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Similarities and Differences between COVID-19-Associated Nephropathy and HIV-Associated Nephropathy

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Abstract
Kidney disease is a major complication of viral infection, which can cause both acute and chronic kidney diseases via different mechanisms such as immune-mediated injury, kidney cell injury from a direct viral infection, systemic effects, and antiviral drug-induced nephrotoxicity. HIV-associated nephropathy (HIVAN), characterized by collapsing focal segmental glomerulosclerosis (cFSGS), has been described 2 decades ago as a major complication of acquired-immunodeficiency syndrome. The pathogenesis of HIVAN has been well studied, including viral entry, host response, and genetic factors. The incidence of this disease has been dramatically dropped with current antiretroviral therapy. In the recent severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) pandemic, acute kidney injury was also found to be a major complication in patients with (coronavirus disease) COVID-19. These patients also developed glomerular disease such as cFSGS in African Americans with apolipoprotein L1 risk alleles, similar to HIVAN. Whether SARS-CoV-2 can infect kidney cells locally remains controversial, but both local infection and systemic effects are likely involved in the pathogenesis of this disease. In this review, we present a comparison of the clinical presentations, pathological findings, disease mechanisms, and potential treatments between HIVAN and COVID-19. Leveraging the knowledge in HIVAN and experimental approaches used to study HIVAN will facilitate the exploration in the pathogenesis of COVID-19-associated kidney disease and improve our management of COVID-19 patients.

Introduction

It is well established that viral infection is a major cause of acute kidney injury (AKI) and chronic kidney disease (CKD). Some viral nephropathy occurs in the general population, while others are found only in immunosuppressive individuals, such as those with a kidney transplant. The criteria used for the diagnosis of viral nephropathy include (1) typical clinical syndrome, (2) specific serological tests, (3) identification of viremia, and (4) detection of viral antigens and host antibodies in the kid-

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ney. Nevertheless, viremia is difficult to detect, since the viral load is usually higher in the tissue (e.g., kidney) than in the circulation. The detection of viruses in specific organs and tissues could also be challenging due to the varying degrees of sensitivity and specificity of the available tests such as polymerase chain reaction, in situ hybridization, immunostaining, or electron microscopy (EM). It should also be noted that while the renal tubular uptake of viral particles is a common finding under EM, it does not necessarily establish an etiological link with renal disease. An etiological link should be confirmed by a complete cure following the eradication of the virus. Among viral nephropathy, HIV-associated nephropathy (HIVAN) has met this criterion. Because of the effective antiviral therapy (ART), the incidence and prevalence of HIVAN have been dramatically decreased [1]. Even in patients with advanced CKD or on dialysis, HIVAN could be reversed or partially reversed by ART [2]. However, such a cause-effect relationship is not fully established for other viral nephropathies, such as hepatitis B- and C-induced glomerulonephritis (GN). Even with new effective direct antiviral agents, hepatitis C-induced cryoglobulinemia and membranoproliferative glomerulonephritis (MPGN) are not significantly improved [3].

The mechanisms of renal injury induced by viral infection are diverse and include immune-mediated, cytotoxic, and systemic effects, as well as antiviral therapy-induced nephrotoxicity. For instance, circulating immune complexes (ICs), consistent with viral antigens or endogenous antigens modified by the virus and host antibodies, are likely responsible for hepatitis C-induced GN, whereas in situ immune-mediated mechanisms involving viral antigens bound to glomerular structures may underlie the pathogenesis of hepatitis B-induced membranous nephropathy (MN) [4]. Cytotoxic effects may occur as a direct result of viral infection and/or expression of viral proteins in kidney cells, or as indirect effects from infiltrated inflammatory cells or mediators released from injured cells in response to viral infection. Both of these mechanisms are likely involved in the pathogenesis of HIV- and COVID-19-associated kidney diseases [5, 6]. AKI is common in patients with infections of Hantavirus, HIV, and coronavirus including severe acute respiratory syndrome and severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). AKI in these patients is caused either by systemic effects, such as multiorgan failure, sepsis, and rhabdomyolysis, or by local cytotoxic effects in kidney cells [7–9]. Many antiviral drugs have been shown to induce nephrotoxicity, and tenofovir, an effective ART for HIV, is a good example of these [10].

