

Narrative Review of Hyperferritinemia, Iron Deficiency, and the Challenges of Managing Anemia in Aboriginal and Torres Strait Islander Australians With CKD



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Aboriginal and Torres Strait Islander Australians (Indigenous Australians) suffer some of the highest rates of chronic kidney disease (CKD) in the world. Among Indigenous Australians in remote areas of the Northern Territory, prevalence rates for renal replacement therapy (RRT) are up to 30 times higher than national prevalence. Anemia among patients with CKD is a common complication. Iron deficiency is one of the major causes. Iron deficiency is also one of the key causes of poor response to the mainstay of anemia therapy with erythropoiesis-stimulating agents (ESAs). Therefore, the effective management of anemia in people with CKD is largely dependent on effective identification and correction of iron deficiency. The current identification of iron deficiency in routine clinical practice is dependent on 2 surrogate markers of iron status: serum ferritin concentration and transferrin saturation (TSAT). However, questions exist regarding the use of serum ferritin concentration in people with CKD because it is an acute-phase reactant that can be raised in the context of acute and chronic inflammation. Serum ferritin concentration among Indigenous Australians receiving RRT is often markedly elevated and falls outside reference ranges within most national and international guidelines for iron therapy for people with CKD. This review explores published data on the challenges of managing anemia in Indigenous people with CKD and the need for future research on the efficacy and safety of treatment of anemia of CKD in patients with high ferritin and evidence iron deficiency.

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KEYWORDS: Aboriginal and Torres Strait Islander Australians; anemia; chronic kidney disease; ESKD and dialysis; ferritin; Indigenous Australians; iron deficiency; hyperferritinemia

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Aboriginal and Torres Strait Islander Australians (herein respectively referred to as Indigenous Australians) suffer some of the highest rates of chronic kidney disease (CKD) in the world. Among Indigenous Australians in remote areas of the Northern Territory, prevalence rates for renal replacement therapy (RRT) are up to 30 times higher than national prevalence.^{1–4} Anemia among patients with CKD is a common complication, and iron deficiency is one of the major causes. Iron deficiency is

also one of the key causes of poor response to the mainstay of anemia therapy with erythropoiesis-stimulating agents (ESAs). Therefore, the effective management of anemia in people with CKD is largely dependent on effective identification and correction of iron deficiency.

The current identification of iron deficiency in routine clinical practice is dependent on 2 surrogate markers of iron status: serum ferritin concentration and transferrin saturation (TSAT)—the ratio of serum iron to the total iron-binding capacity as a percentage. However, questions exist regarding the use of serum ferritin concentration in people with CKD because it is an acute-phase reactant that can be raised in the context of acute and chronic inflammation. Serum ferritin concentration among Indigenous Australians receiving RRT is often markedly elevated⁵ and falls outside reference ranges

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Table 1. Guidelines on target levels of markers of iron status in people with CKD

Guidelines	Continent	Ferritin (µg/l)	TSAT (%)
Canadian Renal Guidelines	Canada	100–500	>20
KDIGO	Worldwide	100–500	>20
ERA–EDTA	Europe	200–300	30–50
CARI	Australia and New Zealand	200–500	30–40
KDOQI	United States	200–500	30–50
UK Renal Association/NICE	United Kingdom	250–500	>20
Japanese Society for Dialysis therapy	Japan	100–300	>20

CARI, Caring for Australasians with Renal insufficiency; CKD, chronic kidney disease; ERA–EDTA, European Renal Association–European Dialysis and Transplant Association; KDIGO, Kidney Disease: Improving Global Outcomes; KDOQI, Kidney Disease Outcome Quality Initiative; NICE, National Institute for Health and Care Excellence; TSAT, transferrin saturation.^{5,22}

The NICE guidelines also recommend offering people with anemia of CKD who are receiving ESAs iron therapy to achieve percentage hypochromic red cell less than 6% (unless ferritin is greater than 800 µg/l) and reticulocyte hemoglobin count or equivalent tests higher than 29 pg (unless serum ferritin is greater than 800 µg/l).

within most national and international guidelines for iron therapy for people with CKD.

Anemia—A Major Complication of CKD

Anemia, a major complication of CKD, is associated with reduced quality of life, increased risk of cardiovascular disease, hospitalizations, cognitive impairment, and mortality.^{6–10} The 2 main causes of anemia in people with CKD are insufficient erythropoietin production by the failing kidneys and/or absolute or functional iron deficiency.^{6,11} The prevalence of anemia in CKD varies from less than 10% in those with stage 1 CKD to more than 50% in those with end-stage kidney disease (ESKD) or on dialysis (Stages 5/5D CKD).^{12,13} ESAs are the main agents for correcting anemia in people with CKD^{14–16} and work most effectively when the patient is replete in iron stores.^{15,17–19} Iron deficiency and its effective identification using current biomarkers and effective administration and use of iron is one of the commonest causes of poor response to ESA therapy.^{20,21}

The effective treatment of anemia in CKD patients therefore requires both the accurate determination of iron status and a safe and effective correction of iron deficiency to achieve and maintain a target hemoglobin level of 100–115 g/l.²² This will ensure avoidance of overtreatment resulting in iron overload, minimize continuing anemia from undertreatment of iron deficiency, and limit inadvertent iron infusions in patients with infections, which can aid bacterial replication.²³

As shown in Table 1, in international clinical practice guidelines on renal anemia management, recommendations regarding iron management are largely dependent on the levels of serum ferritin and TSAT.^{22,24–27} However, the guidelines do not address

variations within populations across these continents, be they ethnicity-based, geographical, social, or environmental.

Iron in CKD

As humans have no endogenous mechanisms for making iron, dietary intake is the only source of iron.²⁸ Therefore, humans need to replace losses of iron by maintaining adequate dietary intake of iron-rich foods such as vegetables and meats. Inadequate access to foods rich in iron in patients with chronic conditions, inflammation, and infections increases the risk of iron deficiency.^{28,29}

In people with CKD, the following are the major causes of iron deficiency in dialysis patients: (i) blood loss for laboratory tests, aggravated by hospitalizations; (ii) gastrointestinal losses (may be exacerbated by systemic anticoagulation during dialysis, and/or the use of maintenance oral anticoagulants or antiplatelet drugs used for the treatment or prevention of cardiovascular disease); (iii) blood losses associated with the hemodialysis procedure, including dialyzer blood loss and blood loss from the arteriovenous fistula or graft puncture site and from catheters; (iv) reduced intestinal iron absorption, at least in part due to increased hepcidin levels, and medications (e.g., proton pump inhibitors and calcium-containing phosphate binders); (v) reduced intake due to poor appetite, malnutrition, and dietary advice (e.g., protein restriction); and (vi) functional iron deficiency that is due to increased levels of hepcidin blocking the release of iron from stores and the reticuloendothelial system despite adequate iron stores.^{11,17,30}

Effective treatment of anemia in patients with CKD is associated with improved quality of life, cardiovascular function, and improved survival.³¹ As described above, effective treatment includes identification and correction of iron deficiency and the use of ESAs as necessary.²² Correction of iron deficiency and maintenance of an iron-replete state are, therefore, key to managing the anemia of CKD.^{14,22,24,17}

Ferritin—More Than a Marker of Iron Status

Ferritin is an intracellular protein that stores excess iron,³² and low serum ferritin is correlated with iron deficiency.^{32,33} However, ferritin is also an acute-phase protein, and increased serum ferritin concentrations, along with increases in other inflammatory markers such as C-reactive protein (CRP), is observed in patients who have inflammation.^{32,34,35} There is also accumulating evidence that high serum ferritin concentrations are independently associated with high rates of hospitalizations,^{36,37} cardiovascular disease,^{38–40} metabolic syndrome,^{41–44} and mortality⁴⁵ (Figure 1).

