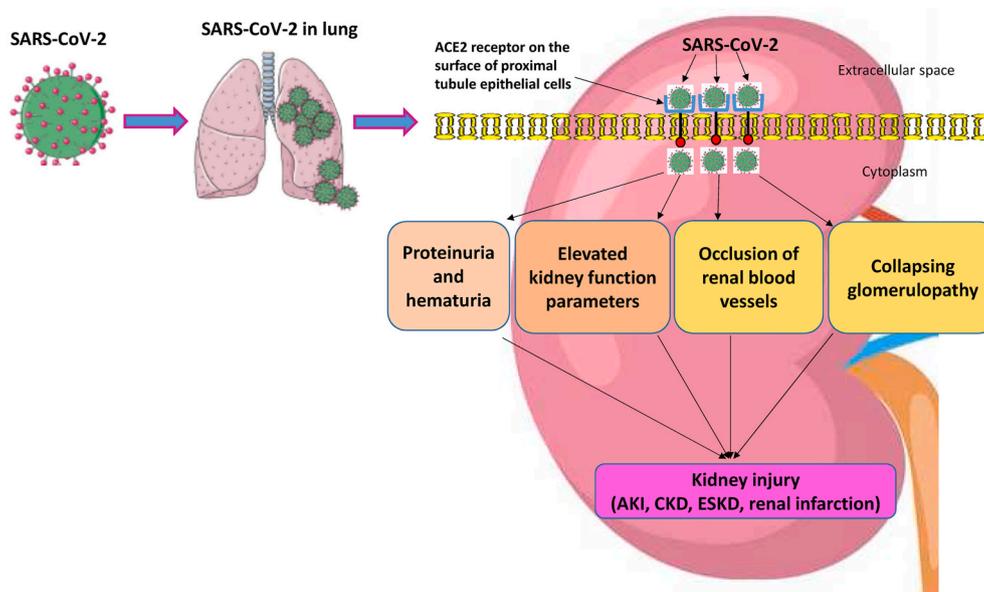**Fig. 1. A diagram showing the attachment of SARS-CoV-2 to the ACE2 receptors expressed on the surface of proximal tubule epithelial cells.** Invasion of the kidneys by SARS-CoV-2 leads to proteinuria, hematuria, abnormal kidney function parameters (urea, creatinine, uric acid and albumin), and occlusion of renal arteries and veins as well as collapsing glomerulopathy as a result of local cytokine storm syndrome.

damage to the kidneys [21,22]. Electron microscopy of kidney biopsies revealed viral-like particles in the glomeruli and renal tubules although the particles were not conclusively that of SARS-CoV-2 [19,22]. The incidence of AKI in COVID-19 patients was also highlighted in 15 separate studies, with an odds ratio (OR) of 18.5% based on COVID-19 severity [21]. The OR for COVID-19 patients with AKI-associated mortality was reported to be as high as 23.95%. In some 710 COVID-19 patients who reported to the hospital, prevalence of elevated markers of renal function such as serum creatinine and blood urea nitrogen (BUN) was 15.5% and 14.1% respectively, with 26.9% of these patients coming in with microscopic hematuria and 44% having proteinuria although the incidence of AKI in these patients was reported as 3.2% [23]. According to this and other supporting data, AKI is likely associated with worse prognosis in COVID-19 patients and increases their mortality rates [24,25]. In a related retrospective analysis of medical records from 85 COVID-19-positive patients in Wuhan from January 17 to March 3, 2020, 27.06% of the patients developed AKI especially among the elderly (59–92 years old) [26]. During this study, varying degrees of tubular necrosis, luminal brush border sloughing and vacuole degeneration was observed in a Hematoxylin and Eosin staining of 6 kidney samples as well as the presence of CD68$^+$ macrophages, CD8$^+$ T cells, CD4$^+$ T cells and CD56$^+$ natural killer cells from deceased COVID-19 patients [26]. In conclusion, COVID-19 infection likely accelerates the development of AKI, especially among elderly patients.

2.2. COVID-19 infection and chronic kidney disease

Patients with chronic kidney disease (CKD) are predisposed to COVID-19 [27]. Emerging reports suggest that patients with pre-existing kidney injuries got worse after testing positive and being admitted to the hospital for COVID-19. In one study, there was an elevation in markers of renal function, elevation of serum D-dimer, pro-inflammatory cytokines particularly interleukin-6 as well as neutrophilia [28]. It is currently unclear as to the extent the virus directly damages renal tubular epithelial cells or whether the kidney injury is secondary to the cytokine storm syndrome [12,29,30]. In a study involving 1603 patients with COVID-19, 21% presented with increased serum creatinine levels while 43.5% of them had a previously diagnosed CKD stage 3 or higher and with higher mortality rates than in the non-CKD group [31]. In these CKD patients (n = 146), urea, serum potassium, urinary proteins, D-dimer, procalcitonin, lactate and troponins levels were elevated while hemoglobin, platelets, albumin and estimated glomerular filtration rate were decreased. Mortality was high in COVID-19 patients with elevated serum creatinine (32.4%) and those with previously diagnosed CKD (41.1%) than those with normal serum creatinine levels (5.8%) [31]. In summary, COVID-19 infection appears to damage the kidney and may accelerate the death of patients with CKD.