A recent SARS-CoV-2 pandemic has hugely impacted the health of millions of people around the world, and that COVID-19 is not merely a respiratory disease but induces multiple organ injury and complications, including the kidney [6]. Recently, several reviews have been published to summarize the COVID-19-associated kidney disease. Our and other laboratories have performed extensive research in HIV-associated kidney disease for the past 2 decades, and we have noted many similarities between HIV- and COVID-19-associated kidney diseases, as well as their distinct features. In this review, we present a comparison between COVID-19- and HIV-associated kidney diseases, and we believe that the approaches that we used to study HIVAN could be applied to address COVID-19-associated kidney disease.

Epidemiology and Clinical Presentations

HIV-Associated Kidney Disease

HIV is part of the family of lentivirus (a subgroup of retrovirus) transmitted as single-stranded, positive-sense, enveloped RNA viruses. About 79.3 million (55.9 million to 110 million) people have become infected with HIV since the start of the epidemic, and about 1.5 million (1.0 million to 2.0 million) people became newly infected with HIV in 2020 [11]. Before the introduction of ART, HIVAN was a unique kidney disease commonly associated with HIV infection, and many of these patients present with massive proteinuria and AKI with rapidly declining renal function [12]. Histologically, HIVAN is characterized as collapsing focal segmental glomerulosclerosis (cFSGS). HIVAN occurred mostly in African Americans with apolipoprotein L1 (APOL1) risk alleles and was a leading cause of end-stage renal disease (ESRD) in African Americans. It has been reported that approximately 6.0–48.5% of HIV-infected patients had a renal disease in Africa and 6.24–83% of these cases were HIVAN [2]. AKI secondary to sepsis was another major complication in sick HIV-infected patients with acquired immunodeficiency syndrome (AIDS) [13]. Numerous forms of the IC-mediated glomerular disease have been reported in HIV-positive individuals [14], referred to as HIV-associated IC kidney disease (HIVICK) with a specific description of the pattern of IC disease in the setting of HIV. HIV-infected patients often have co-infection with hepatitis C and both are known to induce MPGN. The causality of HIV infection and HIVICK has not been fully established. With ART, the incidence and prevalence of HIV have dramatically reduced, and patients with HIV infection live much longer. The spectrum of HIV-associat-

ed kidney disease has also changed significantly in the ART era. The incidence and prevalence of HIVAN and HIV-related AKI dropped dramatically due to the significant viral suppression and rare events of AIDS. Most HIV-infected patients with proteinuria presented with classic FSGS instead of cFSGS. However, the incidence of HIVCK remains unchanged, suggesting that suppression of viral replication does not affect viral-induced IC glomerular disease or HIV infection is not directly responsible for this disease. In addition, with chronic ART use, many patients develop nephrotoxicity related to antivirus drugs [10]. However, the drug-induced nephrotoxicity has been reduced remarkably by the replacement of tenofovir disoproxil fumarate by tenofovir alafenamide [15]. Since HIV patients live much longer, they also suffer from comorbid kidney diseases such as diabetic and hypertensive kidney diseased [16], and recent evidence suggests that chronic HIV infection, even with undetectable viral load, can aggravate the progression of diabetic kidney disease [17]. Therefore, the overall incidence of ESRD in HIV-infected patients remains high. In non-AA populations without APOL1 risk alleles, such as Chinese, HIV-infected patients could develop HIVICK, nephrotoxicity from drugs, and have the aggravation of other kidney diseases. Therefore, HIV infection is also a risk factor for CKD in the Chinese population.

COVID-19-Associated Kidney Disease

Coronaviruses are enveloped, positive single-stranded RNA viruses, similar to HIV, but express a larger number of viral proteins than HIV [18, 19]. The recent pandemic of COVID-19, caused by SARS-CoV-2, has infected over 190 million people worldwide from January 2020 to July 2021 with multiple surges, and this pandemic has not yet ended [20, 21]. AKI has been reported in COVID-19 patients, and the incidence of AKI varies among the regions from 2% in China to 46% in New York City according to our recent study from Mount Sinai Health System [22]. The incidence and the severity of AKI are affected by multiple comorbidity factors such as CKD, hypertension, diabetes, congestive heart failure, and age [23]. AKI occurred in nearly half of all patients hospitalized with COVID-19 and the majority of those admitted to the intensive care unit [22, 24]. AKI is also associated with high mortality [25]. Acute tubular injury (ATI) seems to be the most common finding in patients with COVID-19 and AKI [6]. In a multicenter, observational study of deceased patients with COVID-19 in 3 third-level centers in Mexico City, 78 (92%) were diagnosed with ATI, and ATI grades 2–3 were observed in 42 (49%) out of 85 patients [26]. In some studies, ATI was demonstrated in all patients [27]. These findings on AKI in COVID-19 patients are quite similar to those in sick HIV patients with AIDS. Interestingly, the incidence of COVID-19-related AKI has been dropped recently after more and better treatments are offered to these patients [28]. We hope that similar to HIV-related AKI, the incidence of COVID-19-related AKI will be progressively decreasing when the pandemic is better controlled, and this disease is better treated.

