Prevalence of Anemia among Iraqi Patients after Renal Transplantation

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Summary:

Background: Although the issue of anemia after renal transplantation (RT) has received increasing attention lately, the data on the exact prevalence of post-transplantation anemia (PTA) in the Iraqi patients are limited.

Objective: In this study we sought to determine the prevalence of PTA among Iraqi patients and to correlate the renal allograft function measurements and the use of immunosuppressant with the prevalence of anemia.

Patients and Methods: One hundred and twelve (74 male, 38 female) kidney transplant recipients (KTR) attending the kidney transplant center at surgical specialties hospital were studied. All patients were on maintenance, combined immunosuppressive therapy. The renal function tests [blood urea, serum creatinine, and creatinine clearance] and the hematological tests [Hb, HTC, and white blood cell count (WBC)] were determined in all patients. Anemia was defined according to the gender-specific K/DOQI classification.

Results: In this study, we identified anemia (Hb < 12 g/dl in males and Hb < 11 g/dl in females) in 25% of the patients (28 out of 112).The anemic patients had a significantly higher mean blood urea and serum creatinine levels and lower mean creatinine clearance level than the non-anemic patients. Among the immunosuppressant drugs, patients on tacrolimus combined with mycophenolate mofetil (MMF) had significantly lower Hb and HTC compared with patients without such treatment.

Conclusion: Anemia is common in Iraqi patients after RT. The PTA is associated with impaired renal allograft function when compared with non-anemic RTR. Immunosuppressant including tacrolimus combined with MMF was correlated with decreased Hb and HTC concentrations.

Keywords: Anemia, Renal transplantation, Immunosuppressive drugs.

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Introduction:

Although anemia has been investigated with great interest and intensity in the setting of chronic kidney disease (CKD), studies of the prevalence and clinical relevance of post-transplantation anemia (PTA) were scarce until a few years ago (1). Depending on the definition of anemia and whether hemoglobin (Hb) concentration or hematocrit (HTC) was measured, the prevalence PTA was estimated to be in the range of 20-40 % (2-5). In a previous study, Yorgin *et al.* (2) observed adult kidney transplant recipients (KTR) over a 5-year period and found that 30% of the patients experienced anemia during study period. In another study, Lorenz *et al.* (3) found that prevalence of anemia (Hb<13 g/dl in males and <12 g/dl in females) was 39.7% in KTR. In a large multicentre study, Vanrenterghem *et al*. (4) showed that anemia is present in about 35% of renal transplants and the most powerful predictor among risk factors for PTA was a serum creatinine > 2 mg/dl. Also, Mix *et al.* (5) observed a high prevalence of anemia in KTR at one year (21%) and at 4 years (36%). The different prevalence of anemia found in these studies is likely related to between-study differences in the definition of anemia.

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Following renal transplantation (RT), erythropoiesis begins and level of erythropoietin (EPO) increases to a sustained level in a month and subsequently Hb level increases towards normal within 3 months (6). However, in some KTR, anemia persists or develops following transplantation. Most of them are associated with preoperative blood loss, allograft dysfunction, and acute rejection (7), although some have anemia with normal allograft function as well (8). There are multiple potential causes and correlates of anemia in the KTR. Some factors such as iron and nutrient deficiency, infection, inflammation, blood loss and certain medication are shared with patients suffering from CKD, whereas others are unique to KTR. Examples include rejection episodes, immunosuppressive drugs, antivirals or antibiotics (4, 9). As with CKD, a poorly functioning kidney allograft is a major cause of PTA. This is especially true, as the serum creatinine level rises above 2 mg/dl, which results in reduced EPO production and subsequent anemia. KTR differ from other patients with CKD because they bear the additional burden of therapy with immunosuppressive drugs that may directly exacerbate anemia. The wide variation in the reported prevalence of PTA likely reflects differences in the use of antiproliferative immunosuppressive agents [*e.g.*, azathioprine,

sirolimus, and mycophenolate mofetil (MMF)] that may directly but variably inhibit erythropoeisis (4, 10). Several studies (2, 10) have demonstrated that these drugs are the principal agents that are responsible for late PTA.

Recent studies specifically addressing risk factors for PTA. Shibagaki and Shetty (9) found that in KTR, anemia at 6 months has been associated with reduced renal function. In another study, Chhabra *et al.* (11) showed that PTA is associated with worse patient and graft survival and higher rates of acute rejection when compared with nonanemic KTR.

The present study aimed to estimate the prevalence of PTA in Iraqi patients in a single-center transplant population and to explore possible associations between PTA and renal allograft function measurements and certain immunosuppressive drugs.

Patients and Methods:

During the period between July 2009 till November 2009, 112 adult patients with functioning renal transplants more than 1 month post-engraftment were enrolled in this study. The study sample had been selected from those patients who had attended kidney transplant center at surgical specialties hospital. All patients were on maintenance, combined immunosuppressive therapy as follows: prednisolone was given to all the patients. Fifty patients received cyclosporine A combined with MMF while 37 were given cyclosporine A combined with azathioprine. Twenty five patients received tacrolimus combined with MMF. Detailed medical data of these patients are shown in table 1.

