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ORIGINAL ARTICLE

Iron deficiency anemia and iron losses after renal transplantation

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Summary

Iron deficiency contributes to anemia after transplantation. The magnitude of iron loss from blood loss in the peri-transplantation period has not been quantified. We prospectively estimated phlebotomy and surgical losses over the first 12-weeks following transplantation in 39 consecutive renal transplant recipients on hemodialysis (HD), peritoneal dialysis (PD), or chronic kidney disease (CKD). At transplant, ferritin levels were <200 ng/ml in 51% of the patients, and iron saturation was ≤20% in 44%. CKD patients more commonly had ferritin levels <200 ng/ml than either HD or PD patients (100% vs. 21% vs. 67%, $P < 0.0002$, respectively). Blood loss was similar among HD, PD and CKD patients (833 ± 194 vs. 861 ± 324 vs. 755 ± 79 ml respectively, P = NS), and no difference between deceased and living donor transplant recipients (881 ± 291 vs. 788 ± 162 ml, $P = 0.33$). Based on baseline hemoglobin (Hgb) of 11.8 g/dl, we estimated that an additional 330 mg of iron was needed to normalize hemoglobin to 13 g/dl, and 605 mg to increase hemoglobin to 14 g/dl. Blood and iron losses over the first 12 weeks post-transplant are substantial and may warrant early administration of intravenous iron.

Introduction

Anemia is common after renal transplantation and is frequently under-treated [1–6]. An European study found 38.6% of the 4263 patients who received a kidney transplant within the previous 5 years were anemic (defined as hemoglobin <13 g/dl for men and <12 g/dl for women) [2]. Other studies have also found a high prevalence of anemia among renal transplant recipients, even when graft function was normal [2,6–9]. Anemia is prevalent among these patients despite the rapid increase in endogenous erythropoietin production following successful graft function.

Anemia in chronic kidney disease (CKD) reduces quality of life and is associated with development and progression of left ventricular hypertrophy (LVH). In kidney transplant patients, anemia has been associated with development of post-transplant congestive heart failure [10,11]. Iron deficiency is a major cause of anemia and is independently associated with post-transplant cardiovascular events, the leading cause of death in kidney transplant recipients [8].

The prevalence of iron deficiency, defined as the percentage of hypochromic red blood cells ≥2.5%, in 438 renal transplant recipients was 20% [6]. Shibagaki *et al.* found significant anemia in 192 kidney transplant recipients (hemoglobin <11 mg/dl in women and <12 mg/dl in men) was common at 19.3% at 6 months and 19.8% at 12 months. Only 36% of these anemic patients had their iron profile assessed during their study. Among these, half of them were iron deficient (defined as ferritin <100 μg/dl, or transferrin saturation (TSAT) <20%) [12]. Shah *et al.* studied 1511 renal transplant patients, and found the prevalence of anemia after transplant to be

45.6%. Ferritin levels were measured only in 699 (46%) patients [9].

Major causes for iron deficiency anemia in renal transplant recipients include inadequate iron stores at the time of transplant, surgical blood losses, and frequent post-transplant phlebotomy. With recovery of renal function, erythropoiesis depletes storage iron. Moore *et al.* found that 60% of renal transplant recipients without iron deficiency at the time of transplant became iron-deficient by 6 months post-transplant [13]. Taken together, these studies support that iron deficiency is an overlooked and correctable contributor to post renal transplant anemia.

To determine the magnitude of blood and iron losses in the first 12 weeks following transplant, we performed a prospective observational study of 39 consecutive renal transplant recipients, assessing baseline iron storage markers, and recording actual blood losses via surgery and phlebotomies over the first 12 weeks, and administering intravenous (IV) iron to those found to be iron-deficient.

