Comparison of fractional excretion of electrolytes in patients at different stages of chronic kidney disease

A cross-sectional study

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Abstract

Kidney handling of electrolytes varies in different stages of chronic kidney disease (CKD). Diabetes mellitus (DM) plays an important role in CKD. Fractional excretion (FE) is an important means in clinical practice. The relationship between FE of electrolytes in patients at different stages of CKD is worth further investigating.

We designed a cross-sectional study in 1 teaching hospital, consecutive CKD patients were enrolled between February 2016 and January 2017. Including clinical demographic features, laboratory examination including spot urine electrolytes, blood biochemistries, and relevant medications were determined.

A total of 762 CKD patients completed the study. Of these, 218 (28.6%) had DM. Participants were grouped according to estimated glomerular filtration rate into 7 categories: hyperfiltration (HF), CKD1, CKD2, CKD3a, CKD3b, CKD4, and CKD5. Groups HF, CKD1, 2, 3a, 3b, 4 and 5 contained 83, 143, 192, 94, 82, 82, and 86 patients, respectively. FE of electrolytes tended to increase along with the decline of renal function (CKD1–CKD5) ($P<.001$). The relationship was similar between the DM and non-DM groups. Diabetic patients demonstrated higher FE of magnesium compared with non-DM subjects at CKD2 and CKD5 ($P<.05$).

CKD patients showed a progressive increase in the FE of electrolytes; FE of magnesium seemed to increase more among diabetic patients with CKD, and could be a potential predictor of CKD progression.

Abbreviations: ACR = albumin-to-creatinine ratio, BMI = body mass index, CKD = chronic kidney disease, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, FE = fractional excretion, FEX = fractional excretion of electrolytes, FGF-23 = fibroblast growth factor 23, HF = hyperfiltration, PTH = parathyroid hormone, SCr = serum creatinine, TAL = thick ascending loop of Henle, U = urine, UA = uric acid.

Keywords: chronic kidney disease, fractional excretion, urine biochemistry, urine electrolytes

1. Introduction

The kidney plays a crucial role in the regulation of electrolyte and acid–base homeostasis.[1] To investigate the relationship between blood and urine biochemical changes in patients with kidney disease and electrolyte disorders, it is preferable to perform fraction excretion rate of electrolytes (FEX). The assessment of urine electrolyte excretion rate with either a 24-hour or spot urine collection is a recognized first step.[2–3] Spot
2. Materials and methods

2.1. Study population and data collection

The cross-sectional study protocol was approved by the Ethics Committee on Human Studies at Tri-Service General Hospital, Taipei, Taiwan. All patients were consecutively enrolled from February 2016 to January 2018, with a diagnosis of CKD according to the criteria outlined in Kidney Disease: Improving Global Outcomes. In this study, all CKD patients received their regular medications such as cardiovascular drugs and antidiabetic drugs. Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease Study Group equation in this study: eGFR = 186 × Creatinine^{-1.154} × Age^{-0.203} (× 1 if male, × 0.742 if female). Albuminuria, especially urine albumin-to-creatinine ratio [ACR] > 30 mg/g, is also considered to be a marker of CKD despite being within the normal eGFR range. Each CKD patient in our study had been classified into 1 of 7 groups according to eGFR and [ACR]; these groups were hyperfiltration (HF) (eGFR > 125 mL/min per 1.73 m²), and [ACR] > 30 mg/g), CKD1 (eGFR 90–125 mL/min per 1.73 m²), CKD2 (eGFR 60–89 mL/min per 1.73 m²), CKD3a (eGFR 45–59 mL/min per 1.73 m²), CKD3b (eGFR 30–44 mL/min per 1.73 m²), CKD4 (eGFR 15–29 mL/min per 1.73 m²), and CKD5 (eGFR < 15 mL/min per 1.73 m² or treatment by dialysis). Descriptive features, biochemical data including available blood and spot urine sample results (uric acid, sodium, potassium, chloride, calcium, phosphate, and magnesium), and relevant medications were investigated. Including nephrologists, dietitians, and nurses were involved in this study. Only CKD patients on the educational program for CKD with a fixed diet regimen were included. Patients with definite diagnosis of history of periodic paralysis, Bartter syndrome, Gitelman syndrome, and renal tubular acidosis were not involved in this study. These comorbidities factors may have stronger effects on electrolytes excretion than CKD. To avoid other potential confounders and focus on the target population of stable CKD patients, we excluded patients with acute kidney injury, massive hematuria, renal transplant, dialysis treatment, bladder irrigation, prior creation of a neobladder, pregnancy, obstructive uropathy, and age younger than 18. Medical records including patient characteristics, clinical presentations, laboratory values, and use of diuretic drugs were reviewed.

