Calcimimetics Alter Periosteal and Perilacunar Bone Matrix Properties in Early Chronic Kidney Disease

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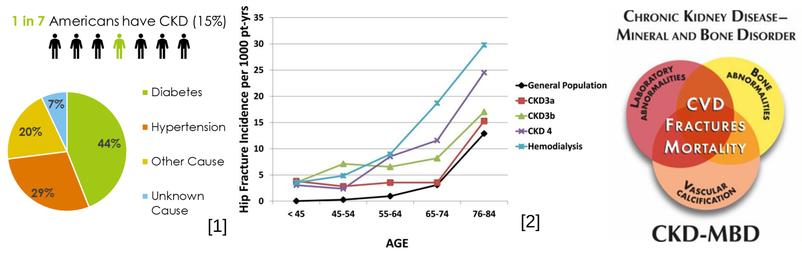
Introduction



- **Goal:** Determine the effects of calcimimetic treatment on structural and tissue-level bone properties in a rat model of early chronic kidney disease

Methods

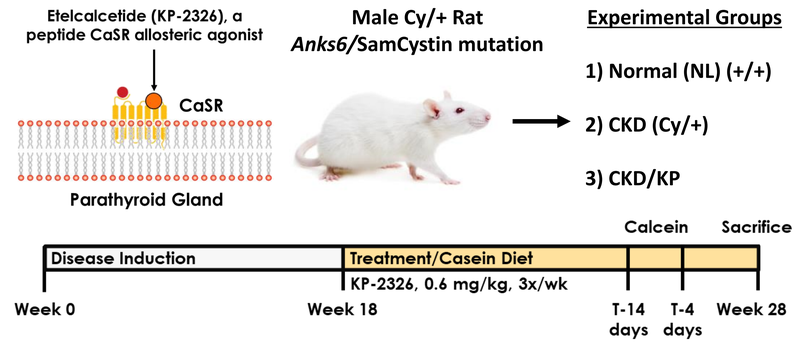


Figure 1: Timeline. Male Cy/+ rats fed a casein-based diet undergo progressive CKD-MBD. 18-week-old rats (N=12) were treated with the calcimimetic KP-2326 (0.6 mg/kg i.p., 3x/wk). N=12 normal littermates and N=12 untreated CKD rats received the casein diet to control mineral intake. Calcein was administered 4 and 14 days prior to sacrifice at 28 weeks.

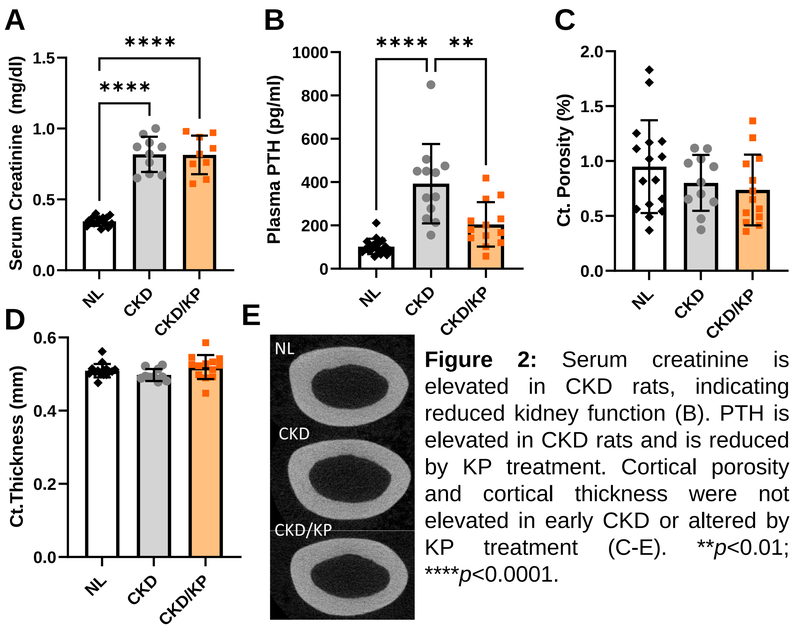


Figure 2: Serum creatinine is elevated in CKD rats, indicating reduced kidney function (B). PTH is elevated in CKD rats and is reduced by KP treatment. Cortical porosity and cortical thickness were not elevated in early CKD or altered by KP treatment (C-E). **p<0.01; ****p<0.0001.

