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A Higher Concentration of Dialysate Magnesium to Reduce the Frequency of Muscle Cramps: A Narrative Review

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Abstract

Purpose of review: Strategies to mitigate muscle cramps are a top research priority for patients receiving hemodialysis. As hypomagnesemia is a possible risk factor for cramping, we reviewed the literature to better understand the physiology of cramping as well as the epidemiology of hypomagnesemia and muscle cramps. We also sought to review the evidence from interventional studies on the effect of oral and dialysate magnesium-based therapies on muscle cramps.

Sources of information: Peer-reviewed articles.

Methods: We searched for relevant articles in major bibliographic databases including MEDLINE and EMBASE. The methodological quality of interventional studies was assessed using a modified version of the Downs and Blacks criteria checklist.

Key findings: The etiology of muscle cramps in patients receiving hemodialysis is poorly understood and there are no clear evidence-based prevention or treatment strategies. Several factors may play a role including a low concentration of serum magnesium. The prevalence of hypomagnesemia (concentration of $<$0.7 mmol/L) in patients receiving hemodialysis ranges from 10% to 20%. Causes of hypomagnesemia include a low dietary intake of magnesium, use of medications that inhibit magnesium absorption (eg, proton pump inhibitors), increased magnesium excretion (eg, high-dose loop diuretics), and a low concentration of dialysate magnesium. Dialysate magnesium concentrations of $\leq$0.5 mmol/L may be associated with a decrease in serum magnesium concentration over time. Preliminary evidence from observational and interventional studies suggests a higher dialysate magnesium concentration will raise serum magnesium concentrations and may reduce the frequency and severity of muscle cramps. However, the quality of evidence supporting this benefit is limited, and larger, multicenter clinical trials are needed to further determine if magnesium-based therapy can reduce muscle cramps in patients receiving hemodialysis. In studies conducted to date, increasing the concentration of dialysate magnesium appears to be well-tolerated and is associated with a low risk of symptomatic hypermagnesemia.

Limitations: Few interventional studies have examined the effect of magnesium-based therapy on muscle cramps in patients receiving hemodialysis and most were nonrandomized, pre-post study designs.

Abrégé

Contexte motivant la revue: Les stratégies visant à atténuer les crampes musculaires sont parmi les principales priorités de recherche des patients hémodialysés. L'hypomagnésémie étant un possible facteur de risque, nous avons procédé à

une revue de la littérature afin de mieux en comprendre l'épidémiologie, et d'examiner la physiologie et l'épidémiologie des crampes musculaires. Nous souhaitions également examiner les données probantes issues d'études interventionnelles portant sur l'effet des thérapies à base de dialysat de magnésium et de magnésium oral sur les crampes musculaires.
Sources: Articles examinés par les pairs.
Méthodologie: Nous avons cherché les articles pertinents dans les principales bases de données bibliographiques, notamment MEDLINE et EMBASE. La qualité méthodologique a été évaluée à l'aide d'une version modifiée des critères de contrôle de la qualité des études de Downs et Black.
Principaux résultats: L'étiologie des crampes musculaires chez les patients hémodialysés est mal comprise et il n'existe aucune stratégie de prévention ou traitement clairement fondé sur des données probantes. Plusieurs facteurs pourraient jouer un rôle, notamment de faibles concentrations sériques de magnésium. La prévalence de l'hypomagnésémie (concentration inférieure à 0,7 mmol/L) chez les patients hémodialysés variait de 10 à 20 %. Une faible consommation de magnésium dans l'alimentation, la prise de médicaments inhibant l'absorption du magnésium (ex. les inhibiteurs de la pompe à protons), l'excrétion accrue du magnésium (ex. dose élevée de diurétiques de l'anse) et une faible concentration de dialysat de magnésium figuraient parmi les causes d'hypomagnésémie. Un taux de dialysat de magnésium inférieur ou égal à 0,5 mmol/L pourrait être associé à une diminution de la concentration sérique de magnésium au fil du temps. Les résultats préliminaires de certaines études observationnelles et interventionnelles suggèrent qu'une concentration sérique plus élevée de magnésium dans le dialysat augmenterait les concentrations sériques de magnésium et pourrait réduire la fréquence et la sévérité des épisodes de crampes musculaires. La qualité des preuves appuyant ce bienfait est cependant limitée. Des essais multicentriques et à plus vaste échelle sont nécessaires pour juger si un traitement à base de magnésium peut véritablement réduire les crampes musculaires chez les patients hémodialysés. Dans les études menées jusqu'à maintenant, l'augmentation de la concentration de dialysat de magnésium semblait bien tolérée et a été associée à un faible risque d'hypermagnésémie symptomatique.
Limites: Peu d'études interventionnelles ont examiné l'effet de la prise de magnésium sur les crampes musculaires des patients hémodialysés, et la plupart de celles-ci constituaient des plans pré- ou post-études non randomisées.