2.2. Data processing and analysis

The following clinical data were analyzed: gender, age, body mass index (BMI), clinical biochemistry, medications including diuretics, and agents for treating hyperuricemia. Particular attention was given to comparing the laboratory data including serum creatinine (SCr), blood urea nitrogen, hemoglobin, electrolytes [sodium (Na+), potassium (K+), chloride (Cl−), calcium (Ca2+), phosphorus (P), magnesium (Mg2+)], biochemistry [uric acid (UA), albumin, total bilirubin], urine biochemistry [urine creatinine (UCr), urine Na+ (UNa), urine K+ (UK), urine Ca2+ (UCa), urine phosphorus, urine Mg2+, and urine uric acid]. Samples of blood and spot urine were simultaneously collected for measurement. Blood and urine biochemistries were determined by automated methods (AU 5800 chemistry analyzer; Olympus, Tokyo, Japan). We used the formula for fraction excretion of electrolytes as FEX (%) = [Urine X (mmol/L, or mg/dL) × serum creatinine (mg/dL)/serum X (mmol/L, or mg/dL) × urine creatinine (mg/dL)] × 100 (%), where X stands for the electrolyte. Thus, the recorded measures included FEUA, FENa, FECa, FEP, and FEMg = [Urine Mg (mg/dL) × serum creatinine (mg/dL)/serum Mg2+ (mg/dL) × urine creatinine (mg/dL)] × 100 (%), where X stands for the electrolyte. Albuminuria is defined as albumin excretion rate of albumin (AER) > 30 mg/g, or urine albumin-to-creatinine ratio (ACR) > 30 mg/g. According to the criteria outlined in Kidney Disease: Improving Global Outcomes, we proposed the classification into 7 groups of different stages of CKD.

2.3. Statistical analysis

Descriptive statistical of categorical variables were reported as numbers and percentage, while continuous variable were expressed as mean ± standard deviation. Patients’ spot urine data were examined with ANOVA in the trend of CKD stage. Furthermore, we divided each CKD stage groups into DM and non-DM, and examined with independent t test. All P values were 2-sided and P < .05 was considered statistically significant. All statistical analyses were performed with IBM SPSS statistical software version 22 for Windows (IBM Corp, Armonk, NY).

3. Results

3.1. Patients’ characteristics

A total of 772 CKD patients were initially included in this study. We then excluded 4 and 6 patients due to missing data on SCr and UCr in this study. Thus a total of 762 patients met the eligibility criteria (Fig. 1). The mean age was 60.94 ± 18.90 years, and 453 patients were male (59.4%). The clinical characteristics of these 762 patients were as follows: 218 patients (28.6%) with DM, 65 (8.5%) with gout, 93 (12.2%) with hyperlipidemia, 341 (44.8%) with hypertension, 158 (20.7%) with cardiovascular disease, 47 (6.2%) with congestive heart failure. There were 129 patients (16.9%) using diuretics. There were 89 patients (11.7%) receiving UA lowering agents, 7 patients (0.9%) taking allopurinol, 50 patients (6.6%) on febuxostat, and 32 patients (4.2%) taking benzbromarone (Table 1).

