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Amount of Magnesium Removed during Predilution Online Hemodiafiltration Compared to Conventional Hemodialysis

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Abstract

Aim: The aim of the study was to investigate how much magnesium is removed with predilution online hemodiafiltration (with or without glucose in dialysate), compared to conventional hemodialysis. **Patients-Methods:** The amount of magnesium removed during different dialysis methods (by collecting all the ultrafiltrate in a volumetric barrel) was studied in 27 dialyzed patients, aged 53 - 92 (mean ± SD = 72.0 ± 11.5, median = 73 years), who were on a dialysis program from 12 to 450 months (92.6 ± 91.6 months). In the first group (Group A), with predilution online hemodiafiltration the dialysate had glucose, in the second also with predilution online hemodiafiltration with the same composition of dialysate but without glucose (Group B) and in the third conventional hemodialysis was used (Group C). We determined serum urea and magnesium before and after the end of each session, as well as the volume of the total ultrafiltrate, as well as its urea and magnesium content. Everyone had one session under the conditions mentioned, which were one week apart. **Results:** Regarding magnesium removal, no significant difference was found with predilution online hemodiafiltration (with and without glucose in dialysate), compared to conventional hemodialysis (p = NS in both cases). The only side effect recorded was hypoglycemia in 3 patients during sessions with glucose-free dialysate, which were treated with intravenous administration of 35% dextrose solution. **Conclusion:** It is concluded that the amount of magnesium removed is not affected by the method of dialysis (predilution online HDF and conventional hemodialysis), nor from the dialysate used (with or without glucose) or the kind of dialyzer (low or high flux), despite the same clearance given for small molecules (Kt/V and URR).

Keywords

Serum Magnesium, Online Hemodiafiltration, Conventional Hemodialysis, Dialysate with Glucose, Dialysate without Glucose, Removed Magnesium

1. Introduction

For normal individuals, the recommended daily minimum magnesium intake is 15 mmol for men and 12 mmol for women [1], although today approximately 7 - 10 mmol of magnesium are ingested and 30% - 50% of this amount is absorbed in the intestine. This amount is difficult to obtain by patients with end-stage renal disease (ESRD), where in addition to reduced dietary magnesium intake (found mainly in the chlorophyll of vegetables), blanching of many foods (which mainly aims to reduce their potassium and phosphate) plays an important role, as does intestinal absorption, which is affected by taking medications such as proton pump inhibitors (PPIs), as well as its renal excretion (when there is residual renal function), in concomitant administration of loop diuretics [2] [3]. However, a key role is also played by the removal of magnesium, mainly through the dialyzer, which may be increased in the presence of hypoalbuminemia and/or metabolic acidosis, leading to a larger fraction of ionized magnesium available for removal by diffusion during the dialysis session. Finally, dialysis methods may also play a role, which have changed over the time (hemodiafiltration with pre- or post-dilution, versus conventional and high flux hemodialysis), as well as the type of membranes used (low versus high flux), with large volumes of substitution fluid, but also dialysate with citrates (which can precipitate magnesium) [3] (one mmol/L of citrate can bind 1.5 mmol/L of calcium and magnesium). Therefore, since now the assessment of serum magnesium status in hemodialyzed patients is a challenge, this study was designed to estimate the magnesium removed during the dialysis session, with dialysate with or without glucose, both in conventional hemodialysis and in predilution online hemodiafiltration (HDF) with dialysate with or without glucose.

2. Patients-Methods

2.1. Patients

The magnesium removed during predilution online HDF and conventional hemodialysis sessions were studied in 27 hemodialyzed patients. Patients over 18 years old, hemodynamically stable, with high blood flow to the dialyzer (at least 400 ml/min) and without active infections were included. Patients with diabetes mellitus, significant liver, heart and lung dysfunction were excluded, as well as those with cognitive impairment and patients unable to provide written informed consent.

The study was completed at the "Dimokrition" Renal Unit of Komotini. It was approved by the Scientific Council of Komotini General Hospital (No. 6/2024, 4/08/2024) and was conducted in accordance with the Declaration of Helsinki and the Guidelines for Ethics in Medical and Health Research Involving Humans. Written consent for participation was obtained from each patient, after being informed about the study and its purpose.

