Anemia Management among Hemodialysis Patients with High Ferritin Levels

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ABSTRACT: **Background:** Anemia management strategies among chronic hemodialysis patients with high ferritin levels remains challenging for nephrologists.

Objectives: To compare anemia management in stable hemodialysis patients with high (≥ 500 ng/ml) vs. low (‹ 500 ng/ml) ferritin levels

Methods: In a single center, record review, cohort study of stable hemodialysis patients who were followed for 24 months, an anemia management policy was amended to discontinue intravenous (IV) iron therapy for stable hemodialysis patients with hemoglobin › 10 g/dl and ferritin ≥ 500 ng/ml. Erythropoiesis-stimulating-agents (ESA), IV iron doses, and laboratory parameters were compared among patients with high vs. low baseline ferritin levels before and after IV iron cessation.

Results: Among 87 patients, 73.6% had baseline ferritin ≥ 500 ng/ml. Weekly ESA dose was greater among patients with high vs. low ferritin (6788.8 ± 4727.8 IU/week vs. 3305.0 ± 2953.9 IU/week, $P = 0.001$); whereas, cumulative and monthly IV iron doses were significantly lower (1628.2 ± 1491.1 mg vs. 2557.4 ± 1398.9 mg, $P = 0.011$, and 82.9 ± 85 vs. 140.7 ± 63.9 mg, $P = 0.004$). Among patients with high ferritin, IV iron was discontinued for more than 3 months in 41 patients (64%) and completely avoided in 6 (9.5%). ESA dose and hemoglobin levels did not change significantly during this period.

Conclusions: Iron cessation in chronic hemodialysis patients with high ferritin levels did not affect hemoglobin level or ESA dose and can be considered as a safe policy for attenuating the risk of chronic iron overload.

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KEY WORDS: anemia, ferritin, hemodialysis, iron

Even though appropriate anemia management has significantly changed over the last decade, effective care remains a challenge for nephrologists treating patients with end stage renal disease (ESRD) who are undergoing hemodialysis. Substantial changes have occurred since targeting high hemoglobin above 12 g/dl by erythropoiesis-stimulating-agents (ESA) was found to be associated with worse outcomes, increased cardiovascular and cerebrovascular events, and death. Keeping hemoglobin levels steady at 10–11.5 g/dl is the current recommendation [1,2]. At the same time, several researchers have raised concerns regarding high dose ESA, which has been associated with malignancy progression and cerebrovascular events [1-3]. This finding led to a U.S. Food and Drug Administration black box warning to recommend the lowest possible ESA dose. However, a short-term, randomized, controlled trial found that intravenous (IV) iron therapy of 1 gram to effectively increase hemoglobin levels, even in patients with ferritin levels 500–1200 ng/ml and transferrin saturation (TSAT) < 25%. Ferritin > 800 ng/ml, did not lead to lower magnitude of response to IV iron [4]. The Dialysis Outcomes and Practice Patterns Study (DOPPS), which evaluated practice patterns in centers around the world, reported increased use of IV iron in parallel with decreased ESA dose and slightly lower median hemoglobin levels [5-7]. This trend was accompanied by mean ferritin levels increasing from 556 to 764 ng/ml, with up to 41% of patients exceeding 800 ng/ml. However, high ferritin levels have been correlated with increased mortality in the hemodialysis population in the United States and Europe, especially when ferritin levels exceed 1200 ng/ml [8,9].

The latest Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for managing anemia in chronic kidney disease patients tried to establish global recommendations [10-12]. According to the guidelines, anemic hemodialysis patients should receive a trial of IV iron before ESA, or if a decrease in ESA dosage is desired, as long as TSAT is ≤ 30% and ferritin is ≤ 500 ng/ml. Once ferritin is > 500 ng/ml, especially if TSAT is > 30%, IV iron therapy should be administered with significant caution. These recommendations are based on sparse data to support an upper ferritin threshold or TSAT levels in which IV iron should be avoided.

