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Efficacy and tolerability of magnesium plus protein for managing hypomagnesemia in pediatric kidney transplant patients

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Abstract

We sought to investigate whether magnesium oxide bound to soy protein (MGP) increases serum magnesium concentrations with less diarrhea compared to commonly prescribed magnesium salts. Subjects were switched to MGP at a near-equivalent daily elemental magnesium dose. Mean serum magnesium levels were compared. If magnesium levels remained <1.7 mg/dL after switching to MGP, subjects were enrolled into Part 2 and received a one-time MGP dose adjustment. The MGP daily dose was increased by 266 mg. For both parts 1 and 2, subjects recorded the number and quality of their stools to assess gastrointestinal (GI) tolerability of MGP. Twelve pediatric kidney transplant recipients completed Part 1. Mean serum magnesium levels increased from 1.61 (SD 0.1) on standard MG to 1.69 (SD 0.1); $t(11) = 2.6$, $P = .02$ on MGP. Five subjects completed Part 2, and all achieved serum magnesium ≥1.7 mg/dL (mean 1.75 mg/dL, SD 0.06; $t(4) = 2.7$, $P = .06$). Subjects reported the same number of, but looser bowel movements with MGP; however, individuals did not perceive intolerable GI symptoms with MGP therapy and all chose to remain on MGP at the end of the study. At an equivalent mg/kg/d dose of elemental magnesium, serum magnesium levels on MGP were significantly higher.

KEYWORDS
calcineurin inhibitors, magnesium, magnesium deficiency

1 | INTRODUCTION

Magnesium is important for the function of many enzymes, especially those with kinase activity.[1-3] Hypomagnesemia leads to increased risk of treatment-resistant hypokalemia and hypocalcemia, cardiac arrhythmias, neuromuscular irritability, and neuropsychiatric symptoms including seizures.[4] Hypomagnesemia post-renal transplant is a well-known problem due to renal magnesium losses with the use of calcineurin inhibitors.[1-4]

Hypomagnesemia is also an independent risk factor for development of NODAT. Cases have been documented in kidney and liver transplant patients.[1,2] A retrospective analysis performed by Hayes and colleagues found low serum magnesium to be an independent risk factor for new-onset diabetes among pediatric renal transplant recipients. An additional finding of this study showed that high tacrolimus trough concentrations conferred additional risk for development of new-onset diabetes.[5] Most concerning are reports of decreased allograft survival in renal transplant patients who have hypomagnesemia.[6,7] Data related to cyclosporine-induced hypomagnesemia suggest that magnesium plays a vital role in attenuation of interstitial fibrosis in cyclosporine-induced nephrotoxicity. Magnesium's proposed antifibrotic effects include decreased

Abbreviations: BSS, Bristol stool scale; CSS, cumulative stool scores; CV, coefficient of variation; EBV, Epstein-Barr virus; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; MGP, magnesium plus protein; NODAT, new-onset diabetes after transplantation; SSS, Stool scoring system.

expression of chemo-attractants and inhibition of macrophage and monocyte recruitment.[7,8] Therefore, appropriate treatment of hypomagnesemia is critical for the health of transplant patients.

Magnesium is a divalent cation that can be combined with different inorganic or organic salts to enhance bioavailability. Correcting hypomagnesemia with oral magnesium supplementation can be challenging due to poor GI absorption. Osmotic diarrhea can occur when a large fraction of unabsorbed magnesium remains in the GI tract.[9] This makes it difficult to titrate oral magnesium therapy to target normal serum magnesium concentrations (1.7-2.2 mg/dL). A supplement with better absorption and less GI side effects is ideal for managing hypomagnesemia. A reduction in the frequency and severity of diarrhea as well as an increased ability to reach and maintain more appropriate magnesium serum levels could significantly improve the health of pediatric renal transplant patients.

MG Plus Protein™ (MGP; Miller Pharmacal Group Inc, Carol Stream, IL, USA) is a supplement in which magnesium oxide, an inorganic magnesium salt, is bound to soy protein.[10] MGP, like all dietary supplements, is not regulated in the same capacity as prescription or over-the-counter medications. It is regulated by the FDA as a dietary supplement and must adhere to Good Manufacturing Practices. Anecdotal reports from healthcare providers report patients are able to attain target serum magnesium concentrations with less diarrhea with MGP when compared to commonly prescribed magnesium salts. These claims have not been formally tested.

