Evaluation of proximal tubule functions at the children with COVID-19 infections: a prospective analytical study

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Research Article

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Abstract

Purpose: There are limited numbers of studies focusing on renal effects of COVID-19 infection and proximal tubular dysfunction in children with COVID-19 infections. In this study, we aimed to evaluate the functions of the proximal tubule in hospitalized children with confirmed acute COVID-19.

Methods: This prospective descriptive study included the children who were hospitalized for confirmed COVID-19 were included. The diagnosis of proximal tubule injury was based on the presence of at least two of the following four abnormalities including abnormal tubular reabsorption of phosphate, normoglycemic glycosuria, hyperuricosuria, and proteinuria.

Results: A total of 115 patients were included in the study. Approximately one-third of the patients had higher serum creatinine levels or proteinuria. Additionally, abnormal renal tubular phosphate loss measured by TMP/eGFR was present in 10 patients (8.7%) and hyperuricosuria was present in 28.6%. Consequently, overall PTD was present in 24 patients (20.8%), and PTD associated with COVID-19 was significantly detected in younger children.

Conclusions: Our findings suggested that one in five children with acute COVID-19 infections had proximal tubular dysfunction. The rate of proximal tubular dysfunctions was not so high as in adults but should be kept in mind. The children with COVID-19 infections should be monitored for recovery of proximal tubular functions.

What Is Known?

- The studies focusing on the renal impairments of COVID-19 were generally in adult patients

What is new?

- Proximal tubular dysfunctions were observed not only in the adults but also in the children.
- The rate of proximal tubular dysfunction in. the children with COVID-19 was lower compared to adults.

Introduction

The clinical course and outcome of coronavirus disease–2019 (COVID-19) in pediatric patients are significantly better compared to adults excluding multisystemic inflammatory syndrome associated in children (MIS-C) associated with COVID-19 (1, 2). Initial studies during the beginning of the pandemic from China and Italy reported that children are mildly affected representing approximately 5% of cases and less than 1% of admissions to a hospital (1, 3). Despite the main clinical presentations are due to pulmonary involvement, extra-pulmonary manifestations including gastrointestinal, cardiovascular, hematological, musculoskeletal, and endocrinology as well as the renal system may be affected (4).

The studies focusing on the renal impairments of COVID-19 were generally in adult patients. In one study including 701 adults with COVID-19, proteinuria and hematuria were the most common clinical findings reported being present in respectively 43.9% and 26.7% of the patients, followed by elevated blood urea nitrogen, elevated serum creatinine levels, and low glomerular filtration rates (5). The most important mechanism for the entry of severe acute respiratory. syndrome coronavirus 2 (SARS-CoV-2) into cells is the angiotensin-converting enzyme 2 (ACE2) receptor and these receptors are mainly found especially in the lung, in addition to the heart, gastrointestinal organs, and also in kidneys (6). The harmful effects of SARS-CoV-2 on the kidney appear clinically as an increase in proteinuria, hematuria, and serum creatinine. The virus particles in the kidney are more common in glomeruli and proximal tubule cells (7). Especially, the reason for the involvement of proximal tubule cells is that ACE2 proteins on the proximal tubule cell surface allow the entry of SARS-CoV-2 viruses (6). Proximal tubules are the part of the kidney where high absorption of albumin, low molecular weight proteins, glucose, amino acids, phosphate, bicarbonate, and uric acid is provided. Proximal tubular dysfunction (PTD) causes proteinuria, hypophosphatemia (decreased tubular phosphorus reabsorption accompanying normal or low serum phosphorus level), hyperuricosuria, neutral aminoaciduria, and normoglycemic glycosuria (8).

There are limited numbers of studies focusing on renal effects of COVID-19 infection and PTD in children with COVID-19 (9–11). In this study, we aimed to evaluate the functions of the proximal tubule in hospitalized children with confirmed acute COVID-19.

Material-methods

This prospective descriptive study was conducted at the University of Health Sciences Dr. Behçet Uz Children's Hospital in İzmir, Turkey, from October 11 through January 31, 2021. The children between one month to 18 years old who were hospitalized in the pediatric infectious diseases ward as a result of confirmed COVID-19 were included in the study. The diagnosis of COVID-19 was confirmed by the quantitative real-time polymerase chain reaction (RT-PCR) positivity. The protocol of RT-PCR was consistent with the recommendation of the WHO (12). In our national and hospital-based protocols, samples for SARS-CoV-2 were indicated for only symptomatic patients. The severity of COVID-19 was defined based on the clinical features, laboratory testing, and chest X-ray imaging, including asymptomatic infection, mild, moderate, severe, and critical cases referring to the previous definitions(13). The urine samples were taken before any medication or intravenous fluid administration.

