

INTRODUCTION

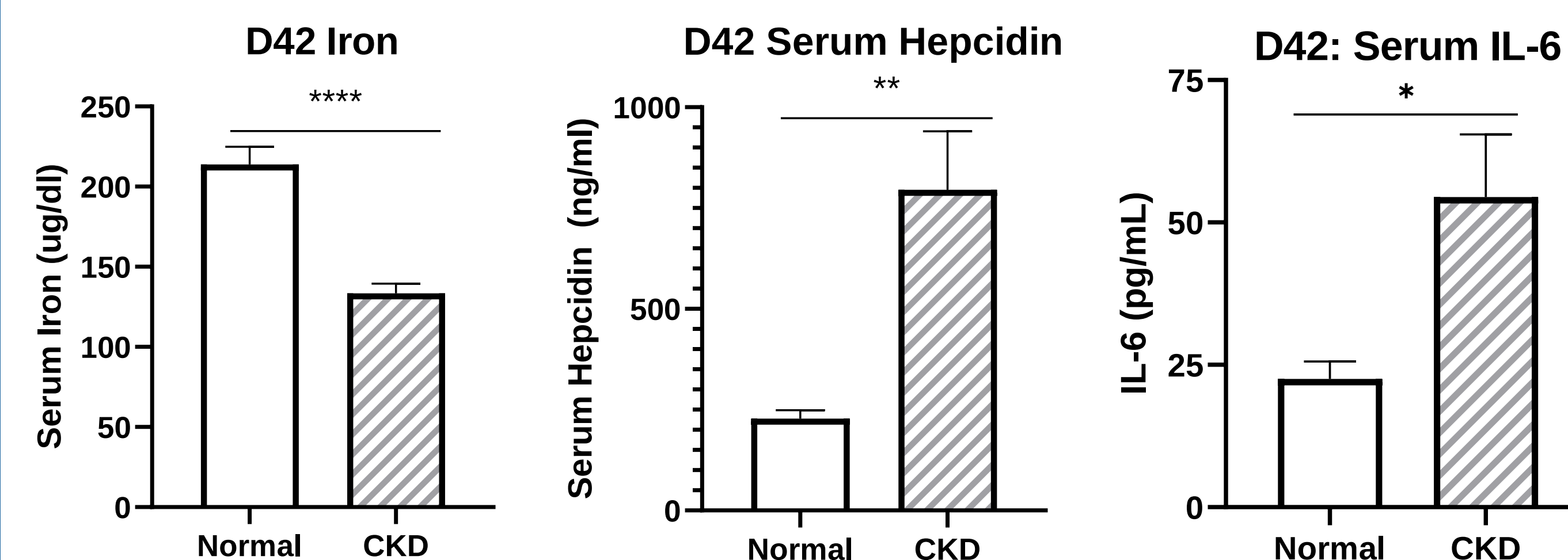
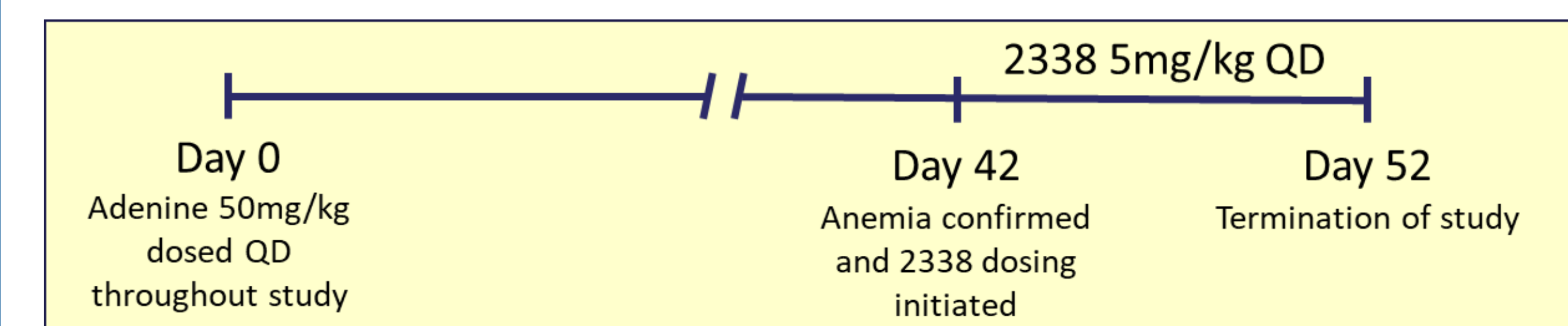
Hepcidin is an endocrine regulator of iron metabolism that, when elevated, can decrease levels of iron available for erythropoiesis resulting in decreased red blood cell production. Signaling through activin-like kinase-2 (ALK2), a TGF- β type 1 receptor, has been implicated in regulation of hepcidin-mediated iron regulation and mobilization; the contribution of ALK2 signaling to hepcidin regulation is complicated by other BMP receptors including ALK3. Activation of type 1 receptors including ALK2 and ALK3, via ligand BMPs and co-receptor hemojuvelin (m-HJV), results in downstream SMAD phosphorylation, increased hepcidin, and decreased serum iron while suppression of the receptor signaling would have the opposite effects.