In this study of pediatric kidney transplant patients at our institution who had low serum magnesium levels (<1.7 mg/dL) on standard magnesium supplements (magnesium chloride, magnesium gluconate, or magnesium oxide), we sought to determine:

1. If an equivalent dose of MGP would increase serum magnesium levels.
2. How well MGP is tolerated compared to standard MG therapy.
3. If, after switching to an equivalent dose of MGP, serum Mg levels were still below 1.7 mg/dL, could that goal be achieved by increasing the dose of MGP by 266 mg of elemental magnesium per day (one 133 mg tablet 2 times per day) without intolerable side effects?

2 | METHODS

This was an Institutional Review Board approved study performed in accordance with the ethical principles of the Declaration of Helsinki of 1975. Eligibility criteria for inclusion were as follows: (i) renal transplant recipient; (ii) average serum magnesium <1.7 mg/dL; (iii) receiving magnesium supplementation; (iv) have stable renal function; and (v) age 5-18 years old; (vi) demonstrate acceptable adherence with immunosuppressive medications. Adherence was determined by self-reporting by patient or caregiver and stable serum tacrolimus concentrations at each clinic visit. We assumed that if patients were adherent to their tacrolimus regimen, then they would be more likely to be adherent with the study medication. Subjects who had an average serum magnesium concentration <1.7 mg/dL at the conclusion of Part 1 of the study were eligible for Part 2 of the study. Exclusion criteria were as follows: (i) average serum magnesium concentration of at least 1.7 mg/dL; (ii) allergy to soy protein; (iii) significant change in renal function due to rejection, pyelonephritis or other cause; (iv) non-adherence with taking the study medication; (v) acute diarrhea within 2 months of study enrollment. Non-adherence was defined as missing more than 2 doses of the study medication within the 7 days before each laboratory assessment on more than one occasion. At our center, all patients who present with acute diarrhea undergo full evaluation for infectious causes. We reviewed each patient's medical records prior to recruitment to ensure that subjects did not have a recent diagnosis of diarrhea. Study enrollment occurred from October 9, 2013, through September 11, 2016. Demographic data, renal function, renal transplant duration, magnesium supplement regimen, other medications that could have affected serum magnesium concentrations (eg, immunosuppressive therapy, proton pump inhibitors, diuretics), and subject/caregiver reported Bristol stool scores were recorded.

The aim of Part 1 of the study was to compare the efficacy of MGP with standard magnesium (standard MG) supplementation. Standard MG was defined as supplementation with any of the following magnesium salts: magnesium chloride, magnesium gluconate, or magnesium oxide. As part of routine clinical practice, all patients with hypomagnesemia are provided a list of high magnesium foods and are encouraged to eat a magnesium-rich diet. Once enrolled in the study, participants were asked to avoid making major changes in their diet.

Serum magnesium concentrations were obtained during routine clinical care. The frequency of laboratory evaluation was determined solely by how long ago the subject had received their kidney transplant or other clinical indications as directed by our Institutional Review Board. Baseline serum magnesium was determined by taking the average of the three most recent serum magnesium values while on standard MG therapy. Serum magnesium concentrations were evaluated at each clinic visit as part of routine care. Following study enrollment, subjects were converted from standard MG therapy to the equivalent elemental magnesium dose with MGP. Each magnesium chloride tablet prescribed to our patients contained 64 mg of elemental magnesium. Each 500 mg of magnesium gluconate contained approximately 27 mg of elemental magnesium. Each 400 mg of magnesium oxide contained approximately 240 mg elemental magnesium.[11] Each MGP tablet contained 133 mg elemental magnesium.[10] After switching to MGP therapy, the next three serum magnesium concentrations were obtained at regularly scheduled clinic visits. These values were averaged to calculate a mean serum magnesium level while on MGP therapy.

