Diurnal variation of magnesium and the mineral metabolism in patients with chronic kidney disease

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Abstract

Increasing levels of magnesium in blood are associated with reduced risk of cardiovascular disease in chronic kidney disease (CKD). Magnesium supplementation may reduce the progression of vascular calcification in CKD. The diurnal pattern and effect of fasting on magnesium in blood and urine in CKD is unknown, and knowledge of this may influence management of magnesium supplementation.

We included ten patients with CKD stage four without diabetes mellitus and ten healthy controls. Participants were admitted to our hospital ward for a 24-h study period. Blood and urine samples were collected in a non-fasting state at 8 o’clock in the morning and every third hour hereafter until the final samples in a fasting state at 8 o’clock the following morning.

We found no diurnal variation in plasma magnesium (p = 0.097) in either group, but a significant diurnal variation in urinary excretion of magnesium (p = 0.044) in both CKD and healthy controls with no significant interaction between the two groups, and thus no suggestion that CKD affects diurnal variation of plasma magnesium or urinary magnesium excretion. The levels of plasma magnesium were not significantly different in fasting and non-fasting conditions.

Magnesium in plasma does not display a significant diurnal variation and can be measured at any time of day and in both fasting and non-fasting conditions. Urinary magnesium excretion displays diurnal variation, which is likely related to increased uptake of magnesium during meals and helps maintain a stable concentration of magnesium in blood.

1. Introduction

Disturbances in mineral and bone metabolism in chronic kidney disease (CKD-MBD) are associated with vascular calcification and stiffness, myocardial hypertrophy, and bone disease, and treatment of these disturbances are believed to prevent cardiovascular events and bone fractures. While the traditional focus of CKD-MBD has been treatment with phosphate binders, activated vitamin D analogues and calcimetics, recent research has highlighted a J-shaped curve which demonstrates that a moderately increased level of serum magnesium (Mg) is associated with a lower risk of cardiovascular events and fractures (Sakaguchi et al., 2014; Negrea et al., 2021; Sakaguchi et al., 2018).

These associations are believed to be related to an inhibitory effect of Mg on vascular calcification (ter Braake et al., 2018; ter Braake et al., 2020; ter Braake et al., 2020a) and an as yet unknown effect of Mg on bone turnover (Diaz-Tocados et al., 2017) (ter Braake et al., 2020b). Therefore, monitoring of Mg in blood and supplementation with Mg may become important parts of the future management of CKD-MBD. Little is known of the diurnal pattern of Mg in chronic kidney disease (CKD). If any diurnal variation exists, this may be important for both treatment decisions and monitoring of therapy.

To further investigate this, we conducted a prospective observational study to assess the diurnal pattern of plasma Mg and urine Mg in CKD and healthy controls, and to compare this with other minerals and
hormones related to CKD-MBD.

2. Material and methods

2.1. Study design and population

This was an investigator-initiated observational controlled clinical trial. We included 10 subjects with stage four CKD and 10 healthy control subjects. Participants with CKD were recruited from the outpatient clinic at Department of Nephrology, Herlev and Gentofte Hospital, Denmark from 1st of November 2018 until 30rd of April 2019. Healthy control participants were recruited through a website for voluntary participation in clinical trials (www.forsoegsperson.dk). Inclusion criteria for subjects with CKD were estimated glomerular filtration rate (eGFR) 15 to 30 mL/min/1.73 m², plasma magnesium between 0.7 and 1.1 mmol/L, plasma ionized calcium between 1.10 and 1.35 mmol/L, and plasma phosphate between 0.7 and 1.8 mmol/L. All on average of measurements over the previous six months. Exclusion criteria were diabetes mellitus, cancer, conditions affecting absorption from the gastrointestinal tract, receipt of a kidney transplant, previous parathyroidectomy, plasma intact parathyroid hormone (PTH) > 600 pg/mL, and current treatment with Mg supplements, calcimetics, or immunsuppressants.