Keywords
hemodialysis, hypomagnesemia, magnesium, muscle cramps, safety

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Introduction

Muscle cramps are sudden, painful, and involuntary muscle contractions that typically occur in the lower extremities.[1,2] Cramps can last seconds to minutes and can occur in the absence of disease, such as during pregnancy or intense athletic activity.[3] Cramps can also occur in the setting of metabolic disorders, motor neuron disorders, and neuropathies.[3] This review focuses on muscle cramps in patients receiving maintenance hemodialysis and on the potential benefit of using a higher concentration of dialysate magnesium to reduce the frequency and severity of muscle cramps.[4,5]

Patients on hemodialysis have prioritized muscle cramps as 1 of the top 3 physical symptoms that should be targeted for novel therapies.[6] Muscle cramps affect 25% to 80% of patients on hemodialysis and are a common reason for stopping a hemodialysis session early.[7-9] Cramps can occur during hemodialysis sessions, in between sessions, and during sleep.[7,8] The resulting discomfort can last up to 72 hours.[1] Patients who have muscle cramps endure a poor quality of life, find it hard to sleep, and experience anxiety and depression.[10,11] Patients who shorten their hemodialysis session because of muscle cramps may find it difficult to achieve their desired body weight by the end of the session.[12]

The pathophysiology of muscle cramping remains poorly understood and there are no proven prevention or treatment strategies. While various therapies have been explored (eg, quinine, carnitine, vitamin E, gabapentin, biotin, exercise, and massage), most have limited effectiveness and some may be unsafe for patients with kidney failure.[8,13-16]

One potential cause of muscle cramping in patients receiving hemodialysis is a low concentration of serum magnesium. A low concentration of serum magnesium is associated with poor health outcomes including muscle cramps.[4,5,17-30] Raising the concentration of magnesium in the dialysate may increase patients' serum magnesium concentration and may improve other health outcomes, such as reduced vascular calcification.[19] We are currently developing a large-scale randomized clinical trial to compare the effect of different concentrations of dialysate magnesium on patient health.

To inform the development of this trial and the decision to include muscle cramps as an outcome in our trial, we conducted a narrative (nonsystematic) literature review on hypomagnesemia and muscle cramps. The objective of this review was to better understand the epidemiology, physiology, and measurement of hypomagnesemia and muscle cramps, and to assess evidence from interventional studies testing the effect of magnesium-based therapy on muscle cramps in patients with and without kidney failure.

Methods

Search Strategy and Review Process

A study author (Varghese) searched for relevant articles in several bibliographic databases (search strategies for MEDLINE and EMBASE are provided in Supplemental Appendix I). Additional articles were found by searching the reference lists of relevant articles and by using the Cited By search function in Google Scholar. The methodological quality of interventional studies was assessed by a study author (Varghese) using a modified version of the Downs and Blacks criteria checklist (summarized in Supplemental Appendix II).[31] This checklist contains 27 criteria to evaluate both randomized and nonrandomized trials. This scale assesses the completeness and clarity of study reporting, external validity, internal validity (eg, bias and confounding), and power. The tool was modified slightly for use in our review. Specifically, the scoring for question 27 dealing with statistical power was simplified to a choice of awarding either 1 or 0 points depending on whether there was sufficient power to detect a clinically important effect. On the modified scale, we gave all included studies a score from 0 to 28, grouped into the following 4 quality levels: excellent (26-28), good (20-25), fair (15-19), and poor ($\leq$14).

After completing and reviewing the search strategy results, we noted the evidence from interventional studies of dialysate magnesium in maintenance hemodialysis patients was quite limited. We then decided to expand the population of interest to include studies of patients not on maintenance hemodialysis, such as pregnant women and older adults (Table 1). The evidence from the interventional studies of both patients on dialysis and nondialysis patient populations, which included the subgroups of pregnant patients and older adults, is summarized in Supplemental Appendix III. We also expanded the study eligibility criteria to include epidemiological studies (eg, cohort and cross-sectional studies). This allowed for a more comprehensive assessment of the relationship between magnesium and muscle cramps.