Clinical studies suggest that about 50% of patients with COVID-19 had proteinuria and hematuria, suggesting a possible glomerular injury [29]. Abnormal urine analysis was associated with increased inflammatory markers and could be used to predict the overall outcomes in these patients with COVID-19 [30]. cFSGS has emerged as a distinct pathology associated with SARS-CoV-2-infected patients with proteinuria [27]. Several investigators have termed this association of cFSGS with SARS-CoV-2 as COVID-19-associated nephropathy because this disease is almost identical to HIVAN [31–33]. These patients were reported almost exclusively in African Americans with APO1 risk alleles similar to cFSGS in HIVAN patients. In addition, other glomerular diseases such as minimal change disease, MN, and lupus nephritis have been also reported in COVID-19 patients, suggesting a potential activation of the immune system in these patients. However, so far, IC-mediated GN has not been reported in COVID-19 patients. It is well known that COVID-19 is associated with endothelial cell injury and a syndrome of hypercoagulability [34]. Several cases of thrombotic microangiopathy (TMA) in the kidney were reported in COVID-19 patients [35]. However, unexpectedly, the incidence of TMA is not common in COVID-19 patients.

The incidence and spectrum of COVID-19-associated kidney disease in patients recovered from acute infection remain to be determined. The current studies with a limited follow-up suggest that about one-third of these patients did not recover their renal function at discharge, many of these patients became CKD, and some of them were dialysis-dependent [22].

Pathology

HIV-Associated Kidney Disease

Collapsing Glomerulopathy

The characteristic pathological manifestation of HIVAN includes cFSGS and associated tubule-interstitial disease. cFSGS is characterized by the glomerular collapse accompanied by prominent hypertrophy and hyperplasia of the podocytes, with the formation of pseu-

docrescents [12, 36]. However, whether the proliferation of podocytes or parietal epithelial cells forms pseudocrescents remains controversial. Eventually, cFSGS may evolve into a more global pattern of glomerulosclerosis. In addition to glomerular injury, the tubulointerstitial disease causes kidney enlargement and hyperechoic appearance by ultrasound and includes interstitial inflammation, tubular atrophy, and microcytic formation [37]. The microcysts may occur in all tubular segments, and viral transcript expression has been detected in cells [38].

HIV-Associated Immune Complex Kidney Disease

HIVICK has histological changes similar to MPGN, immunoglobulin A (IgA) nephropathy, lupus nephritis, or others as observed in the general population.

COVID-19-Associated Kidney Disease

Findings of early studies suggested that ATI, collapsing glomerulopathy or cFSGS, and TMA were the 3 most common kidney biopsy findings associated with COVID-19 infection to date.

AKI with Prominent ATI

ATI features were first reported in the kidney, characterized with the loss of brush border, vacuolar degeneration, dilatation of the tubular lumen with cellular debris, and occasionally even frank necrosis and detachment of epithelium with bare tubular basement membrane as noted in 26 autopsies of patients with COVID-19 by light microscopy in China [39]. Subsequently, several studies demonstrated a similar observation with proximal tubular damage in patients with COVID-19 [27, 40]. In some cases, the degree of ATI was relatively mild compared with the degree of serum creatinine elevation [41], which might be due to the prerenal AKI secondary to hemodynamic changes [27, 42]. Overall, COVID-19 patients may have more severe tubular cell injury than HIV patients.

Glomerulopathy

The most common glomerular disease noted with COVID-19 is cFSGS [43], similar to HIVAN or idiopathic cFSGS. cFSGS has been also reported in patients with other viral infections such as Epstein-Barr virus, cytomegalovirus, and parvovirus B19 infections [44]. In addition, minimal change disease [42], pauci-immune crescentic GN [27], anti-neutrophil cytoplasmic antibody-associated vasculitis [27], anti-glomerular basement membrane disease [45], IgA vasculitis with nephritis [46], MN [42], and acute interstitial nephritis [47] have also been reported in patients with COVID-19 infection. The histological changes in these patients are similar to those observed in non-COVID-19 patients. Whether these immune-mediated glomerular nephritis are similar to HIVCK reported in HIV patients remains further studies.

