Idiopathic Hypokalemia in Lupus Nephritis: A Newly Recognized Entity

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Key Points
- Hypokalemia may occur in patients with lupus nephritis in the absence of renal tubular acidosis (RTA) or other known causes.
- Patients with lupus nephritis and idiopathic hypokalemia have a distinct pattern of markers of autoimmunity.
- Clinically evident RTA in lupus nephritis exhibits a distinct pattern of markers of autoimmunity.

Abstract

Background Various causes of hypokalemia (HK) from renal potassium wasting, including distal renal tubular acidosis (RTA), have been described in lupus nephritis (LN). We report a phenomenon of otherwise unexplained HK among a population with LN.

Methods From our population of 403 patients with LN, we identified a cohort of 20 patients with idiopathic HK, defined by serum potassium <3.5 mmol/L without any apparent explanation. This cohort is compared with 90 LN controls (CON) and ten patients with LN with distal RTA from the same population.

Results The patients with HK had lower median serum potassium compared with CON and RTA subjects (3.26 versus 4.00 versus 3.75 mmol/L, respectively; \( P < 0.001 \)). The median serum bicarbonate was normal in HK and CON, but low in RTA (26.0 versus 25.0 versus 19.4 mmol/L; \( P < 0.001 \)). The median urine pH was abnormally high only in the RTA group (6.00 versus 6.25 versus 6.67; \( P = 0.012 \)). The median serum magnesium was modestly lower in HK compared with the CON and RTA groups (1.73 versus 2.00 versus 1.85 mg/dl; \( P = 0.002 \)). Although both HK and RTA showed a higher rate of seropositivity than CON for anti-Ro/SSA (79% and 80% versus 37%, respectively; \( P < 0.001 \)), only HK revealed a higher rate of seropositivity than CON for anti-RNP (84% versus 42%; \( P = 0.003 \)) and only RTA showed a higher rate of seropositivity than CON for anti-La/SSB (40% versus 12%; \( P = 0.05 \)).

Conclusions A syndrome of idiopathic HK was revealed in 20 out of 403 (5%) of patients within our LN population, and proved to be distinct from the RTA that occurs in LN. Furthermore, it was associated with a distinct pattern of autoantibodies. We speculate that idiopathic HK is the result of a novel target of autoimmunity in LN, affecting renal tubular potassium transport.

Introduction

As in the general population, sustained hypokalemia (HK) in SLE and lupus nephritis (LN) may be due to either extrarenal potassium losses, such as occurs with diarrhea, or from renal losses. Renal potassium wasting may occur in SLE and LN because of exposure to diuretics and corticosteroids, medications commonly used in the management of LN. HK as a result of distal renal tubular acidosis (RTA) is also well described in SLE, with or without LN (1,2).

During the usual care of our large population of patients with LN, we identified a subset of patients with recurrent HK that was not otherwise well explained by extrarenal losses, medications, or RTA. The primary objective of our study was to characterize the patients who exhibit this phenomenon. We also aimed to distinguish this clinical phenotype of patients with LN with idiopathic HK by comparing them with two other groups of patients: patients with LN and overt distal RTA, and a control (CON) group of patients with LN without RTA.

Materials and Methods

This is a retrospective, observational study conducted at Parkland Health and Hospital System in

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Dallas, Texas. The protocol for the study was approved by the institutional review board of the University of Texas Southwestern Medical Center.

Study Population
Electronic health records at Parkland Health and Hospital System were used to identify adult patients diagnosed with LN who were followed in the Parkland Glomerulonephritis Clinic from May 2010 to March 2020. LN was diagnosed from renal biopsy specimens and was classified according to the 2018 International Society of Nephrology/Renal Pathology Society classification criteria (3). CKD and AKI were defined according to the Kidney Disease Improving Global Outcomes definitions (4,5).

We identified idiopathic patients with HK as those with LN who had unexplained and recurrent HK, defined as a serum potassium <3.5 mmol/L in >40% of the laboratory analyses in the 12 months before the initiation of potassium supplements or potassium-sparing diuretics, but without evidence of RTA. Patients with RTA were identified as those with LN, serum bicarbonate <22 mmol/L, and urine pH ≥6.0. CON without evidence of RTA as defined were randomly selected from the total population at a rate of three CON for every patient with HK or RTA. Patients with known or suspected alternate causes of HK, including active diuretic therapy, primary hyperaldosteronism, and chronic diarrhea were excluded from all groups.

Study Outcomes
The primary outcomes of interest were the median serum potassium, serum bicarbonate, and urine pH across the HK, RTA, and CON study groups. Secondary outcomes included the median serum magnesium and the rate of seropositivity for anti-Ro/SSA, anti-La/SSB, and anti-RNP.

