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Graft function in kidney transplant recipients after COVID-19: a brief review

Abstract

The COVID-19 pandemic has left an indelible mark on global healthcare systems, with over 760 million infections and nearly 7 million deaths reported since December 2019. This review delves into the profound impact of COVID-19 on kidney transplant recipients (KTRs), focusing on the pathophysiology of COVID-19-related acute kidney injury (AKI) and the long-term consequences for graft function.

Renal involvement in COVID-19 is frequent, with AKI reported in up to 36.6% of hospitalized patients, carrying an increased risk in those admitted to the ICU and associated with higher mortality. Kidney transplant recipients, in particular, face heightened risks, with AKI present in 64% of admissions, leading to a mortality rate of 20% in hospitalized patients and 50% in ICU admissions. The multifactorial pathogenesis involves direct viral invasion, systemic inflammatory response, and potential nephrotoxic effects of supportive therapies. Kidney biopsy findings reveal acute tubular necrosis, glomerulonephritis, and renal thrombotic microangiopathy as common occurrences. Acute graft rejection is a significant concern, with evidence suggesting an increased frequency in patients with preexisting donor-specific antibodies.

Long-term consequences on graft function are still under study, but available data suggest stable graft function in most recipients at a 6-month follow-up. Vaccination has shown safety for organ transplant recipients, with no reported rejection episodes post-booster vaccination.

In conclusion, the lessons learned from the COVID-19 pandemic underscore the necessity of ongoing research to understand the long-term implications for kidney transplant recipients. These insights will inform future practices, therapeutic interventions, and immunosuppressive strategies in the face of similar infectious disease outbreaks.

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INTRODUCTION

The COVID-19 pandemic has had a profound impact on healthcare systems worldwide. According to the WHO, since December 2019, over 760 million people have been infected, and nearly 7 million have died. As the pandemic unfolded, we learned much about the virus, the acute course of infection, and its long-term complications. We have gained insights into the pathomechanisms of the virus. The kidneys are particularly susceptible to the virus. Renal involvement in COVID-19 is frequent and clinical presentation can range from mild proteinuria to progressive acute kidney injury (AKI). AKI has been reported in up to 36.6% of hospitalized patients, and the risk of its development is increased in individuals admitted to the ICU [1–3]. It is also associated with higher mortality [4]. The risk factors include older age, comorbidities such as diabetes and hypertension, and the presence of pre-existing kidney disease [5].

The pathogenesis of COVID-related AKI is multifactorial. The virus can cause direct injury to renal cells through viral invasion, leading to inflammation, tubular injury, and endothelial dysfunction. Additionally, the systemic inflammatory response triggered by the infection can result in cytokine release, endothelial damage, and microvascular thrombosis, further compromising kidney function. The use of certain COVID-19 supportive therapies, such as antiviral medications and some antibiotics, may also contribute to kidney injury due to their potential nephrotoxic effects [5–8].

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The most frequent biopsy findings were acute tubular necrosis (ATN), glomerulonephritis, and renal thrombotic microangiopathy (TMA) [9–11].

Therefore, kidney transplant recipients (KTRs) require special attention due to their increased risk of infections and potential complications [12]. AKI was present in 64% of KTRs admitted to the hospital. The mortality rate was 20% in hospitalized patients, reaching 50% in the ICU [13]. Understanding the impact of COVID-19 on graft function in KTRs is of utmost importance. This review aims to delve into the available literature and provide insights into the effects of COVID-19, both in the acute phase of the disease and in its long-term consequences.

COVID-19-RELATED AKI PATHOPHYSIOLOGY

According to the Kidney Disease Improving Global Guidelines (KDIGO) 2012, AKI has been defined by changes in kidney function, including serum creatinine (SCr) changes and urine output within 48 hours or 7 days. AKI can have a variety of causes, including specific kidney diseases, such as acute interstitial nephritis, acute glomerular and vasculitic renal diseases; non-specific conditions (e.g., ischemia, toxic injury); as well as extrarenal pathology [14].

As we know, angiotensin-converting enzyme 2 (ACE2) serves as the cellular entry receptor for SARS-CoV-2, and for the endocytosis and membrane fusion, transmembrane serine protease 2 (TMPRSS2) is used. While ACE receptors are present in almost all tissues, ACE2 is found in organs rich in blood vessels, such as the lungs, kidneys (podocytes, mesangial cells, parietal epithelium of Bowman's capsule, proximal cell brush border, and collecting ducts), as well as in the intestines and brain [15]. High level of ACE2 mRNA and protein is expressed in the testis and kidney tissue, not in the lungs [16], therefore the presence of the receptor may explain the most common symptoms associated with the infection, such as respiratory problems, kidney dysfunction, gastrointestinal, and neurological symptoms.