Review

The findings from our literature review are summarized in 6 main content areas:

1. Causes and epidemiology of hypomagnesemia in patients with chronic kidney disease and kidney failure.
2. Physiologic mechanisms linking magnesium and muscle cramps.
3. Assessment of muscle cramps in published studies.
4. Association between a lower concentration of serum magnesium and a higher risk of muscle cramps: Evidence from observational studies.
5. Effect of magnesium-based therapy on muscle cramps: Evidence from interventional studies.
6. Safety of magnesium-based interventions in patients receiving hemodialysis.

Table 1. Components of the Search Strategy Defined by the PICO Framework.

PICO	Definition	Description
P	Patient, population, or problem	Patients receiving maintenance hemodialysis. In addition, we examined other types of patients who suffer from muscle cramps (eg, pregnant women and older adults).
I	Intervention	Increasing the dialysate magnesium concentration in maintenance hemodialysis. In addition, we examined other forms of magnesium supplementation (eg, oral magnesium, intravenous magnesium and magnesium phosphate binders).
C	Control or comparison	Nontreated group or placebo-controlled population.
O	Outcome	Changes in frequency, severity, and duration of muscle cramps.

Causes and Epidemiology of Hypomagnesemia in Patients With Chronic Kidney Disease and Kidney Failure

Magnesium in the human body. Magnesium is the fourth most abundant cation in the human body and the second most abundant intracellular cation (after potassium).[32,33] The average adult human body contains about 22 to 26 g of magnesium; 99% of the body's magnesium is stored in the bone, muscles, and nonmuscular soft tissue, and <1% is in the extracellular fluid. In the extracellular fluid, 65% of magnesium is ionized, 20% is bound to plasma proteins (eg, albumin and globulin), and 15% is bound to molecules such as phosphate (PO_4).[3-33]

The average healthy adult ingests around 12 mmol/day of magnesium, mostly from leafy green vegetables, whole grains, and drinking water.[33] Approximately 30% to 50% of ingested magnesium is absorbed intestinally.[34] The kidneys play an integral role in maintaining magnesium balance within the body, filtering about 84 mmol/day, but reabsorbing most of it, leaving only 3 to 5 mmol/L to be excreted in the urine.[33,35]

Nonionized magnesium is biologically inactive. In contrast, ionized magnesium has many physiological functions, and its serum concentration typically ranges from 0.54 to 0.67 mmol/L.[33,36] It is a cofactor in enzymatic reactions involving energy metabolism, it regulates the passage of electrolytes and other substances through cell membranes, and is a chemical antagonist for calcium in physiological actions along cellular membranes and proteins.[37] The laboratory reference range for the normal concentration of serum magnesium, which includes both ionized and bound forms, is typically 0.65 to 1.05 mmol/L.[38] The majority of the literature studying magnesium and its physiological effects in a clinical context report serum magnesium levels, which are the simplest and most accessible to measure.[30]

Serum magnesium concentrations in patients with chronic kidney disease and kidney failure. In chronic kidney disease, renal function is compromised which can affect the regulation of magnesium. In the early stages of chronic kidney disease, the kidneys compensate by increasing the fractional excretion of magnesium allowing for maintenance of magnesium within the normal physiological range.[39] However, in the later stages of chronic kidney disease, the fractional excretion of magnesium declines, resulting in a net gain of magnesium.[40,41]

As patients progress to end-stage kidney disease and require maintenance hemodialysis, there is some evidence that the average concentration of serum magnesium declines.[42-46] The concentration of serum magnesium in patients receiving maintenance hemodialysis has been quantified in 2 large population-based studies conducted in the United States. In a cohort of 9359 patients, the mean concentration of serum magnesium in the first 90 days after starting hemodialysis was 0.86 mmol/L and the concentration was <0.74 mmol/L in 19% of patients.[27] In another cohort of 27 544 patients who had dialyzed with a dialysate magnesium concentration of approximately 0.50 mmol/L, after an average of 2.5 years on the protocol, the mean concentration of serum magnesium was 0.93 mmol/L, and the concentration was <0.80 mmol/L in 17% of patients.[26]

Defining hypomagnesemia. Hypomagnesemia is typically defined as a serum total concentration below 0.70 mmol/L, and this falls within the normal laboratory reference range of serum magnesium (0.65-1.05 mmol/L).[42,47] While serum magnesium is poorly correlated with total body magnesium,[33,40] multiple studies have shown that patients with lower concentrations of serum magnesium (even within the normal reference range) are at a higher risk of mortality and morbidity compared with patients with normal or high-normal concentrations of serum magnesium (both within and above the normal reference range).[26,27,48] In studies of patients with and without kidney disease, the lowest risk of diabetes and cardiovascular mortality is observed in those with serum magnesium concentrations between 0.78 and 1.11 mmol/L.[29,42,43,49] These data have led some to argue that the lower limit of normal serum magnesium should be increased to 0.8 mmol/L.[42]