Thrombotic Microangiopathy

Pathological analysis of kidneys in COVID-19 patients found that TMA was presented as the primary finding or in combination with other pathologic features like ATI and cFSGS [27, 47]. These patients often had activation of the complement pathway. The activation of the complement components in the blood or a direct result of SARS-CoV-2 infection of endothelial cells through the angiotensin-converting enzyme 2 (ACE2) receptor have been associated with endothelial activation or dysfunction with COVID-19 [48]. Endothelial dysfunction is one of the main mechanisms of COVID-19-associated organ damage including AKI. COVID-19 may aggravate endothelial injury in patients with hypertension, antibody-mediated rejection, and prothrombotic states [47].

It has been reported that HIV can infect endothelial cells, and TMA occurs in HIV-infected patients, especially in children [5].

Pathogenesis

HIV-Associated Kidney Disease

The pathogenesis of HIVAN has been studied over 2 decades, and many findings from HIVAN could be also applied to understand the pathogenesis of CKD in general. The advances in our understanding of the pathogenesis of HIVAN have been made possible by taking advantage of several animal models, such as the HIV-1 transgenic mouse model, referred as Tg26 mice. The major findings on the pathogenesis of HIVAN are summarized below (Fig. 1).

Direct Viral Infection of Kidney Cells

Bruggeman et al. [49] used kidney transplantation between HIV-transgenic mice and their littermates to demonstrate that viral gene expression within the kidney itself contributes to the development of HIVAN, rather than an indirect effect of circulating cytokines. Subsequent studies further confirmed that HIV can infect podocytes, parietal epithelial cells, tubular epithelial cells, T-cells, and macrophages in human HIVAN renal biopsy specimen by in situ hybridizations of viral RNA and immunostaining of viral proteins [50, 51].

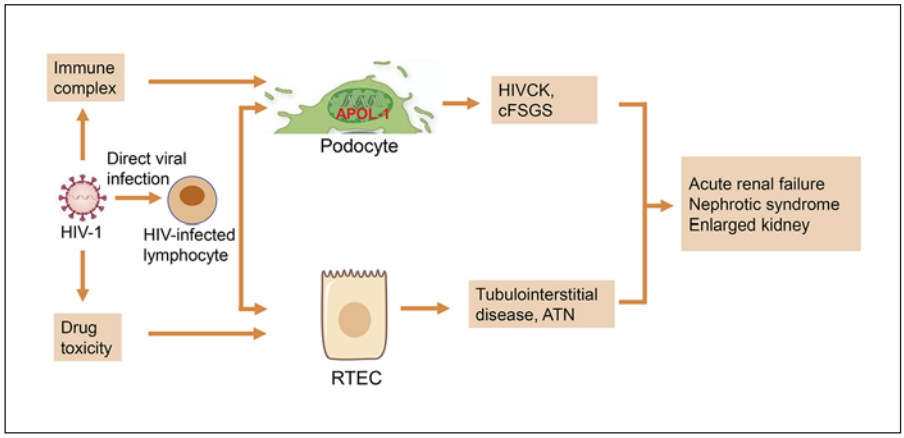

Fig. 1. Summary of HIV-associated kidney disease. HIV-associated kidney disease is caused by direct infection of kidney cells or deposition of IC or drug-toxicity. HIVAN is caused by viral infection of the kidney cells likely through cell-cell transmission between infected lymphocytes and tubular epithelial cells or podocytes. HIVCK, immune-mediated GN in HIV-infected patients, is caused by IC deposition in the glomeruli. Antiviral drugs such as tenofovir can induce nephrotoxicity in HIV patients. The pathological features of HIVAN include cFSGS and tubular dilatation with microcysts. Clinically, these patients present with AKI, nephrotic syndrome, and enlarged kidneys. The pathological and clinical findings of HIVCK are similar to those of other GN. Drug-induced nephrotoxicity presents as ATN, AIN, or Fanconi syndrome. HIV-1: human immunodeficiency virus-1; RTEC: renal tubular epithelial cells; APOL1: apolipoprotein L1; HIVCK: HIV immune complex kidney disease; GN: glomerulonephritis; cFSGS: collapsing focal segmental glomerulosclerosis; ATN: acute tubular necrosis; AIN: acute interstitial nephritis; IC, immune complex.