2.2. Methods

Each patient underwent one session of predilution online HDF, with or without glucose in dialysate (Group A and B, respectively) and one session of conventional hemodialysis with glucose in dialysate (Group C) on midweek days (Wednesday or Thursday), which occurred in random order.

In all patients, low molecular weight heparin (vemiparin) was used as an anticoagulant agent for hemodialysis needs, at doses of 2500 - 3500 IU/session, depending on their dry body weight. The blood flow (pump) was 400 ml/min for all patients in each session, and the dialysate flow was 500 ml/min (all patients underwent dialysis with Nikkiso DBB EXA machines). In all patients, the dialysate had bicarbonate 33 mmol/L, sodium 140 mmol/L, potassium 3 mmol/L, chlorine 110 mmol/L, calcium 1.5 mmol/L, magnesium 0.50 mmol/L, while glucose was 5.6 mmol/L in groups A and C and 0 in group B. For all patients, the duration of the session was four hours.

Polyethersulfone-polynephron filters (ElisioTM Nipro 2.1 m^2 high flux) were used for online HDF. All patients initially underwent one session of predilution online HDF with glucose in the dialysate and then one week later a second session of predilution online HDF with glucose-free dialysate. The same patients underwent one more week later a session of conventional hemodialysis with a dialyzer of the same surface area and composition (Polynephron, low flux 2.1 m^2). The substitution volume used in online HDF was 50% of the pump (*i.e.* 48 L/session).

Serum magnesium and urea levels were determined before the beginning and at the end of the session (after the blood pump was reduced to 50 ml/min for 2 minutes), in a blood sample taken from the same arterial fistula or arterial catheter line. All the ultrafiltrate was collected in a specially constructed, volumetric barrel, where at the end of the session it was stirred well with an electric stirrer for 10 minutes and then a sample was taken for urea and magnesium determination.

To determine the magnesium removed/session, the magnesium of the total ultrafiltrate was determined, from which the amount of magnesium was contained in the dialysate was subtracted (for predilution online HDF: 168 L [120 L of solution + 48 L of substitute] × 1.2 × 10 = 2016 mg/4-hour session and for conventional hemodialysis: [120 L of solution] × 1.2 × 10 = 1440 mg/4-hour session).

The Abbott Alinity C analyzer was used for the laboratory tests of the parameters studied. Urea and magnesium were determined by enzymatic methods.

2.3. Statistical Analysis

The results are expressed as mean ± standard deviation. Adjustment of variables to a normal distribution was done by the Kolmogorov-Smirnov test. The differences between predilution HDF with or without glucose in dialysate and those with conventional hemodialysis were analyzed by dependent paired t-test. The analysis was conducted with the Statistical software SPSS (version 30). A p value < 0.05 was considered statistically significant.

3. Results

The 27 patients in the study ranged from 53 to 92 years old (mean ± SD = 72.0 ± 11.5, median = 73 years) and were dialyzing from 12 to 450 months (92.6 ± 91.6 months). Fourteen had arteriovenous fistula, 1 had a vein graft (PTFE) and 12 had a double lumen jugular vein catheter. The patients' primary renal diseases were unknown in 9, polycystic kidney disease in 4, hypertensive nephrosclerosis in 4, glomerulonephritis in 4, cardiorenal syndrome in 3 and from 1 obstructive nephropathy, interstitial nephritis from lithium and multiple myeloma. 6/25 had residual renal function with eGFR < 3 ml/min (with less than 1000 ml urine/24h), who were also taken loop diuretics. 24/27 patients were receiving PPIs.

Regarding the magnesium removal, it was numerically bigger with predilution online HDF with glucose in dialysate compared to that without glucose (69.4 ± 40.9 vs 61.5 ± 33.2 mmol, p = NS), as well as in comparison with conventional hemodialysis (69.4 ± 40.9 vs 76.1 ± 41.2 mmol, p = NS). There was also no statistically significant difference between predilution online HDF without glucose in dialysate, compared to conventional hemodialysis (61.5 ± 33.2 vs 76.1 ± 41.2 mmol, p = NS), although numerically more magnesium was removed in conventional hemodialysis (**Table 1**). The delivered Kt/V did not differ between sessions with predilution online HDF and conventional hemodialysis (1.82 ± 0.32 vs 1.86 ± 0.35, p = NS), nor did the URR which range from 65.4 to 88.4% (median = 80.8) (p = NS).