Causes of hypomagnesemia in patients receiving hemodialysis. There are multiple potential causes of hypomagnesemia in patients receiving maintenance hemodialysis. Many patients have poor diets and are generally counseled not to take magnesium supplements due to concerns about magnesium

retention in the presence of kidney failure.[50] Hypoalbuminemia is also common in these patients. With 20% to 30% of extracellular magnesium bound to plasma albumin, an increase in ionized magnesium due to hypoalbuminemia contributes to an increase in ultrafiltrable magnesium, which is the only magnesium removed from the body during hemodialysis.[27,42,51] In addition, hypoalbuminemia reduces the Gibbs-Doman effect, where ionized magnesium more freely diffuses from the plasma to the dialysate during hemodialysis when there is less plasma protein.[42] These mechanisms, coupled with lower dialysate magnesium concentrations used by some dialysis centers, can contribute to increased dialytic clearance of ionized magnesium.[39,42]

Many patients also take medications that inhibit magnesium absorption and increase magnesium excretion including proton pump inhibitors and loop diuretics.[48,52-56] Notably, the U.S. Food and Drug Administration issued a safety alert in 2011 warning that long-term use of proton pump inhibitors may lead to hypomagnesemia and increase patients' risk for muscle spasms, arrhythmias, and seizures.[54-56]

A key factor affecting a patient's serum magnesium concentration is the concentration of magnesium in the dialysate. The lower the concentration of dialysate magnesium, the more magnesium is removed from the body during hemodialysis. Over the past 3 decades, there has been some debate on the ideal dialysate magnesium concentration.[57] In the 1970s and 1980s, dialysate magnesium concentrations were more commonly kept at 0.75 mmol/L.[42] As time went on, the concentration was lowered to 0.375 to 0.50 mmol/L, possibly due to beneficial effects seen with a lower dialysate magnesium concentration in relieving uremic pruritus and reducing the risk of osteomalacia.[50,57] However, recent studies show that a higher dialysate magnesium concentration is associated with improved survival and cardiovascular health.[42,57,58]

In Canada and the United States, the dialysate is generally prepared by central suppliers and contains magnesium concentrations of 0.38 mmol/L, 0.50 mmol/L, or 0.75 mmol/L.[18,42,59,60] Currently, most centers use concentrations ≤0.50 mmol/L; however, recent studies show that many patients who dialyze at concentrations ≤0.50 mmol/L will experience a decrease in their serum magnesium concentration over time.[25,57,61]

Effect of increasing the dialysate magnesium concentration on patients' serum magnesium concentrations. Increasing the concentration of dialysate magnesium by 0.25 mmol/L to 0.50 mmol/L generally causes an increase in patients' serum magnesium concentration in the subsequent weeks and months.[18,22,62-64] In a recent trial, 59 patients were randomly allocated to dialyze with a dialysate magnesium concentration of 0.5 vs 1.0 mmol/L for 4 weeks; in the group receiving 1.0 mmol/L, patients' mean serum magnesium levels rose from 0.99 to 1.40 mmol/L.[22] Similar trends have been reported in other prospective studies.[18,62-64]

Of note, in one 10-week study of 15 patients, the dialysate magnesium concentration was reduced from 0.75 mmol/L to 0.25 mmol/L, but patients were given an oral daily dose of 465 g magnesium carbonate. In this study, patients' mean serum magnesium concentration decreased by 0.10 mmol/L (from 1.28 to 1.19 mmol/L).[65] In another study, 16 patients dialyzed with a magnesium-free dialysate for 2.9 years due to concerns of uremic osteodystrophy. This caused a drop of 0.21 mmol/L (from 0.79 to 0.58 mmol/L).[64] However, the initial dialysate magnesium concentration was unclear in this study, making it difficult to quantify a relationship.

Why manipulate dialysate magnesium rather than prescribe oral magnesium supplements? Oral magnesium supplementation is another way to increase serum magnesium concentrations in patients on chronic hemodialysis.[37,66] However, this adds to the overwhelming pill burden that these patients already have; many take 10 or more medications at home each day.[67-69] With more pills comes the potential for medication errors and nonadherence to prescriptions.[69,70] Furthermore, in some countries such as the United States, the cost of supplements may not be covered by insurance.[70,71] Even in countries where medications are covered by a national health system or prescription plan, procuring magnesium tablets may add to the cost and workload of caring for patients on hemodialysis. As with other medications, there is also the potential for shortages and/or quality control issues. Patients placed on oral magnesium supplementation for prolonged periods can develop diarrhea and abdominal pain.[33,72] Finally, long-term use of oral magnesium supplements could lead to altered absorption of other medications and drug-drug interactions.[73,74] In contrast, magnesium is a component of the dialysate that is already incorporated into routine dialysate prescriptions. The prescribed magnesium can be delivered with each scheduled hemodialysis treatment with no additional cost to the patient, payer/insurer, or hemodialysis provider.