OBJECTIVE(S)

To assess the specific effect of ALK2 inhibition on hepcidin and iron mobilization, we tested inhibitors in both naive and diseased animals in a model anemia of inflammation (AI) via induced chronic kidney disease (CKD). AI is characterized by elevated hepcidin and suppressed serum iron levels in addition to hematological changes consistent with anemia.

METHOD(S)

C57BL/6 mice (N=5 in normal groups and N=10 in CKD groups) were dosed daily via PO administration with 50 mg/kg of adenine or vehicle. After 6 weeks of adenine administration, anemia was confirmed in subset of mice. Concomitantly, the remainder of mice began dosing with either vehicle or KTI-2338 5 mg/kg PO daily whilst still receiving daily adenine or vehicle for 10 days. The study was terminated at 52 days and hematology, serum hepcidin, and serum iron levels were assessed.

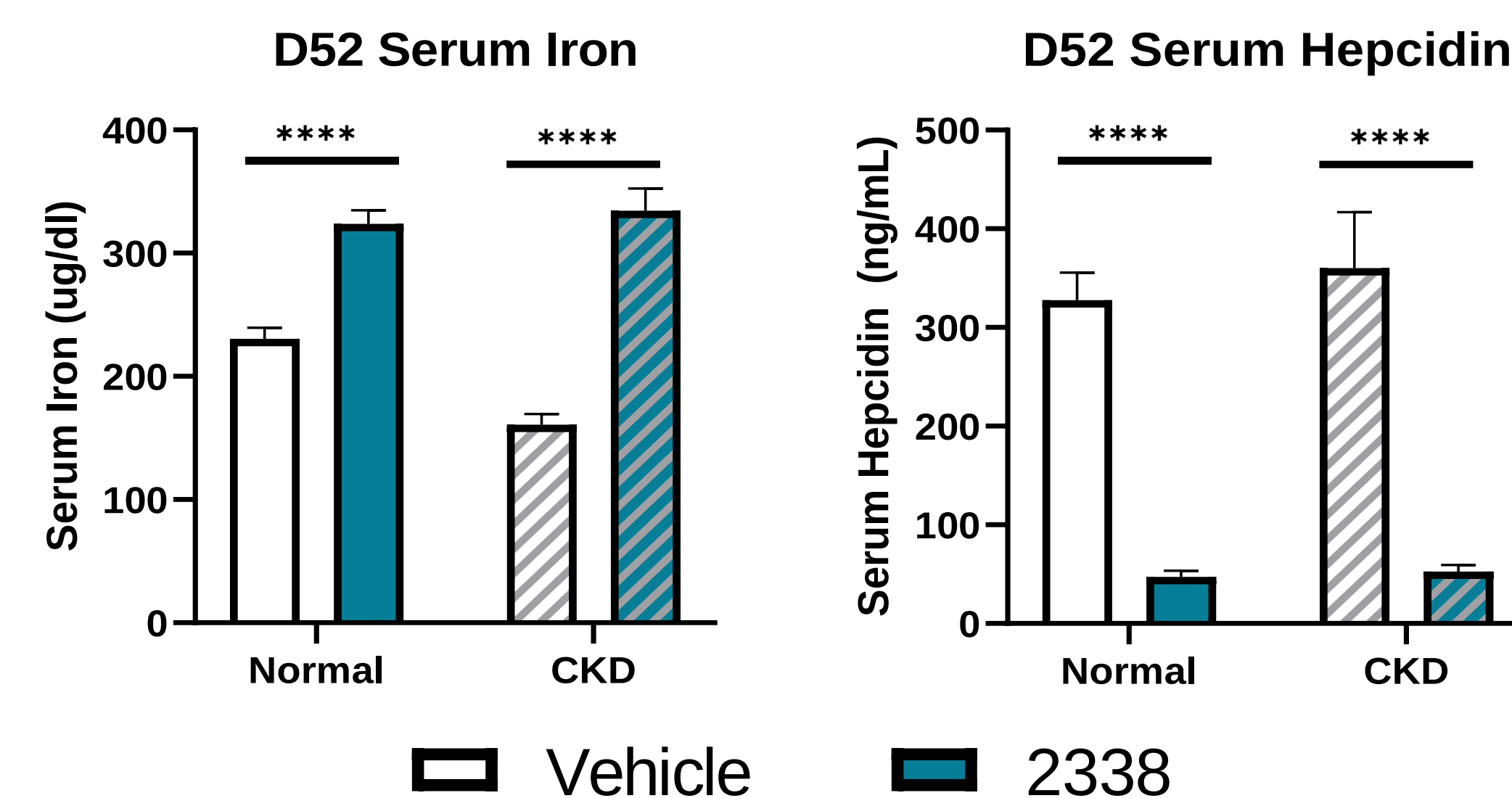


* P < 0.05, ** P < 0.01, **** P < 0.0001 via t-test

RESULT(S)