Of particular importance was the fact that the minimum amount of magnesium removed was <15 mmol/session between all groups, while the median amount of magnesium removed/session ranged from 65 mmol (in online HDF with glucose) to 70.8 mmol in conventional hemodialysis (with the lowest median amount removed again being observed in online HDF).

Table 1. Serum magnesium levels before the beginning of dialysis session and at the end during predilution online HDF (with and without glucose in dialysate) and in conventional hemodialysis (with glucose in dialysate), and the removed amount of magnesium during a dialysis session with those methods of dialysis.

	Predilution online HDF dialysate with glucose (group A)			Predilution online HDF dialysate without glucose (group B)			Conventional hemodialysis (group C)		
n	Mg^{2+} before beginning HDF (mmol/L)	Mg^{2+} after the end of HDF (mmol/L)	Removed amount of Mg^{2+} (mmol)	Mg^{2+} before beginning HDF (mmol/L)	Mg^{2+} after the end of HDF (mmol/L)	Removed amount of Mg^{2+} (mmol)	Mg^{2+} before beginning HD (mmol/L)	Mg^{2+} after the end of HD (mmol/L)	Removed amount of Mg^{2+} (mmol)
1	0.97	0.77	16.3	0.95	0.78	89.6	0.87	0.79	45.4
2	0.94	0.85	87.9	1.06	0.85	83.3	1.20	0.93	113.8
3	1.25	0.80	66.6	1.25	0.82	13.0	1.49	0.80	78.3

Continued

4	0.96	0.75	42.1	0.92	0.73	38.3	1.02	0.73	22.9
5	1.01	0.80	52.4	0.98	0.76	97.5	1.22	0.86	122.2
6	0.64	0.70	17.0	0.60	0.67	10.0	0.80	0.74	14.2
7	0.73	0.69	41.0	0.66	0.68	10.0	0.75	0.75	134.1
8	0.85	0.77	38.3	0.80	0.78	59.6	1.16	0.86	142
9	1.00	0.80	57.4	1.05	0.82	45.4	1.18	0.88	10.0
10	0.91	0.76	65.0	0.88	0.73	38.3	0.88	0.75	50.8
11	1.18	0.84	166.3	1.21	0.75	72.5	1.23	0.85	95.3
12	1.11	0.70	109.2	1.12	0.80	58.8	0.89	0.83	70.8
13	0.84	0.75	78.3	0.69	0.68	15.0	1.12	0.82	68.8
14	0.89	0.79	112.1	0.78	0.69	4.2	0.94	0.76	78.3
15	1.23	0.77	130.4	1.28	0.79	67.1	1.29	0.86	128.8
16	1.06	0.79	104.2	1.07	0.80	73.8	0.88	0.74	15.0
17	1.08	0.85	123.3	0.98	0.79	52.5	1.06	0.84	68.3
18	0.97	0.83	87.9	0.86	0.77	58.3	0.88	0.75	47.5
19	1.16	0.78	68.1	1.17	0.80	117.5	1.14	0.85	124.6
20	1.07	0.77	33.3	1.21	1.06	95.0	1.01	0.71	52.9
21	0.91	0.78	18.2	0.98	0.79	57.0	1.02	0.77	55.0
22	0.95	0.75	14.6	0.99	0.78	38.3	0.89	0.83	88.3
23	1.24	0.81	89.6	1.46	0.83	118.8	1.35	0.88	156.3
24	1.06	0.79	17.1	1.28	0.84	68.8	1.05	0.79	45.8
25	1.29	0.85	134.2	1.00	0.79	109	1.29	0.85	113.8
26	1.08	0.77	38.3	1.19	0.76	65.4	1.22	0.81	78.3
27	0.96	0.79	64.2	1.09	0.82	104.6	1.03	0.83	32.9
Mean ± SD (n = 27) Medium	1.01 ± 0.15 (0.64 - 1.29) 1.0	0.78 ± 0.04 (0.69 - 0.85) 0.78	69.4 ± 40.9 (14.6 - 166.3) 65	1.02 ± 0.20 (0.6 - 1.46) 1.00	0.78 ± 0.07 (0.67 - 1.06) 0.79	61.5 ± 33.2 (4.2 - 118.8) 59.6	1.07 ± 1.18 (0.75 - 1.49 1.05)	0.81 ± 0.05 (0.71 - 0.93) 0.82	76.1 ± 41.2 (10 - 156.3) 70.8
			A − B = NS A − C = NS (0.49) B − C = NS (0.1)	0.00001			0.00001		

