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Kidney in the net of acute and long-haul coronavirus disease 2019: a potential role for lipid mediators in causing renal injury and fibrosis

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Purpose of review
Severe COVID-19 disease is often complicated by acute kidney injury (AKI), which may transition to chronic kidney disease (CKD). Better understanding of underlying mechanisms is important in advancing therapeutic approaches.

Recent findings
SARS-CoV-2-induced endothelial injury initiates platelet activation, platelet–neutrophil partnership and release of neutrophil extracellular traps. The resulting thromboinflammation causes ischemia–reperfusion (I/R) injury to end organs. Severe COVID-19 induces a lipid-mediator storm with massive increases in thromboxane A_2 (TxA_2) and PGD_2, which promote thromboinflammation and apoptosis of renal tubular cells, respectively, and thereby enhance renal fibrosis. COVID-19-associated AKI improves rapidly in the majority. However, 15–30% have protracted renal injury, raising the specter of transition from AKI to CKD.

Summary
In COVID-19, the lipid-mediator storm promotes thromboinflammation, ischemia–reperfusion injury and cytotoxicity. The thromboxane A_2 and PGD_2 signaling presents a therapeutic target with potential to mitigate AKI and transition to CKD. Ramatroban, the only dual antagonist of the thromboxane A_2/TPr and PGD_2/DPr2 signaling could potentially mitigate renal injury in acute and long-haul COVID. Urgent studies targeting the lipid-mediator storm are needed to potentially reduce the heavy burden of kidney disease emerging in the wake of the current pandemic.

Keywords
acute kidney injury, coronavirus disease 2019, prostaglandin D_2, thromboinflammation, thromboxane

INTRODUCTION

Amidst the coronavirus disease 2019 (COVID-19) pandemic, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has caused immense suffering while placing tremendous burden on healthcare systems worldwide. Although mild cases present with common cold symptoms, severe COVID-19 disease is associated with multi-organ failure and dysfunction of the lung, kidney, heart, liver and brain. Acute kidney injury (AKI) has emerged as a common complication in hospitalized patients with severe COVID-19 with acute tubular injury as the major histopathological finding [1,2]. The pathogenesis of COVID-19-induced AKI (CoV2-AKI) is poorly understood.

End organ damage in COVID-19 is fueled by thromboinflammation characterized by platelet and neutrophil activation, and release of neutrophil extracellular traps (NETs) [3▪] (Fig. 1). It has been proposed that thromboinflammation in COVID-19 is mediated by a cytokine storm. However, cytokine release in COVID-19 is comparable to if not lower than the cytokine levels in influenza patients [4], and yet alveolar capillary microthrombi are nine

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KEY POINTS

- Severe COVID-19-induced lipid mediator storm in the lungs is associated with marked increase in thromboxane A_2 (TxA_2), PGD_2 and leukotoxin diols.
- Thromboxane A_2 promotes thromboinflammation and thereby ischemia–reperfusion injury.
- PGD_2/DPr2 signaling promotes a Th2 immune response and apoptosis of renal tubular cells.
- Leukotoxin diols induce mitochondrial dysfunction and cytotoxicity.
- The lipid mediator storm presents a therapeutic target in acute and long-haul COVID-19 with potential to mitigate AKI and transition to CKD.

times more prevalent in COVID-19 compared with influenza [5▪▪]. Emerging evidence supports a lipid-mediator storm fueling maladaptive immune responses and thrombotic events, all of which play a role in thromboinflammation [6▪,7▪▪]. In 33 hospitalized COVID-19 patients requiring mechanical ventilation, lipid analysis of bronchoalveolar lavage fluid (BALF) revealed massive increase in thromboxane levels [7▪▪]. Here, we postulate the possible mechanisms of AKI during acute SARS-CoV-2 infection in the context of the lipid mediator storm. We also speculate on the impact of prolonged lipid mediator storm in the progression of chronic kidney disease in long-haul COVID-19.

CLINICAL SYNDROME OF ACUTE KIDNEY INJURY AND CHRONIC KIDNEY DISEASE IN CORONAVIRUS DISEASE 2019

Although COVID-19 is predominantly a respiratory disorder, the kidney is one of the most common organs affected by COVID-19 second only to the lung [8]. AKI is emerging as a common and important sequelae of COVID-19, with rates as high as 33–43% in hospitalized patients [9–12]. CoV2-AKI may present as collapsing glomerulopathy, acute interstitial nephritis, de novo glomerular disease, prerenal azotemia or acute tubular injury [1,13]. In kidney biopsy, samples from 17 mild COVID-19 patients, acute tubular injury, collapsing glomerulopathy, endothelial injury or thrombotic microangiopathy were the most common histological findings [14]. Interestingly, virus detection was negative in the patient samples [14], and most kidney biopsies performed several weeks after the onset of COVID-19 symptoms failed to show notable SARS-CoV-2 infection [15]. Although some studies have reported SARS-CoV-2 particles in urine samples [16–18] or in kidney glomerular compartments [19], a direct role of the virus in the development of AKI remains to be demonstrated [15].

