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Original Article

Effects of Magnesium Supplementation on Kidney Function and Phosphate Levels in Children with Chronic Kidney Disease and Hyperphosphatemia: A Double-blind Randomized Clinical Trial

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ABSTRACT

Background: Pediatric patients with chronic kidney disease (CKD) who have hyperphosphatemia may experience further deterioration in kidney function. This study aims to investigate the effect of magnesium supplementation on the reduction of phosphate levels and improvement of kidney function in children with CKD and hyperphosphatemia, compared to a placebo. **Methods:** A randomized, double-blind, placebo-controlled trial was conducted at Pediatric Ward in our setting during March-July 2022. We compared oral magnesium supplementation (6 mg/kg body weight/day for two months) with a placebo in children with CKD and hyperphosphatemia (ages 1-18 years old). Patients who were on dialysis and had serum magnesium levels of <1.6 mg/dL and >2.4 mg/dL, and were allergic to magnesium supplementation were excluded. A paired T-test and the Wilcoxon signed-rank test were used for statistical analysis. **Results:** We collected 31 children in the experimental group and 29 children in the placebo group. Phosphate levels were decreased in both the magnesium supplementation and placebo groups (5.4 ± 0.9 to 4.8 ± 1.1 mg/dL; *p*-value = 0.001 and 5.1 ± 0.6 to 4.3 ± 1.2 mg/dL; *p*-value=0.003). However, when compared between groups, the reductions were not significantly different (0.7 vs 0.8; *p*-value=0.935). A significant improvement was found in kidney function in both groups using estimated Glomerular Filtration Rate (eGFR) (83.4±25.3 to 118.8±52; *p*-value=<0.001 and 86.3±28.1 to 96.9 ± 35.8; *p*-value=0.004), and the reductions were significantly different (35.4 vs 10.7; *p*-value=0.045). **Conclusion:** Magnesium supplements have considerably lower phosphate levels and markedly improved kidney function in children with CKD and hyperphosphatemia.

Key words: Children, Chronic Kidney Disease, Hyperphosphatemia, Magnesium, Kidney Function.

INTRODUCTION

Hyperphosphatemia is a cause of morbidity and mortality in children, as well as a challenge in the management of chronic kidney disease (CKD).[1] The pathogenesis of decreased kidney function in children with CKD and hyperphosphatemia is due to decreased levels of *alpha-Klotho*,[2] increased apoptosis of kidney tubular cells,[3] deposition of calcium-phosphate crystals,[4,5] and increased levels of Fibroblast Growth Factor (FGF) 23.[6] Currently, the management of hyperphosphatemia in children with CKD is through the administration of calcium-based-phosphate binders which will cause increased deposition of calcium-phosphate crystals and will aggravate the kidney function itself. [7]

Magnesium (Mg) is a substance that has proven to have protective effects against kidney function deterioration. According to the previous *in-vitro* study, Mg inhibits the vascular calcification process by inhibiting the transformation of amorphous Ca/P into apatite and by forming Mg whitlockite crystals, which will produce deposits that are smaller and more soluble.[5] Magnesium also suppresses profibrotic and proinflammatory cytokine gene expression in tubulointerstitial cells induced by high phosphate levels.[3] Magnesium also has a substantial role in maintaining *alpha-Klotho* expression, a substance that contributes to kidney resistance to various factors that cause kidney damage, including high phosphate levels.[8] At the same time, Mg is also crucial in increasing phosphate excretion in the animal model.[9]

Magnesium supplementation has already been known to have longitudinal effects on CKD and its progression.[9] A low Mg diet is also mentioned to be the risk factor for CKD in the population.[10] Nevertheless, until now, studies regarding Mg supplementation in the pediatric patient with CKD and hyperphosphatemia are still rare. Therefore, the aim of this study is to investigate the effect of magnesium supplementation on the reduction of phosphate levels and improvement of kidney function in children with CKD and hyperphosphatemia, compared to placebo.

MATERIAL AND METHODS

A double-blind randomized controlled trial was conducted. The participants of this study were randomly and blindly assigned to either the experimental or control group. Participants in the experimental group were given oral magnesium supplementation (6 mg/kg body weight/day, max dose of 250 mg/day), while participants in the control group were given the placebo at the same dose as the experimental group. Both treatments were given for 2 months. Kidney function and phosphate levels were checked before the treatments and were evaluated monthly (after 1 and 2 months of treatment). The study was conducted from March to July 2022.

