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Effects of Magnesium Supplementation on the Carotid Intima Media Thickness in Children with Chronic Kidney Disease and Hyperphosphatemia: A Double-blind Randomized Clinical Trial

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ABSTRACT

Background: Hyperphosphatemia has been emphasized to be a significant risk factor for vascular calcification in CKD patients. This study aims to investigate the effect of magnesium supplementation on the reduction of phosphate levels and carotid intima media thickness in children as predictor on vascular calcification with CKD and hyperphosphatemia, compared to a placebo. **Methods:** A randomized, double-blind, placebo-controlled trial was conducted at Pediatric Ward and Outpatient Clinic of Pediatric Nephrology in our setting during October-March 2023. 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 25 children in the experimental group and 25 children in the placebo group. Phosphate levels were decreased in both the magnesium supplementation and placebo groups (6.1 ± 0.79 to 6.0 ± 0.63 mg/dL; p-value = 0.852 and 6.01 ± 0.55 to 5.8 ± 0.64 mg/dL; p-value=0.365). However, when compared between groups, the reductions were not significantly different (0.1 vs 0.21; p-value=0.935). A significant improvement was found in carotid intima media thickness in both groups (0.05±0.01 to 0.05±0.01; p-value=0.000 and 0.05±0.01 to 0.05±0.01; p-value=0.000), and the reductions were significantly different (0.01 vs 0.01; p-value=0.000). **Conclusion:** Magnesium supplements have considerably lower phosphate levels and significantly reduced the thickness on carotid intima media in children with CKD and hyperphosphatemia.
Keywords: Children, Chronic Kidney Disease, Hyperphosphatemia, Magnesium, Carotid Intima Media Thickness.

INTRODUCTION

Chronic kidney disease (CKD) is a significant predictor of cardiovascular disease and is the leading cause of death in patients with end-stage renal disease, who have a 10- to 20-fold increased risk of death compared to the general population based on age and sex.[1] It has recently been reported that atherosclerosis, as assessed by arterial wall thickness and stiffness, is particularly prevalent in CKD patients.[2,3] In the group of all CKD patients, a significant high positive correlation was found between mean carotid intimal-medial thickness (mCIMT) and age, systolic blood pressure, corrected serum calcium, serum phosphorus and calcium phosphate product.[4] Elevated serum phosphate concentrations are a significant risk factor for vascular calcification, an advanced form of atherosclerosis.[5] An increase in serum phosphate levels of 1 mg/dL was associated with an increase in mortality of 18%.[4] Hyperphosphatemia has been reported to be a significant risk factor for vascular calcification, and decreased phosphate levels through phosphate binders have been reported to attenuate vascular calcification.[6]

Although efforts to reduce serum phosphate levels are routine management in patients with kidney disorders, data on the methods used to reduce phosphate levels in pediatric patients with kidney disorders are still very limited. Efforts to provide a low phosphate diet or dialysis itself are still considered less than optimal in reducing serum phosphate levels. Furthermore, although the use of phosphate-binding drugs, such as calcium carbonate, has been widely used in patients with chronic kidney disease, there has been no study proving that these drugs can reduce mortality and cardiovascular events better than placebo.[7] The calcium content in phosphate-binding therapy can also increase blood calcium levels and potentially cause vascular calcification.[8] Recently, magnesium has been highlighted due to its protective effect on kidney function in patients with chronic kidney disease. The death of renal tubular cells and the progression of kidney disease in patients with hyperphosphatemia can be suppressed in patients who have high magnesium levels.[9] Many studies have shown that magnesium can reduce vascular calcification by preventing the formation of calcium phosphate crystals and changes in vascular smooth muscle cells into cells that resemble osteoblasts.[10] Therefore, magnesium is thought to be a substance that has a beneficial effect in reducing kidney damage caused by phosphate. However, in vivo studies on this are still very limited.

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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 3 months. Cardiac ultrasonography and phosphate levels were checked before the treatments and were evaluated after 3 months of treatment). The study was conducted from October to March 2023.

