Scientific Research Publishing

Open Journal of Nephrology, 2026, 16(3), 334-343
https://www.scirp.org/journal/ojneph
ISSN Online: 2164-2869
ISSN Print: 2164-2842

Diagnosis and Management of Hepatic, Endocrine, and Cardiac Complications of Iatrogenic Iron Overload in Renal Patients

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How to cite this paper: El-Reshaid, K., Al-Bader, S., Nasef, H., Ahmad, E. and Abdullah, E. (2026) Diagnosis and Management of Hepatic, Endocrine, and Cardiac Complications of Iatrogenic Iron Overload in Renal Patients. *Open Journal of Nephrology*, **16**, 334-343.
https://doi.org/10.4236/ojneph.2026.163030

Received: June 21, 2026
Accepted: July 19, 2026
Published: July 22, 2026

Abstract

Background: Renal disease is associated with ineffective erythropoiesis. In such patient populations, reports on the extent, complications, and management of iatrogenic iron overload (IO), following repeated blood transfusions and intravenous iron supplementation, are rare. **Patients and Methods**: Over the past 5 years, 3572 patients on different modalities of renal therapies, viz. conservative, maintenance hemodialysis, maintenance peritoneal dialysis, and kidney transplantation, were screened for IO and its subsequent liver, endocrine, and heart complications. Diagnosis of IO was established by high transferrin saturation %, serum ferritin, bone marrow stores, and CT density. Liver disease was suspected with abnormal liver tests and abdominopelvic sonography. After exclusion of other causes of liver diseases, a liver biopsy was done to assess for IO-hepatopathy. In those patients, basal and dynamic hormonal tests as well as echocardiography were used to assess for IO-endocrinopathy and IO-cardiopathy. **Results**: A total of 823 (23%) had IO, of whom 23 patients with severe and long-standing exposure had IO-hepatopathy (6 with severe hemosiderosis and 17 with cirrhosis). In those patients, 2 had pituitary disease and 2 had dilated cardiomyopathy. Weekly phlebotomy for 1 month followed by twice monthly phlebotomy normalized their iron balance by 3 months in all patients with IO and halted the liver, endocrine, and heart complications, in the affected ones, by 42 ± 11 months of follow-up. **Conclusion**: IO-hepatopathy, endocrinopathy, and cardiomyopathy can develop following inappropriate and excessive intravenous iron infusions in renal patients on different RRT. Vigilant monitoring of their hematinic therapy is indicated and

therapeutic phlebotomy is useful in its management.

Keywords

Iron Overload, Phlebotomy, Hemosiderosis, Cirrhosis, Cardiomyopathy, Endocrinopathy, Hematinic Therapy, Renal Patients

1. Introduction

Iron is an essential trace element involved in oxygen transport, mitochondrial energy production, deoxyribonucleic acid synthesis, and host immune defense [1]. Acute iron intoxication is an extremely rare symptomatic emergency that results from accidental or iatrogenic overdose in children [2]. On the other hand, chronic iron overload (IO) is a smoldering disorder with potential for multiple end-stage organ failures, viz., heart, liver, pancreas, and multiple endocrine glands [3]. IO has been reported in patients with (a) hereditary hemochromatosis and (b) repeated blood transfusions in patients with chronic hemolytic anemias and myelodysplastic disorders [4]. In hemochromatosis, excessive oral iron absorption results from a defective hepcidin-ferroprotein control system due to C282Y and H63D mutations in the HFE gene [5]. On the other hand, direct heme-iron in repeated transfusions, which bypasses the hepcidin-ferroprotein gut-control system, is the culprit in the second group [5]. Tissue deposition of iron results in reactive oxygen species with subsequent progressive organ failure [3]. Epidemiological studies from the United States indicate that 1 in every 200 white (non-Hispanic) individuals is affected by IO, yet only 14% are carriers of genetic mutations [6]. The latter indicates the extent of the acquired IO phenomenon. In patients with chronic kidney disease (CKD), the widespread use of erythropoietin has limited the use of IO associated with frequent blood transfusions [7]. However, the risk of IO still remains high with the need to maximize iron dosing with such therapy to overcome functional iron-deficiency anemia and improve its efficacy [8]. Such a functional state, in CKD and cancer, has been attributed to an inflammatory-induced increase in expression of the hepatic protein hepcidin in an interleukin-6-dependent manner with subsequent decrease in the transmembrane iron-transporting protein (ferroportin) in macrophages of the reticuloendothelial system (RES) and hepatocytes [9] [10]. Recent reviews estimated the prevalence of IO-hepatopathy in 10% - 28.6% of patients on maintenance peritoneal dialysis (MPD) and 75% in those on maintenance hemodialysis (MHD) [11]-[13]. In our study, we report the hepatic, endocrine, and cardiac complications of such iatrogenic IO in patients on different renal therapies and provide practical and safe measures for its management.