Most patients who survive CoV2-AKI regain kidney function but up to 30% may remain on dialysis at discharge [20]. Moreover, in a multicenter cohort study of 3099 hospitalized adult COVID-19 patients, one in five patients developed AKI requiring renal replacement therapy (RRT) [11]. Of those who survived and were discharged, one in three remained RRT-dependent at discharge, and one in six remained RRT-dependent 60 days after ICU admission [11]. This raises the specter of transition from acute to chronic kidney disease. Better understanding of mechanisms underlying COVID-19-induced AKI are critical to designing therapeutic strategies.

MECHANISMS OF CORONAVIRUS DISEASE 2019-INDUCED ACUTE KIDNEY INJURY

The mechanisms underlying the development of CoV2-AKI are likely multifactorial, including viral septicaemia, an enhanced inflammatory response, endothelial damage, hypercoagulability, myocardial dysfunction, drug nephrotoxicity and the effects of general hypoxia and dehydration on renal perfusion [21]. Although there is evidence of an association between proinflammatory cytokines and kidney injury [22,23], few patients with COVID-19 exhibit cytokine profiles indicative of cytokine storm syndrome [4]. In fact, patients with COVID-19 exhibited lower cytokine levels than patients with influenza [4]. Therefore, other underlying mechanisms may play a greater role in fueling the thromboinflammation and AKI in COVID-19 as discussed in this review (Table 1).

Endothelial injury and dysfunction

SARS-CoV-2 virus infects endothelial cells causing diffuse endothelialitis, intussusceptive angiogenesis and impaired microcirculation in vascular beds [5▪▪,24,25]. Endothelialitis and pyroptosis lead to release of endothelial microvesicles, which activate leukocytes and platelets through surface interaction, receptor activation, cellular fusion and the delivery of intravesicular cargo [25,26]. Endothelial cell injury, platelet activation, platelet–leukocyte aggregates and thrombosis in severe COVID-19 disease is evidenced by elevated serum levels of soluble P-selectin, von Willebrand factor, soluble thrombomodulin and soluble CD40L [3▪,27▪–29▪]. Endothelial cells and platelets generate TxA_2, a key mediator of platelet activation and thrombosis.