Results

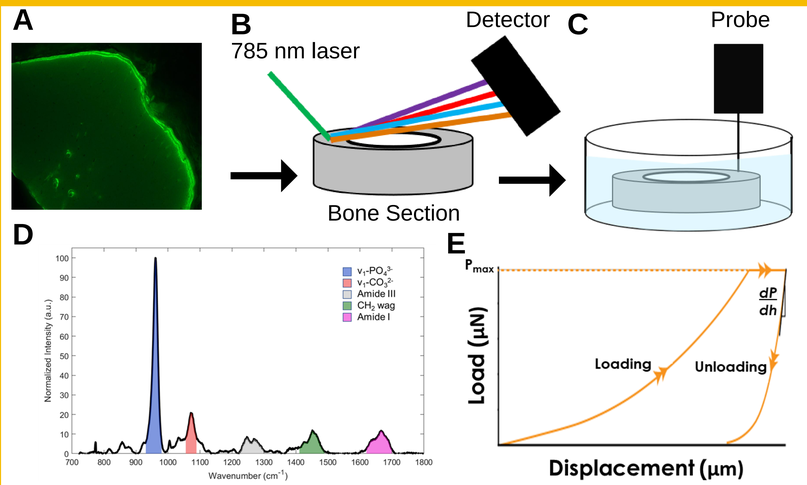


Figure 3: Colocalized Raman Spectroscopy and Nanoindentation. Rat bone sections underwent fluorescent microscopy to select periosteal bone regions between calcein labels (A). Raman spectroscopy was performed at 50x magnification using a 785 nm laser with an 8 second exposure and 8 accumulations. Baseline correcton was performed using an 11th order polynomial, and cosmic rays were removed. Spectral analysis was performed using a custom MATLAB script to assess bone tissue composition with 1 μm resolution (B,D). Nanoindentation was performed in fluid with a diamond spherical probe in the same locations as Raman spectroscopy. Samples were loaded to 1 mN, held for 45 seconds, and unloaded. Mechanical curves were analyzed using Triboscan software (Bruker) to determine tissue-level/intrinsic mechanical properties with a 1 μm resolution (C,E).

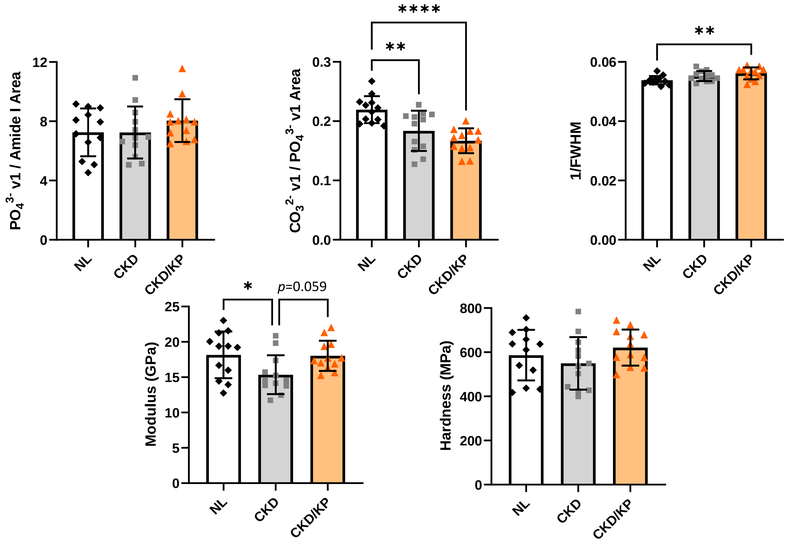


Figure 4: CKD and KP Treatment Alter Periosteal Tissue Properties. Mineral-to-matrix ratio was not altered by CKD or KP (A). Carbonate substitution was significantly reduced by CKD and KP treatment (B) while KP treatment increased mineral crystallinity vs NL (C). Elastic modulus was also significantly reduced in CKD but this was mitigated by KP treatment (D) while no changes were seen in tissue hardness (E). *p<0.05; **p<0.01; ****p<0.0001