3.2. Blood and urine biochemistry

Table 2 presents the distribution of clinical laboratory data. These 762 patients had a mean SCr of 1.85 ± 2.18 mg/dL, mean eGFR of 70.11 ± 48.07 mL/min/1.73 m², mean UA of 6.51 ± 2.82 mg/dL, mean Na+ of 136.60 mmol/L, mean K+ of 3.90 ± 0.81 mmol/L.
mean Cl- of 102.37 ± 9.71 mmol/L, mean Ca²⁺ of 8.97 ± 0.94 mg/dL, mean P of 3.57 ± 1.32 mg/dL, and mean Mg²⁺ of 2.07 ± 0.42 mg/dL. Urine biochemistry revealed a mean UCr of 94.16 ± 80.48 mg/dL, mean urine uric acid of 36.53 ± 26.08 mg/dL, mean UNa of 71.01 ± 40.52 mmol/L, mean UK of 31.11 ± 22.05 mmol/L, mean urine Cl- of 74.82 ± 44.09, mean urine Ca²⁺ of 6.91 ± 6.95 mg/dL, mean UP of 38.46 ± 33.05 mg/dL, and mean urine Mg²⁺ of 5.07 ± 3.71 mg/dL. FEX analysis revealed a mean FEUA of 11.3%, mean FENa of 2.07%, mean FEK of 20.59%, mean FECl of 2.71%, mean FECa of 1.71%, mean FEP of 23.54%, and mean FEMg of

Figure 1. Cross-sectional study design.

| Table 1 | Demographic characteristics in patients at different stages of CKD. |
|---------|-------------------------------------------------------------------|
|         | Total | Hyperfiltration | CKD1 | CKD2 | CKD3a | CKD3b | CKD4 | CKD5 |
|         | n = 762 | n = 83 | n = 143 | n = 192 | n = 94 | n = 82 | n = 82 | n = 86 |
| Age     | 60.94 ± 18.90 | 52.90 ± 24.01 | 51.55 ± 19.06 | 60.23 ± 15.81 | 67.76 ± 16.48 | 67.76 ± 17.84 | 69.91 ± 15.43 | 64.11 ± 16.14 |
| Body mass index (BMI) | 23.75 ± 4.34 | 22.70 ± 4.46 | 23.51 ± 3.94 | 24.58 ± 4.24 | 23.65 ± 4.18 | 24.31 ± 5.10 | 23.15 ± 3.89 | 23.35 ± 4.77 |
| Gender  | Male | 453 (59.4) | 46 (55.4) | 92 (64.3) | 122 (63.5) | 59 (62.8) | 52 (63.4) | 36 (43.9) | 46 (53.5) |
|         | Female | 309 (40.6) | 37 (44.6) | 51 (35.7) | 70 (36.5) | 35 (37.2) | 30 (36.6) | 46 (56.1) | 40 (46.5) |
| Comorbidity | Diabetes mellitus | 218 (28.6) | 12 (14.5) | 22 (15.4) | 47 (24.5) | 36 (38.3) | 36 (43.9) | 30 (36.6) | 35 (40.7) |
|         | Gout | 65 (8.5) | 2 (2.4) | 2 (1.4) | 15 (7.8) | 8 (8.5) | 10 (12.2) | 11 (13.4) | 17 (19.8) |
|         | Hypertension | 93 (12.2) | 5 (6.0) | 18 (12.6) | 29 (15.1) | 12 (12.8) | 8 (9.8) | 8 (9.8) | 13 (15.1) |
|         | Cardiovascular disease | 341 (44.8) | 21 (25.3) | 40 (28.0) | 77 (40.1) | 53 (56.4) | 49 (59.8) | 43 (52.4) | 58 (67.4) |
|         | Coronary artery disease | 158 (20.7) | 7 (8.4) | 16 (11.2) | 25 (13.0) | 29 (30.9) | 31 (37.8) | 21 (25.6) | 29 (33.7) |
|         | Congestive heart failure | 93 (12.2) | 8 (9.6) | 14 (9.8) | 16 (8.3) | 17 (18.1) | 18 (22.0) | 7 (8.5) | 13 (15.1) |
|         | Atrial fibrillation | 42 (5.5) | 6 (7.2) | 4 (2.8) | 7 (3.6) | 10 (10.6) | 5 (6.1) | 7 (8.5) | 3 (3.5) |
|         | Valvular heart disease | 33 (4.3) | 4 (4.8) | 0 | 5 (2.6) | 3 (3.2) | 5 (6.1) | 10 (12.2) | 6 (7.0) |
|         | Human immunodeficiency virus | 17 (2.2) | 2 (2.4) | 9 (6.3) | 4 (2.1) | 1 (1.1) | 0 | 1 (1.2) | 0 |
| Medications | Diuretics | 129 (16.9) | 9 (10.8) | 17 (11.9) | 21 (10.9) | 15 (16.0) | 14 (17.1) | 23 (28.0) | 30 (34.9) |
|         | Uric acid lowering agents | 89 (11.7) | 0 | 6 (4.2) | 19 (9.9) | 8 (8.5) | 15 (18.3) | 18 (22.0) | 23 (26.7) |
|         | Allopurinol | 7 (0.9) | 0 | 0 | 3 (1.6) | 1 (1.1) | 2 (2.4) | 0 | 1 (1.2) |
|         | Febuxostat | 50 (6.6) | 0 | 2 (1.4) | 4 (2.1) | 5 (5.3) | 8 (9.8) | 14 (17.1) | 17 (19.8) |
|         | Benzbromarone | 32 (4.2) | 0 | 4 (2.8) | 12 (6.2) | 2 (2.1) | 5 (6.1) | 4 (4.9) | 5 (5.8) |