Data were extracted from the medical records, capturing the last 3 months of usual ambulatory care for each subject during the period from May 2010 to March 2020. For data with multiple values over that interval, including serum and urine chemistries, BP, and daily prednisone and hydroxychloroquine doses, the 3-month average for that measure was utilized for each subject. Data were censored after reaching any of the following events that could affect potassium or bicarbonate homeostasis: eGFR <60 ml/min per 1.73 m² or exposure to potassium supplements, diuretics (including potassium sparing diuretics), alkali therapy, or calcineurin inhibitors. However, data were not censored during angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) therapy because HK was noted to occur in the HK group despite use of these medications, which would be expected to bias the results to a negative outcome (i.e., no difference between HK and CON). Data during hospitalizations, pregnancy, and periods of Kidney Disease Improving Global Outcomes Stage I or greater AKI were also censored. Most recent serologic test results and renal histology was utilized for each subject, regardless of how far in the past these were obtained, given the infrequency of these tests.

Statistical Analysis
Descriptive analyses were used to summarize baseline characteristics of the subjects by study group. Continuous variables are presented as median (interquartile range) or mean with SD as appropriate and categorical variables are given as proportions. Continuous variables were compared across the three groups using ANOVA or Kruskal-Wallis testing as appropriate, and categorical variables were compared using Pearson’s chi-squared or Fisher’s exact testing. For paired comparisons of continuous variables between groups, the student’s t test was used. Statistical analysis was done using R statistical software version 3.6.1 (R Project for Statistical Computing).

Results
Characteristics of Study Participants
Baseline characteristics of the patients are summarized in Table 1. From the total population of 403 patients, we identified 20 patients with HK and 10 RTA comparators corresponding to a prevalence of 5% and 2.5%, respectively. The distribution of race differed between the three groups, with patients with HK more likely to be Black compared with CON (50% versus 20%, P=0.01).

Overall, immunosuppression regimens were similar between the groups. There were, however, differences noted in the 3-month average daily corticosteroid dose. Compared with HK, the CON group had higher rates of high-dose (≥40 mg/d) steroid exposure (5% versus 16%, respectively; P=0.02). Hydroxychloroquine exposure did not differ between the groups, nor did ACEi and ARB use.

Primary Outcomes
The HK group had a lower median serum potassium compared with CON and RTA subjects (3.26 versus 4.00 versus 3.75 mmol/L, respectively; P<0.001) (Figure 1). The RTA group had a lower median serum bicarbonate compared with HK and CON (19.4 mmol/L versus 26.0 mmol/L versus 25.0 mmol/L, respectively; P<0.001) and a higher median urine pH (6.67 versus 6.25 versus 6.00 P<0.01) (Figure 1). There were no statistically significant between-group differences between HK and CON in serum bicarbonate or urine pH.

Secondary Outcomes
Serum Magnesium Among the Groups
The median serum magnesium level was lower in HK compared with the CON and RTA groups (1.73 versus 2.00 versus 1.85 mg/dl, respectively; P=0.002); however, the median values for all three cohorts were in the normal range (1.7–2.2 mg/dl) (Figure 2). Given the known inhibition of intestinal magnesium absorption by proton pump inhibitors (PPI), rates of active therapy were compared across the groups but did not differ (Table 1). Similarly, PPI exposure did not influence the median serum magnesium within the HK group (1.75 versus 1.75 mg/dl with and without PPI, respectively; P=1.00).

Association Between Autoantibodies and Idiopathic HK
There were remarkable differences in the presence of specific autoantibodies among the groups (Figure 3). Only the HK group had a statistically greater proportion of seropositivity for anti-RNP than CON (84% versus 42%, respectively; P=0.003). Both HK and RTA had greater rates of seropositivity than CON for anti-Ro/SSA (79% versus 80%
versus 37%, respectively; P<0.001) but only RTA had a higher rate of seropositivity than CON for anti-La/SSB (40% versus 12%, respectively; P=0.05).