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Participants

Participants were recruited by consecutive sampling. The inclusion criteria were children aged 1-18 years in the Outpatient Clinic or Pediatric Ward of Dr. Soetomo General Academic Teaching Hospital with CKD and hyperphosphatemia during the time of the study. Patients were diagnosed with CKD if there are abnormalities of kidney structure or function for more than 3 months, with implications for health. Hyperphosphatemia in children was considered if the serum phosphate levels exceed 6.5 mg/dL (1-5 years old), 5.9 mg/dL (6-12 years old), or 4.65 mg/dL (13-18 years old). Patients who underwent dialysis treatment, patients with serum magnesium levels <1.6 mg/dL and >2.4 mg/dL, and patients who were known to have allergy towards magnesium supplementation were excluded.

The sample size was calculated using unpaired sample size formula. The calculated sample size was 20 participants, added with 20% drop out rate.[11] As a result, 60 participants were recruited and using table randomization, was randomly assigned to each group of experimental and control groups.

Research instruments

We created a demographic data set, which included personal information (gender, age, diagnosis, previous medical history, treatment history, nutritional history). Height data was measured using stadiometer in centimeter (cm). The data were used to calculate estimated Glomerular Filtration Rate (eGFR). Phosphate and magnesium data were obtained from blood serum examination. Kidney functions were calculated by eGFR Schwartz formula using serum creatinine and height data.

Magnesium supplementation was given according to daily magnesium supplementation (6 mg/kg body weight/ day, maximum dose 250 mg/ day) using a Magnesium Oxide/Gluconate supplement. The supplement was taken once daily after breakfast. Placebo consisted of *Saccharum lactis* with a dose of 6 mg/kg body weight/ day, maximum dose 250 mg/ day, which was packaged similarly to magnesium supplementation, and was taken once daily after breakfast. All magnesium and placebo supplementations were packaged and numbered according to randomization by computer and given alternately to subjects according to the order in which they participated in the study. Blinding will be carried out on subjects and researchers during the study process.

Human subjects

The study was granted the ethical clearance by the Ethical Committee of Dr. Soetomo General Academic Teaching Hospital (Research ID: 0366/KEPK/II/2022). This study has also been reviewed and approved by the Thai Clinical Trials Registry (TCTR) Committee with reference number TCTR20220708002. Written consent was obtained from participants' guardians and/or parents after they received explanations regarding the study's purpose, procedures, confidentiality, and anonymity. Participants' guardians were also informed about the right to withdraw their children from the study at any time, and they should not have to provide a reason for the withdrawal. All study participants will be checked for serum magnesium levels at each monthly visit for 2 months, and a thorough history-taking will be carried out regarding the appearance of symptoms of magnesium supplementation's side effects, especially gastrointestinal side effects such as diarrhea. If the examination finds that the serum magnesium level exceeds 4.4 mg/dL, the supplementation of the participant will be stopped, and a follow-up examination of magnesium levels will be carried out 2 weeks later. If during the follow-up examination the magnesium level remains above 3.7 mg/dL, the supplementation of the participant will be stopped. In case the serum magnesium level increased but does not exceed 3.7 mg/ dL, the participant will continue magnesium supplementation using half of the usual dose of magnesium supplementation and a follow-up magnesium level check will be carried out 2 weeks later.

Data collection

The demographic data were collected before the intervention began. Body height data were obtained. Blood samples were withdrawn, and were checked for phosphate, magnesium, and creatinine serum. Participants who met the inclusion criteria were randomly assigned to experimental and control groups using randomization table. Each participant's group assignment was blinded from both the participant and the researcher. Both groups were given treatment for two months. Participants were told to come for a monthly visit and were checked for phosphate level, magnesium level, and also kidney function.

Data analysis

All data is recorded in the data collection sheet. The research data were coded, tabulated, and entered into the IBM SPSS Statistics Version 21 software program. Data analysis included descriptive analysis and inferential testing to test the research hypothesis. Descriptive data is presented in the form of tabulations. The inferential test is carried out using a normality test. The paired T-test will be used if the variables were normally distributed, or if the variables were not normally distributed, the analysis will be using the Wilcoxon test. The results of the analysis and the mean difference between the variables were stated to be significant if the p-value <0.05 was obtained.

This study uses the principle of intention to treat analysis. Deceased and drop out participants will still be included in the analysis. Events or complications and factors causing death will also be reported in this study as secondary outcomes. Intention to treat will be calculated on participants who died and dropped out before the end of the study, as long as the initial data from the study were collected and blood phosphate levels and kidney function were obtained.

