Iron deficiency, with and without anaemia, across strata of kidney function in kidney transplant recipients

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Anaemia is highly prevalent in kidney transplant recipients (KTRs), and is associated with an increased risk of adverse outcomes [1]. Similarly, iron deficiency (ID) is highly prevalent in KTRs. The latter is attributable to a combination of multiple causes, including increased hepcidin levels and frequent use of proton-pump inhibitors, which impair iron absorption and frequent use of anticoagulants, which can stimulate iron loss [2, 3]. Until recently, ID was deemed only clinically relevant in the setting of anaemia. We, however, recently showed that ID, independent of anaemia, is associated with an increased risk of death in the patient setting of KTRs [4]. This warrants further investigation into the prevalence of ID, both with and without anaemia, and to ascertain at which stage of kidney function decline these entities become apparent. Hence, in the current study, we aimed to investigate how prevalent ID, with and without anaemia, is in KTRs across strata of kidney function and across chronic kidney disease (CKD) stages.

For this purpose, we used two separately collected cohorts from our University Medical Center in Groningen, which, respectively, include 795 KTRs [TransplantLines Biobank and Cohort Study (TxLines); NCT03272841] and 707 KTRs [TransplantLines Food and Nutrition Biobank and Cohort Study (TxLines-FN); NCT02811835] [5, 6]. The data that support the findings of this study are available from the corresponding author on reasonable request. In brief, all included KTRs, transplanted in the University Medical Center Groningen, were considered stable with a functioning graft ≥1 year beyond transplantation. All KTRs gave written informed consent and approval by institutional review board was obtained in both studies (METC 2008/186 and METC 2014/077). Both studies adhered to the principles of the declaration of Helsinki. Serum iron was measured using a colorimetric assay (all Roche Diagnostics, Mannheim, Germany). Transferrin saturation (TSAT) (%) was calculated as 100 × serum iron (μmol/L)/25 × transferrin (g/L) [7]. ID was defined as TSAT <20% and ferritin <300 μg/L [8]. Renal function was determined by estimating glomerular filtration rate (eGFR) by applying the Chronic Kidney Disease Epidemiology Collaboration equation. Anaemia was defined as haemoglobin <12 g/dL (females) and <13 g/dL (males) [9]. For the current analyses, we excluded KTRs using iron supplementation and/or erythropoietin (n = 67 in TxLines cohort; n = 50 in TxLines-FN cohort) or having missing data on iron status (n = 7 in TxLines-FN cohort), resulting in 728 KTRs and 650 KTRs, respectively. As sensitivity analyses, we used an alternative definition of ID, namely TSAT <20% and ferritin <100 μg/L [10]. Also, we compared prevalences of ID without anaemia in KTRs with those in patients having CKD and in the general population. To this end, we used the Prevention of Renal and Vascular End-stage Disease (PREVEND) study [11]. CKD was defined based on an eGFR <60 mL/min/1.73 m² or albuminuria >30 mg/24 h or albumin-to-creatinine ratio ≥30 mg/g [11]. In CKD, we used the same definitions for ID as in KTRs, whereas in the general population ID was defined as a ferritin <15 μg/L (females) and ferritin <30 μg/L (males) [12].

The baseline characteristics are described in Supplementary data, Tables S1 and S2. The TxLines cohort included 728 KTRs (mean age 56 ± 13 years; 61% males) with mean eGFR of 52.7 ± 17.6 mL/min/1.73 m² and median transplant vintage of 3.8 (1.0–10.0) years. The TxLines-FN cohort included 650 KTRs (mean age 53 ± 13 years; 59% males) with mean eGFR of 54 ± 20 mL/min/1.73 m² and median transplant vintage of 5.3 (1.8–12.0) years. Anaemia was present in 26% and 32%, ID was present in 37% and 30% and ID independent of anaemia was present in 25% and 17% of the two respective cohorts.

We found that in the TxLines cohort, across strata of kidney function, ID independent of anaemia was highly prevalent in
Anaemia and iron deficiency independent of anemia were not highly prevalent (preferentially in early CKD stages, whereas in the general population anaemia was also prominently present across strata of eGFR, whereas in the general population anaemia was also prominently present across strata of eGFR [14, 15]. Recently, we showed an association of ID have underscored the importance of ID independent of anaemia.