Materials and methods

The study was approved by the Washington University Human Research Protection Office. We identified 42 consecutive patients receiving a living or deceased donor renal allograft between January 1 and April 27, 2004 at our center. We excluded three patients from our analysis; one because of primary graft dysfunction, one who received a combined liver-kidney transplant, and one who received IV iron supplementation despite a TSAT of 23%, which was not our usual clinical practice.

Hospital records were reviewed for demographic data, laboratory data, dialysis status prior to transplant, the administration of blood transfusions or IV iron from the time of transplant to 12 weeks following transplant. Blood loss was calculated by adding blood loss during the surgery as stated in the operation report, and the blood volume of all phlebotomies performed. Blood loss from phlebotomy was determined by the fill volume of each phlebotomy tube and accounting for a 10 ml blood volume wasted with clearing of central lines at the time of obtaining blood samples during the hospitalization. Most vials had a 5 ml fill volume, while tacrolimus level samples, type and screens, and cytomegalovirus (CMV) PCR testing vial volumes were 7 ml each.

Standard testing immediately pretransplant included a complete blood count (CBC), type and screen, complete metabolic panel, prothrombin and partial thromboplastin time, final cross-match, lipid panel, human immunodeficiency virus, Epstein-Barr virus, hepatitis B and hepatitis C virus, creatine phosphokinase, lactate dehydrogenase, gamma glutamyl transpeptidase, folate, iron battery, ferritin, vitamin B12, phosphorus, uric acid, and quantitative CMV IgG. Patients typically had a CBC and a renal panel checked four more times during the transplant hospitalization, followed by weekly monitoring of calcineurin inhibitor levels, CBC, renal panel, and CMV testing during the time period studied.

We estimated 1.1 mg of iron per milliliter of packed red blood cells and used an average hematocrit of 35% to calculate the phlebotomy- and bleeding-associated iron losses. The estimated 1.1 mg of iron per milliliter of packed cells was based on 3.3 mg of iron in each gram of hemoglobin or 660 mg of iron in 200 g of hemoglobin [14]. The average volume of packed cells would be 200–250 ml. Thus if there are 3.3 mg iron per 1 g Hgb; if Hgb is 11.5 g/dl, then $(3.3 \times 11.5) = 38$ mg iron in 100 ml of blood. Thus the average blood loss approximately 780 ml blood = 295 mg iron. We estimated additional iron requirements to achieve normalization of hemoglobin of 13 or 14 g/dl from each patient's pretransplant hemoglobin.

Our clinical practice was to administer IV iron (iron dextran, INFeD; Watson Pharmaceuticals [Morristown, NJ, USA]) 1000 mg IV over 6 h after a 25 mg test dose during the transplant hospitalization when immediate pretransplant testing suggested iron deficiency (defined by TSAT ≤20% or ferritin <200 ng/ml). Patients without iron deficiency received no iron.

Thirty-seven patients received thymobglobulin 6 mg/kg over 4 days, one patient received basiliximab 20 mg × 2 doses, and one patient, a recipient of a 2-haplotype living related allograft, received no induction. All patients received tacrolimus with target trough levels of 7–10 ng/ml for the first month and 3–7 ng/ml thereafter. Thirty-two patients received mycophenolate mofetil with an average maintenance dose of 500 mg b.i.d. Seven patients received azathioprine with an average dose of 150 mg/day. Patients who were seropositive or whose donor was seropositive for CMV were randomized to receive prophylaxis with 450–900 mg/day of valganciclovir with the dose adjusted for renal function based or pre-emptive therapy upon detection of a positive CMV-PCR.

No patient was on an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin-receptor blocker (ARB) after transplantation during the study period.

Statistical analysis

Frequencies and means were tabulated for demographic variables and descriptive variables of interest. For all analyses, a limit of $P < 0.05$ was considered statistically significant. Chi-square statistics were calculated for categorical variables of interest. Fisher's exact test was used for contingency tables where any cell had an expected frequency <1 or where ≥20% of cells with expected frequencies were

≤5. One-way analysis of variance (ANOVA) was used to compare means of continuous variables by modality types. Statistical analysis was performed using SAS for Windows software, version 9.1 (SAS Institute, Cary, NC, USA).

