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Changes in Serum Magnesium after Increasing Dialysate Magnesium in Hemodialysis Patients: A Prospective Case Series

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Abstract

Aim: Due to the observation of decreased serum magnesium levels in some patients of our hemodialysis unit, who also had clinical signs of hypomagnesemia, this prospective case series study was designed to investigate if the dialysate magnesium of 0.50 mg/L which we use was sufficient or not for the needs of these patients. This study aimed to evaluate how increasing magnesium dialysate from 0.50 to 0.75 mmol/L affects serum magnesium levels and related symptoms in hemodialysis patients. **Patients-Methods:** Serum magnesium levels were examined in all of our dialyzed patients, with a dialysate magnesium of 0.50 mmol/L, to assess whether these were normal serum magnesium levels and not responsible for clinical manifestations (of hypomagnesemia) that we had found in some of them. Serum magnesium levels were determined before a mid-week dialysis session (Wednesday or Thursday). Those who were below the lower normal limits would be given oral magnesium oxide, initially at a dose of 300 mg/24 hours, and if these were not restored, the drug would be administered at a double dose. If magnesium levels were restored with this dose, the dialysate magnesium would be changed from 0.50 to 0.75 mmol/L, with oral magnesium discontinued. **Results:** Initially, the mean serum magnesium level in the 60 patients was 0.91 ± 0.15 mmol/L (2.18 ± 0.36 mg/dl), with 15 of them having levels below 0.83 mmol/L, with a minimum value of 0.44 and a maximum of 1.29 mmol/L. There was no correlation between the serum magnesium levels and the dialysis method (0.90 ± 0.14 vs 0.90 ± 0.17 mmol/L, p=NS), and no correlation was noted from the presence of diabetes mellitus, hypoalbuminemia, or the existence of diuresis and the use of diuretics. The oral administration of magnesium oxide at a dose of 300 mgx2/24 hours was shown to restore serum magnesium levels, as was the increase in the dialysate magnesium from 0.50 to 0.75

mmol/L (after 4 months, the mean serum magnesium levels were 1.15 ± 0.17 and after another 4 months, were 1.10 ± 0.18 mmol/L). With these serum magnesium levels, no patients had the symptoms of hypomagnesemia that they had when the study began. A small percentage of patients who dialyzed with a dialysate magnesium of 0.75 mmol/L had serum magnesium levels above the normal range (15/60 patients after 4 months on dialysate magnesium 0.75 mmol/L and 9 after another 4 months with the same dialysate), without clinical manifestations of hypermagnesemia. **Conclusions:** It is concluded that the serum magnesium of many dialyzed patients is low when they are being dialyzed with a dialysate magnesium of 0.50 mmol/L, and the use of a dialysate magnesium of 0.75 mmol/L in all patients is, in our opinion, without risk of hypermagnesemia, ensuring many beneficial effects.

Keywords

Serum Magnesium, Dialysate Magnesium, Hypomagnesemia, Online HDF, Conventional Hemodialysis

1. Introduction

For normal individuals, the recommended daily minimum magnesium intake is approximately 150 mmol for men and approximately 120 mmol for women [1], while nowadays approximately 70 - 100 mmol of magnesium is ingested and 30% - 50% of this amount is absorbed in the intestine. This recommended amount is difficult to obtain for patients with end-stage renal disease (ESRD), where, in addition to reduced dietary magnesium intake, the boiling of many foods also plays a role (which mainly aims to reduce their potassium and phosphate intake), as well as its intestinal absorption (*i.e.*, Proton Pump Inhibitors-PPIs) and renal excretion (furosemide in case of existing residual renal function) [2] [3]. Magnesium removal also plays a role, mainly through the dialyzer (filter), which may be increased in case of hypoalbuminemia and/or metabolic acidosis, which are associated with a larger fraction of ionized magnesium available for removal by diffusion during the dialysis session. Finally, dialysis methods have changed over time (hemodiafiltration with pre- or post-dilution), versus high flux and conventional hemodialysis, as well as the type of membranes used (high versus low flux), with large volumes of substitution fluid, but also with citrates in dialysate [3]. Therefore, because nowadays the assessment of serum magnesium levels in hemodialyzed patients is a challenge, this study aimed to evaluate how increasing dialysate magnesium from 0.50 to 0.75 mmol/L affects serum magnesium levels and related symptoms in hemodialysis patients.