Studies in chronic heart failure patients have underscored the importance of ID independent of anaemia with a higher risk of death in KTRs; however, no causality can be attributed to this study due to the observational design [4]. Therefore, randomized controlled trials specifically investigating the relevance of ID independent of anaemia are eagerly needed to assess whether clinicians should be more aware of this entity.

Here, we present data that ID without anaemia in KTRs is especially prevalent in early CKD stages, that is stages I–IIIa. Further research delineating the clinical relevance of this entity seems warranted.

**SUPPLEMENTARY DATA**

Supplementary data are available at ndt online.

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**AUTHORS’ CONTRIBUTIONS**

M.F.E. was responsible for the research idea and study design, and provided supervision or mentorship. G.A., G.v.H., S.J.L.B., and M.F.E. carried out data acquisition. G.A., G.v.H., J.S.J.V., D.J.K., C.A.J.M.G., M.H.d.B., S.J.L.B., and M.F.E. performed data analysis/interpretation. G.A., G.v.H. and M.F.E. carried out statistical analysis. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual’s own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

**CONFLICT OF INTEREST STATEMENT**

J.S.J.V. received consultancy fees from Vifor Pharma. M.H.d.B. has received consultancy fees from Kyowa Kirin, Pharmacosmos, Sanofi Genzyme and Vifor Pharma (all to employer), grant support from Sanofi Genzyme and Vifor Pharma, and served the Advisory Board of Cablon Medical. M.F.E. received speakers’ and consultancy fees from Vifor Pharma and served the Advisory Board of Cablon Medical. The other authors have declared that no disclosures exist.

**REFERENCES**

1. Chhabra D, Grafals M, Skaro AI et al. Impact of anemia after renal transplantation on patient and graft survival and on rate of acute rejection. Clin J Am Soc Nephrol 2008; 3: 1168–1174
2. Douwes RM, Gomes-Neto AW, Eisenga MF et al. Chronic use of proton-pump inhibitors and iron status in renal transplant recipients. J Clin Med 2019; 8: 1382
3. Babitt JL, Lin HY. Mechanisms of anemia in CKD. J Am Soc Nephrol 2012; 23: 1631–1634
4. Eisenga MF, Minović I, Berger SP et al. Iron deficiency, anemia, and mortality in renal transplant recipients. Transplant Int 2016; 29: 1176–1183
5. Eisenga MF, Gomes-Neto AW, Van Londen M et al. Rationale and design of TransplantLines: A prospective cohort study and biobank of solid organ transplant recipients. BMJ Open 2018; 8: e024502
6. van den Berg E, Engberink MF, Brink EJ et al. Dietary acid load and metabolic acidosis in renal transplant recipients. *Clin J Am Soc Nephrol* 2012; 7: 1811–1818
7. Mercadel L, Metzger M, Haymann JP et al.; the NephroTest Study Group. The relation of hepcidin to iron disorders, inflammation and hemoglobin in chronic kidney disease. *PLoS ONE* 2014; 9: e99781
8. Eisenga MF, Van Londen M, Leaf DE et al. C-terminal fibroblast growth factor 23, iron deficiency, and mortality in renal transplant recipients. *J Am Soc Nephrol* 2017; 28: 3639–3646
9. World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. *Vitamin and Mineral Nutrition Information System (VMNIS)*. Geneva: World Health Organization, 2011
10. Locatelli F, Bárany P, Covic A et al.; ERA-EDTA ERBP Advisory Board. Kidney Disease: Improving Global Outcomes guidelines on anaemia management in chronic kidney disease: A European Renal Best Practice position statement. *Nephrol Dial Transplant* 2013; 28: 1346–1359
11. Eisenga MF, Nolte IM, van der Meer P et al. Association of different iron deficiency cutoffs with adverse outcomes in chronic kidney disease. *BMC Nephrol* 2018; 19: 225
12. Jankowich M, Elston B, Evans SK et al. Relationship of iron deficiency and serum ferritin levels with pulmonary hypertension: The Jackson heart study. *PLoS ONE* 2016; 11: e0167987
13. Sangkhae V, Nemeth E. Regulation of the iron homeostatic hormone hepcidin. *Adv Nutr* 2017; 8: 126–136
14. Anker SD, Comin CJ, Filippatos G et al. FAIR-HF trial investigators: ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med* 2009; 361: 2436–2448
15. Klip IT, Comin-Colet J, Voors AA et al. Iron deficiency in chronic heart failure: An international pooled analysis. *Am Heart J* 2013; 165: 575–582.e3

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