Results

Patient demographic data

The average age was 51 ± 15 years old (range: from 19 to 72). Three were black, two were Asian and 34 were Caucasian. Nineteen of the 39 patients were female. Etiologies of renal failure were: diabetes ($n = 7$), hypertension ($n = 9$), diabetes and hypertension ($n = 5$), polycystic kidney disease ($n = 5$), IgA nephropathy ($n = 2$), focal segmental glomerulosclerosis ($n = 2$), reflux nephropathy ($n = 1$), chronic interstitial nephropathy ($n = 1$), thin basement membrane disease ($n = 1$), glomerulonephritis ($n = 2$) and unknown ($n = 4$). Sixteen patients received deceased donor allografts, 12 received living unrelated allografts, and 11 received living related allografts. Prior to transplantation, 19 patients were on hemodialysis (HD), 12 were on peritoneal dialysis (PD), and eight had CKD (estimated glomerular filtration rate < 20 ml/min) (Table 1). Anemia parameters at the time of transplantation are shown in Table 2.

Hemoglobin concentration

At the time of transplant, the average hemoglobin was 11.8 ± 1.7 g/dl (range 8.8 to 15.9 g/dl). The mean hemoglobin 6 weeks post-transplant was 11.5 ± 1.7 g/dl (range from 8.6 to 17.2 g/dl), and 12 weeks post-transplant was 12.2 ± 1.8 g/dl (range: from 7.7 to 17.9 g/dl). The prevalence of anemia (defined by hemoglobin <13 g/dl in men and <12 g/dl in women) was 67% at the time of transplant, 77% 6 weeks post-transplant, and 62% 12 weeks post-transplant. It varied slightly based on renal replacement therapy prior to transplant (Fig. 1). There were no significant differences in hemoglobin level between men and women at the three time points. The mean pretransplant hemoglobin was also similar in those patients on HD, PD or CKD (12.03 vs. 11.77 vs. 11.45 g/dl, P = NS among groups), and between those receiving a deceased donor kidney as compared with a living donor kidney (11.8 ± 1.3 g/dl vs. 11.8 ± 2 g/dl).

Iron assessment

Immediately prior to transplantation, the mean serum ferritin was 326 ± 309 ng/ml (range, from 6 to 962 ng/ml). Men tended to have a higher ferritin level than women, although statistically nonsignificant (415 ± 356 ng/ml vs. 223 ± 224 ng/ml, $P = 0.07$). The average ferritin was much lower in CKD patients (43.9 ng/ml) as compared with HD (518.8 ng/dl, $P < 0.001$) or PD (209.3 ng/ml $P = 0.04$). The overall prevalence of iron deficiency prior to transplant, defined as ferritin <200 ng/ml in HD and PD patients, ferritin <100 ng/ml in CKD patients, was 49% in all 39 patients, and 88% among the CKD patients (Fig. 2).

Table 1. Demographic data.

	Iron-deficient $n = 25$	Non iron-deficient $n = 14$	*P*-value
Age (years ± SD)	51 ± 13	52 ± 18	0.89
Gender			
Male	14 (56%)	6 (43%)	0.43
Ethnicity			
Caucasian	23 (92%)	11 (79%)	0.16*
African American	2 (8%)	1 (7%)	
Asian	None	2 (14%)	
Cause of ESRD			
Diabetes	3 (12%)	3 (21%)	0.82*
Hypertension	4 (16%)	2 (14%)	
GN	2 (8%)	0 (0%)	
PKD	4 (16%)	1 (7%)	
Other	12 (48%)	8 (57%)	
Donor type			
Deceased	10 (40%)	6 (43%)	0.86
Living	15 (60%)	8 (57%)	
Hemoglobin (g/dl ± SD) at the time of transplant			
All	11.7 ± 2.0	12.1 ± 1.1	0.37
HD	12.1 ± 1.8	12.0 ± 1.3	0.93
PD	11.4 ± 2.5	12.4 ± 0.7	0.34
CKD	11.5 ± 1.7	None	N/A
Ferritin (ng/dl)			
All	189.6 ± 233.9	577.0 ± 280.9	0.0003
TSAT (%)			
All	21.1 ± 8.6	33.1 ± 9.9	0.0008
Modality			
HD	9 (36%)	10 (71%)	0.02*
PD	8 (32%)	4 (29%)	
CKD	8 (32%)	0 (0%)	

