GRONINGEN KIDNEY CENTER

C-Terminal Fibroblast Growth Factor 23, Iron Deficiency, and Mortality in Renal Transplant Recipients

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Introduction

Iron deficiency (ID) has been associated with an increased risk of all-cause mortality in renal transplant recipients (RTRs), independent of the presence of anemia. ID promotes cleavage of intact fibroblast growth factor 23 (iFGF23), which in itself is associated with adverse outcomes. We subsequently hypothesized that in RTRs, the relationship between ID and mortality is mediated by FGF23.

Methods

ID was defined as transferrin saturation (TSAT) <20 % and ferritin <300 µg/L. Plasma iFGF23 and cFGF23 (i.e. both intact FGF23 and C-terminal fragments) were measured with enzyme-linked immunosorbent assays. Multivariable Cox proportional hazards analyses were used to assess associations with all-cause mortality. Mediation analysis was performed to evaluate whether the associations between ID and mortality were mediated by FGF23.

Results

We included 700 stable RTRs (median time following transplantation, 5.4 years). Median cFGF23 concentrations were higher in iron deficient compared to non-iron deficient RTRs (223 [131 - 361] vs. 124 [88 - 180] RU/mL; p<0.001), whereas iFGF23 concentrations were similar between groups. In multivariable-adjusted Cox regression analyses, ID was associated with increased mortality (81 events; hazard ratio [HR], 1.95; 95% confidence interval [CI], 1.22-3.10; *P*=0.005). However, this association lost significance after additional adjustment for cFGF23 levels (HR, 1.45; 95%CI 0.87-2.51; *P*=0.15).

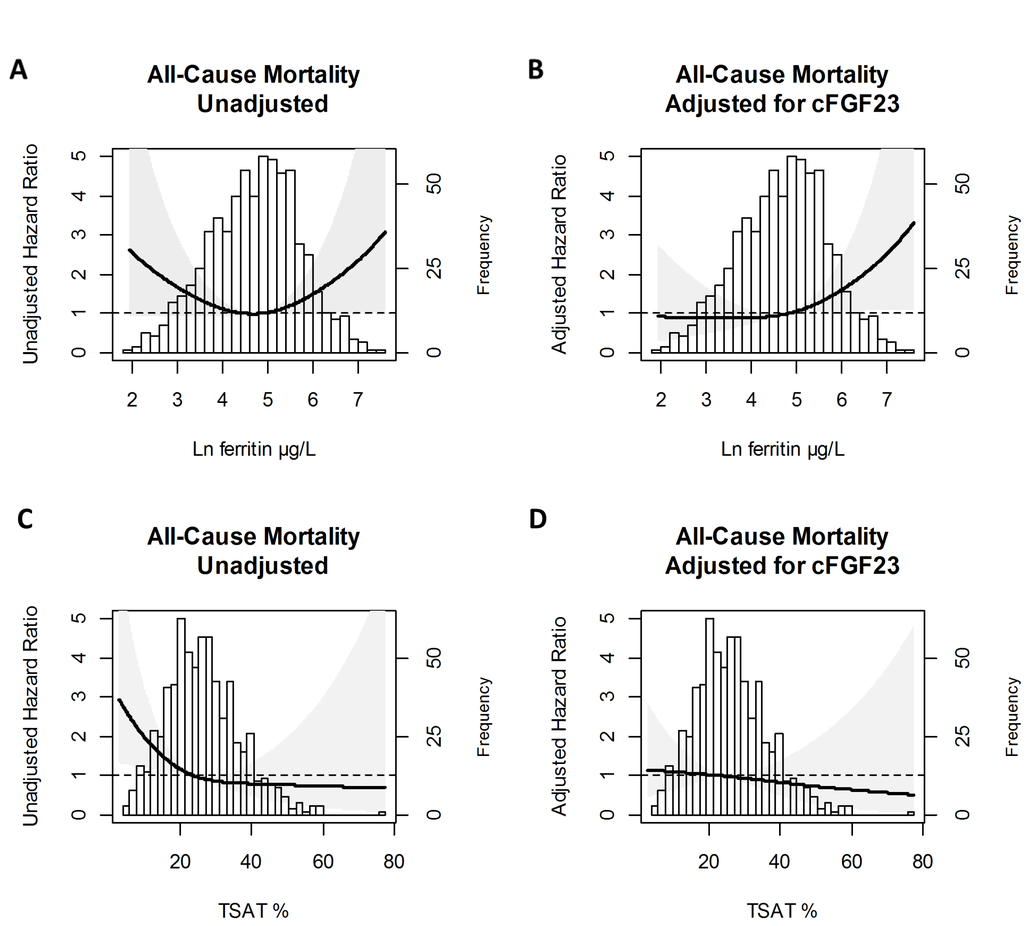
Table 1. Cox regression analysis between ID and mortality

Model	HR (95% CI)	P-value
Univariate	2.04 (1.31-3.16)	0.001
Model 1	1.94 (1.25-3.01)	0.003
Model 2	1.95 (1.22-3.10)	0.005
Model 3	1.94 (1.22-3.10)	0.005
Model 4	1.45 (0.87-2.51)	0.15

Model 1: Adjustment for age and sex;
Model 2: Model 1 + adjustment for eGFR, proteinuria, time since transplantation, primary renal disease, history of cardiovascular disease, and smoking status;
Model 3: Model 2 + adjustment for iFGF23;
Model 4: Model 2 + adjustment for cFGF23

Similar results were found for the associations between the individual iron status components and mortality (Figure 1). In mediation analysis, we found that cFGF23, but not iFGF23, explained 46% of the association between ID and all-cause mortality.
As sensitivity analyses, we repeated the Cox regression analyses between ID and mortality with adjustment for use of ACE-inhibitors or AII-antagonists, hemoglobin, acute rejection, presence of diabetes, use of iron supplements, and hs-CRP, the association remained significant between ID and mortality.

Figure 1. Associations of ferritin and TSAT with mortality, with and without adjustment for cFGF23



Models **A** and **C** are univariate analyses between serum ferritin and TSAT and all-cause mortality. Model **B** and **D** are adjusted for cFGF23.

Conclusion

We found that cFGF23 levels are increased in iron-deficient patients and that cFGF23 is an important mediator in the association of ID with all-cause mortality. Our results underline the strong relationship between iron and FGF23 physiology, and provide a mechanism explaining the relationship between ID and adverse outcome in RTRs.

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