Subjects who remained subtherapeutic (mean serum magnesium value <1.7 mg/dL) by the third serum magnesium level following the conversion from standard MG supplement to the nearest equivalent elemental magnesium dose with MGP were eligible for Part 2 of the study. In a continued effort to correct hypomagnesemia, subjects

enrolled in Part 2 of the study received an increased MGP dose to target serum magnesium concentrations (1.7-2.2 mg/dL) or until the subject developed intolerable GI side effects (per subject or parent's report based on their perception or if they developed diarrhea leading to dehydration). No established standards for adequate dosing of magnesium supplement exist. Patients were prescribed a onetime MGP dose adjustment. MGP doses were increased by one 133 mg tablet twice per day for a total daily elemental magnesium dose increase of 266 mg. The subsequent three serum magnesium concentrations were obtained and documented. Additional analyses of average serum magnesium values during this part of the study were performed in the same manner as described previously.

To assess GI tolerability of MGP, subjects and their caregivers were provided a color printout of the BSS.[12] At study enrollment, subjects and their caregivers were provided written and verbal education regarding reporting of stool frequency and texture using the BSS. The quantity and BSS score of each stool were recorded by the family for 1 week before conversion from standard MG to MGP therapy. At the end of Part 1 of the study, participants were asked to report stool quantity and BSS score for 1 week before the third serum magnesium level while on MGP therapy. Subjects who continued to Part 2 of the study were also asked to report stool quantity and BSS score for 1 week before the third serum magnesium level after their total daily MGP dose was increased by 266 mg. CSS[13] were calculated to assess frequency and form. CSS were calculated using Wijeratne and Leung's novel SSS, which utilizes a 7-point scale (−3 to +3) where −3 corresponds to BSS Type 7 stools, +3 corresponds to BSS type 1, and 0 as BSS type 4.[13] The CSS is the 7-day total after multiplying stool frequency by SSS-scaled form and summating. By centering normal bowel movements on 0, negative CSS values indicate overall diarrheal form and positive CSS values indicate overall more firm, hard stools.

2.1 | Statistical analysis

In our institution, normal serum magnesium is defined as ≥1.7 mg/dL. A retrospective medical chart review of magnesium levels among 29 pediatric kidney transplant patients at our institution showed a mean serum magnesium concentration of 1.65 mg/dL with a standard deviation of 0.18. Based on these values, a power analysis indicated 6 subjects were needed to achieve 80% power in detecting a 20% difference in mean magnesium level using a paired *t* test with a two-tailed alpha of 0.05. These calculations are based on an estimation of expected effect size, as well as a relatively small standard deviation. For these reasons and to help ensure validity, we attempted to recruit all stable pediatric kidney transplant patients on tacrolimus or cyclosporine who were also receiving magnesium supplementation.

Descriptive statistics were used to summarize subject and dose characteristics. Efficacy of MGP therapy over standard MG therapy was evaluated by comparing three-laboratory average serum magnesium levels using a paired *t* test. Additional analyses were performed in the same manner comparing average serum magnesium levels of participants requiring additional MGP dose increases for Part 2 of the study.

Tacrolimus is known to cause magnesium wasting. To determine in our study population whether serum tacrolimus levels correlated with serum magnesium levels, a mixed model with repeated laboratory visits modeled as random effects was used. The CV as a measure for tacrolimus levels[14] during standard MG and MGP therapy was calculated for each subject. The change in CV was compared using a paired *t* test. A mixed model was used to generate an overall correlation coefficient between log-tacrolimus and serum magnesium after controlling for within-subject correlation between laboratories.

The study also aimed to compare GI tolerance between therapies by having the participant describe the texture and quantity of stools and calculating the CSS after change to MGP in Part 1 and after increasing the MGP dose for Part 2. Analyses were completed using either parametric or nonparametric two-sample comparisons, as dictated by the type and frequency of collected data. All analyses included tests ensuring that assumptions were met. Statistical analyses were performed using SAS v9.4 (SAS Institute, Cary, NC, USA) at an a priori alpha level of 0.05.

3 | RESULTS

During the time of this study, our program followed 80 kidney transplant patients. Forty-seven were diagnosed with hypomagnesemia defined as having serum magnesium levels <1.7 mg/dL or serum magnesium levels >1.7 mg/dL while on magnesium supplementation (Figure 1). The majority of patients had serum magnesium levels <1.7 despite diligent attention to encouraging patients to eat a magnesium-rich diet and treating all patients with standard MG supplements. Of these potential subjects for this study, 27 were excluded, most of which were ineligible due to age <5 or >18 years. Twenty subjects were enrolled but 8 had to be excluded due to loss to follow-up (n = 3), non-adherence to all drug regimens including study drug (n = 3) or unstable renal function (n = 2).

