Research Article

Renal Tubular Acidosis in Patients with Systemic Lupus Erythematosus

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Keywords

Glomerular filtration rate · Proteinuria · Renal tubular acidosis · Systemic lupus erythematosus

Abstract

Objective: Renal tubular acidosis (RTA) is a clinical manifestation that occurs with insufficiency in restoring bicarbonate or disruption in hydrogen ion elimination as a result of a disruption in tubulus functions, causing normal anion gap-opening metabolic acidosis. In the present study, we aimed to investigate the prevalence of RTA in the largest systemic lupus erythematosus (SLE) patient population to date. **Materials and Methods:** SLE patients, who were followed up in 2 different healthcare centers, were included. Patients with metabolic acidosis (pH <7.35 and HCO₃ <22 mEq/L) in venous blood gas analysis were determined. The serum and urine anion GAP of these patients were estimated, and the urine pH was assessed. RTA presence was evaluated as metabolic acidosis with a normal serum anion gap and a positive urine anion GAP. **Results:** A total of 108 patients were included in the present study. The mean age of the patients was 41.5 ± 1.2 and 87% were female. The SLE diagnosis duration was 75 ± 5 months. The mean creatinine value was 0.6 ± 0.1 mg/dL and the mean eGFR was 111 ± 2 mL/min. According to the blood gas analysis, 18 patients (16.7% of the total) had RTA. Sixteen of these patients had type 1 RTA and 2 had type 2 RTA; type 4 RTA was not determined in any of the patients. **Conclusion:** RTA should be considered in SLE patients even if they have normal eGFR values. This is the largest study to examine the prevalence of RTA in SLE patients in the literature.

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Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with a broad spectrum of clinical presentations encompassing almost all organs and tissues. The extreme heterogeneity of the disease has caused some investigators to propose that SLE represents a syndrome rather than a single disease. The prevalence rates in lupus are estimated to be as high as 51 per 100,000 people in the USA [1]. The incidence of lupus increased nearly 3-fold in the last 40 years [1]. Sixty-five percent of patients with SLE have a disease onset between the ages of 16 and 55 years.

Renal involvement occurs in 40–70% of all SLE patients and it is a major cause of morbidity and hospital admissions [2]. Immune complex formation/deposition in the kidney leads to intraglomerular inflammation with activation and proliferation of leukocytes [3]. Urinalysis is the most important and effective method to detect and monitor renal activity of disease. Clinical findings such as microscopic hematuria, microalbuminuria, asymptomatic proteinuria, massive proteinuria and nephrotic syndrome, rapidly progressive glomerulonephritis, and acute and chronic renal failure can be seen [4].

Renal tubular acidosis (RTA) is defined as an ion transport disorder in renal tubules. Four types are named and described as follows: distal or type 1 RTA, i.e., a defect in hydrogen ion excretion from the kidneys; proximal or type 2 RTA, i.e., a defect in bicarbonate (HCO_3) reabsorption; mixed or type 3 RTA, i.e., a defect involving both of these; and type 4 RTA, i.e., aldosterone deficiency or resistance [5]. RTA may develop due to idiopathic, familial and secondary causes. Diabetes mellitus, rheumatoid arthritis, Sjögren syndrome, lysosomal storage diseases and drugs are among the common causes of secondary RTA [6–8]. It is known that RTA can be seen in patients with SLE [9]. Studies in the literature are generally in the form of case reports. Although the mechanism of RTA formation in SLE is not clear, different mechanisms have been reported.

Although some studies with small cohorts and several case reports exist in the literature, to the best of our knowledge our study is the largest one to examine the prevalence of RTA in SLE patients.

Materials and Methods

Patients followed-up with the diagnosis of SLE in 2 nephrology and rheumatology units were included in this cross-sectional study. The diagnosis of SLE was based on the diagnostic criteria revised by the American College of Rheumatology in 1997 [10].

Patients with a glomerular filtration rate (GFR) <60 mL/min were not included in this study due to the metabolic acidosis effect of renal failure. In addition, patients diagnosed with diabetes mellitus or Sjögren syndrome and those treated with diuretics, drugs affecting the potassium metabolism, and sodium hydrogen carbonate therapy were not included in this study.