During the study with a glucose-free dialysate, the only side effect recorded was hypoglycemia symptoms (sweating, palpitations, cold palms) in three patients, which was confirmed in all three cases by serum glucose determination, which was found to be <50 mg/dl (<2.78 mmol/L) and treated with intravenous administration of 35% dextrose solution.

4. Discussion

Serum magnesium levels are not related to tissue stores and do not reflect total body stores. Only 1% of total body magnesium is in extracellular fluids and only

0.3% of total body magnesium is in serum, so serum levels are not predictive of total body magnesium. It is also emphasized that serum magnesium can be normal, even in individuals with negative magnesium balance, and most patients with hypomagnesemia are asymptomatic [4]. Finally, it is noted that even when tissue and cellular magnesium are reduced by up to 20%, serum levels may remain normal [5].

Normally, magnesium homeostasis depends on intake, intestinal absorption, release from bone, and renal excretion. In hemodialyzed patients, however, serum magnesium concentration is mainly influenced by its removal by the dialyzer [6].

It was previously thought that hemodialyzed patients tended to develop hypermagnesemia, due to dietary causes and medications (magnesium-containing phosphate binders, etc.). For this reason, and because hypermagnesemia caused osteomalacia and uremic pruritus (as reported in a literature review), which improved after reducing the magnesium concentration of the dialysate, the concentrations in the dialysate generally decreased [7]. Thus, for a long time the general policy in these patients was to avoid magnesium loading via the dialysate.

Hypomagnesemia has been associated with clinical manifestations such as myocardial contractility disorders, intradialytic hemodynamic instability and hypotension [8] [9], cardiac arrhythmia, muscle weakness, tetany, cramps or chronic complications (hypertension, vascular calcifications) [10]. Muscle cramps in hemodialysis are known to lead to non-compliance of patients with treatment, loss of time per session and ultimately to a reduction in the delivered dialysis dose. In hypomagnesemia, oxidative stress and inflammation are also stimulated and endothelial function is impaired, resulting in the occurrence of atherosclerosis. Magnesium is also an important component of bone minerals and hypomagnesemia is associated with suppressed osteoblastic and osteoclastic effects and osteopenia and resistance to the parathyroid hormone (PTH). Severe hypomagnesemia can suppress PTH production at any serum calcium level, leading to relative hypocalcemia [11].

Furthermore, serum magnesium concentration is inversely associated with total and cardiovascular mortality, coronary heart disease, atrial fibrillation and heart failure, while magnesium intake has been inversely associated with ischemic stroke [12] [13]. In fact, in recent years several studies have shown that lower serum magnesium concentrations before hemodialysis are independently associated with higher mortality from all causes, as well as from cardiovascular disease [14]-[16].

Nowadays, the data on magnesium in hemodialyzed patients has changed and the likelihood of detecting hypomagnesemia among them is very high [17] [18]. This is due to the reduced intake of food (due to the reduced magnesium content of vegetables, due to farming reasons), the diets they follow [19], but also to the double blanching of various foods that some people apply, to reduce the amount of potassium and phosphate ingested. Also, an important role is played by the intake of PPIs [20], by most patients, which reduces its intestinal absorption, as well as the administration of loop diuretics to those with residual renal function, which contributes to greater renal excretion of magnesium. In the literature, it was considered that the use of high flux dialyzers and online HDF, where large volumes of the patient's fluids are exchanged with a substitution fluid/session, may also play a role [21], which was not confirmed by our study. Considering all these changes that occurred with the progress of time, it is obvious that dialysate with magnesium 0.50 mmol/L, probably do not serve the needs of these patients [18].

