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Research Article

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What is the Proper Composition of the Dialysate Magnesium and How Much Magnesium is Removed During Pre-Dilution Online Hemodiafiltration?

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Abstract

Aim: *The aim of the study was to determine the ideal dialysate magnesium during hemodialysis, knowing that the solution used is not satisfactory and is often associated with low serum magnesium levels.*

Patients-Methods: *Serum magnesium levels were initially studied in 60 hemodialyzed patients before the beginning of dialysis session with a dialysate magnesium of 1.20 mg/dl. After 6 months from the first blood samples, the dialysate magnesium was changed to 1.80 mg/dl, which continued for the following 6 months, and serum magnesium levels were determined again before the beginning of the dialysis session. In another group of 23 patients was also studied with a pre-dilution online hemodiafiltration session, with a dialysate magnesium of 1.20 mg/dl, during which serum magnesium levels were determined before the beginning of the session and 5 minutes before the end of the dialysis session, as well as the magnesium of the ultrafiltrate collected/session in a barrel.*

Results: *Low serum magnesium levels were found in most patients with the dialysate magnesium of 1.20 mg/dl and with clinical findings in some of them, which improved significantly with an increase of dialysate magnesium to 1.80 mg/dl and reached in most of them above normal range, without showing any clinical side effect. The magnesium removed in an online hemodiafiltration session (pre-dilution) was at least equal to that ingested by a normal person in a 2-days period.*

Conclusion: *Conventional hemodialysis with a dialysate magnesium of 1.20 mg/dl leads many hemodialyzed patients to hypomagnesemia, while the dialysate magnesium of 1.80 mg/dl is well tolerated, safe and does not cause problems for patients. Serum albumin levels affect the amount of magnesium removed during the hemodialysis session. Online HDF (pre-dilution) removes very large amounts of magnesium, capable of removing all the ingested magnesium in two days of food.*

Keywords: Physical Vapor Deposition (PVD), Coating Equipment, Vacuum Technology, Heating Source Technology, Coating Material

1. Introduction

Magnesium is the 8th most abundant element in the Earth's crust. Approximately 99% of the body's total magnesium is found in bone, muscle, and non-muscle soft tissues. Overall, one-third of skeletal magnesium is exchangeable, serving as a reservoir for maintaining normal extracellular levels. Extracellular magnesium represents approximately 1% of the total body magnesium, where it is found free (ionized), bound with proteins, or in compounds with anions such as phosphate, bicarbonate, citrate, or sulfate. Magnesium is found mainly intracellularly, where it is a cofactor in over 300 enzymatic reactions. It is involved in the production of ATP, contributes to the regulation of vascular tone and heart rate. Muscle contraction and relaxation, normal neurological function and the release of neurotransmitters depends on magnesium. It is also important to note that magnesium contributes to platelet-activated thrombosis and bone formation [1]. It plays a role in insulin secretion and inhibits calcium-induced cell death [2].

Magnesium is an important element of the dialysate, since its levels mainly determine clinical manifestations of hypomagnesemia, that constitute a significant problem during the session [3]. However, almost all over the world, a dialysate of the same composition (with 1.20 mg/dl of magnesium) is used, without this having changed for decades, despite the fact that significant changes have occurred regarding magnesium, both in the diet and in medications that were used in the past and others that are used today, but also in the dialysis methods and the type of filters used, which may affect the magnesium in the body. Importantly, interventional studies targeting magnesium balance in hemodialyzed patients are scarce. Therefore, studies in these patients are needed which will examine in depth the composition of the dialysate in relation to magnesium levels, to establish Guidelines for the optimal target serum magnesium level. With these considerations in mind, it was decided to conduct this study, which aimed to investigate the efficacy and toxicity of a dialysate with magnesium of 1.80 mg/dl.

2. Patients-Methods

2.1 Study Design and Setting

This prospective interventional study was performed in «Dimokrition» Renal Unit, Komotini, Greece, from January 2014 to January of 2025 and included 60 hemodialyzed patients form a center. It had two phases, one initially of the serum magnesium level of hemodialyzed patients (dialyzed with a magnesium dialysate of 1.20 mg/dl in) followed by administration of an oral magnesium pill for a period of 6 months, in those (n=6) with very low serum magnesium levels (<1.72 mg/dl). After this period and for another 6 months, a second phase followed, during which the dialysate magnesium for all patients was increased by 50% (from 1.20 mg/dl to 1.80 mg/dl).

The study included hemodialyzed patients who were at least 6 months in dialysis, who were on a program 3 times a week, of at least 4 hours/session. All were stabilized. Excluded from the study patients who were <18 years old, pregnant women, those taking oral or intravenous magnesium, those using laxatives or antacids with magnesium, those with arrhythmias or a major cardiac event 3 months before the start of the study and those who had frequent hypotensive episodes or were hemodynamically unstable. Patients with serious inflammatory diseases and severe dysfunction of the liver, heart and lungs were also excluded.

Patients' magnesium-related medications (PPIs, furosemide, calcineurin inhibitors, magnesium-based phosphate binders), vegetable use and cooking method (especially whether they were boiled before cooking), and patients' symptoms that could be related to magnesium (hypomagnesemia or hypermagnesemia) were recorded. These were reviewed after 6 months of dialysate magnesium increased from 1.20 to 1.80 mg/dl.