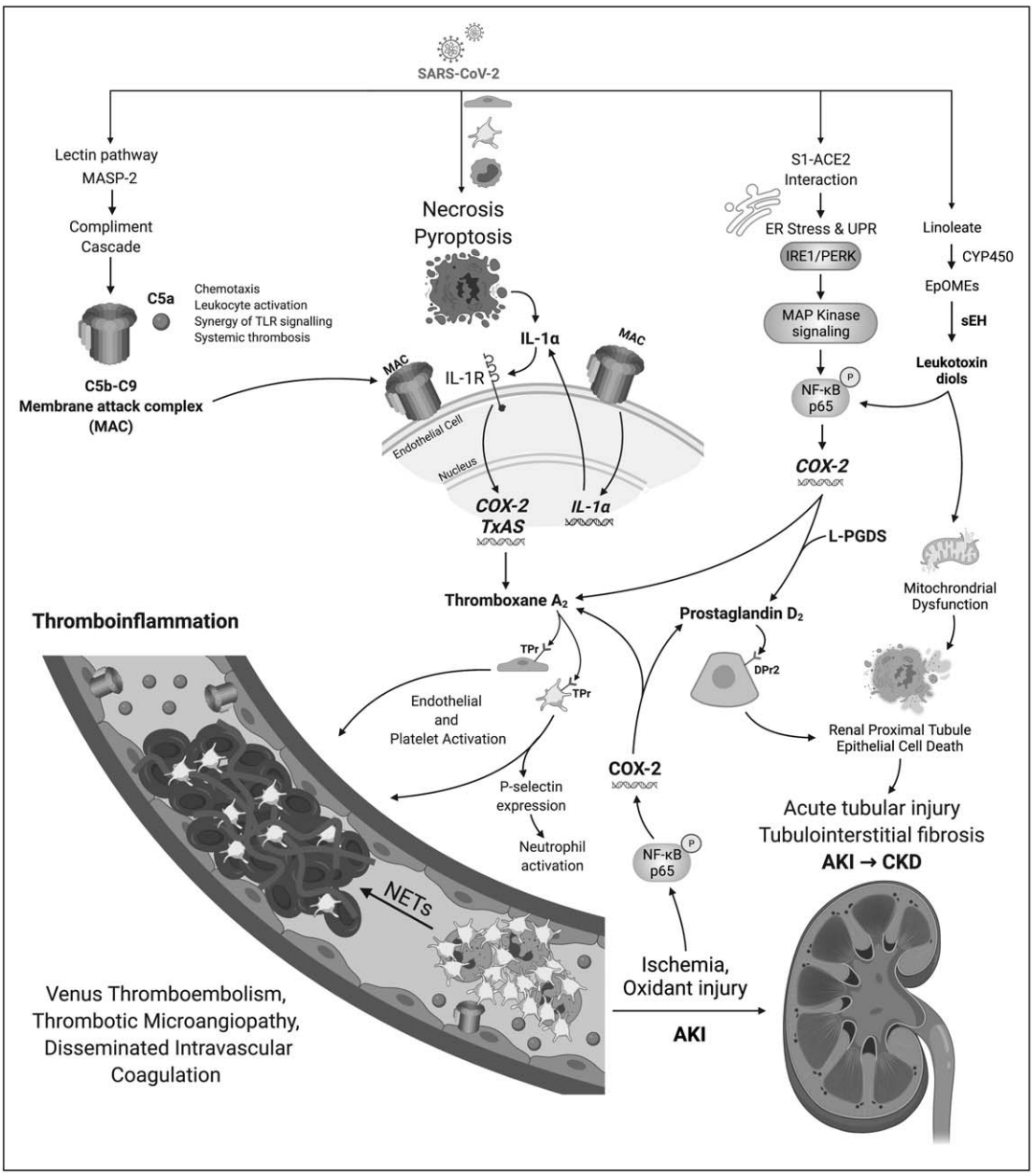

FIGURE 1. Potential mechanisms of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) induced acute kidney injury and transition to chronic kidney disease in long-haul coronavirus disease. SARS-CoV-2 virus binds complement MASP-2, thereby activating the lectin pathways and production of membrane attack complex (MAC) in renal vascular beds and tubuli. MAC synergizes with TLR signaling to promote inflammation, and contributes to chemotaxis, leukocyte adhesion and systemic thrombosis. MAC deposition on endothelial cells along with necrosis and pyroptosis of endothelial cells, platelets and monocytes, leads to IL-1α production and release. In turn, IL-1α stimulates the IL-1 receptor expressed on endothelial cells leading to COX-2 and TxAS expression. Subsequent thromboxane A_2 production induces endothelial and platelet activation via the TPr receptor. Activated platelets express P-selectin leading to platelet–neutrophil partnership, neutrophil activation and release of neutrophil extracellular traps (NETs), which fuel thromboinflammation in COVID-19. Renal ischemia–reperfusion injury as a result of renal thromboinflammation leads to NF-κB p65 phosphorylation. SARS-CoV-2 also directly induces NF-κB p65 phosphorylation via binding of S1 protein to ACE2 leading to ER stress and unfolded protein response (UPR) signaling constituting IRE1 and PERK protein activation, and downstream MAP kinase signaling. NF-κB p65 phosphorylation induces COX-2 expression and eicosanoid production, including upregulation of L-PGDS derived PGD_2. Patients with COVID-19 also exhibit elevated levels of leukotoxin diols. Linoleate is converted into epoxyoctadecenoic acids (EpOMEs) by CYP450 epoxygenase enzymes, and further metabolized into leukotoxin diols by soluble epoxide hydrolase (sEH). PGD_2/DPr2 signaling and leukotoxin diol-induced mitochondrial dysfunction causes renal proximal tubular epithelial cell apoptosis and

Complement activation

Endothelial dysfunction and thrombosis in COVID-19 is also mediated by complement activation (Fig. 1). Nucleocapsid protein of SARS-CoV-2 virus binds to the Mannan-binding lectin-associated serine protease-2 (MASP-2), the lectin pathway's effector enzyme, resulting in complement activation [30]. Kidney biopsies in nine COVID-19 patients reveal enhanced renal complement deposition in vascular beds and tubules, along with glomerular MASP-2 and tubular C5b-9 deposition in the majority of cases [8]. Complement activation and assembly of the MAC C5b-9 is known to promote endothelial damage, thrombosis and renal injury, such as in atypical hemolytic uremic syndrome [31].

In COVID-19 infection, IL-1α release from necrotic and pyroptotic cells is strongly associated with the lung injury and disease severity [32,33]. MAC C5b-9 induces synthesis of IL-1α from porcine endothelial cells, and direct treatment with IL-1α leads to COX-2 but not COX-1 expression [34]. Therefore, complement activation and cellular necrosis-led expression of IL-1α may lead to thromboinflammation via COX-2 mediated thromboxane generation as discussed below (Fig. 1).

Lipid mediator storm promoting thromboinflammation and maladaptive immune response

SARS-CoV-2-induced direct COX-2 expression has been observed in various cell lines and tissues *in vitro* and *in vivo* including cardiomyocytes, Calu-3 and A549 lung cancer cell lines, ciliated lung cells, primary human bronchial epithelial cells, human ACE2-expressing mouse lungs and living human lung slices [35–37]. COX-2 expression is elevated more than four-fold in SARS-CoV-2-infected Calu-3 cells and human lung slices [36] and more than 50-fold in infected cardiomyocytes (Professor Srinivasa T. Reddy, UCLA, personal communication following analysis of the supplemental material in reference [36]) [37].

