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Aspects of kidney damage in covid-19 in patients with comorbid diseases

Nigora Giyosova Odiljonovna

Bukhara state medical institute, Bukhara, Uzbekistan

Abstract. Kidney damage is very likely in people with diabetes who have undergone a new infection, and the risk of developing acute renal injury is associated with mortality. Potential mechanisms of kidney involvement in the clinical picture of the disease may include cytokine damage, cross-organ damage, and systemic effects that determine the treatment strategy. These mechanisms are closely interrelated and are important for individuals on extracorporeal therapy and kidney transplants. Autopsy data provide evidence of SARS-CoV-2 virus invasion into kidney tissue with damage to tubular epithelium cells and podocytes, and red blood cell aggregation in severely COVID-19 patients. By including individuals with chronic kidney disease in planned COVID-19 research protocols, an evidence base for effective and safe treatments can be generated.

Keywords: COVID-19; hypertension, diabetes mellitus; acute kidney injury; dialysis; kidney transplant

Among 5449 patients over the age of 18 years without significant baseline renal problems (ESRD, transplantation kidney) ARD (according to the criteria of the international consortium KDIGO (Kidney Disease Improving Global Outcomes)) developed in 1993 (36.6%). Of these, stage 1 ARD developed in 46.5%, stage 2 - 22.4% and stage 3 - in 31.1%. 14.3% of ARD patients required renal replacement therapy (RRT) [1, 2, 4, 5]. A clear relationship between the development of ARD and the need for mechanical ventilation (ALV) was determined - 89.7% versus 21.7% in persons without mechanical ventilation. It should be noted that ARD in 52.2% of cases developed within 24 hours after intubation [3, 6]. The majority of patients (96.8%) requiring RRT were also on mechanical ventilation [3, 6]. Age, diabetes mellitus, cardiovascular diseases, the Negroid race, hypertension, the need for mechanical ventilation and vasopressor drugs were identified as risk factors for ARD.

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Drugs that block the renin-angiotensin-aldosterone system (RAAS) did not affect the incidence of ARD. 694 (35%) patients with ARD, despite the measures taken, died. Thus, ARD has been defined as a common complication in patients with COVID-19 associated with respiratory failure and poor prognosis [7, 15]. The causes of ARD, given the close relationship with respiratory disorders, could be associated with acute ischemic tubular necrosis, often accompanying systemic collapse. The influence of the prothrombotic status characteristic of COVID-19 is not excluded. A high specific gravity of urine samples and an average urine sodium level <35 mEq / L in patients at the time of ARD development are most indicative of prerenal disorders, but they can also occur in some forms of acute tubular necrosis [8, 10]. These mechanisms are closely interrelated and are especially important for individuals undergoing extracorporeal therapy and with a kidney transplant [11, 13, 16].

In patients with cytokine storm syndrome, ARD can develop as a result of increased vascular permeability, intrarenal inflammation, as part of type 1 cardiorenal syndrome (CRS) [9, 12]. The latter includes systemic endothelial dysfunction, manifested by pleural effusion, edema, intra-abdominal hypertension, fluid loss in "the third space" and hypotension. Extracorporeal membrane oxygenation (ECMO), invasive mechanical ventilation, and continuous RRT can also promote cytokine production [13, 14].

Recent data have confirmed a close relationship between alveolar and tubular injuries in ARDS, determined by medullary hypoxia followed by tubular cell stroke [17]. A retrospective study of 357 patients with ARDS without baseline renal disease showed pneumonia in 83% (as a cause of critical illness) and ARD in 68%. Age, diabetes mellitus, and positive fluid balance were independent factors associated with the development of ARD [18]. A retrospective study of 201 Chinese patients with confirmed COVID-19 pneumonia demonstrated the development of ARDS in 41.8% and ARD in 4.5% of cases with a significant role for age, hypertension and diabetes [19].

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Cross-organ damage also affects the heart-kidney axis (cattle type 1) in patients with COVID-19. Cardiomyopathy and acute viral myocarditis, contributing to the overload of the renal veins, hypotension, renal hypoperfusion, lead to a decrease in the glomerular filtration rate. Rhabdomyolysis, metabolic acidosis, and hyperkalemia are also common in patients with COVID-19 and are associated with hemodynamic instability.

Of particular interest is the work of Chinese researchers who analyzed the autopsy results of 26 patients (19 men, 7 women) with COVID-19 who died from ARDS associated with multiple organ failure [20]. The mean age was 69 years, 11 patients had a history of diabetes mellitus or hypertension, there was no data on the use of RAAS blockers prior to terminal hospitalization, and calcium channel blockers were used to control blood pressure in the hospital. Nine of the 26 patients had clinical signs of renal impairment with a corresponding increase in serum creatinine and / or proteinuria. According to the data of light microscopy, diffuse damage to the proximal tubules, aggregates of erythrocytes in the peritubular capillaries were determined.

According to electron microscopy, clusters of coronavirus particles were detected in the tubular epithelium of the proximal tubules and podocytes. In 3 cases, positive antibodies to the nuclear protein SARS-CoV were determined in the epithelium of the tubules according to the data of immunofluorescence analysis.