HD, hemodialysis; PD, peritoneal dialysis; CKD, chronic kidney disease; TSAT, transferrin saturation; GN, glomerulonephritis; PKD, polycystic kidney disease; SD, standard deviation.
*Fisher's exact test.

Table 2. Hemoglobin, transferrin saturation (TSAT) and ferritin level at the time of kidney transplantation.

	All ($n = 39$)	HD ($n = 19$)	PD ($n = 12$)	CKD ($n = 8$)	*P* value
Hemoglobin (g/dl)	11.8	12.0	11.8	11.5	0.73
TSAT (%)	25.4	26.6	26.4	21.1	0.45
Ferritin (ng/ml)	326.2	518.8	209.3	43.9	<0.0001

HD, hemodialysis; PD, peritoneal dialysis; CKD, chronic kidney disease.

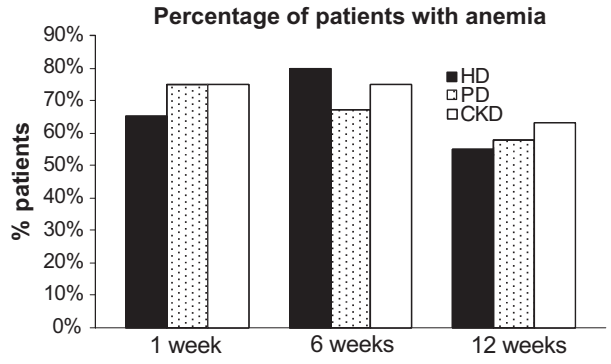

Figure 1 Comparison of percentage of patients with anemia post-transplant defined as hemoglobin <13 g/dl in men and <12 g/dl in women. Modalities are: solid bar, hemodialysis; stripe bar, peritoneal dialysis; chronic kidney disease, white bar.

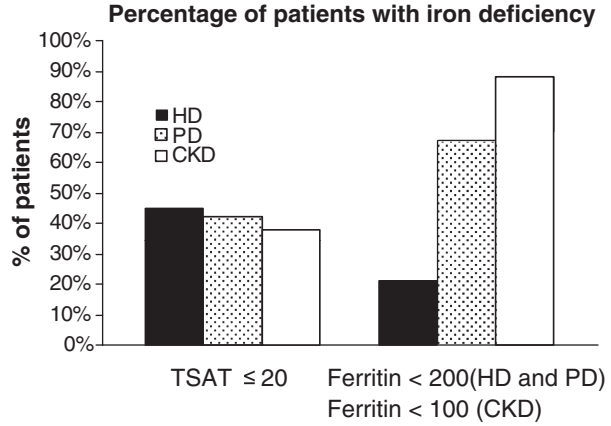

Figure 2 Comparison of percentage of patients presenting with transferrin saturation (TSAT) <20% or percentage with ferritin <100 ng/ml in chronic kidney disease and ferritin <200 ng/ml in hemodialysis or peritoneal dialysis. Modalities are: solid bar, hemodialysis; stripe bar, peritoneal dialysis; chronic kidney disease, white bar.

