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Magnesium Levels in Children with Chronic Kidney Disease Stages 1-3

Niveles de Magnesio en niños con enfermedad renal crónica estadios 1-3

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ABSTRACT

Objective: The objective of this study was to assess serum and urinary magnesium levels in children who have chronic kidney disease stages 1-3. **Methods:** Eighty-seven patients who were followed at pediatric nephrology department for chronic kidney disease were included in the study. Age, gender, magnesium, dietary magnesium, and creatinine levels, and fractionated magnesium excretion for all cases were recorded. Patients with chronic kidney disease and control groups were compared in terms of these data. **Results:** Thirty-nine cases with chronic kidney disease were stage 1, 26 were stage 2, and 22 were stage 3. Average age was 9.9 ± 2.8 years in the control group and 10.2 ± 2.6 years in the chronic kidney disease group. The serum magnesium levels were significantly higher in the stage 3 group than in the control group (P<0.001). Also, in stage 3, fractionated magnesium excretion levels were higher compared to the control group (P<0.001). **Conclusion:** In chronic kidney disease with advancing renal failure, hypermagnesemia is frequently seen. Serum magnesium levels should be measured periodically in all the children with chronic kidney disease stage 3 to investigate magnesium abnormalities and assess clinical results.

KEYWORDS: magnesium; chronic kidney disease stages 1-3; children; homeostasis

RESUMEN

Objetivo: El objetivo de este estudio fue evaluar los niveles de magnesio sérico y urinario en niños con enfermedad renal crónica en estadios 1-3. **Material y métodos:** Se incluyeron en el estudio 87 pacientes que tuvieron seguimiento en el servicio de nefrología pediátrica por enfermedad renal crónica. Se registraron los siguientes datos: edad, sexo, niveles de magnesio, ingesta de alimentos con magnesio, y creatinina, así como también la excreción fraccionada de magnesio para todos estos casos. Sobre la base de dichos datos, se compararon los pacientes con enfermedad renal crónica y los grupos de control. **Resultados:** De los 87 casos de enfermedad renal crónica, 39 se hallaban en estadio 1; 26, en estadio 2, y 22, en estadio 3. La edad promedio fue de 9,9 ± 2,8 años en el grupo control y de 10,2 ± 2,6 años en el grupo de enfermedad renal crónica. Los niveles de magnesio en suero fueron significativamente más altos en el grupo del estadio 3 que en el grupo control (p <0,001). Además, en el estadio 3, los niveles de excreción fraccionada de magnesio fueron más altos en comparación con el grupo control (p <0,001). **Conclusión:** En la enfermedad renal crónica con insuficiencia renal avanzada, se observa con frecuencia una hipermagnesemia. Los niveles séricos de magnesio deben medirse periódicamente en todos los niños con enfermedad renal crónica en estadio 3 para investigar las anomalías del magnesio y evaluar los resultados clínicos.

PALABRAS CLAVE: magnesio; enfermedad renal crónica estadios 1-3; niños; homeostasis

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INTRODUCTION

Magnesium is the second most important intracellular cation in the body, and it is known to have important roles in the synthesis of proteins and in many enzymatic reactions. Two systems which are found to have a role in magnesium homeostasis as the main determiner are those of the gastrointestinal tract and of the kidneys. Previous studies have found that, in moderate level (stage 1-3) chronic kidney disease, fractional magnesium excretion (FEMg) increases to compensate for poor renal functioning for the body to maintain its regular magnesium levels. In advanced stage (stage 4-5) CKD, renal compensation mechanisms have been reported to be insufficient, and hypermagnesemia has been reported to develop as a result.[1-2] The objective of our study is to assess the serum and urinary magnesium levels of children with stage 1-3 CKD, which, according to our literature review, has not been studied before.