The demographic data of the patients (age, sex, disease duration, additional diseases, medications, renal biopsy findings, autoantibody and complement levels, and 24-h urine protein quantity) were obtained from the patient files. All blood samples were obtained from patients in the morning after 12 h of fasting. Biochemical tests in serum (urea, creatinine, sodium, potassium, and chlorine) and urine (sodium, potassium, chlorine, etc.) were studied using the enzymatic colorimetric technique (ADVIA® 1800 Clinical Chemistry System; Siemens, Erlangen, Germany). An ABL800 (Radiometer Medical ApS; Copenhagen, Denmark) device was used for blood gas analysis. All urine analyses were performed on H-800 and FUS-200 automatic modular urine analyzers (Dirui Industry, Changchun, China).

Urine pH, venous blood gas analysis parameters including serum pH values, the HCO_3 concentration, base excess, the presence of metabolic acidosis, which was defined as low HCO_3 (<22 mEq/L) together with low serum pH values (<7.35), were checked at the last follow-up. Patients with metabolic acidosis were further analyzed for urine anion gap (UAG) and serum anion gap (SAG) using the following formulas: UAG =

Table 1. Summary of demographic and laboratory data

Parameter	Value
Age, years	41.5±1.2
Male/female ratio	14/94
Duration of disease, months	75±5
Hypertension, %	30.7
BUN, mg/dL	20±1
Creatinine, mg/dL	0.6±0.1
Potassium, mmol/L	4.2±0.4
Uric acid, mg/dL	4.4±1.3
Albumin, g/dL	4.1±0.1
Hemoglobin, g/dL	12.2±0.1
CRP, mg/L	2.9±0.3
Proteinuria, mg/day	339±68
eGFR, mL/min	111±2
Patients with antinuclear antibody positivity, <i>n</i>	77
Patients with anti-dsDNA positivity, <i>n</i>	28
Patients with low C3 levels, <i>n</i>	23
Kidney biopsy results, <i>n</i>	
Type 2 lupus nephritis	9
Type 3 lupus nephritis	3
Type 4 lupus nephritis	19
Type 5 lupus nephritis	5
Renal tubular acidosis, %	16.7

Values are presented as means ± SD.

$[\text{Na}^+] + [\text{K}^+] - [\text{Cl}^-]$ and $\text{SAG} = [\text{Na}^+] - [\text{Cl}^-] + \text{HCO}_3^-$. SAG values between 7 and 14 were accepted as normal. RTA was defined as metabolic acidosis with normal SAG and positive UAG values. Patients with RTA were further categorized as having type 1 distal RTA if the urine pH was >5.5 and the serum potassium level was low or normal; they were categorized as having type 2 RTA if the urine pH was <5.5 and the serum potassium level was low or normal, and they were considered to have type 4 RTA if the serum potassium level was >5.5 mEq/L [11].

Statistical Analysis

Continuous variables were tested for a normal distribution using Kolmogorov-Smirnov and Shapiro-Wilk tests. We report continuous data as means ± SD. Median values were used when a normal distribution was absent. We compared parametric continuous variables using the *t* test, and the Mann-Whitney U test was used for nonparametric continuous variables. Categorical variables were summarized as percentages and compared with the χ^2 test. *p* < 0.05 was considered statistically significant, and 95% CI were set. All statistical analyses were performed using SPSS version 15 (SPSS, Inc., Chicago, IL, USA).

Results

One hundred eight patients were included in this study. The mean age of the patients was 41.5 ± 1.2 and 87% of them were female. The mean duration of SLE disease was 75 ± 5 months, and 30.7% of patients were hypertensive. There was biopsy-proven SLE nephritis in 36 patients (33%), and the majority of them had class 4 lupus nephritis (55%). Sixty-nine percent of the patients were taking mycophenolate mofetil and a low-dose steroid. The mean creatinine level was 0.6 ± 0.1 mg/dL and the mean eGFR level was 111 ± 2 mL/min. A summary of the demographic and laboratory data is shown in Table 1.