2. Patients-Methods

2.1. Patients

Serum magnesium levels were determined in all patients of our unit (n = 60, 29F, 31M) before the beginning of a mid-week (Wednesday or Thursday) hemodialysis

session. In total, these were examined in all patients (37 on conventional hemodialysis and 23 under online hemodiafiltration-HDF). Patients on dialysis for <12 months were excluded, with no other exclusions for any reason. It was planned to determine serum magnesium levels before the dialysis session and every 4 months in all patients dialyzed with higher magnesium dialysate.

The study was completed at the Chronic Hemodialysis Unit "Dimokritio" of Komotini. It was approved by the Scientific Council of the General Hospital of Komotini (No. 7/2024) and was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Humans. Written consent for participation was obtained from each patient, after they had previously been informed about the protocol.

2.2. Methods

In this prospective case series study, initially, serum magnesium levels were determined in all patients. Those with hypomagnesemic levels (<0.75 mmol/L), with or without symptoms, were administered effervescent magnesium oxide tablets (300 mg, 1 × 1/24 hours), and if serum magnesium levels did not improve after 6 months, the magnesium dosage was doubled, without changing the magnesium of dialysate. Four months after doubling the oral magnesium (300 mg × 2/24 hours), serum magnesium levels improved, so oral magnesium oxide was discontinued and the composition of the dialysate magnesium was changed from 0.50 to 0.75 mmol/L, without changing the rest of the dialysis conditions, methods and dialyzer. The serum magnesium of all patients was determined after 4 and 8 months with the increased magnesium of dialysate (0.75 mmol/L).

Cases of diabetes (the diagnosis was based on medications they were taking and related to diabetes), the presence of residual renal function (diuresis >400 ml/24 hours), whether they were taking furosemide, whether they were taking PPIs, the method of dialysis (conventional hemodialysis or HDF), and the duration of dialysis were recorded.

All patients (n = 60), for the needs of hemodialysis, used low molecular weight heparin (vemiparin) as an anticoagulant agent, in doses of 2500 - 3500 IU/session, depending on their dry body weight. The blood flow (pump) was 400 ml/min for 57, and only 3 had a flow of 350 - 380 ml/min (with arterial negative pressure <−200 mmHg), and dialysate flow was 500 ml/min. In all, the bicarbonates of dialysate were from 29 - 33 mmol/L, the sodium from 138 - 140 mmol/L, the potassium from 2 - 3 mmol/L, the chloride 110 mmol/L, and the glucose 5.6 mmol/L. The duration of the session was four hours (in 57), 4 hours and 30 min in two, and 4 hours and 45 minutes in one. The substitution volume in online HDF with pre-dilution was 50% of the pump, which was basically about 400 ml/min (*i.e.* approximately 48 L/session), and in post-dilution, 25% of the pump (from 22 - 24 L/session). All patients used hemodialysis machines Nikkiso DBB EXA. Polyethersulfone-polynephron dialyzers were used (ElisioTM Nipro 2.1 m^2 high flux and 2.1 m^2 low flux).

The Abbott Alinity C analyzer was used to determine the parameters studied.

Urea and magnesium were determined by the enzymatic method, albumin by a colorimetric method, while potassium was determined by the ion-selective electrode.

2.3. Statistical Analysis

Continuous variables were expressed as mean ± standard deviation or median, according to the normality of the distribution of each variable. The variables of serum magnesium levels follow a normal distribution (Kolmogorov-Smirnov). Comparisons between the groups were performed using the Student's t-test for two independent means. The analysis was conducted with the statistical software MedCalc (version 20.218). Probability values of $p < 0.05$ were considered statistically significant for all comparisons.