Physiologic Mechanisms Linking Magnesium and Muscle Cramps

Mechanisms linking magnesium and muscle cramps. The causes of muscle cramps in general remain poorly understood. In patients receiving hemodialysis, several factors may play a role including rapid fluid removal during hemodialysis, intradialytic hypotension, and deficiencies in carnitine and vitamin C.[13,75] It is also plausible these factors interact to cause cramping in patients. However, to date, prevention strategies targeting these factors have had limited effectiveness for mitigating cramps.[13,76] A low serum magnesium concentration is linked to more cramps in patients receiving hemodialysis as well as in athletes, older adults, and pregnant women.[5,18,77,78] At least 4 physiologic mechanisms may explain how hypomagnesemia contributes to the development of muscle cramps.

First, a magnesium deficiency reduces Na^+/K^+ ATPase activity in muscle cells which prevents the transport of Na^+ ions out of cells, as well as the transport of K^+ ions into cells. The higher ratio of Na^+ to K^+ ions within cells can slightly depolarize the cell membrane, lowering the threshold for nerve stimulation and neurotransmitter release. In this setting, muscle cells have a greater chance of being triggered by various stimuli, which leads to involuntary muscle contractions and cramping.[32,79]

Second, a magnesium deficiency reduces the activity of Ca^{2+} ATPase within muscle cells, which reduces the active transport of calcium ions from the cytosol back into the sarcoplasmic reticulum for storage following a muscle contraction. A magnesium deficiency can also impair the Na^+/Ca^{2+} exchange transporter along the plasma membrane, leading to a greater influx of calcium ions into the cytosol. The surplus of calcium ions within the muscle cell cytosol leads to an excess of ATP and oxygen consumption, which is linked to increased skeletal muscle excitability.[80-82]

Third, hypoparathyroidism can cause muscle cramps.[83,84] Hypomagnesemia may reduce parathyroid hormone secretion and lead to a reversible form of hypoparathyroidism.[85-88] Serum parathyroid hormone levels can quickly return to normal levels within a few days of raising serum magnesium, as well as the associated hypocalcemia that may also contribute to muscle cramps.[45,86] This mechanism is unlikely to be a major factor in patients on maintenance hemodialysis, as chronic kidney disease is known to cause secondary hyperparathyroidism due to low levels of circulating active Vitamin D.[89,90]

Fourth, magnesium may play an indirect role in causing muscle cramps through the regulation of the renal outer medullary K^+ (ROMK) channels located along the distal nephron. When hypomagnesemia occurs, it causes inhibition of these ROMK channels, which are magnesium dependent. This can lead to increased renal secretion of potassium, resulting in hypokalemia. Hypokalemia may affect appropriate depolarization of muscle cells, potentially playing a role in the development of muscle cramps.[34,91,92]

Assessment of Muscle Cramps in Published Studies

The assessment of muscle cramps in published studies is highly variable. Assessments ranged from simple patient self-reports of any cramping to a detailed 17-question survey on various facets of muscle cramping including the duration, frequency, and intensity.[93] Most studies created their own specific questions on muscle cramps, and these were delivered either through a structured patient interview or a patient-reported survey, diary, or log. An example of a nonvalidated but comprehensive cramp assessment in patients receiving hemodialysis is the 10-question assessment designed by Lynch et al (provided in Supplemental Appendix IV).[18] None of the identified studies used any validated measurement tools.

Association Between a Lower Concentration of Serum Magnesium and a Higher Risk of Muscle Cramps: Evidence From Observational Studies

Observational studies of patients receiving hemodialysis. Two cross-sectional studies of patients receiving hemodialysis examined the association between serum magnesium and muscle cramps. In 1 of these studies (n = 231), no association was observed, although only limited data were provided.[94] In the other study (n = 104), 63% of patients indicated they experienced cramps at least once per week, and those with a lower vs higher pre-dialysis serum magnesium concentration ($<$1.34 vs $\geq$1.34 mmol/L) had a higher mean cramp severity score (4.4 vs 2.6 out of 10, respectively; $P < .01$).[69]