SARS-CoV-2-induced cardiomyocyte COX-2 expression is highly correlated with pro-inflammatory genes and signaling pathways including interferon, IL-1β and NF-κB [37,38]. Interestingly, SARS-CoV-2 infection-induced S1-ACE2 receptor interaction leads to NF-κB signaling in various cells including the kidney [39,40]. NF-κB activates COX-2 expression and thromboxane A_2 generation [41], leading to renal ischemia–reperfusion injury (Fig. 1). Inflammation, old age and obesity are additional stimulators of COX-2 expression [42,43]. Canonical NF-κB signaling pathway regulates early phase inflammation in I/R injury [44,45]. In a mouse model of I/R injury induced AKI, widespread NF-κB activation was associated with impaired renal function, tubular apoptosis and neutrophil and macrophage infiltration after I/R injury, all of which were ameliorated by inhibiting expression of NF-κB [45].

In addition to COX-2 expression, SARS-CoV-2 infection inhibits PG-degrading enzyme 15-hydroxyprostaglandin-dehydrogenase (15-PGDH) in Calu-3 cells by about 90% [36]. 15-PGDH is the main enzyme for lipid mediator catabolism [36]. 15-PGDH can accept a wide variety of prostaglandin substrates with a high affinity for PGE_2, $PGF_{2\alpha}$, PGI_2 and 6-keto $PGF_{1\alpha}$, and low affinity for PGD_2 and TxB_2 [46,47].

COX-2 expression and 15-PGDH suppression appear to promote a lipid-mediator storm in severe COVID-19. Archambault and colleagues have measured eicosanoids in the BALF in 33 severely ill patients with COVID-19 within 2 h of initiation of mechanical ventilation, compared with 25 healthy controls. Severe COVID-19 patients had marked increases in fatty acid levels as well as an accompanying inflammatory lipid storm with predominance of cyclooxygenase (COX) metabolites notably $TxB_2 >> PGE_2 > PGD_2$ [7▪▪]. Plasma TxB_2 levels were also markedly increased in severe COVID-19 patients [28▪]. COX-2 mediated thromboxane A_2 generation is thought to be a key catalyst for the prothrombotic state in COVID-19 [27▪]. The involvement of COX-2 derived lipid mediators in the pathogenesis of

death leading to common histological findings in SARS-CoV-2 infection including acute tubular injury. Persistent ischemia–reperfusion injury and apoptosis may lead to tubulointerstitial fibrosis and progression from AKI to CKD. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ACE2, angiotensin-converting enzyme 2; AKI, acute kidney injury; CKD, chronic kidney disease; COX, cyclooxygenase; CYP450, cytochrome P450; EpOMEs, epoxyoctadecenoic acids; ER, endoplasmic reticulum; IFN, interferon; IL, interleukin; IRE1, inositol-requiring enzyme 1; IRF, interferon regulatory factor; L-PGDS, lipocalin prostaglandin D2 synthase; MAPK, mitogen-activated protein kinase; MASP, mannan-binding lectin-associated serine protease; NF-κB, nuclear factor-kappa B; PERK, protein kinase R-like ER kinase; sEH, soluble epoxide hydrolase; TPr, thromboxane A_2 receptor; TxAS, thromboxane A_2 synthase; UPR, unfolded protein response.

Table 1. Renal involvement in coronavirus disease 2019: lipid mediators, pre and inflammatory cytokine, main clinical consequences and therapeutic options