2.4. Ethical Consideration

Ethics committee approval was received for this study from the ethics committee of the Scientific Council of the General Hospital of Komotini (Number of protocol 7/2024, August 16, 2024) in accordance with the International Ethical Guidelines and the Declaration of Helsinki.

3. Results

The study included 60 patients (29F, 31M), who had been on dialysis for 12 - 565 months (mean ± SD = 75 ± 111). Their ages ranged from 39 to 92 years (mean ± SD = 72.3 ± 12.4, median 76 years). Twenty-three were on online HDF (21 post- and 2 pre-dilution) and 37 were on conventional hemodialysis.

Twenty of them had diabetes mellitus; almost all the patients were taking PPIs (56/60). Twenty-one had residual renal function, of whom nine were diabetics and taking furosemide (125 - 500 mg/day) 5F, 4M, and seven out of 60 patients had serum albumin <35 g/L (Table 1).

Initially, all patients were asked about the presence of symptoms of hypomagnesemia, and the following were found: 15 had numbness in the legs, 2 had tremors, 7 had burning sensations, 8 experienced restlessness, and 5 had cramps. For this reason, magnesium levels were initially determined in all patients before the beginning of a mid-week hemodialysis session. The mean magnesium levels in our 60 patients were 0.91 ± 0.15 mmol/L (minimum value 0.44 mmol/L and maximum 1.29 mmol/L), of which 15 had levels below 0.83 mmol/L, with no difference in serum levels between those on conventional hemodialysis and those on online HDF (both with pre- or post-dilution) (0.90 ± 0.14 vs 0.90 ± 0.17 mmol/L, p = NS) (Table 1). Among those with serum magnesium levels below 0.83 mmol/L (8 on conventional hemodialysis and 7 on online HDF), the lowest values were found in five of those on conventional hemodialysis, while the lowest value (0.44 mmol/L) was found in one patient on post-dilution online HDF. Of these six patients who had hypomagnesemia, only 4 were symptomatic (Table 2).

Table 1. The age, the months patients have been on dialysis, patients with diabetes or hypoalbuminemia (albumin <35 gr/L), those taking PPIs, and the dialysis method they used are shown. The serum magnesium levels of the patients before any treatment (with dialysate magnesium 0.50 mmol/L), after 4 months with 0.75 mmol/L dialysate magnesium, and after 8 months with 0.75 mmol/L dialysate magnesium are also shown (CH = Conventional hemodialysis, HDF = Hemodiafiltration).

	Patients (n = 60)	
Demographic data		
Sex (F/M)	(29/31)	
Age mean ± SD (median)	72.3 ± 12.3 (76)	
Months on dialysis (mean ± SD)	(75 ± 111)	
Laboratory exams		
Hypoalbuminemia (Yes/No)	(7/53)	
Serum magnesium levels (mmol/L)		
Before any change (dialysate magnesium 0.50)	0.91 ± 0.15	$P = _{\text{Before-after 4 months}} < 0.00001$
After 4 months, magnesium dialysate 0.75 mmol/L	1.12 ± 0.23	$P = _{\text{After 4 months—after 8 months}} = NS$
After 8 months, magnesium dialysate 0.75 mmol/L	1.10 ± 0.18	
Clinical characteristics		
Diabetes (Yes/No)	(20/40)	
Diabetics taking furosemide (n/60)	(9/20)	
CH/HDF	(37/23)	
Patients taking PPIs (Yes/No)	(56/4)	
Residual renal function (Yes/No)	(21/39)	

The serum magnesium levels of these six patients and their changes with oral administration of magnesium oxide are shown in Table 2:

Table 2. Serum magnesium levels of 6 patients with overt hypomagnesemia before any treatment and after administration of 1 and 2 effervescent magnesium oxide tablets.