RESULTS

We recruited 60 children with CKD and hyperphosphatemia. The majority of the participants were male, and the mean age was 12 years old for the experimental group (magnesium group), and 10.6 years (10 years 7 months) old for the placebo group. The primary diagnosis of participants from both groups was mainly nephrotic syndrome. The initial phosphate level and kidney function were not significantly different between both groups. CKD stages in all participants were also not significant between both groups.

Effects of magnesium supplementation on kidney function

The eGFR of both groups during two months of observation is illustrated in Figure 1. There was significant difference in mean eGFR in experimental group before and after treatment (83.4 ± 25.3 ml/ min/1.73m^2 vs 118.8 ± 52 ml/min/1.73m^2; p-value<0.001). On the other hand, there was also significant difference in mean eGFR in control group before and after treatment (86.3 ± 28.1 ml/min/1.73m^2 vs 96.9 ± 35.8 ml/min/1.73m^2; p-value = 0.004). However, the improvements of eGFR between the experimental and control groups were significantly different (35.4 ml/min/1.73m^2 vs 10.7 ml/min/1.73m^2, p = 0.045) (Table 2).

Effects of magnesium supplementation on phosphate level

Phosphate levels of both groups during two months of observation is illustrated in Figure 2. There was significant difference in mean phosphate level in experimental group before and after treatment (5.4 ± 0.9 mg/dL vs 4.8 ± 1.1 mg/dL; p-value=0.001). On the other hand, there was also significant difference in mean phosphate levels in control group before and after treatment (5.1 ± 0.6 mg/dL vs 4.3 ± 1.2 mg/dL; p-value = 0.003). However, the decrease of phosphate levels between the experimental and control groups were not significantly different (0.7 mg/dL vs 0.8 mg/dL, p = 0.935) (Table 3).

Table 1: Characteristics of subjects.

	Experimental (n=31)	Control (n=29)	p-value*
Age, year *(mean ± SD)*	12 ± 4.5	10.6 ± 4.9	0.235
Sex, n (%)			
Male	18 (58.1)	16 (55.2)	0.821
Female	13 (41.9)	13 (44.8)	
Body weight, kg *(mean ± SD)*	39.7 ± 18.5	33.43 ± 17.1	0.182
Height, cm *(mean ± SD)*	138.5 ± 23.4	130.2 ±22.9	0.173
Diagnosis, n (%)			
Nephrotic Syndrome	12 (38.7)	9 (31)	0.538
Nephritic Syndrome	1 (3.2)	1 (3.4)	
HSP Nephritis	2 (6.5)	1 (3.4)	
Lupus Nephritis	12 (38.7)	10 (34.5)	
Cystitis	1 (3.2)	1 (3.4)	
Nephro/Urolithiasis	1 (3.2)	1 (3.4)	
Anorectal Malformation	2 (6.4)	0 (0)	
Ectopic Kidney	0 (0)	1 (3.4)	
Primary Hypertension	0 (0)	1 (3.4)	
Neurogenic Bladder	0 (0)	1 (3.4)	
Rapidly Progressive Glomerulonephritis	0 (0)	2 (6.8)	
UVJ Stenosis	0 (0)	1 (3.4)	
Initial Phosphate Level, mg/dL *(mean ± SD)*	5.5 ± 0.9	5.1 ± 0.6	0.630
Initial eGFR, ml/min/1.73m^2 *(mean ± SD)*	85 ± 31.9	87.4 ± 24.1	0.740
CKD Stage, n (%)			
I	14 (45.2)	16 (55.2)	0.499
II	14 (45.2)	8 (27.6)	
III	2 (6.5)	4 (13.8)	
IV	1 (3.2)	1 (3.4)	

*p-value is considered significant if < 0.05 by *Chi-square* test

Table 2: eGFR of experimental and control groups and improvement of eGFR on experiment and control groups.

eGFR (ml/min/1.73m^2)	Baseline	After	p-value	Δ	p-value$^+$
Experimental	83.4±25.3	118.8±52	<0.001°	35.4	0.045$^+$
Control	86.3±28.1	96.9±35.8	0.004°	10.7	

$^\circ$significant p-value < 0.05 by Wilcoxon test
$^+$significant p-value < 0.05 by Mann-Whitney U test

