Scientific Research Publishing

Open Journal of Nephrology, 2026, 16(4), 519-526
https://www.scirp.org/journal/ojneph
ISSN Online: 2164-2869
ISSN Print: 2164-2842

Inadequacy in the Management of Anemia in Renal Patients on Different Therapies; Underestimation of the Culprits and Risk of Iatrogenic Iron Overload

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How to cite this paper: El-Reshaid, K., Al-Bader, S., Sallam, H.T. and Ahmad, E. (2026) Inadequacy in the Management of Anemia in Renal Patients on Different Therapies; Underestimation of the Culprits and Risk of Iatrogenic Iron Overload. *Open Journal of Nephrology*, **16**, 519-526.
https://doi.org/10.4236/ojneph.2026.164044

Received: October 16, 2026
Accepted: November 16, 2026
Published: November 19, 2026

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Abstract

Background: Anemia is a common complication of chronic renal disease. Inadequate erythropoiesis due to erythropoietin deficiency, by failing kidneys, is the main culprit that indicates erythropoietin therapy. On the other hand, vitamin B12, folate, and iron are the most essential hematinics for erythropoiesis. Vitamin B12 and folate are water-soluble with adequate renal and dialysis clearance, contrary to intravenous iron supplementation with risk of hemosiderosis and subsequent cirrhosis, cardiomyopathy, and endocrinopathy. Patients and methods: The entry data on anemia and hematinics were assessed in patients referred to our tertiary renal clinic in the past 5 years. Results: A total of 3572 renal patients on different therapeutic modalities were included. Anemia (hemoglobin < 110 g/L) was detected in 715 patients (22%), of whom 123 (4%) had severe anemia (hemoglobin < 100 g/L). In such anemic patients, 278 (14%) had iron deficiency (ID) and 102 (4%) had iron overload (IO). Deficiency of vitamin B12 and folate was detected in 20% and 4%, respectively. A total of 2857 (87%) patients had adequate hemoglobin level (HB > 110 to <120 g/L), yet 447 (14%) were overcorrected. In the latter group, ID was detected in 241 (8%), IO in 26%, B12 deficiency in 570 (20%), and folate in 78 (3%). A total of 2171 (61%) management inadequacies were detected in the screened patients. Conclusion: Vigilance in the diagnosis and management of anemia in renal patients on different therapeutic modalities is indicated to avoid hematinic deficiency, overcorrection, and iatrogenic iron overload.

Keywords

Anemia, Hemosiderosis, Cirrhosis, Iron Depletion, Iron Overload, Vitamin

B12, Folate, Kidney

1. Introduction

At present, nearly 37 million adult Americans have chronic renal disease (CKD) [1]. In such a patient population, anemia is a common complication with a prevalence of 1 in every 7 patients [2]. Inadequate erythropoiesis due to erythropoietin deficiency, caused by the failing kidneys, is the main culprit except for hereditary polycystic kidney disease, which synthesizes such hormone from its plethoric pericystic cells [3]. In general, certain hematinics viz. iron, copper, cobalt, vitamins A, B12, B6, C, E, folic acid, riboflavin, and nicotinic acid are essential for erythropoiesis, yet in patients with CKD, vitamin B12, folate, and iron contribute most [4]. Adequate supplementation of both vitamin B12 and folate is essential since deficiency is associated with impaired DNA synthesis and subsequent defects in myelination (central and peripheral nervous system) as well as erythropoiesis [5]. Data on short- and long-term accidental overdosing of vitamin B12 and folates is inconclusive since they are water soluble and hence have adequate renal and dialysis clearance. On the other hand, iron deficiency is common in patients with CKD due to stress gastric ulcerations, gastrointestinal diseases (especially diverticulosis, polyps, piles), especially in those on maintenance hemodialysis (MHD) with exposure to heparin, as well as blood loss in dialysis tubes and filters [4]. Hence, iron supplementation is essential in the management of renal anemia. Intravenous iron supplementation (IVIS) has been shown to be superior to the oral route in rapid anemia correction, especially in those receiving recombinant erythropoietin (rHuEpo) [4]. Unfortunately, there is no physiological route for removal of iron overload, with risk of iatrogenic iron overload (IO) and subsequent tissue toxicity (hemosiderosis) induced by catalysis of hydroxyl radicals to accelerate lipid peroxidation [6]. Consequently, it increases the risk of heart failure, liver cirrhosis and cancer, arthritis, dyslipidemia, diabetes, and gonadal dysfunction [7]-[9]. Moreover, it may induce several neurodegenerative diseases (e.g., Alzheimer's and Parkinson's diseases) [10]. In this study, we evaluated the prevalence of such hematinic abnormalities in the large number of renal patients referred to our tertiary clinic to assess the risks of their treatment inadequacy.