	Serum magnesium levels (mmol/L)		
Patients	Before any treatment	After 6 months with magnesium oxide 300 × 1 mg/day	After 4 months with magnesium oxide 300 × 2/day
1M	0.44	0.74	0.90
2M	0.70	0.79	1.06
3M	0.62	0.69	0.88
4F	0.67	0.70	0.97
5M	0.71	0.78	1.06
6M	0.70	0.76	1.02
Mean ± SD	0.64 ± 0.09	0.74 ± 0.04	0.98 ± 0.07

Effervescent magnesium oxide tablets were administered (300 mg × 1/24 hours) to the six patients with obvious hypomagnesemia, who continued to be dialyzed with the same magnesium of dialysate (0.50 mmol/L), and serum magnesium levels were determined again after 6 months, without any statistically significant change in their serum magnesium levels (0.64 ± 0.09 vs 0.74 ± 0.04 mmol/L, p = NS), although the clinical icon improved in one patient with numbness, one with cramps, and two with restless legs. The dose of magnesium oxide was then doubled (300 mg × 2/24 hours), and their serum magnesium was re-evaluated after 4 months, where magnesium levels had improved statistically significantly (0.64 ± 0.09 vs 0.98 ± 0.08, p < 0.0001) (Table 2), while the symptoms of hypomagnesemia in all patients were alleviated. This was the reason for increasing the dialysate magnesium to 0.75 mmol/L in all patients (while the magnesium oxide that the six patients were receiving was discontinued), without changing anything else in dialysis conditions, dialyzer, and dialysate. Since then, all patients have continued to be dialyzed with this dialysate magnesium. The serum magnesium of all patients was determined after 4 months (with 0.75 mmol/L magnesium dialysate) and a statistically significant difference was found in comparison with the serum magnesium values with 0.50 mmol/L magnesium of dialysate (0.91 ± 0.15 vs 1.15 ± 0.17, p = 0.0001), where 15 had serum magnesium ≥1.25 mmol/L (from 1.25 - 1.58 mmol/L), while 8 months after the dialysate change regarding the magnesium composition, the serum magnesium levels did not differ from those 4 months before (under 0.75 mmol/L magnesium) (1.12 ± 0.23 vs 1.10 ± 0.18 mmol/L, p = NS), where 9 had ≥ 1.25 mmol/L (range from 1.26 to 1.61 mmol/L), without any symptom of hypermagnesemia (Figure 1).