Lipid mediators	Changes in COVID-19	Receptors	Postulated humoral and cellular mediators	Clinicopathologic outcomes[a]	Antagonists	Effects of antagonism
PGD_2	PGD_2 synthase ↑ [67▪▪] DPr2 ↑ [67▪▪] Plasma PGD_2 ↑ (ST Reddy, personal communication, 2021) BALF PGD_2 ↑ [7▪▪]	DPr1	pVascular/renal superoxide ↓ [127] Blood pressure elevation ↓ [127]	Renoprotective Protection against Age-related hypertension [128] Antifibrotic [129]	Asapiprant Laropiprant	Hypertension [128] Renal inflammation [128]
		DPr2 (CRTH2)	IL-4, IL-5, IL-13 ↑ [72▪–74▪,108] MDSCs ↑ [130,131] Th2 >> Th1 Eosinophilia ↑ [132] Basophilia ↑ Renal apoptosis and fibrosis ↑ [78] IFN-λ ↓ [133]	AKI → CKD [79] Inflammation Collapsing FSGS Acute tubular necrosis Renal fibrosis [79]	Ramatroban Fevipiprant	Th2>>Th1 ↓ [79,134] Renal fibrosis ↓ [79] IFN-λ ↑ → antiviral/renal protection [133,135]
TxA_2	Plasma TxA_2 ↑ [28▪] BALF TxA_2 ↑ [7▪▪] TxA_2 → 11-dehydro-TxB_2 → DPr2 [107] Renal thrombosis (I/R injury)	TPr	Platelet–neutrophil interaction ↑ NETosis ↑ [105] Podoplanin-CLEC2 signaling ↑ [136] Vasoconstriction ↑ NO ↓ [91] TNF-α ↑ [105] ICAM-1, VCAM-1, MCP-1 ↑ [137,138]	I/R injury [139] AKI → CKD Glomerular thrombosis [140] Hypertension [141] GFR ↓ [140] Glomerulosclerosis [141] Cardiac hypertrophy [141]	Ramatroban Seratrodast Ifetroban Terbogrel Ozagrel	Bleeding [142] Thrombo-inflammation ↓ [105,143,144] Oxidative stress ↓ [139,145] Perfusion ↑[b] [141] GFR ↑[b] [141] BP ↓[b] [141] Renoprotective[b] [141]
PGE_2	BALF PGE_2 ↑ [7▪▪]	EPr1	ROS ↑ [146] Fibronectin ↑ [146]	I/R Injury Collapsing FSGS	SC-19220	Renal function ↑ [147] Creatinine/BUN ↓ [147] Glomerulosclerosis ↓ [147]
		EPr4	Podocyte integrity ↑ [148] Inflammatory +/- [149] Fibrosis +/- [149]	Renoprotective [150]	ASP7657	Renoprotective [150] Proteinuria ↓ [150] Anti-inflammatory [150] Antifibrotic [150]
Leukotoxin Diols	12,13-DiHOME ↑ [82▪] 9,10-DiHOME ↑ [82▪]	NA	IL-6 ↑ [83] Renal proximal tubular cell toxicity [84] Mitochondrial dysfunction [84]	AKI Acute tubular necrosis	she inhibitors	Renoprotective [151] Anti-inflammatory [150,151] Antifibrotic [151]
LTC_4, LTD_4, LTB_4, LTE_4	BALF Leukotrienes ↑ [7▪▪]	CysLTr1	MPO ↑ [152] Kidney hemorrhages ↑ [152] Glomerular degeneration ↑ [152]	AKI [124] I/R injury [125]	Montelukast	Oxidative damage ↓ [152] Renoprotective [125]

[a]Proposed clinical or pathologic outcomes based on the changes in cellular or humoral mediators and the disease setting.
[b]Administration of a thromboxane synthase inhibitor.
AKI, acute kidney injury; BALF, bronchoalveolar lavage fluid; BP, blood pressure; BUN, blood urea nitrogen, LT, leukotriene; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; cysLTr, cysteine leukotriene receptor; DiHOMEs, dihydroxyoctadecenoic acids; DPr, prostaglandin D_2 receptor; EPr, prostaglandin E_2 receptor; GFR, glomerular filtration rate; I/R, ischemia–reperfusion; ICAM-1, intercellular adhesion molecule 1; IL, interleukin; MCP-1, monocyte chemoattractant protein 1; MDSC, myeloid derived suppressor cells; MPO, myeloperoxidase; NET, neutrophil extracellular trap; PG, prostaglandin; ROS, reactive oxygen species; sEH, soluble epoxide hydrolase; Th1 and -2, T-helper cell types 1 and 2; TNF-α, tumor necrosis factor alpha; TPr, thromboxane prostanoid receptor; TxA_2, thromboxane A_2; TxB_2, thromboxane B_2; VCAM-1, vascular cell adhesion molecule 1.

COVID-19 associated AKI remains to be investigated.

Thromboxane A_2, a potential promoter of thrombotic events and renal ischemia–reperfusion injury

In addition to pneumonia, SARS-CoV-2 causes a vascular disease leading to thrombotic microangiopathy, pulmonary thrombosis, pedal acro-ischemia ('COVID-toes'), arterial clots, strokes, cardiomyopathy, coronary and systemic vasculitis, bleeding, deep venous thrombosis, pulmonary embolism; and microvascular thrombosis [3▪,5▪▪,28▪,48–50]. Necropsies have revealed inflammatory microvascular thrombi containing neutrophils, platelets and NETs in the pulmonary, hepatic, renal and cardiac microvasculature as the hallmark of severe COVID-19 disease leading to ischemia–reperfusion injury and subsequent multiorgan failure, including AKI [3▪,51,52].

Thromboxane A_2 (TxA_2), a key mediator of thrombosis, is released by platelets, endothelial cells, macrophages and neutrophils [53]. TxA_2 binds to the thromboxane-prostanoid receptor (TPr) on platelets, thereby stimulating platelet activation and aggregation [53]. In patients with acute SARS-CoV-2 infection, elevated TxA_2 is strongly associated with lung lesions and lower peripheral oxygen saturation [54]. This is consistent with pulmonary microvascular thrombi in lung autopsies of severe COVID-19 patients [5▪▪].

