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Renal involvements in COVID-19

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Abstract
COVID-19 is a disease related to an RNA virus, SARS-CoV-2, that affects the respiratory system with a great variability of expression. All the other systems can be affected. Renal involvement is common during COVID-19 and is associated with high morbidity and mortality. The exact mechanism is not well understood, but the virus could directly or indirectly affect the kidney. The common renal impairment is acute kidney injury (AKI) related to acute tubular necrosis (ATN). The other damages are mainly represented by proximal tubulopathy, and COVAN (COVID-19-associated nephropathy), occurring on a pathogenic variant of apolipoprotein L1 (APOL1), a thrombotic microangiopathy (TMA) by endothelial dysfunction and exacerbation or triggering a glomerular disease after vaccination against SARS-CoV-2. Renal involvement should be systematically sought in any patient hospitalized for COVID-19. Appropriate support and follow-up of COVID-19 patients with renal impairment are mandatory.
Keywords: SARS-CoV-2, COVID-19, Acute kidney injury, Proximal tubulopathy, COVID-19-associated nephropathy, Acute tubular necrosis, Thrombotic microangiopathy
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Introduction

A new coronavirus, SARS-CoV-2, identified in December 2019, is an RNA virus responsible for a cluster of pneumonia cases in Wuhan, a city in the Chinese province of Hubei. In 2020, it led to a pandemic that spread to the majority of countries around the world. In March 2020, more than 160 000 cases of the disease caused by this virus (COVID-19) and 6606 deaths have been reported (151 countries and one cruise ship) (1).

Morocco, like the rest of the world, is faced with the spread of this virus, and the first case of this disease was declared on March 2, 2020. Currently, more than 750 million people were infected and 6.8 million have died worldwide. However, in Morocco, more than 1.2 million people were infected and 16.2 thousand died (2). Other coronavirus infections have been reported, SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV), which have infected more than 10 000 people over the past 2 decades, with a mortality of 10% and 37%, respectively (1). COVID-19 has spread rapidly, causing a pandemic of major health and socio-economic severity. It is a contagious disease, spread by human-to-human transmission via respiratory droplets, feces or direct contact, and is characterised by an incubation period of 3 to 14 days (3). Since the start of the pandemic, we have distinguished an evolution over time in five major waves with the appearance of SARS-CoV-2 mutations responsible for different variants with different characteristics regarding viral transmission, expression of the disease and effectiveness of the vaccine, treatment and diagnosis (4). COVID-19 has been reported in all ages including children (1). It mainly affects the respiratory system with variability in clinical expression ranging from the absence of symptoms to severe pneumonia, even multi-organ failure and death with mortality estimated between 2% and 4% (5). Besides respiratory damage, all other organs can be affected: extra-pulmonary manifestations of COVID-19. In fact, SARS-CoV-2 is likely to affect, directly or indirectly, other organs or systems such as the haematological, cardiovascular, renal, gastrointestinal and hepatobiliary, endocrine, neurological, ophthalmological and dermatological systems (6). In this review we focus on aspects of kidney damage linked to COVID-19.

Renal tropism of SARS-CoV-2 and pathogenesis of renal damage

Transmission of the virus occurs mainly through the emission of respiratory droplets from the mouth and/or nose. These droplets hold viral particles could infect a subject by direct contact (direct transmission); either via a surface infected by the nasal, oral or conjunctival mucous membranes (indirect transmission). In order

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Implication for health policy/practice/research/ medical education

Kidney damage in COVID-19 is very varied. The kidney is affected either directly or indirectly. the most common attack is acute kidney injury (AKI) due to acute tubular necrosis (ATN). The renal damage increases mortality and prolongs the duration of hospitalization. A nephrological assessment is necessary in any patient with COVID-19.