Participants

Participants were recruited by consecutive sampling. The inclusion criteria were children aged 4 months-18 years in the Outpatient Clinic and 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 36 participants, added with 20% drop out rate.[11] As a result, 50 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. Carotid intima media thickness were calculated by cardiac echocardiography.

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 was 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: 0799/KEPK/X/2023). This study has also been reviewed and approved by the Thai Clinical Trials Registry (TCTR) Committee with reference number TCTR20240719001. 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 were checked for serum magnesium levels at each monthly visit for 3 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 was stopped, and a follow-up examination of magnesium levels was 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 was stopped. In case the serum magnesium level increased but did not exceed 3.7 mg/dL, the participant continued magnesium supplementation using half of the usual dose of magnesium supplementation and a follow-up magnesium level check was 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 three months. Participants were told to come for a monthly visit and were checked for phosphate level and magnesium level. Echocardiography was done twice during this study, at first month before initiating the treatment and at last month after receiving treatment.

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 carotid intima media thickness were obtained.

RESULTS

We recruited 50 children with CKD and hyperphosphatemia. The majority of the participants were male, and the mean age was 10 years old for the experimental group (magnesium group), and 9.9 years (9 years 9 months) old for the placebo group. The primary diagnosis of participants from both groups was mainly nephrotic syndrome. The initial phosphate level and carotid intima media thickness were not significantly different between both groups. CKD stages in all participants were also not significant between both groups.

Effects of Magnesium Supplementation on Phosphate Level

Serum phosphate levels were measured at two different time points for both groups, as shown in Table 2. In the magnesium supplementation group, there was no significant difference in serum phosphate levels between the two time points, with a p-value of 0.852. Similarly, in the placebo group, no significant difference in serum phosphate levels was

Table 1: Characteristics of subjects.

Characteristics	Control Group (n = 25)	Intervention Group (n = 25)	p-value*
Age, years (mean ± SD)	9.9± 4.4	10.1 ± 4.5	0.876
Gender (n (%))			
Boy	14 (56%)	16 (64%)	0.821
Girl	11 (44%)	9 (36%)	
Body weight, kg (mean ± SD)	33.1 ± 15.4	35.3 ± 15.9	0.954
Height, cm (mean ± SD)	129 ± 21.3	127 ± 26.3	0.731
Glomurular filtration rate (mean ± SD)	50.06 ± 13.9	54.19 ± 10.1	0.541
Diagnosis			
Nephritic lupus	9 (36%)	8 (32%)	0.461
Rapidly progressive glomerulonephritis (RPGN)	1 (3.4%)	2 (8%)	
Poststreptococcal glomerulonephritis (GN)	1 (3.4%)	1 (4%)	
Nephrotic syndrome	10 (40%)	10 (40%)	
Henoch-Schönlein purpura (HSP) nephritis	1 (4%)	1 (4%)	
Hydronephrosis	1 (4%)	0 (0%)	
Nephrolithiasis	1 (4%)	0 (0%)	
Cystitis	1 (4%)	1 (4%)	
Nephritic syndrome	2 (8%)	0 (0%)	
Vesiculolithiasis	0 (0%)	1 (4%)	
Neurogenic bladder	0 (0%)	1 (4%)	
Baseline serum phosphate levels, mg/dL (mean ± SD)	6.01 ± 0.55	6.1 ± 0.79	0.494
Baseline carotid artery intima-media thickness, cm (mean ± SD)	0.05 ± 0.01	0.05 ± 0.01	0.414
Chronic kidney disease stadium (n (%))			
III	22 (92%)	24 (96%)	0.514
IV	1 (4%)	0(0%)	
V	2 (8%)	1 (4%)	
Duration of CKD (n (%))			
< 1 year	5 (20%)	3 (12%)	0.411
1-5 years	12 48%)	18 (72%	
>5 years	8 (32%)	4 (16%	

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

Table 2: Effects of Magnesium on Serum Phosphate Level on Experiment and Control Groups.

	Pre-intervention	Post-intervention	Delta	p-value*
Control group Phosphate levels (mean ± SD)	6.01±0.55	5.8±0.64	-0.21	0.365
Intervention group Phosphate levels (mean ± SD)	6.1±0.79	6.0±0.63	-0.1	0.852

**p*-value is considered significant if < 0.05

Table 3: Effects of Magnesium Supplementation on Carotid Intima-Media Thickness (cIMT) on Experiment and Control Groups.