The participants were admitted to the hospital ward at the Department of Nephrology, Herlev and Gentofte Hospital, Denmark for a 24 h period in order to collect blood and urine samples every third hour. The first samples were collected in a non-fasting state at 8 o’clock in the morning and the last samples collected in a fasting state the following day at 8 o’clock in the morning. Blood samples were drawn from a venous access in the cubital vein. Urine samples were freshly voided samples collected in a bowl.

The participants received three standard hospital meals and a snack in the afternoon. The meals were classic Danish meals, but the exact content of Mg and other nutrients is unknown. The participants were awake during the day and slept during the night in the department. No exercises were performed during the admission. All participants were asked to register their food intake three days prior to the study period, as well as during the 24-h study period. The intake was registered in individual profiles on www.madital.dk and the daily Mg intake was calculated. Patients with CKD are routinely advised to reduce their intake of phosphorus if the levels of phosphate have increased in the blood. The patients were advised to maintain their usual diet prior to the admission.

The study was conducted according to the Helsinki declaration revised October 2013 and was approved by the Danish Data Protecting Agency (case number VD-2018-449) and the local scientific ethics committee (case number H-18037663). We prospectively registered the study at www.clinicaltrials.gov (NCT03698422) on the 8th of October 2018.

2.2. Biochemistry

Plasma Mg was analyzed by Vitros from Johnson & Johnson, Ortho-Clinical Diagnostics. Plasma ionized calcium was analyzed immediately using ABL 835 from Radiometer Medical Aps, Denmark.

Blood samples for later analysis were put on ice right after they were drawn, then centrifuged at 4 °C at 3000 rpm for 10 min and separated plasma was stored at −80 °C. Urine samples from each time point were stored at −80 °C. From this biobank we analyzed plasma intact Fibroblast Growth Factor-23 (FGF23), 1,25(OH)₂ vitamin D and intact PTH, and urine Mg, calcium, phosphate and creatinine. FGF23 and intact PTH were analyzed on a Liaison XL automatic analyzer from Diasorin (Saluggia, Italy) and 1,25 (OH)₂ vitamin D was analyzed using iSYS from Immunodiagnostic Systems Plc (Tyne & Wear, UK). The urinary analyses were performed on Cobas 8000 c702.

The remaining parameters were measured by routine analyses at certified laboratories in the Departments of Biochemistry at Herlev and Gentofte Hospital and Righospitalet, Denmark.

2.3. Outcome measures

The primary end point of this trial was changes in plasma Mg within groups. The secondary end points were the diurnal variation of ionized calcium, phosphate, intact PTH, intact FGF23, and 1,25(OH)₂ vitamin D in patients with CKD and controls.

2.4. Statistics

In a previous trial of subjects with CKD stage 3-4 treated with Mg supplementation (Bressendorff et al., 2017) serum Mg increased by a mean of 0.11 mmol/L and a standard deviation (SD) 0.08 mmol/L. For the longitudinal data analysis, sample size calculations were based on a repeated measure ANOVA with Greenhouse-Geisser correction for non-sphericity. With a power of 0.80, a two-sided significance at 0.05, SD at 0.08, a maximum difference at 0.11 and a correlation between nearest measures at 0.6 and following an autoregressive (AR) structure, a total sample size of 10 subjects in each group was needed. Calculations were performed using SAS version 9.4, PROC GLMPOWER.

Data following a Normal distribution was described as mean ± SD. Non-Normal distributed data was described as median and inter-quartile range. Categorical data was described by number and percentage. Between-group differences for baseline characteristics were analyzed using independent samples t-tests and Mann-Whitney tests for data with Normal and non-Normal distributions, respectively. Fasting and non-fasting samples were compared with paired t-test, and Wilcoxon Signed Rank test as appropriate. The changes within groups and between groups over several timepoints were compared with linear mixed effect models with AR covariance structure. Variables were log-transformed if they did not follow a Normal distribution. Due to age differences between groups, the influence of age was explored by age adjustment post hoc. In addition, to explore if the diurnal rhythm in the parameters could be described by the Cosinor-model, this was applied to examine the presence of a circadian rhythm in plasma Mg and the other measured outcomes using the R package ‘Cosinor2’. All statistical tests were two-sided and p < 0.05 was considered statistically significant.