Table 1: Medical data of the112 kidney transplant recipients.

Variable	Values (Mean ± SD)
Number Male/ Female	74/38
Age (years)	35±10
BMI (kg/m^2)	26.2±4.1
Previous dialysis duration (months)	7±5
Time since transplant (months)	25±21

BMI = body mass index

The renal function tests [blood urea, serum creatinine & creatinine clearance (by Cockcroft and Gault equation)] and the hematological tests [Hb, HTC& white blood cell count (WBC)] were carried out at the laboratory of the kidney transplant center. Anemia was defined as Hb < 12 g/dl for male patients and Hb < 11 g/dl for female patients consistent with the gender-specific K/DOQI (Kidney Disease Outcomes Quality Initiative) guidelines of 2001 (12).Student *t*-tests were used to compare the differences of medical data and the renal function tests between anemic and non-anemic patients. Analysis of variance (ANOVA) was used for comparing indicators of anemia (i.e. Hb and HTC) in the three groups of patients according to the immunosuppressive treatments which they received. A p-value<0.05 was considered significant. All statistics were performed using SPSS software, version 12.

Results:

The biochemical and the hematological features of all 112 KTR included in this study are indicated in Table 2. It is obvious from this table that blood urea level was on the maximal side of the normal range; serum creatinine level was above the normal range; while creatinine clearance was within the normal limit. Regarding the hematological tests (Hb, HTC & WBC), the results revealed that all these parameters were within the normal range.

Table 2: Biochemical and hematological features of all 112 KTR included in this study.

Biochemical and hematological features	Value (Mean ± SD)	Normal range
Blood urea (mg/dl)	44±15	20-45
Serum creatinine (mg/dl)	1.5±0.5	0.7-1.4
Creatinine clearance (ml/min)	75±24	90-125
Hb (gm/dl)	12.6±2.0	12 - 18
PCV (%)	38±6.0	37 - 55
WBC (cells/µL/cu mm)	9000±3400	4,300 - 10,800

In this study, we have shown that the prevalence of anemia among KTR was 25% (28 out of 112) by definition with Hb < 12 g/dl for male patients and Hb < 11 g/dl for female patients. Based on this outcome, the studied cases were divided into two groups: anemic group included 28 KTR and non-anemic group included 84 KTR. When the medical data were compared between these two groups, the results revealed that there were no significant differences in all these data between the anemic and non-anemic patients (Table 3).

Table 3: Comparison of medical data between anemic and non-anemic patients.

Variable		Anemic patients	Non-anemic patients	P value
Gender	Male	65%	67%	NS
	Female	35%	33%	NS
Age (years)		34±9	35±10	NS
BMI (kg/m^2)		24.8±3.7	26.6±4.2	NS
Previous dialysis duration (months)		6±5	5±4	NS
Time since transplant (months)		24±20	22±20	NS

Data are mean ± SD, BMI = body mass index.

Comparison of the results of the renal function tests in the anemic group with the non-anemic group (Table 4) revealed that the levels of blood urea and serum creatinine were significantly higher (P<0.01)

while the level of creatinine clearance was significantly lower (P<0.01) in the anemic group versus the non-anemic group.

Table 4: Comparison of renal function tests between anemic and non-anemic patients.

Renal function tests	Anemic patients	Non-anemic patients	P value
Blood urea (mg/dl)	59±23	40±12	P<0.01
Serum creatinine (mg/dl)	2.0±0.7	1.3±0.4	P<0.01
Creatinine clearance (ml/min)	58±21	81±24	P<0.01

Data are mean ± SD

In order to asses the impact of certain immunosuppressive drugs on development of anemia, the study population was divided according the immunosuppressive treatments which they received into three groups as shown in (Table 5). It is obvious from this table that the third group had lower values of Hb and HTC (p<0.05) compared with the first and the second groups. This means, among the immunosuppressant drugs, we found that both tacrolimus and MMF were associated with lower values of Hb and HCT.

Table 5: Values of Hb and HTC in the three groups of the patients according to their immunosuppressive treatments.

Group	Immunosuppressive treatments	No. of patients	Hb (gm/dl)	HTC (%)
First	Prednisolone, cyclosporine A and mycophenolate mofetil	50	13.3±1.6	41±4
Second	Prednisolone, cyclosporine A and azathioprine	37	13±1.3	40±3
Third	Prednisolone, tacrolimus and mycophenolate mofetil	25	11.3*±0.8	35*±2

∗ Significant difference (P<0.05).