Along with the direct virulence of SARS-CoV-2, systemic hypoxia, hypercoagulation, and possible drug or hyperventilating rhabdomyolysis contributed to acute tubular damage. Thus, this study provides evidence of SARS-CoV-2 invasion of kidney tissue with damage to tubular epithelial cells and podocytes, and erythrocyte aggregation in persons with severe COVID-19.

The long-term consequences of kidney damage in patients who survived after COVID-19 should be the subject of special discussion in the future.

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A particularly vulnerable category in a pandemic is patients receiving programmed hemodialysis. One of the first reports from Wuhan concerned one of 61 dialysis centers, where 37 out of 230 patients and 33 employees developed COVID-19 within a month. The cause of death of 6 out of 7 patients who died was determined to be cardiovascular and not directly related to viral infection. Patients with COVID-19 on hemodialysis showed more pronounced lymphopenia, low levels of proinflammatory cytokines in the blood serum, and relatively mild clinical manifestations compared to other patients with this infection [21].

In hemodialysis centers, the risk of transmission of infection is significantly increased, including to medical personnel, institution workers, patients and their families. The Chinese Nephrological Society and the Taiwan Nephrological Society promptly developed guidelines for dialysis units during the COVID-19 pandemic [22, 23]. Their main provisions were published in the official journal of the International Society of Nephrology "Kidney International" [24]. The recommendations cover the issues of minimizing the spread of infection in dialysis centers (assessing the health of staff and patients before entering the center, identifying patients with suspected COVID-19, observing social distancing whenever possible, personal protective equipment for staff, familiarizing with the symptoms of the disease, using masks, training in social isolation and hand washing, screening for a new coronavirus infection in case of need for surgery, the use of telemedicine for monitoring), issues of transportation, disinfection of devices. Dialysis patients whose family members or caregivers are in “general quarantine” are scheduled to receive RRT as usual for 14 days. In the case of a confirmed diagnosis of infection in a family member or caregiver, the patient is identified as a “contact” and is treated according to appropriate recommendations. For infected patients, it is not recommended to change the place of dialysis, shift and personnel (in order to avoid further spread of infection), as well as use public transport. Protection measures for personnel, other patients, family members should be strengthened, immediate disinfection of devices

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should be observed, distance standards should be observed; dialysis and waiting rooms should be well air-conditioned and ventilated. The problem of reducing the number and / or duration of sessions for patients on chronic dialysis in conditions of an increased demand for RRT, including due to the temporary limitation of the kidney transplant program, cannot be ruled out. It is very important that, like all patients with renal disease, patients on dialysis continue to take all drugs, including those blocking the RAAS, unless their doctor advises them otherwise.

Viral infections are a serious risk of morbidity and mortality in kidney transplant patients. Immunosuppression, which is critical in preventing alloimmune responses, can impair the host's defense mechanisms. COVID-19 progresses faster in immunocompromised people, requiring more frequent admissions to intensive care units and leading to more frequent deaths [25]. Kidney transplant recipients must take all necessary steps to prevent infection. In a series of clinical reports from Europe and the United States [26], the mortality rates of these patients were 23–28%, which is significantly higher than the mortality among ordinary patients infected with COVID-19 (≤5%) [26]. The authors describe various strategies for managing therapy based on a gradual decrease in immunosuppression, depending on the severity of the disease, tARDng into account the risk of acute rejection and graft loss. Interestingly, there was no information about the latter in any of the reports, probably due to the too short observation period. However, serious concerns remain that withdrawing immunosuppressants could aggravate the hyperinflammatory response that develops in the late stages of COVID-19. In addition, the antiviral drugs in standard COVID-19 patient management protocols have a complex history of interactions with various immunosuppressants [23].

The Working Group DESCARTES (Developing Education Science and Care for Renal Transplantation in European States) of the European Renal Association (ERA-EDTA) after intensive discussions, based on the expert opinions of the above publications and recommendations of the relevant communities in France [24], Spain

[23], Great Britain [25], USA [26] formulated proposals for the management of infected patients with kidney transplants (duration of transplantation more than 6 months) [17].

Where possible, risk stratification is recommended based on laboratory parameters (C-reactive protein, interleukin-6 (IL-6), ferritin and D-dimer), reflecting severe inflammation and rapid disease progression.

Unfortunately, no patients with combined kidney and pancreas transplantation have been identified (a particularly severe category for immunosuppression). Probably, before the development of a special program in a pandemic, the management of these patients should be carried out within the framework of the above recommendations.

Thus, in the absence of specific treatment and vaccination, the COVID-19 pandemic caused by the new coronavirus remains a global threat to humanity. The involvement of the kidneys in the clinical picture seems to be more and more significant, and ARD acts as an independent predictor of mortality. In such a situation, people with chronic kidney disease represent a group of particular risk and attention. Only by including them in the planned research protocols for COVID-19 can the evidence base for effective and safe treatments be obtained.

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