Observational studies of women during pregnancy. In 3 observational studies of pregnant women, low serum magnesium concentrations were associated with greater muscle cramping.[95-98] In a prospective cohort study of 160 pregnant women, the proportion experiencing leg cramps during pregnancy was 69% in those with a serum magnesium concentration below 0.52 mmol/L and 25% in those with a concentration $\geq$0.52 mmol/L; $P < .001$.[95] Similar associations were seen in 2 other studies, even when serum magnesium concentrations were within the normal reference range (0.65-1.05 mmol/L).[96-98] For example, in a cross-sectional study of 400 pregnant women in their third trimester, women who experienced any cramps vs no cramps had a lower mean concentration of serum magnesium (0.78 vs 0.82 mmol/L, respectively; $P < .05$).[98] In contrast, 1 prospective cohort study reported no significant difference in the mean concentration of serum magnesium in women who experienced any cramps vs no cramps (serum magnesium concentration of 0.67 vs 0.70 mmol/L, respectively).[96]

Effect of Magnesium-Based Therapy on Muscle Cramps: Evidence From Interventional Studies

Interventional studies of patients receiving hemodialysis. We found 6 interventional studies that examined the effect of different dialysate magnesium concentrations or magnesium-based phosphate binders on patient outcomes.[4,5,18,64,65,99] Only 1 of these studies was specifically designed to assess effects on muscle cramps.[18] In this pre-post study of 62 patients receiving maintenance hemodialysis, patients were surveyed twice about muscle cramps during a 6-month period.[18] The first survey took place while patients were receiving a dialysate magnesium concentration of 0.38 mmol/L and the second survey after the dialysate magnesium concentration was increased to 0.5 mmol/L. The other dialysate constituents stayed the same and patients were not told of the change. Between the first and second surveys, there was a 21% reduction in the frequency of cramps, with the proportion of patients experiencing cramps decreasing from 77% to 56%; $P < .05$. Cramp severity (measured on a 10-point scale of increasing severity) also decreased from

5.3 (standard deviation [SD] 3.6) to 3.9 (SD 3.9); $P < .01$. At the time of the first survey, 23% of patients indicated they had stopped a hemodialysis session early due to cramps, but in the second survey no patients reported doing this.

In the other 5 studies, no details were provided on whether there was a standardized assessment of the frequency and/or severity of muscle cramps, and it is unclear if and how muscle cramps were measured beyond patient self-report. In a pre-post study of 16 patients who received hemodialysis with a magnesium-free dialysate for at least 2 years, patients were switched to a dialysate containing 0.25 mmol/L of magnesium starting in 1982.[64] During the magnesium-free period, serum magnesium concentrations declined in all patients and hypomagnesemia (defined in this study as a serum magnesium ≤0.58 mmol/L) was observed in 11 of 16 patients. The number of cramps was reported as the average number of episodes during 6 consecutive dialysis sessions at both dialysate magnesium concentrations of 0.00 mmol/L and 0.25 mmol/L in 1980 and 1982, respectively. With a concentration of 0.00 mmol/L, muscle cramps were reported by 12 of 16 patients. Of the 11 patients with hypomagnesemia, 9 reported at least 1 muscle cramp (range 1-8 cramps) during 6 consecutive hemodialysis sessions. In contrast, 3 of 5 patients with normal serum magnesium concentrations (≥0.87 mmol/L) reported at least 1 muscle cramp (range 1-2 cramps). In 1982, when the dialysate magnesium concentration was increased to 0.25 mmol/L and muscle cramps were assessed, 3 of 11 patients with hypomagnesemia complained of muscle cramps (range 1-4 cramps), while 0 of 5 patients with normal concentrations of serum magnesium complained of any muscle cramps; $P < .05$.

In a case-report, a 38-year-old male patient dialyzing with a dialysate magnesium concentration of 0.3 mmol/L was experiencing severe muscle cramping in his legs and arms.[5] The patient's pre-dialysis serum magnesium concentration was 1.0 mmol/L; however, his post-dialysis serum magnesium concentration was 0.5 mmol/L. Cramping relief was first achieved after intravenous administration of 10% magnesium sulfate. The concentration of dialysate magnesium was subsequently increased to 0.7 mmol/L, and no further cramping was reported by the patient.