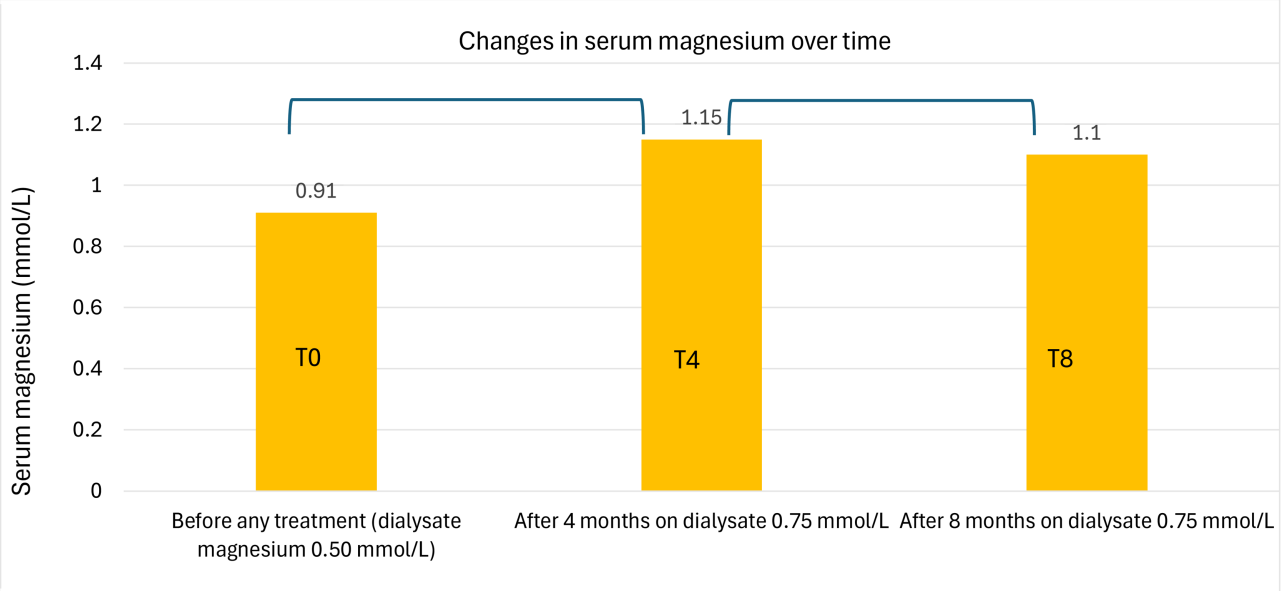

Figure 1. The serum magnesium levels of 60 patients before any treatment (T0) and after 4 (T4) and 8 months (T8) with dialysate magnesium 0.75 mmol/L (p = 0.0001 between serum magnesium levels before any treatment and after 4 months with dialysate magnesium 0.75, and p = NS between serum magnesium levels after 4 months with dialysate magnesium 0.75 and after 8 months with the same dialysate magnesium).

In the initial serum magnesium determination of the 60 patients, no statistically significant difference was found between diabetics (n = 20) and non-diabetics (n = 40) (0.94 ± 0.16 vs 0.89 ± 0.15, p = NS). Also, no difference in serum magnesium levels was noted between those with hypoalbuminemia (n = 7) and those without hypoalbuminemia (n = 53) (0.92 ± 0.15 vs 0.82 ± 0.09 mmol/L, p = NS).

Comparing serum magnesium levels in diabetics with diuresis who were receiving furosemide (n = 9) with the rest of the patients (n = 51), significantly lower levels were found in the former (0.94 ± 0.31 vs 1.15 ± 0.19, $p < 0.005$), only 4 months after changing the dialysate magnesium from 0.50 mmol/L to 0.75 mmol/L.

4. Discussion

Normally, magnesium homeostasis depends on intake, intestinal absorption, release from bones, and renal excretion (approximately 70% - 80% of plasma magnesium is filtered and 95% of it is reabsorbed). In hemodialyzed patients, of course, the serum magnesium levels are mainly influenced by its removal by the dialyzer [4]. That is, the main and determining factor of magnesium balance is the concentration gradient between serum and dialysate, leading to a corresponding loss of magnesium during the session.

As for serum magnesium levels, they are not related to their tissue stores and do not reflect their total reserves in the body. Only 1% of the total body magnesium is in extracellular fluids and only 0.3% of total magnesium is found in serum, because of which its levels in the serum are not predictive of the intracellular or total body magnesium content. It is emphasized that serum magnesium can be normal even in individuals with a negative magnesium balance, while most patients with hypomagnesemia are asymptomatic [5], as we have also found. It is also noted that even when tissue and cellular magnesium are reduced by up to 20%, its serum levels can remain normal [6].

It was previously thought that hemodialyzed patients tended to develop hypermagnesemia due to dietary causes and medications (magnesium-containing phosphate binders, etc.). Thus, due to these concerns and the fact that hypermagnesemia caused osteomalacia and uremic pruritus [7], 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 contraction disorders, intradialytic hemodynamic instability and hypotension, muscle weakness (magnesium is essential for muscle function and vascular tone) [8] [9], arrhythmia, tetany, cramps, or chronic complications (hypertension, vascular calcifications) [10]. Muscle cramps are the second most common intradialytic problem after hypotension and can be the cause of premature discontinuation of the hemodialysis session in a quite large proportion of patients. It is emphasized that these lead to non-compliance of patients with the treatment, loss of dialysis time, and ultimately a reduction in the provided clearance. In a small observational study, increasing dialysate magnesium from 0.375 to 0.50

mmol/L led to a decrease in the frequency of muscle cramps, which even became less severe [11].