Results

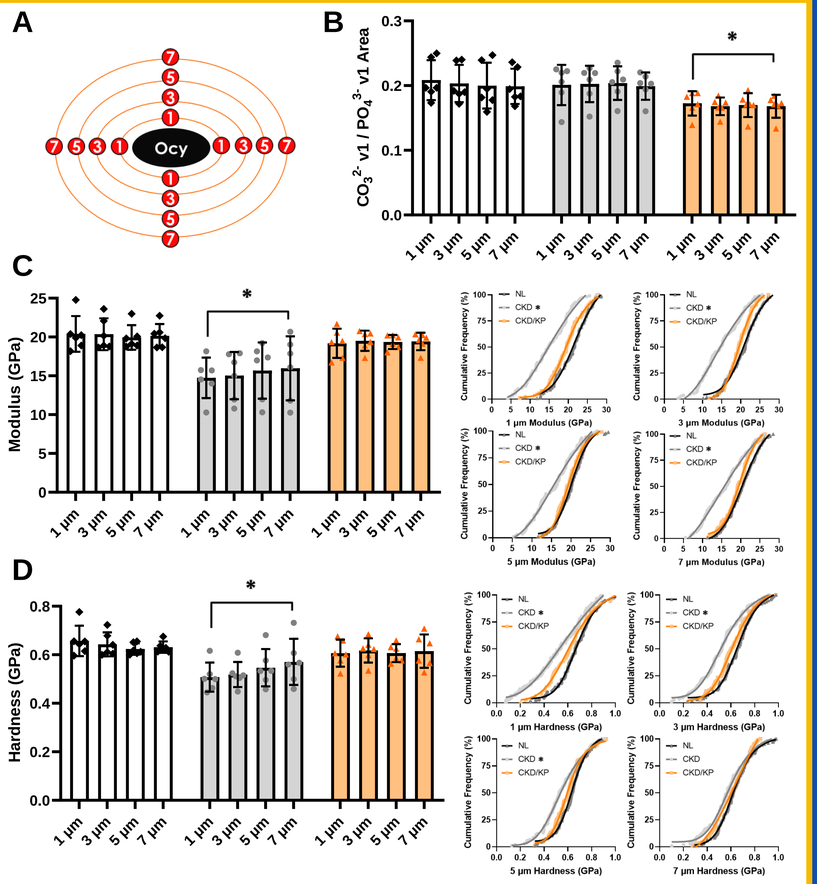


Figure 5: CKD and KP Treatment Alter Perilacunar Tissue Properties. Perilacunar regions were selected 1, 3, 5, and 7 μm from the lacunar wall (A). In perilacunar bone, carbonate substitution was reduced by KP treatment (B). Elastic modulus and hardness were elevated in KP vs CKD (C,D, left). CKD-induced reduction in hardness was limited to 5 μm from the lacunar wall (D, right) *p<0.05; ****p<0.0001.

Conclusions

Outcome Summary vs NL

	CKD		KP	
Structural				
Cortical Porosity	–		–	
Tissue Composition	*Periosteal*	*Perilacunar*	*Periosteal*	*Perilacunar*
Carbonate Sub.	↓	–	↓	↓
Crystallinity	–	–	↑	–
Tissue Mechanics				
Modulus	↓	↓	–	↑
Hardness	–	↓	–	↑ up to 5 μm

References

1. Centers for Disease Control and Prevention. Chronic Kidney Disease in the United States, 2019
2. Moe & Nickolas. CJASN. 2016;11(11):1929-1931