2. Patients and Methods

The study was conducted at Prof. Kamel El-Reshaid's clinic. The clinic was established in 1997 in the center of Kuwait City and has adequate diagnostic and therapeutic facilities to care for out-patients and in-patients with its affiliated hospitals. The study evaluated entry data on anemia management in patients with chronic kidney disease (CKD) undergoing different modalities of renal replacement therapy. The latter included conservative management (CKT), maintenance hemodialysis (MHD), maintenance peritoneal dialysis (MPD), and kidney trans-

plantation (KTx).

2.1. Study Design

Patients with CKD who attended or were referred to the clinic between 1st January 2021 and 31st December 2025 were screened for hemoglobin level (Hb), as well as serum (ferritin, transferrin saturation%, vitamin B12, and folate levels) to assess the prevalence of anemia, extent of hematinic deficiency, and iron overload.

2.2. Specific Definitions

In those patients, adequate hemoglobin level was defined as Hb level > 110 to <120 g/L. Anemia was considered if Hb was <110 g/L, severe anemia if <100 g/L, and overtreatment if Hb > 120 g/L. Iron deficiency (ID) was defined if transferrin saturation was <20% with or without ferritin < 30 μg/L. Iron overload was defined if transferrin saturation was >40% with or without ferritin > 300 μg/L. Low serum levels of vitamin B12 were defined as <148 pmol/L and folate as <4.5 nmol/L.

2.3. Laboratory Investigations

All patients were tested for: a) complete blood counts, b) liver and lipid profiles, c) blood hematinics (serum transferrin saturation %, ferritin, vitamin B12, and folate), d) potential culprits of hemoglobinopathies (endocrine viz. TSH, PTH, and am cortisol), serum aluminum level and protein electrophoresis, as well as autoimmune markers (complement 3 & 4, ANA, ANCA, anti-CCP), antimitochondrial antibodies, and hepatitis (A, B & C) serology. In certain patients, more tests were performed as dictated by the study-exclusion criteria, viz. radiological imaging, hemoglobin electrophoresis, bone marrow biopsy, positron emission tomography, and genetic testing for hemochromatosis (mutations in the HFE gene viz. C282Y & H63D).

2.4. Exclusion Criteria

Patients were excluded from analysis if they had a history of alcohol abuse, infective hepatitis, autoimmune diseases, chronic infection, malignancy, uncontrolled endocrinopathy, as well as those with defective erythropoiesis, viz. hemochromatosis, hemoglobinopathies, dysplastic bone marrow (myelofibrosis, myelodysplasia, multiple myeloma), amyloidosis, malignancy, osteitis fibrosa cystica, and aluminum overload (serum level > 60 μg/L). Patients with unstable KTx (first year or frequent rejections) were also excluded.

2.5. Statistical Analysis

SPSS statistical package version 25 was used for data entry and processing. The p-value < 0.05 was used as the cut-off level for significance. Since all variables were normally distributed, they were expressed as mean + SD and compared using Student's t-test.

3. Results

Over the past 5 years, a total of 3572 patients with CKD were included in the study, of whom 3281 were on CKT, 194 on MHD, 28 on MPD, and 69 with KTx (Table 1).

Table 1. Summary of haematinics abnormalities in the screened renal patients.

Type of renal therapy	CKT	MHD	MPD	KTx
Number of patients*	3281	194	28	69
Anaemic (Hg < 110 g/L)				
Total	644 (20)	37 (19)	**9 (32)**	**25 (36)**
Under-corrected (Hb < 110)	541 (17)	24 (12)	**6 (22)**	**21 (30)**
Poor correction (Hb < 100)	103 (3)	13 (7)	3 (11)	4 (6)
Iron deficient	246 (38)	**25 (6)**	3 (33)	4 (16)
Iron overload	80 (12)	6 (16)	**3 (33)**	**9 (36)**
Iron replete	318 (7)	6 (16)	3 (33)	13 (52)
Low serum vitamin B12	129 (20)	8 (22)	**3 (38)**	5 (20)
Low serum foliate	5 (0.8)	**18 (49)**	2 (22)	6 (24)
Adequate hemoglobin (Hb > 110 g/L)				
Total	2637 (80)	157 (81)	19 (68)	44 (64)
Corrected HB (110 - 120)	2261 (69)	103 (53)	15 (54)	32 (46)
Overcorrected (Hb > 12)	376 (11)	**54 (28)**	4 (14)	12 (18)
Iron deficient	231 (9)	**2 (1)**	3 (16)	5 (11)
Iron overload	665 (25)	34 (22)	**9 (47)**	**23 (52)**
Iron replete	1741 (66)	121 (77)	7 (37)	13 (30)
Low serum vitamin B12	527 (20)	30 (19)	4 (21)	9 (21)
Low serum foliate	**7 (0.3)**	59 (38)	3 (33)	9 (21)

