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ORIGINAL ARTICLE

Renal tubular dysfunction in COVID-19 patients

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Abstract

Introduction SARS-CoV-2 infection can affect other organs aside from those of respiratory system, particularly the kidney, heart, blood, digestive tract, and nervous system. COVID-19 renal compromise consists of different syndromes since proteinuria, hematuria, and acute kidney injury (AKI), until chronic kidney disease. Since COVID-19-induced renal tubular damage has been described as a potential antecedent condition to AKI installation, it was decided to evaluate how COVID-19 affects tubular function.

Materials and method Serum inflammatory parameters, urinalysis, and classical urinary indexes in COVID-19 admitted patients who had neither AKI nor chronic kidney disease (CKD) were evaluated. Statistical analysis was performed by applying Student *t* test.

Results Renal tubular function was evaluated in 41 COVID-19 admitted patients who had neither AKI nor CKD. Patients' mean age was 56 years, males (79%), and with normal creatininemia (0.8 ± 0.2 mg/dL) and eGFR (105.7 ± 6.5 mL/min) values. It was found mild hypocalcemia and a relative increased fractional excretion (FE) of sodium, FE of calcium, FE of phosphorus, calcium-creatinine index, urinary osmolarity, and relative alkaline urine pH values.

Conclusion Tubular dysfunction was documented in COVID-19 patients.

Keywords COVID-19 · Electrolytes · Tubular function

Introduction

SARS-CoV-2 infection can affect other organs aside from those of respiratory system, particularly the kidney, heart, blood, digestive tract, and nervous system [1]. Regarding COVID-19 renal compromise, different syndromes have been reported since isolated abnormal urinalysis, such as proteinuria (60%), albuminuria (35%), hematuria (25%), or their combination (45%) and acute kidney injury (8–30%), with or without renal replacement requirement, until chronic kidney disease [2]. Many pathophysiological mechanisms have been proposed to explain the observed renal damage in COVID-19: First, the viral direct deleterious effect on the kidney. It has been proposed that this cytopathic effect could be mediated by viral binding to angiotensin-converting enzyme II receptors. This mechanism has been histologically documented, such as the loss of the brush border and non-isometric vacuolation in tubules and endothelial damage and microvascular occlusions in glomerular and peritubular capillaries. Additionally, electron microscopy evidenced viral spherical particles in podocytes and the proximal tubular epithelium, associated with pedicels effacement and podocytes detachment from the glomerular basal membrane [3]. However, some authors have been interpreted these particles not as viral fragments but cell organelle ones. Second, there is a series of non-viral pathophysiologic mechanisms of renal damage in COVID-19, as is the case of volume contraction, tissue hypoxia, septic systemic inflammation (cytokines storm), heart failure, rhabdomyolysis, immune complex deposition, harmful mechanical ventilation, and disseminated intravascular coagulation [2, 4].

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Since COVID-19-induced renal tubular damage has been described as a potential antecedent condition to acute kidney injury installation, it was decided to evaluate prospectively how was tubular physiology in admitted COVID-19 adult patients who did not suffer from neither acute kidney injury nor chronic kidney disease.

Materials and method

COVID-19 adult patients (SARS-CoV2 PCR-positive swab) who were admitted in general ward for 1 month (1st April to May, 2020) in Clínica de la Costa, Barranquilla (Colombia), were selected for analyzing their renal tubular function, with the following inclusion and exclusion criteria:

Inclusion criteria

- Serum creatinine < 1 mg/dL
- Age ≥ 18 years

Exclusion criteria

- Acute kidney injury (diagnosis based on KDIGO-2012 criteria) [5]
- Chronic kidney disease (diagnosis based on KDIGO-2013 criteria) [6]
- To be on any medication which could modified tubular function, such as diuretics, proton pump inhibitors, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone antagonists
- Negative to participate in the study

Then, from those patients who were selected, the following parameters were obtained: hemogram; transaminases; D-dimer; ferritin in blood; and sodium, chloride, potassium, calcium, phosphorus, urea, creatinine, glucose, osmolality, and uric acid in blood and spot urine fast samples.

Transtubular potassium gradient (TTKG), calcium-creatinine urinary index, and fractional excretion of all measured electrolytes were obtained (applied formulas are described in the Annex).

A statistical analysis of all serum electrolytes and urinary indexes (mean, standard deviation) was performed by applying Student *t* test.