Based on these clinical guidelines, the anemia management policy in our hemodialysis unit was amended in 2014. All staff nephrologists were instructed to discontinue IV iron therapy for stable hemodialysis patients with hemoglobin levels >10 g/dl and ferritin levels ≥ 500 ng/ml. Simultaneously, patient data were collected and analyzed to determine the preferred anemia management approach in hemodialysis patients with high ferritin levels.

*The first and second authors contributed equally to this study

PATIENTS AND METHODS

STUDY DESIGN

This record-review cohort study of hemodialysis patients treated with chronic hemodialysis was conducted in a single academic center from September 2013 to August 2015. The Meir Medical Center ethics review committee approved the study. Informed consent was not required. During the study period, departmental policy changed to include a recommendation to avoid IV iron therapy for patients with ferritin ≥ 500 ng/ml. Patients were followed until end of the study (August 2015) or until transplantation, death, acute severe illness, or need for more than two units of blood transfused within 1 month. Inclusion criteria were age 18 years or older and hemodialysis treatment longer than 6 months. Exclusion criteria were unstable clinical state defined as recurrent admissions, repeated need for blood transfusions or hemoglobin ≤ 9.0 mg/dl, or carriage of hepatitis. Demographic data extracted from charts included age, duration of hemodialysis prior to study initiation (hemodialysis vintage), cause of ESRD, access type, filter type, weekly hours of dialysis, and smoking habits, in addition to chronic medications including anti-platelets, anti-coagulates, and angiotensin converting enzyme inhibitors or angiotensin receptor blockers. All changes in anemia management, including weekly erythropoietin dose (darbapoetin dose was converted to erythropoietin by a ratio of 1:200) and IV ferric gluconate dosage, were recorded as well as number blood transfusions during the study. Blood test results obtained at the mid-week dialysis session for routine monthly physician rounds were collected for statistical analysis. Blood tests, included complete blood count, reticulocyte hemoglobin content (CHr), liver function tests (GOT, GPT, LDH, ALK Phos), albumin, C-reactive protein (CRP), iron levels, and transferrin. Ferritin, vitamin B12, and folic acid levels were measured every 3 months.

Patients were grouped according to their mid-study ferritin level in September 2014, defined as baseline ferritin level. The study population was divided into a low ferritin group (< 500 ng/ml) and a high ferritin group (≥ 500 ng/ml). Mean ESA dosage, IV iron dosage, and all other laboratory parameters were compared among groups. The change in ferritin level was calculated as the difference between last ferritin measured during the study and the baseline level. The effect of IV iron cessation was assessed among patients with high ferritin levels only. Cessation was defined as therapy being withheld for more than 3 consecutive months. We ensured that a cumulative dose of > 500 mg ferric gluconate was given before discontinuation. Mean change in hemoglobin, weekly ESA dosage, CHr, and TSAT were calculated every 3 consecutive months immediately before and after cessation as long as iron was held or until the end of follow-up. Ferritin level and mean TSAT before iron cessation (baseline) were compared to final levels defined as either the end of follow-up or the resumption of iron therapy.

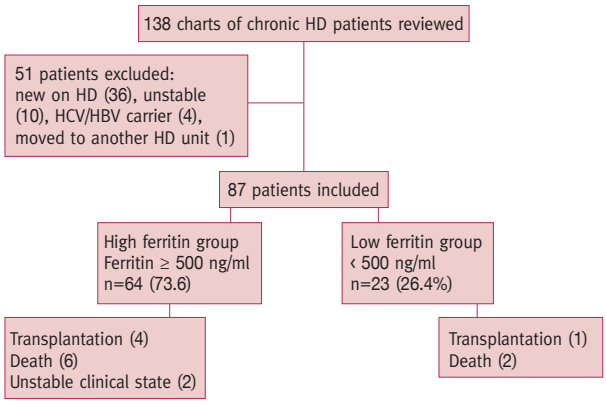
STATISTICAL ANALYSIS

Data are presented as numbers and percentages for non-metric variables and as means and standard deviations for continuous parameters. Metric variables were checked for normality (Shapiro–Wilk test). Mann–Whitney non-parametric test or *t*-test was used to test the difference between two ferritin groups, each when appropriate. Differences among the three groups were tested with one-way ANOVA or Kruska–Wallis test with Bonferroni post hoc correction. Differences in nominal variables were evaluated with chi-square or Fisher's exact test. Multivariate linear regression analysis was used to identify independent predictors that influenced baseline study ferritin levels. Changes in ESA, hemoglobin, TSAT, and ferritin after cessation were analyzed with paired *t*-test, Wilcoxon, and repeated measures. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 23 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