ACE2, converts angiotensin II (AGII) to angiotensin 1-7 (AG1-7), a protein with anti-inflammatory, vasodilatory, antifibrotic, and natriuretic activity [17]. An accumulation of AGII leads to opposite effects. An imbalance in the renin–angiotensin–aldosterone system (RAAS) caused by SARS-CoV-2 results in microcirculatory dysfunction, enhanced inflammatory processes, hypercoagulability, fibrosis, and tissue damage.

TUBULOINTERSTITIAL DAMAGE

Biopsy findings by Su et al. [9] indicate that the SARS-CoV-2 virus can directly infect the renal tubular epithelium and podocytes, which was associated with AKI and proteinuria in COVID-19 patients. A diffuse acute proximal tubular injury with loss of brush border, vacuolar degeneration, luminal dilatation, and even areas of necrosis were observed. Another study by Diao et al. showed SARS-CoV-2 nucleocapsid protein antigen accumulation in kidney tubules [18].

Some authors emphasize other indirect mechanisms potentially leading to tubular injury because they found no viral material in kidney biopsies [19]. Those causes include rhabdomyolysis, renal ischemia, low cardiac output, hypotension, use of mechanical ventilation, and nephrotoxic drugs (e.g. antibiotics). Hypovolemia, due to COVID-19 symptoms, e.g. fever, hyperventilation, vomiting, or diarrhea, was often seen in hospitalized patients [20].

COVID-19-ASSOCIATED GLOMERULOPATHY

Collapsing focal segmental glomerulosclerosis (cFSGS) is one the most frequent COVID-19-associated nephropathy (COVAN) and the most common glomerular pathology in allografts. Pathophysiology is thought to be related to direct viral tropism and immune dysregulation (upregulation of interleukins -1β, -6, -10, and IFN-γ). A high risk of the APOL1 genotype and ethnic susceptibility is described [21]. Even 96% of patients have nephrotic syndrome and about half of patients have hematuria as a clinical manifestation. Other glomerular pathologies that are likely related to SARS-CoV-2 infection include podocytopathies (non-collapsing FSGS and minimal change disease), membranous nephropathy, IgA nephropathy, Pauci-immune crescentic glomerulonephritis, lupus and anti-glomerular basement membrane nephritis, proliferative glomerulonephritis with monoclonal immunoglobulin deposit and TMA. Diseases occurring in transplanted kidneys, besides collapsing glomerulopathy, are IgA nephropathy, lupus nephritis, and TMA [22].

VASCULAR DAMAGE AND TMA

Macro- and microvascular thrombotic events are well-known complications of COV-

ID-19 [23]. Endothelial injury (such as pericyte detachment, subendothelial space expansion, endothelial proliferation without deposits, and foam cell accumulation), caused directly by the virus and a high level of inflammatory molecules, leads to a decrease in vasodilatory agents such as nitrous oxide (NO) and activation of the coagulation cascade [5, 24]. Platelet activation is a result of SARS-CoV-2 binding platelets via ACE2. Endothelial dysfunction may lead to systemic consequences, with renal impairment being a secondary outcome. Alternatively, the damage directly affects the kidney tissue.

In the renal biopsies, a common morphologic finding was erythrocyte stagnation in the lumen of glomerular and peritubular capillaries. Also, the viral particles were found with electron microscopy in the endothelial cells of the kidney [9, 24]. Segmental fibrin thrombi [9] and venous thrombosis were other renal findings [25]. Histopathological studies revealed that various complement pathways were activated in COVID-19 kidneys. In peritubular capillaries, mainly the lectin pathway was activated, in renal arteries partly a classical pathway, whereas, for tubular complement activation, the alternative pathway seems to be crucial [26].

Although various etiologies can cause TMA in native and transplanted kidneys, cases of COVID-19-related disease have been also reported [11, 19, 27–29]. Because of unfavorable outcomes, clinicians should be aware of this renal manifestation of SARS-CoV-2 infection.

DRUG TOXICITY

Tubular necrosis, interstitial nephritis, or thrombotic angiopathy are common causes of parenchymal drug-induced renal injury [30–32]. Reports from biopsies in patients who developed AKI during COVID-19 showed the presence of crystals in the proximal kidney tubules and casts [25]. Among patients hospitalized due to COVID-19, especially in the early stages of the pandemic, a wide range of antibiotics in large quantities were administered. It should be noted that other nephrotoxic drugs such as NSAIDs were also widely used by patients with mild symptoms. Oxalate nephropathy, as a result of excessive vitamin C administration in COVID-19 patients, was reported in addition [33].

