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Research Article

Increased Interleukin-6 as Inflammatory Response and Magnesium Deficiency in Pre-dialysis Chronic Kidney Disease of Indonesian Children

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ABSTRACT

Chronic kidney disease (CKD) is a serious health problem in children, with increasing morbidity and mortality rates throughout the world. Children with CKD tend to experience magnesium (Mg) deficiency that can stimulate an inflammatory response in the body. One of the inflammatory responses is an increase of Interleukin-6 (IL-6). Study to analyze the correlation between Mg and IL-6 in pre-dialysis CKD children. The methods a cross sectional study was conducted in Dr Soetomo General Academic Hospital from November 2018 to April 2019. Children with pre-dialyis CKD were included in this study. Variables of serum Mg level (mg/dL) and inflammatory marker (IL-6) were measured from the blood and analyzed by ELISA method. The correlation between Mg and IL-6 was analyzed with Spearman's correlation test with p <0.05. Result a total of 47 children (27 boys vs 20 girls) between 3 months to 18 years old, with pre-dialysis CKD and no history of magnesium supplementation were included. The primary disease that causes of CKD were lupus nephritis (38.3%), nephrotic syndrome (23.4%), urologic disorder (23.4%), tubulopathy (10.6%) and others (4.3%). The average IL-6 level was 55.42±43.04 pg/dL and Mg level was 2.06±1.54 mg/dL. There were no significant correlation between IL-6 level and Mg level with staging of CKD and duration of illness (p>0.05), but there was a significant correlation between serum Mg level and IL-6 level (r=-0.748; p<0.001). Magnesium levels have a significant inverse correlation with IL-6 levels in pre-dialysis CKD children. The lower the Mg levels in the blood, the higher IL-6 levels and vice versa.

***Keywords**: Chronic kidney disease, Magnesium, Interleukin-6, Children, Elisa method.*

ABSTRAK

Penyakit ginjal kronik (PGK) merupakan masalah kesehatan yang serius pada anak, dengan angka kesakitan dan kematian yang terus meningkat di seluruh dunia. Anak dengan CKD cenderung mengalami defisiensi magnesium (Mg) yang dapat merangsang respon inflamasi dalam tubuh. Salah satu respon inflamasi adalah peningkatan Interleukin-6 (IL-6). Penelitian untuk menganalisis hubungan antara Mg dan IL-6 pada anak PGK pra-dialisis. Metode penelitian cross sectional dilakukan di Rumah Sakit Umum Akademik Dr Soetomo dari November 2018 sampai April 2019. Anak-anak dengan CKD pra-dialisis diikutsertakan dalam penelitian ini. Variabel kadar Mg serum (mg/dL) dan penanda inflamasi (IL-6) diukur dari darah dan dianalisis dengan metode ELISA. Korelasi antara Mg dan IL-6 dianalisis dengan uji korelasi Spearman dengan p<0,05. Hasil total 47 anak (27 laki-laki vs 20 perempuan) antara 3 bulan sampai 18 tahun, dengan CKD pra-dialisis dan tidak ada riwayat suplementasi magnesium dimasukkan. Penyakit utama penyebab PGK adalah lupus nephritis (38,3%), sindrom nefrotik (23,4%), kelainan urologi (23,4%), tubulopati (10,6%) dan lain-lain (4,3%). Rata-rata kadar IL-6 adalah 55,42±43,04 pg/dL dan kadar Mg adalah 2,06±1,54 mg/dL. Tidak terdapat hubungan yang bermakna antara kadar IL-6 dan kadar Mg dengan stadium PGK dan lama sakit (p>0,05), namun terdapat hubungan yang bermakna antara kadar Mg serum dengan kadar IL-6 (r=-0,748; p< 0,001). Kadar magnesium memiliki korelasi terbalik yang signifikan dengan kadar IL-6 pada anak PGK pra-dialisis. Semakin rendah kadar Mg dalam darah, semakin tinggi kadar IL-6 dan sebaliknya.