Inclusion criteria: The patients who were diagnosed with acute COVID-19 infections with RT-PCR and children older than one month up to 18 years, were included.

Exclusion criteria: The patients previously diagnosed with renal disease, the patients who were followed up in the pediatric intensive care unit, or patients with absent data including serum creatinine and routine urinalysis were excluded from the study. Any patients who had medications including hydroxychloroquine before the hospitalization or patients with other chronic diseases were also excluded. The patients with known high phosphate intake were also excluded**.** The patients' urine samples were taken before any

medication or intravenous fluid administration and any patients who did not fulfill the criteria were excluded. The children with the diagnosis of MIS-C were excluded from the study.

The blood and urine samples for initial biochemical parameters and urine analysis including urine electrolytes, protein, glucose, and microalbumin were obtained during the hospitalization. The demographic features of the patients including age, gender, initial serum creatinine levels and electrolytes, uric acid, glucose, and routine urinalysis with microscopy were also recorded to case recording estimated glomerular filtration rate (eGFR), tubular reabsorption of phosphate (TRP), maximum renal tubular phosphate threshold (TmP), renal tubular phosphate loss (TmP/ eGFR), presence of normoglycemic glucosuria, hyperuricosuria were calculated for all patients according to the criteria below.

Definitions

i. Tubular reabsorption of phosphate (TRP): The tubular reabsorption was evaluated by renal tubular phosphate involvement. Approximately 85-95% of the phosphate is reabsorbed from the proximal tubule, thus a TRP rate below 85% was indicated as tubular phosphate leakage (14). This rate was calculated as “100 x [1- {(urinary phosphate X serum creatinine) / (urinary creatinine X serum phosphate)}]”. Serum creatinine and phosphate were expressed as mg/dl (14).

ii. Maximum Renal Tubular Phosphate Threshold (TmP): [Serum phosphate – (urinary phosphate X serum creatinine)]/ urinary creatinine (15)
iii. Renal tubular phosphate loss measured by TmP / eGFR. The values of TmP/eGFR<2.8. mg/dl showed the renal tubular phosphate loss (15)
iv. Normal serum creatinine was defined as 0.2 to 0.4 mg/dL (18 to 35 micromol/L) for infants, 0.3 to 0.7 mg/dL (27 to 62 micromol/L) for children, 0.5 to 1 mg/dL (44 to 88 micromol/L) for adolescents (16).
v. The estimated glomerular filtration rate: was calculated according to the modified Schwartz criteria (17).
vi. Normoglycemic glucosuria: is defined as increased urinary glucose excretion in the presence of normal serum glucose concentration. Glucose positivity in urine with dipstick was planned to be considered significant.
vii. Hyperuricosuria: After the age of three, the value obtained with the formula "uric acid (mg /dL) x serum creatinine (mg /dL) / urine creatinine (mg/dL)", which also uses glomerular filtration rate, is above 0.56 mg / dl as hyperuricosuria (18).
viii. Urinary uric acid/creatinine ratio: It was evaluated and described as normal according to the previous study performed on Turkish children (19).
ix. Hypouricemia: is defined as a serum uric acid level below 2 mg/dl (20).
x. Proteinuria: Upper limit of normal for the spot urine protein-to-creatinine ratio varies by age as following; age 6 to 24 months (infants and toddlers) <0.5 mg protein/mg creatinine; age 24 months to 18 years (children and young adults) <0.2 mg protein/mg creatinine. The spot urine protein-to-creatinine ratio that is indicative of nephrotic range proteinuria is >3 mg protein/mg creatinine (21).

xi. Diagnosis of proximal tubular dysfunction: The diagnosis of proximal tubule injury was based on the presence of at least two of the following four abnormalities (22); including the presence of increased renal tubular phosphate loss, normoglycemic glycosuria, hyperuricosuria, and proteinuria.
Statistical analysis was performed using SPSS statistical software (version 22; SPSS, Chicago, IL, USA). The student's t-test was used to compare continuous parametric variables, the Mann-Whitney U test was used to compare continuous nonparametric variables, and $\chi 2$ or Fisher's exact tests were used when appropriate. A two-tailed p-value of <0.05 was considered to be statistically significant.