2.2 Patients

The age, gender, primary renal diseases of the patients, duration on hemodialysis, medication intake (PPIs, furosemide), boiling of vegetables before cooking, patients with low serum albumin levels (<3.5 mg/dl) and type of dialysis (conventional hemodialysis or online pre-dilution hemodiafiltration-HDF) of both groups are shown in Tables 1 and 2.

A/A						Medication				Symptoms	Serum magnesium (before starting dialysis session)	
	Age/sex	Months on dialysis	Primary renal disease	Vascular access	Dialysis method	PPIs	Furosemide (Yes/No)	Boiling vegetables (Yes/No)	Serum albumin <3.5 (Yes/No)	With dialysate magnesium 1.20 mg/dl	January2024	January 2025
1	68F	8	Unknown	Jugular	HD	YES	No	No	No		2.44	3.14
2	39F	39	Unknown	Femoral	HD	YES	No	YES	No	Leg jerks, legs numbness	2.20	3.57
3	55M	225	Glomerulonephritis	AVF	ONLINE-POST	Yes	No	No	Yes		1.80	2.44
4	73M	8	Hypertensive nephrosclerosis	AVF	HD	No	YES	No	No		2.50	3.02

5	74M	42	Glomerulosclerosis	Jugular	ON-LINE-POST	No	No	No	No	Legs numbness	2.46	2.71
6	82F	45	Diabetic nephropathy	Jugular	ON-LINE-PRE	YES	No	YES	No		3.10	3.80
7	92F	33	Cardiorenal	Jugular	HD	YES	YES	No	No	Legs numbness	1.60	2.32
8	66F	32	Diabetic nephropathy	Jugular	HD	YES	No	No	YES		2.20	2.42
9	82F	26	Unknown	Jugular	HD	YES	No	No	No		2.08	2.62
10	71M	8	Diabetic nephropathy	Jugular	HD	YES	YES	YES	No		2.78	2.82
11	65F	90	Hypertensive nephrosclerosis	AVF	ON-LINE-POST	YES	No	No	No		2.41	2.66
12	77M	26	Unknown	AVF	HD	YES	No	YES	YES		1.68	2.45
13	63M	17	Diabetic nephropathy	AVF	ON-LINE-META	YES	YES	YES	No	Legs numbness	1.90	2.22
14	54F	11	ADPKD	AVF	HD	No	No	YES	No		2.06	2.39
15	92F	9	Unknown	Jugular	HD	No	No	No	No		2.27	3.00
16	53F	73	ADPKD	AVF	ON-LINE-POST	YES	No	YES	No	Cramps	2.20	2.63
17	47F	12	Glomerulonephritis	Jugular	ON-LINE-POST	No	No	YES	No	Leg jerks	2.40	3.30
18	86F	44	Hypertensive nephrosclerosis	AVF	HD	YES	No	No	No		2.40	2.99
19	86M	33	Unknown	AVF	ON-LINE-POST	YES	YES	No	No	Restless legs	2.20	2.41
20	77M	30	Unknown	Jugular	ON-LINE-POST	YES	No	YES	No	Cramps, legs numbness	1.06	2.11
21	81F	12	Unknown	Jugular	HD	YES	No	No	No	Restless legs	2.40	3.47
22	76M	68	Unknown	AVF	ON-LINE-POST	YES	YES	YES	No	Legs numbness	2.14	2.90
23	62M	65	Obstructive nephropathy	AVF	HD	YES	No	No	No		1.90	2.47
24	82M	31	Cardiorenal syndrome	Jugular	HD	YES	No	No	No	Legs numbness	2.10	2.68
25	79M	26	Unknown	Jugular	HD	No	No	No	No		2.58	3.23
26	76M	26	Nephrectomy	AVF	HD	YES	No	No	No		3.10	3.56
27	60M	8	Lithium Nephropathy	AVF	HD	No	No	No	No		2.52	2.79
28	59F	573	SEL	Jugular	ON-LINE-POST	YES	No	No	No	Legs numbness, cramps	1.78	3.10
29	77F	13	Diabetic Nephropathy	Jugular	HD	YES	No	YES	No		2.30	2.96
30	60M	261	Glomerulonephritis	Jugular	HD	YES	No	No	No	Legs numbness	2.20	2.55
31	77F	15	Cardiorenal Syndrome	Femoral V	HD	YES	No	YES	No	Legs numbness	2.10	2.49
32	81M	16	Hypertensive nephrosclerosis	AVF	ΚΛΑΣΙΚΗ	YES	No	YES	No	Restless legs	1.70	2.55
33	73M	166	Glomerulonephritis	AVF	ON-LINE-POST	YES	No	YES	OXI	Legs numbness	2.00	2.68
34	54M	141	Hypertensive nephrosclerosis	AVF	ON-LINE-POST	No	No	YES	No		2.30	2.68