In addition to platelet activation, TxA_2 stimulates expression of thrombotic markers including platelet P-selectin [55], endothelial tissue factor [56–58] and CD40L release [59]. In particular, P-selectin is positively associated with creatinine and BUN, and neutrophil infiltration and extracellular trap release during I/R-induced AKI in mice [60]. Urinary excretion of 11-dehydro-thromboxane B_2, a stable metabolite of TxA_2 is markedly increased in recently hospitalized patients with COVID-19 and is predictive of plasma D-dimer levels, need for mechanical ventilation and mortality [61▪▪]. Additionally, there was a significant positive correlation between urinary 11-dehydro-thromboxane B_2, and urinary liver-type fatty acid binding protein, a marker of renal ischemia and injury [61▪▪]. This suggests that increased generation of thromboxane in COVID-19 is associated with microvascular thrombosis and renal ischemia. Therefore, TxA_2/TPr signaling presents a therapeutic target in COVID-19-associated AKI. Moreover, protracted microvascular thrombosis, evidenced by asymptomatic elevation of D-dimers in 25% patients up to 4 months post-SARS-CoV-2 infection [62] raises the possibility of sustained thromboxane storm and persistent ischemia to the kidneys leading to progression from AKI to CKD (Fig. 1). Further studies are needed to analyze lipid mediators in long-haul COVID-19.

Prostaglandin D_2 signaling as a potential mediator of coronavirus disease 2019-associated acute kidney injury and chronic kidney disease

Prostaglandin D_2 is upregulated during states of ischemia [63,64], and plasma levels of PGD_2 are markedly elevated in severe COVID-19 [7▪▪,36]. PGD_2 is the most abundant prostanoid in the mammalian brain [65] and exerts its main functions through two receptors, DPr1 and DPr2 (aka CRTh2) [66]. In fact, lipocalin PGD_2 synthase and DPr2 expression were elevated in the renal tubules of COVID-19 autopsies [67▪▪]. SARS-CoV-2 infection of Calu-3 lung cells increased PGD_2 secretion more than two-fold [36]. DPr2 expression is upregulated more than 50-fold by TGF-β acting in conjunction with IL-4 [68]. In COVID-19, TGF-β is markedly increased and is in fact a determinant of the maladaptive host immune response [69]. IL-4 levels are also markedly elevated in severe COVID-19 and post COVID where they correlate with the number of circulating endothelial cells [70]. Increased expression of DPr2 receptors in conjunction with local increase in PGD_2 has the potential to massively amplify PGD_2/DPr2 signaling.

PGD_2 via DPr2 is known to induce Th2 cell activation and release of type 2 cytokines including IL-4, IL-5 and IL-13, which promote allergic inflammation [71], a characteristic feature of COVID-19 [72▪]. IL-13 was universally correlated with ARDS, AKI and mortality in COVID-19 [73▪]. Plasma IL-13 levels are associated with need for mechanical ventilation in COVID-19. IL-13 has been recently reported to stimulate hyaluronan accumulation in mouse lungs [74▪].

PGD_2/DPr2 signaling also exerts pro-apoptotic and profibrotic actions on a variety of cells including islet cells, cardiomyocytes and osteoclasts [75–77]. PGD_2/DPr2 signaling promotes apoptosis of cultured pig kidney cells [78]. PGD_2/DPr2 signaling also contributes to tubulointersitial fibrosis following unilateral ureteral obstruction in mice, which was ameliorated either with a DPr2 antagonist or by ablation of IL-4 and IL-13 [79]. Therefore, PGD_2/DPr2 signaling merits examination as a mediator of COVID-19-associated acute kidney injury and progression to CKD (Fig. 1).

Leukotoxin diols as a potential mediator of coronavirus disease 2019-induced renal inflammation and injury

Leukotoxin diols are a metabolite of linoleic acid (18 : 2n6) that is an essential source for long-chain

n-6 polyunsaturated fatty acids. CYP450 epoxygenase enzymes convert linoleate to linoleic epoxides (epoxyoctadecenoic acids, EpOMEs) [80,81]. EpOMEs are further metabolized by soluble epoxide hydrolase (sEH) to leukotoxin diols (dihydroxyoctadecenoic acids, or DiHOMEs) [80,81]. Interestingly, COVID-19 patients have increases in leukotoxin diols, 12,13-DiHOME and 9,10-DiHOME when compared with healthy controls [82▪].

Vascular permeability and stimulation of neutrophil chemotaxis are two vascular actions associated with leukotoxin diols [83]. Endothelial cell activation by leukotoxin diols enhanced nuclear translocation of the transcription factor NF-κB and the inflammatory cytokine IL-6 [83]. Leukotoxin diols also cause mitochondrial dysfunction and extensive cell death at the level of the proximal tubule [84]. Alexander *et al.* [85] have demonstrated that the morphological and molecular profiles of severe COVID-19 renal injury resemble sepsis-induced renal injury including microvascular dysfunction, inflammation and molecular reprograming but mitochondrial injury is more severe. These actions on the vascular endothelium and renal proximal tubule epithelial cells are consistent with the pathophysiology of AKI (Fig. 1).

