

# Novel treatment with sucrosomial magnesium for hypomagnesemia in Familial Hypomagnesemia with Hypercalciuria and Nephrocalcinosis (FHHNC)

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## Research Article

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# Abstract

**Introduction:** Familial Hypomagnesemia with Hypercalciuria and Nephrocalcinosis (FHHNC) is a rare autosomal recessive disorder caused by mutations in the *CLDN16* and *CLDN19* genes, which encode claudins essential for paracellular magnesium and calcium reabsorption in the thick ascending limb. This defect results in significant renal magnesium loss, hypercalciuria, and progressive nephrocalcinosis, often leading to chronic kidney disease (CKD). Conventional magnesium supplementation is challenging due to its low bioavailability and frequent gastrointestinal side effects.

**Case Presentation:** a 22-year-old female patient diagnosed with FHHNC had been on multiple magnesium supplementation regimens with poor gastrointestinal tolerance, leading to malabsorption, underweight and poor control on magnesium metabolism. She was given sucrosomial magnesium, a recent formulation designed to enhance bioavailability while minimizing gastrointestinal side effects, resulting in improving symptoms and biochemical blood tests.

**Conclusions:** This case highlights the potential benefits of sucrosomial magnesium in managing patients with FHHNC, improving adherence and reducing treatment-associated adverse effects.

## Summary - What's new

Sucrosomial magnesium offers a promising alternative for managing FHHNC, enhancing magnesium bioavailability while reducing gastrointestinal side effects. This case report highlights its effectiveness in stabilizing magnesium levels, improving adherence, and alleviating associated symptoms.

## Introduction

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) is a rare genetic disorder characterized by a defect in the paracellular reabsorption of magnesium and calcium in the thick ascending limb (TAL) of the nephron [1].

Paracellular reabsorption is the primary mechanism in the TAL, where a positive luminal voltage, generated by the sodium-potassium-chloride cotransporter (NKCC2), drives magnesium and calcium across tight junctions. Mutations in *CLDN16* and *CLDN19*, which encode claudins 16 and 19 – key regulators of tight junction selectivity in the thick ascending limb – disrupt this process, leading to excessive urinary loss of magnesium and calcium. Magnesium reabsorption in the nephron can also occur via transcellular reabsorption, primarily in the proximal tubule and distal convoluted tubule, mediated by TRPM6 and TRPM7 channels. However, this mechanism alone is not enough to compensate for defective paracellular transport. Chronic hypomagnesemia triggers secondary hyperparathyroidism, further exacerbating calcium excretion and promoting nephrocalcinosis and renal dysfunction [2].

FHHNC can be detected perinatally, but the median age of onset is 5 years [1], presenting with clinical symptoms such as polyuria, polydipsia, and, less frequently, urinary tract infections and lithiasis. Ultrasonography reveals characteristic calcifications in the neonatal kidneys, sometimes described as having a flower petal-like appearance. Biochemical assessments typically confirm hypomagnesemia with

hypermagnesiuria, hypercalciuria, and mild metabolic alkalosis. Historically, genetic testing for FHHNC was limited during the early 2000s. However, since then, several variants and mutations in *CLDN16* and *CLDN19* have been identified. Mutations in *CLDN19* are typically more severe, often associated with ocular involvement and a more rapid progression to CKD.

Although the genetic tubulopathies Bartter and Gitelman syndromes can also present with electrolyte abnormalities and hypomagnesemia, FHHNC is uniquely associated with pronounced nephrocalcinosis and hypercalciuria. Bartter syndrome generally manifests with hypercalciuria but normal magnesium levels, whereas Gitelman syndrome is associated with hypomagnesemia but typically low urinary calcium excretion. While metabolic alkalosis is a common feature of Bartter and Gitelman syndromes due to renal sodium and chloride wasting, leading to volume contraction and secondary hyperaldosteronism, it is typically less pronounced in FHHNC. Another similar genetic tubulopathy is Dent disease, characterized by high phenotypic variability. It can present with hypercalciuria, nephrocalcinosis, and nephrolithiasis, along with low-molecular-weight proteinuria and, in some cases, phosphaturia, aminoaciduria, and glycosuria (incomplete Fanconi syndrome) [3]. Given the overlap between these tubulopathies, genetic testing is crucial to achieve a correct diagnosis.