35	65M	139	Unknown	AVF	ON-LINE-PRE	YES	No	YES	No		2.19	2.96
36	79M	164	Unknown	AVF	HD	YES	No	No	No		1.80	2.32
37	77M	29	Hypertensive nephrosclerosis	Jugular	HD	YES	No	No	No	Insomnia	1.90	2.61
38	78F	19	Hypertensive nephrosclerosis	Jugular	HD	No	YES	No	No		2.10	2.85
39	83M	29	Diabetic nephropathy	Jugular	HD	YES	No	No	No		2.10	2.49
40	71M	474	Glomerulonephritis	AVF	ON-LINE-POST	YES	No	YES	No	Restless legs	1.90	2.80
41	72F	429	Glomerulonephritis	AVF	ON-LINE-META	No	No	No	No		3.00	3.80
42	86M	84	Glomerulonephritis	Jugular	HD	YES	No	No	No		1.90	2.39
43	77F	11	Diabetic nephropathy	Jugular	HD	YES	YES	YES	No		2.32	2.56
44	85F	19	Unknown	Jugular	HD	YES	No	No	No		2.30	3.02
45	62F	19	Unknown	Jugular	HD	No	No	No	No	Legs numbness	2.50	3.10
46	72M	85	ADPKD	AVF	ON-LINE-POST	YES	No	YES	No		1.90	2.51
47	86F	52	Unknown	Jugular	HD	YES	No	No	No		2.03	2.67
48	77F	8	Myeloma	Jugular	HD	No	No	No	YES		1.72	2.58
49	85F	80	Chronic pyelonephritis	AVF	ON-LINE-POST	YES	YES	YES	No		2.20	2.89
50	85M	21	Diabetic nephropathy	Jugular	HD	YES	No	No	No	Legs numbness, Restless legs	1.60	1.86
51	60F	28	Diabetic nephropathy	Jugular	ON-LINE-POST	YES	No	YES	No	Legs numbness, Restless legs	2.40	2.98
52	78M	77	Diabetic nephropathy	AVF	HD	YES	No	No	No		2.10	2.47
53	89F	40	Hypertensive nephrosclerosis	Femoral	HD	YES	No	No	YES	Legs numbness	2.06	2.30
54	44F	23	Diabetic Nephropathy	AVF	ON-LINE-POST	YES	YES	No	No		2.09	2.28
55	87F	69	Unknown	AVF	HD	YES	No	No	No		2.92	2.97
56	87M	42	Hypertensive nephrosclerosis	Jugular	ON-LINE-POST	No	No	No	YES		2.20	3.13
57	71F	8	Diabetic nephropathy	Jugular	HD	YES	YES	No	YES		2.19	2.05
58	55	80	Glomerulonephritis	AVF	ON-LINE-POST	YES	No	No	No		2.10	2.79
59	64M	184	ADPKD	AVF	ON-LINE-POST	No	No	YES	No	Restless legs	2.00	2.79
60	64F	34	Unknown	Jugular	HD	YES	No	No	No		2.26	2.92

Table 1: Age, Gender, Primary Renal Disease, Vascular Access, Months In Dialysis, Medication of Patients (Furosemide, PPIs), Boiling of Vegetables by Patients Before Cooking, Hypoalbuminemia, Serum Magnesium Levels at the Beginning of the Study Before the Starting of Dialysis Session (With Dialysate Magnesium 1.20 mg/dl) and after One Year (After Dialyzing for 6 Months with Dialysate Magnesium 1.80 mg/dl), are Shown

	Age/Sex	Primary renal disease	Vascular access	Months in dialysis	Serum magnesium pre dialysis (mg/dl)	Serum magnesium end session (mg/dl)	Magnesium removed (mg/ session)
1	71M	Glomerulonephritis	AVF	437	2.42	1.93	804
2	54M	Hypertensive Glomerulosclerosis	AVF	141	2.25	2.05	790
3	72F	Glomerulonephritis	AVF	429	3.01	1.93	736
4	55F	Glomerulonephritis	AVF	80	2.30	1.81	677
5	71M	Glomerulonephritis	AVF	474	2.42	1.93	804
6	92F	Cardiorenal syndrome	Jugular	33	1.54	1.69	617
7	77M	Unknown	Jugular	30	1.74	1.65	617
8	72M	ADPKD	AVF	85	2.04	1.84	688
9	65M	Unknown	AVF	139	2.40	1.91	714
10	64M	ADPKD	AVF	184	2.18	1.82	732
11	82F	Hypertensive Glomerulosclerosis	AVF	45	2.97	1.97	719
12	81F	Unknown	ARV	12	2.67	1.67	838
13	73M	Glomerulonephritis	AVF	166	2.01	1.84	809
14	79M	Unknown	AVF	164	2.14	1.90	845
15	81M	Hypertensive Glomerulosclerosis	AVF	16	2.60	1.93	680
16	65M	Hypertensive Glomerulosclerosis	AVF	90	2.55	1.89	826
17	54F	ADPKD	AVF	11	2.58	2.03	872
18	77M	Hypertensive Glomerulosclerosis	Jugular	28	2.32	1.99	866
19	60M	Lithium nephropathy	AVF	8	2.78	1.86	792
20	85F	Unknown	Jugular	19	2.57	1.85	680
21	77F	Myeloma	Jugular	8	2.19	1.86	640
22	77F	Cardio-renal syndrome	Femoral	15	2.28	1.79	653
23	87F	Unknown	AVF	69	2.97	1.94	870
	72.6±10.3 (55-92) MEDIAN=73		Femoral=1 Jugular=5 AVF=17	116±139 (8-474)	2.39±0.39	1.87±0.10	751±82

Table 2: Age, Gender, Primary Renal Disease, Vascular Access, Months in Dialysis, Magnesium Levels Before the Start and After the End of the Online Pre-dilution HDF Session, As Well As the Amount of Magnesium Removed During the Session, are Shown