2. Patients and Methods

The study was conducted by Prof. Kamel El-Reshaid's clinic. The clinic was estab-

lished 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.

2.1. Study Protocol

At the start, all patients with CKD on different RRT who attended or were referred to the clinic between 1st January 2021 and 31st December 2025 were screened for IO and its subsequent hepatopathy (liver hemosiderosis and cirrhosis). Diagnosis of IO was considered if high serum levels of (a) transferrin saturation% (>40%) and (b) ferritin (>1110 μg/L) were present in patients who had not received intravenous iron for >12 weeks [14] [15]. Moreover, it was confirmed by high CT density (>70 Hounsfield units) and grade 6 bone marrow iron stores [16].

2.2. Assessment for Complications of IO

Diagnosis of liver disease was established by abnormal liver on: (a) serum tests that showed high transaminases, alkaline phosphatase, and gamma-glutamyl transferase, and/or (b) abdominopelvic sonography viz. abnormal liver size/shape, enlarged spleen, and ascites. After exclusion of other liver-disease etiologies (Vida infer); liver biopsy was done in the selected patients to assess the etiology of their liver disease, acquired hemosiderosis, and cirrhosis [17]. Endocrine tests included: (a) pancreas: hemoglobin A1c, C-peptide, insulin, pancreatic elastase, amylase, and lipase, (b) thyroid viz. TSH with free T3 and T4, (c) early morning serum cortisol and ACTH for adrenal gland, (d) pituitary: IGF, FSH, LH, ACTH, prolactin, and copeptin, and (d) gonads: sex hormones (testosterone in males, estradiol and progesterone in females). Dynamic tests included: (a) gonadotropin-releasing hormone (GnRH), (b) synthetic adrenocorticotrophic hormone 1 - 24 (ACTH) stimulation tests, and modified glucose tolerance test (MOGTT). Dynamic endocrine testing was done by blood sample collected prior to the scheduled dialysis session, followed by intravenous injection of 100 μg of GnRH and 250 μg of ACTH. Blood sample collection was done at time 0, 30 minutes, and 60 minutes. MOGTT was performed 1 week after completion of GnRH and ACTH stimulation tests. Patients were given 1 g/kg glucose syrup and blood samples were collected at start, after 1 and 2 hours, for assessment of glucose and insulin. The response to stimulatory tests was considered adequate if a minimum of: (a) 100% increment in LH was achieved after 2 hours of GnRH injection, (b) 200% increase in plasma cortisol levels after 2 hours of ACTH injection, and (c) 100% increase in free insulin after 2 hours of oral glucose ingestion. Moreover, echocardiogram was used to assess the myocardium.

2.3. Exclusion Criteria

To assess for IO-hepatic disease, patients were excluded if they had clinical evidence, laboratory tests, serological markers, genetic mutations, and radiological images indicating alcohol abuse, autoimmune diseases, chronic infection, malig-

nancy, were on immunosuppressive therapy, 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) [18]-[20]. Patients with previous non-IO endocrinopathy and heart disease were excluded from such assessment.