2.3. COVID-19 infection and diabetic nephropathy

COVID-19 patients with comorbidities are more likely to show a more severe clinical picture of the infection with high mortality rate. Most of the available data highlight diabetes mellitus as one exceptional comorbidity associated with more severe COVID-19 and mortality [32]. A survey done in the United Kingdom showed that out of 23,804 patients with COVID-19 dying in hospitals, 1.5% had type 1 diabetes mellitus and 32% had type 2 diabetes mellitus, with 3.5 and 2.03 times the odds of dying compared to patients without diabetes mellitus respectively [33]. It has been observed that patients with diabetes mellitus have a severe and fatal manifestation of COVID-19 infection with increased ACE2 production in the kidney as an adaptive response to elevated levels of angiotensin I and II, which in effect facilitates the entry of SARS-CoV-2 into host cells [34]. This phenomenon enhances a progressive decline in renal function in diabetic patients characterized by an increase in serum creatinine, uric acid, BUN, proteinuria and a decrease in estimated glomerular filtration rate [32]. A molecular study revealed that the enhanced progressive decline in renal function in COVID-19 patients with diabetes mellitus could be due to upregulation of genes that influence viral infection pathways in diabetic nephropathy [35]. For example, proximal tubular epithelial cell (PTEC) gene, which is co-expressed with ACE2, may exhibit cellular interplay between mechanism that enhance viral infection and host immune responses [35]. Thus, COVID-19 increases the severity of the manifestations of diabetes mellitus, which may then contribute to death of the diabetic patient.

2.4. COVID-9 infection and renal cancer

Cancer patients undergoing cancer chemotherapy are among those likely to be easily infected with SARS-CoV-2 due to drug-related immunosuppression [36,37]. Globally, renal cell carcinoma (RCC) represents the 6th and 10th most diagnosed cancer in men and women, and accounts for 5% and 3% of all cancers in males and females respectively [38]. A recent study revealed predominant expression of coronavirus receptors (CoV; DPP4, ANPEP, ENPEP) in clear cell RCC and also in other forms of renal cancers such as papillary and chromophobe subtypes [39]. This finding confirms increased risk of SARS-CoV-2 infection in these groups of patients, and has left physicians and other stakeholders to debate whether or not to continue or stop cancer therapy. Considering the risk of cancer progression after stopping or delaying therapy especially deterioration of metastatic conditions, it is recommended that cancer patients receiving curative treatment should continue their treatment regardless of the potentially high risk of COVID-19 infection during their chemotherapy [40]. However, delaying or minimizing elective surgical procedures in patients with stable cancer as well as in those patients at high risk of ending up in the intensive care units following surgery has been strongly recommended as a strategy to mitigate the COVID-19 crisis [40]. In the light of these strategies, recommendations for the deferment for cytoreductive nephrectomy in patients with RCC in this COVID-19 era and replacement with systemic therapy for patients with intermediate to poor-risk disease has been made [41]. Current data from a study gives both medical practitioners and patients some hope, as surgery can be safely delayed in a subgroup of patients with RCC to between 3 and 6 months without significant sacrifice in overall survival [42]. Overall, patients with RCC and other forms of renal cancer, who are undergoing cancer chemotherapy are at a higher risk of COVID-19 infection, which could further exacerbate their kidney condition.

2.5. COVID-19 infection and kidney infarction

An increased risk of the formation of blood clot has previously been noted with SARS and MERS, and this is one proposed cause of pre-renal injury in COVID-9 patients [43,44]. The lodging of thrombi in the renal vessels and kidneys increases the likelihood of kidney damage and possibly kidney death due to kidney infarction. This finding supports the observation where platelet-rich fibrin microthrombi scattered in peritubular capillaries and tubules in kidneys of deceased COVID-19 patients [45]. In some COVID-19-positive patients, changes in blood coagulation parameters have been observed [46,47]. Disseminated intravascular coagulopathy (DIC; a condition of overactive clotting factors) is observed in COVID-19 patients, particularly in the critically ill patients. DIC arises from cytokine storm syndrome-induced hemophagocytosis and acute consumptive coagulopathy, which leads to enhanced platelet activation, fibrin and thrombus formation [45]. A cross-sectional study from April 13–24 in 2020 revealed elevation of markers of endothelial cells and platelet activation such as von Willebrand factor antigen, coagulation factors and fibrinolytic enzymes [48]. These coagulation anomalies were reported in a 71-year-old COVID-19-positive patient, who exhibited thromboembolic events such as ascending aortic thrombosis, renal infarction and a corresponding hypercoagulable state [49]. However, this may seem a little presumptuous given that the coagulation anomalies were reported in

only one patient and over a short period (10 days). In a nutshell, COVID-19 infection increases the likelihood of formation of blood clots in the renal vessels and kidney, which may lead to kidney infarction and possibly death of the patient.