A total of 138 electronic medical records for chronic hemodialysis patients were reviewed. Among these, 51 were excluded from analysis: 36 had been undergoing hemodialysis for less than 6 months, 10 were unstable as defined in exclusion criteria, 4 were carriers of hepatitis virus B or C, and 1 patient moved to another dialysis facility. A total of 87 patients were included in the cohort. At baseline, 64 (73.6%) had ferritin levels ≥ 500 ng/ml and were defined as the high group, 23 (26. 4%) had ferritin levels < 500 ng/ml and were defined as the low group. Fifteen patients (17%) did not complete the study, eight died, and five received a transplant. Follow-up was discontinued in two patients due to acute illness [Figure 1]. Demographic characteristics of patients are presented in Table 1. Hemodialysis vintage was the only demographic parameter that was statistically dif-

Figure 1. Study flowchart



HD = hemodialysis, HBV = hepatitis B virus, HCV = hepatitis C virus

Table 1. Baseline clinical characteristics of study population stratified by ferritin level

Characteristic	Low ferritin (< 500 ng/ml) N=23	High ferritin (≥ 500 ng/ml) N=64	*P* value
Mean age, years	66.4 ± 13	65.5 ± 13.3	0.775
Dialysis vintage, months	16.61 ± 15.04	38.67 ± 33.2	0.003
Mean hours of dialysis per week	11.2	11.6	0.391
ESRD etiology (%)			
Diabetes mellitus	45%	50.0%	
Hypertension–nephrosclerosis	22.7%	14.1%	
Glomerulonephritis	13.6%	9.4%	
Polycystic kidney disease	9.1%	6.3%	
Unknown	0.0%	10.9%	
Others	4.5%	7.8%	
Blood access (%)			
Permacath	30.4%	20.3%	0.504
AV fistula	60.9%	64.1%	
AV Graft	8.7%	15.6%	
Filter type (%)			
High efficiency	78.3%	68%	0.435
High flux	21.7%	31.3%	
Smoker (%)			
Yes	18.2%	14.1%	0.732
No	81.8%	85.9%	
Aspirin (%)			
Yes	59.1%	57.8%	0.916
No	40.9%	42.2%	
Clopidogrel (%)			
Yes	18.2%	14.1%	0.372
No	81.8%	85.9%	
Warfarin (%)			
Yes	9.1%	9.4%	1
No	90.9%	90.6%	

ESRD = end stage renal disease

ferent in the two groups. Patients with high ferritin levels were on hemodialysis longer than patients in the low group (38.67 ± 33.2 months vs. 16.61 ± 15.04 months, respectively, $P = 0.003$).

Mean erythropoietin dose per week was lower in the low group compared to the high group, 3305 ± 2953.9 IU/week vs. 6788.8 ± 4727.8 IU/week, respectively, $P = 0.001$ [Table 2]. Total cumulative iron dose and monthly iron dose were significantly higher in patients within the low group compared to the high group, 2557.4 ± 1399 mg (follow-up 19.1 ± 5.5 months) vs. 1628.2 ± 1491 mg (follow-up 21.2 ± 4.3 months), $P = 0.01$; 140.7 ± 63.9 mg per month vs. 82.9 ± 85 mg per month, $P = 0.004$, respectively. The percentage of months that IV iron was given during the study was also significantly higher in the low ferritin group, 64.3% ± 30.4% vs. 34.9% ± 26.2%, $P = 0.001$[Table 2]. Hemoglobin level was kept within the recommended range in both groups but was significantly higher in the low group as compared to the high group (11.4 ± 0.6 g/dl vs. 11.0 ± 0.6 g/dl, $P = 0.01$); however, TSAT was similar in the two groups (24.1% ± 6.5% vs. 26.7% ± 6.5%, $P = 0.102$) [Table 2]. By the end of the study, ferritin levels had decreased significantly in the high ferritin group as compared to baseline, -228.48 ± 302.8 ng/ml, but remained above 500 ng/ml [Table 2].