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Kata Kunci: *Penyakit ginjal kronis, Magnesium, interleukin-6, Anak, Metode Elisa*

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INTRODUCTION

Chronic kidney disease (CKD) is a serious health problem in adults and children, with increasing morbidity and mortality rates throughout the world[1]. The number of CKD patients globally in 2019 was 13.4% (11.7 - 15.1%) of the world's population[2] with the amount in pediatric patients is quite high[3]. Moreover, the number of children with CKD in 2011 was 11-12 children per 1 million in CKD stages 3-5, .8 children per 1 million in CKD stages 3-5 (Europe), 5.7 children per 1 million (America), and 38 children per 1 million (Middle East and South Asia)[3].

Chronic inflammation that occurs in CKD patients can increase the risk of disease becoming more severe and worsening of glomerular filtration rate[1]. Children with CKD often have decreasing magnesium (Mg) levels. About 65% of Mg in the body is found in bones, 34% in smooth muscle and the remaining 1% is in plasma and interstitial fluid[4]. Magnesium deficiency can stimulate an inflammatory response and may influence the defense mechanism of human body[5].

The inflammatory response in CKD patients is indicated by high levels of proinflammatory cytokines, including interleukin-6 (IL-6) that are associated with morbidity and mortality[6,7]. Interleukin 6 is a dissolved IL-6 mediator with pleiotropic effect on inflammation, immune response, and hematopoiesis. Interleukin 6 is produced quickly and temporarily in response to infection and tissue injury, contributes to host defense through stimulation of acute phase responses, hematopoiesis, and immune reactions[8].

Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, is the first referral hospital in East Java, Indonesia. The number of pediatric CKD patients in 2018 was 102 patients. Most patients were often being admitted to treatment ward with inflammatory problems as many as 72.4%. Based on the description above and limited studies, the researchers focusing on correlation between Mg and IL-6 levels in pre-dialysis pediatric CKD patients in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

METHODS AND MATERIALS

Participants

Participants in this study were children diagnosed with CKD[9]. The inclusion criteria were children aged 3 months to 18 years, diagnosed with CKD, in pre-dialysis. Children having received Mg supplementation and having an infection (fever/ temperature >37.5ºC and high leukocyte levels) were excluded. Their parents were given an explanation regarding participant rights and obligations. All parents were also required to fill out an informed consent sheet.

Design

An analytic observational study was conducted using cross sectional design. The research was carried out at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, from November 2018 to April 2019 (figure 1). This research had been declared to meet ethical requirements by the Ethics Commitee Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (0835/KEPK/XII/2018). Participants were chosen based on consecutive random sampling. The number of participants in this study were 47 participants. Participants were first identified for characteristics and then measured for Mg and IL-6 levels.

The examination of IL-6 and Mg levels were perform at Clinical Pathology laboratorium of Dr. Soetomo General Academic Hospital. Measurement of IL-6 levels used ELISA test kits-Quantikine HS human IL-6 immunoassay (Elabscience Biotechnology Co., Ltd, Wuhan,

