Nephrol Dial Transplant (2021) 36: 2342–2344
doi: 10.1093/ndt/gfab173
Advance Access publication 4 May 2021

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

Gizem Ayerdem[1,*], Gaston van Hassel[1,*], Joanna Sophia J. Vinke[1], Daan J. Kremer[1], Carlo A.J.M. Gaillard[2], Martin H. de Borst[1], Stephan J.L. Bakker[1] and Michele F. Eisenga [1]

[1]Division of Nephrology, Department of Internal Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands and [2]Division of Internal Medicine and Dermatology, University Medical Center Utrecht, University of Utrecht, Utrecht, The Netherlands

*These authors contributed equally to this work.
Correspondence to: Michele F. Eisenga; E-mail: m.f.eisenga@umcg.nl

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, ferritin using an immunoassay and transferrin using an immunoturbidimetric 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 m^2 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 m^2 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 m^2 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

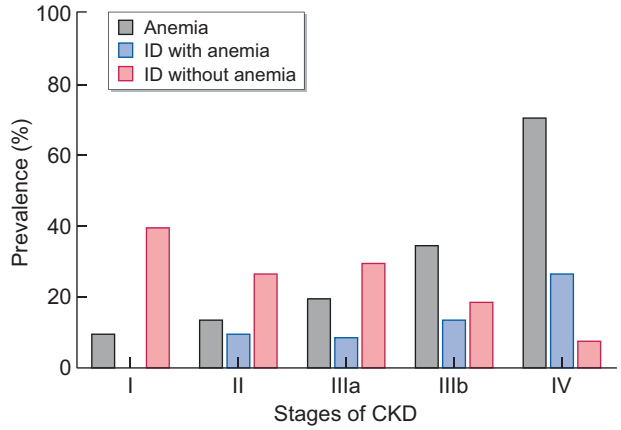

FIGURE 1: Prevalence of anaemia and ID, with and without anaemia, across CKD stages in the TransplantLines Biobank and Cohort Study (TxLines). Prevalence of anaemia is displayed as grey, anaemia in combination with ID is displayed as blue and ID without anaemia is displayed as red. CKD stage V is not shown as only five kidney transplant recipients were present in this specific group.

the early stages of CKD, with prevalences of >25% in almost all strata of eGFR 50 to >90 mL/min/1.73 m^2 (Supplementary data, Table S3). Across further degrees of kidney dysfunction, anaemia became more prevalent and presence of ID independent of anaemia decreased. Similarly, in the TxLines-FN cohort, the highest prevalence of ID independent of anaemia was present in the same group of KTRs with eGFR 50 to >90 mL/min/1.73 m^2 (Supplementary data, Table S4).

When subdividing kidney function into CKD stages, in both cohorts ID independent of anaemia was most prevalent in CKD stages I and II (Figure 1 and Supplementary data, Figure S1). In the TxLines cohort, ID, independent of anaemia, was also the most prevalent in CKD stage IIIa (Figure 1). With advancing of the CKD stage, anaemia was more prevalent, whereas the prevalence of ID without anaemia diminished.

In sensitivity analyses, using the alternative definition for ID, we found a similar pattern for ID without anaemia with higher prevalence in early stages of CKD (Supplementary data, Tables S3 and S4). In CKD patients present in the general population cohort ($n = 962$; Supplementary data, Table S5), ID without anaemia was also prominently present across strata of eGFR, preferentially in early CKD stages, whereas in the general population ($n = 5182$; Supplementary data, Table S6) ID without anaemia was not highly prevalent (≤5% across strata of eGFR 60 to >90 mL/min/1.73 m^2).

In this study, we show that ID independent of anaemia is highly prevalent in KTRs, with particularly high prevalence at early stages of CKD and frequencies approaching 25% of the population. At lower degrees of kidney function, anaemia becomes more overt and ID without anaemia is less frequently encountered. It should be kept in mind that anaemia is an end stage of depleted iron stores, and that besides erythropoiesis iron plays a pivotal role in many cellular processes, including synthesis of DNA, electron transport and cellular proliferation and differentiation [13]. Studies in chronic heart failure patients have underscored the importance of ID independent of anaemia [14, 15]. Recently, we showed an association 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 present 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.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

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, Bárány 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

Received: 25.11.2020; Editorial decision: 9.4.2021