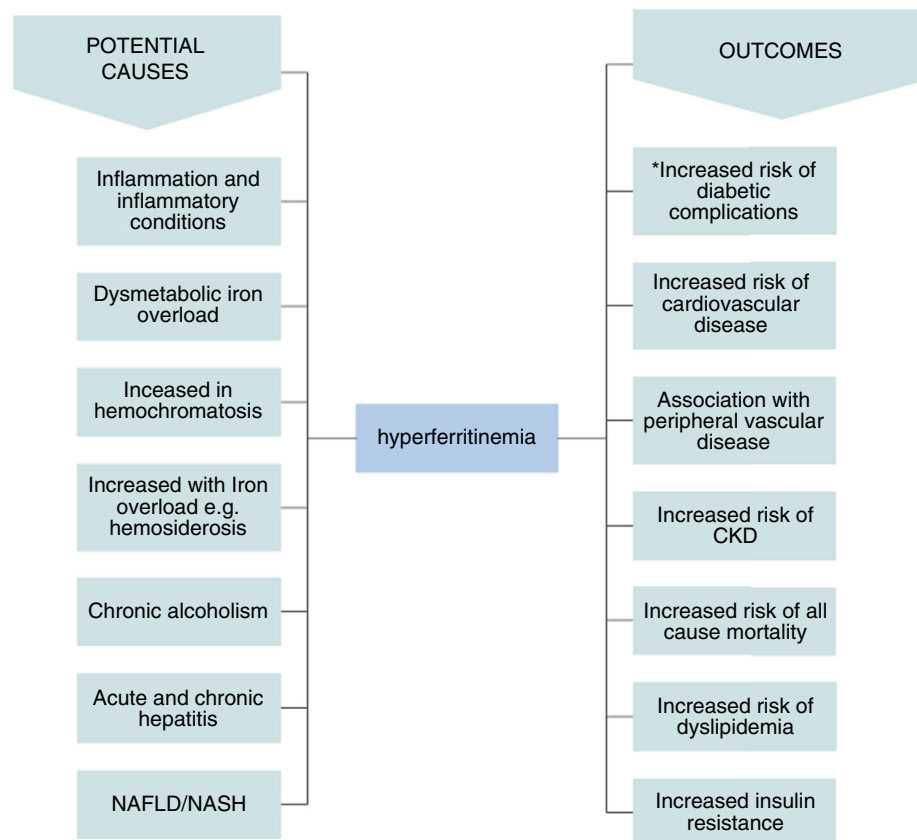


Figure 1. Associations of high serum ferritin concentrations in patients with chronic kidney disease (CKD). *There is conflicting evidence on this association, with some studies suggesting high serum ferritin as associated and others suggest no association. NAFLD/NASH, nonalcoholic fatty liver disease / nonalcoholic steatohepatitis.

Our work, and that of other researchers, has shown that iron deficiency, hyperferritinemia, and evidence of recurrent infection and/or inflammation coexist among adult Indigenous Australians, particularly in those with dialysis-dependent ESKD.^{5,46-48}

Challenges With Measuring Serum Ferritin Concentrations in Patients With CKD

There is no gold standard assay for measuring serum ferritin. Immunoassay methods are typically available to measure serum or plasma ferritin. These immunoassays could be broadly categorized into radiometric, nonradiometric, and agglutination assays. To improve the comparability between assays, the World Health Organization (WHO) Expert Committee on Biological Standardization established international reference materials.⁴⁹⁻⁵¹ The WHO recommendation is that one method does not appear to be superior to another and that all methods are acceptable if a commutable material traceable to the WHO international reference standard is used to calibrate the assay. However, their strong recommendation is that once a method has been selected, that same method should be used for the follow-up of individuals and populations. A recent systematic review assessing the performance and

comparability of laboratory methods for measuring ferritin concentrations in human serum or plasma concluded that laboratory methods most used to determine ferritin concentrations have comparable accuracy and performance.⁵⁰ This heterogeneity in ferritin measurement methods creates challenges in clinical decisions in iron deficiency and overload. The challenges are further accelerated in inflammatory states and in people with CKD where levels of serum ferritin are generally higher than the reference ranges determined by the WHO. Performance of different methods need to be evaluated to determine clinical decision limits in people with CKD.

High Prevalence of CKD, Anemia, and Inflammation Among Indigenous Australians of the Northern Territory

ESKD prevalence rates in Indigenous Australians are more than 6 times those for non-Indigenous Australians and, in remote areas, are up to 30 times higher than the national average^{4,52,53} (Figure 2). ESKD impacts Indigenous Australians at a younger age and disproportionately affects women.^{4,52} In the Northern Territory (NT), demand for dialysis treatment and the associated expenditure has increased relentlessly over

Prevalence of dialysis-dependent patients by state, 1998–2018

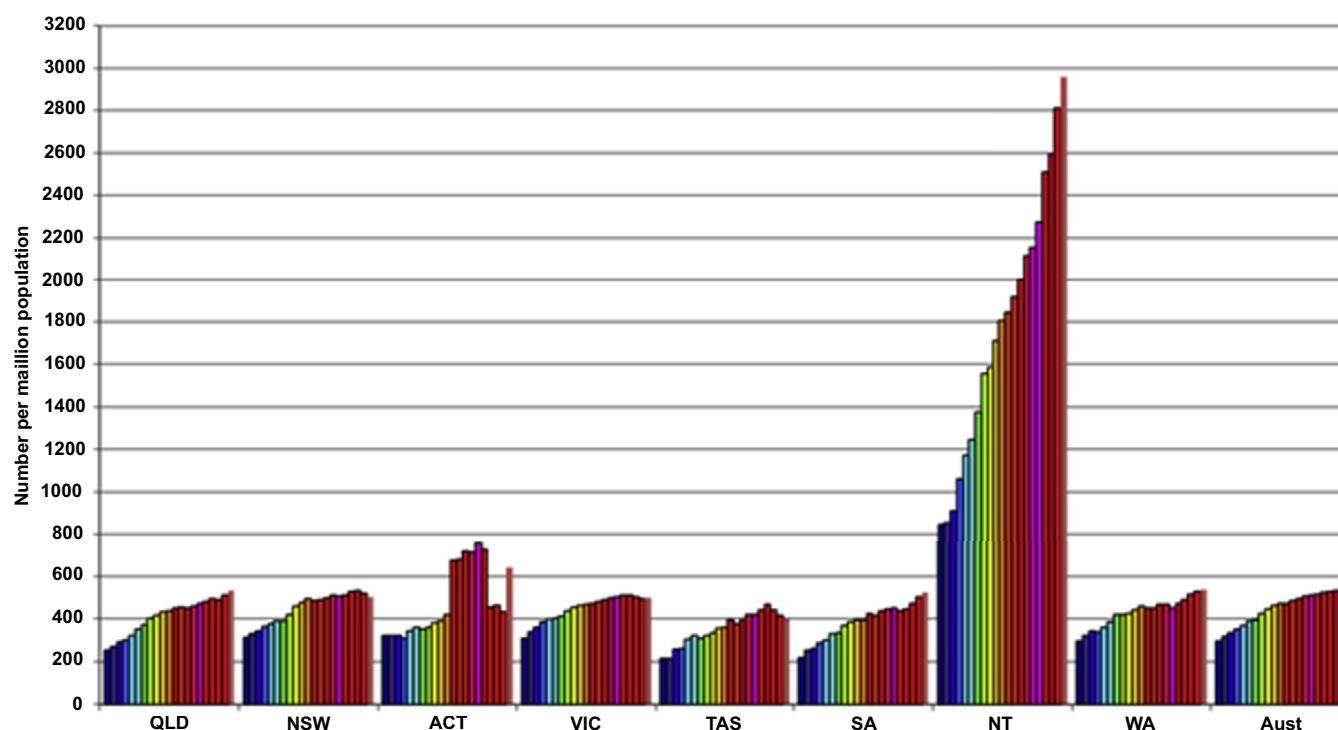


Figure 2. The prevalence of dialysis requiring end-stage kidney disease showing rates of between 1800 and 2000 per million population in the NT. Each bar represents the year from 1998 to 2018. ACT, Australian Capital Territory; Aust, Australia; NSW, New South Wales; NT, Northern Territory; QLD, Queensland; SA, South Australia; TAS, Tasmania; VIC, Victoria; WA, Western Australia

recent decades.⁵⁴ Admission for dialysis treatment comprises 50% of all NT hospital admissions.⁵⁴