The optimal concentrations of magnesium in serum and in the dialysate have not yet been determined, as the current Guidelines for conventional hemodialysis do not recommend specific concentrations of magnesium in the dialysate, while its usual composition varies from 0.25 - 1.0 mmol/L [18]. It has also been found that the frequently used magnesium concentration of 0.50 mmol/L usually leads to hypomagnesemia [22]. Thus, even today there is confusion regarding the ideal magnesium concentration of the dialysate and in many countries, as in ours, the commonly used magnesium concentration is that of 0.50 mmol/L.

Regarding the removal of magnesium through the dialyzer in conventional hemodialysis, during a session, the serum magnesium is not fully "available" for removal, because approximately 25% is bound to proteins (mainly albumin) and 5-16% to anions, such as bicarbonates, phosphate radicals and citrates [23]. Of course, the amount of magnesium removed by the dialyzer depends mainly on its concentration in the dialysate. And although the fraction of magnesium that can be filtered during hemodialysis is <1% of the total body magnesium, as magnesium is mainly found intracellularly, cumulatively small magnesium losses over time can be magnified by a shift towards lower overall dietary magnesium intake [23]. Regarding the amount of magnesium in the predilution online HDF sessions, a numerically higher amount of magnesium removed (p = NS) was observed when the dialysate contained glucose (69.4 ± 40.9 mmol/session), compared to the session with a dialysate without glucose (61.5 ± 33.2 mmol/session), although according to the literature, in the presence of glucose in the dialysate should be lower the extracellular magnesium (because there is glucose excreted insulin—in non-diabetics—which moves magnesium intracellularly) [24]. However, some studies on the effect of magnesium on insulin secretion and blood glucose control in diabetics and non-diabetics found a correlation [25], while others did not find a significant correlation [26].

Currently, a dialysate magnesium with a concentration of 0.50 mmol/L is widely used in conventional hemodialysis. Leenders *et al.* used a dialysate magnesium of 0.50 mmol/L in 34 hemodialyzed patients and found a mean decrease in serum magnesium concentration after the session of 0.10 mmol/L (while in this study with predilution online HDF [with and without glucose in the dialysate] we found a mean decrease of >0.20 mmol/L) (**Table 1**). Of the 34 patients, 25 patients were receiving oral PPIs, 18 diuretics and one patient a calcineurin inhibitor (CNI) [27]. They concluded that the above medications may be one of the main reasons for the relatively low blood magnesium concentration in this group (something that may have also occurred in our patients, because 24/27 were taking PPIs and 6/27 were also taking loop diuretics), all thought they were taking a tablet with 200 mg of magnesium/24 hours.

In contrast, a Chinese center retrospectively collected magnesium data from 148 hemodialyzed patients who were dialyzed with 0.50 mmol/L magnesium dialysate. The mean serum magnesium concentration before hemodialysis was 1.11 ± 0.14 mmol/L. The prevalence of hypermagnesemia was 73.65% and 2 patients had hypomagnesemia (1.35%). After the hemodialysis session, serum magnesium concentration was significantly lower when conventional hemodialysis was used. Patients in this study had slightly higher serum magnesium concentration, but also more patients with hypermagnesemia. This was attributed to the fact that they had younger patients (who have better magnesium intake), only 5 were taking PPIs and 40 patients were only doing 2 dialysis sessions/week [28].

There are finally insufficient data on the optimal serum magnesium concentration, how this concentration should be adjusted, and what the magnesium dialysate should be. In a study that increased the magnesium concentration of dialysate from 0.50 to 0.75 mmol/L, the ionized magnesium concentration before dialysis increased statistically significantly from 0.53 ± 0.12 to 0.66 ± 0.02 mmol/L after 24 months, without clinical signs of magnesium toxicity [29]. However, findings from other studies suggest that it may be important to maintain serum magnesium concentrations before the dialysis at 1.13 - 1.25 mmol/L in patients undergoing conventional hemodialysis [30] [31], as was the case in most of our study patients, without any symptoms of hypermagnesemia [18].