This study was approved by Ethical Committee of Clinica de la Costa, Barranquilla (Colombia), and informed consent was obtained from all patients.

Results

In this study, renal tubular function was evaluated in 41 noncritical COVID-19 patients who were admitted between April and May 2020 in Clinica de la Costa in Barranquilla, Colombia. Blood and urine samples were taken 24 h after patients' admission, and no one suffered from acute kidney injury or chronic kidney disease when they were evaluated. The main comorbidities in this studied group were hypertension (58%), obesity (40%), and diabetes mellitus (23%).

The patients' main symptoms were fever (100%), dyspnea (85%), marked asthenia (48%), and myalgia (40%). No patients required mechanical ventilation.

Patients' mean age was 56 ± 18 years, with a clear predominance of males (79%), and their average creatininemia, uremia, and eGFR (CKD-EPI) values at admission were 0.8 ± 0.2 mg/dL, 47 ± 10 mg/dL, and 105.7 ± 6.5 mL/min/1.73 m^2, respectively. Patients' main urinalysis alteration was proteinuria (1.5 ± 5 g/L), while neither hematuria nor glucosuria was documented. Regarding other detected alterations different from renal ones, leukocytosis (leukocytes: 12,680 ± 8,366 mm^3), anemia (hematocrit: 10.9 ± 2.6), hyperglycemia (glycemia: 161 ± 89 mg/dL), and elevated transaminases (GOT: 115 ± 18 UI/L, GPT: 103 ± 20 UI/L) were observed. Besides, elevated serum parameters of systemic inflammation were documented, such as C-reactive protein: 15.6 ± 11 mg/L (normal value: ≤ 1.7 mg/L), ferritin: 909 ± 165 ng/mL (normal value: 6–137 ng/mL), and D-dimer: 3619 ± 583 ng/mL (normal value: 0–500 ng/mL). Finally, regarding electrolyte alterations, in fast samples, mild hypocalcemia and increased fractional excretion (FE) of sodium, FE of calcium, FE of phosphorus, calcium-creatinine index, and high urine pH values were found, compared to their habitual values in healthy individuals (Tables 1 and 2).

Discussion

There is growing evidence that COVID-19 can induce renal damage leading to different renal syndromes since abnormal urinalysis, whose more prevalent form is proteinuria, to acute kidney injury. This latter condition is more frequent in critically ill patients, and is considered a poor prognostic factor due to its association to high mortality (91%) [7].

Table 1 Serum electrolyte parameters

Parameters	Mean	SD	Normal values
Uric acid (mg/dL)	3.7	1.3	3–7
Serum osmolarity (mOsm/L)	297	9	280–300
Serum sodium (mmol/L)	139	5	135–145
Serum potassium (mmol/L)	4.3	0.8	3.5–5.5
Serum chloride (mmol/L)	104	5	95–106
Serum calcium (mg/dL)	8.1	1.3	8.5–10.5
Serum magnesium (mg/dL)	2.1	0.4	1.9–2.5
Serum phosphorus (mg/dL)	3.8	1.8	2.5–4.5

Table 2 Urinary indexes

Parameters	Mean	SD	Normal value (fast sample)
FE uric acid (%)	14	7	8
Urinary osmolarity (mOsm/L)	686	291	> 350
FE sodium (%)	1.4	1.1	0.5–1
FE potassium (%)	6	3	10
TTKG	1.2	0.5	4
FE chloride (%)	0.6	0.2	0.5–1
FE calcium (%)	2.1	4	0.8
Calcium-creatinine index	0.26	0.6	> 0.11
FE magnesium (%)	1.8	1.6	3
FE phosphorus (%)	35	5	˂20
Urinary pH	6	0.7	4

FE fractional excretion

COVID-19-associated renal damage has been interpreted as multivariate, although the high prevalence of proteinuria, even in a setting of normal renal function, has been interpreted as induced by fever, inflammation, and its consequent glomerular hyperfiltration [7–11]. Several COVID-19-inducing kidney damage mechanisms have been proposed, as follows: [2, 11–21].