to get in the host cell, SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as the main cellular receptor. It is a transmembrane protein of the zinc metalloprotease family. In physiology, ACE2 plays a role in the regulation of the renin-angiotensin-aldosterone system (RAAS) by inactivating angiotensin I and II to angiotensin 1-9 and angiotensin 1-7 respectively. The spike (S) protein of the virus binds to ACE2 which is cleaved by the membrane protease TRMPSS2 (transmembrane protease serine 2) leading to its activation with conformational modification of the receptor allowing entry of the virus into the host cell (6). SARS-CoV-2 has been identified in urine, and in kidney damage during COVID-19 (7), suggesting that the kidney could be a coronavirus target. The exact mechanism of kidney damage remains unknown, but the virus could directly or indirectly affect the kidney. Direct damage may be the result of a virus cytotoxic effect and this is also explained by the presence of the viral ACE2 receptor and its co-receptors on the surface of kidney cells. The binding of SARS-CoV-2 to its ACE2 receptor causes an increase in angiotensin II levels leading to vasoconstriction, dysfunction of glomerular hemodynamics, inflammation and fibrosis (6). Indeed, the virus is likely to affect several structures of the kidney, including the glomerulus, the tubule and the renal vessels. Indirect damage could be induced by hypoxia related to pulmonary damage or related to systemic consequences of the viral infection, such as severe hemodynamic changes with prolonged hypotension or even multi-organ damage in the context of cytokine storm, occurrence of rhabdomyolysis or iatrogenic nephrotoxicity related to an antiviral treatment or vaccination (Figure 1).

Acute kidney injury (AKI) associated with COVID-19

Renal damage was described during the COVID 19 pandemic, initially in severe forms with AKI then secondarily in less severe forms such as proteinuria and hematuria. This renal damage is a poor prognostic factor for the overall survival of patients (8). Prevalence of AKI in COVID-19 is variable, depending on the studies and ranging from less than 5% to 37% (8-10). A meta-analysis of 30675 patients hospitalized for COVID-19 found that AKI occurs in approximately one in three patients with a prevalence of 28% and a necessity for renal replacement therapy (RRT) of 9% (11). In critical care patients, its prevalence is 46% and a use of RRT in 19% cases (11). A high prevalence of AKI, above 50%, has been reported in Europe and the United States (10,12). AKI is diagnosed within 5 to 9 days following hospital admission with a median of 21 days following symptoms onset, and a duration of progression more than seven days (13). This AKI increases the hospital stay and the cost of care and is associated with high morbidity and mortality. A meta-analysis of 58 studies including 13452 patients showed that AKI significantly increases the risk of mortality (OR 5.73, 95% CI: 3.75 to 8.77) in patients infected with coronavirus (14). In another meta-analysis, mortality in patients with COVID-9 who presented with AKI was 52% (OR 15.27, 95% CI: 4.82-48.36) [15]. AKI requiring extra renal replacement therapy further increases all-cause hospital mortality (OR 3.43, 95% CI: 2.02-5.85) (13). The risk factors for this AKI are aged, male gender, comorbidities (diabetes, high blood pressure,

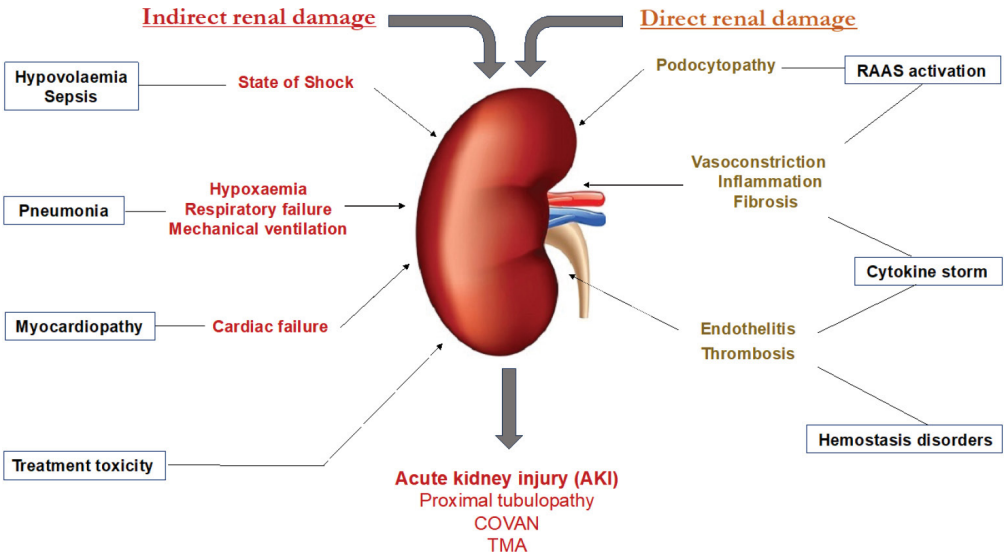

Figure 1. Pathophysiology of renal damages during COVID-19. Abbreviations: COVAN, COVID-19 associated nephropathy, TMA, Thrombotic microangiopathy; RAAS, Renin-angiotensin-aldosterone system.