Values are expressed numbers (percentages) or mean ± standard deviation.
6.6%. FEUA and FECA, which reached its nadir in CKD2, but FEX results tended to increase from CKD1 to CKD5 and had statistical significance ($P < .001$) (Table 2). To eliminate the effects of diuretics, we further excluded the 129 patients (16.9%) who were using diuretics. Our analysis of the remaining 633 patients not using diuretics revealed similar trends in FEX results (Fig. 2).

3.3. Differences in FEX among CKD patients with and without diabetes mellitus (DM)

We further analyzed the remaining 633 patients for any differences in FEX between diabetic ($n=161$) and nondiabetic ($n=472$) patients. No obvious differences in FEX between the 2 groups were noted, but FEMg had a relatively higher value in diabetic patients. And this difference reached significance in CKD2 and CKD5 ($P < .05$) (Fig. 3).

4. Discussion

In this cross-sectional, we investigated the correlations of renal excretion of different electrolytes in patients at different stages of CKD. The major significant findings of this study were as follows:

The existence of certain differences in FEX results associated with different stages of CKD was established. Values of FEX for most electrolytes tended to increase during progression through the CKD stages (i.e., values were lowest in CKD1 and highest in CKD5); DM and non-DM patients had some differences in the FEX results associated with the different stages of CKD. The overall trends in FEX during CKD progression were the same in DM and non-DM patients. In the following subsections, our findings regarding each electrolyte and the major 2 findings in the study will be reviewed and discussed.

4.1. Uric acid (UA) handling in CKD

In this study, we observed that uricosuria was higher in stages HF and CKD1 than in CKD2, which may be attributed to glomerular hyperfiltration. The cause of the drop in FEUA in CKD2 and CKD3b still needs to be determined; we speculated, however, that possible causes may include impaired tubular secretion, increased tubular resorption, or a combination of these. Kannangara et al. [20] have suggested that measuring FEUA through spot urine sampling could overcome some of the uncertainties related to the inconvenience and frequent unreliability of 24-hour urine collection.
FEUA is approximately independent of glomerular kidney function for subjects with reasonable renal function. The kidney plays an important role in the regulation of UA by reabsorbing around 90% of filtration and is also responsible for 60% to 70% of total body UA excretion. In adult humans, FEUA is around 10% (range 7% to 12%); this figure is usually higher in women than in men. FEUA is higher in children, averaging 35% in newborns, 13% to 26% in children less than 1 year old, and then decreasing progressively to adult levels in spite of increasing UA filtered load.[21–23] Renal UA handling involves a complex interplay of absorptive and secretory transport pathways, primarily in the renal proximal tubule; this process is mediated by incompletely understood molecular mechanisms. It is possible that impairment of the absorptive pathways in CKD3b results in the observed increase of FEUA. FEUA has been shown to remain quite stable, increasing only marginally even when GFR is down to 30 mL/min.[21]

