Magnesium plasma concentration in haemodialysis patients treated at a single dialysis unit

Stężenia magnezu w surowicy pacjentów leczonych powtarzanymi hemodializami w jednym ośrodku

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Keywords
magnesaemia, haemodialysis, renal failure

Słowa kluczowe
magnezemia, hemodializoterapia, niewydolność nerek

Summary
Introduction. Mineral disorders are common in dialysed people, but serum magnesium concentration is only seldom monitored in this group of patients. The negative consequences of magnesium deficiency are proved, and in dialysed patients higher concentration of magnesium correlates with lower mortality and morbidity.

Aim. Retrospective examination of plasma concentrations of magnesium determined in adult patients dialysed in one big dialysis unit in Warsaw, and evaluation of some factors that could influence or determine its concentration.

Material and methods. Retrospective observational study – the results of the first plasma magnesium concentration measured between January 1, and June 30, 2015 in all patient on chronic haemodialysis therapy were extracted from the database.

Results. We examined 168 patients dialysed with the use of dialysis fluid magnesium concentration of 0.5 mmol/l. The mean magnesium plasma concentration was 0.87 ± 0.114 mg/dl. In 22 patients (13.09%) mild hypermagnesaemia (not above 1.3 mmol/l) and in 3 patients hypomagnesaemia (1.78%) were diagnosed. In 56 out of 143 patients (38.5%) with normomagnesaemia, the serum magnesium concentration was lower than 0.83 mmol/l. Serum magnesium concentration was significantly lower in patients presenting with diabetes.

There was statistical correlations between plasma concentration of magnesium and creatinine \( r = 0.47 \), and nPCR \( r = 0.3, p < 0.001 \), but not with the Kt/V, which suggests that nutrition has stronger impact on magnesium concentration than dialysis dose.

Conclusions. Since hypomagnesaemia is harmful, and mild hypermagnesaemia seems to pose no danger to dialysed patients and could be even protective, serum magnesium concentration should be monitored in these patients to avoid magnesium deficiency, especially in malnourished patients, those with small muscle mass or with diabetes.

Streszczenie

Wstęp. Zaburzenia gospodarki magnezowej są częste u chorych dializowanych, a jednak stężenie magnezu jest rzadko monitorowane w tej grupie chorych. Opisano wiele niekorzystnych konsekwencji niedoboru magnezu, natomiast w grupie chorych dializowanych wyższe stężenia magnezu korelują z mniejszą śmiertelnością i chorobowością.

Cel pracy. Zbadanie retrospektywnie stężenia magnezu oraz próba znalezienia czynników mogących na nie wpływać, w populacji dorosłych osób dializowanych w dużym ośrodku dializ w Warszawie.

Materiał i metody. Retrospektywne badanie obserwacyjne. Z bazy danych wszystkich pacjentów przewlekli dializowanych wyekstrahowano wyniki pierwszych oznaczeń stężenia magnezu w surowicy w okresie 01.01.2015 -3 0.03.2015.

 Wyniki. Zbadano 168 pacjentów dializowanych przy użyciu płynu dializacyjnego ze stężeniem magnezu 0,5 mmol/l. Średnie stężenie magnezu w surowicy wynosiło 0,87 ± 0,114 mmol/l.

U 3 (1,78%) osób stwierdzono hipomagnezemię, a u 22 (13,09%) łagodną, nieprzekraczającą 1,3 mmol/l hypermagnezemię. U 56 pacjentów spośród 143 z normomagnezemią (38,5%) stężenie magnezu było niższe niż 0,83 mmol/l. Stężenie magnezu było zazwyczaj niższe w grupie osób z cukrzycą.

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INTRODUCTION
Magnesium is the second most abundant cation in the intracellular space and the fourth most abundant in the body. Magnesium is essential in many important biochemical reactions, including all ATP transfer reactions. Disorders of magnesium homeostasis are common in dialysis patients but magnesium does not receive much attention from most clinicians taking care of these patients.