Ethical consent: This study was approved by the Local Ethical Committee of Dr. Behcet Uz Children's Training and Research Hospital with the registration number 452, approval number 166, and date 09.24.2020

Results

In this study, 115. hospitalized patients fulfilling the criteria were included in the study.

The demographics of the study population:

Seventy-three (63.5%) patients were male and 42 (47.9%) were female. The median age of patients was 10 years (range 1 months to 17 years). Regarding the age distribution, 18 (15.7%) of the patients were under one-year-old and 68 (59.1%) were 12 years and older. The median bodyweight of the patients was 39.0 kg (range 3.9 to 115 kg) and median height was 145 cm (range 54 to 186 cm). Totally 15 patients (13.0%) had Body Mass Index (BMI) ≥ 25. Eight patients(6.9%) were overweight (BMI= 25-29.9) and seven patients (6.0%) were obese(BMI ≥ 30).

The most common symptom of the patients was fever (44.3%, 51 patients) and cough (41,7%, 48 patients) followed by headache (25.2%, 29 patients), myalgia (21.7%, 25 patients), sore throat(16.5%, 19 patients), diarrhea (15.6%, 18 patients), chest pain(14.0%,16 patients), anosmia (13.2%, 15 patients)followed by the symptoms reviewed at table-1 (Table-1).

The baseline characteristics of the laboratory tests

The average serum creatinine level was 0.6 ± 0.1 mg/dl (range from 0.4 to 1.00 mg/dl) and 38 patients (33.0%) had elevated creatinine levels (Table-2). The mean serum phosphate level was 4.5±0.8 mg/dl (table-1). Hypophosphatemia was present in 10 patients (8.7%) of the total patients. All serum biochemical parameters evaluated in the study were reviewed in table-1. The mean eGFR was 85.98±18.38 (range 44.6 to 131.4).

Evaluation of diagnostic criteria for proximal tubular injury.

The median urinary protein/ urinary creatinine ratio was 0.17 (ranging from 0.03 to 2.62) indicating 39 (33.9%) patients had proteinuria. The mean age in the patients with proteinuria was 87.54± 68.98 months (1 month to 17 years) and without proteinuria was 118.57± 68.71 months (range 2 months to 17 years),

and significantly lower in the proteinuria group(p=0.024). In the patients without proteinuria, 15.8% (12 patients) of the patients had microalbuminuria (Table-3).

Tubular phosphate leakage measured by TRP was present in 27 (23.5%) patients. Additionally TMP/eGFR values revealed abnormal renal tubular phosphate loss (<2.8. mg/dl) at 10 patients (8.7%) and normal range at 105 patients (91.3%). Hypophosphatemia was present in 10 patients (8.7%) of the total patients. Two patients (1.73%) had normoglycemic glycosuria. Hyperuricosuria was present at 28.6% (33 patients) of the population. The median age in the patients with hyperuricosuria was 4 years (range 1 month to 16 years) and 12,5 years (range 2 months to 17 years) at the patients without hyperuricosuria, and significantly lower in the patients with hyperuricosuria (p<0.001). The rate of patients with hypouricemia was 4.3% (n=5 patients) and with hyperuricemia was 4.3% (n=5 patients).

Evaluation of patients for proximal tubule dysfunction:

As reviewed in Table-3, 7 patients (6.0%) had both proteinuria and increased renal tubular phosphate loss measured by TmP/eGFR, 18 patients (15.6%) had both proteinuria and hyperuricosuria, 3 patients (2.6%) had both increased renal tubular phosphate loss and hyperuricosuria. The rate of proximal tubular pathology depending on the presence of two diagnostic criteria positivity was 24 patients (20.8%) (Table-3). The rate of patients having at least three diagnostic criteria positivity was 4 patients (3.5%) (Table-3).

The rate of male patients was 58.3% (14 patients) in the PTD group and 64.8% (59) in the patients with normal proximal tubule function, and no significant difference was present between these two groups (p>0.05). The median age was 6 years (range 1 month to 17 years) at the patients with PTD and 10 years (2 months to 17 years) at the patients. without PTD, and the age was significantly lower in the patients with PTD (p=0.028).