2.6. COVID-19 infection and end-stage renal disease

Information on COVID-19 in end-stage renal disease (ESRD) is limited but rapidly evolving. ESRD patients have a higher chance of contracting COVID-19 due to suppression of the immune system, which is associated with ESRD [50,51]. While there is no evidence-based solution to this concern, patients who are at high risk of progressing to ESRD without immediate treatment are being advised to postpone treatment until their local transmission rates of COVID-19 are low. Further evidence of the impact of COVID-19 on ESRD patients was reported where a higher rate of in-hospital death of COVID-19 patients with ESRD compared to those without ESRD in a retrospective study in the United States [52]. This observation was in agreement with that of an independent study, where the researchers evaluated clinical characteristics, laboratory measures and clinical outcomes in 759 hospitalized COVID-19 patients out of which 45 had ESRD [53]. The authors reported that COVID-19 patients with ESRD had significantly increased leukocyte count, C-reactive protein, lactate dehydrogenase and ferritin, and markedly reduced serum albumin and thrombocytopenia with a higher in-hospital mortality (18%) compared to their counterparts without ESRD (10%) [53]. Another study also reported that COVID-19-positive patients who had ESRD and on dialysis had better outcomes than ESRD patients who were not on dialysis [54]. They attributed their observation to a possible "pre-conditioning", where underlying chronic inflammation in ESRD patients on dialysis attenuates the inflammatory response from the COVID-19 infection. It is important to note that the spread of COVID-19 in some dialysis centers is on the rise (e.g. Italy), which is partly due to the difficulty in applying social distancing protocols [55] while it is lower in other centers (e.g. Abu Dhabi, United Arab Emirates) due to rapid isolation of COVID-19 patients within their dialysis centers [56]. Taken together, COVID-19 infection worsens kidney condition of ESRD patients, and may lead to increased mortality.

2.7. COVID-19 infection and kidney transplantation

Kidney transplant patients are currently at a higher risk of COVID-19 infection and its associated mortality, as these patients have a spectrum of kidney diseases and comorbidities such as hypertension, diabetes, obesity that requires kidney transplantation [57,58]. Hence, kidney transplant surgeons have been advised to suspend kidney transplantation during this pandemic due to poor outcomes, especially in high-risk older recipients with comorbidities. This unfortunate obstacle to such an important life-saving procedure is due to possible donor to recipient viral transmission or members of the transplant team serving as vectors of the SARS-CoV-2. Suspension of kidney transplantation during the pandemic will have a negative impact on the transplant waiting list, thereby increasing morbidity and mortality [59]. SARS-CoV-2 has a higher tropism for the kidney, where it has been shown to replicate in about 30% of COVID-19 patients [60]. In 12 transplant centers in the United States, Italy, and Spain, Cravedi et al. [61] reported a high COVID-19-related mortality and AKI rate in adult kidney transplant recipients. This observation supports previous findings in which a very high early mortality (28%) was recorded among kidney transplant recipients with COVID-19 in the United States compared to 8–15% mortality of COVID-19 mortality among the general population [62] and dialysis patients on the waiting list for kidney transplantation [63]. The high COVID-19-related mortality in this group of patients is mainly due to advanced age and frailty [63]. In conclusion, patients who have undergone kidney transplantation have a high COVID-19-related mortality risk, which are driven by factors such as immunosuppression therapy, comorbidities, advanced age and frailty.

3. A special case of COVID-19-associated nephropathy in people of African ancestry

Genetic variants of apolipoprotein L1 (APOL1), which greatly increases the risk of kidney diseases, are found only in people of African descent [64]. The APOL1 alleles became common in Sub-Saharan Africa due to protection conferred by these alleles against the pathogen that causes African sleeping sickness (trypanosomiasis). Studies in recent times suggest that black people living in Sub-Saharan Africa have high predisposition to kidney disease as do African Americans, and that these two groups (African Americans and Black Africans) have common genetic susceptibilities. Two APOL1 susceptibility gene variants (G1 and G2) are linked with hypertension-associated CKD, collapsing focal segmental glomerulosclerosis and HIV-associated nephropathy [65–67]. The APOL1 kidney risk variants encode circulating APOL1, which functions as a trypanolytic factor capable of killing the trypanosome parasites in the human serum [64]. These APOL1 risk variants developed some 10,000 years ago in Sub-Saharan Africa where trypanosomiasis was endemic. Thus, APOL1 gene is an innate immunity gene common in people of African ancestry.