- SARS-CoV-2 cytopathic activity. Podocytes and proximal tubule cells have an abundant expression of angiotensin 2-converting enzyme receptor and TMPRSS2 coreceptor, which are considered putative receptors of the virus, mediating cell entry by endocytosis.
- Myoglobin-induced renal damage secondary to rhabdomyolysis.
- Tissue hypoxia secondary to severe hypoxemia.
- Cytokine storm, which involves interleukin 6 (IL-6), interleukin 7 (IL-7), interleukin 2 (IL-2), tumor necrosis factor-alpha (TNFα), monocyte chemoattractant protein-1 (MCP-1), and G-SCF (granulocyte-colony stimulating factor).
- Nephrotoxic drugs (AINES, antiviral drugs, etc.).
- Immune complex renal deposition.

Our studied population had symptoms (fever, myalgia, dyspnea) and comorbidities (hypertension, obesity, diabetes mellitus) characteristically described in those COVID-19 patients who required hospital admission [11, 16]. In this study, there was a series of findings which could be interpreted as signs of tubular dysfunction in the setting of COVID-19, as follows (Tables 1 and 2):

- Urine calcium excretion was inadequately high since calcium should be being saved in a setting of hypocalcemia.
- Urine sodium and phosphorus excretion values were inadequately high since they should have been lower in a setting of fast urine samples.
- Urine pH was inadequately high (relatively alkaline) in a setting of fast urine samples.

Al these findings could be explained by a relative tubular incapability to reabsorb an adequate amount of sodium, calcium, and phosphorus and to secrete an adequate amount of protons in a setting of systemic inflammation induced by COVID-19 infection. In this sense, there are reports describing COVID-19-induced tubular structural and functional alterations, particularly in proximal tubules (Fanconi syndrome) in the literature [18–20]. It should be taken into account that 25-(OH) vitamin D_3, in complex with its plasma carrier, is filtered through the glomerulus and reabsorbed in the proximal tubules by the endocytic receptor megalin. Since this process is needed to preserve 25-(OH) vitamin in order to deliver it to the cells as 1,25-(OH)2 vitamin D_3 precursor, then COVID-19-induced tubular damage could lead to inadequate hypercalciuria in patients [21].

Werion et al. have reported viral injury at the initial part of proximal tubules in the kidneys from COVID-19 patients, where brush border loss, acute tubular necrosis, intraluminal debris, and a marked decrease in the expression of megalin (multi-ligand receptor of tubular transport system), associated to hypouricemia with inappropriate uricosuria, were documented [22]. Fukao et al. have reported that severe COVID-19 patients without acute kidney injury had significantly elevated tubular injury markers, such as urinary live-type fatty acid binding protein (L-FABP), β2 microglobulin, and urinary N-acetyl-β-D-glucosaminidase (uNAG). Besides, they documented that these markers were significantly associated with IL-6 levels [23]. Therefore, inflammation has been highlighted as one of the main tubular damage-inducing mechanisms in COVID-19, and our studied population has significantly high serum levels of inflammatory markers such as C-reactive protein, ferritin, and D-dimer. Serum C-reactive protein and ferritin elevation has been explained by SARS-CoV-2-induced inflammatory response. Particularly, it has been proposed that elevated ferritin could come from the acute destruction of hepatocytes, macrophages, or cells of the bone marrow induced by systemic stimulation of cells of innate immunity (e.g., macrophages). The above mentioned can explain the elevated transaminases (hepatitis) levels and the anemia (inflammatory induced erythropoietin resistance) observed in our studied patients. Furthermore, innate immunity secretes cytokines which generates inflammation, and also stimulates adaptive immunity response which secretes more cytokines giving place to a spiral of inflammation which ends in the phenomenon called cytokine storm, and consequently

tissue damage [24–32]. There is a close interaction between immune system and coagulation in response to infection, and D-dimer increase, which was documented in our studied population, is a marker of thrombin generation, fibrinolysis, and endothelial damage [28]. Thus, high D-dimer serum levels could signify a mechanism of tubular damage by microthromboembolic activity [22].

Conclusion

Tubular dysfunction was documented in COVID-19 patients.

Annex

- Transtubular potassium gradient (TTKG)
  TTKG: urine potassium/serum potassium × serum osmolarity/urine osmolarity
- Calcium-creatinine index (CaCr)
  CaCr: urine calcium/urine creatinine
- Fractional excretion (FE) of X
  (X): sodium, potassium, chloride, calcium, phosphorus, magnesium, urea, uric acid

FE X: urine X/serum X × serum creatinine/urine creatinine

Declarations

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the patient.

Conflict of interest The authors declare no competing interests.

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