Twelve pediatric kidney transplant patients completed Part 1 of the study; however, one subject developed *Clostridium difficile* diarrhea before their third serum magnesium level while on MGP. For this individual, only the first two serum magnesium values while on MGP were included in analyses. At the completion of Part 1 of the Study, 6 of 12 subjects did not reach the goal serum magnesium level of ≥1.7 mg/dL; however, only 5 subjects completed Part 2 of the study where the dose of MGP was increased by 266 mg/d of elemental magnesium to determine if that would increase their serum magnesium levels to the goal of ≥1.7 mg/dL.

Table 1 lists baseline information along with the distribution of standard MG salt forms and other prescribed medications that could affect serum magnesium concentrations. Mean eGFR at baseline and at the conclusion of Part 1 of the study were 75 (SD: 30) mL/min/1.73 m^2 and 73 (SD: 29) mL/min/1.73 m^2, respectively, indicating that renal function was relatively good (mild stage 2 chronic kidney disease) and did not change appreciably during the course of the

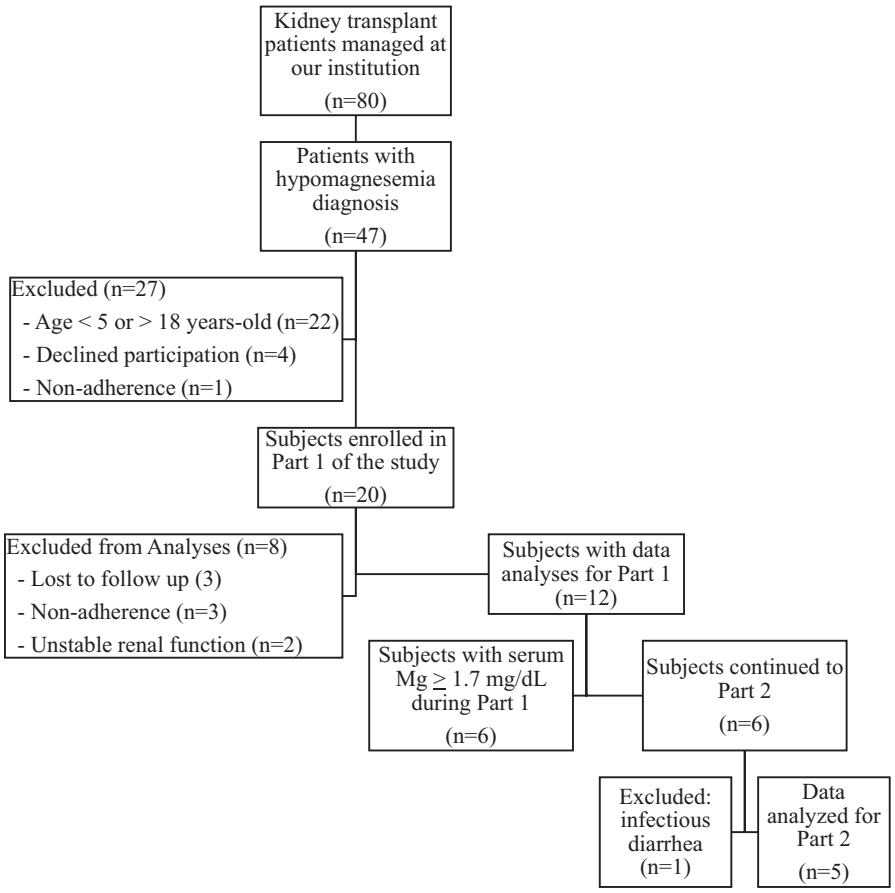


FIGURE 1 Consort diagram of enrollment

study in subjects who completed the study. Table 2 lists the amount time that had elapsed between the start of each magnesium therapy and serum magnesium values.

Tacrolimus is known to cause magnesium wasting. Tacrolimus levels were log-transformed to normalize the distribution. The estimated correlation coefficient between log-tacrolimus and serum magnesium was −0.28, indicating that higher tacrolimus levels were weakly correlated with lower serum magnesium levels. All subjects who received medications other than a calcineurin inhibitor that could affect serum magnesium levels remained on the same doses of these medications throughout the duration of the study, with the exception of 4 subjects who were prescribed mycophenolate. Three of these subjects were prescribed higher doses of mycophenolate (due to weight gain and resolution of subclinical EBV infection) while on MGP compared to baseline while one subject had their mycophenolate dose decreased while on MGP therapy (due to neutropenia and subclinical EBV infection).