Anemia is also common among Indigenous Australians, with prevalence rates higher than 50% in some cases associated with chronic illness.^{55,56} Evidence from our work and other researchers has shown the coexistence of iron deficiency, evidence of recurrent infection, and/or inflammation in adult Indigenous Australians particularly in those with dialysis dependent ESKD.^{5,46–48,55,57,58}

Inflammation is also common among Indigenous Australians with chronic conditions.^{59–62} The high prevalence of chronic inflammation among those with CKD is associated with major adverse clinical outcomes such as all-cause hospitalizations and cardiovascular events.^{63–67}

High Prevalence of Iron Deficiency Anemia Among Indigenous Australians in the NT

Several studies have shown high prevalence of iron deficiency in Indigenous children and young people across Australia.^{68,69} Evidence also suggests that iron deficiency is the most common cause of anemia in Indigenous Australians of all ages⁷⁰ and that anemia is common among Indigenous people of Northern Australia and is likely to be highly prevalent in those

with CKD.^{57,71} Data from the Australian Bureau of Statistics suggest that prevalent rates of iron deficiency anemia among adults are as high as 7.6%, which is twice that of non-Indigenous Australians, and rates can be as high as 29.6% among those with diabetes and CKD.⁷² This is thought to be driven mainly by nutritional factors and infectious disease. Evidence suggests that Indigenous Australians with advanced CKD or ESKD are likely to have higher risk of iron deficiency anemia.^{55,57} This may account, in part, for the high resistance to ESA therapy we observed in a recent study.⁵

Measurement of Iron Status in People With CKD

The most accurate and direct measurement of human iron stores is achieved by directly measuring the level of iron in bone marrow biopsy and/or liver biopsy.⁷³ However, these are invasive high-risk procedures that are rarely used in clinical practice. As a result, surrogate measures of iron stores have been used in clinical practice since the 1970s.^{32,74}

The combination of serum ferritin levels and TSAT is used worldwide in renal anemia management guidelines (Table 1). Low TSAT and low serum ferritin are indicative of iron deficiency.^{17,75} However, recent published evidence suggests that TSAT is a better marker of iron status than ferritin and is more

Table 2. Current protocol for iron infusion in hemodialysis patients in renal units across the Northern Territory of Australia

Regimen	Iron studies result	IV iron dose
A	TSAT <25 and Ferritin <500 (notify doctor before administering a third consecutive regime A)	Iron 200 mg 3 times/wk over 14 d (total 6 doses) (repeat iron studies 2 weeks post sixth dose—withdraw iron until results known)
B	TSAT <25 and ferritin <1000	Iron 200 mg weekly
C	TSAT 26–50 and ferritin <1000	Iron 100 mg weekly
D	TSAT <50 and ferritin <1500	Iron 50 mg weekly
E	TSAT >50 and or ferritin >1500 with normal CRP	No replacement
F	TSAT >50 and or ferritin >1500 with elevated CRP	Withhold and repeat iron studies after 14 d without receiving iron

1. Measure iron studies and CRP 3-monthly.
2. Withhold IV iron 14 d before iron studies and 14 d post blood transfusion.
3. Ferritin > 1500 no iron replacement.

CRP, C-reactive protein; IV, intravenous; TSAT, transferrin saturation.

Units of TSAT as a percentage, ferritin in micrograms per liter, elevated CRP >20 mg/dl.

predictive of the response to treatment of anemia in maintenance hemodialysis (MHD) patients.^{74,76}

Standard clinical care recommends therapeutic supplementation of iron for CKD patients until pre-determined targets of these measures are achieved. Internationally, the target levels vary (Table 1). There are no recommendations to vary targets according to ethnic groups.

Uncertainty Regarding the Use of Serum Ferritin Levels as a Marker of Iron Status in Indigenous Australians

Low serum ferritin is a marker of iron deficiency.^{24,32,74,77,78} However, as an acute-phase protein, increased serum ferritin concentration, along with increases in other acute-phase reactants such as CRP, is observed in patients who have inflammation.^{35,67,79}

Therefore, there is uncertainty regarding the usefulness of serum ferritin as a marker of iron stores in states of chronic inflammation and chronic infections. As a result of this uncertainty, a clinical practice guideline from the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom discourages the use of either ferritin or TSAT alone to determine iron status in people with CKD although several expert opinions have suggested revising this such that if serum ferritin is low, this alone is sufficient to confirm iron deficiency and the need for therapy.²⁴

Among Indigenous Australians on MHD, a population known to have a heavy burden of cardiovascular and infectious diseases, hospitalizations, and premature mortality,⁸⁰ we have shown that anemia coexists with ESA therapy hyporesponsiveness, hyperferritinemia, and high serum CRP.^{5,46} High serum ferritin levels have been recognized in this population for almost 20 years. Given the coexistence of chronic conditions, chronic inflammation, and hyperferritinemia, there is significant

clinical uncertainty regarding the appropriate management of anemia in Indigenous CKD and ESKD patients.

NT Renal Services have developed an iron management protocol to guide iron replacement that addresses the particular burden of comorbidities seen within the NT dialysis population. There are no other iron management protocols in Australia or internationally that address the safe use of iron in CKD and ESKD patients with high serum ferritin levels above 500 µg/l associated with low TSAT (Table 2).

In a study of the effectiveness of this protocol in correcting iron deficiency in 197 NT patients on MHD, we found patients were poorly responsive to ESA treatment and received higher annual doses of iron treatment both in absolute terms and relative to the hemoglobin response.⁵ Furthermore, in another cohort of more than 1500 NT patients on MHD, we showed that high serum ferritin levels in Indigenous patients were only partly explained by iron sufficiency as indicated by low TSAT.⁴⁶ However, because of the retrospective study design, we could not determine whether iron overload, which is a clear risk in this situation, was also present. Despite this, the higher iron doses observed suggest iron overload is a potential harm. We concluded that the administration of iron among Indigenous patients on MHD with hyperferritinemia needs to be prospectively studied to avoid adverse infections,⁴⁸ cardiovascular, and clinical outcomes associated with iron overload.^{5,46}

The 2 studies also showed a lack of correlation between serum ferritin and CRP. This lack of correlation raises the question whether hyperferritinemia observed in Indigenous patients with CKD/ESKD may be explained by factors other than inflammation.^{5,46}

Other Measures of Iron Status

The uncertainty regarding the use of serum ferritin levels to guide iron therapy in patients with hyperferritinemia raises questions regarding whether other measures of iron status should be considered.⁵ These include percentage hypochromic red cells,⁸¹ reticulocyte hemoglobin content (CHr),⁸² soluble transferrin receptor (sTfR),⁸³ and hepcidin.⁸⁴

Overall, the CHr is a better predictor of response to intravenous (IV) iron treatment and has less variability than ferritin and TSAT especially in states of inflammation, resulting in better diagnostic accuracy for iron status.^{74,82} CHr is approved both in the United States and Europe as marker of functional iron deficiency with a diagnostic threshold of 29 pg. It has one of the best specificities of greater than 90%. The NICE guidelines suggest using CHr as it is also available on most analyzers in the laboratories. However, there is no agreed value that provides the best balance between its sensitivity and specificity. In the context of our

patients with high serum ferritin, CHr may still provide better interpretation of iron status.