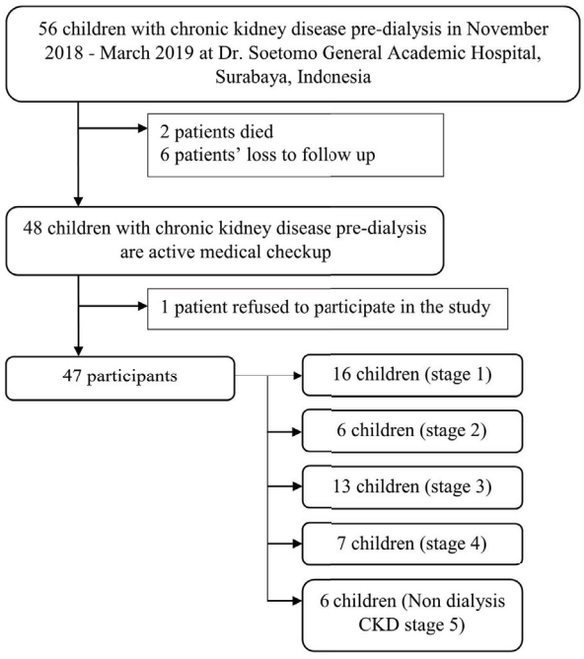

Figure 1. Participant requitment process in this study

Hubei, China), during which participants were taken for venous blood. Blood samples were centrifuged at 3000 rpm for 15 minutes. The serum samples were collected and stored at -80°C in the laboratory of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. The results of IL-6 measurement were categorized into 3 groups: high (≥4.5 pg/dL), normal (1.8-2.3 pg/dL), and low (<1.8 pg/dL). Magnesium levels were measured using photometry method with EXL dimension analyzer (Siemens Healthcare Diagnostics, Erlangen, Germany). The measurement results were categorized into 3: group high (≥1.6 mg / dL), normal (1.2-1.6 mg / dL), and low (<1.2 mg / dL)[4].

Statistical Analysis

The results were displayed in figures and tables. The data were analyzed using IBM SPSS Statistics software version 22.0 (IBM Corp., Armonk, NY, USA). Analysis of correlation between Mg and IL-6 with staging of CKD and duration of illness, between Mg and IL-6 were carried out using Spearmen correlation test. The $p<0.05$ showed a significant correlation, while $p \geq 0.05$ indicated no significant correlation.

RESULTS

Characteristics of Participants

Table 1. Demographics Characteristics of Pre-dialysis CKD Children

Characteristics	n (%)
Sex	
Male	27 (57.45)
Female	20 (42.55)
Age (years)	
< 10 years	14 (29.79)
10-18 years	33 (70.21)
Duration of illness	
< 1 year	18 (38.30)
1-5 years	21 (44.68)
>5 years	8 (17.02)
Etiology	
Lupus Nephritis	18 (38.30)
Nephrotic Syndrome	11 (23.40)
Urological Disorders	11 (23.40)
Tubulopathies	5 (10.64)
HSP nephritis	2 (4.26)
CKD stage	
Stage I	16 (34.04)
Stage II	6 (12.77)
Stage III	12 (25.53)
Stage IV	7 (14.89)
Stage V	6 (12.77)
Mg	
Low	25 (53.19)
Normal	16 (34.04)
High	6 (12.77)
IL-6	
Low	4 (8.51)
Normal	0 (0.00)
High	43 (91.49)

CKD = Chronic kidney disease

Most children were boys of about 27 (57.45%) children. There were 33 children belonged to age group of 10-18 years (70.21%) (Table 1). The average age was 147.81±55.20 months, while mean age of boy and girl were 140.89±60.63 months and 157.15±46.76 months, respectively. There were 21 (44.68%) children suffered from CKD for 1-5 years in, followed by children who experienced illness <1 year of about 18 (38.30%) children (Table 1). The average time of experiencing CKD was 30.64±30.97 months. The average time of male and female participants duration of illness was 26.44±20.67 months and 36.30±40.97 months, respectively. The most common underlying disease in this study was lupus nephritis in 18 (38.30%)

children, followed by nephrotic syndrome and urological abnormalities, each occured in 11 (23.40%) children (Table 1).

The Correlation between Magnesium and IL-6 Levels with staging of CKD

The Mg level in CKD stage 1 was 1.75±0,4 mg/dL, CKD stage 2 was 1.71±0,4 mg/dL, CKD stage 3 was 2.79±2.93 mg/dL, CKD stage 4 was 1.7±0.5 mg/dL and CKD stage 5 was 1.92±0,7 mg/dL (figure 2a). The IL-6 level in CKD stage 1 was 54±41.3 pg/dL, CKD stage 2 was 38.3±33.7 pg/dL, CKD stage 3 was 48.8±44.8 pg/dL, CKD stage 4 was 64.7±31.7 pg/dL and CKD stage 5 was 78.8±64.0 pg/dL (p=0.994, Figure 2b). There were no significant correlation between magnesium and IL-6 levels with staging of CKD (Figure 2a and 2b).