The CV as a measure for tacrolimus levels was calculated.[14] Tacrolimus levels were available for 11 out of 12 subjects as one subject was on cyclosporine. During Part 1 of the study, 7 subjects had 6 separate tacrolimus measurements, and 4 of the subjects had 5 levels measured. For standard MG therapy, the mean tacrolimus CV was 30 (SD 16) with a range of 11-58. For MGP therapy, the mean tacrolimus CV was 24 (SD 16) with a range of 4-55. Using a paired-samples *t* test, the intrasubject CV of tacrolimus level did not change significantly during the time the subject was taking standard MG therapy compared to the time taking MGP therapy, $t(10) = 0.8$, $P = .4$.

During standard MG therapy, the mean elemental magnesium dose was 6.22 (SD 3.9) mg/kg/d. Subjects were switched to MGP at a dose as close as practical to the same daily elemental magnesium dosing regimen, but since the pill sizes are different, the dose was not exactly the same. The mean elemental magnesium dose following the switch to MGP was 6.28 (SD 3.8) mg/kg/d. The mean change from standard MG to MGP therapy was 0.06 (95% CI: −0.14 to 0.25) mg/kg/d, which was not significantly different using a paired-samples *t* test, $t(11) = -0.7$, $P = .5$.

Table 3 lists the mean serum magnesium levels for each laboratory measurement in Part 1 of the study with standard MG and MGP therapy. A paired-samples *t* test was conducted to compare average serum magnesium levels on standard MG and the near-equivalent dose of MGP. There was a statistically significant increase in mean serum magnesium levels with MGP compared to standard MG therapy, increasing from a mean value of 1.61 mg/dL (SD 0.1) on standard MG to 1.69 mg/dL (SD 0.1) with MGP therapy; $t(11) = 2.7$, $P = .02$. All but 2 study participants had higher average serum magnesium concentrations while on MGP compared to standard MG supplement. Figure 2 shows serum magnesium values at baseline and following the switch to MGP for all 12 subjects who completed Part 1 of the study.

3.1 | Stool frequency and quality analysis during Part 1 of the study

Participants documented stool frequency and form according to the BSS during the final 7 days of standard MG and MGP therapy. Ten out of 12 provided complete records during Part 1 of the study. Two participants were not analyzed in this aim due to incomplete records: One subject provided data only during standard MG therapy while the other subject did not provide any stool records. Another subject's stool data were excluded due to developing infectious diarrhea during the week of recording stool frequency and form for MGP therapy. For the remaining 9 participants, the median bowel movement per week for standard MG and MGP therapies was 12 (IQR 7-16) and 8 (IQR 7-14), respectively. This difference was not statistically different, Wilcoxon signed-rank S=−4.5, P=.4.

Collectively, 33% of stools on standard MG therapy were categorized as normal (BSS type 4) with 30% as firm (BSS types 1-3) and 37% as loose (BSS types 5-7). On MGP therapy, 52% were normal with 12% as firm and 36% loose (Table 4). BSS types were not equally distributed between MG and MGP therapies, exact Pearson chi-square test, $P < .001$. To test a participant's average form and frequency of bowel movements and the potential change between therapies, CSS[13] were calculated as described in the Methods section. The mean CSS for standard MG therapy was −4.8 (SD 27), while the mean CSS for MGP therapy was −6.4 (SD 18). The change between therapies was −1.67, indicating overall looser bowel movements on MGP therapy, although this difference was not statistically significant, $t(8)$=0.2, P=.9.