Discussion:

Although the issue of anemia after RT has received increasing attention of late, the data on the exact prevalence of PTA in the Iraqi patients are limited. In this study, we found that PTA (Hb < 12 g/dl for male patients and Hb < 11 g/dl for female patients) is a common condition found in KTR, identifiable in 25% of this study population. Other studies have found a similar prevalence of PTA, namely between 20 and 40% (2-5). In a previous study, Mix *et al.* (5) were able to evaluate the prevalence of anemia in KTR at some stage in their transplant history. They found that 48% were anemic at time of transplantation, but only 21% were at 1 year after the procedure. Again, 4 year after RT, the prevalence had risen to 36%. The authors suggested that the usual time course of anemia after RT is the development of anemia early after RT followed by recovery and then in the longer terms an increased risk for anemia. Early after transplantation, blood loose related to the surgical procedure and subsequent inflammation lead to anemia. Also the effects of delayed graft function, induction therapy causing bone marrow suppression may play an important role in the development of anemia during this period (1). Winkelmayer *et al.* (13) reported that the majority of KTR do not have normal renal function as measured by estimates of Glomerular filtration rate (GFR), and poorer renal function has been associated with lower HTC in this population in a similar manner to native kidney disease. Sun *et al.* (6) indicated that as early as approximately 2 moths after transplantation, a normal HCT might be expected in patients without graft failure and iron deficiency. The study by Chadban *et al.* (14) revealed that with the subsequent decrease in renal function that most patients experience, anemia once again develops associated with decreased transplant function. Although clearly associated with GFR, anemia occurs earlier in KTP compared with in patients with CKD. Although it is difficult to compare each of these studies because of the different definitions of anemia and timing of checking it, the overall picture that can be gleaned from all the studies including ours allows the general conclusion that anemia is prevalent in KTR, either early or late after transplantation. Reported causes of anemia in KTR are many. In the early postoperative period, anemia is the consequence of blood loss, graft failure to generate enough EPO, and drugs that inhibit bone marrow erythropoisis (15). Late PTA has been attributed to renal dysfunction, antiviral agents, infections, and the use of immunosuppressive drugs (16).The role of endogenous EPO production in the setting of PTA has not been fully explained and few studies have included serum EPO levels in their analyses (6, 17). In a previous study, Nampoory *et al.* (17) concluded that relative or absolute EPO deficiency can persist in KTR despite restoration of normal renal function. Also, Al-Uzri *et al.* (18) reported that whereas endogenous production of EPO commonly begins within the first day after RT, complete restoration of EPO synthesis depends mostly on recovery of graft function. It well described that production of EPO depends on allograft function (8). In this study, we did not find any significant differences in the medical data (age, gender, BMI, previous dialysis duration, and time since transplantation) between the anemic and non-anemic patients. Regarding of the gender difference, this finding is consistent with those of the large European study which did not show any gender difference in the prevalence of anemia (4). However, Shibagaki and Shetty (9) observed that more females than males had PTA, while other studies showed higher prevalence of anemia in males (2, 3). In the current study, we noted a strong correlation between level of renal function and anemia; with the anemic group having

a high significantly higher blood urea and serum creatinine levels and lower creatinine clearance. Similar to our observations, other studies (2-4) have identified direct associations between PTA and decreased levels of kidney function. Also, Winkelmayer and Chandraker (1) found that the important- and related-determinant of PTA is transplant function, so they suggested that the best prevention of PTA is preservation of transplant function. Anemia in chronic allograft injury may accelerate the decline in renal function by limiting oxygen delivery to tissues, particularly to the tubulointerstitum. In turn, hypoxia contributes to the formation of reactive oxygen species, which adds further insult to renal tissues and induces the release of proinflammatory molecules that recruit inflammatory cells into the interstitium (19). In KTR, the hypoxic damage may be potentiated by the use of immunosuppressive drugs and by the concomitant presence of congestive heart failure, which reduces renal blood flow (20). Regarding the impact of certain immunosuppressive drugs on development of anemia, our results are in contrast to those of Sinnamon *et al.* (21) whose data found no evidence that specific immunosuppressive regimens contributed significantly to PTA. However, we observed a relationship between anemia and immunosuppressive regimens in the KTP. Among the immunosuppressant drugs, we found that both tacrolimus and MMF were associated with lower values of Hb and HCT in the studied cases. In a previous study, Winkelmayer *et al.* (13) evaluated the role of six individual immunosuppressants on HCT and found MMF and tacrolimus to be independently associated with lower HTC. Both drugs, however, had been implicated in development of PTA in earlier studies (22, 23). Our results did not reveal azathioprine as a risk factor for PTA, which is at odds with a previous study (3) that has reported such an association, but it confirms findings of other studies (4, 13). Immunosuppressive drugs contribute to the development of anemia through a variety of mechanisms. The antiproliferative agents (*e.g.*; azathioprine, sirolimus and MMF) are known to cause anemia through direct suppression of the bone marrow (4, 10). MMF is a potent antimetabolite, used increasingly in RT as part of a standard triple drug immunosuppressive regimen [in combination with a calcineurin inhibitor (cyclosporine or tacrolimus) and corticosteroids]. MMF may induce anemia by a direct myelosuppressive effect (24). Multiple clinical studies comparing MMF to azathioprine have demonstrated efficacy of MMF for the prevention of acute rejection episodes and treatment failures, while maintaining a good safety profile (25, 26). Tacrolimus is more often associated with leukopenia but it was also associated with the development of PTA according to several studies (22, 23).

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