HEPCIDIN, ERYTHROPOIETIN, INFLAMMATION, FERRITIN AND IRON STORES IN RENAL ANEMIA

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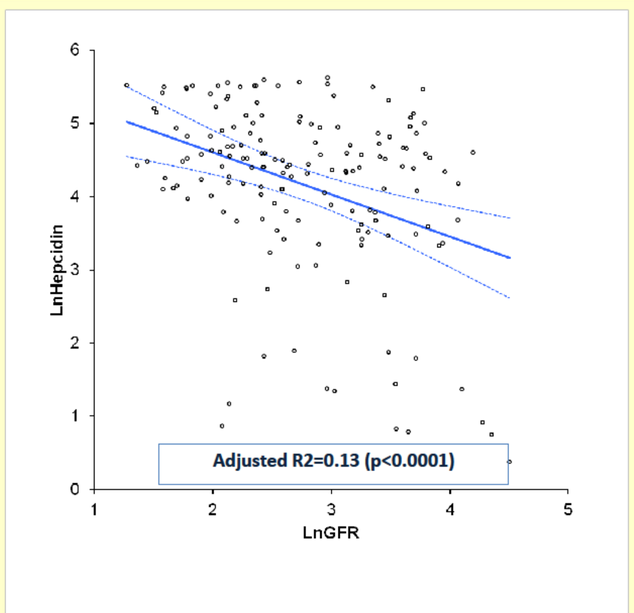
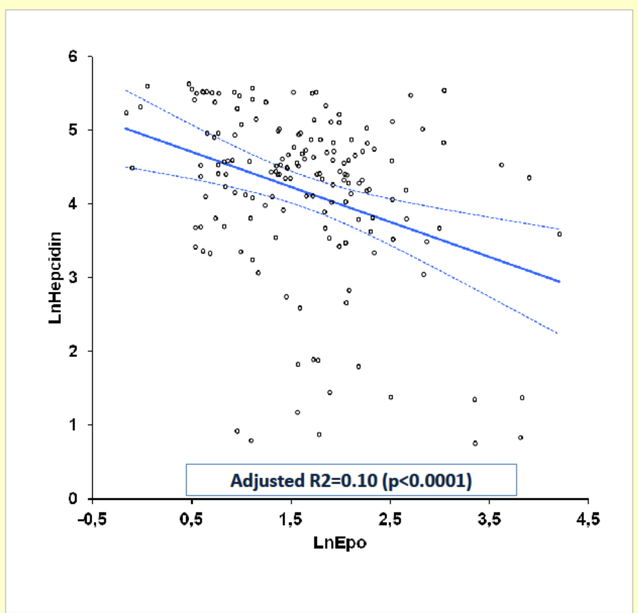
BACKGROUND

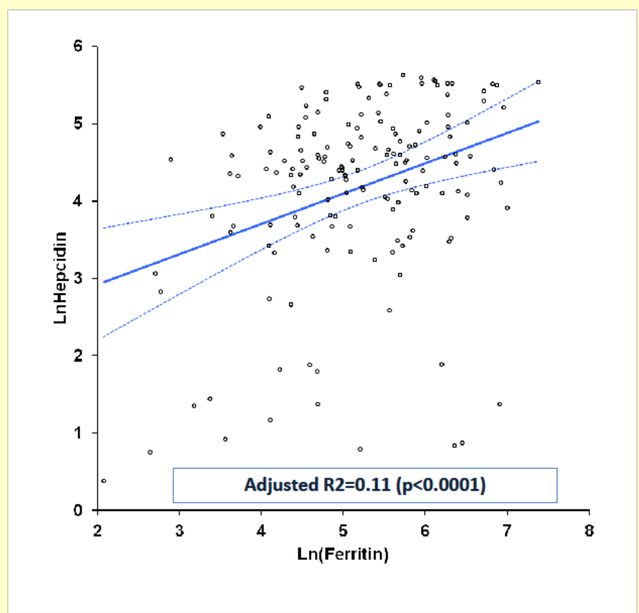
Renal anemia results from a combination of inadequate stimulation of erythropoiesis, iron deficiency and inflammation-induced defective iron mobilization from macrophages. As the interplay between erythropoietin (Epo), hepcidin and inflammation driven by the declining renal function induces increase in serum ferritin, higher serum ferritin can be attributed either to replete iron stores or to inflammation. We aimed to evaluate the relationships between hepcidin, erythropoietin, inflammation (C- reactive protein - CRP) and serum ferritin in anemic non-dialysis chronic kidney disease (CKD) patients.

METHODS

One hundred sixty two non-dialysis patients with renal anemia, iron and erythropoietin free (52% males, 25% diabetes mellitus) entered this prospective single center study. Serum hepcidin and erythropoietin were measured by ELISA, and ferritin, transferrin and CRP, by immunoturbidimetric methods. Transferrin saturation index (TSAT) was calculated as the percentage of serum iron from total serum iron binding capacity. Data are presented as mean (median) and 95% confidence intervals of the mean (median) and were logarithmated as appropriate for regression analysis.







Investigated parameters in the whole cohort

Parameter	Median (95% CI)
Patients number (%)	162 (100%)
Age (years)	67 (63-70)
Gender (% male)	52%
eGFR (mL/min)	14.2 (12.0-18.0)
Hb (g/dL)	9.4 (9.2-9.8)
Transferrin (mg/dL)	208 (198-217)
TSAT (%)	14.9 (12.5-17.5)
Ferritin (ng/mL)	181 (152-251)
Erythropoietin (mU/mL)	4.9 (4.3-5.9)
Hepcidin (ng/mL)	83.3 (76.3-94.5)
CRP (ng/mL)	7.6 (6.0-10.0)

Determinants of hepcidin levels

Determinants	B (95% CI)	Sig.
(Constant)	4.14 (2.75 to 5.52)	0.000
Ln (GFR)	-0.30 (-0.56 to -0.05)	0.02
Ln (Epo)	-0.36 (-0.57 to -0.14)	0.001
Ln (Ferritin)	0.28 (0.10 tp 0.46)	0.003
Adjusted R Square 0.21; p<0.0001		
Dependent variable: Ln (Hepcidin)		
Predictors: (Constant), Transferrin, Age, Ln (CRP), Ln (Epo), Ln(Hb), Ln (GFR), Ln (Ferritin)		

RESULTS

Hepcidin was higher in this cohort - of an old age (67 [63-70] years), anemic (9.4 [9.2-9.8] g/dL) with advanced CKD (eGFR 14.2 [12.0-18.0] mL/min) and only moderate inflammation (CRP 7.6 [6.0-10.0] ng/mL) - than reported in the general population (83.3 [76.3-94.5] vs. 18-22 ng/mL).

In bivariate analysis, hepcidin levels were inversely related to renal function (eGFR) and EPO levels, and directly to iron stores (ferritin) and iron available for erythropoiesis (transferrin), but not to inflammation (CPR). However, the correlations were not impressive. Thus, renal function, directly or via suppressed erythropoietin production, and iron status seem more important than inflammation in defining hepcidin levels.

The independent determinants of hepcidin levels were the decline in renal function, the decrease in erythropoietin levels and the increase in serum ferritin in a model of logistic regression which explained only 23% of hepcidin variability. To note, CRP was not retained neither in that model.

CONCLUSIONS

The increase in hepcidin levels in CKD patients is related to the decline in renal function and is probably mediated by the decreased erythropoietin production. Hepcidin seems to react adequately to iron stores, and as this reaction is independent of inflammation, high ferritin levels in CKD patients with moderate inflammation suggest iron stores repletion rather than inflammation.

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