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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)”<sup>1</sup> that we read with great interest. Indeed, magnesium is effective against elastic tissue calcification in PXE mouse models<sup>1</sup>. However, in this study, we regret that magnesium treatment results only in a trend towards improvement<sup>1</sup>. 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)<sup>2</sup>. Importantly, magnesium-element amount is depending from its form<sup>2</sup>. Magnesium bioavailability corresponding to the absorbed quantity is the most relevant pharmacological parameter in magnesium-salt selection<sup>2</sup>. The authors used magnesium-oxide, one of the cheapest available salts, with a relatively high content in magnesium, but with a low bioavailability<sup>2</sup>. Indeed, excessively high magnesium content may have a laxative effect. Hence, the necessity for dose-splitting<sup>2</sup>. Magnesium-citrate has the highest bioavailability of all magnesium-salts, compared to chelated forms and magnesium-oxide<sup>2</sup>. In a randomized, placebo-controlled study 46 healthy subjects received daily 300 mg doses of magnesium-citrate or magnesium-oxide<sup>3</sup>. Saliva, blood, and 24-hour urine samples were taken at baseline, 24-hours and 60-days<sup>3</sup>. 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 ( $p=0.006$ ) supplementation<sup>3</sup>. This study showed that magnesium-citrate is more soluble than magnesium-oxide<sup>3</sup>, hence its higher absorption rate as demonstrated by higher plasma concentration and urinary excretion outcomes than magnesium-oxide at various time-points after administration<sup>3</sup>. Thus available

data suggest that magnesium-citrate is better suited to therapeutic and supplementary use<sup>3</sup>. Furthermore citric acid, as a low molecular weight organic acid, promotes magnesium absorption by increasing its solubility<sup>3,4</sup>. Additionally, citrate is a major substrate in cellular energy metabolism and other cellular processes, binding calcium and inhibiting nucleation and calcium crystal growth<sup>4</sup> which is the desired outcome for PXE. A recent study found that citrate inhibited calcification in CKD patient urine<sup>4</sup>. Also, potassium-magnesium-citrate is an effective prophylaxis against recurrent calcium-oxalate nephrolithiasis<sup>4</sup>, 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 model<sup>4</sup>.

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 mortality<sup>5</sup>, 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 status<sup>5</sup>.

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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