chronic kidney disease, overweight), Afro-American ethnicity, severity of hypoxia on admission and the use of mechanical ventilation (10). In severe forms of COVID 19, viral replication could contribute to tissue damage such as acute tubular necrosis (ATN) and glomerulosclerosis (16). AKI could be induced by hypovolaemia secondary to digestive disorders, high fever or sepsis in multi-vascular patients. Specific cardiac lesions such as myocarditis, acute ischaemic heart disease or cardiac arrhythmia during a severe form of viral infection, complicated by left heart failure and acute cardio-renal syndrome, could also induce an AKI. Right heart failure during pulmonary embolism in COVID-19 might possibly be complicated by AKI. The nephrotoxic treatments used (antibiotics, iodinated contrast products, antivirals) could promote or worsen AKI. ATN, which can be ischaemic or toxic, is the common identified lesion during organic AKI and does not present particular clinical or histologic characteristics. Myoglobin casts induced by rhabdomyolysis complicating COVID-19 and crystals related to drug toxicity have been described (17). The management of AKI in the context of COVID-19 is based on preventive and/or symptomatic treatment given that there is no specific treatment. The objective of preventive treatment is individualized volume management and correction of hypovolaemia. However, non-invasive ventilation and continuous RRT methods could reduce the risk of AKI and prevent its complications by limiting the cytokine storm and the renal hemodynamic effects of mechanical ventilation (10,18). Regarding RRT, the time initiation and methods should be the same as those applied to sepsis (19). Concerning extracorporeal circuit (ECC) coagulation, Helms et al reported a 96.6% prevalence of filter thrombosis in patients with COVID-19. These data could suggest optimizing prevention through regional anticoagulation with citrate in addition to general anticoagulation when indicated (20). RRT should be considered in patients with volume overload, particularly those with refractory hypoxemia. Continuous RRT methods are the preferred modalities in hemodynamically unstable patients with AKI and COVID-19. They help control the inflammatory cascade reaction by eliminating toxins and waste from damaged cells and regulate hydro-electrolyte disturbances and acid-base balance. Rizo-Topete LM et al (21) discuss the indications for dialysis according to hemodynamic instability and volume overload that are common in patients with AKI and COVID-19. Thus, they specify that continuous RRT methods should be the first treatment option if available. It is interesting to note that Sohaney et al (22) were able to preserve the lifetime of the ECC in COVID-19 patients in AKI and treated with continuous veno-venous hemodiafiltration with regional citrate anticoagulation (CVVHDF-RCA), and found no association between ultrafiltration and improvement of respiratory parameters.