3. Results

Baseline characteristics of the study participants are presented in Table 1. The control group consisted of more females than the CKD group.

We compared blood markers of mineral metabolism at 8 o’clock in the morning in fasting and non-fasting states and found no within-group differences in any of these parameters (Table 2).

The overall levels of plasma Mg (p = 0.204) and urine Mg/creatinine ratio (p = 0.150) were similar between CKD and controls (Fig. 1A and B), which persisted after adjustment for age differences between groups (p = 0.751 and p = 0.070). We analyzed the overall influence of time on plasma Mg in both groups combined and found no significant influence of time on the plasma Mg (p = 0.997), which suggests that there is no diurnal variation in plasma Mg. However, we did find a significant overall influence of time on the urinary excretion of Mg (log urine Mg/creatinine ratio) (p = 0.044), suggesting that there is a diurnal variation in the urinary excretion of Mg. We found no significant time × group interaction in the mixed model analysis of plasma Mg (p = 0.181) or urinary Mg excretion (log urine Mg/creatinine) (p = 0.125), which persisted after adjustment for age differences between groups (p = 0.181 and 0.125), and thus no suggestion that CKD affects diurnal variation of plasma Mg or variation in urinary Mg excretion. These findings were confirmed by the cosinor analysis, which revealed no significant diurnal variation in plasma Mg (p = 0.66), but a significant diurnal variation in...
Loop diuretics or thiazides were prescribed to six patients in the CKD group. Data presented as number (percentages), mean ± standard deviation or median and interquartile range.

Table 1 Baseline demographics.

|                      | CKD (n = 10) | Controls (n = 10) | Comparison between groups (p-value) |
|----------------------|--------------|------------------|-----------------------------------|
| Sex (male)           | 9 (90%)      | 5 (50%)          | 0.141                             |
| Age (years)          | 72 ± 8       | 41 ± 10          | <0.001                            |
| Body mass index (kg/m²) | 27.5 ± 4.1    | 25.5 ± 3.8       | 0.160                             |
| Smoking              | 9 (90%)      | 2 (20%)          | NA                                |
| Co-morbidities       |              |                  |                                   |
| Hypertension         | 8 (80%)      | 1 (10%)          | 0.001                             |
| Heart failure        | 1 (10%)      | 0 (0%)           | 1.000                             |
| Dyslipidemia         | 1 (10%)      | 0 (0%)           | 1.000                             |
| Coronary artery disease | 1 (10%)    | 0 (0%)           | 1.000                             |
| Cause of CKD         |              |                  |                                   |
| Polycystic kidney disease | 2 (20%)   | –                |                                   |
| Obstructive nephropathy | 1 (10%)    | –                |                                   |
| Infection            | 1 (10%)      | –                |                                   |
| Rhabdomyolysis       |              |                  |                                   |
| Glomerulonephritis   | 1 (10%)      | –                |                                   |
| Post-operative        | 1 (10%)      | –                |                                   |
| complication          |              |                  |                                   |
| Unknown              | 4 (40%)      | –                |                                   |
| Estimated glomerular filtration rate (mL/min/1.73 m²) | 27 ± 8 | 105 ± 10 | <0.001 |
| Plasma magnesium (mmol/L) | 0.90 ± 0.06 | 0.83 ± 0.08 | 0.045 |
| Urine magnesium/creatinine (mmol/µmol) | 0.37 | 0.35 | 0.796 |
| Plasma ionized calcium (mmol/L) | 1.18 ± 0.03 | 1.17 ± 0.03 | 0.628 |
| Urine calcium/creatinine (mmol/µmol) | 0.10 | 0.30 | 0.089 |
| Plasma phosphate (mmol/L) | 1.09 ± 0.16 | 1.15 ± 0.13 | 0.452 |
| Urine phosphate/creatinine (mmol/µmol) | 2.06 | 1.62 | 0.190 |
| Plasma intact PTH (pg/mL) | (60.2–100.5) | 39.7 | 0.024 |
| Plasma intact FGF-23 (pg/mL) | (49.5–197.8) | 40.0 | 0.005 |
| Plasma 1,25(OH)₂ vitamin D (nmol/L) | (61.5–78.5) | 59.2 | 0.019 |
| Plasma bicarbonate (nmol/L) | 23.1 ± 1.4 | 24.2 ± 0.8 | 0.061 |
| Magnesium intake (mg/day) | 237 ± 67 | 288 ± 87 | 0.319 |
| Diuretics            | 7 (70%)      | 0                | 0.003                             |
| Loop diuretics       | 6 (60%)      | 0                |                                   |
| Thiazides            | 1 (10%)      | 0                |                                   |
| Aldosterone antagonist | 1 (10%)     | 0                |                                   |
| Proton pump inhibitors | 2 (20%)      | 0                | 0.474                             |
| Sodium bicarbonate   | 2 (20%)      | 0                | 0.474                             |
| Phosphate binders    | 3 (30%)      | 0                | 0.211                             |
| Native vitamin D     | 4 (40%)      | 0                | 0.087                             |
| Active vitamin D     | 4 (40%)      | 0                | 0.087                             |