Although the percentage hypochromic red cell measure produces comparable or somewhat better results than CHr, samples need to be analyzed on site by the laboratory technician, which may affect reproducibility of measures between and within individuals, making its widespread adoption difficult in our setting where most samples need transporting to laboratories at distant sites.

sTfR levels are not affected by inflammation.⁸⁵ This may suggest sTfR as the best marker in our setting.⁸⁵ However, sTfR is very sensitive to erythropoiesis and can be affected by administration of ESAs. This raises uncertainty for its use in determining iron status in patients receiving these drugs.⁸⁶ It may still be useful in those not yet receiving ESAs as part of an evaluation to determine the baseline for subsequent iron therapy. Ritchie et al showed that sTfR was a more reliable adjunctive measure of iron status than serum ferritin in Aboriginal children in tropical Australia.⁵⁸ This needs to be explored in our CKD and hemodialysis patients, most of whom are Indigenous.

Hepcidin, a protein synthesized by the liver, regulates both absorption of iron from the intestine and release of intracellular iron into plasma from the reticuloendothelial cells following recycling of erythrocytes. It reduces the expression of ferroportin, a regulating protein for cellular iron export. Hepcidin-25 synthesis is enhanced by iron itself and by inflammation, and is downregulated by anemia, hypoxia, bleeding, iron deficiency, erythropoietin, and increased medullary erythropoiesis.^{74,87} As a key regulator of iron homeostasis, it would be an ideal measure. However, its use is not readily available in clinical practice, and current available assays for measuring blood levels of hepcidin have high variability and at present are not useful in the clinical setting because of this variability.⁸⁸ Studies suggest that its use may be mainly limited to distinguishing simple functional iron deficiency from those with reticuloendothelial blockade.⁸⁹ Its potential use in our patients needs to be explored. However, some studies have shown no correlation between hepcidin levels and other markers of iron stores and function, casting doubt on its potential usefulness in hemodialysis patients.⁷⁴

The use of these measures in patients with CKD and MHD from the NT is unknown. Assessing their potential use may provide additional certainty regarding the safe use of iron in our patients.

Other Recognized Causes of Raised Ferritin Beyond Inflammation

In addition to inflammation, the classical causes of hyperferritinemia include chronic alcoholism, acute

and chronic hepatitis, dysmetabolic syndrome (often associated with dysmetabolic iron overload or nonalcoholic fatty liver disease / nonalcoholic steatohepatitis), genetic hemochromatosis, and secondary hemosiderosis.^{90,91} Confirmation of causes of hyperferritinemia in CKD and ESKD requires further evaluation.^{5,46} One potential and unexplored cause is the association with metabolic syndrome and type 2 diabetes mellitus in Australian Indigenous patients.^{41,43,44,92,93} Metabolic syndrome and diabetes are highly prevalent conditions among Indigenous ESKD patients,⁹⁴ but the association with raised serum ferritin has not been investigated. Examining the association of ferritin with more specific inflammatory markers such as interleukin-6 (IL-6), tumor necrosis factor receptor 1 (Tnfr1), serum tumor necrosis factor (TNF) alpha, and interleukin-1 (IL-1) will help to confirm if the ferritin is due to causes other than inflammation. The potential association of hyperferritinemia, liver function, and progression of CKD also needs investigation (Figure 1).

Iron Overload and Other Clinical Outcomes in CKD and ESKD Patients With High Serum Ferritin

The liver is the main site of iron storage, and liver iron concentration is a valuable marker of total body iron stores, which can be measured noninvasively and accurately by quantitative magnetic resonance imaging in iron overload disorders including dialysis patients.^{95,96} Recent studies of liver iron stores in dialysis patients by quantitative magnetic resonance imaging and susceptometry have revealed a high frequency of radiologic hemosiderosis (affecting up to 66% of the 500 dialysis patients in a pooled analysis of 11 published radiologic studies on liver iron concentration), therefore questioning the potential hazards of routine indiscriminate administration of high-dose IV iron in this setting.^{97,98}

A recent study showed that serum ferritin level of 200–500 µg/l correctly reflected liver iron stores as assessed by magnetic resonance imaging in hemodialysis patients without overt inflammation or malnutrition. The authors concluded that the results strongly suggest that current ferritin target values should be lowered to avoid iron overload.⁹⁹ However, ferritin levels in their patients were much lower than in our Indigenous MHD patients.

Another study had the contrasting conclusion that transferrin saturation and serum ferritin levels were poor markers of liver and cardiac iron deposition in MHD subjects.¹⁰⁰ The authors recommended that in patients with high serum ferritin receiving iron

treatment, it will be crucial to monitor iron overload by measuring liver iron.^{100,101}

Some studies have shown that iron treatment is associated with adverse effects especially if doses of >1000 mg are administered over ≤ 6 months.¹⁰² These include increased infection,¹⁰³ cardiovascular complications, and hospitalizations.²⁵ In 32,435 hemodialysis patients in 12 countries in the Dialysis Outcomes and Practice Patterns Study, compared with average IV iron doses of 100–199 mg/mo (the most common dose range), case mix-adjusted mortality was similar for the 0-, 1–99-, and 200–299-mg/mo categories but significantly higher for the 300–399-mg/mo (hazard ratio [HR] 1.13, 95% confidence interval [CI] 1.00–1.27) and ≥ 400 -mg/mo (HR 1.18, 95% CI 1.07–1.30) groups. Associations with cause-specific mortality (cardiovascular, infectious, and other) were generally similar to those for all-cause mortality. The hospitalization risk was elevated among patients receiving ≥ 300 mg/mo compared with 100–199 mg/mo (HR 1.12, 95% CI 1.07–1.18). The recommendation from this study was that a well-powered clinical trial to evaluate the safety of different IV iron-dosing strategies in hemodialysis patients was urgently needed.¹⁰⁴

However, a recent large clinical trial, the PIVOTAL study, indicated that high doses of IV iron of up to 3164 mg per annum were safe and efficacious. This trial was a multicenter, open-label noninferiority trial with blinded endpoint evaluation, which randomized 2141 UK hemodialysis patients either to high-dose IV iron-sucrose originator (Venofer; $n = 1093$ patients) or to low-dose IV iron-sucrose originator (Venofer; $n = 1048$) for a median follow-up of 2.1 years. In the group with high-dose iron, Venofer was given in a proactive fashion: patients were scheduled to receive 400 mg/mo of iron-sucrose originator, up to a ferritin level of 700 ng/ml or a transferrin saturation $\geq 40\%$, whereas patients in the low-dose iron group were administered Venofer (0–400 mg monthly) in a reactive fashion aimed at maintaining ferritin >200 ng/ml or a transferrin saturation >20%. The primary endpoint was a composite of nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or death, whereas secondary endpoints included death, infection rate, and ESA dose. The trial demonstrated noninferiority ($P < 0.001$) with a slight superiority ($P = 0.04$) related to fewer cardiovascular events (fatal and nonfatal myocardial infarction; HR 0.69, 95% CI 0.52–0.93) or hospitalizations for cardiac failure (HR 0.66, 95% CI 0.46–0.94). The trial also confirmed that maintenance iron therapy was better than an iron loading strategy for sparing ESA requirements (–19.4%). Interestingly, the trial also confirmed the lack of toxicity in dialysis patients of IV iron

dosages <300 mg/mo, as shown by DOPPS. Patients enrolled in the proactive high-dose arm received an average monthly dose of 264 mg (interquartile range 200–336 mg) whereas patients in the low-dose reactive arm received 145 mg monthly during the trial (interquartile range 100–190 mg).¹⁸ However, this landmark clinical trial was mainly in Europeans and excluded patients with serum ferritin >700 $\mu\text{g/l}$.¹⁸