In general population and in the CVD patients’ hypomagnesaemia is a significant predictor of increased cardiovascular morbidity and mortality, favours the reduction of HDL and the increase of LDL and TG, increases oxidative stress and inflammation, platelet aggregation and insulin resistance (1). To the contrary, higher magnesium levels are correlated with better outcomes (2, 3). Dietary magnesium intake was inversely associated with mortality risk in people at high risk of cardiovascular disease (4) and in general population (5). Because of beneficial effect of magnesium on the cardiovascular mortality risk reduction and the incidence of diabetes mellitus, it is suggested that lower limit of normal plasma magnesium concentration should be increased from 1.7 to 2 mg/dl (0.7 and 0.83 mmol/l, respectively).

In people with CKD magnesium balance is related to diminished excretion by the kidneys, depressed intestinal magnesium absorption due to a deficiency of active vitamin D (6), poor nutrition, acidosis and the following reduced absorption, and drugs: diuretics, proton pump inhibitors or phosphate binders (7, 8).

In dialysed patients the important additional determinant of magnesium balance is magnesium concentration in the dialysate. In spite of lack of kidney function, in people on dialysis magnesium concentration in plasma could be normal, below or above normal.

A number of investigations conducted during the last 15 years showed beneficial effect of magnesium in preventing vascular calcification in vitro and in vivo in animal studies, and the deleterious effect of hypomagnesaemia (9-11). Increased magnesium levels in dialysed patients in comparison to lower levels are correlated with better outcomes including mortality (2, 3). A convincing proof that supplementation of magnesium, or administration it in order to increase its level is save and beneficial health-wise is unfortunately lacking. The biggest anxiety concerns the incidence of hypermagnesaemia in HD patients and it’s influence on patient status, especially on bone metabolism. However, it is reasonable to avoid hypomagnesaemia in that special group of patients, and to monitor its concentration on regular basis.

AIM
We decided to examine retrospectively the plasma concentrations of magnesium determined in dialysed patients in one big dialysis unit in Warsaw, and to evaluate some factors that could influence or determine its concentration.

MATERIAL AND METHODS

The results of first magnesium plasma concentration determined between January 1, and June 30, 2015 were extracted from the database. All of the 168 patients on chronic RRT program due to end stage renal disease, dialysed in the ambulatory Warsaw dialysis unit-Diaverum were included into the study – there were 72 women (42.86%) and 96 men (57.14%).

All patients were dialysed with the use of dialysis fluid magnesium concentration of 0.5 mmol/l. Dialysate flow was fixed for all patients at 500 ml/min. Most patients – 85%, were dialysed with calcium dialysate concentration of 1.25 mmol/l, and 15% with 1.5 mmol/l.

Statistical analysis
Statistical analyses were performed using STATISTICA v 12 statistical software, using correlation tests and multiple regression analysis. All reported P values were 2-sided, and values of P < 0.05 were considered statistically significant. Analysis of the correlation between magnesium and BMI, BSA, nPCR, creatinine, and urea was performed.

RESULTS
In 168 patients the median age was 68 years: 73 years for women, and 65 for men. The causes of renal disease are presented in table 1. The anthropometric, nutritional and dialysis efficacy indices are given in table 2.

The most frequent cause of renal failure (47 patients) was diabetes (20.8%), but the diabetes was diagnosed in patients 65 (38%: M 44.6% and F 55.4%), of whom 51 (78%) were receiving insulin therapy. The prevalence of diabetes was 30% (29/96) in men and 50% (36/72) in women. In 18 patients diabetes was considered comorbidity. The mean age of patients with diabetes was 68 years, without diabetes 65 years.

