Stable Calcium Isotopes: a novel biomarker of bone mineralization in children with chronic kidney disease

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In chronic kidney disease (CKD) dysregulated calcium (Ca) homeostasis is associated with reduced bone mineral density (BMD) and vascular calcification. However, radiological measures and biomarkers do not allow accurate evaluation of BMD.

We measured Ca isotope ratios ($\delta^{44/42}Ca$) by MC-ICP-MS in blood and urine. Bone Ca gain and loss is calculated using a box model based on Ca kinetics. Ca absorption from bones increases $\delta^{44/42}Ca_{Blood}$ and $\delta^{44/42}Ca_{Urine}$, resorption decreases these fractions.

104 children in CKD4-5 and on dialysis (CKD4-5D), 40 controls and 100 adults underwent Ca isotope measurement, bone biomarkers, dual energy x-ray absorptiometry (DXA) and tibial peripheral quantitative CT scan (pQCT).

In healthy children $\delta^{44/42}Ca_{Blood}$ and $\delta^{44/42}Ca_{Urine}$ were higher than in adults ($p<0.0001$), reflecting Ca uptake during bone formation. Since urinary Ca excretion is impaired in CKD, $\delta^{44/42}Ca_{Blood}$ was higher and $\delta^{44/42}Ca_{Urine}$ lower in children with CKD4-5D compared to controls ($p<0.001$ for both).

In CKD2-5D $\delta^{44/42}Ca_{Blood}$ positively correlated with cholecalciferol ($p=0.01$) and alfacalcidol ($p=0.002$) doses, implying increased bone Ca uptake when Ca bioavailability is increased. $\delta^{44/42}Ca_{Blood}$ positively correlated with biomarkers of bone formation (alkaline phosphatase, $p=0.05$) and negatively with bone resorption markers (PTH, $p=0.013$, TRAP5b, $p<0.001$, CTX, $p=0.006$). $\delta^{44/42}Ca_{Blood}$ positively correlated with tibial cortical BMD-Z-score ($p=0.006$, $R^2=0.39$), and DXA hip BMD-Z-score ($p=0.02$). On multivariable linear regression analysis significant and independent predictors of tibial cortical BMD-Z-score were $\delta^{44/42}Ca_{Blood}$ ($\beta=0.68$, $p=0.006$) and PTH ($\beta=0.39$, $p=0.04$), together predicting 67% of the variability in BMD.

Ca isotope ratios provide a novel, non-invasive method of assessing bone mineralization. Further studies are in progress to define optimal levels of $\delta^{44/42}Ca_{Blood}$ that can guide safe and effective treatment to prevent Ca deficiency or overload.