Discussion

In this prospective study, PTD was evaluated in children with COVID-19. Approximately one-third of the patients had higher serum creatinine levels or proteinuria. Additionally, abnormal renal tubular phosphorus loss measured by TMP/eGFR was present in 10 patients (8.7%) and hyperuricosuria was present in 28.6%. Consequently, overall PTD was present in one of the five patients, and PTD associated with COVID-19 was significantly detected in younger children.

Some studies reported the kidney as a specific target for SARS-CoV-2 infection(23–26). The postmortem examination of the kidney revealed the accumulation of SARS-CoV-2 antigens in the renal epithelial cells(23). Despite the published articles, limited studies are emphasizing the effect of COVID-19 on proximal tubule functions (7, 22, 27). Detection of viral particles of SARS-CoV-2 in the proximal tubular epithelium and podocytes associated with foot process effacement, vacuolation, and detachment of podocytes from the glomerular basement membrane showed the involvement of the proximal tubules by SARS-CoV-2(26). Another renal impairment was SARS-CoV-2-related acute kidney injury and generally reported from critically ill patients (28, 29). In our patient's group, we didn’t observe any acute kidney

injury related to SARS-CoV-2. This is mainly due to the properties of the study group. In our study. we mainly focused on children who didn't require intensive care unit admission, which were less likely to effect from COVID-19 infections.

Werion et al. reported that 70-80% of the patients with COVID-19 had low-molecular-weight proteinuria, and 46% and 19% of the patients had an inappropriate urinary loss of uric acid and had phosphate, respectively (7). In another study, it was reported that 75% of the patients with COVID-19 had at least two of the four criteria for PTD (22). The recent studies reported that the patients requiring pediatric intensive care units were more likely to have signs of renal involvement such as proximal tubule injury (22). However, although the current study applied similar diagnostic criteria, the rate of PTD was 20.8% and lower compared to that study mentioned above. The higher rates of PTD in that previous study might have been depending on the limited number of patients and more of the patients followed up in the intensive care unit which was different from our study (22). As a result of having comorbid diseases and also much more nephrotoxic drugs administration to the patients in the intensive care unit may be associated with a higher rate of PTD. For this reason, to provide homogeneity of the study group and to prevent any possible confounding in our study, the patients in the intensive care units, patients receiving any nephrotoxic drugs, and patients with comorbid diseases were excluded. Thus, it may be speculated that PTD may be detected in a considerable rate of children with COVID-19, and including patients in intensive care units would probably increase the rate of PTD.

Our study revealed that the proximal tubule dysfunction is not only present in adults but also present in children with COVID-19. Children were reported to have fewer symptoms compared to adults and the attributable mortality in the children was far away from low compared to adults (30). Although the pathogenesis of age-related differences of severity was not clearly understood, the variety of ACE2 and TMPRSS2 was one of the important candidates for pathogenesis (31). One of the most popular hypotheses, depended on increased expression and affinity of ACE in addition to MTMPRSS2 with age, while against hypothesis supported the anti-inflammatory properties of ACE2(32–35). Proximal tubular cells were reported to express ACE2 and TMPRSS2 intensely thus resulting in them as a good target for SARS-CoV-2 at the early stage. (36). Besides ACE2 is present in the renal cells, such as the parietal epithelium of Bowman's capsule, collecting ducts, a thick ascending limb of Helen, podocytes, proximal cell brush border, and mesangial cells, suggesting multiple sites are the target for SARS-CoV-2(37). Also as postulated above, the increased affinity of the spike protein of SARS-CoV-2 to ACE was associated with disease severity (38). A relatively low rate of PTD in children compared to adult studies supported this hypothesis. On the other hand, the significantly younger age in the. patients with PTD supported the ACE-related hypothesis and suggested unexplored complex mechanisms and interactions besides SARS-Cov-2 and ACE receptors on the proximal tubule cells.

One of the definition criteria for PTD was normoglycemic glycosuria. Werion et al, reported that although other elements of PTD were present in the patient cohort with different rates, no normoglycemic glucosuria was recorded (7). While, Korman et al, reported that normoglycemic glucosuria was present in 11 of the patients (28%) and most of the patients in this group were from intensive care units (22). In our

study only 2 patients (1.73%) had normoglycemic glucosuria, suggesting the children had also a low rate compared to most of the adult studies. According to us, the difference between the adults and children regarding PTD and COVID-19 infections in the literature had several reasons. Besides the better prognosis of the COVID-19 infections, the relatively low burden of chronic diseases, and related medications, low rate of intensive care, and mechanical ventilation requirement at the children are the main reason for the difference.