The mean magnesium plasma concentration in the first measurement in 2015 was 0.87 ± 0.114 mg/dl.
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In 22 patients hypermagnesaemia – (13.09%) and in 3 patients hypomagnesaemia (1.78%) were diagnosed. In 56 out of 143 patients (38.5%) with normomagnesaemia, the serum magnesium concentration was lower than 0.83 mmol/l. In 28 of 65 patients presenting with diabetes (43.08%) plasma magnesium concentration was lower than 0.83 mmol/l. This was insignificantly more (chi² = 2.94, p > 0.05), as compared to patients with no diabetes – 31 of 103 patients (30.10%). Magnesium plasma concentration in patients with diabetes was significantly lower, than in patients without diabetes (0.85 mmol/l, SD 0.094 and 0.89 mmol/l, SD 0.123, respectively; p < 0.05).

Multiple regression analysis showed statistical correlations between plasma concentration of magnesium and creatinine (r = 0.47, fig. 1), and with protein catabolic rate per normalized body weight – nPCR (r = 0.3, fig. 2) (p < 0.001). The correlation between plasma magnesium and creatinine levels, and nPCR was strong in both groups – with and without diabetes. There was present also a quite strong correlation between magnesium concentration and urea (r = 0.3) and phosphate concentration (r = 0.29). Considering the strong co-linearity of these two parameters to plasma creatinine, both did not reach statistical significance in the multiple regression model. The correlation between plasma magnesium concentration and Kt/V was weak (r = -0.05). There was no correlation between magnesium and calcium and PTH.

Table 1. Causes of chronic haemodialysis in the cohort studied.

<table>
<thead>
<tr>
<th>ESRD cause</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>20.83%</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>17.26%</td>
</tr>
<tr>
<td>Hypertension/angiosclerosis</td>
<td>17.26%</td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>10.12%</td>
</tr>
<tr>
<td>Autosomal dominant polycystic kidney disease</td>
<td>4.76%</td>
</tr>
<tr>
<td>Other 7.14%:</td>
<td></td>
</tr>
<tr>
<td>- familiar nephropathy</td>
<td></td>
</tr>
<tr>
<td>- granulomatosis with polyangitis</td>
<td></td>
</tr>
<tr>
<td>- myeloma multiplex</td>
<td></td>
</tr>
<tr>
<td>- amyloidosis</td>
<td></td>
</tr>
<tr>
<td>- haemolytic-uremic syndrome</td>
<td></td>
</tr>
<tr>
<td>- kidney cancer</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>19.05%</td>
</tr>
</tbody>
</table>

Table 2. The anthropometric and nutritional indicators, and dialysis efficacy data.

<table>
<thead>
<tr>
<th>Parameters measured</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height [cm]</td>
<td>163.7</td>
<td>10.40</td>
</tr>
<tr>
<td>BMI [kg/m²]</td>
<td>26.35</td>
<td>5.512</td>
</tr>
<tr>
<td>Body surface area [m²]</td>
<td>1.79</td>
<td>0.222</td>
</tr>
<tr>
<td>Body mass increase between treatments [%]</td>
<td>2.1</td>
<td>1.41</td>
</tr>
<tr>
<td>RR systolic [mmHg]</td>
<td>137.7</td>
<td>23.63</td>
</tr>
<tr>
<td>RR diastolic [mmHg]</td>
<td>75.4</td>
<td>13.79</td>
</tr>
<tr>
<td>MAP [mmHg]</td>
<td>96.18</td>
<td>15.302</td>
</tr>
<tr>
<td>Duration of treatment (months)</td>
<td>33.6</td>
<td>33.53</td>
</tr>
<tr>
<td>Weekly time of treatment (min)</td>
<td>736.8</td>
<td>59.66</td>
</tr>
<tr>
<td>Time of one treatment (min)</td>
<td>247.2</td>
<td>12.19</td>
</tr>
<tr>
<td>Blood flow [mL/min]</td>
<td>337.4</td>
<td>24.02</td>
</tr>
<tr>
<td>EPO [U/week]</td>
<td>4612</td>
<td>1796.5</td>
</tr>
<tr>
<td>URR</td>
<td>0.719</td>
<td>0.090</td>
</tr>
<tr>
<td>Kt/V</td>
<td>1.52</td>
<td>0.361</td>
</tr>
<tr>
<td>Ca-S [mmol/L]</td>
<td>2.12</td>
<td>0.166</td>
</tr>
<tr>
<td>PHOS-S [mmol/L]</td>
<td>1.71</td>
<td>0.448</td>
</tr>
<tr>
<td>PTH-S [pg/mL]</td>
<td>385.8</td>
<td>274.72</td>
</tr>
</tbody>
</table>
| EPO – erythropoietin, Ca-S – serum calcium prior to HD session, PHOS-S – serum phosphate prior to HD session, PTH-S – intact parathormone

