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Investigating the drivers of Ca isotope variability in human urine in healthy individuals

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While calcium isotopes ($\delta^{44/42}Ca$) in blood and urine are emerging as a potential clinical tool for monitoring bone mineral balance (BMB) (e.g., [1-3]), the baseline $\delta^{44/42}Ca$ variability among healthy individuals remains understudied. In theory, however, numerous aspects of an individual's demographic, health status, diet or lifestyle can influence $\delta^{44/42}Ca_{urine}$. Here, we provide an update on our Caltech Bone Health Study [3], reporting $\delta^{44/42}Ca_{urine}$ data from 81 new individuals (age 18-76). We identify three attributes (active vitamin D deficiency, vegetarian diet, and being post-menopausal) that systematically affect an individual's $\delta^{44/42}Ca_{urine}$, with vegetarians and vitamin D deficient individuals exhibiting heavier $\delta^{44/42}Ca_{urine}$ values than their age-matched control groups and post-menopausal women showing lighter $\delta^{44/42}Ca_{urine}$ values.

Combining our results with available literature data, we investigate the fundamental drivers of $\delta^{44/42}Ca_{urine}$variability, both during Ca homeostasis in general and in response to the attributes identified above in particular. Modeling the impact of kidney function on Ca isotopes as a Rayleigh distillation, we find that a fractionation factor of 0.99972 (or -0.3 ‰) during Ca reabsorption in the kidneys reproduces the relationship between $\delta^{44/42}Ca_{urine}$ and Ca excretion values in the available data. Changes in Ca reabsorption rates in the kidney drives $\delta^{44/42}Ca_{urine}$ variability, though within a typical range of reabsorption rates, the initial isotope composition ($\delta^{44/42}Ca_{serum}$) exerts the strongest control on inter-individual $\delta^{44/42}Ca_{urine}$ variability. Importantly, $\delta^{44/42}Ca_{urine}$ variations in 3 post-menopausal women from 3 separate studies cannot be explained by the same model, pointing to a different mechanistic control of $\delta^{44/42}Ca_{urine}$ in these subjects. These results impose practical considerations for the use of Ca isotopes in human urine as a biomarker of BMB, which will be discussed at the conference.

[1] Skulan & DePaolo (1999) Calcium isotope fractionation between soft and mineralized tissues as a monitor of calcium use in vertebrates. *PNAS* 96, 13709–13713.

[2] Eisenhauer et al. (2019) Calcium isotope ratios in blood and urine: a new biomarker for the diagnosis of osteo- porosis. *Bone Rep* **10**, 100200.

[3] Tissot et al. (2024) Magnitude and timescales of Ca isotope variability in human urine: implications for bone mass balance monitoring. *Metallomics* **16**, mfae050.