Table 2 Fasting does not affect magnesium and other markers of the mineral metabolism in plasma.

|                      | CKD Non-fasting | Fasting | Control Non-fasting | Fasting |
|----------------------|-----------------|---------|---------------------|---------|
| Magnesium (mmol/L)   | 0.90 ± 0.06     | 0.89 ± 0.08 | 0.83 ± 0.08         | 0.84 ± 0.07 |
| Ionized calcium (mmol/L) | 1.18 ± 0.03 | 1.17 ± 0.02 | 1.17 ± 0.03         | 1.18 ± 0.02 |
| Phosphate (mmol/L)   | 1.09 ± 0.16     | 1.12 ± 0.21 | 1.15 ± 0.13         | 1.09 ± 0.15 |
| Intact PTH (pg/mL)   | 76.6 ± 00.5     | 76.9 ± 0.6  | 39.7 ± 0.37         | 37.6 ± 0.37 |
| Intact FGF23 (pg/mL) | 142.0 ± 0.4    | 139.5 ± 0.4 | 40.0 ± 0.37         | 40.3 ± 0.37 |
| 1,25(OH)₂ vitamin D (nmol/L) | 65.0 ± 0.9 | 67.0 ± 0.9  | 116.0 ± 0.94        | 104.5 ± 0.94 |

Plasma levels of markers of mineral metabolism at 8 o’clock in the morning showed no significant within-groups differences between fasting and non-fasting states. Data are presented as mean ± standard deviation or median and interquartile range.

PTH, parathyroid hormone; FGF23, fibroblast growth factor 23.

Our study explored the diurnal variation of Mg and found no evidence of a diurnal variation in plasma Mg in either CKD or healthy controls. We did, however, find a diurnal variation in the urinary excretion of Mg in both groups. We did, however, find a significant time * group interaction for the diurnal variation of plasma Mg (p = 0.0075) and ionized calcium (p = 0.098). We also found no difference in the overall urinary phosphate excretion (log urine phosphate/creatinine) (p = 0.696) between CKD and control groups, whereas the urinary calcium excretion was higher in the control group (log urine calcium/creatinine) (p = 0.041) compared with the CKD group (Fig. 1D and F).

Data presented as mean ± standard deviation or median and interquartile range.

PTH, parathyroid hormone; FGF23, fibroblast growth factor 23.

The overall levels of log PTH (p = 0.001) and log FGF23 (p = 0.001) were significantly higher and the overall level of 1,25(OH)₂ vitamin D (p = 0.016) was significantly lower during the 24-h period in the CKD group compared with the control group (Fig. 2A, B and C).

We found a significant influence of time on the levels of log PTH (p = 0.0071), 1,25(OH)₂ vitamin D (p = 0.001), but only a borderline significant influence of time on log FGF23 (p = 0.052). However, the cosinor analysis revealed a diurnal variation for all variables (log PTH (p < 0.001), 1,25(OH)₂ vitamin D (p = 0.001) and log FGF23 (p = 0.0005)). The mixed model analysis showed no significant time * group interaction for log PTH and log FGF23 but did show a significant time * group interaction for 1,25(OH)₂ vitamin D (p = 0.004), suggesting that CKD affects the diurnal variation of 1,25(OH)₂ vitamin D, but not the diurnal variation of PTH and FGF23.