3. Methods

Patients in group A were dialyzed with a dialysate individualized in terms of sodium (138-140 mEq/L), potassium (2.0-3.0 mEq/L), calcium (6.0-7.5 mg/dl), and bicarbonates (30-33 mEq/L), but with the same concentration of glucose (100 mg/dl) and magnesium (1.20 mg/dl). The filters used were polyethersulfone (polynephron), with a surface area of 2.1 m^2, low flux, for conventional hemodialysis and 2.5 m^2, high flux, for online pre-dilution HDF. Most patients (n=46) used vemiparin (2,500-3,500 IU/session) as an anticoagulant for dialysis session, 9 used classic heparin (unfractionated), and 5 used fondaparinux. The blood pump (blood supply) for 54 of them were 400 ml/min and in the remaining 6 350-380 ml/min, while the dialysate supply was 500 ml/min for all.

All patients in group B had a dialysate of the same composition (sodium 140 mEq/L, potassium 3.0 mEq/L, bicarbonates 33 mEq/L, calcium 6.0 mg/dl, magnesium 1.20 mg/dl and glucose 100 mg/dl). The filters used were also polyethersulfone (polynephron), high flux, with a surface area of 2.1 m^2 and the duration of the session was 4 hours for all. The anticoagulant used for dialysis session was vemiparin (2,500-3,500 IU/session) in 19 patients,

classic heparin in 2 and fondaparinux in 2. The blood pump supply was in all sessions 400 ml/min and the dialysate pump 500 ml/min for all. Everyone did online pre-dilution HDF and the substitution volume was for any of them 48 L/session.

It was initially planned in group A to determine serum magnesium levels on midweek days (Wednesday or Thursday), before the beginning of the session and before any intervention. Patients who were found to have particularly low serum magnesium levels (<1.72 mg/dl, n=6) and had symptoms of hypomagnesemia were administered effervescent magnesium oxide tablets (Orbimag 300 mg, 1x1/24 hours for 6 months), during which they continued to be dialyzed with the already used dialysate (with magnesium 1.20 mg/dl). No one's dialysis program conditions, medications, method or filter were changed. After this period, and after the serum magnesium levels was checked in the 6 patients with very low magnesium levels and it was found that it did not change substantially, the magnesium in the dialysate was changed to 1.80 mg/dl, with which the patients continued to dialyzed for the following 6 months, at which time a second blood sample was taken for serum magnesium before the start of dialysis session.

In group B of patients with online pre-dilution HDF, serum magnesium was determined midweek (Wednesday or Thursday) before the start of the session, with a dialysate magnesium of 1.20 mg/dl, and 5 min before its end, as well as the removed magnesium during a 4-hour session, in the total ultrafiltrate.

The ultrafiltrate was collected in a specially made volumetric barrel, where its volume was determined. After the end of the session and after thoroughly stirring the ultrafiltrate with an electric stirrer for 10 minutes, a sample was taken to determine the magnesium concentration. Restless legs, leg tremors and numbness, the presence of arrhythmias and frequent intradialytic hypotension episodes were considered symptoms of hypomagnesemia. Nausea, hot flashes, headache, lethargy and drowsiness, hypocalcemia, hypotension and bradycardia were defined as possible manifestations of hypermagnesemia. Magnesium was determined in all cases by enzymatic method.

4. Statistical Analysis

Data was analyzed using SPSS for Windows (edition 22.0, IBM SPSS Statistics. IBM Corp., Armonk, New York, USA). Quantitative data are presented as mean and standard deviation (mean±SD). Comparison of quantitative data between groups was made using t-test for independent and dependent samples and paired t-test. Statistically significant changes were considered with a significance level of $p < 0.05$.

4.1 Ethical Committee

This prospective study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects and was approved by the Scientific Council of the General Hospital of Komotini, Greece (registration number 3/2024).

5. Results

Detailed patient data (age, gender, primary renal disease, vascular access, months on dialysis, type of dialysis, taking PPIs or furosemide, cooking method of vegetables and legumes, patients with hypoalbuminemia, symptoms of hypomagnesemia in patients with low serum magnesium levels and dialysate magnesium of 1.20 and 1.80 mg/dl) that were involved in the study are shown in Table 1. Of the patients in group A, 37 were on conventional hemodialysis and 23 were on online HDF (21 with post-dilution and 2 with pre-dilution). In post-dilution the substitution volume was 25% of the pump (≥24 L/session) and in pre-dilution 50% of the pump (≥48 L/session).

Of the patients in group A, 23, 13 men and 10 women, aged 55 to 92 years (median age 73 years), who had been on a dialysis program for 8 to 573 months (mean±SD=116±139), were additionally studied with an online pre-dilution HDF session, during which the ultrafiltrate was collected to determine the amount of magnesium removed (Group B).

Residual diuresis (>400 ml/24 hours) was present in 11/60 (33.3%) patients. Proton pump inhibitors (PPIs) were used by 46/60 (76.7%), two patients (3.3%) were using a phosphate binder with magnesium (calcium acetate and magnesium carbonate, tabl Osvaren 435+235 mg) and 11/60, i.e. all those who had diuresis (18.3%) were receiving furosemide (of these, 2 were not receiving PPIs, while the remaining 9 were receiving both). None of the patients received any type of intravenous magnesium supplement after increasing the dialysate magnesium to 1.80 mg/dl.