Abbreviations: CKT: chronic kidney therapy, MHD: maintenance haemodialysis, MPD: maintenance peritoneal dialysis, KTx: kidney transplant, Hb: haemoglobin, *Patient numbers expressed as: number (% of total), Numbers highlighted in **bold** express statistically significant data ($p < 0.05$).

3.1. Hematinic Abnormalities in Anemic Patients

A total of 2411 (67%) had adequate anemia correction, yet 715 (20%) had anemia, of whom 123 (3%) had severe anemia. It was more prevalent in those on MPD and KTx. Patients on MHD tend to be less ID, and those on MPD and KTx were IO. The prevalence of low serum vitamin B12 and folate was similar in all groups and was at 20% - 22% and 22% - 24%, respectively. However, low serum folate was common in those on MHD (49%).

3.2. Hematinic Abnormalities in Non-Anemic Patients

A total of 2637 (80%) patients had hemoglobin levels > 110 g/L, yet 376 (11%) had

it overcorrected, especially in those on MHD who were less likely to be ID. Patients on MPD and KTx were more IO at 47% and 52%, respectively. In this group, deficiency of vitamin B12 was similar to the anemic group. However, folate deficiency was less corrected except for those on CKT.

3.3. Summed Hematinic Abnormalities

As seen in Table 2, 61% of all patients had hematinic abnormalities, which was 58% in those receiving CKT, compared to 94%, 107%, and 100% in those on MHD, MPD, and KTs, respectively.

Table 2. Haematinic abnormalities in the screened renal patients.

		Hematinic abnormalities					
Patient's treatment groups							
Haemoglobin level	Number	Iron-overload	Iron-replete	Iron-depleted	Low vitamin B12	Low Folate	Group-summed abnormalities
Conservative kidney therapy							
Hg > 120	376 (12)	93 (24)	272 (72)	11 (4)	75 (20)	1 (0.3)	180 (49)
Hg 110 - 120	2261 (69)	572 (25)	1469 (65)	220 (10)	452 (20)	6 (0.3)	1250 (55)
Hg < 110	541 (16)	77 (4)	291 (34)	173 (32)	108 (20)	2 (0.4)	360 (67)
Hg < 100	103 (3)	3 (3)	27 (26)	**73 (71)**	21 (20)	3 (3)	**100 (97)**
Total	3281	745 (23)	2059 (63)	477 (14)	656 (20)	12 (0.4)	1890 (58)
Maintenance haemodialysis							
Hg > 120	**54 (28)**	**32 (59)**	22 (41)	0	10 (19)	21 (39)	**63 (117)**
Hg 110 - 120	103 (53)	2 (2)	99 (96)	2 (2)	20 (19)	38 (37)	63 (60)
Hg < 110	24 (12)	4 (16)	5 (21)	15 (63)	5 (21)	**11 (56)**	**35 (146)**
Hg < 100	13 (7)	2 (15)	1 (8)	**10 (77)**	3 (23)	7 (54)	**22 (169)**
Total	194	40 (21)	127 (65)	27 (14)	38 (20)	77 (40)	182 (94)
Maintenance peritoneal dialysis							
Hg > 120	4 (14)	**3 (75)**	1 (25)	0	1 (25)	1 (25)	**5 (125)**
Hg 110 - 120	15 (54)	6 (40)	6 (40)	3 (20)	3 (20)	2 (13)	14 (93)
Hg < 110	6 (21)	**3 (50)**	2 (33)	1 (17)	2 (33)	1 (17)	**7 (117)**
Hg < 100	3 (11)	0	1 (33)	**2 (67)**	1 (33)	1 (33)	**4 (133)**
Total	28	12 (43)	10 (36)	6 (21)	7 (25)	5 (18)	30 (107)
Transplant patients							
Hg > 120	12 (18)	7 (59)	4 (33)	1 (8)	3 (25)	2 (17)	13 (108)
Hg 110 - 120	32 (46)	16 (50)	12 (38)	4 (12)	6 (19)	7 (22)	33 (103)
Hg < 110	21 (30)	3 (14)	12 (57)	6 (29)	4 (19)	4 (19)	17 (81)
Hg < 100	4 (6)	0	1 (25)	**3 (75)**	1 (25)	**2 (50)**	**6 (150)**
Total	69	26 (38)	29 (42)	14 (20)	14 (20)	15 (22)	69 (100)
Grand total	3572 (100)	823 (23)	2225 (62)	524 (15)	715 (20)	109 (3)	2171 (61)