Recent studies suggest that people with high/low renal risk alleles for APOL1, who are COVID-19-positive, may have a high risk of developing renal failure, proteinuria and hematuria. There are six case reports of collapsing glomerulopathy among COVID-19 patients of African ancestry, with severe AKI and nephrotic range proteinuria, two of whom carried APOL1 renal risk genotypes [68–71]. APOL1 coding variants have been associated with collapsing glomerulopathy among individuals with untreated HIV infection or undergoing interferon treatment. There is a high frequency of APOL1 risk genotypes among African Americans (~13%) and West Africans (~25%), with lower frequencies found in East and South Africans [64,72,73]. Collapsing glomerulopathy has been described in 24 cases of COVID-19 infection; 23 out of the 24 (95.8%) cases were Africans or African American and 1 was Indian, 18 patients had APOL1 gene variants (12 were G1:G1 and 6 were G1:G2) [16]. This suggests that one of the major risk factors for AKI in patients with COVID-19 infection is black race [74]. Individuals with high renal risk alleles for APOL1 who have COVID-19 infection may be at increased risk of developing AKI, proteinuria and hematuria and consequent chronic kidney disease. A likely mechanism may be upregulation of APOL1 mediated by cytokines resulting from the SARS CoV-2 infection. This hypothesis requires investigation. In addition, innate immune response to SARS CoV-2 infection can drive the APOL1 kidney disease in patients with APOL1 high risk genotypes. The later argument is based a case series of collapsing glomerulopathy linked to interferon therapy [75].

4. Hydrogen sulfide as a potential therapy against COVID-19 infection

A search for antiviral agents is currently underway in the face of the alarming rate of global COVID-19 infections. Just recently, ritonavir-boosted nirmatrelvir was granted emergency use authorization by the United States Food and Drug Administration (FDA) for the treatment of mild to moderate COVID-19 cases. Prior to this, remdesivir, an orphan antiviral drug originally developed to treat Ebola virus disease and Marburg virus infections (via inhibition of the viral RNA-dependent RNA polymerase), was the only drug approved by United States FDA for the treatment of COVID-19 in symptomatic patients [76]. This antiviral drug was administered along with convalescent plasma. In addition, a host of vaccine candidates have been approved and distributed for global use to curb the spread of SARS CoV-2.

4.1. Endogenous and exogenous sources of hydrogen sulfide

In the search for antiviral agents for effective treatment of COVID-19, hydrogen sulfide (H_2S), a pungent-smelling gas which gained notoriety for several centuries for its toxicity and death among industrial and agricultural workers, is emerging as a potential candidate drug. Over the last two decades, however, H_2S has moved past its historic notorious label as a gas which was once feared, to an intracellular messenger molecule that plays important roles in cellular homeostasis and impacts physiological and pathophysiological conditions, including regulation of the renal system [77]. H_2S possesses important therapeutic properties including antiviral, anti-inflammatory, anti-thrombotic and antioxidant properties, which are important for any drug candidate against COVID-19. Endogenous H_2S is produced in mammalian cells by four enzymatic pathways. The first two pathways involve the use of the substrate L-cysteine, a sulfur-containing amino acid, in the presence of two cytosolic enzymes cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE) while the third pathway uses the mitochondrial enzyme 3-mecaptopyruvate sulfurtransferase (3-MST) and the intermediate product 3-mecaptopyruvate (from L-cysteine). The fourth enzymatic pathway uses D-cysteine, an enantiomer of L-cysteine, and the peroxisomal enzyme D-amino acid oxidase (DAO) [78–81]. Reduced production of endogenous H_2S and expression of these H_2S-producing enzymes have been associated with various pathologies of the organ system including the renal system. Whereas the distribution of these H_2S-producing enzymes are tissue specific, we and others have previously reported that all the four enzymes are abundantly expressed in the glomerular and tubular compartments of the kidney [81–84]. This makes the kidney is a richer source of endogenous H_2S production compared to other organs.

In addition to its endogenous production, H_2S is also administered exogenously in its gaseous form (though less ideal) and via H_2S donor compounds. These H_2S donors include water-soluble, fast-releasing but short-lasting H_2S donors such as the inorganic sulfide salts, sodium hydrosulfide (NaHS) and sodium sulfide (Na_2S) [85]. There is also water-soluble, slow- and controlled-releasing, long-lasting H_2S donor donor GYY4137 [86], and mitochondrially-targeted slow-releasing donors AP39 and AP123 [87], which augment mitochondrial H_2S production by 3-MST and provide an effective and longer treatment time in experimental models of kidney diseases including acute kidney injury, chronic kidney disease, diabetic nephropathy, hypertensive kidney injury, renal cancer, drug-induced nephropathy, renal ischemia-reperfusion injury and kidney transplantation. As already discussed in previous sections, all these renal pathologies are worsened by COVID-19 infection. Also, several organic small-molecules H_2S donors have been developed [134,135]. While these H_2S donors are limited to only preclinical studies, thiosulfate, a major H_2S oxidation product in the form of sodium thiosulfate (STS), is an FDA-approved drug already in clinical use for treatment of calciphylaxis in ESRD patients and other clinical situations [88]. Other clinically viable H_2S donor drugs such as ATB-346 (H_2S-generating naproxen molecule) and zofenopril (FDA-approved antihypertensive drug that increases H_2S release) are currently in human clinical trials for gastric ulcer, osteoarthritis, chronic pain, cardiovascular diseases and type 2 diabetes mellitus (www.clinicaltrials.gov).