**Studies of Renal Potassium Handling in HK**

Among the 20 patients with idiopathic HK, nine had assessments of renal potassium handling during concurrent HK (Table 2). All demonstrated renal potassium wasting as revealed by urine potassium to creatinine ratio >15 mmol/g, transtubular potassium gradient >3, or 24-hour urine potassium >20 mmol/d. Six patients underwent testing for primary hyperaldosteronism, all with negative studies. All 20 patients ultimately required either potassium supplementation or mineralocorticoid antagonist therapy to maintain normokalaemia (data not shown), despite an 85% rate of ACEi or ARB use.

| Characteristic | Hypokalemia | Renal Tubular Acidosis | Control | P Value |
|---------------|-------------|------------------------|---------|---------|
| N             | 20          | 10                     | 90      |         |
| Female, n (%) | 19 (95)     | 10 (100)               | 75 (83) | 0.26    |
| Age at diagnosis, mean (SD) | 33.20±9.53 | 31.90±9.11             | 30.82±11.22 | 0.66 |
| Race, n (%)   |             |                        |         | 0.05    |
| Black         | 10 (50)     | 3 (30)                 | 18 (20) |         |
| Hispanic White| 8 (40)      | 6 (60)                 | 65 (72) |         |
| Other         | 2 (10)      | 1 (10)                 | 7 (8)   |         |
| SBP (mm Hg), median (IQR) | 118.50 (116.50–130.50) | 124.50 (117.75–132.25) | 121.00 (115.00–135.00) | 0.85 |
| DBP (mm Hg), median (IQR) | 77.00 (71.25–81.75) | 81.00 (76.50–87.00) | 75.00 (70.00–85.00) | 0.19 |
| Class of LN, n (%) | 2 (10) | 1 (10) | 4 (4) |         |
| Proteinuria without renal biopsy | 0 (0) | 1 (10) | 0 (0) |         |
| Protein/creatinine ratio (g/g), median (IQR) | 0.73 (0.17–1.54) | 0.38 (0.16–1.30) | 0.37 (0.13–1.88) | 0.98 |
| Current prednisone dose (mg/d), n (%) | 14 (70) | 8 (80) | 72 (80) | 0.02 |
| <20           | 1 (5)       | 0 (0)                  | 14 (16) |         |
| 20–39         | 5 (25)      | 2 (20)                 | 4 (4)   |         |
| ≥40           |             |                        |         |         |
| HCQ dose (mg/d), n (%) | 2 (10) | 1 (10) | 13 (14) | 0.53 |
| 0             | 1 (5)       | 0 (0)                  | 14 (16) |         |
| 200           | 1 (5)       | 0 (0)                  | 14 (16) |         |
| 300           |             |                        |         |         |
| 400           | 10 (50)     | 4 (40)                 | 14 (16) |         |
| Current immunosuppression, n (%) | 3 (15) | 2 (20) | 3 (3) | 0.22 |
| Azathioprine  |              |                        |         |         |
| CYC           | 2 (10)      | 0 (0)                  | 9 (10)  |         |
| MMF           | 8 (40)      | 4 (40)                 | 51 (51) |         |
| Other immunosuppressive | 1 (5) | 0 (0) | 5 (6) |         |
| No immunosuppression | 6 (30) | 4 (40) | 22 (24) |         |
| Current PPI therapy, n (%) | 9 (45) | 4 (40) | 33 (37) | 0.81 |
| Current ACEi/ARB therapy, n (%) | 17 (85) | 6 (60) | 56 (90) | 0.13 |
| History of kidney stone disease, n (%) | 0 (0) | 4 (40) | 1 (1) | <0.001 |
| History of overlap syndrome, n (%) | 1 (5) | 3 (30) | 7 (8) | 0.08 |
| Serum creatinine (mg/dl), median (IQR) | 0.74 (0.62–0.85) | 0.91 (0.78–1.03) | 0.73 (0.62–0.88) | 0.08 |
| Serum phosphate (mg/dl), median (IQR) | 3.25 (2.80–3.55) | 3.15 (2.54–3.50) | 3.40 (3.03–3.90) | 0.01 |
| Serum 25-OH vitamin D (ng/ml), median (IQR) | 17.4 (15.4–22.5) | 30.5 (24.6–38.78) | 23.8 (16.6–30.4) | 0.02 |
| Serum PTH (pg/ml), median (IQR) | 41.0 (24.0–55.8) | 31.0 (20.1–39.7) | 38.5 (27.1–56.9) | 0.26 |

The categorical outcome measures were compared between the three groups using chi-squared test or Fisher’s exact test, whereas the one-way ANOVA or Kruskal-Wallis test was used to compare continuous outcome measures. SBP, systolic BP; IQR, interquartile range; DBP, diastolic BP; LN, lupus nephritis; HCQ, hydroxychloroquine; CYC, cyclophosphamide; MMF, mycophenolate mofetil; PPI, proton pump inhibitor; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; PTH, parathyroid hormone.