Leukotrienes as potential mediators of coronavirus disease 2019-induced oxidative stress and acute kidney injury

Leukotrienes, notably LTB_4, LTE_4 and eoxin E_4 are significantly increased in the BALF of severe COVID-19 patients [7▪▪]. Leukotrienes have been implicated in renal disease. In rat model of glomerular nephritis, administration of antirat glomerular basement membrane antibodies led to urinary excretion of LTC_4, LTE_4 and acetylated LTE_4 concomitantly with increased renal LTC_4 synthase activity [86]. Moreover, in a mouse model of renal–ischemia reperfusion, inhibition of leukotriene biosynthesis attenuated oxidative stress, histopathological markers of tissue damage, cytokine release and damage to renal function [87]. Therefore, leukotrienes likely play a key role in renal ischemia–reperfusion-induced AKI.

Other lipid mediators of uncertain significance in causing renal injury in coronavirus disease 2019

Many other lipid mediators have been reported to be increased in the lungs and plasma of COVID-19 patients but their role in causing renal injury in acute and long-haul COVID remains to be defined. These mediators include PGE_2, specialized pro-resolving mediators, D-series resolvins and protectin D1 [7▪▪,36].

Nitric oxide deficiency

Nitric oxide (NO) has been implicated in many physiological functions in the kidney [88], and is known to ameliorate renal injury in ischemic acute renal failure [89]. On the other hand, NO deficiency characterizes transition to chronic kidney disease and adverse kidney events [88,90].

SARS-CoV-2 virus-induced endothelial injury and pyroptosis is associated with inhibition of nitric oxide synthesis. Furthermore, TxA_2 directly inhibits endothelial and inducible nitric oxide synthase [91,92]. Conversely, NO phosphorylates TxA_2 receptor (TPr) and thereby inhibits platelet activation [93] whereas seratrodast or ramatroban as TPr antagonists enhance NO generation [91]. Therefore, TPr antagonism could potentially increase NO production and thereby mitigate AKI in COVID-19.

THERAPIES TARGETING THE LIPID MEDIATOR STORM AND ACUTE KIDNEY INJURY IN CORONAVIRUS DISEASE 2019

Therapies targeting the lipid mediator storm have been proposed in COVID-19. In a prospective study, Hong *et al.* treated ordinary, severe and critically ill COVID-19 patients with the COX-2 inhibitor, Celecoxib [94]. In ordinary COVID-19 cases, patients taking Celebrex did not progress to severe disease compared with 15.7% of ordinary cases under routine treatments. Moreover, none of the severe COVID-19 cases with full dose Celebrex treatment progressed to critical illness. Concern has been raised that blocking upstream mediators including COX-2 and COX-1 may result in more challenges than cures because of their broad inhibition of several essential prostanoids including vasodilatory prostacyclin [95].

Dexamethasone is effective in lowering 28-day mortality and need for renal replacement therapy in hospitalized patients [96]. The efficacy of dexamethasone may stem from inhibition of the lipid mediator storm [7▪▪]. Dexamethasone destabilizes β-globin–Cox-2 reporter mRNAs [97] and upregulates annexin A1 expression [98], thereby inhibiting COX-2 and phospholipase A_2 expression, respectively, and thereby eicosanoid production.

In contrast to dexamethasone, low-dose aspirin failed to limit 28-day mortality, progression to invasive mechanical ventilation or need for renal dialysis in hospitalized COVID-19 patients [99]. This may be because of failure of low-dose aspirin in high thromboxane states, as has been reported in the obese and elderly [100,101]. NF-κB has also served as a therapeutic target in COVID-19, and NF-κB antagonism may ameliorate I/R by downregulating COX-2 expression and TxA_2 production [102].

It has been proposed that blocking the deleterious effects of PGD_2 and TxA_2 with the dual DPr2/TPr antagonist Ramatroban might be beneficial in COVID-19 [7▪▪]. Ramatroban as a TPr antagonist is 100 times more potent than aspirin in inhibiting platelet aggregation and P-selectin expression [103,104]. In addition to its antiplatelet action, ramatroban also improves vascular responsiveness; while inhibiting endothelial surface expression of ICAM-1 and VCAM-1; inhibiting MCP-1 expression in response to TNF-α or platelet-activating factor; and inhibiting macrophage infiltration [103]. In a rat model of endotoxic shock, ramatroban prevented hypotension and reduced mortality by 45%; effects attributable to marked reduction in myeloperoxidase levels in lungs, ileum and heart and more than 90% reduction in plasma TNF-α levels [105]. It is notable that infliximab, a TNF inhibitor used in auto-immune conditions, such as Crohn's disease and rheumatoid arthritis is being tested in the WHO-sponsored SOLIDARITY trial [106].

