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Do diabetes and nutrition status determine plasma magnesium concentration in patients on chronic renal replacement therapy?

Czy cukrzyca i stopień odżywienia warunkują stężenie magnezu w osoczu chorych przewlekle leczonych powtarzanymi hemodializami?

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Keywords

magnesium, magnesaemia, haemodialysis, diabetes, diet

Słowa kluczowe

magnez, magnezemia, hemodializa, cukrzyca, dieta

S u m m a r y

Introduction. Magnesium depletion negatively impacts the cardiovascular system, inflammation, insulin resistance and diabetes – in patients on chronic haemodialysis it is linked to worse prognosis and inflammation, and the magnesaemia correlates with protein intake (nPCR) and creatininaemia.

Aim. To verify which elements of the standard set of clinical data used for assessment of nutrition status, correlate best with plasma magnesium in diabetic and non-diabetic patients on chronic haemodialysis program.

Material and methods. Single-unit observational study, based on standard laboratory and clinical parameters obtained at the beginning of a single midweek haemodialysis session for routine cyclic workup in patients on regular chronic haemodialysis.

Results. Out of 147 adult patients on regular chronic haemodialysis (males 83, females 64; median age 68 years) 57 had diabetes. Hypomagnesaemia was diagnosed in 2 (1.19%), and hypermagnesaemia in 39 (23.21%). Serum magnaesium concentration was < 0.83 mmol/l in 32 patients (21.77%) – 16 with, and 16 without diabetes (28 and 17.8% of all patients with and without diabetes, respectively). The only variables correlating with magnesaemia were nPCR, plasma creatinine and albumin (R2 = 0.32). Within each tertile of magnesaemia, none of the predialysis blood parameters analysed differed in patients with diabetes from that in patients with no diabetes, with an exception for urea and phosphate concentrations, higher in patients with diabetes within the tertile 2.

Conclusions. Better diet results in better nutrition and higher magnesium serum concentration in haemodialysis patients, which might prevent, or diminish inflammation also in patient with diabetes. The efficacy of dialysis seemed of lesser importance.

S t r e s z c z e n i e

Wstęp. Niedobór magnezu negatywnie wpływa na układ sercowo-naczyniowy, odczyn zapalny, oporność na insulinę oraz na przebieg cukrzycy. U pacjentów hemodializowanych wiąże się to z gorszym rokowaniem i stanem zapalnym, a magnezemia koreluje ze spożyciem białek (nPCR) i kreatyninemią.

Cel pracy. Ocena korelacji z magnezemią okresowo badanych parametrów odżywienia i efektywności dializy u przewlekle leczonych dializami pacjentów chorych na cukrzycę i bez cukrzycy.

Materiał i metody. Jednoośrodkowe badanie obserwacyjne oparte o standardowe badania laboratoryjne i kliniczne uzyskiwane w czasie okresowej oceny pacjentów hemodializowanych.

Wyniki. Spośród 147 dorosłych pacjentów przewlekle leczonych powtarzanymi hemodializami (83 mężczyzn, 64 kobiety; mediana wieku 68 lat) 57 miało cukrzycę. Hipomagnezemię rozpoznano u 2 (1,19%), a hipermagnezemię u 39 (23,21%) osób. Stężenie magnezu w surowicy < 0,83 mmol/l miało 32 pacjentów (21,77%) – 16 z cukrzycą i 16 bez cukrzycy (odpowiednio 28 i 17,8% wszystkich pacjentów z cukrzycą i bez cukrzycy). Z magnezemią korelowały jedynie nPCR oraz stężenia kreatyniny w surowicy i albumin w osoczu (R2 = 0,32). W każdym tercylu magnezemii żaden z parametrów we krwi, Kt/V ani nPCR u pacjentów z cukrzycą nie różnił się istotnie od obserwowanych u pacjentów bez cukrzycy, za wyjątkiem wyższego stężenia fosforanów i mocznika w 2. tercylu.

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Wnioski. Lepsza dieta to lepszy stopień odżywienia i wyższe stężenia magnezu w surowicy pacjentów hemodializowanych, co może chronić przed stanem zapalnym lub go zmniejszać, także u pacjentów z cukrzycą. Sprawność dializy wydaje się być mniej istotna w tym względzie.

INTRODUCTION

Disorders of magnesium homeostasis are common in HD patients, but usually remain undiagnosed and left uncorrected, because the serum magnesium concentration is not routinely monitored. 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, and diabetes incidence (1-3). To the contrary, higher magnesium levels, and higher magnesium dietary intake correlate with better outcomes (4-7).