4.2. Sodium (Na⁺), chloride (Cl⁻), and potassium (K⁺) handling in CKD

In our study, we observed a relatively high FENa in the HF group compared with the CKD1 group. Salt wasting in renal disease results from the inability of the distal nephron either to increase its sodium absorptive capacity proportionate to an increase in sodium delivery out of the proximal nephron or to generate maximal concentration gradients between tubular fluid and blood.[24–26] The relatively high urine Na⁺ in HF associated with CKD has been proposed to be due to increased osmotic load per nephron. CKD patients typically maintain serum Na⁺ balance until late stages of the disease.[27,28] The mechanisms suggested to be involved in further urine Na⁺ loss in CKD include osmotic diuresis, tubular injury, and inability to acutely shut off natriuretic forces. Urine Na⁺ excretion is typically coupled with urine Cl⁻. However, urine Na⁺ and Cl⁻ excretion are usually both high and coupled in CKD patients.[27–29]

We found in the present study that FEK tends to increase during progression through stages CKD1 to 5. Serum K⁺ level reached a peak at CKD5. Previous studies have revealed that urine K⁺ excretion ability is diminished due to decreased renal mass, administration of renin-angiotensin-aldosterone system inhibitors, and the presence of DM.[12,30,31] Urine K⁺ excretion depends on aldosterone action, which results from adequate sodium delivery to the distal tubule and the cortical collecting duct. Urine flow in residual nephrons is adaptively enhanced due to a decrease in tubular Na⁺ reabsorption; this adaptive mechanism can further contribute to the preservation of urine K⁺ excretion at CKD3b, even with a significant decrease in the urine K⁺ concentration.[31,32]

Figure 3. Comparison of fractional excretion (FE) of electrolytes among CKD patients with (n = 161) and without (n = 472) diabetes mellitus (DM). Differences were compared using the independent t test, and * presented P < .05. CKD = chronic kidney disease.
In the early stages of CKD, serum P remains in the normal range due to an increase in urine P excretion by FGF-23. In addition, hyperparathyroidism secondary to CKD leads to inhibition of urine P reabsorption and consequently to an increase in FEP. Evenepoel et al. have demonstrated higher FEP in patients with both high serum FGF-23 and high PTH level. Together, PTH and FGF-23 could promote urine P wasting through internalization of sodium phosphate cotransporters IIa and IIc from the proximal tubular apical membrane, which may explain the observed increase in FEP. Metabolic acidosis per se can stimulate phosphaturia, which helps remove acid from the bloodstream. Overt phosphaturia, however, can contribute to renal tubular damage and renal fibrosis through the formation of calcium phosphate crystals via oxidative stress. Urine P excretion per creatinine clearance could be a useful indicator that early
intervention for phosphate restriction is needed in CKD patients.\textsuperscript{[41]}

4.4. Magnesium (Mg$^{2+}$) handling in CKD

In our study we observed a tendency toward decreased urine Mg$^{2+}$ concentration and increased FEMg along with CKD progression. FEMg is higher in HF than in CKD1. The increased filtrated load of Mg$^{2+}$ per nephron via a paracellular pathway is aided by a chemical gradient generated by sodium gradient-driven water transport that increases intraluminal magnesium as well as lumen positivity.\textsuperscript{[35]}