4.2. Antiviral action of H_2S and its underlying mechanisms in relation to COVID-19 infection

Burgeoning evidence shows that H_2S donors such as NaHS and GYY4137 exhibit excellent effects against the family of enveloped RNA viruses of which SARS-CoV-2 is a member [89–92]. Also, natural sources of exogenous H_2S such as diallyl sulfide, diallyl disulfide and diallyl trisulfide, which are derived from garlic, have been reported to reduce viral load of cytomegalovirus (another enveloped virus) in infected organs of humans and rodents [93]. Furthermore, sinigrin, a precursor of

the H_2S donor allyl isothiocyanate, and obtained from the root extract of *Isatis indigotica* plant for Chinese traditional medicine [94], inhibited the function of 3-chymotrypsin-like protease, the main protease of SARS-CoV, which caused the 2002–2004 outbreak of severe acute respiratory syndrome [95].

There are several mechanisms that underlie the antiviral action of H_2S. Firstly, the antiviral activity of H_2S has been suggested to be partly linked to its antioxidant property - activating and increasing the levels of other antioxidants including glutathione (GSH), the most abundant naturally occurring antioxidant in the body, which inhibits overproduction of reactive oxygen species (ROS; a destructive mediator in tissue injury) and its consequent oxidative stress [96,97]. Interestingly, ROS-induced oxidative stress has been associated with viral infection in the kidney [98], impairing the kidney's antioxidant defense system. Moreover, Kim et al. [97] recently predicted in their study involving high-throughput artificial intelligence-based binding affinity that GSH interacts with and possibly inhibits the action of ACE2 and TMPRSS2, the two proteins that facilitate SARS-COV-2 entry into the kidney. Secondly, findings from a very recent study shows that H_2S also exhibits its antiviral activity against SARS-CoV-2 by inhibiting TMPRSS2 in human airway epithelial cells and possibly interfering with ACE2 and potentially blocking the attachment of the virus to these host proteins [99], and thereby inhibiting entry of the virus into the host cell (Fig. 2). However, a previous study reported that administration of H_2S via its donor molecule NaHS upregulated carotid ACE2 expression and reduced organ damages in a mouse model of carotid artery ligation [100]. These contradictory findings could be attributed to the different context of H_2S application, as the former study used human respiratory epithelial cells and lung tissue samples from patients undergoing segmental/lobar pulmonary resections, whose pharmacological response to H_2S donors may be different from that of the mice carotid artery endothelial cells used in the latter study. Moreover, while two H_2S donors (NaHS and GYY4137) were administered in the former study, only one H_2S donor (NaHS) was used in the latter study, which could suggest that increased H_2S level in the former study may have accounted for the decreased expression of the TMPRSS2 (and possibly ACE2) proteins while a decreased H_2S level could result in increased expression of these host proteins in the latter study. A recent molecular dynamics simulation study showed that reduction of disulfides in ACE2 and S protein of SARS-CoV-2 into sulfydryl groups impairs the binding of the S protein of SARS-CoV-2 to ACE2 [101]. Interestingly, administration of N-acetylcysteine (NAC; an antioxidant H_2S donor and a source of cysteine for endogenous GSH production) disrupted the disulfides, leading to inhibition of SARS-CoV-2 entry into the host cell [102]. This could also partly explain why the antiviral action of H_2S is suggested to be linked to its antioxidant property through increased GSH production. Moreover, NAC is a known mucolytic agent that breaks disulfide bonds in mucus, making it less viscous and easier to be expelled by other mucoactive agents (expectorants and mucokinetics) together with the action of the ciliary apparatus of the respiratory system. Thus, H_2S facilitates elimination of potentially harmful viruses such as SARS-CoV-2, suggesting its antiviral action in COVID-19.

