Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

positives) of CKD in the aging group of a population studied, particularly those without proteinuria, hematuria, or overt hypertension who are considered to be healthy older people who will never die of renal failure.[8] When Jonsson *et al.* considered age-adapted eGFR thresholds, the age-standardized prevalences of CKD was 3.2% for men and 4.0% for women, again clearly lower prevalences of CKD than in the vast majority of previous studies.

Such inaccurate CKD 3A labeling in older individuals without proteinuria/hematuria (85.9%)[2] or hypertension (61.3%)[2] has undesirable effects, such as unnecessary anxiety, unneeded additional investigations, and even loss of insurability.

The single threshold of eGFR <60 ml/min per 1.73 m^2 also leads to underdiagnosis (false negatives) of CKD in younger individuals with an eGFR >60 ml/min per 1.73 m^2 and who are below the third percentile of their age/sex category (Figure 1). The use of a third-percentile eGFR level, based on age- and sex-specific reference values of eGFR for a particular population, as cutoff or an age-adapted threshold staging allows the detection of these false positives and negatives. These eGFR curves of many different populations in the world are currently available in the literature.[8]

Although these simple concepts have been supported for several years by solid publications in the best journals of medicine and nephrology, the scientific renal community has not arrived at a consensus regarding the interpretation of a particular eGFR and its clinical consequences. However, some light is appearing at the end of the tunnel. recently

The Global Burden of Disease Chronic Kidney Disease Collaboration wrote:[9] "Most data sources reporting the prevalence of nonfatal CKD are cross sectional and do not repeat serum creatinine and urine ACR measurements over 3 months, as suggested by KDIGO guidelines, to confirm the chronicity of abnormalities. Studies suggest that use of one measurement of decreased eGFR to characterize CKD might overestimate prevalence by 25%–50%. Therefore, it is possible that the results of our analysis represent an overestimate of CKD prevalence. Future analyses of the global burden of CKD should investigate developing a methodology to correct prevalence estimates."

Jonsson *et al.* have added new relevant data contributing to the realization of the above-defined wish in the near future.

DISCLOSURE

All the authors declared no competing interests.

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Proximal tubular dysfunction in patients with COVID-19: what have we learnt so far?

Fabian Braun[1], Tobias B. Huber[1] and Victor G. Puelles[1]

Recent studies have reported a variety of urine abnormalities in patients hospitalized due to severe acute respiratory syndrome coronavirus 2 infection. In a single-center study from Belgium, Werion *et al.* present a concise investigation of tubular dysfunction in patients with coronavirus disease 2019, identifying potential risk factors for increased disease severity. These data complement current evidence regarding severe acute respiratory syndrome coronavirus 2 presence and potential infection in the kidney.

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The characterization of the potential effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in extrapulmonary organs is a matter of great interest worldwide. It has been reported that

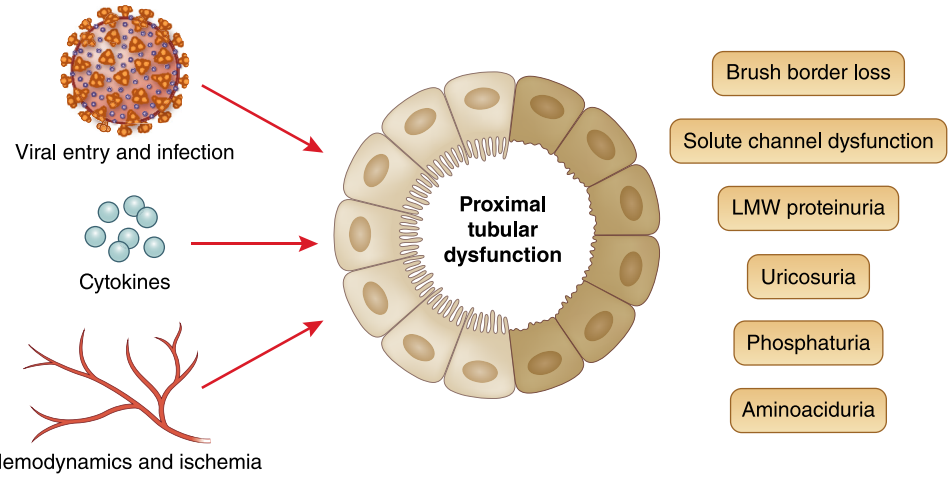

Figure 1 | Potential pathophysiological mechanisms driving coronavirus disease 2019 (COVID-19)–related proximal tubular dysfunction. To date, 3 pathomechanisms, including viral entry and infection, cytokine-mediated injury, and hemodynamic factors and ischemia, appear to be most plausible to cause proximal tubular dysfunction in patients with COVID-19. While each of them can explain tubular dysfunction, it is also possible that these factors coexist and interact with each other during the complex clinical course of COVID-19. In the cohort investigated by Werion *et al.*,[3] these functional alterations included low molecular weight (LMW) proteinuria, inadequate handling of uric acid or phosphate, and the loss of neutral amino acids into the urine.

close to 40% of hospitalized patients with severe courses of coronavirus disease 2019 (COVID-19) develop acute kidney injury during hospitalization.[1] Furthermore, other studies have shown additional signs of kidney injury, including hematuria and proteinuria.[2] Given the devastating nature of this pandemic and the unknown future health sequelae of COVID-19, the nephrology community has wisely turned its attention into the potential effects of SARS-CoV-2 in the kidney.