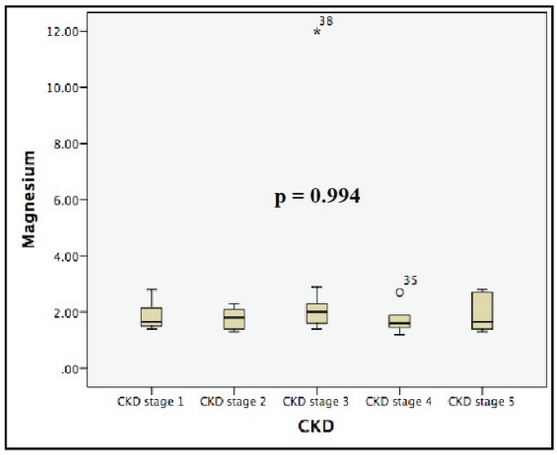

Figure 2a. Magnesium Level (mg/dL) Based on Staging of CK

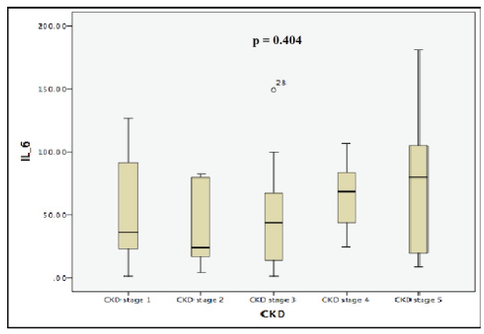

Figure 2b. IL-6 Level (pg/dL) Based on Staging of CKD

The average figure Ff There were no significant correlation between magnesium and IL-6 levels with staging of CKD (Figure 2a and 2b).

The Correlation between Magnesium an IL-6 Levels with Duration of Illness

The average Mg level in <1 year duration of CKD was 1,8±0,53 mg/dL, 1-5 years was 2,15±2,06 mg/dL, and > 5 years was 1,8±0,34 mg/dL (Figure 2c). The average IL-6 level in < 1 year duration of CKD was 53,6±46,3 pg/dL, 1-5 years was 59,6±41,6 pg/dL, and > 5 years was 44,7±43,3 pg/dL (p=0.883, Figure 2d). There were no significant correlation between magnesium and IL-6 levels with the duration of illness (Figure 2c and 2d).

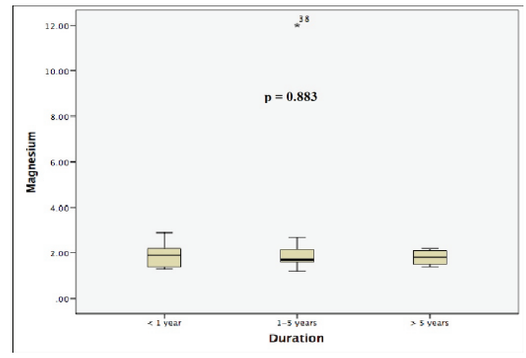

Figure 2c. Magnesium Level (mg/dL) Based on Duration of CKD

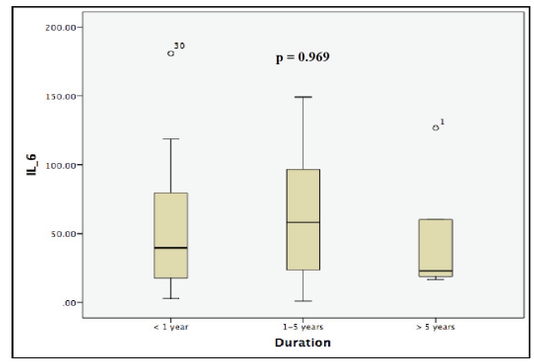

Figure 2d. IL-6 Level (pg/dL) Based on Duration of CKD

Correlation between Magnesium and IL-6 Levels

The average IL-6 level was 55.42±43.04 pg/dL, that was categorized into high IL-6 level. The average IL-6 level in boys and girls were 63.89±46.82 pg/dL and 43.98±35.30 pg/dL, respectively. Most children had high IL-6 levels in 43 (91.49%) children (Table 1). The average Mg level in boys and girls were 2.17±2.01 mg/dL and 1.90±0.46 mg/dL, respectively. Most participants had low Mg level in