*Overlap syndrome includes any of the following: rheumatoid arthritis, mixed connective tissue disease, Sjogren’s syndrome, interstitial lung disease, dermatomyositis.*

Other Notable Between-group Differences

The median serum phosphate was lower in the HK and RTA groups, compared with CON (3.25 versus 3.15 versus 3.40 mg/dl, respectively; P=0.01). The median 25-hydroxyvitamin D level was lower in HK compared with...
RTA and control (17.4 versus 30.5 versus 23.8 ng/ml; *P* < 0.02). There was, however, no significant difference in the median serum parathyroid hormone level (Table 1). We analyzed the groups for the occurrence of some expected comorbidities, including autoimmune overlap syndromes and kidney stones. Nephrolithiasis or nephrocalcinosis occurred in none of the HK cohort and in 1% of the CON, but was documented in 40% of the RTA cohort (*P* < 0.001). Overlap syndromes, defined as SLE with comitant Sjögren’s syndrome, mixed connective tissue disease, rheumatoid arthritis, interstitial lung disease, or dermatomyositis, occurred in a larger proportion of RTA subjects, but this did not reach statistical significance.

**Discussion**

This is the largest study in the literature to identify and describe a unique subset of adults with LN with idiopathic HK. The present analysis not only introduces the novel finding of idiopathic HK in LN, but it also begins to explore its mechanisms. These patients manifested clinically relevant HK, sometimes even <3 mmol/L, and universally eventually required either maintenance potassium supplementation or a potassium-sparing diuretic. This was despite 85% of them being on ACEi or ARB therapy, which tends to raise the serum potassium. The fact that potassium-sparing diuretics could ameliorate the HK was indicative that renal potassium loss was the cause of this phenomenon. Indeed, inappropriate potassium wasting was revealed in all nine HK subjects who had assessments of renal potassium handling (Table 2).

As a first step of phenotyping this phenomenon of idiopathic HK, we set out to distinguish it from the HK that can occur in association with distal RTA. Distal RTA as a cause of HK is well described in association with autoimmune conditions, including SLE (6). Rigorous evaluation by provocative testing may not uncommonly reveal renal acidification defects (1,7–9). However, clinically overt RTA in SLE and LN is rare. For instance, in a retrospective review of a large health system in Taiwan spanning more than two decades, Li et al. (10) identified only six patients with overt RTA in those with SLE, five of whom had LN. A recent cross-sectional study involving 108 patients with SLE in two hospitals in Turkey reported a significantly larger prevalence of overt RTA (17%). A little over half of the patients in this study had biopsy-proven LN (11). Differences in ethnicity and study methodology may explain the variation in the occurrence of overt RTA in our study and those cited. With ten patients (representing a prevalence of 3%), our study is one of the largest LN cohorts with clinically overt RTA that has been described. We defined patients with RTA as those with low serum bicarbonate and inappropriately high urine pH. Interestingly, we found that although some patients with RTA did exhibit HK, as a group their median serum potassium was not statistically different from CON. As expected, the occurrence of kidney stones or nephrocalcinosis, a key feature of distal RTA, was higher in the RTA group. In contrast, the HK group exhibited a lower median serum potassium and a serum bicarbonate and urine pH that was...
indistinguishable from CON, with no nephrocalcinosis or nephrolithiasis.

We next evaluated for differences in demographics, clinical status, and drug exposures between the HK, RTA, and CON groups as a further means to infer disease mechanisms. An obvious possible explanation for HK was from the mineralocorticoid effects of prednisone (12). This was ruled out by the fact that compared with HK, the CON group was on a higher 3-month average daily prednisone dose. Further, there were no meaningful differences in current immunosuppressive or hydroxychloroquine therapy.

The finding of idiopathic HK more commonly in Black patients is remarkable because of the known influence of race on LN. Black race is considered a risk factor for more severe LN, poor response to therapy, and mortality (13). Additionally, some studies suggest distinctive patterns of distribution in autoantibodies by race. In a study in Oklahoma, McCarty et al. (14) found the occurrence of anti-Ro/SSA, anti-RNP, and anti-Smith to predict severe and progressive LN in Black patients. However, a contemporaneous study on the basis of a cohort in Louisiana countered this finding (15). More recent studies from the United States and the United Kingdom have also found higher occurrences of anti-Ro/SSA, anti-RNP, and anti-Smith in Black patients with severe LN and Afro-Caribbean people with SLE (13,16). Although we do not report the racial distribution of these autoantibodies in our study, it is certainly remarkable that the higher rates of occurrence of anti-Ro/SSA and anti-RNP and Black race associate with HK in our population of LN.