In patients undergoing high flux hemodialysis, using dialysate magnesium of 0 mg/dl, 0.6 mg/dl (0.25 mmol/L) and 1.8 mg/dl (0.75 mmol/L) in 8 cases, net magnesium removal was found to be 486 ± 44 mg (20 ± 0.75 mmol), 306 ± 69 mg (5.25 ± 1.19 mmol) and 56 ± 50 mg (0.96 ± 0.86 mmol), respectively ($p = 0.001$) [10]. We found a loss/session of 69.4 ± 40.9 mmol with a dialysate containing glucose and 61.5 ± 33.2 mmol with a dialysate without glucose, while with conventional hemodialysis, we found a loss of 76.1 ± 41.2 mmol (range of values from 10 to 156.3 mmol/session).

Although several reports have been published on serum magnesium levels in hemodialyzed patients, only a few have evaluated magnesium levels in online HDF. In postdilution, which is the main method used in Europe, a large volume of substitution fluid is directly introduced into the blood. It has been hypothesized that with the large loss of albumin (for every 1 g/dl increase in albumin, the serum magnesium level increases by approximately 0.2 mg/dl) [16], magnesium bound to it is removed during the session. However, the significance of this albumin loss on serum magnesium levels remains unknown, although we did not find it to affect the levels of magnesium removed (compared the predilution online HDF with substitution volume of 48 L/session to conventional hemodialysis). Tanaka *et al.* who studied 18 patients undergoing online HDF (with a substitution volume of 60 - 84 L in predilution and 8 - 16 L in postdilution), with the classic dialysate or with citrate in dialysate, found that online HDF had a negligible effect on ionized magnesium (however, the use of the citrate in dialysate reduced ionized magnesium levels, possibly due to chelation) [32].

What was interesting is that in our study, the median amount of magnesium removed in predilution online HDF with glucose in dialysate was 65 mmol/session, without glucose in dialysate it was 59.6 mmol/session, and in conventional hemodialysis a numerically higher median removal was found (70.8 mmol/session). The minimum removed amounts of magnesium were also important, where in predilution online HDF they even reached levels of 4.2 mmol/session (in group B) and 10 mmol/session in conventional hemodialysis, while the maximum amount removed in predilution was 118.8 mmol (Group B) and 156.3 mmol in conventional hemodialysis [18]. The question that arises, however, is what is the reason for the loss of a numerically significantly smaller amount of magnesium in predilution online HDF with or without glucose in the dialysate (Groups A or B) compared to conventional hemodialysis? The dialyzer is certainly not to blame (sieving coefficient-SC, since the magnesium molecule is very small and easy to pass through the pores of each dialyzer). Insulin is also not to blame (since glucose was present in both groups A and C in dialysate), which when present increases the intracellular transport of magnesium, but also leads to a reduced loss of these ions [33]. Finally, the numerically higher removal of magnesium in conventional hemodialysis cannot be explained by the fact that 25% of it is bound to albumin, which would perhaps increase its loss in online HDF where there is a greater loss of albumin through the dialyzer.

The fact that normal individuals consume 7 - 10 mmol of magnesium daily and of this amount, 30% - 50% is absorbed in the intestine, while an average of around 7 mmol of magnesium is lost daily with the dialyzer (both in online HDF and in conventional hemodialysis), suggests that this loss cannot be replaced by food intake, because these individuals are not vegetarians (therefore have a reduced intake), almost all take PPIs (which reduce magnesium absorption from the intestine), and some also takes loop diuretics (which increase magnesium excretion through the kidneys, when there is residual renal function). Thus, with this loss, it is obvious that these patients should rather have tissue hypomagnesemia, when they are dialyzed with a magnesium dialysate of 0.50 mmol/L.

It is concluded that in non-diabetic hemodialyzed patients, magnesium removed with conventional hemodialysis is numerically greater than that with predilution online HDF with or without glucose in the dialysate, with the same given clearance, which indicates that the glucose content of dialysate and the SC of the membranes does not affect the removal of magnesium through the dialyzer. Also, magnesium removed with any type of dialysis (predilution online HDF with or without glucose in the dialysate or conventional hemodialysis) is rather greater, compared to the usually ingested and removed through the dialyzer (with the same dialysis conditions provided). This must be considered, since such an amount cannot be normally ingested by these patients, which certainly leads them to tissue hypomagnesemia.

5. Limitations

The number of patients studied has been a relatively small, and perhaps if there were more of them there would be a statistically significant difference in the levels of magnesium removed by the various methods studied.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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