25 participants (53.19%), followed by normal Mg in 16 participants (34.04%; Table 1).

The distribution of data was abnormal. The results of statistical analysis using Spearman correlation test showed a significant relationship between average Mg levels and average IL-6 levels ($p<0.001$), with correlation coefficient value of -0.748. This indicated a strong negative correlation between average Mg and average IL-6 levels in the blood. The lower Mg levels will further increase IL-6 levels as a proinflammatory mediator and vice versa (Figure 3a). There were no significant correlation between average of Mg ($p=0.994$) and IL-6 levels ($p=0,404$) with staging of CKD (Figure 3b and 3c), between average of Mg ($p=0,883$) and IL-6 ($p=0,969$) with duration of illness (Figure 3d-e).

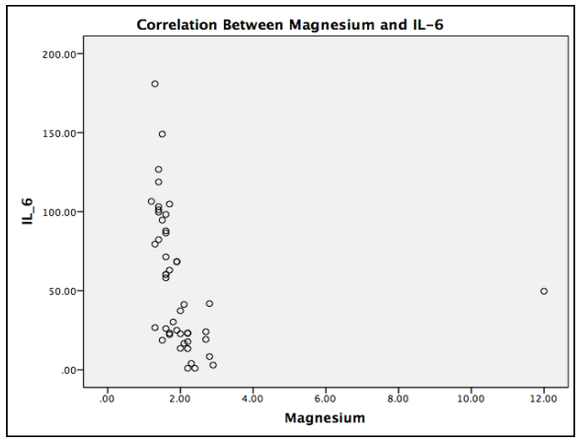

Figure 3a. Correlation between Mg (mg/dL) and IL-6 (pg/dL) in Pre-dialysis CKD Children (r = -784; p = 0.001)

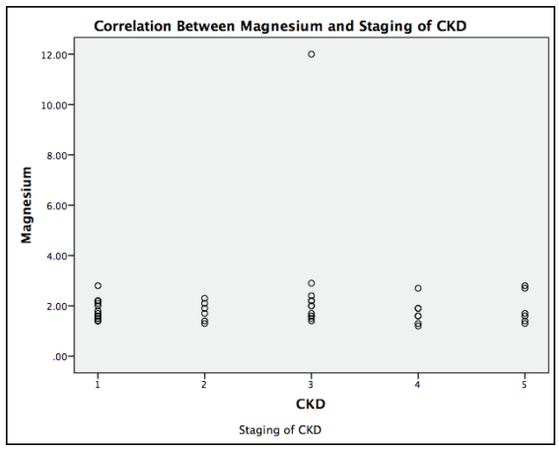

Figure 3b. Correlation between Mg (mg/dL) and Staging of CKD (r = 0,01; p =0.994)

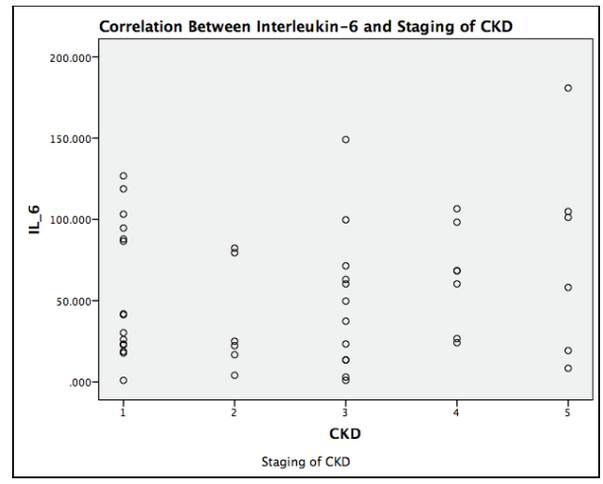

Figure 3c. Correlation between IL-6 (pg/dL) and Staging of CKD (r = 0.125; p =0.404)