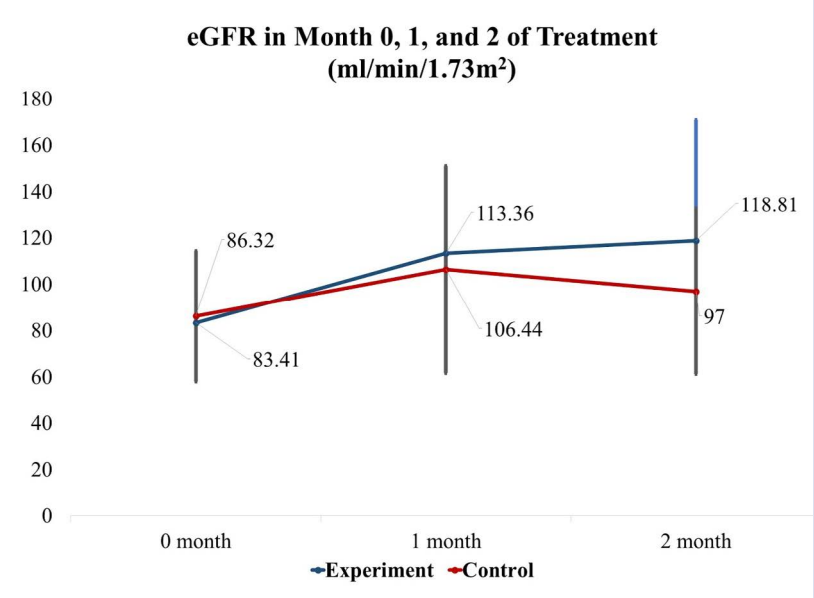

Figure 1: eGFR of experimental and placebo groups on month 0, 1, and 2 of treatment

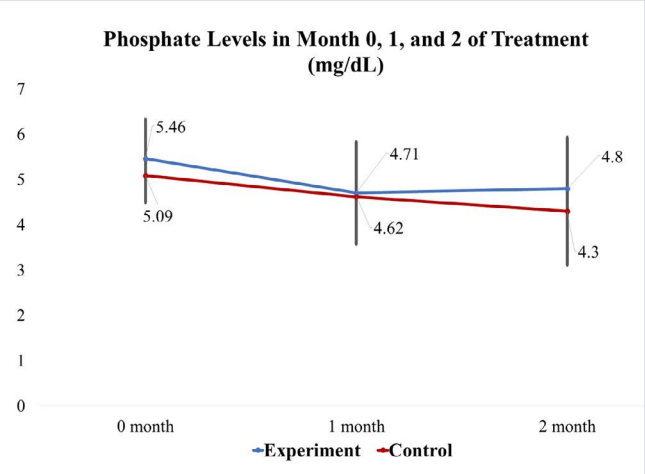

Figure 2: Phosphate levels of experimental and control group on month 0, 1, and 2 of treatment

Table 3: Phosphate levels of experimental and control groups and decrease of phosphate levels on experiment and control groups.

Phosphate (mg/dL)	Baseline	After	p-value	Δ	p-value
Experimental	5.4±0.9	4.8±1.1	0.001*	0.7	0.935
Control	5.1±0.6	4.3±1.2	0.003*	0.8	

*significant *p-value* < 0.05 by Paired T-test

DISCUSSION

The average age of participants was 11.3 years, dominated by male. It was also found in this study that most of the participants were patients with chronic glomerular kidney disease (Nephrotic Syndrome, Nephritic Syndrome, HSP Nephritis, and Lupus Nephritis). This is in accordance to previous finding where demographically, most patients who experience hyperphosphatemia are older and as many as 52% are male.[12] Another study states that blood phosphate levels are significantly higher in children with oligo/anuria and in children with glomerular disease.[13]

The majority of participants who experienced hyperphosphatemia were patients with CKD with normal kidney function (Stage I CKD). This result is supported by Moon (2019),[12] which found that hyperphosphatemia can occur in patients with good initial kidney function and then significantly lead to worse end kidney function. This suggests that hyperphosphatemia may occur in patients with good initial renal function. The same study also mentioned an increased risk of ESKD in the group with high serum phosphate levels, compared to the group with normal serum phosphate levels,[12] regardless of the group's initial kidney function.

Effects of magnesium supplementation towards kidney function

Our study found that magnesium supplementation could improve kidney function in patients with CKD stage I-IV. This is also in line with previous retrospective cohort study that recruited 311 CKD patients with eGFR level > 15 ml/min/1.73m^2 or those who were not on dialysis, and concluded that the risk of end stage kidney disease (ESKD) was increased significantly in patients with higher serum phosphate levels and lower serum magnesium than in patients who had higher serum high phosphate levels and high serum magnesium. This suggests that magnesium is protective against the risk of worsening CKD caused by high serum phosphate levels.