PTH could affect the renal handling of magnesium at the distal convoluted tubule in a fashion similar to its effect on calcium, so it is possible that the increase in filtered Mg$^{2+}$ per nephron has a greater effect on FEMg and overshadows the effect of PTH.\textsuperscript{[42]} Futrakul et al investigated patients with nephrotic syndrome in search of the most sensitive markers of tubular dysfunction. FEMg is considered a sensitive index for the detection of early abnormality of tubular structure and function. The improvement of renal perfusion and function after recovery from renal injury is associated with increased GFR and decreased FEMg.\textsuperscript{[43–45]}

Different segments of the nephron have different propensities to ischemia. The straight proximal tubule and the thick ascending loop of Henle (TAL) are the 2 segments that are most sensitive to ischemia. Urine Mg$^{2+}$ reabsorption in the TAL and that in the distal tubule are load-dependent. The major portion of urine Mg$^{2+}$ reabsorption occurs in TAL, FEMg is considered a marker of intact tubulointerstitial structure in patients with glomerular disease. FEMg could be useful as an index to diagnose early-stage tubular dysfunction or as an indicator of residual tubular damage. FEMg can potentially reflect not only the presence or absence of tubulointerstitial fibrosis but also the severity of CKD.\textsuperscript{[43–46]}

Diabetic glomerulopathy is common in the early stages of diabetic nephropathy; however, tubulointerstitial fibrosis may be prominent in advanced diseases.\textsuperscript{[47]} In our study, FEMg increased more markedly among diabetic patients, suggesting that diabetic patients might have more tubulointerstitial disorder.

To the best of our knowledge, this is the first report of large populations to investigate the correlations of renal excretion of different electrolytes in patients at different stages of CKD. However, there are some limitations of this study. First, we did not collect the 24-hour urine samples to assess FEX. Nevertheless, 24-hour urine collection is frequently limited by patients’ adherence and may have some potential mistakes in clinical practice. Second, the values of FEX may have been influenced by medications such as antihypertensive drugs, bicarbonates and polystyrene sulfonate, acid-base, volume status, blood biochemistry, and several physiologic factors including age, gender, nutrition, exercise, timing of specimen collection, diet, and various diseases. This may be another limitation in this study.

In conclusion, we investigated the relationship between urine electrolytes and FEX at different stages of CKD. FEX tended to increase along with the reduction of GFR, and the trends observed over the course of CKD progression were similar in DM and non-DM patients. DM patients might have higher FEMg compared with non-DM subjects. FEMg could be a potential predictor of CKD progression.

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References

\textsuperscript{[1]} Dhondup T, Qian Q. Electrolyte and acid-base disorders in chronic kidney disease and end-stage kidney failure. Blood Purif 2017;45:179–88.

\textsuperscript{[2]} Tanaka T, Okamura T, Miura K, et al. A simple method to estimate population 24-h urinary salt potassium excretion using a casual urine specimen. J Hum Hypertens 2002;16:97–103.

\textsuperscript{[3]} Brown JJ, Dyer AR, Chan Q, et al. Group, Estimating 24-hour urinary sodium excretion from casual urinary sodium concentrations in Western populations: the INTERSALT study. Am J Epidemiol 2013;177:1180–92.

\textsuperscript{[4]} Zhang T, Chang X, Liu W, et al. Comparison of sodium, potassium, calcium, magnesium, zinc, copper and iron concentrations of elements in 24-hr urine and spot urine in hypertensive patients with healthy renal function. J Trace Elem Med Biol 2017;44:104–9.

\textsuperscript{[5]} Mill JG, Rodrigues SL, Baldo MP, et al. Validation study of the Tanaka and Kawasaki equations to estimate the daily sodium excretion by a spot urine sample. Rev Bras Epidemiol 2015;18(suppl 2):224–37.

\textsuperscript{[6]} Ilch JZ, Blanusa M, Orlic ZC, et al. Comparison of calcium, magnesium, sodium, potassium, zinc, and creatinine concentration in 24-h and spot urine samples in women. Clin Chem Lab Med 2009;47:216–21.

\textsuperscript{[7]} Wu KL, Cheng CJ, Sung CC, et al. Identification of the causes for chronic hypokalemia for chronic hypokalemia: importance of urinary sodium and chloride excretion. Am J Med 2017;130:846–55.