The mechanism by which infection occurs remains an enigma since these cells do not normally express CD4, the primary receptor for HIV-1, or the co-receptors CCR5 (C-C Motif Chemokine Receptor 5) and CXCR4 (C-X-C Motif Chemokine Receptor 4) [52, 53]. However, it is reported that HIV could infect renal tubular epithelial cells (RTECs) in CD4-independent pathways and that incubation of HIV-infected macrophages with tubular epithelial cells resulted in the direct transfer of HIV to RTECs via cell-to-cell intimate contact [51]. Transfer of HIV directly from infected lymphocytes to uninfected lymphocytes or RTECs was also reported, and this process was shown to be more efficient than infection by cell-free virus [54]. A recent study elucidated that podocytes could be productively infected, and the HIV envelope gene and cell surface proteoglycans determined the ability of cell-free HIV-1 to infect these podocytes [55]. TNF-α facilitated HIV infection and subsequent integration of HIV-1 into the podocyte DNA.

It is worth noting that the presence of HIV-1 proviral RNA was detected in renal epithelial cells even in patients with undetectable levels of viral RNA in the peripheral blood [50]. Further, Marras et al. [52] revealed evidence for kidney-specific viral evolution, suggesting the existence of a renal viral reservoir. Importantly, studies showed that infected RTEC can also transfer HIV to uninfected T lymphocytes [56]. Canaud et al. [57] found that 13 of 19 HIV-positive patients who had undetectable plasma HIV RNA at the time of kidney transplantation had detectable HIV RNA in either podocytes or RTECs after transplant, and this has been further confirmed by another recent study [58]. Collectively, therapies aimed at fully curing HIV infection will need to include strategies to eliminate HIV infection in the kidneys.

Genetics – APOL1

The APOL1 risk alleles are known as G1 and G2, whereas G0 signifies the nonrisk APOL1 allele. In general, 2 risk alleles (genotypes G1/G1, G2/G2, or G1/G2) are rendered as high-risk variants of APOL1 [59]. Early evidence found that classic HIVAN predominantly occurs in individuals of African descent [60]. The genetic predisposition to HIVAN among patients of African descent associates with high-risk variants in the APOL1 gene [61] because APOL1 kidney risk alleles are detected only in African descent [62]. APOL1 was strongly associated with HIVAN, with about 29-fold higher odds in AA [62] and 89-fold higher odds in Black South Africans [63]. Subsequent studies have confirmed the strong association between the high-risk genotypes and the diagnosis of HIVAN [64].

The mechanism of APOL1-mediated kidney disease is currently not completely clear. It is postulated that high

expression of APOL1 can induce kidney cell toxicity through the creation of ion channels in membranes, disrupting the endo-lysosomal function, altering autophagy, and inducing inflammatory cell death [65]. About 13% of black individuals in the USA have the high-risk genotype [2]. However, not all individuals with high-risk genotypes develop kidney disease, suggesting that disease expression requires a "second hit," such as viral infections and other kidney disease risk factors.

Local Response

Viral replication is not necessary for the HIVAN phenotype [66], and that the expression of viral genes such as negative regulatory factor (Nef) and/or viral protein R is required and sufficient to generate the full HIVAN phenotype in rodents [67]. Infection of podocytes with Nef activates the Src-dependent signal transducer and activator of transcription 3 (Stat3) and mitogen-activated protein kinase 1/2 pathways, which are associated with the proliferation and/or dedifferentiation of podocytes [68]. Consistently, both phospho-mitogen-activated protein kinase 1/2 and phospho-Stat3 were enhanced in kidney podocytes from HIV-1 transgenic mice and HIVAN patients [68]. On the contrary, reduction of Stat3 activity could alleviate kidney injury in HIV-1 transgenic mice in vivo [69]. Nef-induced Ras-related C3 botulinum toxin substrate 1 activation and Ras homolog family member A inhibition mediated loss of stress fibers and increased lamellipodia in HIV-infected podocytes [70]. Viral protein R could induce persistent activation of extracellular signal-regulated kinase, activating caspase 8-mediated cleavage of Bcl-2 interacting domain to truncated Bcl-2 interacting domain, subsequently leading to Bcl-2-associated X protein-mediated mitochondrial injury and apoptosis in renal tubular epithelial cell [71].

Inflammation also plays a key role in the pathogenesis of HIVAN. HIV infection can cause increased expression of pro-inflammatory mediators in renal cells [72]. In a mouse model of HIVAN, there is persistent activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) in renal epithelial cells, which led to apoptosis via upregulating the expression of Fas and Fas ligand [73]. Inhibition of NF-κB by pharmacologic methods was reported to reduce renal injury in HIV-induced kidney disease [74].