Autoantibodies may have a pathogenic role in the renal manifestations of autoimmune disease. For instance, anti-dsDNA plays a role in the pathogenesis of LN and is associated with increased disease activity (17). Alternatively, autoantibodies may simply serve as disease markers. In Sjögren’s syndrome for example, some authors have reported an association between urine acidification defects and the presence of anti-La/SSB, although the pathogenic mechanism typically involves other autoantibodies directed to H-ATPase, anion-exchange protein, or carbonic anhydrase (18–22). The association of RTA in Sjögren’s syndrome with anti-La/SSB, however, is not a consistent finding (23). Ours is the first study to suggest an association between clinically overt RTA and the occurrence of anti-Ro/SSA and anti-La/SSB antibodies in LN. Furthermore, although the prevalence of anti-Ro/SSA, anti-La/SSB, and anti-RNP in our LN cohort is comparable to what is reported in the literature (24), the association of
idiopathic HK in LN with the presence of autoantibodies to Ro/SSA and RNP is a novel finding. Although there is clearly a trend that anti-RNP positivity was able to discriminate between the HK and the RTA that we describe in LN, this did not reach statistical significance. No prior reports have suggested an association between anti-Ro/SSA, anti-La/SSB, and anti-RNP with tubular transport defects in LN.

Although the HK cohort did not exhibit overt hypomagnesemia, the serum magnesium was significantly lower compared with the other two groups. The possibility of an intestinal malabsorption related to PPI therapy as an explanation for this finding is argued against given the similar 3-month average serum magnesium with and without PPI exposure in the HK group. Chronic diarrhea as an alternate cause was excluded by history. Hypomagnesemia is a known cause of HK through magnesium’s role in modulating renal outer medullary K⁺ channel conductance (25). The relatively lower serum magnesium in HK was not to the extent that one would expect it to cause hypokalemia. However, we recognize that serum magnesium may not always reflect total body magnesium content (26).

Combining the finding of a slightly lower serum magnesium in patients with HK together with the novel patterns of autoantibodies in this group perhaps provides further insight into the mechanisms. We hypothesize that an acquired immune-mediated impairment in distal convoluted tubule transport explains this phenotype, albeit the defect must be incomplete. Others have described an acquired Gitelman’s syndrome–like phenotype in the setting of autoimmunity. Most of these reports have been in patients with Sjögren’s syndrome, although associations with systemic sclerosis and SLE have also been reported (27–32). To rigorously prove the hypothesis that this is an acquired form of Gitelman’s syndrome, we would need to detect an autoantibody to sodium-chloride cotransporter, and show there was a deficiency of this transporter in the distal convoluted tubule in the absence of SLC12A3 mutations.

Limitations of the study arise from its retrospective design. Therefore, we could not perform rigorous studies of renal potassium and magnesium handling or provocative testing to conclusively rule out the presence of RTA in patients with idiopathic HK. Further studies including formal assessments of renal electrolyte handling, genotyping, and immunohistochemistry for renal tubular transport proteins are needed to definitively describe this phenomenon. Another limitation of the analysis is the stringent criteria that were used to define the HK and RTA groups. This may have led to the underestimation of the occurrence of idiopathic HK and RTA. However, this study also has several unique strengths. The large size of our population of patients with LN has afforded us the opportunity to describe this somewhat uncommon phenomenon of idiopathic HK and find meaningful differences from the larger group. Our data are also the largest report from North America on overt RTA in LN to date. Finally, we are also the first to report on the association of autoantibodies with distinct tubular transport defects in LN.

From our large population of patients with LN, we have reported on a novel finding of idiopathic HK and explored its clinical features and autoantibody associations. Idio-pathic HK is a clinically relevant phenomenon in LN. Although we offer a preliminary hypothesis for the pathophysiology of this entity, further research is required to define its mechanisms.

Disclosures
All authors have nothing to disclose.

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Author Contributions
E. Adomako, S. Bilal, and K. Sambandam conceptualized the study; E. Adomako, S. Bilal, A. Malik, and K. Sambandam were responsible for data curation; E. Adomako, Y.-I. Liu, K. Sambandam, S. Shastri, and P. Van Buren were responsible for formal analysis; K. Sambandam was responsible for funding acquisition; E. Adomako, S. Bilal, Y.-I. Liu, A. Malik, K. Sambandam, S. Shastri,
and P. Van Buren were responsible for investigation; E. Adakomo and K. Sambandam were responsible for methodology; K. Sambandam was responsible for project administration, resources and provided supervision; Y.-I. Liu was responsible for the software; E. Adakomo and K. Sambandam wrote the original draft; E. Adakomo, K. Sambandam, S. Shastri, and P. Van Buren reviewed and edited the manuscript.

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