Table 2. Comparison of the data in 2 groups involving patients with and without RTA

	RTA (+) (n = 18)	RTA (-) (n = 90)	p value
Age, years	45.1±2.4	40.8±1.3	0.13
Duration of disease, months	73.4±13.9	75.8±5.7	0.66
Hypertension, %	44.4	27.8	0.13
BUN, mg/dL	21.2±4.1	20.5±1.1	0.47
Creatinine, mg/dL	0.6±0.1	0.6±0.1	0.28
Albumin, g/dL	4.1±0.1	4.1±0.1	0.86
Hemoglobin, g/dL	12.1±0.3	12.2±0.1	0.86
CRP, mg/L	2.5±0.5	2.9±0.4	0.64
Proteinuria, mg/day	558±268	301±65	0.36
eGFR, mL/min	98±5	114±2	0.01
Serum sodium, mEq/L	141±3	140±11	0.94
Urine sodium, mEq/L	88±45	95±56	0.59
Serum chlorine, mEq/L	107±4	107±8	0.33
Urine chlorine, mEq/L	112±57	121±66	0.65
Serum potassium, mEq/L	4.4±0.1	4.3±0.1	0.13
Urine potassium, mEq/L	30.9	46.9	0.44
Serum PH	7.31±0.29	7.37±0.04	<0.001
Urine PH	6	5.9	0.26
Serum anion gap	11.3±2.0	13.3±3.7	0.033
Urine anion gap	17	0.4	0.03

Values are presented as means ± SD.

According to the blood gas analysis, 18 patients (16.7%) had RTA. The level of serum anion gap was 11.3 ± 2 , and the urine anion gap was 17 (10–29.8) in patients with RTA. Sixteen of those patients had type 1 RTA and 2 had type 2 RTA. Type 4 RTA was not seen in any patient. The mean age of the patients with RTA was 45.1 ± 2.4 years and the mean disease duration of those patients was 73.4 ± 13.9 months. There were 10 patients diagnosed with SLE nephritis by biopsy, and those patients were taking mycophenolate mofetil. When the patients with and without an RTA diagnosis were compared, there were no differences in terms of age, sex, duration of disease, treatment, or complement and autoantibody levels. Although the proteinuria amount of the patients with RTA was higher than in those without RTA, this difference was not found to be statistically significant. Although the eGFR levels of both groups were quite good, the eGFR levels of the patients with RTA were significantly lower. The serum pH and HCO_3 levels in the RTA group were significantly lower than those in the non-RTA group. There were no statistical differences between the 2 groups in terms of serum creatinine, serum and urine chlorine (107 ± 4 vs. 107 ± 8 and 112 ± 57 vs. 121 ± 66 mEq/L, respectively), serum and urine sodium (141 ± 3 vs. 140 ± 11 and 88 ± 45 vs. 95 ± 56 mEq/L, respectively), urine potassium levels (30.9 [22.5–64.8] vs. 46.9 mEq/L [25.4–75.4]) and urine pH (6 [6–6.5] vs. 5.9 [5.5–6.5]) ($p > 0.05$). A comparison of the data in 2 groups involving patients with and without RTA is shown in Table 2.

Discussion

The presence of RTA in patients with SLE has been previously reported in case reports. In this cross-sectional study, we aimed to investigate the incidence of RTA in a large population of SLE patients, and we detected that the incidence was remarkable at a rate of 16.7%.

SLE is a multisystem autoimmune disease with an unknown etiology. In the course of the disease, it is not wrong to say that the kidney is the organ that affects mortality and morbidity. The kidneys are among the most important organs during active disease [12]. The rates of renal involvement during the course of SLE are very variable and have been reported to be 25–60% in adults and 30–80% in children [13]. It was suggested that this ratio may be as high as 75–100% by biopsy. The severity of the disease varies from silent kidney disease to end-stage renal failure. In patients with urinary proteinuria, the presence of erythrocyte cylinders, detection of hematuria, pyuria, an increase in serum creatinine, a decrease in serum complement-3 (C3) and complement-4 (C4) levels, a decrease in creatinine clearance, and hypertension should suggest renal involvement [14]. Patients with renal involvement should have an early diagnosis and treatment should be initiated. In 10–30% of those patients, end-stage renal failure occurs despite appropriate treatment. The 15-year survival rate has increased to 80% with new treatment methods [15].

RTA refers to a group of disorders characterized by a defective renal acid-base regulation. The normal urine acidification capacity is impaired and results in a net acid retention and hyperchloremic metabolic acidosis. Acid-base imbalance occurs despite a normal or mildly reduced GFR. RTA is classified into 4 main forms, i.e., distal, proximal, mixed, and hyperkalemic RTA. Distal RTA is associated with a reduced urine acid secretion, proximal RTA is characterized by impaired HCO_3 reabsorption, and hyperkalemic RTA is an acid-base disorder generated by aldosterone deficiency or resistance [5]. Type 1, 2, 4 RTA cases have been reported as accompanying SLE, in the literature, and type 1 RTA has been detected in the majority of these cases. In our study, type 1 RTA was seen in 16 out of 18 patients with RTA. The development of type 4 RTA in SLE is extremely rare, though there are several case reports in the literature [16]. Aldosterone deficiency and/or resistance is responsible for its mechanism. None of our patients had type 4 RTA.