Thirdly, the antiviral action of H_2S involves Toll-like receptors (TLRs), a class of pattern recognition receptors (PRRs) that initiate innate immune response for early immune recognition of a pathogen. Following release of viral RNA (i.e. pathogen-associated molecular pattern) into host cells, it is recognized by PRRs such as TLRs in the host immune cells, which activates production and secretion of large amounts of proinflammatory cytokines and chemokines responsible for cytokine storm and organ damage as seen in the various kidney conditions discussed in previous sections [103]. Chen and colleagues [104] recently reported that deficiency in endogenous H_2S level contributes to sepsis-induced myocardial dysfunction (SIMD) in humans and mice via increased expression of TLRs. However, administration of NaHS in SIMD mice inhibited TLR pathway and prevented TLR-mediated inflammation. Although this study was not in relation to viruses, it is likely that
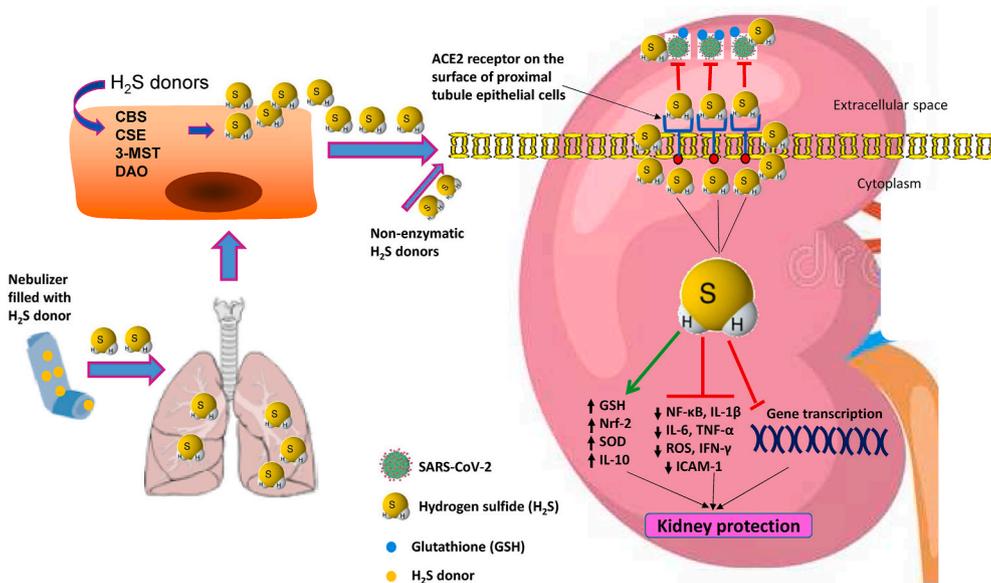
Fig. 2. Possible mechanism of action of H₂S against SARS-CoV-2. Administration of H₂S donors may increase endogenous production of H₂S by cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE), 3-mecaptopyruvate sulfurtransferase (3-MST) and D-amino acid oxidase (DAO) and may also activate non-enzymatic pathway. H₂S interacts with angiotensin-converting enzyme 2 (ACE2) and TMPRSS2 (not shown) and may block the binding of SARS-CoV-2 to these host cell proteins, thereby inhibiting entry of the virus into the host cell. H₂S may also alter SARS-CoV-2 membrane and inhibits its gene transcription including inhibiting the activation of nuclear factor-kappaB (NF-κB). In addition, H₂S may activate antioxidant pathway, leading to increased levels of antioxidant enzymes such as glutathione (GSH), nuclear factor-erythroid factor 2-related factor 2 (Nrf2) and superoxide dismutase (SOD), and suppressing overproduction of reactive oxygen species (ROS). Furthermore, H₂S may inhibit pro-inflammatory pathway, resulting in reduced production of pro-inflammatory mediators such as interleukin-1beta (IL-1β), IL-6, tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ) and intercellular adhesion molecule-1 (ICAM-1) while activating anti-inflammatory pathway which increases production of IL-10.

antiviral action of H₂S involves the same mechanism. Besides, H₂S has been reported to inhibit activation and nuclear translocation of nuclear factor-kappaB (NF-κB; an inflammatory-related transcription factor) and thereby suppressing the transcription of pro-inflammatory genes, leading to inhibition of the secretion of virus-induced chemokines and cytokines [89]. Fourthly, post-mortem examination of transplanted kidney, lungs and heart of COVID-19 deceased patients revealed endotheliitis and accumulation of apoptotic bodies [105], suggesting that inflammation of the endothelium (an important gatekeeper of cardiovascular health and homeostasis) and apoptotic cell death contributed to dysfunction or malfunction of these organs in the COVID-19 patients, which resulted in death of these patients. As a potential therapy for COVID-19 patients, there are studies showing the ameliorative effect of H₂S endothelial dysfunction in cardiovascular disorders such as hypertension, atherosclerosis, hyperhomocysteinemia as well as in diabetes [106,107]. Besides, overactivation of the sympathetic nervous system has recently been implicated in COVID-19 patients with pre-existing chronic lung diseases, kidney diseases, cardiovascular pathologies, obesity and diabetes mellitus through factors including ACE2 imbalance, which contributes to organ damage in these patients [108]. Interestingly, H₂S donors such as NaHS are well-known to suppress sympathetic activation [85,109–111], and therefore inhibition of sympathetic outflow could be a potential therapeutic mechanism by H₂S donors for COVID-19 patients.

Another mechanism underlying the antiviral action of H₂S in relation to COVID-19 involves interaction with endoplasmic reticulum (ER) stress-related proteins. A recent preliminary virtual screening study in patients with COVID-19 pneumonia revealed higher gene expression and serum concentrations of glucose-regulated protein 78 (GRP78; an ER stress protein and the host cell surface protein to which the Spike protein of SARS-CoV-2 binds as revealed by molecular docking) compared to pneumonia patients without COVID-19 [112]. There are studies showing the inhibitory action of H₂S donors on GRP78 and other ER stress-related proteins in experimental models of human diseases. Yi et al. [113] reported that administration of NaHS downregulated the expression of GRP78 and other ER stress-related proteins and inhibited uranium-induced apoptosis of rat renal proximal tubular epithelial cells and mitigated ER stress via activation of Akt/GSK-3β/Fyn-Nrf2