The details of magnesium absorption in the gastrointestinal tract are not fully understood – an active transport occurs in the ileum, and the passive absorption in other parts of the small intestine uses (8, 9). The enterocyte apical membrane hosts two magnesium channels of the melastatin subfamily of transient receptor potential channels: TRPM6 which is located in the colon endothelial cells (and also in the distal convoluted tubule of the nephron), and the TRPM7 which is present in various parts of the small intestine (and in many other cells). TRPM6 activity is modulated by estrogens and by dietary magnesium restrictions, which increase the activity of the channel. Many other factors: age, vitamin D, gastrointestinal diseases, drugs (IPP, some phosphate binders) also affect absorption of magnesium (10).

Nowadays people on dialysis are getting older, so it is reasonable to ask, if the standard of care to use magnesium concentration of 0.5 mmol in dialysate, made many years ago, is not too low nowadays and may results in dangerous hypomagnesaemia, especially in patients presenting with diabetes.

During the first 6 month of 2015 we found, that low-normal magnesium concentrations (below 0.83 mmol/l) and hypermagnesaemia affected every second patient at our haemodialysis unit (38.5 and 13.1% respectively). The serum magnesium correlated significantly with nPCR and serum creatinine, but not with dialysis dose, which suggested that in patients on regular chronic haemodialysis the nutritional status prevailed over dialysis efficacy in determining magnesaemia (Daniewska D. et al.: Magnesium plasma concentration in haemodialysis patients treated at a single dialysis unit. in press - this issue, p. 704).

AIM

To verify which elements of the standard set of clinical data used for assessment of nutrition status correlate best with plasma magnesium in patients on chronic haemodialysis program.

MATERIAL AND METHODS

Single-unit observational study, based on standard laboratory and clinical parameters obtained at the beginning of a single midweek haemodialysis session for routine cyclic workup in patients on regular chronic haemodialysis. Standard laboratory procedures at "Diagnostyka Laboratoria Medyczne" were used for both pre- and post-dialysis laboratory tests. The relevant anthropometric and dialysis data were extracted from medical records.

Statistical analysis

Statistical analyses, including the description sample statistics, correlation tests and multiple regression analysis, were performed using STATISTICA v 12 software. Analysis of the correlation between magnesium and BMI, BSA, nPCR, creatinine, and urea was also done. Additional analysis of difference of the mean by diabetes status was made within the three groups separated by magnesaemia tertiles. The differences of mean between the tertiles, were not analysed. All reported P values were 2-sided, and values of $P < 0.05$ were considered statistically significant.

RESULTS

In August, 2015 the routine workup was done in 147 adult patients on regular chronic haemodialysis (males 83, females 64), aged 23-94 years (median 68 years). Out of these patients, 57 have been previously diagnosed with diabetes. At the workup hypomagnesaemia was diagnosed in 2 patients (1.19%), and hypermagnesaemia in 39 (23.21%). Serum magnaesium concentration was low (< 0.83 mmol/l) in 32 patients (21.77%) – 16 presenting with, and 16 without diabetes (28 and 17.8% of all patients with and without diabetes, respectively). Basic clinical and dialysis data are given in table 1. Table 2 contains the results of blood/plasma/serum concentrations of the parameters routinely analysed.

The relation between the serum magnesium concentration and each measured parameter revealed strong association of magnesaemia with the nPCR, and with the pre-dialysis concentrations of serum urea, creatinine, phosphates, and plasma albumin. Further analysis of these associations using the stepwise multiple regression reduced to only three, the number of variables presenting statistically significant correlation with serum magnesium concentration. These were: nPCR, and the concentrations of serum creatinine and of plasma albumin. A model based on these three variables was highly significant (R full model = 0.57, p < 0.0001, R2 = 0.32). Figure 1 pictures the strong correlation of serum magnesium and plasma albumin.

Plasma magnesium in patients with diabetes was similar to that in patients without diabetes (0.90 +/- 0.126 mmol/l and 0.94 +/- 0.132 mmol/l, respec-

Table 1. Basic anthropometric and haemodialysis data collected at the workup.

Anthropometric and haemodialysis data	Mean	Standard deviation
Body Mass Index (BMI) [kg/m^2]	27.19	5.900
Body surface [m^2]	1.78	0.22
Intra-dialysis weight gains [%]	2.91	1.29
BP systolic [mmHg]	134.48	22.15
BP diastolic [mmHg]	74.11	13.02
Mean Arterial Pressure (MAP) [mmHg]	94.23	14.57
Therapy duration [months]	38.82	33.31
Weekly dialysis time [min]	737.38	59.88
Single session time [min]	246.9	11.51
Blood flow [mL/min]	338.81	23.99
Urea Reduction Rate (URR)	0.718	0.094
Kt/V for urea	1.52	0.38
nPCR [g/kg/24 h]	0.870	0.240

Table 2. Laboratory data collected at the workup.