4. Discussion

Our study explored the diurnal variation of Mg and found no evidence of a diurnal variation in plasma Mg in either CKD or healthy controls. We did, however, find a diurnal variation in the urinary excretion of Mg in both groups. In addition, we observed diurnal variations in plasma phosphate, ionized calcium, urinary excretion of
Fig. 1. Diurnal pattern of magnesium, calcium and phosphate in blood and urine among subjects with CKD and healthy controls.
Plasma magnesium (A), urine magnesium/creatinine ratio (B), plasma ionized calcium (C), and urine calcium/creatinine ratio (D), plasma phosphate (E), and urine phosphate/creatinine ratio (F).

Data depicted as mean ± standard deviation or median and interquartile range.
○ CKD group (n = 10) ● Healthy controls (n = 10).
phosphate and calcium, plasma PTH, FGF23 and 1,25(OH)2 vitamin D, as well as evidence of a disturbance by CKD on the diurnal pattern of plasma 1,25(OH)2 vitamin D and urinary excretion of calcium.

So far, there is no known hormonal regulation of Mg homeostasis. We speculate that plasma Mg is maintained at a stable level by transient increases in urinary Mg excretion associated with gastrointestinal absorption of Mg during meals. A recent study (Nie et al., 2018) has demonstrated that in conditions of low Mg in diet, uromodulin (UMOD) is upregulated and secreted in the lumen of the thick ascending limb (TAL) of the loop of Henle and physically interacts with the apical Mg-channel transient receptor potential melastatin 6 (TRPM6) in the distal convoluted tubules (DCT) to inhibit endocytosis of TRPM6 and thereby increase Mg reabsorption in the DCT. This suggests a feedback system between the TAL and DCT by which fluctuations in systemic Mg affect the secretion of UMOD and activity of TRPM6 to maintain Mg balance. How fluctuations in Mg are sensed by the TAL is presently unknown and it is possible that a yet unknown Mg-regulating hormone exists. The observed variations in urinary Mg in our study are relatively small and unlikely to be of clinical significance.

Hypocalcemia stimulates renal calcium and Mg reabsorption in the TAL via the calcium-sensing receptor (Ferre et al., 2012) and the patients with CKD in our study all had secondary hyperparathyroidism with low-normal or overt hypocalcemia as well as elevated PTH. It is unknown if these levels of calcium in plasma affect renal Mg handling in CKD or whether this is affected by other hormones related to CKD-MBD. Given that we observed no significant differences in urinary excretion of Mg between CKD and controls, any effects mediated by the calcium-sensing receptor on renal Mg handling in the TAL in our study are likely too small to be of clinical significance.

In contrast to extracellular Mg, intracellular Mg has been shown to exhibit a circadian rhythm related to diurnal variations in metabolic demands and the interactions between Mg and adenosine triphosphate-dependent enzymes (Feeney et al., 2016). Patients with diabetes mellitus are known to have lower levels of serum Mg independent of kidney function (Dewitte et al., 2004), and TRPM6 is among the most downregulated genes in advanced versus early diabetic kidney disease (Fan et al., 2019) suggesting a possible mechanism for Mg wasting in diabetic kidney disease. Therefore, we specifically excluded patients with diabetes mellitus from this study, in order to investigate the effects of CKD on Mg independent of diabetes mellitus.