2.4. Treatment Protocol

In patients with IO, oral and intravenous iron were avoided, and periodic phlebotomy was performed. The latter consisted of the removal of 450 ml of the patient's blood per session weekly for 1 month, followed by twice monthly until TS% & SF levels were normalized. Deficiencies in vitamin B12 and folates were corrected periodically, and subcutaneous erythropoietin (Darbepoetin alpha) was used to maintain an adequate hemoglobin level (110 - 120 g/L) [21] [22].

2.5. Follow up

Patients were assessed clinically as well as by laboratory testing (complete blood count, TS%, SF, liver function) every week for 1 month, then every 2 weeks for the subsequent 2 months. Radiological tests, viz. abdominal ultrasound (to assess for liver, spleen, and ascites) and CT (to assess for liver CT density), were performed at the start and after 3 months. Upper GI endoscopy was done when indicated.

2.6. 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. Comparison of changes with time, following therapy, and between groups was done using the t-test for two dependent means and for two independent ones.

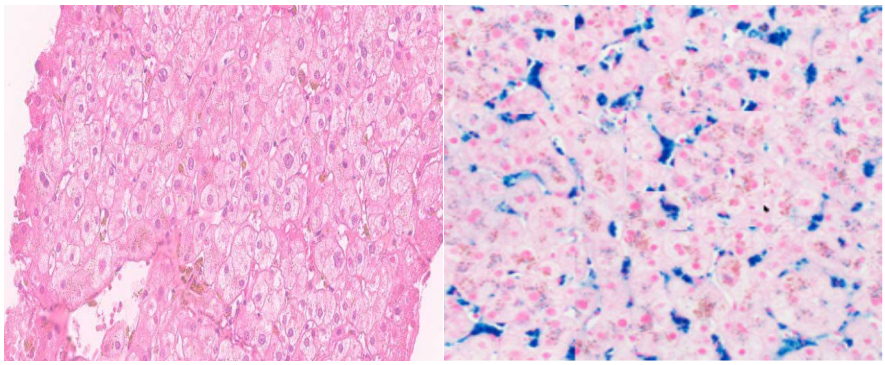
3. Results

A total of 3572 CKD patients on RRT (CKT: 3281, MHD: 194, MPD: 28, and KTx: 69) were screened during the past 5 years. As seen in **Table 1**, IO was detected in 823 (23%) of the total patients; of whom 745 (23%) were on CKT, 40 (20%) on MHD, 12 (43%) on MPD, and 26 (38%) with KTx (**Table 1**). Among these IO patients, 23 (3%) fulfilled the strict criteria for inclusion of IO-liver disease with (a) high TS, SF, and bone marrow iron stores, (b) high liver CT density, abnormal liver function/abdominopelvic sonography, and (c) lack of exclusion diseases, which was further confirmed by liver biopsy.

3.1. Liver Biopsy

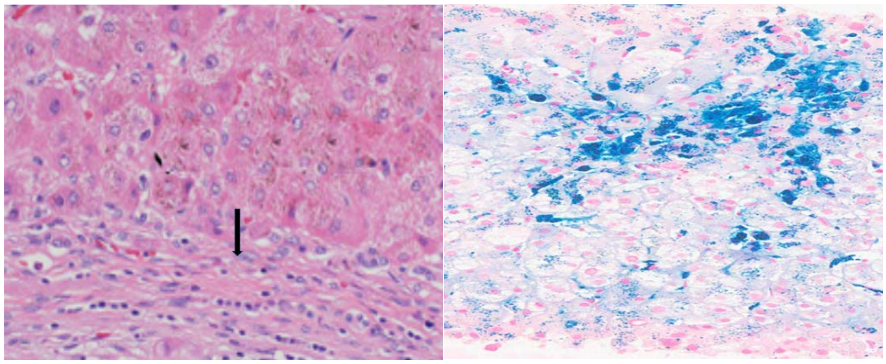
In the 23 patients with IO and liver disease, liver biopsy showed diffuse: (a) iron deposition in the sinusoidal Kupffer cells (severe hemosiderosis) in 6 patients

(Figure 1), and (b) iron-loaded hepatocytes with a variable degree of cirrhosis in the other 17 patients (Figure 2).