Regarding boiling vegetables and legumes, 22/60 boiled them (21 only once and one twice). No difference was found in the magnesium levels of the patients (who boiled or did not boil their vegetables), both with a dialysate magnesium of 1.20 mg/dl and with a dialysate magnesium of 1.80 mg/dl (p=NS in both cases).

Regarding serum albumin levels below 3.50 (n=7) or above this value (n=53), marginal significance was found, with those with hypoalbuminemia having lower serum magnesium levels when dialyzed with a dialysate magnesium of 1.20 mg/dl (t-test, p=0.064), while with the dialysate magnesium of 1.80 mg/dl the difference was statistically significant, with patients with hypoalbuminemia having lower serum magnesium levels (t-test independent samples, 2.48±0.30 Vs 2.79±0.40, p=0.029).

Serum magnesium levels were determined before the beginning of dialysis session (on January 2024), when hemodialysis was performed with a dialysate magnesium of 1.20 mg/dl (group A). At this determination, 6 patients had magnesium <1.72 mg/dl, 15 had it below <2.00 mg/dl and only 5 had it above 2.60 mg/dl. Of the 2 patients receiving magnesium as a phosphate binder, one had a serum magnesium of 2.40 with the dialysate magnesium of 1.20 mg/dl and 3.30 mg/dl with the dialysate magnesium of 1.80 mg/dl.

In July 2024, i.e. after 6 months of oral administration of magnesium (effervescent magnesium oxide tablets), we found no

significant improvement in the serum magnesium levels of the 6 patients, compared to the results with the 1.20 mg/dl dialysate magnesium (t-test dependent samples, p=NS), therefore the dialysate magnesium was changed to 1.80 mg/dl (in July 2024). In blood samples taken six months later (January 2015), statistically significantly higher serum magnesium levels were found in the samples of the second period compared to the first (January 2024) (t-test dependent samples, 2.18±0.36 Vs 2.76±0.40, p<0.0001). Specifically, 36 patients had serum magnesium before the start of the dialysis session above 2.60 mg/dl (13 above 3.00 mg/dl), with the minimum value being equal to 1.86 mg/dl only in one patient and the maximum being equal to 3.80 mg/dl in two patients. However, no clinical manifestations of hypermagnesemia, nor toxic serum magnesium levels were detected in any of our patients. The symptoms of hypomagnesemia of all our patients were relieved at the end of the study and they continue to be well.

Examining the impact of the presence of residual diuresis along with the use of diuretics (furosemide) by these patients, it was found that in the 11 with diuresis the serum magnesium levels with dialysate magnesium 1.20 mg/dl did not differ significantly from those of patients who did not have diuresis. Also, the serum magnesium levels with dialysate magnesium 1.80 mg/dl of those with diuresis, compared to those without diuresis, did not differ significantly (t-test independent samples, p=NS).

Examining magnesium levels in group A between those who underwent conventional hemodialysis (n=37) or online HDF (n=23), no difference was found, both in serum magnesium levels with a dialysate magnesium of 1.20 and with a dialysate magnesium of 1.80 mg/dl (t-test independent samples, p=NS in both cases).

Regarding group B (under Online HDF), with a dialysate magnesium of 1.20 mg/dl, significantly higher serum magnesium levels were also found, between values at the beginning of the session versus at the end of this (Paired t-test, 2.39±0.39 Vs 1.87±0.10, p<0.0001). The amount of magnesium removed in one online pre-dilution HDF session was 751±82 mg (from 617 to 872 mg (mean±SD=751±82 mg).

6. Discussion

Magnesium is found in most human foods, such as meat, green vegetables, and grains. In normal individuals, the recommended daily dietary intake of magnesium is approximately 300-400 mg for adult women or men [2]. Apparently, hemodialyzed patients consume less magnesium, due to a special diet that limits vegetables, but also due to the way they are cooked (double or triple boiling) to avoid hyperkalemia [4].

In the past, hemodialyzed patients were found to have a positive magnesium balance, despite the special diet (non-vegetarian) and the boiling of vegetables, which lose a lot of their magnesium. In addition to the dietary magnesium intake, which was previously higher than today (at that time, fruits and vegetables were harvested more maturely from the plants or trees and had time to absorb more magnesium from the ground), but also due to the higher magnesium content of the ground that existed then, than what exists today. Hypermagnesemia was also since the phosphate binders used in the past were mainly magnesium compounds (a medication of calcium acetate and magnesium carbonate is now used for this purpose today, by a very small number of patients). On the other hand, sevelamer hydrochloride, which was previously marketed and used as a phosphate binder in hemodialyzed patients, was associated with an increase in serum magnesium concentration, due to bile salts, thus increasing the amount of free magnesium available for absorption [5]. Also, perhaps due to concerns about hypermagnesemia causing osteomalacia and a literature reference that reported improvement in uremic pruritus after reducing the dialysate magnesium concentration (from approximately 1.80 mEq/L, changed to 0.60 mg/dl), a low magnesium diet and dialysate magnesium around 1.20 mg/dl were established [6,7].