Electrolyte and acid-base disorders are key components of each disorder. RTA is often detected incidentally after laboratory tests, but some patients present with clinical features such as poor growth, dehydration, or an altered mental state [5]. RTA may develop due to idiopathic, familial, and secondary causes. Diabetes mellitus, rheumatoid arthritis, Sjögren syndrome, sarcoidosis, storage diseases (such as cystinosis and Wilson disease), and drugs (lithium, amphotericin b, and trimethoprim) are among the secondary causes [17, 18]. SLE is also among the secondary causes of RTA. In some studies, it has been reported that SLE constitutes 12% of distal RTA causes [19].

There may be glomerular, tubular, or interstitial involvement of the kidneys in SLE patients. In particular, tubular and interstitial involvement may lead to RTA and/or hyperkalemia.

The only study investigating tubular defects in SLE was performed by Kozeny et al. [20]. Kozeny et al. [20] found distal RTA in 8 (26%) out of 30 SLE patients undergoing a renal biopsy. In that study, no relation was detected between glomerular findings and the presence of RTA. In our study, there was biopsy-proven SLE nephritis in 10 out of 18 patients diagnosed with RTA. It should be kept in mind that, RTA may be present synchronously in patients with lupus nephritis. The pathogenesis of RTA development in SLE is unknown. RTA is also seen in autoimmune diseases such as RA and Sjögren syndrome, and it is thought that hypergammaglobulinemia and immunological factors may be responsible for the pathogenesis in RTA [20]. Again, it is thought that, antibodies against the carbonic anhydrase enzyme, or tubulointerstitial inflammation may have a role [20]. It has been suggested that a high disease activity score may be a risk factor for RTA development in SLE patients [21], but supporting studies are needed. In our study, when SLE patients with and without an RTA diagnosis were compared, there were no differences in terms of age, sex, duration of disease, or autoantibody and complement levels. The proteinuria amounts of the patients with RTA were higher (statis-

tically insignificant); however, it was shown that most of the patients in this group had a previous glomerular involvement. Although, the GFR values of both groups were in the normal range, there was a significant difference between the GFR levels in the 2 groups and the GFR level was lower in group with an RTA diagnosis. It has been suggested that glomerular function has a minimal or no effect on the development of RTA. In the study conducted by Kocyigit et al. [22] and our previous study [11] on renal transplant patients, it was shown that the GFR has an effect on RTA development. Supporting studies on this subject are also needed.

Our study has some limitations. Blood gas analysis and serum and urine anion gap measurements were performed one time. Since kidney biopsy is invasive and its absolute indications did not exist in all of the patients, the severity of glomerular and tubular damage could not be evaluated by kidney biopsy in all of the patients. Another limitation is that we may not have been able to identify all patients who may have incomplete distal RTA. An ammonium chloride (NH_4Cl) loading test is useful in such cases. These patients may not have a pH level below 7.35 or a decrease in HCO_3 in their serum, and metabolic acidosis can be induced by applying NH_4Cl (0.1 g/kg for 3 days). Under these stimulated acidemia conditions, if the urine pH level is above 5.3, it indicates distal RTA.

In conclusion, we showed that the incidence of RTA was not negligible in a large proportion of the SLE patients, whose GFR levels were within the normal ranges. We think that the evaluation of SLE patients, especially those with metabolic acidosis or potassium imbalance in this respect, would be useful, and supporting studies on this subject are needed.

Statement of Ethics

The study protocol was performed in accordance with the Declaration of Helsinki. The Ethics Committee of the Medical Faculty of Kahramanmaraş Sutcu Imam University approved the study protocol (KSU KAEK: 2018/31). Written informed consent was obtained from all subjects before enrollment into this study.

Conflict of Interest Statement

The authors declare that they have no conflict of interests.

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Author Contributions

Data collection, data analysis: F.N.S., F.S., D.T., G.Y.C., A.Y., S.G.B., E.A., and A.C. Data collection, data analysis, conception or design, authorship: N.E., O.G., and O.A.

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