High serum ferritin is also an independent predictor of mortality, cardiovascular disease, and hospitalizations.^{36,40,105} NT patients on MHD for ESKD are already at high risk of infections such as high rates of melioidosis during the wet season and cardiovascular disease.^{47,48}

Current Treatment of ESKD Patients With Anemia, High Ferritin, and Low TSAT

As outlined above, the paucity of published evidence has motivated the development of the current NT iron management protocol to guide the safe administration of iron in MHD patients with serum ferritin levels >500 $\mu\text{g/l}$ associated with low TSAT (Table 2). The evidence from our 2 recent studies suggests that even this protocol may be contributing to higher and potentially harmful total doses of iron in NT patients on MHD.^{5,46}

Patients with anemia, TSAT <30%, and serum ferritin levels <500- $\mu\text{g/l}$ levels fall within national and international guidelines. They are treated with ESA and iron therapy to maintain hemoglobin between 100 and 115 g/l, a ferritin of 200–500 $\mu\text{g/l}$, and TSATs of 20%–30%.^{17,26,27}

In patients with high serum ferritin >500 $\mu\text{g/l}$, most guidelines discourage iron administration.^{16,22} The only evidence for iron administration under these circumstances is from 2 small clinical studies from North America, only one of which was a randomized controlled trial.^{106,107} The Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE) study evaluated the safety and efficacy of IV iron therapy in anemic hemodialysis patients treated with epoetin, who had higher serum ferritin levels, but low to normal TSAT. The DRIVE study was an open label study, which randomized 134 patients to an IV iron group and a control group (62 patients in each group). The primary outcome was the difference between treatment groups in hemoglobin change from baseline to week 6. They also assessed the safety of administration of iron. This study showed that the IV administration of ferric gluconate (125 mg for 8 treatments) was superior to no iron therapy in anemic dialysis patients receiving adequate epoetin dosages with a ferritin 500–1200 ng/mL and TSAT $\leq 25\%$.¹⁰⁶ In our patient population,

however, only 5.6% of the Indigenous patients would fit the entry criteria for the DRIVE study.⁵

The follow-up DRIVE II study was a 6-week observational extension of DRIVE comparing the extended effects of ferric gluconate or no iron on epoetin doses and the mean change between treatment groups in hemoglobin from the end of DRIVE to the end of DRIVE II. They concluded that ferric gluconate maintained target hemoglobin and allowed lower ESA doses in anemic hemodialysis patients with low TSAT and high serum ferritin levels up to 1200 ng/mL.^{106,107} These 2 studies partly informed the development of the current NT treatment protocol, which was tailored to the high levels of serum ferritin in NT MHD patients (Table 2). This review of evidence re-emphasizes the current lack of evidence to guide treatment in our patient population because of the hyperferritinemia.

A recent epidemiologic study analyzed the influence of 5 commonly used strategies of iron utilization (a set of decision rules with levels of iron status tests and corresponding iron dosing approaches) including very high dosage of IV iron inspired by DRIVE in US patients in a cohort of 18,697 USRDS patients who started hemodialysis between 2009 and 2012. The authors analyzed mortality and infection-related hospitalization in a dynamic Cox marginal structural model, after multiple adjustments for factors contributing to strategy initiation and deviation. When compared to the strategy that recommended less intensive treatment at lower ferritin levels, strategies using a large amount of iron at high levels of ferritin and transferrin saturation inspired by the DRIVE trial demonstrated an increased risk of all-cause mortality (60-day risk difference: 1.3% [0.8%–2.1%]; 120-day risk difference: 3.1% [1.0%–5.6%]). These strategies with high IV iron use inspired by the DRIVE trial were also associated with an elevated risk of infection-related morbidity and mortality.¹⁰⁸

Rationale for Studies to Assess the Causes of Hyperferritinemia and Generate Evidence Regarding Safety and Efficacy of Iron Therapy in Indigenous Australians With CKD

There is a strong rationale for assessing the potential causes and associations of hyperferritinemia in Indigenous patients with CKD/ESKD as uncertainty persists regarding its use as a measure of iron status:

- (i) Anemia is particularly common among Indigenous ESKD patients from the NT. Iron deficiency, highly prevalent among Indigenous Australians, causes poor response to ESAs. The accurate diagnosis of iron deficiency depends on serum ferritin levels. However, the coexistence of hyperferritinemia,

inflammation, and chronic infections complicates the diagnosis of iron deficiency in Indigenous patients with CKD/ESKD. Evidence-based guidelines are needed to support best practice clinical care in CKD/ESKD patients with hyperferritinemia. Serum ferritin levels and TSAT, which are used to guide iron treatment, might be inadequate as measures of iron status. Evidence from our recent studies showed that a significant number of Indigenous patients on MHD are not adequately treated for anemia due to hyperferritinemia, and there is associated uncertainty regarding the benefits and harms of treatment.^{5,46} The best available RCT evidence guiding iron therapy in patients with high ferritin cannot be applied to treatment of NT Indigenous patients. Only approximately 1 in 20 of our Indigenous patients would fit entry criteria for these studies.^{106,107}

- (ii) There are significant risks of adverse outcomes in Indigenous patients receiving iron. The high iron dose received and the hyperferritinemia may predispose patients to bacterial infections, cardiovascular disease and metabolic syndrome observed in Indigenous patients with CKD/ESKD.
- (iii) Examining the association of hyperferritinemia and biomarkers of inflammation with progression of CKD to ESKD and clinical outcomes such as cardio/peripheral vascular disease, infections, and hospitalizations will further improve the understanding of the clinical significance of the hyperferritinemia.
- (iv) Studies assessing the performance and comparability of the different ferritin measurement methods in people with CKD are also needed.
- (v) Considering the high prevalence of diabetes mellitus and metabolic syndrome in this Indigenous Australian population, we may hypothesize a high prevalence of hepatic steatosis as encountered in dialysis patients more and more frequently in developed countries as well as dysmetabolic iron overload.^{109,110} There is a need to identify those patients with these underlying liver diseases, to adapt iron dosage and to monitor the safety of IV iron in this setting. This peculiar safety issue seems particularly relevant since indiscriminate IV iron has recently been shown to either trigger or aggravate NAFLD in dialysis patients suggesting a double-edged iron sword.^{111,112}
- (vi) MRI-R2* Relaxometry, using multipeak fat spectral modeling (General Electric: IDEAL-IQ), has recently been shown to accurately measure hepatic iron load in dialysis patients by comparison with quantitative histology. This suggests that MRI-R2* Relaxometry with multipeak fat spectral modeling could be particularly useful in the population of

Indigenous Australians for decision, choice, and follow-up of iron therapy. This will need evaluation in future studies.⁹⁶

Conclusions

A significant evidence gap exists, and there is clinical equipoise or uncertainty regarding the potential benefits or harms of iron therapy in Indigenous ESKD patients with hyperferritinemia. We need to explore the clinical significance of high serum ferritin levels and generate clear evidence to guide clinical decision making regarding the need for iron therapy.