Many kidney recipients take angiotensin-converting enzyme inhibitors (ACEI) and angiotensin-receptor blockers (ARBs), among other reasons, due to arterial hypertension or even to ameliorate the toxicity of CNI. At the beginning of the pandemic, it seemed that these medications could be dangerous. However, researchers found no significant association between ACEI or ARB use with the risk of COVID-19 and its severity [34, 35].

ACUTE GRAFT REJECTION

In Daniel et al. study the most common cause of allograft dysfunction after COVID-19 among 18 KTRs was an acute rejection with arthritis. And there was no evidence of direct viral invasion in the kidneys [36]. In May et al. study the most common diagnosis (61.4%) in allograft biopsies was also a rejection of a transplanted kidney. Subsequently, 17 out of 44 patients had an antibody-mediated rejection, 6 were diagnosed with an acute T cell–mediated rejection, and 4 with an antibody and a T cell–mediated rejection simultaneously. And there was an increased frequency of transplant rejection in patients with COVID-19, compared to that in pre-pandemic biopsies [37]. Authors suggest that SARS-CoV-2 infection acts as a second hit in patients with preexisting donor-specific antibodies [36]. However, there is a possibility of immune stimulation of alloantibody production during viral infection [38].

It is also important to pay attention to immunosuppressive strategies, especially when it is known that triple immunosuppression has an impact on reducing seroconversion in vaccinated patients [39]. Mycophenolic acid (MPA) has demonstrated antiviral activity against various viruses, including MERS-CoV, human coronavirus (HCoV) strains such as HCoV-OC43 and HCoV-NL63, dengue virus, and mouse hepatitis virus. A study by Kato et al. revealed anti-SARS-CoV-2 activity comparable to that against MERS-CoV, albeit at significantly higher dosages than therapeutically relevant [40]. Notably, an in vitro study found that MPA inhibits SARS-CoV-2 replication in VeroE6/TMPRSS2 cells, although antimetabolites were most frequently withdrawn due to their impact on inhibiting T-cell function and proliferation [41, 42]. But what is important in terms of graft rejection, is that minimizing the immunosuppressive regimen did not affect kidney function in the long term [43].

AKI OUTCOMES IN KTRS

COVID-19-induced AKI in KTRs can have detrimental effects on both the trans-

planted kidney and the overall health of the individual. The risk factors for AKI in this population, like the general, include older age, comorbidities such as diabetes and hypertension, and the presence of pre-existing kidney disease. However, compared with the general population, KTRs have a lower average kidney function reserve; thus, they are more susceptible to AKI [44]. The severity of renal impairment can vary, ranging from mild dysfunction to complete renal failure requiring temporary or permanent dialysis. Among KTRs, AKI occurred in 44% of patients, with 30% of them requiring kidney replacement therapy. Dialysis was needed in 12% of all KTRs, and 8% lost graft function [45]. While 21.8% of patients had an increase in creatinine of more than 25% compared to their pre-COVID-19 baseline creatinine level, graft survival was good in most patients who survived COVID-19. Graft failure within 3 months of follow-up was rare and occurred at a similar rate in non-hospitalized patients (0.7%) and hospitalized patients who were not admitted to the ICU (1.0%). In patients admitted to the ICU, 10.7% experienced irreversible graft function loss within 3 months after COVID-19 presentation, while 89.4% had a functioning graft. Only 0.8% of kidney transplant recipients from the ERACODA (European Renal Association COVID--19 Database) had biopsy-proven acute rejection during SARS-CoV-2 infection, but all of them had a functioning graft after 3 months of follow-up [46].

Prompt recognition and management of AKI in KTRs with COVID-19 are crucial because the highest mortality was observed in this cohort. Worsening renal function, as indicated by increased KDIGO stage, was associated with increased mortality [5, 44, 46, 47].

It's worth noting that, although at the beginning of the pandemic, the incidence of AKI among KTRs reached as high as 50%, in subsequent waves, a slight decrease was observed [48].

DISTANT CONSEQUENCES

Unfortunately, long-term observations of kidney function are limited. In a 6-month follow-up, graft function remained stable in most kidney transplant recipients [49, 50]. Only 7.7% had allograft dysfunction, and 2 out of 8 patients remained dialysis-dependent [51]. Our recent study revealed that only males with acute course of COVID-19 had a statistically significant relative eGFR decrease one year after infection onset [52].

