Comment on "Magnesium supplementation in the treatment of pseudoxanthoma elasticum:" Is magnesium oxide the best choice?

To the Editor: We read with great interest Rose et al's[1] report on their randomized controlled trial on magnesium supplementation to treat pseudoxanthoma elasticum (PXE). Indeed, magnesium is effective against elastic tissue calcification in PXE mouse models.[1] However, in this study, we regret that magnesium treatment results in only a trend toward improvement.[1] So, various factors might account for lack of statistical effect beyond a small sample size. Magnesium supplements and magnesium salt are combinations of magnesium and other minerals and come in 4 different forms: insoluble inorganic salts (oxide carbonate hydroxide), soluble inorganic salts (chloride sulfate), soluble organic salts (citrate lactate gluconate), and soluble organic complexes (glycinate bisglycinate).[2] Importantly, the amount of magnesium absorbed by the patient depends on its form.[2] Magnesium bioavailability, or the quantity absorbed, is the most relevant pharmacologic parameter in magnesium salt selection.[2] The authors used magnesium oxide, one of the cheapest available salts, which has a relatively high magnesium content but low bioavailability.[2] Indeed, excessively high magnesium content might have a laxative effect. Hence, the necessity for dose splitting.[2] Magnesium citrate has the highest bioavailability of all magnesium salts, compared with chelated forms and magnesium oxide.[2]

In a randomized, placebo-controlled study, 46 healthy participants received daily 300-mg doses of magnesium citrate or magnesium oxide.[3] Saliva, blood, and 24-hour urine samples were taken at baseline, 24 hours, and 60 days. The magnesium content in the 60-day urine sample was higher in the patients taking magnesium citrate than the patients taking magnesium oxide.[3] Magnesium citrate treatment induced higher mean serum magnesium concentrations than magnesium oxide treatment after 24-hour ($P = .026$) and 60-day ($P = .006$) supplementation.[3] Magnesium citrate is more soluble than magnesium oxide; hence, its higher absorption rate as demonstrated by higher plasma concentration and urinary excretion outcomes than magnesium oxide at various time points after administration.[3] Thus, available data suggest that magnesium citrate is better suited to therapeutic and supplementary use.[3]

Citric acid, a low-molecular-weight organic acid, promotes magnesium absorption by increasing its solubility,[3,4] and citrate is a major substrate in cellular energy metabolism and other cellular processes that can bind calcium and inhibit nucleation and calcium crystal growth,[4] which is a desired outcome for PXE. In a recent study, citrate was found to inhibit calcification in the urine of a chronic kidney disease patient.[4] Also, potassium magnesium citrate is an effective prophylaxis against recurrent calcium oxalate nephrolithiasis,[4] a complication frequently observed in PXE patients. Furthermore, magnesium citrate has been shown to protect against vascular calcification in the adenine-induced chronic renal failure rat model.[4]

Magnesium should remain a new treatment option for PXE calcification, yet larger studies are required. We suggest considering magnesium citrate, the highest bioavailable magnesium salt for treatment of PXE calcification, in future clinical trials. Because vascular calcification is a well-known predictive risk factor of subsequent cardiovascular mortality,[5] changes in vascular calcification could constitute a trial endpoint.

Magnesium balance in PXE patients should additionally constitute a secondary endpoint. Therefore, serum magnesium concentration, red blood cell magnesium concentration, and 24-hour urinary magnesium excretion are potentially useful biomarkers of magnesium status.[5]

Given the rarity of PXE and the few patients involved, it is time to combine efforts for a cure, and we call for international multicenter trials encompassing all PXE patient associations.

The authors wish to thank the Patients' Association PXE France, the Fondation Groupama, and the Centre Hospitalier Universitaire de Rennes – Corect for their support for our work. The authors wish to thank Ms Hazel Chaouch for formatting this article and English language corrections.

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Funding sources: None.

Conflicts of interest: None disclosed.

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https://doi.org/10.1016/j.jaad.2019.05.106