Dual DPr2/TPr antagonism would not only block the activity of both TxA_2 and PGH_2 on platelets and vessels but abrogate the effects of 11-dehydro-thromboxane B_2, a stable metabolite of TxA_2 and a full agonist of the DPr2 receptor for PGD_2 [107]. Ramatroban is a potent inhibitor of IL-4, IL-5 and IL-13 production induced by PGD_2 [108], and therefore, a promising therapy for the maladaptive immune response in severe COVID-19. Ramatroban (Baynas, Bayer Yakuhin Ltd., Japan) has been safely administered for the treatment of allergic rhinitis in Japan since 2000 [103]. Ramatroban exhibits surmountable binding to TPr [109], and reversible antiplatelet action [103]. This is of advantage in the event of bleeding complications reported in 5.6% of critically ill COVID-19 patients [110].

There is increasing evidence of ongoing lung inflammation in patients with long-haul COVID, which may culminate in lung fibrosis [111,112]. There is no animal model of long-haul COVID to date. However, an animal model of silicosis exhibits massive increases in lung PGD_2 and TxA_2 associated with lung inflammation and fibrosis [113▪▪]. In this model, ramatroban reduced macrophage, lymphocyte and neutrophil infiltration of the lungs while inhibiting TNF-α, IL-6, IL-1β, IL-18 and NLRP3 activation, thereby reducing inflammation, fibrosis and cardiopulmonary dysfunction [113▪▪]. Therefore, ramatroban is a promising candidate for chemoprophylaxis and treatment of lung and cardiac injury in COVID-19 thereby mitigating secondary kidney injury.

Soluble epoxide hydrolase inhibitors (sEHIs) have two activities that could be beneficial in COVID-19-induced AKI. Inhibition of sEH can lower linoleic-derived leukotoxin diols and increase arachidonic acid-derived epoxyeicosatrienoic acids (EETs) [81]. The therapeutic benefits for sEHIs have been demonstrated in several animal models of kidney disease including AKI [81,114]. Cisplatin-induced AKI was opposed by sEH inhibition with decreased NF-κB activation and TNF-α inflammation [115,116]. The conversion of AKI to chronic kidney disease can also be opposed by sEHIs. Renal fibrosis induced by unilateral ureter obstruction is prevented by sEH inhibitor administration, which was attributed to increased EET levels and decreased inflammation associated with decreased neutrophil influx [117]. Antifibrotic actions for sEHIs can be attributed to suppression of epithelial to mesenchymal transition by increasing E-cadherin, decreasing α-SMA and preventing the phenotype transition [117,118]. These kidney animal model studies have demonstrated that sEHIs provide renal protection through anti-inflammatory and antifibrotic mechanisms.

Development of sEHIs have been tested in clinical trials and SEHIs did not demonstrate major side effects or toxicity [119,120]. Interestingly, a major finding for the human clinical trial with GSK2256294 found improved endothelial function in obese smokers assessed by forearm blood flow response to the vasodilator bradykinin [121]. These actions on endothelial function would be beneficial in COVID-19-induced AKI. Taken together, sEHIs ability to lower leukotoxin diols and increase EETs have vascular, inflammatory, and epithelial actions that could treat COVID-19-induced AKI and prevent the progression to CKD.

In view of the massive increase in leukotrienes in patients with severe COVID-19, Montelukast, a cysteinyl leukotriene receptor 1 antagonist has recently been shown to reduce clinical deterioration in hospitalized patients with COVID-19 in a small retrospective study [122]. In a rat model of chronic renal failure, montelukast attenuated oxidative damage, myeloperoxidase, LTB_4, cytokine levels, reduced glutathione, and finally, damage to glomerular structure [123]. Moreover, in a rat model of lipopolysaccharide-induced sepsis, Montelukast reduced renal injury, and levels of inflammatory and oxidative stress markers [124]. Montelukast also reduced AKI induced by rhabdomyolysis or intestinal ischemia in rats [125,126].

CONCLUSION

SARS-CoV-2 infection induces a lipid mediator storm with massive increases in pulmonary and systemic thromboxane A_2, PGD_2 and leukotoxin diols. Thromboxane A_2 and PGD_2 appear to play a

key role in COVID-19-associated thromboinflammation and maladaptive immune response, respectively while leukotoxin diols induce mitochondrial dysfunction and cytotoxicity. The lipid mediators may promote AKI, renal fibrosis and development of CKD. Approaches targeting the lipid mediator storm merit further exploration in order to reduce the heavy burden of kidney disease emerging in the wake of the current pandemic.

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Conflicts of interest

A.G. and K.C.C. have filed a patent on the use of ramatroban for COVID-19. Other authors declare no conflict of interest. Thromboxane A_2 and prostaglandin D_2 receptor antagonists are under investigation and not approved for the treatment of COVID-19.

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