Abstract Type : Poster exhibition
Abstract Submission No.: A-0193
Abstract Topic : Non-dialysis CKD

Association Between a-Klotho and Bone Mineral Density Decline Rate in Chronic Kidney Disease Patients: Findings from KNOW-CKD

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Objectives : Chronic kidney disease (CKD) is associated with an increased risk of bone mineral density (BMD) loss, leading to fractures and osteoporosis. α-Klotho, a circulating protein with potential protective effects on bone metabolism, has been suggested to influence BMD. However, its role in BMD decline among CKD patients remains unclear. This study investigates the association between α-Klotho levels and the rate of BMD decline.
Methods : A total of 1,185 CKD patients were included in this longitudinal study. BMD measurements were obtained at baseline and after four years. The associations between serum α-Klotho levels at baseline and the BMD decline rate was assessed using multiple linear regression models. To determine the interaction between time and α-Klotho, we included a year*log α-Klotho interaction term in the model.
Results : The baseline-adjusted analysis demonstrated that BMD declined significantly over time (β = -3.448 per year, 95% CI: -5.494 to -1.401, $p < 0.001$). The year*log α-Klotho interaction term showed a significant positive association with BMD decline rate (β = 0.463, 95% CI: 0.134 to 0.791, p = 0.0058), suggesting that higher α-Klotho levels were associated with a slower rate of BMD loss. Visual analyses confirmed a dose-dependent relationship, with higher α-Klotho tertiles exhibiting less BMD decline rate.
Conclusions : This study provides that higher α-Klotho levels are associated with a reduced rate of BMD decline in CKD patients. These findings highlight the potential role of α-Klotho in bone health preservation and suggest that it may serve as a biomarker or therapeutic target for managing CKD-related bone loss.

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Table 1. Association between α-Klotho and BMD decline rate

Variable	β (Estimate)	95% CI	*p* value
(Intercept)	90.453	81.066 to 99.84	<0.001
Year	**-3.448**	**-5.494 to -1.401**	**<0.001**
year: log α-Klotho	**0.463**	**0.134 to 0.791**	**0.006**
α-Klotho	-0.239	-1.175 to 0.697	0.617
Age	-0.014	-0.043 to 0.014	0.329
Sex	-0.729	-1.570 to 0.112	0.089
BMI	0.057	-0.027 to 0.141	0.185
Smoking (former)	-0.037	-0.953 to 0.88	0.937
Smoking (never)	-0.732	-1.553 to 0.09	0.081
eGFR	0.026	0.013 to 0.04	<0.001
UPCR	0.026	-0.272 to 0.324	0.862
Serum albumin	0.152	-1.013 to 1.317	0.798
DM	0.533	-0.198 to 1.265	0.153
Serum calcium	1.224	0.399 to 2.049	0.004
Serum phosphorus	-0.934	-1.499 to -0.37	0.001
25-OH-Vitamin D3	0.001	-0.045 to 0.048	0.954
PTH	0.005	-0.002 to 0.013	0.184
Serum ALP	-0.0003	-0.005 to 0.005	0.903
log FGF23	0.082	-0.05 to 0.214	0.221

Multiple linear regression analysis was performed to examine the relationship between BMD decline rate and α-Klotho levels, including interaction term between year and log-transformed α-Klotho. The regression results show estimates (β) for each variable, with 95% confidence intervals (CI) and p-values.
Abbreviations: ALP, alkaine phosphatase; BMD, bone mineral density; BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular fitration rate; PTH, parathyroid hormone; UPCR, urine protein-to-creatinine ratio

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Figure 1. Relationship Between a-Klotho and Adjusted BMD Slope