In contrast to Mg, we observed significant diurnal variations for all the measured minerals and hormones related to CKD-MBD. Previous studies have demonstrated diurnal variations in plasma phosphate, PTH and FGF23 in humans (Isakova et al., 2012; Ix et al., 2014) and animals (Nordholm et al., 2019), which are affected by CKD and progressively higher content of phosphate in diet. Animals with CKD in particular exhibit abolishment and augmentation of diurnal variation in plasma phosphate and FGF23, respectively, with increasing phosphate content in diet. Also, a recent study in rats demonstrated that CKD causes disturbances in genes related to circadian rhythms in the parathyroid glands (Egstrand et al., 2020). The subjects in our study were given regular hospital meals during the 24-h observational period but were not asked to adhere to a specific diet as part of the study (e.g. high, normal or low phosphate diets). However, patients with CKD are asked to adhere to a low phosphate diet as part of general dietary advice in CKD, and this might explain the lack of abolished diurnal variation in plasma phosphate and FGF23, respectively, with increasing phosphate content in diet. Also, a recent study in rats demonstrated that CKD causes disturbances in genes related to circadian rhythms in the parathyroid glands (Egstrand et al., 2020). The subjects in our study were given regular hospital meals during the 24-h observational period but were not asked to adhere to a specific diet as part of the study (e.g. high, normal or low phosphate diets). However, patients with CKD are asked to adhere to a low phosphate diet as part of general dietary advice in CKD, and this might explain the lack of abolished diurnal variation in plasma phosphate and FGF23, respectively, with increasing phosphate content in diet. Also, a recent study in rats demonstrated that CKD causes disturbances in genes related to circadian rhythms in the parathyroid glands (Egstrand et al., 2020).

Diurnal variation in 1,25(OH)2 vitamin D3 with a pattern similar to the findings in the present study has previously been described in healthy persons (Jones et al., 2017) but has not been examined in CKD. The blunted rise in the morning and as such an altered diurnal pattern of
1,25(OH)2 vitamin D in CKD is in line with the findings by Isakova et al. (Isakova et al., 2012) who found less postprandial increase in serum calcium in CKD, which was normalized when calcitriol was given as a dietary supplementation. These changes in the diurnal variation of 1,25 (OH)2 vitamin D may be due to changes in the diurnal activity of the vitamin D activating enzyme CYP27B1 or the vitamin D inactivating enzyme CYP24A1, or changes in their stimuli. Although the diurnal pattern of PTH and FGF23 was not significantly different in the present study, other studies demonstrated a disturbed circadian rhythm of these vitamin D regulating hormones in CKD. We speculate that the less pronounced pattern of urinary calcium excretion in CKD is due to reduced postprandial intestinal calcium absorption due to reduced levels of 1,25 (OH)2 vitamin D.

The main finding of clinical significance in our study is the observation that plasma Mg does not seem to exhibit any diurnal variation or be influenced by fasting, and thus blood samples for plasma Mg can theoretically be drawn at any time of day and in both fasting and non-fasting states. This might simplify the conduct of clinical trials investigating the effects of Mg modulation, although we have not examined the diurnal variations during Mg supplementation. Further research is needed if blood samples are to be used to monitor plasma Mg during diurnal variations during Mg supplementation. This might simplify the conduct of clinical trials investigating the effects of Mg modulation, although we have not examined the fasting states. Fasting did not affect plasma Mg and is therefore not necessary when measuring plasma Mg. Any possible effect of Mg supplementation on the diurnal pattern of plasma Mg requires further study.

In conclusion, plasma Mg does not appear to have any diurnal variation in either CKD without diabetes mellitus or healthy controls, while urinary excretion of Mg exhibits a diurnal variation, which is likely related to transient increases in total body Mg in relation to meals. Fasting did not affect plasma Mg and is therefore not necessary when measuring plasma Mg. Any possible effect of Mg supplementation on the diurnal pattern of plasma Mg requires further study.

Authors’ contribution

IB, DHA, KO and TWK designed the study. AAJ and IB performed the clinical work and data collection. NRJ performed the biochemical assessments and interpretation. IB, DHA, TWK, AN, SE, and KO analyzed and interpreted the data. AAJ, IB, DHA, AN and SE drafted the manuscript. The final paper was approved by all the authors.

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CRediT authorship contribution statement

Astrid Sand Møller: Data curation, Funding acquisition, Investigation, Project administration, Writing – original draft, Writing – review & editing.

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Declaration of competing interest

Diasorin donated the kits for analysis of intact PTH, intact FGF23 and 1,25(OH)2 vitamin D.

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