All these pathological processes in kidney cells in response to HIV infection play an important role in the pathogenesis of HIVAN. Proliferation and/or dedifferentiation and abnormal cytoskeleton integrity in podocytes can cause cFSGS, and the expression of pro-inflammatory factors in RTECs leads to tubulointerstitial disease, including tubulointerstitial inflammation, atrophy, and fibrosis.

Drug Toxicity from HIV Therapy

Tenofovir, used in combination with other antiretroviral agents, is an effective therapy for HIV infection. Clinical studies suggest that the use of tenofovir induces Fanconi syndrome, increases AKI, and aggravates the progression of CKD in HIV patients likely through causing tubular cell damage by altering mitochondrial function [75].

COVID-19-Associated Kidney Disease

Unlike HIVAN, the pathogenesis of COVID-19-associated kidney disease remains unclear with very limited studies (Fig. 2). In addition, we do not have good in vitro and animal models to study this disease. However, the approaches that we took to study HIVAN could be applied to study COVID-19 kidney disease.

Direct Viral Infection of Kidney Cells

It has been debating whether SARS-CoV-2 could directly infect kidney cells. The high expression of ACE2, the receptor of SARS-CoV-2, in the kidney cells suggests that the kidney should be a target of SARS-CoV-2 infection. The presence of SARS-CoV-2 or viral particles in the kidneys detected by immunohistochemistry, in situ hybridization, RT-PCR, and EM [39, 76] provide evidence of direct infection of the kidney by SARS-CoV-2. SARS-CoV-2 virus isolated from an autopsied kidney tissue in affected patients was able to infect nonhuman primate kidney tubular epithelial cells, providing perhaps the strongest evidence for kidney infection [76]. Local infection of SARS-CoV-2 in the kidney cells is also supported by recent studies showing that SARS-CoV-2 can infect human kidney cells cultured in vitro or in organoids, although the infection efficiency was low [76]. A recent study suggested that a higher SARS-CoV-2 viral load in urine sediments from COVID-19 patients correlated with increased incidence of AKI and mortality [77], suggesting that there is a correlation between viral infection and kidney disease. However, this evidence has been challenged since the above positive findings in kidneys were mainly obtained from autopsy samples and the specificity of immunostaining and electron microscopic findings of SARS-CoV-2 in the kidney samples have been also argued. Conversely, several studies found no evidence of SARS-CoV-2 in kidney biopsies from patients with COVID-19 infection [27, 42, 78].

Several key questions remain unanswered. It is known that viremia is rare in COVID-19 patients, and therefore,

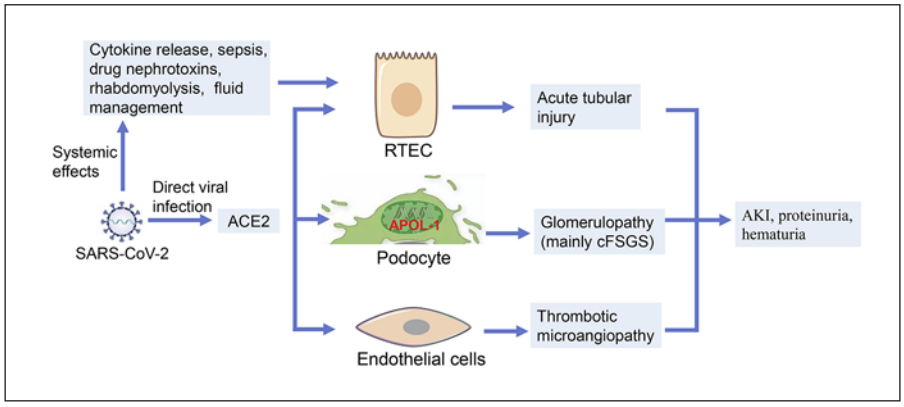

Fig. 2. Summary of COVID-19-associated kidney disease. SARS-CoV-2 may directly infect RTECs, podocytes, and endothelial cells through ACE2 receptor. The local infection and the systemic effects caused by SARS CoV-2 jointly cause acute tubular injury, cFSGS, and thrombotic microangiopathy. Clinically, these patients present with AKI, with or without proteinuria and hematuria. SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2; ACE2, angiotensin-converting enzyme 2; RTEC, renal tubular epithelial cells; APOL1, apolipoprotein L1; cFSGS, collapsing focal segmental glomerulosclerosis; AKI, acute kidney injury; ATI, acute tubular injury.