ANTIVIRAL DRUGS AND VACCINATION

ANTIVIRAL DRUGS

Following the latest guidelines from the National Institutes of Health (NIH), USA, nonhospitalized patients with mild to moderate COVID-19 who are immunocompromised, should be treated with antiviral drugs at the doses and durations recommended for the general population [53]. The recommended first-line therapy is ritonavir-boosted nirmatrelvir (Paxlovid), initiated as soon as possible and within 5 days of symptom onset. However, it is crucial to note that ritonavir is a potent inhibitor of CYP3A and may increase concentrations of certain concomitant medications during the treatment course and for about 3 days after ritonavir is discontinued. As a result, general guidance for coadministering Paxlovid with concomitant medications includes temporarily withholding certain immunosuppressive agents (e.g., tacrolimus, everolimus, sirolimus) or reducing the dosage (e.g., cyclosporine), monitoring the patient closely for toxicities, and performing therapeutic drug monitoring during and after the 5-day treatment course of Paxlovid [54]. However, outpatient administration of Paxlovid, with monitoring of immunosuppressive drug levels in non-hospital settings, may pose challenges. An alternative option remains the selection of intravenous administration of remdesivir or appropriate monoclonal antibody therapy to avoid significant drug-drug interactions, as stated in the statement from the American Society of Transplantation [55]. Such an approach may be organizationally easier and safer for the patient. Another option is Molnupiravir, initiated as soon as possible and within 5 days of symptom onset, although it appears to have relatively low efficacy in the high-risk population, according to the same document. In the treatment of hospitalized patients with COVID-19, commonly used drugs are dexamethasone (a moderate inducer of CYP3A4), and interleukin-6 inhibitors (which may lead to increased metabolism of CYP substrates). Clinicians should closely monitor the serum concentrations of calcineurin and mammalian target of rapamycin (mTOR) inhibitors when these drugs are used [53]. The toxicity of calcineurin inhibitors (CNI) can occur as vasoconstriction, TMA, tubular vacuolization, epithe-

lial necrosis, loss of brush border, athero- and arteriohyalinosis, tubular atrophy, and interstitial fibrosis [56].

VACCINES

Clinical data indicate that the mRNA vaccine and the viral vector vaccine have provided excellent protection in humans [57, 58], but specific groups, such as organ transplant recipients, have been excluded from most clinical trials.

The research has shown that lower seroconversion in this vulnerable group is due to the administration of immunosuppressants, especially MMF/MPS [39, 59–62]. Other factors identified in studies include older age and steroid treatment [39], diabetes, worse kidney function, and anti-thymocyte globulin treatment during the past year [61–63]. Since even 35–50% of organ transplant recipients did not respond after the second vaccine dose, current knowledge suggests the necessity and recommendation of booster doses [62–67].

Centers for Disease Control and Prevention (CDC) recommends using only three products: updated 2023–2024 formula of mRNA vaccines — SPIKEVAX (Moderna) and COMIRNATY (Pfizer-BioNTech), or protein subunit vaccine — NUVAVAX Adjuvanted. Simultaneously, the CDC recommends specific vaccination schedules for immunocompetent individuals, with at least one dose of the updated COVID-19 vaccine [68]. A large Israeli study suggests a benefit of administering COVID-19 boosters every 6 months in groups with the highest risk of COVID–19–related hospitalization or death [69].

There are no studies indicating changes in the function of the transplanted kidney after vaccination. However, available publications demonstrate the safety of vaccines for organ transplant recipients [61, 64]. In the Taheri article, it was noted that "no rejection episodes or graft failure post-booster vaccination were reported" [65]. Retrospective studies have shown reduced mortality in vaccinated immunosuppressed patients [70].

CONCLUSION

With each subsequent wave of infections, the number of infected organ transplant recipients increased. Simultaneously, their hospitalization and mortality rates decreased as a consequence of the natural evolution of the virus as well as the introduction of protective vaccinations, and the emergence of effective antiviral drugs [71]. However, it is important to remember the particular situation of patients using immunosuppressive drugs, which due to numerous interactions may act toxically. Telemedicine, enabling coordinated outpatient care, also significantly impacted this trend. Remote monitoring technologies can facilitate regular follow-ups, reduce the burden of hospital visits, and provide interventions when necessary [72].

Even though WHO declared the end of the COVID-19 pandemic on May 5, 2023 [73], in November and December 2023, Poland recorded the highest number of infections in the last six months [74]. Therefore, it is important to remember the importance of preventive measures. According to NIH guidelines, patients should take precautions to reduce the risk of infection (wearing masks, practicing good hand hygiene, avoiding crowded places) as well as protective vaccinations should be administered. Due to the lower seroconversion rate, additional doses are recommended for immunocompromised individuals [53].

The lessons learned during the SARS-CoV-2 pandemic can also contribute to shaping future practices and preparedness for similar infectious disease outbreaks. Understanding the potential long-term implications of the infection for kidney transplant recipients is essential. Solid long-term studies are necessary to assess the durability of graft function and long-term outcomes in this vulnerable population. Understanding the mechanisms by which COVID-19 affects graft function will help guide therapeutic interventions and refine immunosuppressive strategies in the future.

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