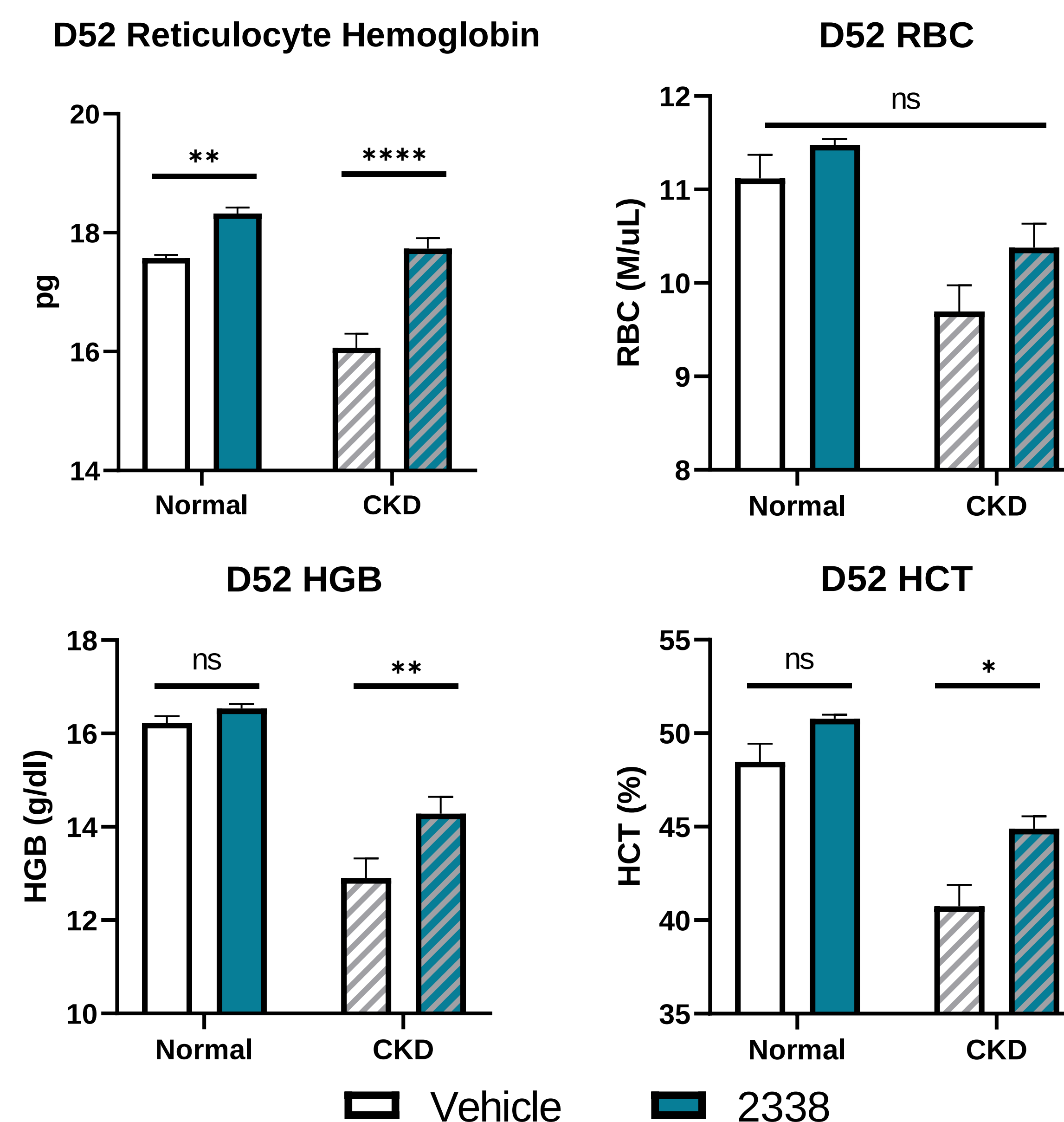
10 days of therapeutic dosing following confirmation of anemia at Day 42 with KTI-2338 resulted in elevation of serum iron and suppression of serum hepcidin beyond baseline levels in both normal and CKD mice. At study termination, CKD mice receiving KTI-2338 had serum iron values 108.2% higher than CKD mice receiving vehicle. Additionally, serum hepcidin was decreased by 85.4% over CKD vehicle mice.