Hypomagnesemia also stimulates oxidative stress and inflammation and impairs endothelial function, resulting in atherosclerosis. Magnesium is also an important component of bone minerals, and hypomagnesemia is associated with suppressed osteoblastic and osteoclastic activity, osteopenia, and resistance to parathyroid hormone. Higher serum magnesium concentrations have been shown to be associated with lower parathyroid hormone levels in hemodialyzed patients [12] [13]. Although several studies have shown that low serum magnesium levels in hemodialyzed patients are associated with increased parathyroid hormone [14], others do not support this [15], while one study found no correlation between magnesium and serum parathyroid hormone concentrations [16].

In an observational study with hemodialyzed patients, an inverse association was found between plasma magnesium concentrations and the occurrence of arrhythmias [17]. Furthermore, in a short, randomized crossover study in hemodialyzed patients, a dialysate magnesium of 0.75 mmol/L compared to 0.50 mmol/L reduces pulse wave velocity, *i.e.*, reduces vascular stiffness [18].

Finally, 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 correlated with ischemic strokes [19] [20]. In fact, in recent years, several studies have shown that lower plasma magnesium concentrations before hemodialysis sessions are independently associated with higher all-cause and cardiovascular mortality [21].

Nowadays, the data on magnesium in hemodialyzed patients has changed, and the probability of detecting hypomagnesemia among them is very high, as we have also found. This is due to the reduced intake (due to the reduced magnesium content of vegetables, because of soil content in magnesium, but also to the diet followed) and the double boiling of various foods, to reduce potassium and phosphate intake. Also important is the use of PPIs (which are usually taken by almost all of these patients, as happened in ours), which reduces its intestinal absorption, as well as the administration of loop diuretics (furosemide) in those with residual renal function, which contributes to larger renal excretion of magnesium (its reabsorption occurs in the thick ascending limb of the loop of Henle and furosemide inhibits the electrical gradient that is necessary for it). In particular, with regard to diabetic hemodialyzed patients (who may constitute up to 50% of hemodialyzed patients in each renal unit), hypomagnesemia is very often observed, which is attributed to osmotic diuresis (if there is residual renal function), which causes high renal excretion of magnesium, but also to the lack of sensitivity to insulin, which affects the intracellular movement of magnesium and therefore leads to the increased concentration and loss of extracellular magnesium (insulin regulates the activity and expression of the transient receptor potential channel melastatin [6TRPM6], which regulates magnesium reabsorption in the intestine and kidneys) [22]. Other mechanisms include hyperfiltration, increased urine flow (in patients

with residual renal function), and reduced intestinal absorption due to autonomic neuropathy [23]. In 1979, Mather *et al.* determined plasma magnesium levels in 582 unselected diabetic outpatients and 140 controls and found that mean levels were significantly lower in diabetics than in controls, with 25% of diabetics having values lower than those found in controls. They also noted that plasma magnesium levels in diabetics were inversely related to glycemic control (*i.e.*, poor glycemic control was associated with lower serum magnesium levels). However, the problem of hypomagnesemia in those patients is not easily recognized, also because serum magnesium levels were rarely determined by doctors in dialysis units [24]. In our patients, no difference in serum magnesium levels was noted between those with and without diabetes, maybe because of the small sample of patients. However, in our 9 diabetic patients receiving furosemide (when dialyzed with 0.75 mmol/L dialysate magnesium, compared with 51 patients who did not have the combination of diabetes and furosemide), statistically significantly lower magnesium levels were found in diabetics.