DISCLOSURE

All the authors declared no competing interests.

REFERENCES

- Li L, Guthridge S, Li SQ, et al. Estimating the total prevalence and incidence of end-stage kidney disease among Aboriginal and non-Aboriginal populations in the Northern Territory of Australia, using multiple data sources. *BMC Nephrol*. 2018;19:15.
- You J, Zhao Y, Lawton P, et al. Projecting demands for renal replacement therapy in the Northern Territory: a stochastic Markov model. *Aust Health Rev*. 2018;42:380–386.
- Hoy WE. Kidney disease in Aboriginal Australians: a perspective from the Northern Territory. *Clin Kidney J*. 2014;7:524–530.
- Hoy WE, Mott SA, Mc Donald SP. An expanded nationwide view of chronic kidney disease in Aboriginal Australians. *Nephrology (Carlton)*. 2016;21:916–922.
- Majoni SW, Ellis J-A, Hall H, et al. Inflammation, high ferritin, and erythropoietin resistance in indigenous maintenance hemodialysis patients from the Top End of Northern Australia. *Hemodial Int*. 2014;18:740–750.
- Fishbane S, Spinowitz B. Update on anemia in ESRD and earlier stages of CKD: core curriculum 2018. *Am J Kidney Dis*. 2018;71:423–435.
- Rao M, Pereira BJG. Optimal anemia management reduces cardiovascular morbidity, mortality, and costs in chronic kidney disease. *Kidney Int*. 2005;68:1432–1438.
- Kovesdy CP, Trivedi BK, Kalantar-Zadeh K, Anderson JE. Association of anemia with outcomes in men with moderate and severe chronic kidney disease. *Kidney Int*. 2006;69:560–564.
- Sato Y, Fujimoto S, Konta T, et al. Anemia as a risk factor for all-cause mortality: obscure synergic effect of chronic kidney disease. *Clin Exp Nephrol*. 2018;22:388–394.
- Stauffer ME, Fan T. Prevalence of anemia in chronic kidney disease in the United States. *PLoS One*. 2014;9, e84943.
- Babitt JL, Lin HY. Mechanisms of anemia in CKD. *J Am Soc Nephrol*. 2012;23:1631–1634.
- Pendse S, Singh AK. Complications of chronic kidney disease: anemia, mineral metabolism, and cardiovascular disease. *Med Clin North Am*. 2005;89:549–561.
- Ryu SR, Park SK, Jung JY, et al. The prevalence and management of anemia in chronic kidney disease patients: result from the KoreaN Cohort Study for Outcomes in Patients With Chronic Kidney Disease (KNOW-CKD). *J Korean Med Sci*. 2017;32:249–256.
- Padhi S, Glen J, Pordes BAJ, Thomas ME. Management of anaemia in chronic kidney disease: summary of updated NICE guidance. *BMJ*. 2015;350:h2258.
- Drüeke TB. Anemia treatment in patients with chronic kidney disease. *N Engl J Med*. 2013;368:387–389.
- Locatelli F, Nissenson AR, Barrett BJ, et al. Clinical practice guidelines for anemia in chronic kidney disease: problems and solutions. A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*. 2008;74:1237–1240.
- Macdougall IC, Bircher AJ, Eckardt KU, et al. Iron management in chronic kidney disease: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. *Kidney Int*. 2016;89:28–39.
- Macdougall IC, White C, Anker SD, et al. Intravenous iron in patients undergoing maintenance hemodialysis. *N Engl J Med*. 2019;380:447–458.
- Macdougall IC. Intravenous iron therapy in patients with chronic kidney disease: recent evidence and future directions. *Clin Kidney J*. 2017;10(suppl 1):i16–i24.
- Agarwal R. Iron deficiency anemia in chronic kidney disease: uncertainties and cautions. *Hemodial Int*. 2017;21(suppl 1):S78–S82.
- Rosati A, Ravaglia F, Panichi V. Improving erythropoiesis stimulating agent hyporesponsiveness in hemodialysis patients: the role of hepcidin and hemodiafiltration online. *Blood Purif*. 2018;45:139–146.
- Locatelli F, Barany P, Covic A, et al. 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.
- Cherayil BJ. The role of iron in the immune response to bacterial infection. *Immunol Res*. 2011;50:1–9.
- Ratcliffe LE, Thomas W, Glen J, et al. Diagnosis and management of iron deficiency in CKD: a summary of the NICE guideline recommendations and their rationale. *Am J Kidney Dis*. 2016;67:548–558.
- Feldman HI, Santanna J, Guo W, et al. Iron administration and clinical outcomes in hemodialysis patients. *J Am Soc Nephrol*. 2002;13:734–744.
- Moist LM, Troyanov S, White CT, et al. Canadian Society of Nephrology commentary on the 2012 KDIGO Clinical Practice Guideline for Anemia in CKD. *Am J Kidney Dis*. 2013;62:860–873.
- Macginley R, Walker R, Irving M. KHA-CARI Guideline: use of iron in chronic kidney disease patients. *Nephrology (Carlton)*. 2013;18:747–749.
- Anderson GJ, Frazer DM. Current understanding of iron homeostasis. *Am J Clin Nutr*. 2017;106(suppl 6):1559s–1566s.
- World Health Organization. *WHO Guideline on Use of Ferritin Concentrations to Assess Iron Status in Individuals and Populations*. Geneva: World Health Organization; 2020.
- Macdougall IC, White C, Anker SD, et al. Randomized trial comparing proactive, high-dose versus reactive, low-dose