\textsuperscript{[8]} Li F, Guo H, Zou J, et al. The association of urinary sodium and potassium with renal acidosis in patients with chronic kidney disease. Kidney Blood Press Res 2018;43:3110–21.

\textsuperscript{[9]} Walsh PR, Tse Y, Ashton E, et al. Clinical and diagnostic features of Bartter and Gitelman syndromes. Clin J Kidney J 2018;11:902–9.

\textsuperscript{[10]} Xu H, Hashem A, Witas A, et al. Fibroblast growth factor 23 is associated with fractional excretion of sodium in patients with chronic kidney disease. Nephrol Dial Transplant 2019;34:2051–7.

\textsuperscript{[11]} Jiménez Villodres M, García Gutiérrez G, García Frías P, et al. Fractional excretion of phosphorus and vascular calcification in stage 3 chronic kidney disease. J Investig Med 2019;67:674–80.

\textsuperscript{[12]} Ueda Y, Oosawara S, Ito K, et al. Changes in urinary potassium excretion in patients with chronic kidney disease. Kidney Clin Pract 2016;35:78–83.

\textsuperscript{[13]} Hameda M, Utsunomiya K, Koya D, et al. A new Classification of Diabetic Nephropathy 2014: a report from Joint Committee on Diabetic Nephropathy. J Diabetes Invest 2015;6:242–6.

\textsuperscript{[14]} Isakova T, Nikolov TL, Denburg M, et al. KDOQI US Commentary on the 2017 KDIGO Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease– Mineral and Bone Disorder (CKD-MBD). Am J Kidney Dis 2017;70:737–51.
[15] Levey AS, Coresh J, Balk E, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med 2003;139:137–47.

[16] Vassalotti JA, Centor R, Turner BJ, et al. Practical approach to detection and management of chronic kidney disease for the primary care clinician. Am J Med 2016;126:135–62.

[17] Phelps KR, Lieberman RL. Fractional excretion and reabsorption in chronic kidney disease. Clin Nephrol 2012;77:484–90.

[18] Kroll MH, Elin RJ. Relationships between magnesium and protein concentrations in serum. Clin Chem 1983;31:244–6.

[19] Mateu-de Antonio J. New predictive equations for serum ionized calcium. Clin Chem 1985;31:244–6.

[20] Bobulescu IA, Moe OW. Renal transport of uric acid: evolving concepts and uncertainties. Adv Chronic Kidney Dis 2012;19:358–71.

[21] Maesaka JK, Fishbane S. Regulation of renal urate excretion: a critical review. Am J Kidney Dis 1998;32:917–33.

[22] Sorensen LB, Levinson DJ. Origin and extrarenal elimination of uric acid in man. Nephron 1975;14:7–20.

[23] Combs S, Berl T. Dysnatremias in patients with kidney disease. Am J Med 2016;126:153–76.

[24] Coleman AJ, Arias M, Carter NW, et al. The mechanism of salt wastage in chronic renal disease. J Clin Invest 1966;45:1116–25.

[25] Brosius FC, Lau K. Low fractional excretion of sodium in acute renal failure: role of timing of the test and ischemia. Am J Nephrol 1986;6:450–7.

[26] Zarich S, Fang LS, Diamond JR. Fractional excretion of sodium. Exceptions to its diagnostic value. Arch Intern Med 1985;145:108–12.

[27] Combs S, Berl T. Dysnatremias in patients with kidney disease. Am J Kidney Dis 2014;63:294–303.

[28] Weir MR, Rolfe M. Potassium homeostasis and renin-angiotensin-aldosterone system inhibitors. Clin J Am Soc Nephrol 2010;5:531–48.

[29] Llamas G, Liberopoulos E, Barkas F, et al. Diabetes mellitus and electrolyte disorders. World J Clin Cases 2014;2:488–96.

[30] Kamel KS, Quagggin S, Scheich A, et al. Disorders of potassium homeostasis: an approach based on pathophysiology. Am J Kidney Dis 1994;24:597–613.