* P < 0.05, ** P < 0.01, **** P < 0.0001 via two-way ANOVA



Further, therapeutic dosing resulted in improvement of hematologic parameters measured. Hemoglobin, hematocrit, red blood cell counts, and reticulocyte hemoglobin content was increased by 10.9%, 10.3%, 7.2%, and 9.9%, respectively, in CKD mice treated with 2338 over CKD vehicle mice.

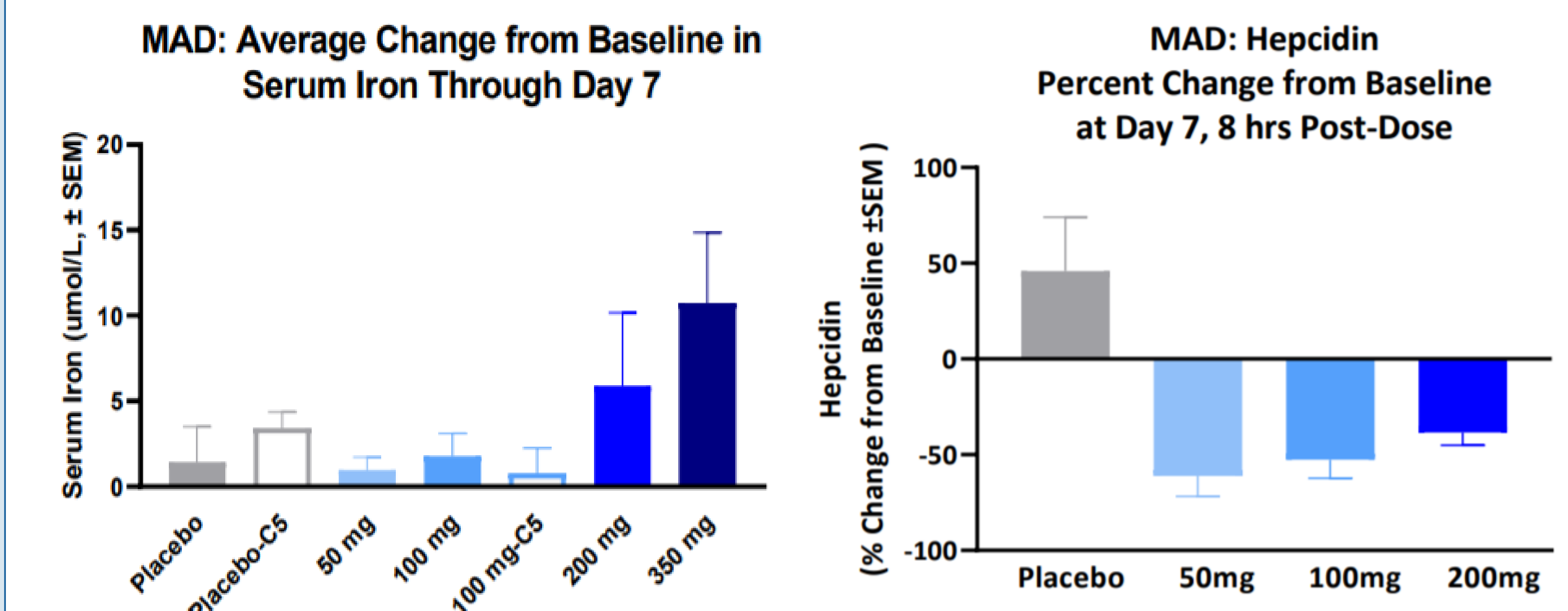
* P < 0.05, ** P < 0.01, **** P < 0.0001 via two-way ANOVA



CONCLUSION(S)

Herein, we have evaluated the utility of ALK2 inhibition in a model of anemia arising from high hepcidin due to chronic inflammation. We have characterized that inhibition of ALK2 signaling contributed to an improvement in hematologic parameters, including hemoglobin (HGB), hematocrit (HCT), red blood cell counts (RBC) and reticulocyte hemoglobin content. Additionally, we observed a decrease in serum hepcidin and increase in serum iron levels. Though the use of a selective ALK2 targeted biologic does not completely preclude involvement of other BMP receptors such as ALK3, these data support our assertion that ALK2 signaling is an integral part of hepcidin-mediated iron mobilization and that targeting ALK2 inhibition (with a small molecule inhibitor or a neutralizing monoclonal antibody) could potentially treat anemia of high hepcidin.

Finally, KER-047, an investigational compound structurally related to KTI-2338, was observed to increase serum iron levels and decrease serum hepcidin levels in a Phase I clinical trial of healthy volunteers. Taken together, these data substantiate the role of ALK2 signaling in anemia arising from high hepcidin and illustrate that specific ALK2 inhibition could potentially treat these diseases.



REFERENCES

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