MATERIAL AND METHODS

Eighty-seven patients who were followed at pediatric nephrology department for CKD and ninety-four healthy children as a control were included in the study. The healthy control group consisted of healthy volunteers, without a chronic disease and drug use and those with similar demographic characteristics to the patient group. Glomerular filtration rates (GFR) were calculated via the Schwartz method. According to GFR, CKD was classified as stage 1 (GFR≥90), stage 2 (GFR between 89-60), or stage 3 (GFR between 59-30) [stage 3a:59-45; stage 3b:44-30].[3] Age, gender, and levels of sodium, potassium, calcium, phosphorus, magnesium, creatinine, as well as FEMg and dietary magnesium levels of all participants were recorded. The normal range of serum magnesium level was accepted as 0.65-1.05 mmol/L (1.5-2.3 mg/dL).[4] A 24-h dietary recall form was prepared and given to either the children themselves or to their parents to document food consumption and its ingredients (including fluid and beverage) in both patient and control group for 3 day before urine and blood sampling. Magnesium levels in the food lists of all cases were calculated by a dietician, and averages were taken and recorded for each case. An informed consent form was signed to each participant. Approval for this study was given by the local Ethical Board (2014/586).

The data were analyzed with an SPSS Statistics 20 program. Averages, standard deviations, and percentages were calculated as descriptive statistics. A One-way-ANOVA was used for statistical comparisons, $p<0.05$ values were accepted as significant.

RESULTS

Eighty-seven children with CKD and 94 healthy children (the control group) were included in our study. The demographic characteristics and laboratory findings of all groups are summarized in **Table 1.** Thirty-nine of the CKD cases were stage 1, 26 were stage 2, and 22 were stage 3. The average age of the control group was 9.9 ± 2.8 years; the average age of the patient group was 10.2±2.6 years.

FEMg: Fractional magnesium excretion, GFR: Glomerular filtration rate, ᵡ: minimum-maximum levels of the parameters. *P<0.001 vs Control, &P<0.05 vs Stage 3a and 3b, P<0.001 vs Stage 2, 3a and 3b, ¥P<0.001 vs Control, Stage 1 and 2, §P<0.05 vs Control, αP<0.001 vs Stage 2, 3a and 3b, £P<0.001 vs Stage 3a and 3b.

No significant differences were found between the control group and those with stage 1 and stage 2 CKD in terms of serum magnesium levels. Significant differences were found between the control group and those with stage 3a and 3b CKD (P<0.001). Serum magnesium levels were found to be significantly high in those with stage 3a and 3b CKD when compared with the serum magnesium levels of the other groups (P=0.003 for stage 3a vs. stage 1, P=0.001 for stage 3b vs. stage2 and P=0.019 for stage 3a vs stage 2, P=0.006 for stage 3b vs stage 2).

When FEMg of the patient group was compared with FEMg of the control group, it was found to be mildly high (but not significantly) for those with stage 1 and stage 2 CKD. FEMg were higher in patients with CKD stage 3a than control, CKD stage 1 and 2 patients (P<0.001). Patients with CKD stage 3b had have higher level of FEMg than control (P=0.004). No significant differences were found between the control group and CKD groups in terms of serum sodium, potassium, calcium and phosphorus, and dietary magnesium levels **(Table 1)**. Also, none of the patients were receiving magnesium therapy.

Table 1. Demographic characteristics and laboratory findings of the study population