Table 2. Anemia management parameters stratified by ferritin level

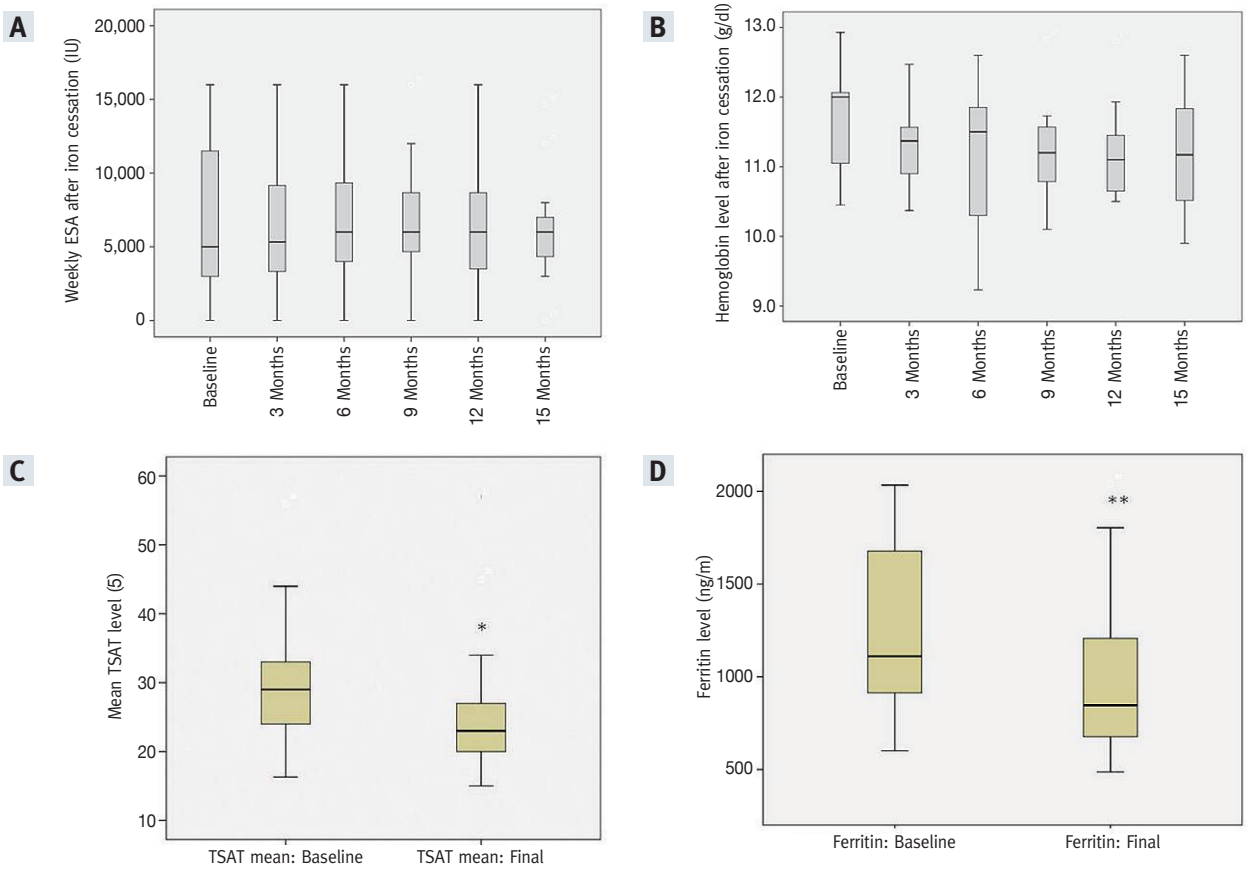
Parameter	Low ferritin (< 500 ng/ml) N=23	High ferritin (≥ 500 ng/ml) N=64	*P* value
Follow-up, months	19.1 ± 5.5	21.2 ± 4.3	0.070
Mean ESA per week (IU)	3305.0 ± 2953.9	6788.8 ± 4727.8	0.001
Cumulative iron dose (mg)	2557.4 ± 1398.9	1628.2 ± 1491.1	0.011
Monthly iron dose (mg)	140.7 ± 63.9	82.9 ± 85.0	0.004
Months received iron (%)	64.3 ± 30.4	34.9 ± 26.2	0.0001
Hemoglobin (g/dl)	11.4 ± 0.6	11 ± 0.6	0.010
CHr	30.9 ± 2.1	31.9 ± 2.0	0.041
TSAT (%)	24.1 ± 6.5	26.7 ± 6.5	0.102
Baseline ferritin level (ng/ml)	303.7 ± 151.2	1019.6 ± 431	
Last ferritin level (ng/ml)	368.1 ± 214.4	791.2 ± 358.5	
Difference between last and baseline ferritin levels (ng/ml)	62.39 ± 219.12	-228.48 ± 302.8	0.007
Albumin (g/dl)	3.7 ± 0.4	3.8 ± 0.2	0.040
C-reactive protein (mg/dl)	1.4 ± 1.1	1.6 ± 1.5	0.446