(a) normal histology on H&E stain (b) diffuse amorphous iron-containing clumps of hemosiderin (blue deposits) in sinusoidal Kupffer cells (arrow) on Perls' Prussian blue stain.

Figure 1. Liver biopsy micrographs of patients with renal iron overload.



(a) bridging fibrosis (Arrow) on H&E stain (b) diffuse and mixed (sinusoidal Kupffer cells and hepatocytes) amorphous iron-containing clumps of hemosiderin (blue deposits) (Arrow) on Perls' Prussian blue stain.

Figure 2. Liver biopsy micrographs of patients with iron overload in renal disease.

3.2. Comparison of IO-Groups

Those patients were classified into three groups, viz. without hepatic disease, with acquired hemosiderosis, and with cirrhosis. The demographic data of the three patient groups were compared with regard to duration of renal disease, duration of IO treatment, clinical cirrhosis, and response to therapy (Table 1). Significantly longer duration of RRT as well as higher serum TS%, ferritin, and CT-density were observed in those with cirrhosis compared to those with acquired hemosiderosis, followed by those without liver disease. The latter two groups had a higher female predominance compared to those with cirrhosis. Overt cirrhotic disease, viz. clinical, laboratory indices, and/or radiological, was evident in 12 of the 17 cirrhotic patients and in none of the other two groups. As seen in Table 2, patients with biopsy-proven liver disease: (a) higher serum TS%, ferritin, and CT-density were most evident in patients on MPD, and (b) higher response to therapy (holding iron supplementation and phlebotomy) was more effective in patients on MHD.

3.3. Testing for Endocrinopathy

Endocrine testing showed normal sex hormones in male patients, indicating an intact pituitary-gonadal axis. In female patients, 2 KTx patients were < 40 and had adequate sex hormones and an intact GnRH stimulation test. On the other hand, low levels of sex hormones with high gonadotrophins indicated primary gonadal failure, except for 2 MPD patients with low gonadotrophins, indicating a diseased anterior lobe of the anterior pituitary gland that failed to increase following GnRH stimulation tests. Moreover, they had low IGF and inappropriately low TSH in the face of low free T4, indicating pituitary disease. Copeptin levels were normal in all patients, indicating an intact posterior lobe of the pituitary gland. The ACTH stimulation test produced an adequate increment in plasma cortisol, indicating intact adrenal function. For assessment of endocrine function, 6 patients with long-standing diabetes mellitus were excluded from assessment of beta-cell function yet had pancreatic elastase, amylase, and lipase, indicating intact stromal exocrine function. The remaining patients had normal endocrine and exocrine function on testing.

3.4. Cardiac Assessment

Seven patients had a history of ischemic heart disease, and localized wall motion abnormalities were excluded from the study, as well as 2 patients with aortic stenosis. In the remaining patients, 2 patients on MPD showed features of dilated cardiomyopathy that were slowly progressive on follow-up and without history or laboratory indicators of viral myocarditis.

3.5. Treatment Outcome

Treatment was tolerated in all patients. It led to significant and rapid laboratory improvement in all parameters (TS%, SF, BM iron stores, and CT density) within 3 months (Table 1 and Table 2, Figure 3). Moreover, over a period of 42 ± 11 months, no new cases of hepatic, endocrine, or cardiac disease had evolved. None of the patients with (a) hemosiderosis had developed clinical, laboratory, or radiological evidence of cirrhosis, (b) overt and non-overt cirrhotic disease had manifested disease progression, and (c) endocrine or cardiac disease had manifested disease progression.

Table 1. Demographic characteristics and response to phlebotomy in iron-overloaded renal patients on different RRT.