	Pre-intervention	Post-intervention	Delta	p-value*
Control group cIMT (mean ± SD)	0.05±0.01	0.04±0.01	-0.01	0.000
Intervention group cIMT (mean ± SD)	0.05±0.01	0.04±0.01	-0.01	0.000

**p*-value is considered significant if < 0.05

observed, with a p-value of 0.365. The difference in serum phosphate levels within the magnesium group was 0.1 mg/dL, while in the placebo group, the difference was 0.21 mg/dL.

Effects of Magnesium Supplementation on Carotid Intima-Media Thickness (cIMT)

In the magnesium supplementation group, a significant reduction in carotid intima-media thickness (cIMT) was observed, with a p-value of <0.05. The placebo group also showed a significant difference in mean cIMT, with a p-value of <0.05. The change in cIMT in both the magnesium and placebo groups was 0.01 mm (Table 5.2). However, phosphate levels did not show a significant pre-and post-treatment difference in the control group (Table 2).

DISCUSSION

The study observed a significant reduction in carotid artery intima-media thickness (cIMT) in the magnesium group, suggesting magnesium inhibits vascular calcification by preventing the

transformation of amorphous calcium/phosphate into apatite and forming Mg whitlockite crystals. Magnesium also inhibits circulating calciprotein particle (CPP) formation, prolonging the conversion of primary to secondary CPP in serum.[16] This finding supports previous studies indicating magnesium's role in reducing vascular calcification and suggests its benefit in CKD by reducing vascular calcification in a dose-dependent manner.[17]

Additionally, animal studies have shown that magnesium can prevent vascular calcification, with increased magnesium intake reducing calcium content in vascular tissues and magnesium restriction accelerating calcification.[18] Magnesium's roles include enhancing vascular endothelial function, reducing inflammation and oxidative stress, and protecting against vascular calcification.[19] Low serum magnesium levels in CKD are linked to worse cardiovascular outcomes.[20]

Oral magnesium supplementation has been shown to reduce arterial stiffness and cardiovascular disease risk factors in CKD patients, with studies demonstrating a reduction in carotid-femoral pulse wave velocity and a correlation with reduced left ventricular mass index.[21] Magnesium's protective effects on vascular calcification and arterial stiffness are crucial in CKD, where cardiovascular risks are elevated.[22]

During the study, one subject in the treatment group reported experiencing nausea, though no vomiting was observed. Generally, magnesium supplementation is well tolerated by the body; however, it can cause gastrointestinal symptoms such as diarrhea, nausea, and vomiting in some individuals.[23] At the conclusion of the treatment period, only one subject in the treatment group had elevated magnesium levels. Hypermagnesemia, defined as a serum magnesium level exceeding 2.6 mg/dL, is typically asymptomatic or presents with mild symptoms such as nausea, vomiting, and dizziness if levels are below 7 mg/dL. Severe hypermagnesemia, with magnesium levels above 12 mg/dL, can lead to cardiovascular complications including hypotension and arrhythmias, as well as neurological disturbances. Extremely high magnesium levels (exceeding 15 mg/dL) pose serious risks, potentially causing cardiac arrest and coma.[24]

This study found no significant difference in phosphate level reduction between the magnesium and placebo groups. In CKD, decrease in phosphate levels who have been given magnesium supplementation can occur due to several physiological mechanisms related to the interaction between magnesium and phosphate in the body. Magnesium can form a complex with phosphate in the digestive tract, which reduces the absorption of phosphate from food. This complex is insoluble and is excreted in the feces, thereby lowering phosphate levels in the blood.[11]

Magnesium affects the secretion of parathyroid hormone (PTH). In chronic kidney disease, PTH levels are often elevated (secondary hyperparathyroidism), which causes the release of phosphate from the bones. Magnesium supplementation can decrease PTH secretion, which in turn reduces phosphate release from bones and lowers blood phosphate levels.[12]