*Table 1. Differential diagnosis of tubulopathies*

| <b>Feature</b>                                                    | <b>Bartter syndrome</b>                                                               | <b>Gitelman syndrome</b>                                                      | <b>Dent disease</b>                                                                          | <b>Familial hypomagnesemia with hypercalciuria (FHHNC)</b>                                                            |
|-------------------------------------------------------------------|---------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|
| <b>Age of Onset</b>                                               | Neonatal/ early childhood                                                             | Late childhood/ adolescence                                                   | Childhood                                                                                    | Infancy/ early childhood/adulthood                                                                                    |
| <b>Pathogenesis</b>                                               | Defective sodium-potassium-chloride cotransporter (NKCC2) in the thick ascending limb | Defective sodium-chloride cotransporter (NCC) in the distal convoluted tubule | Mutations in <i>CLCN5/OCRL</i> affecting endocytosis and trafficking in the proximal tubular | Mutations in <i>CLDN16</i> and <i>CLDN19</i> impairing magnesium and calcium reabsorption in the thick ascending limb |
| <b>Magnesemia/ Magnesiuria</b>                                    | Normal or mild hypomagnesemia, variable magnesiuria                                   | Moderate to severe hypomagnesemia, increased magnesiuria                      | Normal magnesemia, variable magnesiuria                                                      | Severe hypomagnesemia, pronounced magnesiuria                                                                         |
| <b>Calcium Metabolism (Calcemia/ Calciuria/ Nephrocalcinosis)</b> | Normal or hypercalciuria, nephrocalcinosis common                                     | Hypocalciuria, nephrocalcinosis rare                                          | Hypercalciuria, nephrocalcinosis frequent                                                    | Hypercalciuria, nephrocalcinosis present in most cases                                                                |
| <b>Metabolic Alkalosis</b>                                        | Present                                                                               | Present                                                                       | Absent                                                                                       | Mild or absent                                                                                                        |
| <b>Blood Pressure</b>                                             | Normal or low                                                                         | Normal or low                                                                 | Normal                                                                                       | Normal or low                                                                                                         |
| <b>Sodium Loss</b>                                                | High                                                                                  | Moderate                                                                      | Mild                                                                                         | High                                                                                                                  |

## Case Report

A 22-year-old female was diagnosed with FHHNC at 14 months of age based on some biochemical analysis that showed severe hypomagnesemia and hypercalciuria performed for a urinary tract infection. Renal ultrasound revealed extensive nephrocalcinosis. Genetic testing was unavailable at that time. During infancy, she experienced a seizure preceded by paresthesia, with serum magnesium levels around 0.40 mEq/L.

Between the ages of 15 and 20 years, she had multiple episodes of recurrent renal colic and nephrolithiasis. Laboratory follow-up showed persistent hypomagnesemia, hypercalciuria, and elevated parathyroid hormone (PTH) levels indicative of secondary hyperparathyroidism. Serial ultrasounds demonstrated cortical thinning and medullary hyperechogenicity. A resistivity index of approximately 0.68 bilaterally was reported, with greater involvement of the right kidney, correlating with the predominance of right-sided renal colic episodes.

Since childhood, she was prescribed with various formulations of magnesium supplement, however, adherence was difficult due to severe gastrointestinal side effects (chronic diarrhea, abdominal discomfort) resulting in malabsorption. She was first treated with magnesium sulfate, which caused significant diarrhea and failed to correct serum magnesium levels. Later, she was stabilized on 8 g/day of galenic preparations of magnesium glycosulfate (eight sachets per day), resulting in asymptomatic hypomagnesemia [4]. To mitigate nephrocalcinosis, she was also prescribed a thiazide diuretic combined with amiloride 5/50 mg, half a tablet twice daily. Despite the treatment with amiloride, daily potassium supplementation with potassium chloride 600 mg remained necessary.

Upon transition to our adult Nephrology Unit, the FHHNC diagnosis was confirmed by genetic testing that revealed the presence of variants of CLDN16. The patient's renal function remained stable, with an estimated glomerular filtration rate (eGFR) >60 mL/min, and presenting persistent microalbuminuria. Her blood pressure was consistently low (90/60 mmHg), and she experienced episodic paresthesia, tension-type headaches, and vitamin D deficiency. A 2021 DEXA scan indicated normal bone mineral density (BMD).

In 2024, due to poor tolerability of conventional oral magnesium salts, she was switched to a sucrosomial magnesium formulation, resulting in significantly improved gastrointestinal tolerance and adherence. Within six months, serum magnesium levels stabilized, PTH levels declined, and potassium supplementation was discontinued. The patient reported an overall improvement, reduced gastrointestinal symptoms, and no electrolyte imbalance-related events. Her BMI increased from 17.7 to 19. Laboratory assessments confirmed stable renal function and maintained serum magnesium around 1.00 mEq/L. A parathyroid ultrasound in 2024 showed no signs of primary hyperparathyroidism. She is currently continuing treatment with three sachets per day of sucrosomial magnesium dissolved in 500 mL of water throughout the day, along with vitamin D supplementation to manage secondary hyperparathyroidism.

Thiazide diuretic plus amiloride was discontinued during the summer due to two episodes of symptomatic hypotension (60/45 mmHg). Following its withdrawal, urinary calcium levels slightly rose from a median of 180 mg/die to 220 mg/die (normal <250 mg/die), but no further episodes of renal colic were observed. Additionally, magnesium wasting was reduced after the discontinuation of the thiazide diuretic, from a median of 24 mEq/die to a median of 16 mEq/die. Vitamin D dosing needed careful adjustment: the initial 10,000 IU/week triggered recurrent nephrolithiasis, so it was lowered to 8,750 IU/week, stabilizing vitamin D levels

and preventing further colic episodes for over 12 months. Regular physical activity was encouraged to support bone health.

