Anemia Among Long-Term Renal Transplant Recipients

A. Ghafari and N. Noori-Majelan

ABSTRACT

Background. The effects of anemia on cardiovascular disease among the end-stage renal disease (ESRD) population suggest that it may be one of the major factors explaining this complication among kidney transplant recipients. Systematic investigation into the prevalence of posttransplantation anemia (PTA) is therefore of critical importance.

Materials and Methods. This cross-sectional study of data from 650 patients followed at a single outpatient transplant clinic utilized the guidelines of the American Society of Transplantation to define anemia as a hemoglobin (Hb) ≤130 g/L in men or ≤120 g/L in women.

Results. Among the 39% of patients who were anemic, the prevalence was greater in women than in men. Serum Hb concentrations significantly correlated with the glomerular filtration rate (GFR), serum transferrin, the use of angiotensin converting enzyme inhibitors and mycophenolate mofetil therapy. Upon multivariate analysis, the GFR, serum transferrin, potential nutritional markers, chronic inflammation, and iron deficiency were independently and significantly associated with the presence of anemia. Erythropoietin was administered to 15 (5.7%) anemic patients.

Conclusions. PTA is a prevalent, undertreated condition. Based on our results, we suggest that protein/energy malnutrition and/or chronic inflammation were independently associated with anemia.

ANEMIA in chronic kidney disease (CKD) is strongly associated with significant cardiovascular morbidity,[1] hospitalization,[2] and mortality.[3] Correction of anemia with iron or erythropoietin (EPO) has been shown to reverse left ventricular hypertrophy in CKD.[3] Cardiovascular disease (CVD) is the leading cause of mortality among kidney transplant recipients; the death rate from this cause in this population is twice as high as in the general population.[4] Hence, it should be advisable to prevent/treat posttransplantation anemia (PTA). In this cross-sectional study, we approached 650 adult renal transplant patients followed at a single outpatient transplant center to determine the prevalence and clinical correlates of PTA.

MATERIALS AND METHODS

Sample of Patients and Data Collection

All adult patients (N = 650) who were regularly followed at a single kidney transplant outpatient clinic were included in a cross-sectional study between April 2005 and February 2006; 635 (97.8%) patients received living donor renal transplantations. Data were extracted from patient hospital charts. Demographic information and details of medical history collected at enrollment included: age, gender, etiology of end-stage renal disease (ESRD), and presence of diabetes mellitus. We analyzed the serum hemoglobin (Hb), iron indices (serum iron, serum transferrin, transferrin saturation [TSAT]), serum creatinine, blood urea nitrogen, serum albumin and C-reactive protein (CRP). Based on the glomerular filtration rate (GFR), patients were stratified into CKD stages as suggested by the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines[9]: group 1, GFR >60 mL/min; group 2, GFR 30 to 59 mL/min; or group 3, GFR <30 mL/min. Transplant-related data extracted from the medical records included: time of transplantation, medications (including current immunosuppressive combination), use of recombinant human EPO, and iron therapy.

From the Nephrology Department (A.G.), Urmia University of Medical Sciences, Urmia, Iran, and the Nephrology Department (N.N.-M.), Yazd University of Medical Sciences, Yazd, Iran.

Address reprint requests to Ali Ghafari, Nephrology Department, Emam Hospital, Ershad St, Urmia University of Medical Sciences, Urmia 5715943394, Iran. E-mail: ghaf_ali@yahoo.com

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Definition of Anemia

Anemia was defined according to the American Society of Transplantation as an Hb ≤130 g/L for adult males, or ≤120 g/L for adult females.[10] Anemic patients were divided into 3 subcategories to assess the severity: 1, mild for males, Hb >120 g/L (≤130 g/L), and females, Hb >110 g/L (≤120 g/L); 2, moderate for males, Hb >110 g/L (≤120 g/L), and females, Hb >100 g/L (≤110 g/L); and 3, severe for males, Hb ≤110 g/L, and females, Hb ≤100 g/L.