Patient's groups*	Gender (F/M)	Age (years)	Type of RRT	Duration of RRT (months)	Response to phlebotomy								
					Serum ferritin		Transferrin saturation%		Bone marrow iron		CT density		
					Start	3 months	Start	3 months	Start	3 months	Start	3 months	12 months
I-IO—yet without liver disease	461/339	49 ± 9	739/745CKT, 30/40MHD, 9/12MPD, 22/26KTx	76 ± 19*	1431 ± 86	412 ± 54	42 ± 8	24 ± 5	6	3.1 ± 0.2	73 ± 7*	69 ± 6*	52 ± 4*

Continued

II- With hemosiderosis	5/1	50 ± 6	3/6CKT, 2/10MHD, 0/3MPD, 1/4KTx	84 ± 18*	1773 ± 47	495 ± 80	47 ± 1	25 ± 3	6	3.6 ± 0.5	82 ± 4	71 ± 5	63 ± 5
III- With cirrhosis	7/10	56 ± 11	3/6CKT, 8/10MHD, 3/3MPD, 3/4KTx	99 ± 15*	2090 ± 29	570 ± 139	55 ± 3*	26 ± 2	6	3.8 ± 0.7	84 ± 5	73 ± 5	65 ± 5
Statistical difference		NS		p < 0.05	p < 0.01	NS	p < 0.001	NS	NS	NS	<0.01	<0.05	<0.05

Abbreviations: RRT; renal replacement therapy, RD; renal disease, F; female, M; male, SF, CT; computed tomography; RRT: renal replacement therapy, CKT: conservative kidney therapy, MHD: maintenance haemodialysis, MPD: maintenance peritoneal dialysis, KTx: kidney transplantation. Data expressed as mean ± standard deviation with NS; not significant, (*) significant difference.

Table 2. Demographic characteristics and response to phlebotomy in iron overload patients with hepatic disease on different renal replacement therapies (RRT).

Patient's RRT*	Gender (F/M)	Age (years)	Duration of RD (months)	Response to phlebotomy								
				Serum ferritin		Transferrin saturation%		Bone marrow iron		CT density		
				Start	3 months	Start	3 months	Start	3 months	Start	3 months	12 months
I-CKT	3/3	53 ± 8	89 ± 17*	1948 ± 187	496 ± 80	54 ± 2	24 ± 3	6	3.7 ± 0.8	83 ± 1	74 ± 3	65 ± 4
II- MHD	4/6	55 ± 6	99 ± 16	1907 ± 24	585 ± 132	55 ± 2	26 ± 2	6	4 ± 0.7	83 ± 3	69 ± 4*	59 ± 6*
III- MPD	2/1	74 ± 2*	82 ± 19	2143 ± 389*	557 ± 97	61 ± 6*	26 ± 2	6	3.6 ± 0.5	90 ± 7*	75 ± 3	62 ± 2
IV- KTx	3/1	44 ± 7	100 ± 14	1945 ± 182	590 ± 177	54 ± 6	26 ± 3	6	3.5 ± 0.6	85 ± 5	71 ± 7	65 ± 5
Statistical difference		p < 0.05	NS	p < 0.01	NS	p < 0.001	NS	NS	NS	p < 0.05	p < 0.05	<0.05

Abbreviations: RD; renal disease, F; female, M; male, SF, CT; computerized tomography, Rx: phlebotomy treatment, RRT: renal replacement therapy, CKT; conservative kidney therapy, MHD; maintenance haemodialysis, MPD; maintenance peritoneal dialysis, KTx; kidney transplantation. Data expressed as mean ± standard deviation with NS: statistically not significant, (*) significant.