TABLE 1 Baseline data for study subjects

Characteristic	Median (IQR)
Age at study enrollment, y	13.5 (9.8-16)
	No. (%)
Female	2 (16.7)
Male	10 (83.3)
Deceased donor kidney transplant	9 (75)
Living donor kidney transplant	3 (25)
Time from kidney transplant to study enrollment, median (IQR), y	2.7 (0.9-4.8)
Type of standard MG supplement	
Magnesium chloride	9 (75)
Magnesium gluconate	1 (8.3)
Magnesium oxide	2 (16.7)
Other medications that may affect serum magnesium	
Calcineurin inhibitors	
Cyclosporine	1 (8.3)
Tacrolimus	11 (91.7)
Antiproliferative agent	
Azathioprine	1 (8.3)
Mycophenolate mofetil	4 (33.3)
Mycophenolate sodium	7 (58.3)
Others	
Hydrochlorothiazide	1 (8.3)
Omeprazole	3 (25)
Polyethylene glycol	3 (25)

3.2 | Part 2. Change in serum magnesium levels with an increased dose of MGP

After Part 1 of the study, 5 eligible subjects had not achieved the target serum magnesium level of ≥1.7 mg/dL. All 5 subjects had their MGP dose increased by 266 mg per day (given as an additional 133 mg tablet twice daily) as Part 2 of the study. All subjects achieved average serum magnesium concentrations within target range with this MGP dose increase. Subjects were on an average elemental magnesium dose of 12.8 mg/kg/d at the end of Part 2 of the study. The mean serum magnesium level for these 5 subjects while on standard MG was 1.59 mg/dL (SD 0.13). Following the switch to MGP during Part 1 of the study, the mean serum magnesium level was 1.6 mg/dL (SD 0.04) and rose to 1.75 mg/dL (SD 0.06) during Part 2 when the dose of MGP was increased.

Only 3 subjects reported stool data for Part 2 of the study. Because of the small sample, statistical analyses of stool data were not possible. The overall trend of CSS scores with the increased MGP dose did not suggest worsening of GI symptoms and, surprisingly, bowel movements of all 3 subjects seemed to have moved toward becoming more firm and less frequent after the MGP dose was increased (Figure 3). None of these subjects reported any side effects with the increased dose of MGP. Furthermore, all of the subjects enrolled in this study (both parts 1 and 2) chose to continue MGP at the end of the study rather than reverting to standard MG therapy.

TABLE 2 Time elapsed betweesn magnesium therapy and serum magnesium values

	Standard MG therapy	MGP therapy
	Time elapsed, median (IQR) days	Time elapsed, median (IQR) days
Duration of magnesium therapy before the first serum magnesium value (Laboratory 1)	417 (168-831)	26 (14-35)
Duration between laboratory 1 and laboratory 2	28 (24-46)	41 (35-43)
Duration between laboratory 2 and laboratory 3	31 (19-80)	31 (20-38)

TABLE 3 Change in mean serum magnesium concentration from standard MG to MGP

	Standard MG			MGP		
Measurement	1st	2nd	3rd	1st	2nd	3rd
n	12	12	12	12	12	11
Serum magnesium level at each clinic visit (SD)	1.58 (0.15)	1.68 (0.19)	1.58 (0.12)	1.67 (0.14)	1.71 (0.13)	1.68 (0.18)
Mean serum magnesium level (SD)	1.61 (0.1)			1.69 (0.1)		

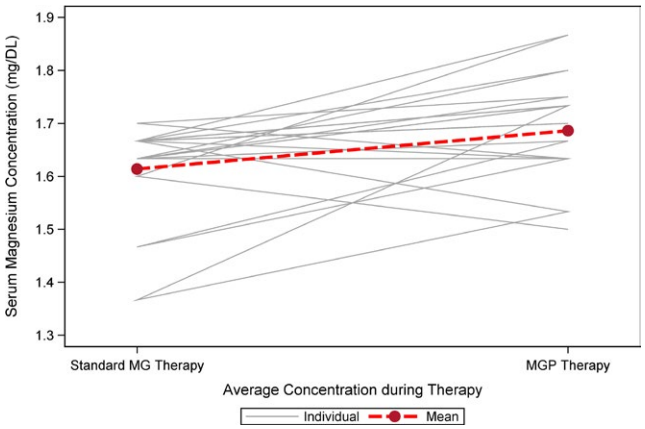


FIGURE 2 Paired profiles for average serum magnesium values with standard MG compared to MGP during Part 1. Solid gray lines represent individual subjects' trend in mean serum magnesium levels while on standard MG and after conversion to MGP therapy. The red dash line represents the group's average change in mean serum magnesium levels while on standard magnesium supplement and after conversion to MGP therapy

Overall, while the study sample size was small, Part 2 of this study demonstrates that it is possible to reach target magnesium levels by increasing the MGP dose without intolerable GI side effects.