Ongoing management includes monitoring calciuria levels. If calciuria rises significantly, thiazide diuretic reintroduction will be considered. However, there is no immediate need to reinstate it, as the long-term effects of thiazides in FHHNC are controversial [1]. Should renal colic symptoms recur, a temporary suspension of vitamin D may be considered, and potassium citrate initiated to address potential lithogenic factors. Additionally, DEXA scans will be conducted every two years to ensure stable bone mineral density and annual ultrasound evaluations will monitor renal morphology and function.

## Discussion

Gastrointestinal absorption is the only non-invasive route for magnesium replacement. High

oral doses of magnesium are required for the treatment of FHHNC, which often causes significant gastrointestinal side effects, particularly diarrhea, leading to further magnesium

losses. The introduction of the recent formulation, sucrosomial magnesium, enhances absorption and reduces side effects. Magnesium formulations used in FHHNC found in literature and from our experience are resumed in Table 2.

Unlike conventional magnesium salts, sucrosomial magnesium encapsulates the mineral in a phospholipid matrix, facilitating transport across the intestinal epithelium via endocytosis rather than relying on passive diffusion. This mechanism enhances bioavailability and bypasses the limitations of traditional magnesium supplements, which often lead to osmotic diarrhea due to unabsorbed magnesium in the gut lumen [2]. Sucrosomial magnesium with its innovative formulation has been shown to be effective both in the rare genetic tubulopathies Bartter’s and Gitelman’s syndromes and in kidney transplant patients [5].

*Table 2. Comparison of Magnesium Formulations*

| Formulation                   | Approx. Elemental Mg Content                        | Bioavailability                              | Notable Side Effects / Notes                                                                                                                                       |
|-------------------------------|-----------------------------------------------------|----------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Magnesium Oxide</b>        | ~241 mg of Mg/standard tablet                       | <b>Extremely Low</b>                         | Can cause significant gastrointestinal distress (diarrhea). Often poorly absorbed.                                                                                 |
| <b>Magnesium Citrate</b>      | Highly variable (e.g., ~90–300 mg per dose)         | <b>Good/Moderate</b>                         | Mild laxative effect. Better solubility in water than many inorganic salts; sometimes used to help reduce risk of nephrolithiasis.                                 |
| <b>Magnesium Sulfate</b>      | ~240 mg per 10 mL                                   | <b>Moderate to High</b>                      | Can cause gastrointestinal distress, especially in high doses. Used intravenously in acute settings.                                                               |
| <b>Magnesium Pidolate</b>     | ~370 mg of Mg daily with 3 vials                    | <b>Moderate</b> (not extensively quantified) | Frequently reported GI side effects (e.g., diarrhea) and intolerance.                                                                                              |
| <b>Magnesium Glycosulfate</b> | Varies by preparation; e.g. up to several grams/day | Not specifically quantified                  | Pronounced GI effects (diarrhea, abdominal cramps) and malabsorption.                                                                                              |
| <b>Magnesium Bisglycinate</b> | Varies; often ~100–200 mg elemental Mg per dose     | Considered <b>High</b>                       | Amino acid–chelated form. Generally well tolerated, with fewer laxative effects compared to inorganic salts. Recommended when GI side effects limit higher doses . |
| <b>Sucrosomial Magnesium</b>  | ~375 mg of Mg per sachet                            | <b>High</b>                                  | Sucrosomial technology encapsulates magnesium oxide in a phospholipid membrane, enhancing absorption and reducing GI discomfort.                                   |

A specific therapy for this syndrome does not currently exist. Typical management includes magnesium supplementation, large fluid administration, thiazide and alkali citrate therapy, and potassium supplementation if needed. Magnesium management in this syndrome is particularly challenging, due to both the heterogeneity of magnesium urinary loss among patients, who may exhibit variable severity phenotypes [1-2] and the different effectiveness of magnesium salts prescribed, often limited by gastrointestinal side effects. The recommended daily magnesium requirement is approximately 300–400 mg for healthy adults. Each sachet of sucrosomial magnesium is designed to provide this daily magnesium intake, however, in this clinical case, due to elevated magnesiuria, three sachets per day are necessary, dissolved in a 500 mL bottle of water and consumed throughout the day to improve the compliance.

One crucial aspect often overlooked in the literature is the impact of chronic hypomagnesemia and gastrointestinal intolerance on nutritional status and body weight. Persistent diarrhea can be both physically debilitating and socially distressing, causing embarrassment and limiting daily activities. In this case, the switch to sucrosomial magnesium was associated with a significant weight gain (from a BMI of 17.7 to 19), improving well-being and nutrient absorption.

## Conclusion

Sucrosomial magnesium has the potential to be a superior alternative for managing hypomagnesemia in FHHNC. Its enhanced bioavailability and reduced gastrointestinal side effects improve treatment adherence and overall patient outcomes.

## Declarations

Conflict of interest: the author declares no conflict of interest.

Author contribution: ES and DDP wrote the manuscript. LAC and FN supervised paper writing. ES, DDP, LAC, LFS and MC supervised the clinical case.

All authors read and approved the final manuscript.

Ethics approval and consent to participate: authors confirm that the appropriate ethical approval has been received from University of Padua and that the study is conformed to the declaration of Helsinki.

Consent for publications: written informed consent was obtained from the patient.

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