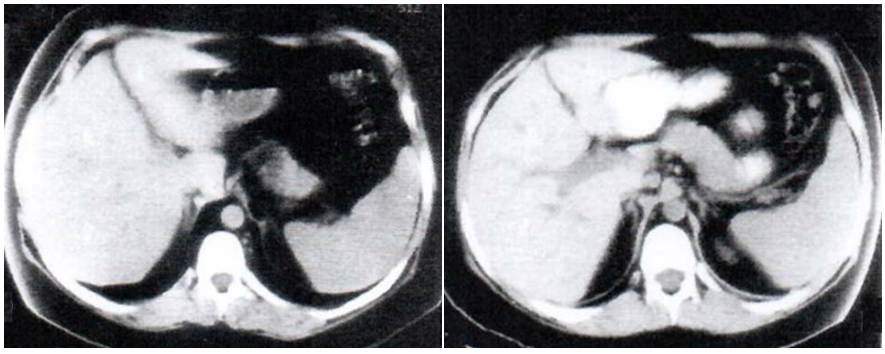


Figure 3. CT scan of the liver in a renal patient with iron overload, showing a decrease in hepatic CT density from 86 HU at the start (A) to 75 HU after repeated phlebotomy (B).

4. Discussion

In our study, we have shown that IO is prevalent (23%) in patients on different modalities of RRT. Moreover, screening our patients for 5 years disclosed that

biopsy-proven IO-hepatopathy (liver hemosiderosis and even cirrhosis) was prevalent among 3% of patients who lacked hemochromatosis genes. In our patients, IO may have been associated with previous blood transfusions, yet the study was conducted after the availability of erythropoietin, which incriminates more the ill-advised intravenous iron supplementation [23]. The latter may have been due to (a) avoidance of early erythropoietin therapy for financial reasons, (b) attempts to "boost" erythropoietin effect and hence limit its use and cost by keeping higher levels of iron stores, and (c) inadequate screening and treatment of other hematinics (vitamin B12 and folates) [20]. Unfortunately, such practice is hazardous without adequate and periodic monitoring of blood hemoglobin level, serum TS% and ferritin, at least on a monthly basis, and vitamin B12 and folates every 3 months [21]. In our study, we aimed at hemoglobin levels > 100 g/L to improve oxygen-carrying capacity and < 120 g/L to avoid ischemic complications in this patient population [22] [24]. Moreover, in our methodology, we screened for IO by using both TS% and SF since the latter is elevated in inflammation, alcohol consumption, and liver disease [25]. Furthermore, confirmation was done by measurement of bone marrow iron stores and CT-density. In screening for liver disease, transaminases were done to reflect on hepatocyte injury, and we used both GGT and alkaline phosphatase to reflect on IO-infiltrative disease. Alkaline phosphatase is not liver-specific and can be elevated in bone diseases [26]. Moreover, for definitive IO-hepatopathy, liver biopsy was essential [17]. In our study, we confirmed the risk of hepatic, endocrine, and cardiac disease associated with long-standing and severe IO [11]-[13] [21]. Moreover, we showed that IO-hepatopathy is the most common complication of IO and may precede the development of endocrine and cardiac IO-disease, since the latter complications were limited only to those with heavy IO-hepatopathy. With regards to therapy of IO in our patient population, we used a modified protocol of IO-chelation with periodic phlebotomy, similar to that in hemochromatosis patients [27]. We avoided chelating agents that bind to serum iron and enhance its excretion in urine and stool, viz. deferoxamine and oral agents (deferasirox and deferiprone), as well as gut-related polymeric chelators, for their renal mode of action, slow action, side effects, and cost [4]. We applied (avoidance of iron supplementation and periodic phlebotomy) yet added (a) anemia correction by erythropoietin and (b) correction of other common hematinics (vitamin B12 and folate). We showed that such therapy, if started early, can reverse IO and halt the progression of liver disease. The latter was more effective in those on MHD with more blood loss during hemodialysis sessions.

5. Conclusion

IO-hepatopathy, endocrinopathy, and cardiomyopathy can develop following inappropriate and excessive intravenous iron infusions in renal patients on different RRT. Vigilant monitoring of their hematinic therapy is indicated, and therapeutic phlebotomy is useful in its management.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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