Fig. 1. Plasma magnesium and creatinine concentrations in 168 patients on regular haemodialysis treatment (CI – confidence interval).
Further to the detection of strong correlation between plasma magnesium and creatinine concentration the risk for hypermagnesaemia in relation to creatinine was evaluated. The resulting ROC curve is presented on figure 3. For the cut-off point set at plasma creatinine of 6.5 mg/dl the sensitivity and specificity for diagnosing hypermagnesaemia were 95% and 63%, respectively (AUC 0.83).

BMI in patients with diabetes was higher in comparison to patients without diabetes (p = 0.00005) but plasma creatinine was lower (p = 0.002). Concentrations of calcium, phosphate, haemoglobin and nPCR did not differ significantly between the groups.

DISCUSSION

In dialysed patients the magnesium balance results from diminished or lacking excretion by the kidneys, depressed intestinal magnesium absorption, poor nutrition, drugs (diuretics, proton pump inhibitors, others) and the concentration of magnesium in dialysate, which affect magnesium diffusion during dialysis.

The ultrafilterable magnesium, which can be removed on dialysis is the ionized one (60 to 70% of plasma magnesium) and complexed with non-protein anions such as bicarbonate, phosphate and citrate (about 10% of plasma magnesium). The rest of magnesium is bound to albumin and not ultrafilterable.

During haemodialysis a small amount of magnesium could be removed by ultrafiltration, but the concentration gradient between plasma magnesium and dialysate magnesium concentration is the main force influence magnesium flux in HD patients.

Taking into account the Donnan factor (different distribution of proteins between plasma and dialysate influence ion transport through the membrane of dialyzer) one can calculate, that to let magnesium diffuse from the blood to dialysate its concentration in dialysate should be lower by more than 3% than that of the ultrafilterable plasma magnesium.

Dialysis with magnesium concentration of 0.5 mmol/l allows to remove magnesium from the blood, and to avoid hypermagnesaemia, but in small group of dialysed patients results in hypomagnesaemia. In our results most of the patients were normomagnesaemic prior to HD session. Only 3% of patients were overtly hypomagnesaemic, but almost 36% of patients had magnesium concentration
in plasma lower than 0.83 mmol/l, which many authors consider the lowest acceptable value in dialysed patients.

Despite the use of hypomagnesic dialysis fluid, the mild hypermagnesaemia ensued in 22 patients, however of the maximum concentration lower than 1.3 mmol/l.

Hypermagnesaemia has been described by others also with the use of magnesium dialysate concentration of 0.75 mmol/L – in both the PD and the HD patients (12-14). In one other report when a lower dialysate concentration (0.5 and/or 0.25 mmol/L) was used the results were not as much consistent, but it is pointed out that hypomagnesaemia can occur especially, when the dialysate with magnesium concentration of 0.25 to 0.5 mmol/l is used (15). Besides of dialysate concentration, number of other factors like diuretics, nutrition, disorders of gastrointestinal tract, affect the magnesium balance in HD/PD patients. Nowadays the role of proton pump inhibitors, widely used in HD patients, in inhibiting absorption of magnesium and resulting in positive correlation with hypomagnesaemia incidence in these patients (7, 8).

According to our results, serum magnesium level correlated with nPCR and creatinine, suggesting that nutrition has strong impact on magnesium balance.