Nowadays, dietary magnesium intake is much lower (less magnesium is found in plant foods) [8]. It is also believed that the introduction of processed foods in the 20th century led to a decrease in magnesium intake compared to the previous century (over 40% of Germans had a magnesium deficiency) [9]. Also, the aforementioned magnesium phosphate binders are no longer used, while drugs that reduce magnesium absorption from the intestine are used by almost all patients (PPIs), which predispose to hypomagnesemia [10-13]. Furthermore, hemodialyzed patients usually have severely reduced intestinal magnesium absorption, compared to healthy individuals, possibly due to a deficiency of active vitamin D [14]. The importance of residual renal function in magnesium balance should not be forgotten, where, if present, the use of diuretics also plays a role (we did not find any effect of diuresis and furosemide on serum magnesium levels, perhaps due to the size of the sample studied). Perhaps the dialysis method currently used by many patients (hemodiafiltration with its models, compared to conventional hemodialysis), with high-flux filters that are different from those used in the past (with larger diameter pores), also plays a role.

For these reasons, low serum magnesium levels are increasingly being observed in hemodialyzed patients. This may contribute to the loss of patients due to sudden deaths from arrhythmias, which could be attributed to hypomagnesemia or to the combination of hypomagnesemia and hypokalemia, which is also a problem in hemodialysis [2,15,16]. Indeed, researchers have found that hypomagnesemia worsens both atrial and ventricular arrhythmias associated with hypokalemia. In fact, a recent meta-analysis reported a 30% increase in cardiovascular disease for every 0.49 mg/dl decrease in serum magnesium levels within the normal range [17]. However, if we consider that avoiding hypokalemia at the end of the dialysis session in the hemodialyzed patient is quite difficult, the detection of hypomagnesemia in a routine check is an important reason to improve serum magnesium levels at the end of the session. Unfortunately, despite these changes that have occurred, even today the magnesium levels of the dialysate used remain low (most commonly 1.20 mg/dl in the majority renal units in the world). If we also consider the fact that serum magnesium

levels are rarely determined (perhaps never in many hemodialysis units), it becomes clear how dangerous hypomagnesemia is in these patients.

Therefore, the role of dialysate magnesium in serum magnesium levels is dominant. Bibliographic data showed that hypomagnesemia occurs in 5% of patients undergoing conventional hemodialysis with a dialysate magnesium of 1.20 mg/dl, while some have argued that the use of a low-magnesium dialysate (1.20 mg/dl) is a risk factor for hypomagnesemia [11,18,19]. With these bibliographic data and with the data from the serum magnesium exams before the start of the conventional hemodialysis session of our patients, where only 5 had serum magnesium more than 2.60 mg/dl, the need to increase the dialysate magnesium is obvious, which we did immediately, changing the 1.20 mg/dl that we had in the dialysate in 1.80 mg/dl. With this change, we achieved very good serum magnesium levels (10 patients had serum magnesium before the beginning of the session between 1.86-2.50 mg/dl, 36 had above 2.60 mg/dl [13 above 3.00 mg/dl], with a maximum value of 3.80 in two patients), without clinical events of hypermagnesemia.

However, the importance of other parameters of the dialysis session should not be overlooked. Thus, the impact of the bicarbonates of the dialysate should be considered, which affects the number of anionic sites of albumin, which when reduced, also reduces the bound with the serum magnesium, resulting in an increase in the magnesium that can be filtered and removed through the dialyzer. In fact, fluctuations in the concentration of ionized magnesium by 0.29 mg/dl per unit change of pH have been shown. When serum albumin levels are also reduced, the serum magnesium increases and its removal during dialysis is facilitated, as was also shown by our results.

Of course, glucose in the dialysate also plays a role, stimulating insulin secretion. The latter increases cellular magnesium uptake in tissues sensitive to glucose and an increase in insulin resulting from hyperglycemia could reduce the concentration of magnesium in the serum (moving it intracellularly), which means a smaller amount of magnesium will be available for removing through the filter. The relationship between hypomagnesemia and disorders of glucose metabolism in diabetes mellitus is quite well documented and is inversely correlated with glycemic control [20,21]. And this parameter did not appear to affect the serum magnesium levels of our patients, possibly again due to the size of the sample we studied. Other factors that could affect magnesium removal besides composition of dialysate include the rate of blood and dialysate supply to the filter, but no studies have been conducted on these factors.

It is therefore a given that the daily intake of magnesium should be removed, both in normal individuals and in hemodialyzed patients by the intestine and kidneys (but also by a dialysis method). Considering that 35-90% of the daily intake of magnesium is excreted in the feces, it is obvious that several mg of magnesium remains to be excreted through the kidneys (or through via the dialysis filter). In hemodialyzed patients, the serum magnesium concentration depends mainly on the removing through the filter [22]. The dialysate composition is supposed to allow for optimal electrolyte exchange between the blood and the dialysate. In the last 10 years, the dialysate has been modified mainly regarding the concentration of calcium and the bicarbonates. Of course, since 2014, a higher concentration of dialysate magnesium has been recommended (2.40 mg/dl in conventional hemodialysis, in addition to the usual content of 1.20 mg/dl used as a classical dialysate and 1.80 mg/dl which is rarely used) [7]. However, there are no data and specific guidelines and for dialysate magnesium in hemodiafiltration.