Immunosuppression and Anemia Management

Immunosuppressive therapy generally consisted of prednisolone, cyclosporine (CsA), and mycophenolate mofetil (MMF) or azathioprine (AZA). The use of EPO, angiotensin converting enzyme inhibitors (ACEI), and oral iron supplementation was also assessed.

Statistical Analysis

Statistical analysis was performed using the SPSS 10.0 software (SPSS Inc, Chicago, Ill, United States). Continuous variables were compared with the Student t test or the Mann-Whitney U test; categorical variables, with the chi-square test or Fisher exact test, as appropriate. ANOVA testing with Bonferroni correction for multiple comparisons was used to analyze the relationship between continuous and categorical variables. Univariate analysis was performed using Pearson or Spearman correlation analysis, as appropriate. For multivariate analysis, linear or logistic regression was used.

RESULTS

Baseline patient characteristics of the study population and of groups with different degrees of anemia are shown in Table 1. For the total sample, the mean age was 43 ± 12 years, and included 52% of men. Mean GFR was 64 ± 33 mL/min, and mean time since transplantation was 63 ± 51 months (Table 1). The most prevalent underlying kidney disease in the sample was chronic glomerulonephritis (23%). The prevalence of other kidney diseases included: diabetic nephropathy, 16%; hypertensive nephropathy, 14%; autosomal dominant polycystic kidney disease, 8%; chronic pyelonephritis, 8%; other (or unknown) underlying kidney disease, 31%. Among the patients, 592 (91%) were taking prednisolone; 618 (95%), CsA; 377 (58%), MMF; and 253 (39%), AZA.

Prevalence of Anemia

Mean Hb for the total sample was 139 ± 32 g/L (males: 141 ± 37 g/L; females: 129 ± 28 g/L; $P < .005$). Overall we defined 254 patients (39%) as anemic (Table 1). Among the total population, 137 patients (21%) had mild; 78 (12%) moderate; and 39 (6%) severe anemia.

Correlates of Anemia

Upon bivariate analysis, there was no correlation between age and Hb level. Anemia was more prevalent among women than men (45% vs 33%; $P < .01$). Among all patients, 98 (15%) were iron deficient (TSAT <20%). Iron deficiency was more prevalent among women than men (19% vs 12%; $P < .05$). Upon bivariate analysis, serum transferrin was positively correlated with albumin ($r = .254$, $P < .001$) and negatively with CRP ($r = -.2.11$, $P < .001$). Serum albumin levels positively correlated with Hb ($r = .214$, $P < .001$) and negatively with CRP ($r = -.154$, $P < .001$). Upon multivariate linear regression analysis (dependent variable: serum transferrin), CRP and albumin remained significantly and independently associated with serum transferrin after controlling for potential confounding variables ($\beta = -.173$, $t = -2.64$, $P < .001$) and ($\beta = .184$, $t = 3.86$, $P < .001$). For the whole population, there

Table 1. Characteristics of the Study Population

	Total Population (N = 650)	Not Anemic (n = 396; 61%)	Mild Anemia (n = 137; 21%)	Moderate Anemia (n = 78; 12%)	Severe Anemia (n = 39; 6%)	*P*
Female (%)	48	41	55	57	61	<.05
Age (y) (mean ± SD)	43 ± 12	41 ± 13	44 ± 14	39 ± 15	42 ± 13	NS
Diabetes mellitus (%)	16	18	11	9.5	13	
Time since transplantation (months) (mean ± SD)	63 ± 51	61 ± 46	60 ± 31	58 ± 41	64 ± 53	NS
Glomerular filtration rate (mL/min) (mean ± SD)	64 ± 33	62 ± 31	58 ± 28	52 ± 37	51 ± 27	<.01
Serum albumin (g/L) (mean ± SD)	41 ± 3	41 ± 2	39 ± 3	36 ± 2	37 ± 3	<.01
C-reactive protein (g/L) (mean ± SD)	5 ± 1.3	6 ± 1.7	8 ± 1.2	9 ± 23	9 ± 25	<.01
Serum transferrin (mean ± SD)	2.6 ± 0.3	2.5 ± 0.4	2.3 ± 0.3	2.2 ± 0.4	2.1 ± 0.5	<.01
Serum iron (mean ± SD)	20 ± 8	20 ± 6	19 ± 7	19 ± 5	18 ± 7	NS
Transferrin saturation (TSAT) (mean ± SD)	37 ± 12	36 ± 16	37 ± 19	36 ± 10	35 ± 14	NS
Immunosuppressants (%)						
Steroids	91	90	89	90	88	NS
Cyclosporine (Neoral)	95	93	94	92	93	NS
Mycophenolate mofetil	58	59	63	66	69	.03
Azathioprine	39	36	37	35	36	NS
ACEI (%)	23	21	27	29	31	<.01
Prevalence of iron deficiency (%) (transferrin saturation <20%)	9	11	10	13	10	NS