Immediately prior to transplant, the mean TSAT was 25.4 ± 10.6% (range, from 6 to 60%). Overall 44% of patients at the time of transplant had a TSAT<20% and there were no significant differences based on TSAT among different renal replacement modalities (HD 26.6% vs. PD 25.3% vs. CKD 21.1% P = NS (Fig. 2). Men had a similar TSAT as women (24 ± 8.8% vs. 27 ± 12.6%; P = 0.24) and did not differ by renal replacement therapy modality.

The average blood loss during the transplant surgery was 179 ± 133 ml (range: from 43 to 600 ml). The average blood loss over the 12-week period (including surgical blood loss and phlebotomy blood loss) just after transplantation was 823 ± 226 ml. The total blood loss ranged from 612 to 1854 ml (in a patient with a prolonged hospital course post-transplant). The total blood loss corresponds to an average iron loss of 317 ± 87 mg during the 12 weeks immediately following the transplant, with a range from 239 to 714 mg. Blood losses were similar among HD, PD and CKD patients (833 ± 194, 861 ± 324, and 755 ± 79 ml, respectively, P = NS). Blood losses were not significantly different between deceased donor transplant and living donor transplant recipients (881 ± 291 vs. 788 ± 162 ml, P = 0.33). Blood losses were similar between the group that received IV iron and the group that did not receive IV iron (780 ± 269 vs. 851 ± 178 ml, P = 0.38).

We estimated an overall need of 330 mg of additional iron to normalize hemoglobin from 11.8 to 13 g/dl, and 605 mg to increase hemoglobin up to 14 g/dl. Therefore the average iron requirement to raise hemoglobin to 13 or 14 g/dl and maintain the pretransplant iron status over the first 12 weeks would be 647 mg (317 + 330 mg) and 922 mg (317 + 605 mg), respectively.

Nineteen iron-deficient patients received IV iron supplementation. No adverse reactions to the IV iron infusion were observed. Overall, 37% of patients receiving IV iron achieved a hemoglobin level greater than 12 g/dl at 6 weeks and 58% at 12 weeks post-transplant. For patients who did not receive IV iron, 30% achieved a hemoglobin level greater than 12 g/dl at 6 weeks and 50% at 12 weeks. However, there was no statistical difference when comparing the proportion of patients who had >12 g/dl hemoglobin level at 6 weeks (P = 0.90) or at 12 weeks (0.86) among those who did or did not receive IV iron.

At the time of transplant, mean hemoglobin did not differ between patients who received IV iron as compared with those who did not receive iron (11.7 ± 2.2 g/dl vs. 12.0 ± 1.2 g/dl respectively, P = 0.62). Mean hemoglobin concentrations were the same at 6 weeks post-transplant (11.9 ± 1.7 vs. 11.0 ± 1.6 g/dl, P = NS) and at 12 weeks post-transplant (12.3 ± 1.8 g/dl vs. 12.2 ± 1.8 g/dl, P = 0.21) (Fig. 3). Hemoglobin increased at 6 weeks in the IV iron group and decreased in the 'no iron' group (Fig. 3).

Renal function

Delayed graft function (DGF) did not vary by iron deficiency. Of the 25 with iron deficiency, three (12%) had DGF and of the 14 noniron-deficient, two (14%) had DGF, P = 1.0. Delayed graft function occurred in one (6.7%) of those who were anemic at 6 weeks as compared with four (16.7%) of those who were not anemic at 6 weeks, P = 0.63. There was no difference in the incidence of DGF or slow graft function among those who remained anemic at 6 weeks as compared with those who were not anemic as assessed by the MDRD equation (Table 3). However, serum creatinine concentrations were