4 | DISCUSSION

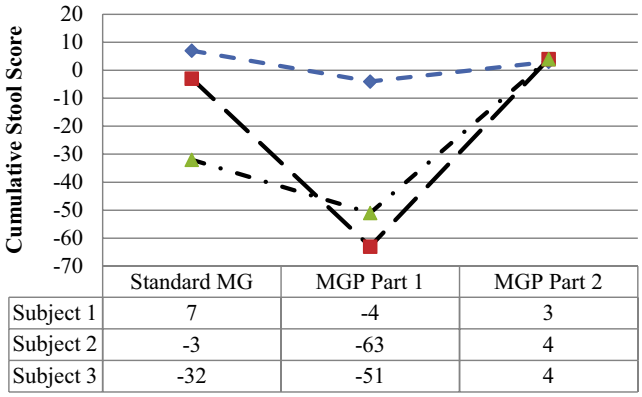
Hypomagnesemia is a common finding following renal transplantation. One pediatric study identified hypomagnesemia in 41% of renal transplant recipients.[15] The condition is most prevalent during the first few months following allograft transplantation; however, it has been reported that a fair percentage of patients develop hypomagnesemia refractory to oral magnesium supplementation; adult data suggest that more than 20% of patients have persistent hypomagnesemia many years post-transplant.[7] The use of calcineurin inhibitors is a well-known cause of hypomagnesemia.[16,17] This is due to renal magnesium wasting.[7,16,17] Magnesium wasting is likely due to downregulation of magnesium transport proteins in the distal collecting tubule by calcineurin inhibitors.[16] Tacrolimus therapy has a higher prevalence of hypomagnesemia compared to cyclosporine therapy.[7,15] In our population, we found that out of 80 pediatric renal transplant patients, 47 (59%) either had serum magnesium levels <1.7 or were on magnesium supplementation with serum levels ≥1.7 mg/dL. Therefore, assessment of efficacy and tolerability of various magnesium preparations to optimize the chance of normalizing serum magnesium levels is of the utmost importance in solid organ transplantation.

MG Plus Protein™ (MGP) is magnesium oxide bound to soy protein. Anecdotal reports claim that this formulation provides better magnesium absorption with fewer side effects than other magnesium preparations. However, this claim has not been formally tested. Data from the present study showed statistically significant increases in serum magnesium concentrations when subjects were placed on a near-equivalent mg/kg/d of elemental magnesium with MGP. The serum magnesium levels of almost all subjects increased after switching from standard MG therapy to MGP. The mean change in serum magnesium from 1.61 mg/dL for standard MG therapy to 1.69 mg/dL during MGP therapy represents a 5% increase. Our prestudy power analysis was based on an increase of 20%, which would have brought the mean serum magnesium level to the middle of the target range. Our estimated sample size to detect a 20% change was 6, which we doubled to ensure sufficient power if the effect was not as large. The 5 subjects who did not reach a serum magnesium level of ≥1.7 mg/dL during Part 1 of the study were able to achieve that level with a single increase in MGP daily dose that was well tolerated.

Hypomagnesemia has been reported as a risk factor for the development of NODAT and tubulointerstitial fibrosis; however, a causal relationship and etiology of this association are not known. Van Laecke et al[2] reported that hypomagnesemia in liver transplant patients is associated with risk for NODAT; patients developing NODAT had an average post-transplant magnesium level of 1.87 mg/dL while the patients who did not develop NODAT had an average magnesium level of 1.95, or a 0.08 mg/dL difference. This implies that improvements in magnesium levels may be associated with lower risk of NODAT. Further studies are warranted to identify the causal relationship between hypomagnesemia and NODAT and to assess the effect of magnesium supplementation on this condition. In the current study, we demonstrated that converting from standard MG supplement to MGP increased the average serum magnesium level from 1.61 to 1.69 mg/dL (a 0.08 mg/dL improvement). We were able to normalize the magnesium levels in all of the subjects in Part 2 of the study without intolerable side effects. Given the possible association between low post-transplant serum magnesium concentrations and NODAT, adequate treatment should be considered to avoid hypomagnesemia in these patients.