Other kidney damage associated with COVID-19

Proteinuria is quickly emerged as a characteristic of SARS-CoV-2 kidney damage. This proteinuria is reported in 18 to 65% of cases depending on the series with two types identified, high-flow proteinuria made of albumin reflecting glomerular damage, and commonly low-flow proteinuria, indicating tubular damage. Regarding hematuria, its prevalence is 17 to 41% (13,14,23). Leukocyturia is reported in 47% of patients admitted to intensive care for COVID-19 (24). In the context of Fanconi syndrome related to SARS-CoV-2 proximal tubular attack, tubular proteinuria (88%), phosphaturia (55%), hyperuricemia (43%) and normoglycemic glycosuria (30%) were reported (24). These abnormalities were more frequent and more severe in patients admitted to intensive care, and preceding the appearance of severe AKI during hospitalization (24). Glomerular damage, characterized by high-flow proteinuria commonly associated with AKI, has been less frequently described during biopsy series. Collapsing focal and segmental glomerulosclerosis (FSGS) is the main glomerular lesion found during COVID-19 (known as COVAN: COVID-19-associated nephropathy) (25,26). An association between a pathogenic variant of apolipoprotein L1 (APOL1) and this FSGS was highlighted in the work of Wu et al (26). In the study by May et al which involved 240 native renal biopsies and 44 renal allograft biopsies, COVAN was the most frequent glomerular involvement in COVID-19 patients who had a native renal biopsy, noted in 62 cases (25.8%). However, 96.8% of COVAN cases had concomitant ATN lesions. Concerning renal allograft biopsies, the most frequent histologic diagnosis was humoral rejection in 38.6%, cellular rejection in 13.6% and mixed rejection in 9.1%. An ATN lesion was noted in 27.3% of renal allograft biopsy cases (27). Other glomerular disorders have been described, notably podocytopathy in the context of minimal changes disease (MCD) or primary non-collapsing FSGS, extra capillary pauci-immune glomerulonephritis and membranous glomerulopathy, noted respectively in May's series in 7.5% (4.6% and 2.9%), 4.6% and 4.6%, suggesting a possible role of the virus as a triggering factor for immunological diseases with renal expression (27). Endothelial and vascular damage have been described in COVID-19 patients. However, severe virus infection is associated with endothelial activation and endotheliitis which could be induced by inflammation, cytokine storm and/or direct endothelial cell virus cytotoxicity (28,29). In this context, thrombotic microangiopathy (TMA) lesions are possible, sometimes associated with cortical necrosis (29). May et al were noted TMA in 2.1% of cases (27). Fibrin thrombi with glomerular ischemia, linked to thrombotic activation during COVID-19, have also been described (30). In biopsy series, chronic lesions in addition to acute lesions were found such as nephroangiosclerosis or diabetic glomerulosclerosis, confirming the susceptibility of

patients with comorbidities (diabetes, high blood pressure and chronic kidney disease) to develop a severe form of COVID-19 commonly associated with AKI (27,30,31).

After the start of vaccination against the virus, several cases of exacerbation or new appearance of glomerular diseases have been reported. The introduction of new RNA vaccines has raised several questions about the occurrence of renal side effects following vaccination. All approved vaccines have been implicated; however, the most frequent cases were observed after RNA vaccines, Pfizer-BioNTech BNT162b2 and Moderna mRAN1273 (32). This could be partly explained by the wide use of these RNA vaccines. The interesting aspect of COVID-19 vaccine-associated glomerulopathy or CVAGD (COVID 19 vaccine-associated glomerular disease) is that the most frequently reported cases are either IgA nephropathy (IgAN) or MCD. The time to onset of IgAN is 1 to 2 days after a second dose of BNT162b2 or mRAN1273. However, MCD occurs within a median of 7 days after the first dose (32). Other types of glomerulopathy have been reported, in a small proportion of cases, after a short period following vaccination, notably scleroderma renal crisis, but most often after 2 weeks (membranous glomerulopathy, anti-neutrophil cytoplasmic antigen associated vasculitis, anti-glomerular basement membrane disease, lupus nephritis and IgG4 related renal disease) (32). Given the low number of reported cases and the delay in the occurrence, after vaccination, of these immunologically mediated glomerulopathies, it is difficult to consider with certainty a causal link to these data. However, these data must lead to pharmacovigilance analyses with the aim of clarifying whether these reported cases are just associations or whether a causal link exists with certainty.

Conclusion

Kidney damages associated with COVID-19 are very varied. The common lesion is AKI due to ATN which is associated with a poor prognosis. Several mechanisms are involved in the occurrence of this AKI. Among these mechanisms, direct damage to the renal parenchyma by viral invasion, deregulation of the RAAS, thrombosis; and non-specific indirect mechanisms observed depending on the context (multiorgan failure, nephrotoxicity). Other disorders are mainly represented by proximal tubulopathy, COVAN on a genetic basis of APOL1 and new appearance or exacerbation of glomerulopathy after vaccination. It is necessary that a nephrological assessment must be indicated at least initially (proteinuria, urinary sediment, renal function) in any patient hospitalized for COVID-19. Finally, long-term care and monitoring of patients who have developed kidney damage following COVID-19 is mandatory.

Authors' contribution

Conceptualization: Taoufiq Aatif.
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Supervision: Taoufiq Aatif, Driss El Kabbaj.
Validation: Taoufiq Aatif.
Writing–original draft: Taoufiq Aatif.
Writing–review & editing: Taoufiq Aatif, Driss El Kabbaj.

Conflicts of interest

The authors declare that they have no interest link.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely
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