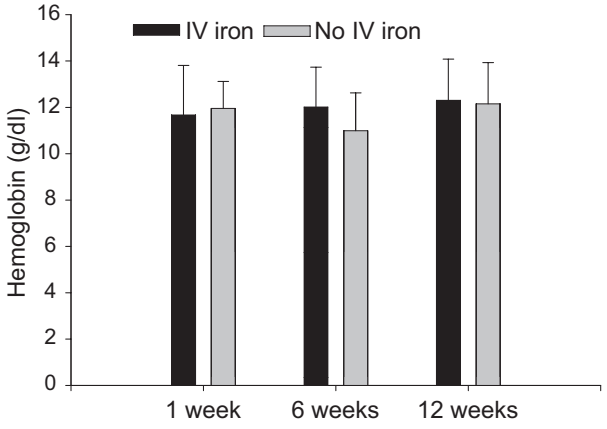

Figure 3 Comparison of hemoglobin between patients who received intravenous (IV) iron versus patients who did not receive IV iron.

Table 3. Renal function among those who were and who were not anemic at 6 weeks.

	Anemic at 6 weeks				
	Yes (n = 15)		No (n = 24)		
Variable	Mean	SD	Mean	SD	P-value
Scr-pod 5	1.55	1.68	2.30	2.17	0.261
Scr-2 weeks	1.12	0.25	1.85	1.67	0.044
Scr-4 weeks	1.10	0.23	1.42	0.47	0.008
Scr-12 weeks	1.14	0.21	1.40	0.55	0.041
MDRD-pod 5	58.73	22.47	57.02	34.74	0.866
MDRD-2 weeks	60.07	16.50	59.50	34.43	0.945
MDRD-4 weeks	59.60	16.01	62.50	25.84	0.699
MDRD-12 weeks	59.93	17.46	62.13	25.08	0.769

Scr, serum creatinine; pod, post operative day; MDRD, estimated glomerular filtration rate as per the modification of diet in renal disease 6-variable equation [15].

statistically lower among those who remained anemic at 2, 4, and 6 weeks as compared with those who were not anemic at these time-points; see Table 3 [15].

Effect of immunosuppression on anemia

Administration of azathioprine or mycophenolate mofetil did not affect anemia. Of those who received azathioprine 14.3% were anemic at 6 weeks post-transplant as compared with 40.0% of those who received mycophenolate mofetil (MMF), $P = 0.36$. This relationship was also not statistically significant at 12 weeks post-transplant, $P = 0.66$.

Effect of valganciclovir on anemia

None of those who received valganciclovir were anemic at 6 weeks post-transplant as compared with 41.7% of those who did not receive valganciclovir at 6 weeks post-transplant, $P = 0.$ 0.27. This was also not significant at 12 weeks, $P = 0.56$.

Discussion

Consistent with previous studies, we found a high prevalence of anemia (67%) and iron deficiency (44%) in patients presenting for transplant at our center. One contribution to the high incidence of anemia following transplant despite return of endogenous erythropoietin production may be insufficient iron. Previous studies have found that iron status is frequently not evaluated in the transplant population [3,4,9]. Even when greater attention is focused on anemia before and after kidney transplantation, iron deficiency remains common in the early months post-transplant. Iron deficiency can result in iron-restricted erythropoiesis, as has been observed in dialysis patients [16].

Our novel report quantifies the magnitude and sources of blood and iron losses in the post-transplant period. We found significant blood loss in the immediate peri-transplant period, largely through standard phlebotomy for allograft function and immunosuppressant drug level monitoring. An additional significant amount of iron is required to increase hemoglobin from the range of 10–12 g/dl common in CKD patients prior to transplant, to the normal range expected in a patient with a well functioning graft. In addition, premenopausal women may have return of menses and thus lose iron. In all, the average post-transplant patient has an iron requirement approaching 1 g.

Previous work has shown maximal oral iron absorption to be 3 mg/day in states of iron deficiency [17]. As the iron deficit was estimated at approximately 600–900 mg, it would take at least 60–90 days of maximal iron absorption to provide this deficit. Nevertheless, oral iron can cause gastrointestinal side-effects leading to poor adherence and in anemic CKD patients is not particularly effective in increasing hemoglobin, TSAT, or ferritin and it may bind to immunosuppressive agents, although this is controversial [18,19].