pathway, a protective molecular pathway. This *in vitro* result supports a previous result by Wei et al. [114] who observed attenuation of hyperhomocysteinemia-induced cardiomyocyte injury following H₂S administration in rats. Administration of NaHS also markedly inhibited cigarette smoke-induced overexpression GRP78 and other markers of ER stress-mediated apoptosis and prevented lung tissue damage [115]. These pieces of experimental evidence suggest that H₂S donors could be potential antiviral agents that serve to treat COVID-19 patients by preventing entry of SARS-CoV-2 into host cells via inhibition or downregulation of the expression of GRP78 and other ER stress-related proteins, thereby preventing apoptosis and organ damage. In addition to all these mechanisms, we also reported that H₂S decreases renal expression of kidney injury molecule (KIM-1; a biomarker of human renal proximal tubular injury) [83,116], which has recently been found to be associated with COVID-19 nephropathy and potential receptor for SARS-CoV-2 entry into renal and lung cells [117]. Renal and lung epithelial cells of humans and mice co-expressed KIM-1 and SARS-CoV-2 Spike protein [118], suggesting that KIM-1 could directly bind to SARS-CoV-2 Spike protein following its induction by AKI or other pathological conditions involving the kidney, as this interaction was inhibited by anti-KIM-1 antibodies and the KIM-1 inhibitor, TW-37 [118]. Yang et al. [119] also implicated KIM-1 and ACE2 in a synergistic interaction which mediated the invasion of SARS-CoV-2 in kidney cells and worsened COVID-19 infection in the kidney. We recently showed that activation of endogenous H₂S production by dopamine administration increases renal expression of H₂S-producing enzymes (CBS, CSE and 3-MST) and serum H₂S level and decreases renal KIM-1 expression, leading to increased kidney protection in a rat model of deep hypothermia/rewarming-induced AKI [83]. We also observed decreased expression of KIM-1 in renal tubules and preservation of renal structures following administration of 5′-adenosine monophosphate, which correlated with increased renal H₂S-producing enzymes and serum H₂S level in a hamster model of therapeutic hypothermia [116]. These observations together with other potential mechanisms that decrease KIM-1 expression in kidney and lung tissues suggest that H₂S may offer a new therapy for COVID-19-associated nephropathy and pneumopathy. Other mechanisms underlying the antiviral action of H₂S or H₂S donors include inhibition of gene transcription along with

antiviral immunosuppressive effect, as was reported in human cyto-megalovirus [120] and alterations of the viral membrane, as XM-01 (an H2S donor) inhibited the activities of enveloped viruses but had no effect on non-enveloped viruses [121]. The findings from all these studies strongly suggest that H2S donors could serve a therapeutic purpose in COVID-19 and its complications including COVID-19-associated nephropathy (Fig. 2).

4.3. H2S as a potential biomarker in determining final outcome of COVID-19 infection

Although there is currently no studies on effect of H2S on COVID-19-associated nephropathy, recent clinical study in a cohort of patients with COVID-19 pneumonia showed that circulating H2S level was significantly higher along with increased lymphocyte count and reduced serum interleukin-6 (IL-6; an inflammatory marker) in survivors of the disease compared to healthy controls and those who died of the disease [122]. This observation suggests that H2S could be a potential biomarker to determine the final outcome of pneumonia caused by COVID-19. It is important to note that IL-6 is considered a major pro-inflammatory mediator in the cytokine-storm syndrome that causes respiratory failure and COVID-19-associated mortality [123]. There are studies including ours, showing that H2S is a potent inhibitor of pro-inflammatory pathway by inhibiting pulmonary and renal IL-6 and several other pro-inflammatory mediators such as IL-2, tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), intercellular adhesion molecule-1 (ICAM-1) and NF-κB while simultaneously increasing the levels of anti-inflammatory cytokines [124,125]. Therefore, the findings by Renieris et al. [122] may suggest that the increased serum H2S level in the COVID-19 survivors could be due to increased endogenous H2S production from the lungs and perhaps the kidneys and other tissues to suppress production of IL-6 and other pro-inflammatory mediators which are yet to be investigated. This is in agreement with the a study by Li and colleagues [89] who observed reduced endogenous H2S production and downregulation of CSE mRNA and protein expression (H2S-producing enzyme) in airway epithelial cells infected with respiratory syncytial virus, the virus commonly associated with upper and lower respiratory tract infections in children of which there is no vaccine or effective treatment. Further evidence of the involvement of H2S in virus-induced respiratory condition was reported when increased viral replication and airway inflammation was observed in CSE knockout mice infected with respiratory syncytial virus compared to wild-type mice [90]. Interestingly, treatment with the H2S donor, GYY4137, markedly reduced the viral replication of not only respiratory syncytial virus but also human metapneumovirus and Nipah virus, which correlated with decreased production of pro-inflammatory mediators and improvement in airway dysfunction [90]. These findings provide strong evidence of the antiviral property of H2S, which could be a potential therapeutic agent against COVID-19. In addition, administration of NAC to 10 patients with severe COVID-19 significantly improved clinical and biochemical parameters [126] as well as clinical improvement in a critically ill COVID-19 patient with multisystem organ dysfunction, who was treated with intravenous administration of NAC (75 mg/kg over 4 h, then 35 mg/kg over 16 h, followed by 17 mg/kg over 24 h on day 2) along with low-dose hydroxychloroquine [127]. This finding is supported by another case of a severely ill COVID-19 patient who was cured and discharged following administration of NAC inhalation solution [128]. However, a recent double-blind, randomized controlled trial in which intravenous administration of NAC (14 g/kg in the first 4 h and 7 g/kg in the next 16 h) to severe COVID-19 patients in late stage of the disease showed no clinical benefits compared to placebo group [129]. This contradictory result could be attributable to differences in the dose of NAC and treatment regimen, synergistic effect with hydroxychloroquine, and the timing of NAC administration, as the latter study administered NAC later than 7–10 days after the onset of COVID-19 symptoms compared to the former study. It further suggests that the aforementioned factors are crucial in the treatment of COVID-19 patients with NAC or other H2S donors, and should be matched with concurrent medical treatments. These clinical outcomes have led to conduction of several clinical trials with NAC to determine the most appropriate timing of administration in various stages of COVID-19. In the face of the potential positive role of H2S in COVID-19 cases, Dominic et al. [130] recently refuted the report of Renieris et al. [122] by showing low circulating H2S levels in Caucasian and African American COVID-19 patients compared to healthy controls and fatal cases. This conflicting finding could be due to important determinants such as age, race, sex, comorbidities (e.g. diabetes and hypertension) and stage of COVID-19 infection, which were not reported in the former study. Another important factor for consideration is the differences in the method of serum H2S measurement, as H2S decay was so fast in the latter study and may not have been very accurate. Besides, the authors of the latter study did not include high performance liquid chromatography (a new method of H2S quantification in biological systems) in their serum H2S measurement, which their counterparts in the former study did, although both studies used the common monobromobimane method of H2S measurement. This discrepancy in the two studies requires additional investigations, and should take into consideration all important determining factors of H2S, to establish the exact role of H2S in determining the final outcome of COVID-19 infection.