Serum/plasma/blood concentration	Mean	Standard deviation
Calcium [mmol/L]	2.17	0.168
Phosphates inorganic [mmol/L]	1.71	0.46
Parathormone [pg/mL]	385.791	274.723
Urea pre-HD [mg/dl]	99.99	32.55
Urea post-HD [mg/dl]	28.52	14.69
Creatinine [mg/dl]	6.77	2.59
Plasma albumin [g/dl]	4.06	0.363
Haemoglobin [g/dl]	10.56	1.140

tively; p = 0.111). There were also no differences between the two groups in plasma urea, creatinine, phosphates, and nPCR.

In order to extract the impact of diabetes on magnesaemia the whole group was divided into tertiles using serum magnesium concentrations as denominator. The results are presentented in table 3. Within each tertile none of the parameters analysed in patients with diabetes differed significantly from that in patients with no diabetes, with the exception for urea and phosphate predialysis concentrations, which were in patients presenting with diabetes, significantly higher within the tertile 2.

DISCUSSION

Our results confirm the previous observations, including ours, that disorders of magnesium concentration are common in dialysed patients, and correlate with such nutrition indices as nPCR and creatinine. These observations were further supported in our group of patients by the positive correlation between plasma albumin and serum magnesium concertations. The other two important parameters relating to patients' diet, i.e. plasma urea and phosphate concentrations prior to dialysis, were significantly associated with the magneseamia in whole group only if evaluated separately. The multiple correlation analysis indicated that serum creatinine prevailed over the phosphate and urea in relation to magnesaemia. The main dietetic sources of magnesium are whole grains, nuts, and green leafy vegetables (11), and patients on dialysis are discouraged to take them in. We did not evaluate our patients' diet, so we cannot apportion the differences observed to the diet variety.

It is well known, that patients presenting with diabetes tend to become hypomagnesaemic. Interestingly diabetic patients within the 1. and 3. tertile of magnesaemia had all parameters measured similar to those of patients with no diabetes. In tertile 2. the urea and phosphate concentrations were lower in patients with no diabetes, which might indicate that their protein consumption was lower than that in diabetic patients. Serum predialysis urea, creatinine and phosphate, in diabetic patients was highest in tertile 3. of magnesae-

Table 3. Plasma/serum/blood conctentration in patients presenting with diabetes as compared to those with no diabetes within the tertiles of magnesaemia levels.

Serum/ plasma/ blood	Tertile 1		Tertile 2		Tertile 3	
	D (-) Mean ± SD	D (+) Mean ± SD	D (-) Mean ± SD	D (+) Mean ± SD	D (-) Mean ± SD	D (+) Mean ± SD
Mg	0.792 ± 0.056	0.790 ± 0.056	0.920 ± 0.036	0.911 ± 0.039	1.080 ± 0.085	1.075 ± 0.088
U	86.9 ± 33.70	96.8 ± 32.69	87.22 ± 31.04	104.43 ± 22.000*	112.81 ± 27.92	120.14 ± 38.57
Cr	6.06 ± 1.99	5.56 ± 1.50	5.94 ± 2.99	6.31 ± 3.07	9.02 ± 2.55	7.64 ± 1.72
Hb	10.5 ± 1.36	10.28 ± 1.15	10.56 ± 1.11	10.36 ± 1.07	10.84 ± 1.12	10.58 ± 0.84
Alb	3.8 ± 0.51	3.96 ± 0.42	4.06 ± 0.39	3.97 ± 0.26	4.28 ± 0.33	4.12 ± 0.34
Ca	2.13 ± 0.16	2.13 ± 0.17	2.18 ± 0.18	21.20 ± 0.15	2.23 ± 0.17	2.16 ± 0.16
PO4	1.57 ± 0.40	1.53 ± 0.24	1.51 ± 0.34	1.72 ± 0.32*	2.04 ± 0.52	1.94 ± 0.62
URR	0.717 ± 0.100	0.702 ± 0.098	0.717 ± 0.110	0.715 ± 0.084	0.728 ± 0.095	0.729 ± 0.067
Kt/Vu	1.499 ± 0.376	1.452 ± 0.365	1.520 ± 0.400	1.499 ± 0.342	1.571 ± 0.422	1.561 ± 0.318
nPCR	0.765 ± 0.217	0.822 ± 0.193	0.788 ± 0.243	0.901 ± 0.162	0.986 ± 0.247	1.034 ± 0.263