ESA = erythropoiesis-stimulating-agents, CHr = reticulocyte hemoglobin content, TSAT = transferrin saturation

In the low ferritin group, levels had increased by a mean of 62.4 ± 219.1 ng/ml. Multi-variable logistic regression analysis demonstrated association of baseline ferritin levels with dialysis vintage (β coefficient 0.311, $P = 0.003$), followed by total IV cumulative iron dose given during follow-up (β-coefficient -0.269, $P = 0.006$), mean weekly ESA dose (β coefficient 0.23, $P = 0.05$), and change between last and baseline ferritin levels (β coefficient) -0.19, $P = 0.039$.

IV iron cessation for longer than 3 consecutive months was documented in 41 patients in the high ferritin group (≥ 500 ng/ml). All had received a cumulative iron dose of more than 500 mg during the 6 months prior to cessation. Mean follow-up after IV iron cessation was 11.1 ± 5.3 months (median 10.5 months). Neither hemoglobin level nor weekly erythropoietin dosage changed significantly after iron therapy was withheld [Figure 2]. Ferritin levels, TSAT, and CHr decreased from baseline to final study measurements, 1265 ± 440.4 ng/ml to 957 ± 389.6 ng/ml, $P = 0.0001$; 30% ± 11% to 24% ± 8%, $P = 0.016$; and 32.7% ± 1.65% to 30.95% ± 2.03%, respectively, $P = 0.011$ [Figure 2]. IV iron therapy was reinitiated in 11 patients (26.8%) with a mean of 8.27 ± 3.88 months (range 4–16 months). Ferritin and TSAT levels at this time did not differ from ferritin and TSAT levels among patients in whom iron was not restarted (815 ± 302 ng/ml vs. 894 ± 365.5 ng/ml, $P = 0.606$; 23.5% ± 6.7% vs. 25.7% ± 9.2% $P = 0.474$, respectively). Only three patients (7%) required a blood transfusion during the cessation period, which was followed by re-initiation of IV iron therapy. Six patients (9.4%) in the high group did not receive any IV iron or blood transfusion during a mean follow-up of 23 ± 3.7 months. Initial ferritin level among these patients was 1511.2 ± 552.8 ng/ml (range

Figure 2. IV iron discontinuation for longer than 3 consecutive months was documented in 41 patients within the high ferritin group (≥ 500 ng/ml) **[A]** Weekly erythropoietin dosage calculated as mean of every 3 consecutive months **[B]** Hemoglobin level calculated as mean of every 3 consecutive months **[C]** Mean TSAT level at baseline versus final level. Baseline was defined as the mean of 3 months before cessation of iron therapy. Final was defined as the mean of the last 3 months before the end of the follow-up or the restarting of iron therapy **[D]** Ferritin levels at baseline adjacent to iron cessation vs. final either at the end of the follow-up period or adjacent to the restart of iron therapy.
Data are expressed as mean ± standard deviation
*P < 0.05 compared with baseline TSAT
**P < 0.05 compared with baseline ferritin level



ESA = erythropoiesis-stimulating-agents, TSAT = transferrin saturation

843 ng/ml to 2279 ng/ml), which had decreased to 1003.7 ± 735.2 ng/ml by the end of the study.

