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Comment on: **Magnesium supplementation in the treatment of Pseudoxanthoma Elasticum: Is magnesium-oxide the best choice?**

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Dear Editor,

Rose et al. conducted the randomized controlled trial “Magnesium supplementation in the treatment of Pseudoxanthoma Elasticum (PXE)”¹ that we read with great interest. Indeed, magnesium is effective against elastic tissue calcification in PXE mouse models¹. However, in this study, we regret that magnesium treatment results only in a trend towards improvement¹. So, various factors may account for lack of statistical effect beyond a small sample size. Magnesium supplements or magnesium-salt, a combination of magnesium and other minerals, come in four different forms: i) insoluble inorganic-salts (oxide-carbonate-hydroxide); ii) soluble inorganic-salts (chloride-sulfate); iii) soluble organic-salts (citrate-lactate-gluconate); and iv) soluble organic complexes (glycinate-bisglycinate)². Importantly, magnesium-element amount is depending from its form². Magnesium bioavailability corresponding to the absorbed quantity is the most relevant pharmacological parameter in magnesium-salt selection². The authors used magnesium-oxide, one of the cheapest available salts, with a relatively high content in magnesium, but with a low bioavailability². Indeed, excessively high magnesium content may have a laxative effect. Hence, the necessity for dose-splitting². Magnesium-citrate has the highest bioavailability of all magnesium-salts, compared to chelated forms and magnesium-oxide². In a randomized, placebo-controlled study 46 healthy subjects received daily 300 mg doses of magnesium-citrate or magnesium-oxide³. Saliva, blood, and 24-hour urine samples were taken at baseline, 24-hours and 60-days³. At 60-days urinary magnesium excretion was higher with magnesium-citrate than with magnesium-oxide. Magnesium-citrate induced higher mean serum magnesium concentration than magnesium-oxide following 24-hour ($p=0.026$) and 60-day ($p=0.006$) supplementation³. This study showed that magnesium-citrate is more soluble than magnesium-oxide³, hence its higher absorption rate as demonstrated by higher plasma concentration and urinary excretion outcomes than magnesium-oxide at various time-points after administration³. Thus available

data suggest that magnesium-citrate is better suited to therapeutic and supplementary use³. Furthermore citric acid, as a low molecular weight organic acid, promotes magnesium absorption by increasing its solubility^{3,4}. Additionally, citrate is a major substrate in cellular energy metabolism and other cellular processes, binding calcium and inhibiting nucleation and calcium crystal growth⁴ which is the desired outcome for PXE. A recent study found that citrate inhibited calcification in CKD patient urine⁴. Also, potassium-magnesium-citrate is an effective prophylaxis against recurrent calcium-oxalate nephrolithiasis⁴, a complication frequently observed in PXE patients. Furthermore, magnesium-citrate has been shown in a recent study to protect against vascular calcification in an adenine-induced chronic renal failure rat model⁴.

Magnesium should remain a new treatment way 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. Since vascular calcification is a well-known predictive risk factor of subsequent cardiovascular mortality⁵, 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-hours urinary magnesium excretion are potentially useful biomarkers of magnesium status⁵.

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.

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Not Applicable

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Conflict of Interest

All authors declare they have no conflict of interest to disclose.

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