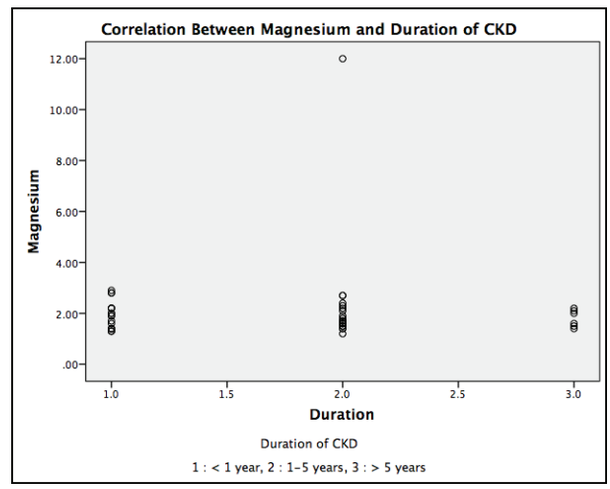

Figure 3d. Correlation between Magnesium (mg/dL) and duration of CKD (r = -0.22; p =0.883)

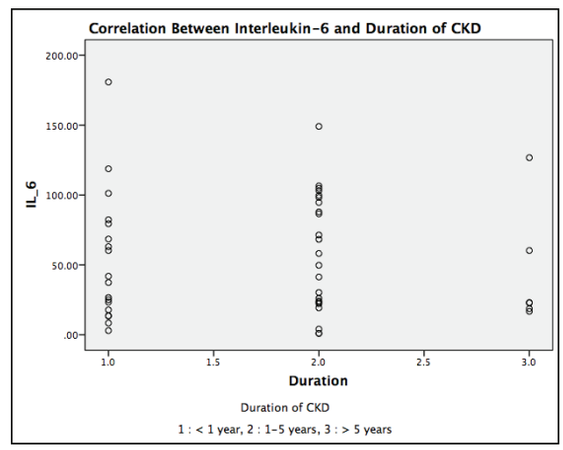

Figure 3e. Correlation between IL-6 (pg/dL) and duration of CKD (r = -0.006; p =0.969)

DISCUSSION

This study found that most participants had low Mg level <1,8 mg/dL. Similar findings were obtained in Swaminathan's study [10], in which CKD patients with hypomagnesemia were higher than normal or high Mg levels. In stage 1-3 CKD patients, there is an increase in fractional Mg excretion as compensation for decreased or loss of kidney function to maintain normal serum magnesium levels in the blood. In CKD with Glomerular Filtration Rate (GFR) <10ml/min/1.73m^2, this compensatory mechanism is less effective (insufficient) to prevent an increase Mg levels in the blood[5]. One of the causes of hypomagnesemia in this study might be caused by calcineurin inhibitors (cyclosporine) administration as a sparing agent for steroid therapy in children with resistant steroid nephrotic syndrome. Visscer et al.'s study[5] stated that hypomagnesemia can be caused by drugs such as thiazide group, proton pump inhibitors, antibiotics, aminoglycoside groups and calcineurin inhibitors. Hypomagnesemia in CKD patients can also be caused by impaired intestinal absorption of Mg due to vitamin D deficiency, therefore routine vitamin D testing is needed in children with CKD[11,12]. In addition, hypomagnesemia is one of the early predictors of the risk of cardiovascular and cardiovascular disease in CKD patients[5].