Most importantly, the use of high flux dialyzers, where large volumes of the patient's fluids are replaced with a substitution fluid, contributes to a much greater loss of magnesium per session. Considering all these changes that have occurred over time, it is obvious that dialysate with magnesium of 0.50 mmol/L probably does not serve the needs of these patients. Of course, the optimal concentrations of magnesium in plasma 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, where the usual content varies from 0.25 - 1.00 mmol/L [25], and even today there is confusion regarding the ideal magnesium of the dialysate in hemodialysis. It was also found that the commonly used dialysate magnesium of 0.50 mmol/L, in many countries, including ours, often leads to hypomagnesemia [26].

Regarding the removal by the filter in conventional hemodialysis during a dialysis session, serum magnesium is not fully "available" for excretion, because it is approximately 25% bound to proteins (mainly albumin) and 5% - 16% to some anions, such as bicarbonate, phosphate radicals, and citrate [27]. The amount of magnesium removed by the dialyzer depends on its concentration in the dialysate. This means that in cases of hypoalbuminemia, patients have more magnesium unbound to proteins and therefore more available for removal. However, in our study, no difference was found in serum magnesium levels between those with hypoalbuminemia and those without it, perhaps due to the small sample of patients in the study.

Currently, in patients undergoing conventional hemodialysis, some believe that low serum magnesium levels in patients using 0.50 mmol/L dialysate magnesium are due to medications (PPIs, loop diuretics) [28]. In a study, a 4-week increase in the magnesium concentration in the dialysate from 0.50 to 1.00 mmol/L resulted in a 0.4 mmol/L increase in predialysis plasma magnesium concentration and achieved a mean predialysis plasma magnesium concentration of 1.4 ± 0.2 mmol/L [12].

Also, in a Japanese study, in patients undergoing conventional hemodialysis, the average plasma magnesium concentration of 142,555 hemodialyzed patients was 1.09 mmol/L, but it should be noted that most dialysis units there use a dialysate magnesium of 1.0 mmol/L [29]. In a US study, in 21,534 hemodialyzed patients the average plasma magnesium concentration was 0.92 ± 0.16 mmol/L, where patients who were dialyzed with higher dialysate magnesium also had higher serum magnesium levels [21]. Furthermore, those who noted hypermagnesemia in a large percentage of their patients (73.65%) attributed it to the fact that most of their patients were young, consumed a higher amount of magnesium, and did not take PPIs, while 40/148 of their patients underwent only 2 dialysis session per week [16].

Finally, there are insufficient data on the optimal plasma magnesium concentration, and this concentration must be regulated in some way. However, in a study that increased the dialysate magnesium from 0.50 to 0.75 mmol/L, the predialysis serum ionized magnesium concentration increased statistically significantly from 0.53 ± 0.12 to 0.66 ± 0.02 mmol/L after 24 months, without clinical signs of hypermagnesemia [30]. Also, two studies that described magnesium concentrations before and after the end of the hemodialysis session, with a dialysate magnesium of 0.75 mmol/L, reported a constant mean plasma magnesium concentration during hemodialysis, ranging from 1.10 to 1.21 mmol/L [9], results with which we also agree.

However, given the increased prevalence of hypomagnesemia and its enhancing effect on potassium transport, it has been suggested that the usual prescription of dialysate magnesium should be higher than 0.50 mmol/L, especially among patients who are hypokalemic and those with a high gradient serum-dialysate potassium. In particular, Küchle *et al*. showed that with 0.75 mmol/L dialysate magnesium, serum magnesium concentrations can be increased to consistently high normal levels in all patients, without notable side effects [31], something that others agree with [9] [32], but also, we observed (about 10 of our patients had serum magnesium at the border of mild hypermagnesemia without clinical manifestations). It has even been suggested that serum magnesium levels up to 1.50 mmol/L are not associated with clinical manifestations of hypermagnesemia [33]. This may suggest a protective effect of slightly elevated serum magnesium concentrations in hemodialyzed patients. In fact, a large-scale American study showed that mortality in hemodialyzed patients increased when serum magnesium concentration was low [21]. The above studies support the idea that hemodialyzed patients may require a slightly higher plasma magnesium level than healthy individuals.