Thus, while normal serum magnesium levels in the general population are currently considered to be 1.70-2.40 mg/dl, the optimal serum magnesium levels and the ideal dialysate magnesium concentration for hemodialyzed patients are unclear. Kato et al. in 1650 hemodialyzed patients studied retrospectively, found a median serum magnesium levels of 2.50 mg/dl before the beginning of session, with dialysate magnesium of 2.40 mg/dl [23,24].

Overall, the data today suggests the risk of an increasing depletion of magnesium in hemodialyzed patients when conventional dialysis dialysate are used, especially in patients with poor nutrition and in those taking proton pump inhibitors (we did not see a significant effect of PPIs on serum magnesium balance, perhaps due to the small number of our patients). Nephrologists should be aware of this possibility and consider avoiding dialysate with low magnesium levels, monitoring serum magnesium for hypomagnesemia and the effects of any treatment with adjustments to the dialysate or oral supplements. We did this after determining serum magnesium levels in all of our patients (due to some symptomatology of some of them that suggested hypomagnesemia).

The choice of dialysate magnesium by nephrologists is ultimately difficult, because several factors must be considered. Early signs of magnesium deficiency include loss of appetite, nausea, vomiting, fatigue and weakness. As it worsens, numbness, tingling, muscle twitching, cramps may occur, seizures, sudden changes in behavior, personality changes, arrhythmias, coronary spasms and intradialytic hypotension [10,25-28]. However, even in patients with severe hypomagnesemia, clinical signs associated with magnesium deficiency may be absent [29]. In our patients, we observed the following clinical findings: numbness or tingling and burning in the feet, muscle twitching, restless legs, cramps and arrhythmias.

Chronic magnesium deficiency causes chronic inflammation, oxidative stress, insulin resistance, osteoporosis and bone fractures, which do not occur in mild hypermagnesemia [4,30,31]. It also increases the incidence of diabetes mellitus, infectious and cardiovascular diseases [32,33]. Magnesium also plays a role in vascular aging (due to its reduction, it is likely to occur prematurely and is more severe in patients with CKD compared to the general population). Kato et al. from the Japanese hemodialysis database (J-DOPPS), found a negative correlation between low serum

magnesium levels and response to erythropoietin, while they found opposite results with slightly elevated serum magnesium levels [24]. In the literature, patients with serum magnesium concentrations ≤1.50 mg/dl or ≤1.80 mg/dl were considered hypomagnesemic [34,35].

In contrast, higher dialysate magnesium appears to be safe and beneficial. Plasma magnesium levels of up to 4.80 mg/dl are common in hemodialyzed patients and are usually asymptomatic [6]. Studies have shown that it may be important to maintain serum magnesium concentrations before hemodialysis session at 2.70-3.00 mg/dl [36]. In the study of Leenders et al. with 34 hemodialyzed patients, as well as in others, it was found that higher serum magnesium concentration before hemodialysis session was associated with lower overall mortality, cardiovascular mortality and sudden death [4,37,38]. Also, in an interventional study the increased dialysate magnesium concentration from 1.20 to 1.80 mg/dl, the concentration of ionized magnesium before hemodialysis session is increased statistically significantly after 24 months, without clinical signs of hypermagnesemia and without toxic magnesium levels being detected. Having found low serum magnesium levels, these researchers simply suggested the use of a higher dialysate magnesium (1.80 mg/dl), a method that has now been shown to safely increase serum magnesium levels, which was also confirmed by our findings (we restored the serum magnesium levels of all patients and eliminated their symptoms of hypomagnesemia) [39].

More recently, Ohya et al. examined 1231 hemodialyzed patients and found that higher serum magnesium levels predicted lower PTH levels even after adjusting for other factors, such as serum calcium and phosphate levels and the use of calcimimetics [39]. As a divalent cation, magnesium can bind to calcium receptors in the parathyroid glands and is thought to thereby reduce PTH release [4]. Data from the study of Kusic et al. showed that the mean total serum magnesium concentration in the group with higher dialysate magnesium exceeded the range of normal serum magnesium levels, both before and after the hemodialysis session, but no signs and symptoms of hypermagnesemia were observed [40]. In line with these findings, studies examining the preferred magnesium levels in hemodialyzed patients have suggested that higher serum magnesium levels may be beneficial, even for them [36,41]. In fact, Sakaguchi et al. reported that the optimal total serum magnesium concentration should be above the range of normal levels in healthy individuals to be protective against cardiovascular morbidity and mortality, with even moderate hypermagnesemia being associated with improved survival [36,42]. It is generally accepted that slightly elevated magnesium is beneficial for hemodialyzed patients [43]. As the patients in the study by Kusic et al. showed no signs of hypermagnesemia during the 1-year follow-up, it seems that clinically recognizable manifestations of hypermagnesemia may depend on extremely high serum magnesium levels (above 4.80 mg/dl) rather than moderately high ones (<2.80 mg/dl), especially over a period longer than 1 year [40,44,45]. The most significant increase occurs in the first six months after the start of treatment. This is in good agreement with the findings of Filiopoulos et al., who followed patients for 4 months [46]. We, too, with the several cases with elevated serum magnesium values (levels up to 3.80 mg/dl) with the 1.80 mg/dl dialysate magnesium, did not observe any clinical manifestations or side effects of hypermagnesemia in any patient.

Knowing this data and the relatively low serum magnesium levels in almost all our patients (with the dialysate magnesium of 1.20 mg/dl), some of whom also had symptoms (both during the session and outside of dialysis) related to hypomagnesemia, such as restless legs, involuntary leg jerks, and numbness, we increased the magnesium solution to 1.80 mg/dl.