it is unclear where these viruses in urine come from. Another question is what routes the virus uses to infect kidney cells. It remains to be determined whether SARS-CoV-2 could infect kidney cells like HIV through macrophages or T cells. It will be also critical to establish good animal models of COVID-19-related kidney disease which will help determine whether local infection versus system effects contribute to the pathogenesis of COVID-19-associated kidney disease. Current evidence suggests that SARS-CoV-2 is likely able to infect kidney cells but with low efficiency and may only be transiently in certain patients with a high viral infection. The low infection efficiency of SARS-CoV-2 might also be related to the lack of co-expression of ACE2 and TMPRSS2, the cleavage enzyme for spike protein in the tubular cells [79].

Genetics – APOL1

Similar to HIVAN, most of the reported COVID-19-associated cFSGS is AA with APOL1 risk allele [42, 78, 80]. However, one report indicated that the transplanted patients with low-risk G0/G2 genotype or heterozygous expression of wild-type and G1 variants, developed cFSGS in the context of COVID-19 infection [81], suggesting that one risk allele may be enough to cause kidney disease in COVID-19 patients. Further studies are required to understand how SARS-CoV-2 interacts with APOL1 to induce cFSGS in COVID-19 patients. It has been postulated that systemic effects such as cytokine storm also contribute to the pathogenesis of cFSGS in these patients by stimulation of APOL1 expression [31].

Local Response

It is known that SARS-CoV-2 can induce cell death, but such evidence is unclear in renal cells. How different viral proteins induce kidney cell damage requires further studies.

Drug Toxicity from COVID-19 Therapy

Drug toxicity may also contribute to the occurrence of AKI, which has been supported by the presence of crystals in the proximal kidney tubules and casts in COVID-19 patients [82]. Administration of vancomycin, colistin, and aminoglycosides increased the risk of AKI in COVID-19 patients [83]. Cases of AKI associated with antivirals used to treat COVID-19 in patients were also reported, including remdesivir [84], lopinavir, and ritonavir [85]. Remdesivir may damage mitochondrion in renal tubule epithelial cells to cause nephrotoxicity [6]. However, the exact mechanisms of kidney cell injury induced by these drugs require further studies.

Systemic Effects

In addition to the sepsis and septic shock that we observed in the regular intensive care unit or AIDS patients, there are several unique features in COVID-19 patients which could cause AKI. Cytokine release syndrome, also termed "cytokine storm," has been reported in patients with COVID-19 [86]. Many pro-inflammatory cytokines including IL-2, IL-7, IL-10, granulocyte cell-stimulating factor, IFN-γ, IP-10, MCP1, MIP1A, and TNF-α were elevated in plasma or kidney tissues in patients with COVID-19 infection [78, 87].

The combined effects of cytokine release syndrome with complement and coagulation cascades contributed to the kidney injury [88]. The infection of endothelial cells and the complement system activation trigger endothelial dysfunction. Pro-inflammatory cytokines can cause degradation of endothelial glycocalyx and alteration of the coagulation system, which amplify the vicious cycle leading to the disruption of vascular integrity and formation of thrombosis. The dysfunction of endothelial cells also promotes infiltration of neutrophils with subsequent release of reactive oxygen species and neutrophil extracellular traps, ultimately aggravating endothelial cell injury [89]. It has been shown that SARS-CoV-2 infection induces degradation of ACE2 leading to the dysregulation of the renin-angiotensin-aldosterone aystem (RAAS) which may predispose to vasoconstriction in renal vessels [90] and reduction of local blood flow to the outer medulla [91]. In addition, respiratory failure in patients with severe COVID-19 caused generalized hypoxemia and hypercapnia, which are also related to tubular damage [92]. Hypoxemia and hypercapnia, together with the decrease of blood supply to the kidney, increase the risk of ischemic damage. Alveolar cell damage has been reported to contribute to the damage in renal endothelium, glomeruli, and tubules [92]. Rhabdomyolysis is responsible for kidney injury in some COVID-19 patients.

Treatment

HIV-Associated Kidney Disease

Current guidelines recommend ART to be the mainstay of treatment if HIVAN was diagnosed, irrespective of CD4+ lymphocyte count [93]. ART has been demonstrated to improve kidney function in patients with HIV-associated CKD. Early evidence indicated that RAAS blockade [94] and corticosteroid [95] attenuated kidney injury in HIVAN patients. And corticosteroids and RAAS blockade are considered as an adjunct to ART in those with a biopsy-proven HIVAN [93]. In addition, kidney transplantation has been demonstrated to be beneficial for ESRD patients with well-controlled HIV.