Patients may benefit from administration of IV iron, as we employed in our clinical practice during the transplant hospitalization. We noted no problems related to administration of 1 g of INFeD in the immediate postoperative period. Use of the higher molecular weight iron dextran, Dexferrum, should be avoided because of an unacceptably high rate of severe reactions [20]. Ferric gluconate or iron sucrose can also be administered intravenously as smaller doses each hospital day.

In our nonrandomized study, postoperative administration of IV iron to patients considered to be iron-deficient

was associated with higher hemoglobin at 6 weeks as compared with those not considered iron-deficient and not given iron (11.9 ± 1.7 vs. 11.0 ± 1.6 g/dl). Similar hemoglobin levels were present at 12 weeks post-transplant. While this trend at 6 weeks may be because of an erythropoietic effect of the IV iron, it may also reflect the limited ability to identify iron deficiency by serum ferritin and TSAT testing, or variation caused by other factors, which can influence anemia, such as immunosuppressant medications and infections. Alternatively, inflammatory cytokines, such as interleukin-6 or tumor necrosis factor, which were not measured but are elevated in end-stage renal disease (ESRD) and transplant patients, may have impaired the erythropoietic response.

A limitation of our study is that it was not a randomized study to investigate the impact of IV iron on the recovery of anemia in those who were or were not identified as having iron deficiency at the time of presentation for renal transplantation. A better study would have been to randomize patients who were iron-deficient to receive or not to receive IV iron. It was our clinical experience that patients who were treated with iron recovered from their anemia more quickly and more completely than those who were not treated with IV iron that led to this observational study. The observation that patients who were iron-deficient and treated with IV iron had numerically higher hemoglobin concentrations at 6 weeks tends to support our clinical impression. Another relevant study would be to administer IV iron to all patients regardless of identified iron deficiency. Although this would go beyond a clear clinical indication, it is a study worth pursing in the future.

There were no differences among induction or maintenance immunosuppression among those who were or were not anemic at 6 weeks. Most of our patients received thymoglobulin and none received sirolimus. Thus, we were unable to investigate adequately the use of other commonly administered immunosuppressive maintenance regimens on the treatment of anemia.

Although we did not investigate the use of ACE-I or ARB at the time of presentation for transplantation, it is unlikely that use of these drugs would have influenced our observations given that the half-life of these drugs is 6–12 h.

An important concern with iron supplementation is the development of post-transplant erythrocytosis. None or our patients developed erythrocytosis. Furthermore, in previous studies, discontinuation of iron was usually followed by a decrease in hemoglobin 4 weeks later [4,7].

This is the first study to document that despite increased attention to iron deficiency among CKD and ESRD patients, iron deficiency is common in patients presenting for renal transplantation. This study documents that the magnitude of blood and iron loss with surgery and routine phlebotomy for post-transplant monitoring contribute to anemia. Finally, IV replacement of iron among those who were iron-deficient at the time of transplant was associated with equalization of hemoglobin concentrations by 12 weeks as compared with those who were not iron-deficient and did not receive iron. Anemia, however, persisted in both groups. Anemia predisposes to LVH. LVH is a major risk factor for cardiovascular mortality and which the vast majority of ESRD patients have. Cardiovascular death is the leading cause of graft loss among renal transplant recipients and whether correction of anemia will decrease this requires further study. The optimal hemoglobin concentration in renal transplant recipients remains to be determined.

In conclusion, routine assessment of iron stores in the post-transplant period is indicated. Given the large iron losses and large iron needs following renal transplantation, further studies assessing the risks and benefits of peri-operative IV iron therapy are warranted.

Authorship

SZ: analyzed data, wrote the manuscript. DWC: analyzed data, wrote the manuscript. HJ: collected, analyzed data, wrote the manuscript. RS: collected data. AGB, PE: analyzed data. DCB: collected, analyzed, wrote the manuscript.

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