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POSTER ABSTRACTS

102.IRON HOMEOSTASIS AND BIOLOGY

Moderate Iron Deficiency Does Not Potentiate Renal or Cardiac Calcification and Subsequent Tissue Injury in Mouse Models of CKD

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Chronic kidney disease (CKD) is a public health challenge that affects over 26 million Americans and many more worldwide. Many develop renal and cardiac calcification, which promotes arterial wall stiffness. These structural changes of the vasculature contribute to hypertension and heart failure, increasing the risk of premature death.
Dysregulated iron homeostasis also occurs in many patients with CKD, and iron deficiency and anemia are common complications that are independently associated with CKD progression, cardiovascular disease and all-cause mortality. Furthermore, lower transferrin saturation (TSAT) levels are independently associated with higher coronary artery calcification scores in CKD patients receiving hemodialysis. However, whether iron deficiency and/or anemia directly contribute to the pathogenesis of calcification in CKD is unknown. We examined the effects of iron deficiency on renal and cardiac calcification, and tissue injury in mouse models of CKD.
We used a dietary model of progressive CKD: 8-week-old male C57BL/6J mice were fed for 8 weeks a customized 0.2% adenine-rich diet that was either iron-replete (100 ppm iron; "adenine-IR" group) or iron-deficient (4 ppm iron, "adenine-ID" group). Control mice were fed a diet without adenine, but with matching iron content (iron-replete "CTRL-IR" and iron-deficient "CTRL-ID" groups). Compared to CTRL-IR mice, CTRL-ID mice developed widespread tissue iron deficiency and anemia as expected. Surprisingly, despite 8 weeks of low iron diet which led to lower serum iron and worse anemia, adenine-ID mice had similarly high liver iron as adenine-IR mice, similar expression of transferrin receptor 1 (marker of tissue iron deficiency) in kidney or heart, and similarly elevated liver hepcidin mRNA. This suggests that hepcidin induction in this CKD model likely protected tissues from iron depletion, at least on the time scale of the experiment. Calcification in adenine mice was evident but was similar between adenine-ID and adenine-IR mice, as observed by the comparable expression of calcification markers in kidney and heart (*Runx2, Sox9, Opn*). Additionally, markers of kidney function (BUN and serum creatinine), kidney injury (*Kim1, Lcn2*) and cardiac injury(*Myh7*) were also comparable between adenine-ID and adenine-IR mice. Inflammation and fibrosis were increased in kidney and heart of adenine mice in general, but once again similar between adenine-ID and adenine-IR mice (serum IL-6, *Tnfa*, *Tgfb Col1a1).*
We then employed a genetic model of progressive CKD – constitutive *Col4a3* $^{-/-}$ mice (Alport syndrome, life expectancy in this model ~11 weeks of age), and fed male mice either an IR or ID diet for 7 weeks. Diets were started in juvenile mice (4-week-old), a strategy known to exacerbate the effect of ID diet on tissue iron deficiency and anemia. Despite this, Alport-ID and Alport-IR mice still displayed similar liver iron levels and liver hepcidin expression. Alport-IR and -ID groups also had comparable renal and cardiac calcification, injury, inflammation and fibrosis.
Altogether, our findings in two different mouse models of CKD indicate that moderate iron deficiency does not potentiate renal or cardiac calcification and subsequent tissue injury. Our data suggest that despite causing hypoferremia and anemia, chronically elevated hepcidin in CKD might delay the development of tissue iron deficiency in the liver, kidney and heart, and potentially protect against deleterious vascular changes and subsequent tissue injury.

Disclosures Ganz: *Ionis Pharmaceuticals:* Consultancy; *Disc Medicine:* Consultancy; *Silarus Therapeutics:* Current equity holder in private company, Membership on an entity's Board of Directors or advisory committees; *Intrinsic LifeSciences:* Current equity holder in private company, Membership on an entity's Board of Directors or advisory committees.

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