TABLE 4 Frequency of Bristol stool types for standard MG and MGP therapy for Part 1 of the study

Stool index (All subjects)	Type 1	Type 2	Type 3	Type 4	Type 5	Type 6	Type 7
Standard MG							
Count	15	1	18	37	7	4	31
Row percent	13%	1%	16%	33%	6%	3%	27%
MGP							
Count	0	2	10	53	17	2	17
Row percent	0%	2%	10%	52%	17%	2%	17%



	Standard MG	MGP Part 1	MGP Part 2
Subject 1	7	-4	3
Subject 2	-3	-63	4
Subject 3	-32	-51	4

FIGURE 3 CSS for subjects completing Part 2. The blue dash line with blue diamonds represents the trend in CSS for subject #1 the black dash line with red squares represents the trend in CSS for subject #2 the black dash line with dots and green triangles represents the trend in CSS for subject #3. Standard MG: CSS for study subjects while on standard magnesium supplement. MGP Part 1: CSS for study subjects following conversion from standard magnesium supplement to magnesium plus protein at a near-equivalent daily elemental magnesium dose. MGP Part 2: CSS for study subjects who did not achieve mean serum magnesium >1.7 mg/dL at the end of Part 1 of the study and who were prescribed a onetime MGP dose adjustment

4.1 | Limitations

Limitations of this study include use of serum magnesium concentrations as a clinical marker for magnesium status. Serum magnesium poorly correlates to total body magnesium concentrations; however, it is the most widely used method for clinical assessments of magnesium deficiency.[3] Magnesium is primarily an intracellular cation that is stored in bone and soft tissue. Only one percent of total body magnesium is present in the blood making it difficult to accurately assess total body magnesium concentrations.[3,18,19] A clinical study comparing serum magnesium concentrations to clinical symptoms of magnesium deficiency in 3894 patients reported that at a serum magnesium cutoff value of 0.75 mmol/L (1.82 mg/dL), approximately 50% of patients had clinical magnesium deficiency. At a cutoff value of 0.7 mmol/L (1.7 mg/dL), 90% of patients had clinical magnesium deficiency.[3,20] Given this information, it may be that while MGP raised serum magnesium levels, patients who achieved a minimum serum magnesium target value of 1.7 mg/dL may still have clinical magnesium deficiency requiring higher magnesium doses.

There is a risk that once subjects are enrolled in a study, they will comply with their medications better while in the study. Measures to assess adherence to study medications are associated with some inherent limitations. Interviewing subjects and their caregivers was an easy and low-cost method; however, there is a possibility for subjects to inaccurately report adherence to the study medication. In this study, no subjects reported having intolerable diarrhea on standard MG treatment at the time of enrollment and none reported intolerable side effects while on MGP either. Thus, relief of GI symptoms would not be a motivation for changing compliance. As an objective secondary measure of adherence, we evaluated tacrolimus CV while on standard MG and with MGP. The CV of tacrolimus did not change while on standard MG compared to MGP. However, the tacrolimus CV only provides indirect evidence of a change in compliance pattern after starting the study.

Reliance on study subjects' and caregivers' reports related to stool form and consistency for 1-week duration resulted in a number of missing data. This particular component of the study had lower patient participation. Some subjects may have neglected to record or report stool data unless GI symptoms were perceived to be problematic; also, study subjects complained that recording of their stool quality for a week was unpleasant, leading to lower participation. Of note, none of the subjects taking MGP developed GI symptoms severe enough to consider them intolerable and all chose to continue on MGP rather than switch back to other forms of magnesium supplementation at the end of the study.

This was a single-center study with a small number of subjects. Future studies involving multiple sites with a larger number of participants are warranted in light of the serious health concerns that correlate with hypomagnesemia in solid organ transplant recipients.

5 | CONCLUSIONS

Hypomagnesemia is a common finding following renal transplantation. Variations among the different magnesium salt forms such as oral bioavailability, percent of oral absorption, and diarrheal potential influences dosing. At an equivalent mg/kg/d dose of elemental magnesium, MGP was associated with statistically significantly higher serum magnesium concentrations compared to standard MG

supplementation. At equivalent elemental magnesium dose, subjects on MGP reported fewer, but looser stools, although this difference was not statistically significant. Furthermore, for those subjects who did not achieve the goal of serum magnesium level ≥1.7 mg/dL after switching to MGP all were able to meet that goal with only one total daily dose adjustment of MGP without developing intolerable GI side effects.

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