A significant difference of eGFR improvement was reported in our findings, which represents kidney function, between experimental and control group. This corresponds to previous cohort studies which independently evaluated the association between dietary magnesium intake and the risk of developing CKD incidents. A study from The Healthy Aging in Neighborhoods of Diversity across the Life Span involving 1,252 African-American and Caucasian urban residents with an estimated glomerular filtration rate (estimated GFR) ≥ 60 mL/min/1.73 m^2, demonstrated that low magnesium intake (measured using food recall over the last 24 hours) was associated with a rapid decrease in estimated GFR (decreased estimated GFR ≥ 3% per year).[14] A study reported that dietary magnesium intake of 0.581 mg/day reduced the risk of CKD incidents by around 60% followed up for 5.1 years.[15] Additionally, it was also found that patients with lower baseline serum magnesium levels experienced a decrease in GFR more rapidly.[16] Another retrospective cohort study also found that the risk of ESKD was increased significantly in patients with higher serum phosphate levels and lower serum magnesium than in patients who had higher serum high phosphate levels and high serum magnesium. An *in vitro* study also concluded that patients in the group with higher phosphate serum and lower magnesium levels had a 2.07-fold higher risk of developing ESKD than patients with high serum phosphate levels and high serum magnesium levels in the fully adjusted model (95% CI: 1.23-3.48).[3]

Effects of magnesium supplementation towards phosphate level

Phosphate levels were observed to be significantly lower in both the experimental and control groups in this investigation. This is in accordance to the theory that human's body is capable of excreting 90% of phosphate through kidney and gastrointestinal tract. Serum phosphate levels are maintained through a complex interaction between intestinal absorption of phosphate, renal excretion of phosphate, and transcellular movement of phosphate that occurs between the intracellular fluid and phosphate stores in bone.[17]

There was no significant difference in serum phosphate level reduction between the experimental and control groups in this study. This is in line with the theory that phosphate metabolism is a complex process involving the presence of several hormones (such as parathyroid and FGF-23), vitamin D, and calcium. Magnesium is known to directly increase phosphate excretion through the kidneys and intestines.[9] On the other hand, other study has also found that low serum magnesium levels can increase levels of FGF-23 which is a phosphaturic hormone, and inhibit the action of vitamin D, which will lower blood phosphate levels.[18] Further research is needed to study about the potential mechanism of magnesium in regulating phosphate serum level.

CONCLUSION

The outcomes showed that magnesium supplementation had a significant effect on improving the kidney function of children with CKD and hyperphosphatemia However, there was no statistically significant difference in the reduction of phosphate levels between the experimental and control groups. On the other hand, magnesium supplementation also lowers phosphate levels in children with CKD and hyperphosphatemia. Magnesium supplementation may be considered a supportive treatment to improve kidney function in pediatric patients with hyperphosphatemia and renal impairment. Given the chronicity of poor renal function and the causes of hyperphosphatemia, additional research is required to confirm the findings with a larger sample size.

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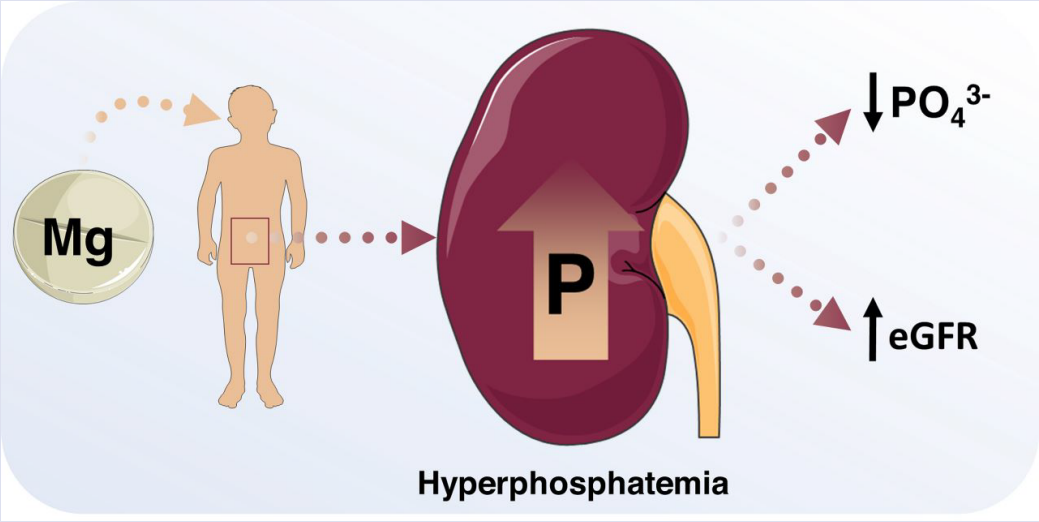
GRAPHICAL ABSTRACT



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