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CALCIUM ISOTOPE RATIOS IN SERUM ARE THE STRONGEST PREDICTOR OF BONE CALCIUM BALANCE IN PATIENTS ON DIALYSIS

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Background and Aims: Dysregulated mineral homeostasis is common in chronic kidney disease (CKD) and associated with bone demineralization and vascular calcification. The balance between bone formation and resorption, which reflect the bone calcium (Ca) balance (BCaB), cannot be determined without bone biopsy which is invasive and not easily repeatable. Recently, we have shown that stable (i.e. non-radioactive) Ca isotopes, ^{42}Ca and ^{44}Ca, can be measured in serum and their ratio ($\delta^{44/42}Ca_{serum}$) quantitatively determines net bone gain or loss of Ca. Thus, when bone formation exceeds bone resorption, the net BCaB is positive and $\delta^{44/42}Ca_{serum}$ is high, and when bone resorption is the predominant process $\delta^{44/42}Ca_{serum}$ is low compared to age-matched controls. In this study we compared $\delta^{44/42}Ca_{serum}$ against $\delta^{44/42}Ca_{bone}$ and arterial biopsy samples ($\delta^{44/42}Ca_{artery}$) and the sensitivity of $\delta^{44/42}$Ca in predicting changes in bone histology.

Method: Adults receiving chronic dialysis who underwent bone and arterial biopsies at the time of kidney transplantation were recruited. Patients who had parathyroidectomy or received cinacalcet or anti-resorptive agents were excluded. All participants had Dual Energy X-ray Absorptiometry (DXA) of the hip and lumbar spine. Ca^{44} and Ca^{42} measurements were performed in serum and bone and arterial biopsy samples using a multi-collector inductively-coupled plasma mass spectrometer (*Thermo Fisher Scientific, Germany*).

Results: Nineteen patients, median age 59.8 years, 84% male, median time on dialysis 3.3 years were included. $\delta^{44/42}$Ca was significantly higher in serum compared to bone or arterial biopsy samples ($p < 0.0001$), with the lowest isotope ratios in bone (Fig. 1A). $\delta^{44/42}Ca_{bone}$ was significantly lighter than $\delta^{44/42}Ca_{artery}$ ($p = 0.0002$; Fig. 1B). $\delta^{44/42}Ca_{bone}$ correlated positively with the osteoblastic markers BAP and P1NP ($p = 0.0006$, $R^2 = 0.51$ and $p = 0.009$, $R^2 = 0.31$) and inversely with PTH and the osteoclastic marker RANKL ($p = 0.0017$, $R^2 = 52$ and $p = 0.02$, $R^2 = 0.29$ respectively; Fig. 2). Both the DXA hip and lumbar spine T-scores and z-scores correlated positively with $\delta^{44/42}Ca_{bone.}$ $\delta^{44/42}Ca_{serum}$ showed an inverse correlation with the osteoid area ($p = 0.04$, $R^2 = 0.22$) and a positive correlation with the absolute mineralized area and the trabecular thickness ($p = 0.0004$, $R^2 = 0.58$ and $p = 0.013$, $R^2 = 0.34$ respectively. The were no significant correlations with $\delta^{44/42}Ca_{artery}$. On multivariable linear regression analysis significant predictors of $\delta^{44/42}Ca_{serum}$ were $\delta^{44/42}Ca_{bone}$ ($p = 0.018$, 95%CI −1.35 to −0.16), age ($p = 0.02$, 95%CI 0.002 to 0.02) and BAP ($p = 0.019$, 95%CI 0.04 to 0.38), together predicting 71% of the variability in $\delta^{44/42}Ca_{serum}$. The only significant predictor of $\delta^{44/42}Ca_{bone}$ was the $\delta^{44/42}Ca_{serum}$: $p = 0.004$, 95%CI −1.6 to −0.37, model $R^2 = 69\%$.

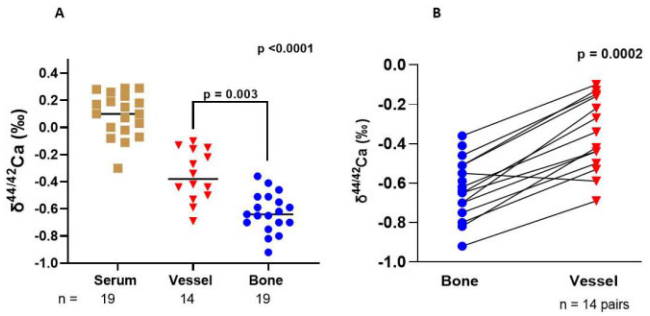

Figure 1:

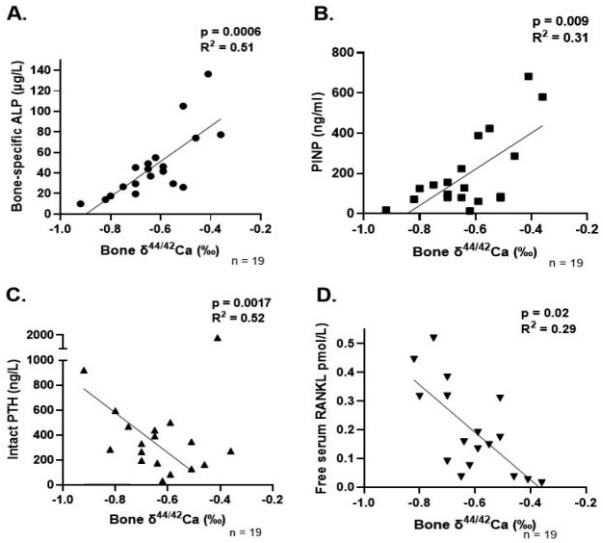

Figure 2:

Conclusion: $\delta^{44/42}Ca_{serum}$ is a significant and independent maker of BCaB, correlating with bone histology measures, and may provide a more sensitive measure than DXA or bone biomarkers. Further studies are required to determine the clinical utility of using $\delta^{44/42}Ca_{serum}$ to guide management of mineral bone disease in CKD.

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