Research indicates magnesium can affect kidney function in phosphate reabsorption. Under normal conditions, the kidneys filter phosphate and most of it is reabsorbed back into the body.[13] On the gastrointestinal tract, magnesium can also have a laxative effect, which can speed up intestinal transit and reduce the absorption time of phosphate from food.[14,15]

This study represents the first randomized controlled trial (RCT) to assess the effects of magnesium supplementation on carotid artery intima-media thickness and phosphate levels in pediatric patients with chronic kidney disease (CKD) and hyperphosphatemia. It employed echocardiographic parameters to measure carotid intima-media thickness and included patients with decreased Glomerular Filtration Rate (GFR), recognizing that impaired renal function can occur even with a normal GFR calculation. Nevertheless, the study's inability to categorize samples based on the underlying causes of hyperphosphatemia may limit the generalizability of the findings.

CONCLUSION

Significant differences were observed in carotid artery intima-media thickness between the placebo and magnesium groups in children with chronic kidney disease (CKD) and hyperphosphatemia. Additionally, magnesium supplementation have considerably lower phosphate levels among pediatric patients with chronic kidney disease (CKD) and hyperphosphatemia. Magnesium supplementation could be considered as a supportive treatment to potentially improve renal function in pediatric patients with hyperphosphatemia and renal impairment.

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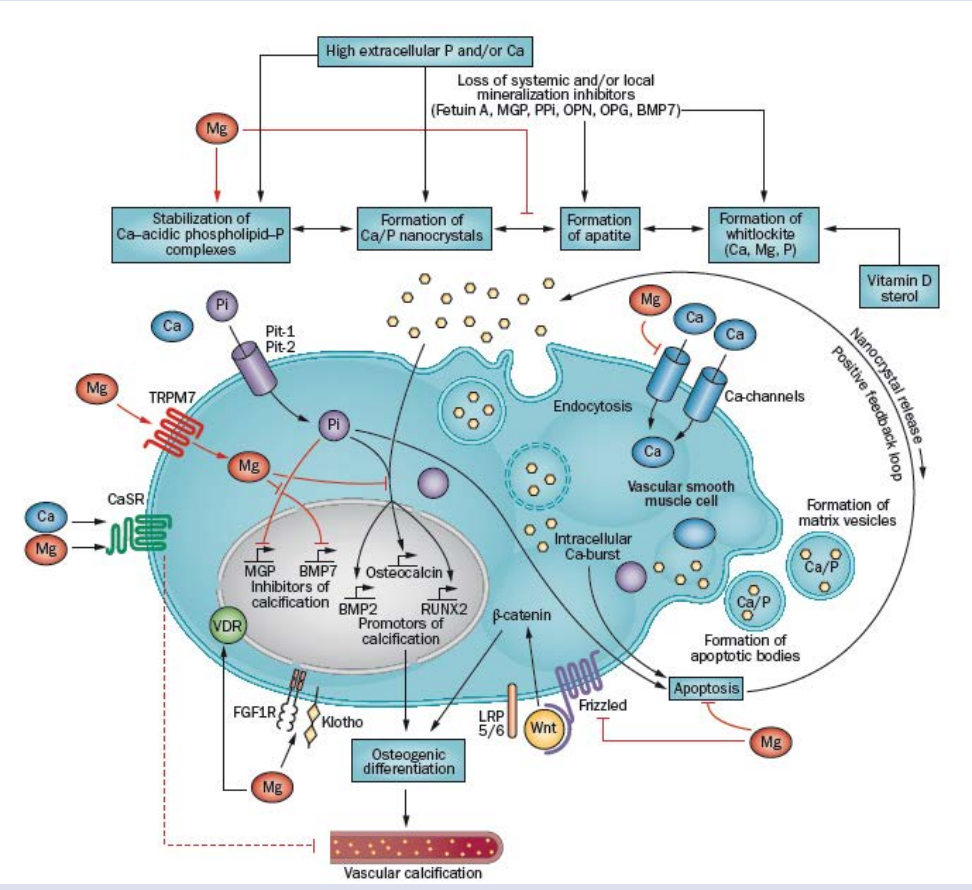
GRAPHICAL ABSTRACT



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