DISCUSSION

This observational study describes anemia management among a cohort of prevalent hemodialysis patients from September 2013 to August 2015. During the study, the KDIGO guidelines [13] were implemented in the hemodialysis unit and a trial of iron cessation was advocated for stable patients with high ferritin levels (≥ 500 ng/ml). Nonetheless, treatment decisions were authorized by staff nephrologists according to each patient's medical condition and laboratory results. Patients were grouped according to baseline ferritin levels into high (≥ 500 ng/ml) or low (< 500 ng/ml). The high group included 73.6% of the cohort, 67% of this group had ferritin levels ≥ 800 ng/ml. Dialysis vintage was the only baseline parameter that significantly correlated with ferritin levels; that is, a longer dialysis period prior to the study initiation was associated with higher ferritin levels. Neither CRP nor albumin correlated with ferritin levels.

Serum ferritin concentration results from leakage of tissue ferritin (intracellular iron storage) and constitutes a marker of iron status [13,14]. However, ferritin is also an acute phase reactant and can be increased as a result of inflammation and malnutrition, as was demonstrated in maintenance hemodialysis patients [15-17]. The finding that ferritin levels did not correlate with CRP or albumin concentration in our cohort

suggests that by excluding unstable patients (those with low inflammation markers) we eliminated their contribution to ferritin levels. We tend to think that the high ferritin level among our cohort, which included prevalent, stable hemodialysis patients, is mostly indicative of large, cumulative iron exposures during the pre-dialysis and dialysis periods, secondary to previous liberal use of IV iron in our unit prior to the study period. The global increase in serum ferritin levels among hemodialysis patients correlated with worldwide anemia management trends and was attributed to increased iron administration [5,7,16,18]. The latest DOPPS report presented in Vienna in 2016 [19] demonstrated an increase in ferritin level between phase 4 (2009–2011) and phase 5 (2012–2015) from a mean of 620 ng/ml to 800 ng/ml. This increment correlated with an increased monthly IV iron dose, with approximately 30% of patients receiving monthly doses of 400 mg iron or more. However, a large study that analyzed the relation between iron administration and ferritin level demonstrated an initial increase in ferritin attributed to high iron doses followed by a continued high ferritin level that was not explained by iron administration but was attributed to low doses of ESA [16]. This theory disagrees with our findings, which demonstrated a direct relation between weekly ESA dose and ferritin levels among patients with high ferritin, suggesting functional iron deficiency among this group.

As expected, total IV iron over the study period and monthly IV iron dose given to patients with high ferritin levels were significantly lower than doses given to patients with low ferritin. However, the high group received significantly larger weekly ESA doses than patients in the low group. Mean hemoglobin levels and TSAT were not significantly different in the two groups. The observation in which patients with high ferritin levels received significantly larger ESA dose suggests hypo-responsiveness to ESA and the presence of functional iron deficiency among this group. Functional iron deficiency is caused by sequestration of iron within the reticuloendothelial system, primarily due to inflammation. Hepcidin, which was found to be up-regulated in response to increased circulating and stored iron levels as well as to inflammation and infection, is believed to be fundamental to the development of functional iron deficiency [13,20,21]. Unfortunately, hepcidin levels were not measured in this cohort. The DOPPS study demonstrated significant concordance between IV iron and ferritin levels. Much lower correlation with TSAT suggested that hepcidin diverts the administered iron directly into storage sites and thus has a lower effect on TSAT levels [5]. Among our cohort, TSAT did not differ significantly in the two groups .This finding supports the weak association between TSAT and iron storage compared to serum ferritin levels.