*0.01 < p < 0.05

Mg – magnesium [mmol/l], U – urea [mg/dl], Cr – creatinine [mg/dl], Hb – haemoglobin [g/dl], Alb – albumin [g/dl], Ca – calcium [mg/dl], PO4 – phosphate [mg/dl], URR – urea reduction rate, Kt/Vu – Kt/V for urea, nPCR – normalised protein catabolic rate [g/kg/24 h]

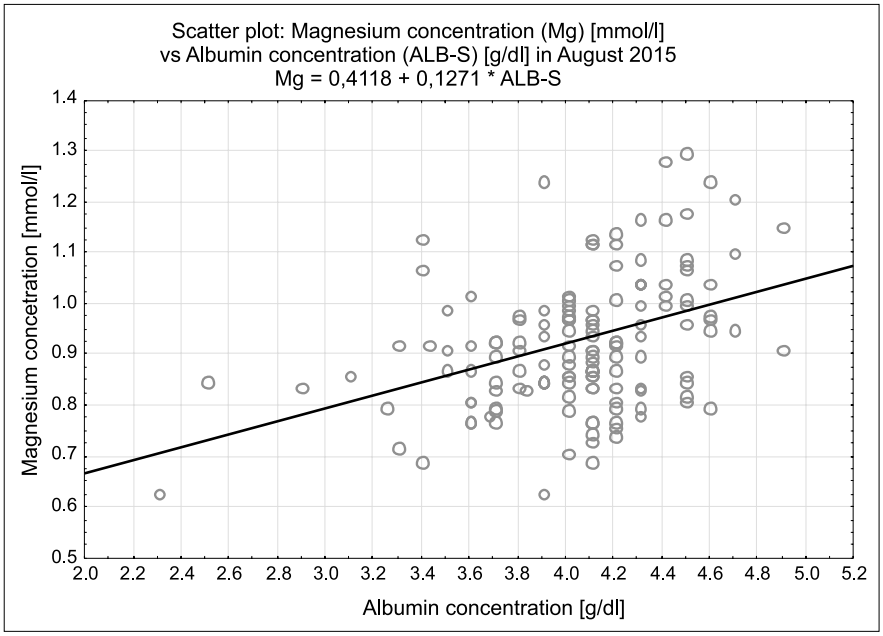

Fig. 1. Pre-dialysis plasma magnesium and albumin concentrations in a cohort of 147 adult haemodialysis patients.

mia and lowest in the 1. one. The same holds true for patients with no diabetes. However, in patients with no diabetes the aforementioned values were similar in tertile 2. to those in tertile 1., and reached the values intermediate between tertiles 1. and 3. in patients with diabetes. This could explain, partly, the observed dissimilarity of tertil 2. with the 1. and 3. The other possible factor for the observed discrepancy, could be the statistically insignificant unevenness in distribution of diabetes between the tertiles. Unfortunately the numbers of patients under study were to small to perform the detailed analysis of this concept, which calls for further studies.

We found a strong correlation between concentration of albumin and magnesium. One can only speculate, that higher level of magnesium prevented inflammation and MIA syndrome in our patients and resulted in higher creatininaemia, for the efficacy of treatment measured with Kt/V was similar. Also, the higher level of albumin could reflect this inflammation protective role of magnesium, as a factor preventing cachexia and promoting calorie and protein intake. So we assume, that better nutrition could reflect lower inflammation – or the opposite. However, many published data indicate the anti-inflammatory effect of magnesium, and suggest that deficiency of magnesium is responsible for inflammatory state (12-16). Thus we suggest, like others (17, 18), that higher plasma magnesium levels prevent inflammation accompanying the malnutrition. We assume we could observe it in our patients both, with and with no diabetes.

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 (19-21). It is suggested that insulin resistance and chronic hyperglycaemia might contribute to the development of hypomagnesaemia (21, 22), but this phenomena are not fully understood.

CONCLUSIONS

The results of our observational study, with all limitations of that approach, suggest that better diet results in better nutrition and higher magnesium serum concentration, which prevents, or diminishes inflammation. The efficacy of dialysis seemed of lesser importance. The above holds true also for patients presenting with diabetes. As a far consequence of this finding the use of higher magnesium concentration in dialysis fluid might be advised by future guidelines.

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received/otrzymano: 02.09.2015
accepted/zaakceptowano: 26.09.2015