Our study had several limitations, including a limited number of measurements for some markers, lack of renal biopsy, and failure to demonstrate SARS-Cov-2 at the proximal tubule cells, as well as the single-center design of the study. However, the results of the current study may be more reliable because of providing more unvarying groups by the exclusion of the patients in intensive care units who may have more possible confounding factors. A better marker such as low molecular weight proteins including beta-2 microglobulin and retinol-binding protein might be more helpful, however during the study period, we were not able to reach these sophisticated tests. However, up to our knowledge, this is the first large study focusing on the effect of SARS-CoV-2 infections on the proximal tubule functions in children with COVID-19 infections, and our result may play a role in developing a screening test. Also, the longer follow-up of the patients for recovery of PTD was missing, which would be planned in the future.

In conclusion, our findings suggested that 20.8% of the children with COVID-19 infections had proximal tubular dysfunction. Proximal tubular dysfunctions were observed not only in the adults but also in the children. Children with COVID-19 infections should be followed up for recovery of proximal tubule dysfunction. More detailed studies for the evaluation of renal effects of SARS-CoV-2 on pediatric patients are essential.

Abbreviations

COVID-19: coronavirus disease 2019

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

ACE2: Angiotensin-converting enzyme 2

PTD: Proximal tubular dysfunction

RT-PCR :Real-time polymerase chain reaction

MIS-C: Multisystem inflammatory syndrome in children

eGFR: Estimated glomerular filtration rate

TRP:Tubular reabsorption of phosphate

Declarations

- Funding: N/A
- Conflicts of interest/Competing interests: Ilker Devrim had educational grant from BD and Ilker Devrim has educational webinars for BD. However, all authors have no conflicts of interest about this manuscript
- Availability of data and material: if required the authors can provide the data.
- Code availability: custom code
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Tables

Table 1: The symptoms at admission at children with COVID-19 infections

Comorbidities	N(%)
Fever	51(44.3)
Cough	48 (41.7)
Headache	29 (25.2%)
Myalgia	25(21.7%)
Sore throat	19(16.5)
Diarrhea	18 (15.6%)
Chest pain	16 (14.0)
Anosmia	15 (13.2)
Vomitting	9 (7.8)
Nasal discharge	8(6.9)
Rash	2(1.7)

Table-2: Baseline characteristics of the 115 patients with **serum biochemical parameters and** urinalysis

			Minimum-maximum
Serum creatinine, mg/dl	Mean	0.6 ± 0.1	0.4 - 1.00
Serum Calcium, mg/dl	Mean	9.3 ± 0.6	7.3 - 10.5
Serum Phosphate , mg/dl	Mean	4.5 ±0.8	1.0- 6.6
Serum Sodium, mmol/L	Mean	138.4±2.4	129-142
Serum Potassium, mmol/L	Mean	4.4 ± 0.5	3.3-6.1
Serum Clor, mmol/L	Mean	105.6±3.1	95-114
Serum Glucose, mg/dl	Mean	102.9±21.0	73-227
Serum Ure, mg/dl	Mean	10.7±6.9	2.0-63.0
Serum Uric acid, mg/dl	Mean	4.1±1.4	1.0-9.8
Serum Proteinin, gr/dL	Mean	7.0±0.8	4.1-8.3
Serum Albumin, gr/L	Mean	4.3±0.5	2.4-5.0
eGFR, ml/min per/ 1.73 m2	Mean	85.98 ± 18.38 ml/min per 1.73 m2	44.6 -131.4 ml/min per/ 1.73 m2
Urinary protein/ urinary creatinine ratio	Median	0.1740	0.03 - 2.62

Table-3: The distribution of the patients with COVID-19 infections for the diagnostic criteria for proximal tubule dysfunction.

*The gray shaded cells, showed the 24 patients (20.8%) with PTD depending on two positivity of diagnostic criteria.

Diagnostic criteria for proximal tubule dysfunction.	Hyperuricosuria	Proteinuria	Renal tubular phosphorus loss	Normoglycemic glycosuria	Number of cases
	-	-	-	-	59
	-	-	+	-	2
	-	+	-	-	16
*	-	+	+	-	4
	-	+	+	+	1
	+	-	-	-	14
*	+	-	+	-	1
*	+	+	-	-	15
*	+	+	-	+	1
*	+	+	+	-	2
					115