- intravenous iron supplementation in hemodialysis (PIVOTAL): study design and baseline data. *Am J Nephrol*. 2018;48:260–268.
31. Palaka E, Grandy S, van Haalen H, et al. The impact of CKD anaemia on patients: incidence, risk factors, and clinical outcomes—a systematic literature review. *Int J Nephrol*. 2020;2020:7692376.
 32. Wang W, Knovich MA, Coffman LG, et al. Serum ferritin: past, present and future. *Biochim Biophys Acta*. 2010;1800:760–769.
 33. Ponka P, Beaumont C, Richardson DR. Function and regulation of transferrin and ferritin. *Semin Hematol*. 1998;35:35–54.
 34. Kell DB, Pretorius E. Serum ferritin is an important inflammatory disease marker, as it is mainly a leakage product from damaged cells. *Metallomics*. 2014;6:748–773.
 35. Kalantar-Zadeh K, Kalantar-Zadeh K, Lee GH. The fascinating but deceptive ferritin: to measure it or not to measure it in chronic kidney disease? *Clin J Am Soc Nephrol*. 2006;1(suppl 1):S9–S18.
 36. Kato S, Lindholm B, Yuzawa Y, et al. High ferritin level and malnutrition predict high risk of infection-related hospitalization in incident dialysis patients: a Japanese prospective cohort study. *Blood Purif*. 2016;42:56–63.
 37. Kuragano T, Matsumura O, Matsuda A, et al. Association between hemoglobin variability, serum ferritin levels, and adverse events/mortality in maintenance hemodialysis patients. *Kidney Int*. 2014;86:845–854.
 38. Depalma RG, Hayes VW, Chow BK, et al. Ferritin levels, inflammatory biomarkers, and mortality in peripheral arterial disease: a substudy of the Iron (Fe) and Atherosclerosis Study (FeAST) Trial. *J Vasc Surg*. 2010;51:1498–1503.
 39. Lien CT, Lin KC, Tsai YF, et al. Serum ferritin is associated with progression of peripheral arterial disease in hemodialysis patients. *Clin Exp Nephrol*. 2015;19:947–952.
 40. Williams MJ, Poulton R, Williams S. Relationship of serum ferritin with cardiovascular risk factors and inflammation in young men and women. *Atherosclerosis*. 2002;165:179–184.
 41. Abril-Ulloa V, Flores-Mateo G, Solà-Alberich R, et al. Ferritin levels and risk of metabolic syndrome: meta-analysis of observational studies. *BMC Public Health*. 2014;14, 483–483.
 42. Brudevold R, Hole T, Hammerstrom J. Hyperferritinemia is associated with insulin resistance and fatty liver in patients without iron overload. *PLoS One*. 2008;3:e3547.
 43. Jehn M, Clark JM, Guallar E. Serum ferritin and risk of the metabolic syndrome in U.S. adults. *Diabetes Care*. 2004;27:2422.
 44. Jin Y, He L, Chen Y, et al. Association between serum ferritin levels and metabolic syndrome: an updated meta-analysis. *Int J Clin Exp Med*. 2015;8:13317–13322.
 45. Kim T, Streja E, Soohoo M, et al. Serum ferritin variations and mortality in incident hemodialysis patients. *Am J Nephrol*. 2017;46:120–130.
 46. Majoni SW, Lawton PD, Barzi F, et al. Assessing the association between serum ferritin, transferrin saturation, and C-reactive protein in Northern Territory Indigenous Australian patients with high serum ferritin on maintenance haemodialysis. *Int J Nephrol*. 2017;2017:5490963.
 47. Majoni SW, Hughes JT, Heron B, Currie BJ. Trimethoprim+sulfamethoxazole reduces rates of melioidosis in high-risk hemodialysis patients. *Kidney Int Rep*. 2018;3:160–167.
 48. Chalmers RM, Majoni SW, Ward L, et al. Melioidosis and end-stage renal disease in tropical northern Australia. *Kidney Int*. 2014;86:867–870.
 49. Hamwi A, Endler G, Rubi K, et al. Reference values for a heterogeneous ferritin assay and traceability to the 3rd International Recombinant Standard for Ferritin (NIBSC code 94/572). *Clin Chem Lab Med*. 2002;40:365–370.
 50. Garcia-Casal MN, Peña-Rosas JP, Urrechaga E, et al. Performance and comparability of laboratory methods for measuring ferritin concentrations in human serum or plasma: a systematic review and meta-analysis. *PLoS One*. 2018;13, e0196576.
 51. WHO Team Nutrition and Food Safety. *WHO Guideline on Use of Ferritin Concentrations to Assess Iron Status in Individuals and Populations*. Geneva: WHO; 2020.
 52. Australia and New Zealand Dialysis and Transplant Registry (ANZDATA): End Stage Kidney disease in Aboriginal and Torres Strait Islander Australians. In: McDonald S, ed. *ANZDATA 42nd Annual Report 2019 (Data to 2018)*. Adelaide, South Australia: South Australian Health and Medical Research Institute (SAHMRI); 2019.
 53. Gillian Gorham SWM, Paul Lawton, Sarah Brown, et al. Interesting times—evolution of dialysis in Australia's Northern Territory (1980–2014). *RSA J*. 2018;14:108–116.
 54. Australian Health Ministers' Advisory Council. *Aboriginal and Torres Strait Islander Health Performance Framework 2017 Report*. Canberra: AHMAC; 2017.
 55. Hopkins RM, Gracey MS, Hobbs RP, et al. The prevalence of hookworm infection, iron deficiency and anaemia in an aboriginal community in north-west Australia. *Med J Aust*. 1997;166:241–244.
 56. Pasricha SR, Flecknoe-Brown SC, Allen KJ, et al. Diagnosis and management of iron deficiency anaemia: a clinical update. *Med J Aust*. 2010;193:525–532.
 57. Watson DS, Tozer RA. Anaemia in Yirrkala. *Med J Aust*. 1986;144(suppl):S13–S15.
 58. Ritchie B, McNeil Y, Brewster DR. Soluble transferrin receptor in Aboriginal children with a high prevalence of iron deficiency and infection. *Trop Med Int Health*. 2004;9:96–105.
 59. Moscovis SM, Cox A, Hall ST, et al. Effects of gender, cytokine gene polymorphisms and environmental factors on inflammatory responses. *Innate Immun*. 2015;21:523–530.
 60. Tong SY, van Hal SJ, Einsiedel L, et al. Impact of ethnicity and socio-economic status on *Staphylococcus aureus* bacteremia incidence and mortality: a heavy burden in Indigenous Australians. *BMC Infect Dis*. 2012;12:249.
 61. McDonald SP, Hoy WE. Interfaces between cardiovascular and kidney disease among Aboriginal Australians. *Adv Chronic Kidney Dis*. 2005;12:39–48.
 62. O'Rourke S, Steffen C, Raulli A, Tulip F. Diabetic major amputation in Far North Queensland 1998–2008: what is the Gap for Indigenous patients? *Aust J Rural Health*. 2013;21:268–273.
 63. Kapellas K, Jamieson LM, Do LG, et al. Associations between periodontal disease and cardiovascular surrogate