Two pre-post studies examined the clinical effects and tolerability of dialyzing at different dialysate magnesium concentrations (including a magnesium-free dialysate) in patients who were concurrently taking magnesium carbonate phosphate binders.[4,65] In the first study,[4] 15 patients who had been receiving maintenance hemodialysis with a dialysate magnesium concentration of 0.7 mmol/L (1.8 mg/dL) were switched to a magnesium-free dialysate for 2 weeks. After this change, 8 of 15 patients complained of widespread cramping in both the upper and lower extremities within the first hour of hemodialysis treatment. Two patients were unable to complete the 2-week protocol due to the severity of their muscle cramps. In all cases, the cramping stopped within 15 to 30 minutes of dialysis after changing back to a dialysate magnesium concentration of 0.7 mmol/L (1.8 mg/L). In the following 2-week period, 13 of 15 patients received hemodialysis with a dialysate magnesium concentration of 0.2 mmol/L (0.6 mg/dL). The authors indicated that no cramping or other adverse reactions were reported by any patients during this second 2-week period. In the second study,[65] 15 patients had their dialysate magnesium concentration reduced from 0.75 mmol/L to 0.25 mmol/L for several weeks while taking a magnesium carbonate phosphate binder; no muscle cramps were reported by patients after the change.

In a randomized controlled trial of 255 patients dialyzing with a dialysate magnesium concentration of 0.5 mmol/L, patients were randomly allocated to receive an oral magnesium phosphate binder (235 mg/day magnesium carbonate combined with 435 mg/day calcium acetate) or sevelamer hydrochloride (800 mg/day) for 24 weeks.[99] At the end of the trial period, mean serum magnesium concentrations were 1.3 mmol/L and 1.0 mmol/L in these groups, respectively. The authors indicated that no adverse effects differed between groups, including muscle spasms or cramps.

Interventional studies of women during pregnancy. We found 4 interventional studies that tested the effect of oral magnesium supplements on leg cramps during pregnancy.[100-103] While 3 studies reported that oral magnesium therapy significantly reduced leg cramps,[100-102] the methodological quality of 2 of these studies was poor (key details were missing [see Supplemental Appendix IIIb]) and these 2 studies are not discussed here.[100,101] Only 1 of the 4 studies provided adequate detail on the randomization procedure, concealment, and blinding—in this double-blind trial, 86 pregnant women with leg cramps (≥ twice per week) were allocated to receive magnesium bisglycinate chelate (300 mg/day) or placebo for 4 weeks.[102] The primary outcome, a 50% reduction in the self-reported number of leg cramps during week 4, occurred in 37 of 43 (86%) women allocated to receive magnesium and in 26 of 43 (61%) women allocated to receive placebo; $P < .01$.

In contrast, no effect of magnesium therapy on cramping was observed in the study by Nygaard et al.[103] In this double-blind randomized controlled trial, 45 pregnant women who had leg cramps at least twice per week were allocated to receive magnesium citrate/lactate (360 mg/day) or placebo for 2 weeks. Only 38 of 45 patients who completed the study were analyzed, and more withdrawals occurred in the placebo group. The mean number of days and nights with leg cramps during the 2-week intervention period was 9.5 (SD 5.1) in the group allocated to magnesium and 7.7 (4.7) in the group allocated to placebo. No change in serum magnesium was observed between baseline and follow-up and it is possible that 2 weeks was not sufficiently long enough to observe an effect.

Interventional studies of older adults. We found 4 randomized controlled trials examining the effect of magnesium-based therapy vs placebo on muscle cramping in older adults

(all trials excluded patients with advanced chronic kidney disease—see Supplemental Appendix IIIc).[93,104-106] Three of the trials specifically examined the effect of magnesium therapy on nocturnal cramping (or cramping while at rest). No trial reported a significant effect of magnesium-based therapy on cramp frequency or pain intensity.

Trial sample sizes ranged from 42 to 94 participants and the mean age ranged from 62 to 69 years. Oral magnesium supplements were used in 3 trials (1 with magnesium oxide [865 mg/day][93] and 2 with magnesium citrate [1800 mg/day[106] and 300 mg/day[104]]), and 1 trial administered intravenous magnesium sulfate (5000 mg/day for 5 consecutive days).[105] Two of the studies were cross-over trials, where participants underwent 4 weeks of oral magnesium or placebo supplementation separated by a washout period.[104,106] All trials measured participant outcomes after 4 weeks of follow-up. Methodological limitations of these studies include small sample sizes, attrition bias, and short-term follow-up (quality assessment provided in Supplemental Appendix II).