The pathological characteristics of COVID-19 also includes coagulopathy, during which there is progression of thrombosis and generation of DIC with increased platelet–leukocyte aggregates, which promote coagulation and vascular inflammation in the glomeruli of critically ill patients, and partly accounts for COVID-19-related mortality [131]. Hence, inhibiting platelet–leukocyte aggregates is a therapeutic interest in COVID-19 patients, especially those with kidney conditions. Emerging evidence using animal and human whole blood shows that H2S donors such as NaHS and GYY4137 inhibit the coagulation system by preventing DIC formation and platelet-leukocyte aggregation, and facilitate thrombolysis, leading to impairment in thrombus stability [132,133]. Therefore, these findings about the thrombolytic or anti-thrombotic property of H2S could advance its potential clinical utility by COVID-19 patients.

5. Conclusion

Symptomatic COVID-19 patients develop renal complications and patients with pre-existing renal conditions also have a high chance of disease progression and mortality. Currently, there are no approved drugs that offer renal protection in COVID-19 patients although ritonavir-boosted nirmatrelvir and remdesivir, and a number of vaccines have been approved by United States FDA for emergency use. With a new viral pandemic which has significant renal involvement, there is a need for future studies to determine the risk factors of kidney disease among COVID-19 patients. It is important to also determine the link between genetic polymorphisms and the risk of developing kidney diseases among certain races of people including those of African ancestry, who have genetic polymorphisms to kidney diseases, and to know whether there is an association between APOL1 high-risk carriers and risk of developing COVID-19-associated nephropathy. As the search for pharmacological agents for effective treatment of COVID-19 is underway, there are studies that are suggesting the potential clinical use of H2S donors, as these agents fall under all three classifications of COVID-19 treatment - antiviral treatment, cytokine storm treatment, and thrombosis treatment. A growing body of evidence show that H2S donors interact with ACE2, TMPRSS2 and other potential SARS-CoV-2 receptors on the host cell surface, alter SARS-CoV-2 membrane, thereby inhibiting the entry of the virus into the host cell and consequently preventing its replication (assembly and release). This mechanism is thought to suppress SARS-CoV-2-induced inflammatory pathway, leading to organ protection (Fig. 2). Other studies also suggest inhibition of gene transcription by H2S donors along with antiviral

immunosuppressive effect. In the light of these mechanisms of the antiviral action of H_2S donors, more experimental and clinical studies with H_2S donors, especially those that are already FDA-approved and are in human clinical trials such as STS, NAC, ATB-346 and zofenopril, should be considered for preventive treatment or effective therapy against COVID-19 infection, and should include their use in nebulizer for aerosol inhalation into the lungs and dissemination to extra-pulmonary organs such as the kidney.

Funding sources

Author contributions

GJD conceived and designed the research; GJD, KKA and BOO drafted the manuscript; GJD prepared the figures; GJD, SA, VB and AS reviewed and edited the manuscript; All authors approved the final version of the manuscript.

Declaration of competing interest

The authors have no conflict of interest to declare.

Acknowledgement

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