Parameters	Control (n:94)	Stage 1 (n:39)	Stage 2 (n:26)	Stage 3a (n:13)	Stage 3b (n:9)
Gender (female %)	55	51	65	38	55
Age (years)/χ	9.9±2.8/5-16	9.5±2.9/5.3-16.3	10.5±2/6.9-15.1	11.7±2.2/7.2-15.2	10±2.2/6.9-13.8
Dietary magnesium levels (mg/day)//χ	158±34/84-260	158±43/86-264	155±21/121-186	151±23/114-200	155±16/135-175
Sodium (mg/dL)//χ	139±3/134-144	138±2/135-142	139±2/135-143	138±2/136-141	138±1/136-140
Potassium (mg/dL)//χ	4.2±0.5/3.5-5.4	4.1±0.5/3.6-4.9	3.9±0.2/3.5-4.3	4.3±0.6/3.7-5.3	4.3±0.5/3.7-5.2
Calcium (mg/dL)//χ	9.7±0.5/8.5-10.5	9.5±0.5/8.6-10.5	9.6±0.5/8.6-10.4	9.3±0.4/8.8-10.1	9.3±0.5/8.6-10
Phosphorus (mg/dL)//χ	5.0±0.7/3.8-6.5	5.4±0.7/3.8-6.8	5.3±0.6/4.3-6.7	5.2±0.8/4.1-6.8	5.3±0.9/4.3-6.4
Magnesium (mmol/L)//χ	0.91±0.10/0.70-1.10	0.91±0.06/0.76-1.10[&]	0.92±0.09/0.78-1.20[&]	1.03±0.07/0.92-1.15*	1.06±0.10/0.94-1.24*
Creatinine (mg/dL)//χ	0.63±0.09/0.40-0.87[¶]	0.66±0.07/0.50-0.82[¶]	1.02±0.26/0.69-1.62	1.70±0,31/1.40-2.30	1.88±0.31/1.50-2.50
FEMg (%)//χ	2.5±0.5/1.26-3.69	2.9±0.8/1.30-4.80	3.0±0.9/1.32-5.12	4.9±2.2/2.10-10.40[¥]	3.9±2.2/1.35-7.21[§]
GFR (ml/min/1.73 m²)/χ	122±13/102-168[α]	123±17/98-158[α]	75±8/63-88[£]	52±5/45-58	37±4/32-42

DISCUSSION

In this study, it was found that, in the early stages of CKD, serum magnesium levels and urinary magnesium excretion was not significantly different than those of healthy individuals. Although urinary magnesium excretion increased with advanced renal failure, this did not prevent serum magnesium elevation, and, toward the third stage of renal failure, serum magnesium and urinary magnesium excretion elevations began to become evident. As our study results demonstrate, in early-stage CKD patients, decreases in mg excretion result from the deterioration of renal function. This can be compensated by increasing the fractionated mg excretion and the serum mg level can be kept within normal ranges.[5] Magnesium fulfils various intracellular functions. It regulates enzyme stabilization in ATP production reactions, calcium antagonization in muscle contractions, insulin signal transduction, and cell proliferation. In addition, it is important for membrane transport and cell adhesion. Approximately 99% of the body's magnesium is found in bones, muscles, and non-muscular soft tissues. Approximately 1% of the magnesium in the body is extracellular magnesium; it is mainly found in serum and erythrocytes. Although it does not reflect total body magnesium, the serum magnesium test is the most used test for magnesium measurement.[4, 6-9] We also used serum magnesium measurements since they are inexpensive but useful.

The intestinal system, bones, and kidneys play roles in magnesium homeostasis. Magnesium is absorbed from the intestines, stored in the bones, and excreted by the kidneys. Intestinal magnesium excretion occurs mainly through passive paracellular mechanisms. Renal excretion plays a vital role in the maintenance of magnesium balance despite intestinal intake. More than 90% of the filtered magnesium in the body is reabsorbed in the passive paracellular style. This reabsorption is realized at a distal convoluted tubule by magnesium-specific transporters. With the loss of renal functions, a significant decrease in the body's ability to excrete magnesium occurs. While renal function losses are compensated for by FEMg in mild forms of stage 1-3 CKD, it results in hypermagnesemia in advanced forms of stage 4-5 CKD, as this mechanism is insufficient for dealing with advanced CKD.[10-14] In our study, serum magnesium levels were found to be within normal ranges for those with stage 1 and stage 2 CKD. For participants with stage 3 CKD, serum magnesium levels were found to be significantly higher compared with the control group. As previously shown, when kidney failure

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progresses to stage 4-5, a decrease in urinary magnesium excretion and an increase in serum magnesium level are observed.[1-2] In line with this, in our study, patients with CKD 3a had slightly high FEMg and low serum Mg compared to patients with CKD3b which is close to CKD stage 4, however, both did not reach statistical significance. In accordance with the literature on the topic, FEMg levels were found to be higher in the CKD groups than in the control group. In the CKD groups, the stage of the disease and the increase in FEMg levels paralleled one another.