Two systematic reviews and meta-analyses (a patient-level[107] and simulated meta-analyses)[78] analyzed several of the studies discussed above.[78,107] The results of the patient-level meta-analysis (excluding pregnant women) reported that the percentage change in number of cramps per week at 4 weeks (magnesium vs placebo) was −3.9% (95% confidence interval: −21.1% to 13.3%). The authors of both reviews concluded that magnesium-based therapy is unlikely to provide a clinically meaningful protective effect against muscle cramps in older adults. One review suggested that the results of the trials of pregnancy-associated muscle cramping were inconclusive,[107] while the other concluded that magnesium supplementation may have a small protective effect against cramping during pregnancy; however, the clinical significance is uncertain.[78]

Safety of Magnesium-Based Interventions in Patients Receiving Hemodialysis

Although magnesium-based dialysate therapy is considered low risk, the development of hypermagnesemia is a concern for patients with kidney failure.[40] Symptoms of hypermagnesemia include lethargy, flaccid paralysis, and confusion; however, these symptoms do not generally begin until the serum magnesium concentration exceeds 2.0 mmol/L.[22,108] In rare cases, hypermagnesemia has been associated with heart block, cardiac arrest, and respiratory difficulties.[109] Serum magnesium levels above the laboratory reference range (0.65-1.05 mmol/L) were reported in 2 of 6 studies of magnesium-based therapy in patients receiving hemodialysis.[18,99] In the study by Lynch et al,[18] where the dialysate magnesium concentration was increased from 0.38 mmol/L to 0.50 mmol/L for 3 months, 2 of 62 participants developed a serum magnesium >1.05 mmol/L. In the study by De Francisco et al,[99] patients in 1 group received 435 mg of calcium acetate with 60 mg of elemental magnesium (CaMg) and patients in the second group received 800 mg of sevelamer-HCl as daily phosphate binders; both groups dialyzed with a dialysate magnesium concentration of 0.50 mmol/L. In these groups, the mean number of patient visits with a serum magnesium concentration above 1.05 mmol/L was 8 and 4, respectively. In both studies, all episodes of hypermagnesemia appeared to be asymptomatic.

Adverse events related to magnesium-based therapy appear to be rare. In the study of 255 patients receiving hemodialysis by De Francisco et al, 4 patients in the CaMg group and 9 patients in the sevelamer-HCL group dropped out due to adverse events. Gastrointestinal adverse events were more commonly reported in the sevelamer-HCL group than the CaMg group (23.6% vs 13.6%, respectively).[99] In the other study using an oral magnesium phosphate binder, no gastrointestinal or other adverse side effects were noted.[65] The 5 other studies that modulated the dialysate magnesium concentration at some point during their protocol reported no other notable side effects.[4,5,18,64]

Conclusion

We conducted this narrative literature review to better understand the physiology, epidemiology, and measurement of hypomagnesemia and muscle cramping in patients receiving hemodialysis, and to assess evidence from interventional studies on the effect of magnesium-based therapy on muscle cramping.

In summary, the physiology of muscle cramping remains poorly understood, and there are no proven prevention or treatment strategies. Hypomagnesemia appears to be a potential risk factor for cramping, although several other factors may play a role and/or interact. Causes of hypomagnesemia in patients receiving hemodialysis include poor diet, use of medications that inhibit magnesium absorption (eg, proton pump inhibitors) or increase magnesium excretion (eg, high-dose loop diuretics), and a low dialysate magnesium concentration. Many patients who dialyze at concentrations ≤ 0.5 mmol/L will experience a decrease in their serum magnesium concentration over time. Evidence from observational and interventional studies suggests that increasing the concentration of dialysate magnesium can raise patients' serum magnesium concentrations and this may reduce the frequency and severity of muscle cramping; however, the methodological quality of studies conducted to date is poor and the assessment of cramping is highly variable. Few interventional studies have been conducted and most used a nonrandomized, pre-post study design. In patients without kidney disease, there is inconsistent limited evidence that magnesium-based therapy provides a clinically meaningful protective effect against muscle cramps.

Increasing the concentration of dialysate magnesium appears to be well-tolerated and is associated with a low risk of symptomatic hypermagnesemia. While it is also

possible to raise the concentration of patients' serum magnesium through oral supplementation, using hemodialysis to do this is simpler for the patient and safer; it adds no additional cost for patients, does not add to a patient's pill burden, is not dependent on patient adherence to taking pills, and avoids adverse side effects that may be associated with oral magnesium supplementation such as gastrointestinal upset. Large multicenter randomized controlled trials will improve our understanding as to whether a higher vs lower concentration of dialysate magnesium reduces muscle cramps in patients receiving hemodialysis. Future trials should attempt to develop a robust instrument to measure the various facets of muscle cramps, examining factors such as cramp frequency, severity, duration, timing, and location.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Consent for publication was agreed to by all of the involved authors.

Availability of Data and Materials

Not applicable.

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Supplemental Material

Supplemental material for this article is available online.

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