The results of this study indicated that most participants experienced increasing IL-6 levels as one of the proinflammatory cytokines. Increased levels of IL-6 in CKD patients are most often caused by increased oxidative stress activity, chronic inflammation and fluid overload[13]. The decreased clearance of IL-6 results from impaired renal function[14]. Their study stated that increasing IL-6 levels in CKD patients were associated with the severity of metabolic acidosis and serum bicarbonate levels`[15]. In addition, high levels of IL-6 are also caused by the activity of lupus nephritis and nephrotic syndrome[14,16].

Patients with nephrotic syndrome also have increased IL-6 levels. A study conducted by Subandiyah et al. found a significant increase in IL-6 levels in patients with steroid-resistant nephrotic syndrome compared to steroid sensitive nephrotic syndrome[17]. Jafar et al.'s study obtained similar findings, stating that increasing IL-6 levels were found in patients with idiopathic nephrotic syndrome that was related to the therapeutic response[18]. Interleukin-6 expression in the urine and renal tissues was correlated with proteinuria in minimal changes disease rats [19].

Cunningham et al. found that the quantitative excretion of magnesium tends to decrease in CKD stage 4 dan 5 and cannot be compensated by an increased fractional excretion of magnesium[12]. In this study, there was no correlation between average magnesium level and staging of CKD, it might be due to several factors such as less of magnesium intake, calcineurin inhibitors (cyclosporine) administration and malabsorbtion in majority of children. Study by Magno et al. found the correlation of IL-6 dependent on the type of kidney disease and overlapping conditions such as hypertension and diabetes, but not by duration and staging of CKD. The measurement of IL-6 independently associated with mortality in patient with chronic kidney disease[20,21,22]20,21,22. It also can be used to explain that there were no correlation between average level of magnesium and IL-6 with duration of illness.

Statistical analysis showed a significant relationship between decreased Mg levels and increased IL-6 levels. Lower Mg level will cause higher IL-6 levels, which indicates a more severe inflammatory process. Measurement of Mg levels is affordable and can be used as an early predictor the severity of inflammatory process in pre-dialysis children with CKD. Magnesium is an important element that the body needs as a cofactor for >300 enzymatic reactions. Magnesium is needed for biochemical functions of various body metabolism pathways. Enzyme systems that involve magnesium include protein synthesis, muscle contraction, nerve function, controlling blood sugar, hormone receptor binding, regulating blood pressure, stimulating cardiovascular work, transmembrane ion flux, and connecting calcium. In addition, Mg has an important role in energy production in the body such as having a crucial role in the ATP metabolism (adenylate cyclase), oxidative phosphorylation, and glycolysis.

Another function of Mg is to play a role in the process of RNA and DNA synthesis[23,24,25]3,24,25. Whereas, IL-6 is a dissolved IL-6 mediator with pleiotropic effect on inflammation, immune response, and hematopoiesis[8].

Kidneys have an important role in maintaining levels or concentrations of magnesium in the blood. The ability to regulate magnesium level will decrease along with decrease in kidney function. In addition, there is a decreased ability to absorb Mg in the intestine in CKD children when compared to normal children. The use of drugs as proton pump inhibitors (PPI) in CKD also reduces the ability of intestine to absorb magnesium. In patients who have undergone both hemodialysis and peritoneal dialysis, hypomagnesemia often results from the use of low-magnesium dialysate (low-Mg dialysate) fluids[5].

CONCLUSION

Magnesium levels have a significant inverse correlation with IL-6 levels in pre-dialysis CKD children. Hypomagnesemia is associated with increased levels of IL-6 proinflammatory cytokines. Further research is needed to examine the role of magnesium with cardiovascular disease in children with CKD who do not yet have symptoms and signs.

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CONflICT OF INTEREST

Astrid Kristina Kardani, Jusli Aras, Risky Vitria Prasetyo, Ninik Asmaningsih Soemyarso, and Mohammad Sjaifullah Noer declare that they have no conflict of interest this publication.

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