[31] Komaba H, Fukagawa M. FGF23–parathyroid interaction: implications in chronic kidney disease. Kidney Int 2010;77:292–8.

[32] Isakova T, Wahl P, Vargas GS, et al. Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. Kidney Int 2011;79:1370–8.

[33] Blaine J, Chonchol M, Levi M. Renal control of calcium, phosphate, and magnesium homeostasis. Clin J Am Soc Nephrol 2015;10:1257–72.

[34] Alexander RT, Cordat E, Chambrey R, et al. Acidosis and urinary calcium excretion: insights from genetic disorders. J Am Soc Nephrol 2016;27:3511–20.

[35] Oliveira RB, Cancela AL, Gracioli FG, et al. Early control of PTH and FGF23 in normophosphatemic CKD patients: a new target in CKD-MBD therapy? Clin J Am Soc Nephrol 2010;5:286–91.

[36] Kuro-O M. A phosphate-centric paradigm for pathophysiology and therapy of chronic kidney disease. Kidney Int Suppl 2013;3:420–6.

[37] Evenepoel P, Meijers B, Vaeve L, et al. Fibroblast growth factor-23 in early chronic kidney disease: additional support in favor of a phosphate-centric paradigm for the pathogenesis of secondary hyperparathyroidism. Clin J Am Soc Nephrol 2010;5:1268–76.

[38] Nitta K, Nagano N, Tsuchiya K. Fibroblast growth factor 23/Klotho axis and phosphate homeostasis. Clin J Am Soc Nephrol 2015;10:1257–72.

[39] Kawasaki T, Maeda Y, Matsuki H, et al. Urinary phosphorus excretion per creatinine clearance as a prognostic marker for progression of chronic kidney disease: a retrospective cohort study. BMC Nephrol 2015;16:116.

[40] Dai LJ, Ritchie G, Kerstan D, et al. Magnesium transport in the renal distal convoluted tubule. Physiol Rev 2001;81:51–84.

[41] Furrakul P, Yenrudi S, Futrakul N, et al. Tubular function and magnesium transport in the renal distal convoluted tubule. Physiol Rev 2001;81:51–84.

[42] Mai A, Ali I, Chaudhry K, et al. Magnesium and kidney function parameters in nondiabetic chronic kidney disease. Clin Nephrol 2012;77:484–90.

[43] Isakova T, Wahl P, Vargas GS, et al. Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. Kidney Int 2011;79:1370–8.

[44] Blaine J, Chonchol M, Levi M. Renal control of calcium, phosphate, and magnesium homeostasis. Clin J Am Soc Nephrol 2015;10:1257–72.

[45] Alexander RT, Cordat E, Chambrey R, et al. Acidosis and urinary calcium excretion: insights from genetic disorders. J Am Soc Nephrol 2016;27:3511–20.

[46] Oliveira RB, Cancela AL, Gracioli FG, et al. Early control of PTH and FGF23 in normophosphatemic CKD patients: a new target in CKD-MBD therapy? Clin J Am Soc Nephrol 2010;5:286–91.

[47] Kuro-O M. A phosphate-centric paradigm for pathophysiology and therapy of chronic kidney disease. Kidney Int Suppl 2013;3:420–6.

[48] Evenepoel P, Meijers B, Vaeve L, et al. Fibroblast growth factor-23 in early chronic kidney disease: additional support in favor of a phosphate-centric paradigm for the pathogenesis of secondary hyperparathyroidism. Clin J Am Soc Nephrol 2010;5:1268–76.

[49] Nitta K, Nagano N, Tsuchiya K. Fibroblast growth factor 23/Klotho axis and phosphate homeostasis. Clin J Am Soc Nephrol 2015;10:1257–72.

[50] Kawasaki T, Maeda Y, Matsuki H, et al. Urinary phosphorus excretion per creatinine clearance as a prognostic marker for progression of chronic kidney disease: a retrospective cohort study. BMC Nephrol 2015;16:116.