Although several reports have been published on magnesium levels in hemodialyzed patients, only a few have evaluated them in online HDF. In post-dilution HDF, which is the best dialysis method in Europe, a large volume of substitution fluid enters the blood directly. Tanaka *et al*. studied 18 patients undergoing online HDF (with replacement of 60 - 84 L in pre-dilution and 8 - 16 L in post-dilution), with the classic dialysate or with a dialysate containing citrate. They found that

online HDF had a negligible effect on ionized magnesium and calcium (however, the use of citrate in dialysate reduces ionized magnesium levels, probably due to chelation). That is, in this study, when using an acetate-based dialysate (classical solution), it was found that there was no difference between the five dialysis conditions examined (*i.e.*, HDF with pre- or post-dilution, HDF with higher or lower volumes of substitution fluids, and conventional hemodialysis) in the concentrations of serum ionized magnesium or calcium levels after the dialysis session. However, when a dialysate containing citrate was used, the concentration of ionized magnesium in the serum after the end of hemodialysis decreased to a level below the corresponding one in the dialysate containing citrate, possibly due to chelation of magnesium by citrate [34]. Our results (where citrate was not present in the dialysate) confirm that the dialysis method does not affect serum magnesium levels; however, our sample was not large enough and perhaps in the future, other studies with a larger number of patients will fully clarify the issue of the relationship of the dialysis method with serum magnesium levels.

It has been hypothesized that with the increased loss of albumin, magnesium bound to it is removed during the session [34]. Others agree that cotransport causes a negative magnesium balance, regardless of the concentration of this ion in the dialysate [35], while those who used a citrate dialysate did not find such an effect, apparently due to magnesium chelation [34]. The effect of albumin loss through the dialyzer on serum magnesium levels remains unknown, however.

In our study with pre-dilution online HDF (with ≥48 L of substitution volume), it was found that the loss of magnesium in dialysate ranged from 17 to 166.3 mmol/session with a dialysate containing glucose and from 95 to 118.8 mmol per session with a dialysate without glucose (unpublished data), which indicates that the loss is very large, considering that these patients cannot be vegetarians, where magnesium is abundant, and almost all were taking PPIs, with some also taking loop diuretics. Thus, with this loss, it is obvious that these patients should have tissue hypomagnesemia when dialyzed with 0.50 mmol/L dialysate magnesium.

In our study, we initially found low serum magnesium levels in several of our patients, especially in those who had diabetes and were also receiving furosemide. Oral magnesium administration at a dose of 300 mg × 2/24 hours may be a solution. However, by increasing the dialysate magnesium from 0.50 mmol/L to 0.75 mmol/L, we restored serum magnesium levels in all our patients (having caused mild asymptomatic hypermagnesemia in a few patients). This may be of prospective importance for limiting the complications of hypomagnesemia and improving patient survival, as other studies have shown [36] [37].

It is concluded that the serum magnesium levels of many dialyzed patients are low, and the use of a 0.75 mmol/L dialysate magnesium is currently necessary to be applied to all patients, without restrictions and fear of hypermagnesemia, because it ensures many beneficial effects.

Limitations of the study: First, the patients were from a single center and the sample was relatively small; second, there was no randomization of the patients

and all of them participated in the study; and third, there was no control group because it was considered unethical to exclude patients from treatment.

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Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Authors' Contributions

Konstantinos S. Mavromatidis: Contributed to the study design, analyzed and interpreted the data, drafted and revised the manuscript, and approved the final version. **Irini M. Kalogiannidou:** Contributed to the study design, collected and analyzed the data, revised the manuscript, and provided critical input to the study. **Pelagia A. Kriki:** Contributed to analyzing the data and conducting literature searches. **Emine S. Impis**: Contributed to sample and data collection. **Gkiounai S. Katzel Axmet:** Assisted with data collection, data analysis and interpretation, and literature searches.

Conflicts of Interest

The authors have no conflicts of interest to declare. They had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. The results in this paper have not been published previously, in whole or in part.

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