The capacity of magnesium excretion deteriorates as GFR decreases. In early stage of CKD, increased FEMg prevents an increase in serum magnesium concentration due to the loss of renal function and keeps balance serum magnesium level within normal range. In advanced CKD, both FEMg and serum magnesium concentration is increased because of destroyed compensatory mechanisms and impaired tubular reabsorption.[1, 15] Especially in stage 5 CKD patients, in which creatinine clearance falls below 10 mL / min, this decrease becomes more evident. On the other hand, with the decrease in renal functions, tubular mg reabsorption is disturbed and an increase in fractionated mg excretion occurs. However, this increase in fractionated mg excretion cannot prevent the increase in serum mg concentration.[1, 5] In our study, we think that both increased serum magnesium and FEMg in CKD stage 3 patients are resulted from inappropriate compensatory mechanism and deterioration of tubular reabsorption.

Different studies have reported that the factors influencing serum magnesium levels in dialysis patients depend on magnesium in the dialysate, diet, and on the use of drugs containing magnesium.[5, 16-17] In our study, the level of dietary magnesium was calculated in the control and patient groups, and no significant differences were found. In addition, none of the patients used magnesium-containing drugs.

In many clinics, serum magnesium concentration is not measured routinely in patients and, thus, most magnesium anomalies are not found. Clinical symptoms of magnesium anomalies (i.e., hypomagnesemia or hypermagnesemia) can be non-specific, similar, or dissimilar. Depending on the severity of the magnesium anomaly, lack of appetite, weakness, cramps, seizures, changes in character, arrhythmia, loss of deep tendon reflexes, hypotension, hypotonia, respiratory depression, and even comas may develop.[18-19] Symptomatic hypomagnesaemia is often accompanied by additional laboratory abnormalities including hypokalemia, hypocalcemia, and metabolic alkalosis. Therefore, if the patients have hypokalemia, hypocalcemia, and metabolic alkalosis and comorbidity that increases the risk of hypomagnesemia by decreasing intestinal absorption of magnesium such as chronic diarrhea, regular use of proton-pump inhibitors or increasing urinary excretion such as diuretics and nephrotoxic medications, serum magnesium level should be measured in even asymptomatic patients.[20]

Clinical findings of hypermagnesemia vary according to serum magnesium level. Mild hypermagnesemia (<2.88 mmol/L) is generally asymptomatic. Decreased reflexes, worsening of the confusional state, urinary retention, constipation, hypotension, bradycardia, and blurry vision may be seen in moderate hypermagnesemia (2.88-4.94 mmol/L). Severe hypermagnesemia (>4.94 mmol/L) can cause life threatening arrhythmia, coma, and muscle paralysis.[1] In our study, we did not find any patients having hypermagnesemia.

Various epidemiological studies have shown mild hypermagnesemia to have positive effects on cardiovascular disease and mortality, while hypomagnesemia has been shown to be a risk factor for cardiovascular and some metabolic diseases. In some in vitro and animal studies, magnesium was shown to have a protective role in vascular calcification through multiple molecular mechanisms. Firstly, magnesium inhibits magnesium calcium phosphate crystals from turning into apatite crystals. Secondly, it functions as a calcium antagonist and, thus, prevents calcium access to cells. Thirdly, it restores the balance between calcium promoter and inhibitor expressions. Furthermore, clinical studies have proven magnesium to have protective effects on vascular calcification. Hypomagnesemia has been associated with high blood pressure. A reverse association was found between serum magnesium levels and systolic blood pressure. At the same time, hypomagnesemia has been defined as a major risk factor for atherosclerosis.[21-26]

Present study has some limitations. The first is that the number of cases in the patient group was low, especially in stage 3. The second is that patients with CKD stage 4-5 were not included in the study. Therefore, we could not generalize our study results for all CKD stages.

CONCLUSION

In conclusion, renal response is protected in the early stages of CKD. In the advanced stages, however –especially stage 3b– the body's renal compensation mechanism is insufficient for the maintenance of magnesium levels, and a tendency for hypermagnesemia emerges. Thus, for patients who have stage 3 CKD, serum magnesium levels should be checked regularly to protect these patients from life-threatening complications.

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