Werion *et al.*[3] provide systematic evidence of proximal tubule dysfunction in a well-characterized cohort of patients diagnosed with COVID-19 that required hospitalization. Among the features of proximal tubule dysfunction, hypouricemia with inappropriate uricosuria was independently associated with overall disease severity and with an increased risk of respiratory failure requiring invasive mechanical ventilation. These findings are certainly a step forward in our understanding of extrapulmonary manifestations of COVID-19 and also provide a unique opportunity to discuss the current evidence regarding SARS-CoV-2 infection and its role in kidney injury.

What did the study show?

While there have been several studies depicting the presence of potential SARS-CoV-2 particles by electron microscopy, and SARS-CoV-2 protein or RNA or both in kidney tubular cells,[4–6] functional changes remained incompletely understood.

Werion *et al.*[3] provide unique evidence of a distinct tubular phenotype in a subset of patients with COVID-19 who were hospitalized at a tertiary care center in Belgium. The majority of 49 patients showed features of proximal tubular dysfunction, including low molecular weight proteinuria, deficiency in uric acid and phosphate handling, and neutral aminoaciduria in specific urine analyses. Furthermore, fractional uric acid excretion of >10% in the presence of hypouricemia was reported, postulating that this may serve as a risk factor for the need of mechanical ventilation, disease severity, and death.

A strength of this study is that the patient cohort is well characterized with an extensive clinical description and a broad range of outcomes at the end of the investigation period. Thus, we believe that inadequate uric acid handling can be considered as a potential predictor of clinical outcome. However, these observations remain limited as larger and prospective studies will be required to provide further validation.

Another interesting finding of this study are the similarities between proximal tubular dysfunction in patients with COVID-19 and other types of tubular injury, including Dent disease and toxic acute tubular necrosis due to tenofovir exposure, 2 entities characterized by low molecular weight proteinuria. The investigators propose a novel injury mechanism after SARS-CoV-2 entry, which is based on expression data and functional network analysis between *ACE2* and solute channel genes (i.e., *SLC6A19* and *SLC22A12*), suggesting that this could be one of the ways the virus is directly affecting tubular function. This provocative hypothesis certainly merits more in-depth analysis and careful experimental characterization.

It is worth noting that dysfunctional channel activity may also be a

consequence of cytokine imbalances due to systemic inflammation or hemodynamic changes (or both) leading to periods of ischemia. The investigators provide evidence of tubular damage with debris in the lumen of dilated tubules, brush border loss, and denuded basement membranes. Furthermore, thorough electron microscopy analyses were performed, identifying potential viral particles with trilaminar envelopes and projections from their surface in vacuoles or cisternae of the endoplasmic reticulum in proximal tubular cells. While this is not conclusive, it provides at least indirect evidence and suggests a potential role for viral infection in proximal tubuli.

However, precisely defining the cause of tubular dysfunction may not necessarily modify a potential approach for clinical stratification in hospitalized COVID-19 cases. For example, a diagnostic strategy could involve a first step based on routine blood analysis for uric acid to identify patients at risk (i.e., with hypouricemia) and a urine analysis to determine the fractional uric acid excretion as a second step for at-risk patients. This may expand the range of diagnostic algorithms proposed for patients with COVID-19.[7]

How does this study build on existing data?

The presence of SARS-CoV-2 in the kidney has been documented with multiple complementary techniques (e.g., RNA and protein detection) as highlighted by some examples from several groups around the world.[4–6] However, identification of SARS-CoV-2 particles by electron microscopy, or the presence of viral RNA or proteins, should not be considered conclusive evidence of infection. Importantly, a recent report has documented replication-competent SARS-CoV-2 isolated from a postmortem kidney[8]—a finding that cannot be explained by viral remnants or inactive virus passively up-taken in the kidney. While the cellular target of SARS-CoV-2 replication in the kidney is still unclear, the most logical target is the tubular system. The study by Werion *et al.*[3] adds to this theory as it provides functional and clinical evidence for the pathophysiological changes triggered by SARS-CoV-2 infection.

Some studies also have failed to identify SARS-CoV-2 renal tropism, for example.[9] An important caveat should be considered: All tissue-based studies attempt to identify processes based on a "snapshot," and as such, we do not know what happened before and we do not know what will happen later. This means that event frequency, timing, and location play central roles in positive detection. Unfortunately, event frequency is unknown and hard to predict. Perhaps we are assuming that proximal tubular infection should be comparable to infection of the respiratory tract. If this is an infrequent or highly dynamic process, then sample size and location within the kidney will significantly affect the sensitivity of any method. Furthermore, the clinical course at the time of sampling can also mask viral identification (i.e., extensive proximal tubular damage during episodes of acute kidney injury).

Finally, it will be important to remain open to the possibility that multiple factors contribute to the same pathophysiological finding. For example, it is likely that this pattern of proximal tubular dysfunction described by Werion *et al.*[3] is explained by a combination of viral infection, cytokine effects, and hemodynamic changes associated with critical-ill status (Figure 1). However, despite of our current level of uncertainty, the fact to the matter is that a subset of patients with COVID-19 who developed signs of proximal tubular dysfunction during their disease course, which at the very least merits open discussions regarding the need to implement precise protocols to identify at-risk patients and validation of these findings by larger prospective studies.

DISCLOSURE

All the authors declared no competing interests.

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