Iron therapy among patients within the high ferritin group varied. The majority underwent a trial of iron cessation. Cessation for more than 3 consecutive months was documented in 41 patients (64%) and did not cause significant changes in hemoglobin levels or weekly ESA doses. As expected CHr, TSAT, and ferritin levels decreased significantly from baseline to final measurements. However, mean TSAT and ferritin level were still high at final measurements, 24 ± 0.08% and 957 ± 389.6 ng/ml, respectively, which suggests large iron stores despite cessation of iron. On average, iron was withheld for 11.1 months. Re-initiation of iron therapy was not guided by TSAT or ferritin levels, suggesting other factors such as the rate of hemoglobin decline, clinical symptoms, or additional blood tests that were not assessed in our study. Within the high ferritin group, six patients (9.4%) did not receive any iron therapy during 23 ± 3.7 months of follow-up. Ferritin levels among this group were significantly higher, suggesting large iron stores that could be used for prolonged periods without iron administration.

Iron loss among hemodialysis patients varies greatly. It is affected by many factors, including antiplatelet and anticoagulant therapy, dialysis access, co-morbidities, and frequency of blood sampling [13]. Previous studies demonstrated that iron loss ranges from 1 to 5 grams per year [22,23]. Since this component as well as iron storage and functional iron deficiency are not accurately assessed, response to iron cessation could not be predicted. However, our findings support a trial of iron cessation among stable hemodialysis patients with high ferritin levels. Iron cessation was found to be safe and helpful in reducing the risk of excessive iron administration without the threat of decreased hemoglobin or increased ESA dose. We think that once iron was discontinued in stable hemodialysis patients the excessive iron storage was utilized, as seen by decreased serum ferritin levels.

This study had several limitations. Its small sample size lowered sensitivity to detect modest differences in patient groups, as was observed in other large population-based studies [16,18,24]. The observational nature of this study permits potential bias to interfere with the results. This bias could be due to varying approaches by different physicians or to additional blood test results that might have influenced physicians' decisions, which were not fully integrated into the study.

This study was designed to follow a cohort of prevalent, stable hemodialysis patients. Patients who experienced recurrent or prolonged admission were excluded from the study. This design limits the ability to generalize our findings to incident, peritoneal, or other dialysis patients. Unfortunately, we did not measure hepcidin levels in the study population. High hepcidin levels in parallel with high ferritin levels could help define the subgroup of patients with functional iron deficiency. The PIVOTAL study [25] is an ongoing clinical trial, which includes 2080 hemodialysis patients across 55 sites in the U.K. who were randomized to a high- versus a low-dose IV iron regimen with a planned follow-up of 2 to 4 years. Hard endpoints such as death, myocardial infarction, strokes, heart failure, and infections are being assessed. This study completed its recruit-

ment during 2016 and its results will hopefully constitute an important landmark for guiding the preferred usage of iron administration among the hemodialysis population.

CONCLUSIONS

The latest KDIGO guidelines [13] recommend avoiding administration of IV iron in patients with ferritin > 500 ng/ml. However, since the DRIVE study [4] showed an increase in hemoglobin in response to IV iron even in patients with ferritin > 500 ng/ml, the KDIGO suggested a therapeutic trial of additional iron for selected patients with ferritin > 500 ng/ml. Data to support the upper ferritin limit above which IV iron should be withheld are insufficient. Our study demonstrated that patients with ferritin levels > 500 ng/ml who were adequately given lower dose of IV iron received significantly larger mean weekly ESA doses compared to patients with low ferritin level. Discontinuing iron among patients with high ferritin levels was safe and did not affect hemoglobin level or ESA dosage; whereas, CHr, TSAT, and ferritin levels gradually decreased.

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"Your success and happiness lies in you. Resolve to keep happy, and your joy and you shall form an invincible host against difficulties"

Helen Keller, (1880–1968), American author, political activist, and lecturer. She was the first deaf-blind person to earn a bachelor of arts degree

"The diversity of the phenomena of nature is so great, and the treasures hidden in the heavens so rich, precisely in order that the human mind shall never be lacking in fresh nourishment"

Johannes Kepler, (1571–1630), German mathematician, astronomer, and astrologer