The similar results, were presented by Liu et al. (16). They examined 92 HD patients, in patients who were hypomagnesaemic, serum Mg, creatinine, albumin, pre-albumin levels, nPCR, dietary protein intake, triceps skin fold thickness, mid-arm circumference, mean mid-arm circumference, subjective global assessment scores, and Kt/V were lower than in hypermagnesaemic patients. In our group the correlation between the Kt/V and magnesium was negligible. Also other group find that low s-Mg level was independently associated with malnutrition (also with inflammation, arterial stiffening and risk of death) (17). All these data support our impression based on the relation of magnesaemia to creatinine, nPCR but not to Kt/V, that plasma magnesium is higher in patients with bigger muscle mass, independently from dialysis dose. Malnutrition and inflammatory state are common in dialysed patients, thus that group is at higher risk of hypomagnesaemia and it consequences. In general population is suggested that the deficiencies in magnesium status depend mostly on inappropriate diet and this problem is increasing in older people (18), who generally take more processed food and less whole grains and green vegetables (19).

We found a tendency to lower plasma magnesium in patients with diabetes. Type 2 diabetes is often accompanied by alteration of Mg status. An increased prevalence of Mg deficit has been identified in diabetic patients, especially in those with poorly controlled glycaemia, with longer duration of the disease and with the presence of vascular disease (20-23). It is suggested that insulin resistance and chronic hyperglycaemia might contribute to the development of hypomagnesaemia (16, 24). Because insulin has been implicated in enhancing renal magnesium reabsorption, insulin deficiency or resistance could promote urinary magnesium excretion. However, most dialysed patients had lost kidney function and this explanation could be appropriate only to minority of them with residual renal function. On the other hand dietary Mg deficiency may cause insulin resistance (25-27). In rats, Mg supplements were able to postpone the onset of diabetes (28). In young, African Americans (without diabetes) low dietary Mg was associated with insulin resistance (21). Deficiencies of Mg status have been correlated with the risk of developing diabetes type 2 or glucose intolerance (29, 30).

The relationship between low magnesium concentration and haemodynamic instability – tendency to hypotension, arrhythmia, and worse cardiac contractility in HD patients is well known (31, 32), so it is advised not to use low magnesium concentration in dialysate in patients with frequent intra dialytic hypotension.

The number of experimental studies reporting inhibitory effects of magnesium on vascular calcification in normal and/or uremic animals, is ever increasing (9-11) and in in vitro models (11). The increasing number of epidemiologic studies shows correlations between higher serum magnesium levels, and lower incidence of CVD and mortality (33). A large study conducted with 142,555 haemodialysis patients from nationwide registry-based cohort in Japan to determine whether hypomagnesaemia is an independent risk for increased mortality in this population showed that hypomagnesaemia was significantly associated with an increased risk of mortality in haemodialysis patients. Moreover among patients with serum phosphate levels of ≥ 6.0 mg/dl, the cardiovascular mortality risk significantly decreased with increasing serum magnesium levels (2).

In the light of the knowledge about the role of magnesium in homeostasis and of many reported observations presenting that lower levels of magnesium are correlated with worse outcomes, but supplementation of magnesium has beneficial effect, it seems reasonable to avoid low-normal level of magnesium in plasma in dialysed patients, and to adjust the concentration of magnesium in dialysate to each patient.

CONCLUSIONS

Plasma concentration of magnesium in HD patients using dialysate with magnesium concentration of 0.5 mmol/l is seldom above the normal, and hypomagnesaemia or low-normal magnesaemia can occur in these patients. The nutritional status and diabetes are important factors influencing the magnesium concentration in dialysed patients independent from dialysis dose. Since hypomagnesaemia is harmful, and mild hypermagnesaemia seems not dangerous to dialysed patients, and could be even protective, more careful adjustment of dialysate magnesium concentration would be appreciated.
BIBLIOGRAPHY


MAGNESIUM PLASMA CONCENTRATION IN HEMODIALYSIS PATIENTS TREATED AT A SINGLE DIALYSIS UNIT

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