was a significant correlation between GFR and Hb (r = .376, $P < .01$). When analyzed individually, only MMF was associated with more frequent anemia ($P < .01$; Table 1); Therapy with ACEI, which was prescribed in 163 patients (25%), was associated with lower mean serum Hb levels: 130 ± 23 vs 133 ± 15 g/L ($P < .05$).

Multivariate Analysis

To analyze the complex relationship between anemia (Hb as the dependent variable) and the multiple, potentially relevant covariables, we used linear regression analysis. In this model (r = .383, $P < .01$), serum transferrin, gender, GFR, serum albumin, iron deficiency, ACEI, and MMF were significantly and independently associated with blood Hb (Table 2).

Management of Anemia

Among all patients, 66 (10%) were given iron supplementation. Only 22 (22.5%) of the 98 iron-deficient patients received iron therapy and 18 (7%) of the 254 anemic patients were treated with EPO.

DISCUSSION

We observed that PTA was a common condition with a 39% incidence among our kidney transplant recipients. The prevalence of PTA was similar to previously published data.[5,7] Although iron deficiency is one potential cause of PTA, it has rarely been analyzed in this context. Mix et al[6] reported that iron stores were examined in only 12% of their 240 patients. In our analysis, iron deficiency was a significant predictor of PTA even after controlling for potential covariables (Table 2). Importantly, in our study serum transferrin level was one of the strongest independent predictors, of Hb or anemia even after statistical correction for other variables. Serum transferrin is a marker of nutritional status and its level is negatively regulated by inflammation.[8] Upon multivariate analysis of our dataset, serum transferrin value was significantly and independently predicted by both albumin and CRP. When the interaction of these variables was analyzed in a multivariate model, serum transferrin, gender, GFR, serum albumin, iron deficiency, ACEI, and MMF remained significant independent predictors of Hb (Table 2). Consistent with previous studies,[5,7,11] Hb levels were significantly and independently predicted by GFR in our population. The prevalence of anemia was markedly increased with declining renal function. Immunosuppressive drugs, specifically AZA and MMF, were associated with PTA in some[5,12] but not other[13] studies. We observed an association between MMF prescription and Hb level. In this study, the use of ACEI was associated with a lower Hb level, an association that remained significant even upon multivariate analysis. In our population, 10% of patients were given iron supplementation. Only 22.5% of iron-deficient patients received iron therapy, and 7% of anemic patients were treated with EPO. Further prospective studies are needed to determine specific therapeutic targets as well as the effects and cost-effectiveness of EPO therapy based upon clinical outcome measures.

Table 2. Linear Regression Model of Serum Hemoglobin as the Dependent Variable (r = .383, $P < .01$)

	β	t	P
Serum albumin	.067	1.876	.034
Serum C-reactive protein	.047	.357	.311
Serum transferrin	.345	5.422	<.01
Age	.043	1.321	.212
Gender	−.305	−8.255	<.01
Iron deficiency (transferrin saturation <20%)	.063	3.104	.018
Glomerular filtration rate	.123	5.324	<.01
Time since transplantation	−.023	−.431	.641
ACEI	.243	5.765	<.01
Mycophenolate mofetil	.143	5.312	<.01

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