- measures among Indigenous Australians. *Int J Cardiol.* 2014;173:190–196.
64. Barr ELM, Barzi F, Hughes JT, et al. High baseline levels of tumor necrosis factor receptor 1 are associated with progression of kidney disease in indigenous Australians with diabetes: the eGFR follow-up study. *Diabetes Care.* 2018;41:739–747.
 65. Skilton MR, Maple-Brown LJ, Kapellas K, et al. The effect of a periodontal intervention on cardiovascular risk markers in Indigenous Australians with periodontal disease: the Peri-oCardio study. *BMC Public Health.* 2011;11:729.
 66. Barr EL, Maple-Brown LJ, Barzi F, et al. Comparison of creatinine and cystatin C based eGFR in the estimation of glomerular filtration rate in Indigenous Australians: the eGFR study. *Clin Biochem.* 2017;50:301–308.
 67. Arnold LW, Hoy WE, Wang Z. The association between C-reactive protein levels and the risk for chronic kidney disease hospitalizations in adults of a remote Indigenous Australian community—a prospective cohort study. *Nephrology (Carlton).* 2017;22:699–705.
 68. Brewster DR. Iron deficiency in minority groups in Australia. *J Paediatr Child Health.* 2004;40:422–423.
 69. Udovicich C, Perera K, Leahy C. Anaemia in school-aged children in an Australian Indigenous community. *Aust J Rural Health.* 2017;25:285–289.
 70. Erber WN, Buck AM, Threlfall TJ. The haematology of indigenous Australians. *Hematology.* 2004;9:339–350.
 71. National Health and Medical Research Council, Australian Government. *Nutrition in Aboriginal and Torres Strait Islander Peoples.* Canberra: National Health and Medical Research Council, Australian Government; 2000.
 72. 4727.0.55.003 - Australian Aboriginal and Torres Strait Islander Health Survey: Biomedical Results, 2012-13, ANAEMIA. Available at: <http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/4727.0.55.003~2012-13~Main%20Features~Anaemia~116>.
 73. Johnson-Wimbley TD, Graham DY. Diagnosis and management of iron deficiency anemia in the 21st century. *Therap Adv Gastroenterol.* 2011;4:177–184.
 74. Gaweda AE. Markers of iron status in chronic kidney disease. *Hemodial Int.* 2017;21(suppl 1):S21–S27.
 75. Yamamoto H, Nishi S, Tomo T, et al. 2015 Japanese Society for Dialysis Therapy: guidelines for renal anemia in chronic kidney disease. *Renal Replace Ther.* 2017;3:36.
 76. Gaweda AE, Bhat P, Maglinte GA, et al. TSAT is a better predictor than ferritin of hemoglobin response to epoetin alfa in US dialysis patients. *Hemodial Int.* 2014;18:38–46.
 77. Cavill I. Iron status as measured by serum ferritin: the marker and its limitations. *Am J Kidney Dis.* 1999;34:s12–s17.
 78. Thomas C, Thomas L. Biochemical markers and hematologic indices in the diagnosis of functional iron deficiency. *Clin Chem.* 2002;48:1066.
 79. Ho JCL, Stevic I, Chan A, et al. Serum ferritin is not sensitive or specific for the diagnosis of iron deficiency in patients with normocytic anemia. *Blood.* 2015;126:955.
 80. Australian Institute of Health and Welfare. *Aboriginal and Torres Strait Islander Health Performance Framework 2017 Report: Northern Territory.* Canberra: Australian Institute of Health and Welfare; 2017.
 81. Braun J, Lindner K, Schreiber M, et al. Percentage of hypochromic red blood cells as predictor of erythropoietic and iron response after i.v. iron supplementation in maintenance haemodialysis patients. *Nephrol Dial Transplant.* 1997;12:1173–1181.
 82. Mittman N, Sreedhara R, Mushnick R, et al. Reticulocyte hemoglobin content predicts functional iron deficiency in hemodialysis patients receiving rHuEPO. *Am J Kidney Dis.* 1997;30:912–922.
 83. Markovic M, Majkic-Singh N, Subota V. Usefulness of soluble transferrin receptor and ferritin in iron deficiency and chronic disease. *Scand J Clin Lab Invest.* 2005;65:571–576.
 84. Young B, Zaritsky J. Hepcidin for clinicians. *Clin J Am Soc Nephrol.* 2009;4:1384–1387.
 85. Tarng DC, Huang TP. Determinants of circulating soluble transferrin receptor level in chronic haemodialysis patients. *Nephrol Dial Transplant.* 2002;17:1063–1069.
 86. Wish JB. Assessing iron status: beyond serum ferritin and transferrin saturation. *Clin J Am Soc Nephrol.* 2006;1(suppl 1):S4–S8.
 87. Daher R, Manceau H, Karim Z. Iron metabolism and the role of the iron-regulating hormone hepcidin in health and disease. *Presse Med.* 2017;46(12, pt 2):e272–e278.
 88. Macdougall IC, Malyszko J, Hider RC, Bansal SS. Current status of the measurement of blood hepcidin levels in chronic kidney disease. *Clin J Am Soc Nephrol.* 2010;5:1681.
 89. Larson DS, Coyne DW. Understanding and exploiting hepcidin as an indicator of anemia due to chronic kidney disease. *Kidney Res Clin Pract.* 2013;32:11–15.
 90. Lorcerie B, Audia S, Samson M, et al. Diagnosis of hyperferritinemia in routine clinical practice. *Presse Med.* 2017;46(12, pt 2):e329–e338.
 91. Ricchi P, Meloni A, Spasiano A, et al. The impact of liver steatosis on the ability of serum ferritin levels to be predictive of liver iron concentration in non-transfusion-dependent thalassaemia patients. *Br J Haematol.* 2018;180:721–726.
 92. Padwal MK, Murshid M, Nirmale P, Melinkeri RR. Association of serum ferritin levels with metabolic syndrome and insulin resistance. *J Clin Diagn Res.* 2015;9:BC11–BC13.
 93. Sun L, Franco OH, Hu FB, et al. Ferritin concentrations, metabolic syndrome, and type 2 diabetes in middle-aged and elderly Chinese. *J Clin Endocrinol Metab.* 2008;93:4690–4696.
 94. Valery PC, Moloney A, Cotterill A, et al. Prevalence of obesity and metabolic syndrome in Indigenous Australian youths. *Obes Rev.* 2009;10:255–261.
 95. Paisant A, d'Assignies G, Bannier E, et al. MRI for the measurement of liver iron content, and for the diagnosis and follow-up of iron overload disorders. *Presse Med.* 2017;46(12, pt 2):e279–e287.
 96. Rostoker G, Laroudie M, Blanc R, et al. Histological scores validate the accuracy of hepatic iron load measured by signal intensity ratio and r2* relaxometry MRI in dialysis patients. *J Clin Med.* 2019;9:17.
 97. Rostoker G, Griuncelli M, Loridon C, et al. Hemodialysis-associated hemosiderosis in the era of erythropoiesis-

- stimulating agents: a MRI study. *Am J Med.* 2012;125:991–999.e991.
98. Rostoker G, Vaziri ND. Risk of iron overload with chronic indiscriminate use of intravenous iron products in ESRD and IBD populations. *Heliyon.* 2019;5, e02045.
99. Rostoker G, Griuncelli M, Loridon C, et al. Reassessment of iron biomarkers for prediction of dialysis iron overload: an MRI Study. *PLoS One.* 2015;10, e0132006.
100. Holman R, Olynyk J, Kulkarni H, Ferrari P. Characterization of hepatic and cardiac iron deposition during standard treatment of anaemia in haemodialysis. *Nephrology.* 2017;22:114–117.
101. Ramanathan G, Olynyk JK, Ferrari P. Diagnosing and preventing iron overload. *Hemodial Int.* 2017;21(suppl 1):S58–S67.
102. Fishbane S, Mathew A, Vaziri ND. Iron toxicity: relevance for dialysis patients. *Nephrol Dial Transplant.* 2014;29:255–259.
103. Ishida JH, Johansen KL. Iron and infection in hemodialysis patients. *Semin Dial.* 2014;27:26–36.
104. Bailie GR, Larkina M, Goodkin DA, et al. Data from the dialysis outcomes and practice patterns study validate an association between high intravenous iron doses and mortality. *Kidney Int.* 2015;87:162–168.
105. Pourmoghaddas A, Sanei H, Garakyaraghi M, et al. The relation between body iron store and ferritin, and coronary artery disease. *ARYA Atheroscler.* 2014;10:32–36.
106. Coyne DW, Kapoian T, Suki W, et al, DRIVE Study Group. Ferric gluconate is highly efficacious in anemic hemodialysis patients with high serum ferritin and low transferrin saturation: results of the dialysis patients' response to IV Iron with Elevated Ferritin (DRIVE) Study. *J Am Soc Nephrol.* 2007;18:975–984.
107. Kapoian T, O'Mara NB, Singh AK, et al. Ferric gluconate reduces epoetin requirements in hemodialysis patients with elevated ferritin. *J Am Soc Nephrol.* 2008;19:372–379.
108. Li X, Cole SR, Kshirsagar AV, et al. Safety of dynamic intravenous iron administration strategies in hemodialysis patients. *Clin J Am Soc Nephrol.* 2019;14:728–737.
109. Chinnadurai R, Ritchie J, Green D, Kalra PA. Non-alcoholic fatty liver disease and clinical outcomes in chronic kidney disease. *Nephrol Dial Transplant.* 2019;34:449–457.
110. Deugnier Y, Bardou-Jacquet É, Lainé F. Dysmetabolic iron overload syndrome (DIOS). *Presse Med.* 2017;46(12, pt 2): e306–e311.
111. Rostoker G, Loridon C, Griuncelli M, et al. Liver iron load influences hepatic fat fraction in end-stage renal disease patients on dialysis: a proof of concept study. *EBioMedicine.* 2019;39:461–471.
112. Chinnadurai R, Macdougall IC, Kalra PA. Treatment of anaemia in end-stage renal disease: a double-edged iron sword? *EBioMedicine.* 2019;40:31–32.