*Patient numbers expressed as: number (% of total); Numbers highlighted in bold indicate statistically significant data ($p < 0.05$).

Anemia overcorrection was more common in patients on MHD (28%) compared to other renal treatment modalities (12% - 18%). In that group, overcorrection was associated with IO (59%). In MPD patients, IO was common at 75% in overcorrected patients, and ID in severely anemic patients at 67%. Anemic KTx patients were more likely to be ID (75%) and folate deficient (50%).

4. Discussion

The ideal treatment of anemia of CKD is exogenous erythropoietin (rHuEpo) administration with its established safety and efficacy [11]. However, two issues should be respected in its management: a) avoidance of overcorrection with the risk of precipitating cardiovascular ischemic complications in a population with premature atherosclerosis, and b) adequate correction of the essential hematinics to ensure its adequate response and avoid iatrogenic iron overload induced by overzealous IVIS. Hence, vigilant monthly assessment of a) hemoglobin level, and b) hematinics level is essential [12]. Our study showed significant inadequacies in anemia management in our area by an independent tertiary unit. Such inadequacies include a) persistent anemia and even severe cases, b) induction of relative polycythemia in this patient population associated with costly rHuEpo use, c) lack of correction of hematinics viz. vitamin B12 and folate with risk of myelopathy as well as poor response to rHuEpo with ID, and d) prevalent IO with overzealous IVIS [13]. The latter was the culprit since the study was conducted after the widespread use of rHuEpo and limited blood transfusion [11]. Moreover, primary hemochromatosis was excluded in our patients by testing for hemochromatosis alleles (HFE gene) that encodes the transmembrane enteric iron-uptake protein regulator (HFE protein) [13]. Our study disclosed four major issues in "vigilant" anemia management in renal patients viz. a) vague definition levels of (hemoglobin and hematinics), b) ill-defined measures of iron status, c) inherent abnormalities akin to renal patients in different dialysis modalities viz. excessive iron and folate losses in MHD as well as bone marrow suppression in KTx patients, and d) underestimation of risks of IO, limiting it only to primary hemochromatosis [14]. In our study, we used serum transferrin saturation and ferritin, as simple and practical tests, to assess iron stores. Moreover, we acknowledged their limitations, especially recent (within 1 month) IVIS in both, and ferritin with inflammatory states (infection, autoimmune, and malignancy) [15]. Serum iron should not be used since it fluctuates even with recent oral intake. Recently, we showed that, even in the absence of primary hemochromatosis, overzealous IVIS in renal patients is associated with IO and subsequent risks of liver, heart, and endocrine disease similar to those with thalassemia, myelodysplastic syndrome, myelofibrosis, sideroblastic anemias, sickle cell disease, and pyruvate kinase deficiency [8] [16]. Moreover, we advocated periodic phlebotomies, with adequate rHuEpo therapy, to limit such complications in renal patients [8]. Our study has certain limitations: a) though it had large entry data yet was from a single outpatient referral center, b) it did not include the impact of co-morbidities, c) it had small clinic

data which represents actual form has few limitations, and d) it had small peritoneal-dialysis and transplant subgroups.

5. Conclusion

Vigilance in the diagnosis and management of renal anemia is indicated to avoid inadequacy in its correction, hematinic deficiency, and iatrogenic iron overload.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

Conceptualization & writing (original draft preparation): Kamel El-Reshaid and Shaikha Al-Bader. Patient follow up and data collection: Shaikha Al-Bader, Hossameldin Tawfik Sallam, Ehab Ahmad. Final draft preparation, review and editing: Kamel El-Reshaid. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare that they have no potential conflicts of interest related to the contents of this article.

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