COVID-19-Associated Kidney Disease

Specific management guidelines for the treatment or prevention of COVID-19-related kidney disease are currently lacking. Early and close monitoring of creatinine levels along with urine output [29], supportive care, and careful post-hospitalization care [22] are recommended in COVID-19 AKI patients, which are not very different from those with non-COVID-19 AKI. Limiting indications for intubation and mechanical ventilation have contributed to the decreased rate of AKI over the course of the pandemic [96]. Of note, the increased risk of coagulopathy in AKI patients with COVID-19 should be taken into consideration, while deciding to introduce RRT [97]. Recent studies reported evidence to support the protective effect of glucocorticoid [98] and tocilizumab [28] (a recombinant humanized anti-IL-6 receptor monoclonal antibody) on the kidney in COVID-19 patients with AKI. However, such evidence is weak and needs to be further confirmed. Antiviral drugs are currently introduced to treat COVID-19-related AKI, such as remdesivir, which was reported to be effective as an initial treatment for AKI patients without a concomitant liver disease [99]. Favipiravir has also been used to treat COVID-19 patients with AKI; however, its efficacy remains to be confirmed [100].

Conclusion

There are several similarities between HIV-associated and COVID-19-associated kidney diseases (Table 1) such as disease spectrum including AKI and cFSGS and its pathogenesis involving in APOL1 risk alleles and probably a local infection of the virus. In addition, both patients with suppression of HIV viral replication and patients with recovery from COVID-19 could suffer from CKD. However, there are also several differences between them (Table 1). First, SARS-CoV-2 viral infection is usually cured with or without treatment by developing neutralizing antibodies, while the HIV can be only suppressed by ART without a cure. Second, the mechanisms by which the 2 viruses enter renal cells are different. SARS-CoV-2 may enter into proximal renal tubular epithelial cells through ACE2 receptors. HIV infects kidney cells when the virus is delivered directly from infected lymphocytes to tubular epithelial cells. Third, although both HIV and COVID-19 patients have a depletion of immune cells, COVID-19 patients develop the cytokine storm, while HIV patients do not. Fourth, it is recognized that HIV-associated kidney disease is caused mostly by local infection. However, COVID-19-associated kidney disease is likely caused by both local infection and systemic effects. Taken together, a comparison between these 2 diseases could help us to better understand the characteristics of COVID-19-associated kidney disease and better manage these patients.

Table 1. Comparison between COVID-19- and HIV-associated kidney diseases

	COVID-19-associated kidney disease	HIV-associated kidney disease
Virus	Lentivirus, enveloped, positive single-stranded RNA viruses	Coronaviruses, enveloped, positive single-stranded RNA viruses
Incidences	2~46% COVID-19 patients	6~48.5% HIV-infected patients
Clinical presentations	AKI, proteinuria, hematuria	AKI, proteinuria, enlarged kidney
Pathology	ATI, cFSGS, MCD, MN, lupus nephritis, and TMA	cFSGS, HIVCK, ATN, tubulointerstitial disease
Infection of kidney cells	Unknown, likely via ACE2	Yes, via cell-cell transmission (lymphocytes-kidney cells)
APOL1 risk alleles	Yes for cFSGS	Yes for cFSGS
Systemic effects	Yes with cytokine storm	Yes with sepsis
Drug toxicity	Yes, but not well-determined	Yes with tenofovir and others
CKD	AKI to CKD or AKI on CKD	Affect CKD progression
Treatment	No effective antiviral drugs, transient infection with development of neutralizing antibodies, vaccine available	Effective viral suppressive drugs, persistent and not curable, kidney is viral reservoir, no vaccine

AKI, acute kidney injury; CKD, chronic kidney disease; APOL1, apolipoprotein L1; cFSGS, collapsing focal segmental glomerulosclerosis; HIVCK, HIV-associated immune complex kidney disease; ATN, acute tubular necrosis; MN, membranous nephropathy; TMA, thrombotic microangiopathy; MCD, minimal change disease; ATI, acute tubular injury; HIV, human immunodeficiency virus.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Conflict of Interest Statement

All authors in this article declare that they have no competing financial interests. J.C.H. is currently an associate editor of this journal.

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Author Contributions

A.C., L.Y., K.L., and J.C.H. drafted, edited, and revised manuscript; A.C. and L.Y prepared figures; A.C., L.Y., K.L., and J.C.H. approved the final version of the manuscript.

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