Regarding dialysis methods, they have changed over time, using high-flux membranes and hemodiafiltration using large volumes of substitution fluid, where the assessment of magnesium levels is challenging [47]. Of course, the literature data on the impact of the dialysis method on magnesium levels are few. Thus, Kusic et al. studied serum magnesium levels (and magnesium levels in their red blood cells) in 43 hemodialyzed patients with conventional hemodialysis, using dialysate magnesium of 1.20 and 2.40 mg/dl. Total serum magnesium was 2.73±0.46 mg/dl before and 2.28±0.38 mg/dl after the end of dialysis session in patients using 1.20 mg/dl dialysate magnesium ($p < 0.001$), while it was 3.53±0.6 mg/dl before and 3.58±0.43 mg/dl after the dialysis session in patients using 2.40 mg/dl dialysate magnesium ($p<0.001$). They concluded that patients using a lower dialysate magnesium had serum magnesium levels that remained within the normal range and decreased after the end of dialysis session, while in the group with a higher dialysate magnesium, serum magnesium levels exceeded the normal range before and after dialysis session. The post-session decreases in total serum magnesium levels when using a 1.20 mg/dl dialysate magnesium was also reported by Leenders et al., who argued that the 1.20 mg/dl dialysate magnesium is too low [41]. Kusic et al. also did not observe clinical signs and symptoms of hypermagnesemia during the use of the higher dialysate magnesium, despite the high total serum magnesium levels, as we also noted and we agree with them [41]. The results of this study are consistent with previously reported data from Kuchle et al. who compared the use of a low (1.20 mg/dl) and a higher (1.80 mg/dl) dialysate magnesium, as we did. They determined the serum magnesium levels before the session of 205 hemodialyzed patients, with a dialysate magnesium of 1.20 mg/dl and found them lower, compared to age-matched patients not undergoing hemodialysis, with several clearly hypomagnesemic [40]. Others studied the impact of a dialysate magnesium of 1.80 mg/dl (on safety and serum magnesium levels) in 34 patients over a 30-month period. They did not record any obvious side effects or other laboratory abnormalities (in calcium, phosphate and parathyroid hormone). In summary, the higher dialysate magnesium was found to be safe and did not allow for magnesium loss during dialysis [22].

Finally, the amount of magnesium removed by conventional hemodialysis depends on its concentration in the dialysate (dialysate with magnesium 1.80 mg/dl) and can remove up to 565 mg of magnesium/session [2].

Tanaka et al. studied hemodialyzed patients with a combination of dialysis methods (online pre-dilution hemodiafiltration with substitution volume of 60 and 84 L/session and then post-dilution online HDF with substitution volume of 8 and 16 L/session and then with conventional hemodialysis (the same program once with classical dialysate composition and the other with citrate in dialysate), which cannot be compared with our results which involved only conventional hemodialysis with two different dialysate magnesium and a single session with online per-dilution HDF [48]. With such a program in 4-hour sessions, with a blood pump of 280 ml/min and a dialysate flow of 500 ml/min, in 6 patients and with a dialysate magnesium of 1.20 mg/dl with acetate, they found that 129±97 mg of magnesium were removed in pre-dilution and 102±72 in post-dilution/session (p=NS), without having collected the hole ultrafiltrate, claiming that in their hospital the partial collection of the ultrafiltrate did not have large difference in the magnesium levels of the hemodialyzed patients from the total ultrafiltrate concentration. It is noted, however, that the total magnesium levels in all patients before the session were <2.70 mg/dl, which was probably lower than the magnesium levels of our patients [48]. Of course, the comparison with our results is not safe, since they also used acetates in the solution, as well as because the different blood flow to the filter (280 Vs 350-400) and the substitution volume in ours were 48 L and not 60 L. Nevertheless, the amount removed that they found was much smaller than that which we found. And despite what they claim about the reliability of the partial collection of the ultrafiltrate, we collected the entire volume of this and there we determined the magnesium that was removed, which means that our method is more accurate.

It is concluded form our study that: a) Conventional hemodialysis with a dialysate magnesium of 1.20 mg/dl leads many hemodialyzed patients to low serum magnesium levels, even symptomatically, b) dialysate magnesium of 1.80 mg/dl is well tolerated, safe and does not cause any problems in patients, c) serum albumin levels affect the amount of magnesium removed during the hemodialysis session, d) while borderline low serum magnesium levels cause symptoms, elevated levels (above the upper normal limits) do not cause any symptoms, e) online pre-dilution HDF loses very large amounts of magnesium, capable of removing magnesium ingested with food in two days and f) guidelines should be established for the dialysate magnesium and nephrologists should stop using the 1.20 mg/dl dialysate magnesium, because major changes have occurred in people's lives and in the treatment of hemodialyzed patients over time, which have led to a decrease in their serum magnesium levels, which after the session may even be fatal.

Limitations of the study The study has some limitations. First, the number of patients studied was relatively small. Second, total serum magnesium was measured and not ionized magnesium or red blood cell magnesium levels, which is more representative. And third, the amount of magnesium removed in a conventional hemodialysis session was not studied to determine whether there is a difference between this and online pre-dilution HDF in the amount of magnesium removed/session.

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