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Characteristics of Anemia and Iron Deficiency After Kidney Transplant

Jong Cheol Jeong[a], Han Ro[b,*], Jaeseok Yang[c], Kyu Ha Huh[d], Jae Berm Park[e], Jang-Hee Cho[f], Sik Lee[g], Seung-Yeup Han[h], and Curie Ahn[c], KNOW-KT Study Group

[a]Department of Internal Medicine, Ajou University School of Medicine, Suwon, Republic of Korea; [b]Department of Internal Medicine, Gachon University Gil Medical Center, Incheon, Republic of Korea; [c]Transplantation Center, Seoul National University Hospital, Seoul, Republic of Korea; [d]Department of Transplantation Surgery, Severance Hospital, Yonsei University Health System, Seoul, Republic of Korea; [e]Department of Surgery, Sungkyunkwan University, Seoul Samsung Medical Center, Seoul, Republic of Korea; [f]Department of Internal Medicine, Kyungpook National University Hospital, Daegu, Republic of Korea; [g]Department of Internal Medicine, Chonbuk National University Hospital, Jeonju, Republic of Korea; and [h]Department of Internal Medicine, Keimyung University, Dongsan Medical Center, Daegu, Republic of Korea

ABSTRACT

Background. Numerous studies have shown that iron deficiency is common in patients with end-stage renal disease. However, change of iron deficiency after kidney transplant (KT) is not fully understood. This study was undertaken to examine sequential changes of iron level after KT.

Methods. A total of 1080 KT recipients enrolled in a multicenter observational cohort study between July 2012 and August 2018. A total of 786 patients with transferrin saturation and ferritin level at pretransplant and 1 year after KT were reviewed. Iron deficiency was defined as ferritin <200 ng/mL and total saturation of transferrin (TSAT) < 20%. Anemia was defined as hemoglobin (Hb) < 13 g/dL (male) or <12 g/dL (female).

Results. Hemoglobin at 1 year after KT was higher than Hb at KT (13.64 [SD, 1.87] g/dL vs 10.53 [SD, 1.63] g/dL; $P < .001$). The TSAT decreased from baseline at 1 year after KT (33.89% [SD, 18.73%] vs 29.09% [SD, 14.54%]; $P < .001$), and ferritin level decreased from baseline at 1 year (190.63 [SD, 217.43] ng/mL vs 141.39 [194.25] ng/mL; $P < .001$). In patients with anemia at pretransplant, the group with anemia at 1 year after KT (persistent group) and the group without anemia at 1 year after KT (improved group) were compared. The persistent group showed higher pretransplant TSAT, lower 1-year TSAT, and lower estimated glomerular filtration rate at 1 year after KT than the improved group. In multivariate analysis, low ferritin at KT, low TSAT at 1 year, and high ferritin at 1 year were the risk factors for low Hb level at 1 year after adjusting multiple variables.

Conclusion. Anemia improved within 1 year after KT, although patients with iron deficiency increased. While ferritin reflected the inflammatory status, low TSAT at 1 year after KT was a risk factor for anemia at 1 year after KT.

ANEMIA is common in patients with chronic kidney disease, and it is well known that anemia is improved after kidney transplant (KT) [1]. However, anemia did not improve in all KT patients, and in some patients anemia persisted or worsened after KT. In patients with chronic kidney disease, the major cause of anemia is erythropoietin deficiency, but an additional important cause is iron deficiency [2]. Therefore, the role of iron deficiency in the

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*Address correspondence to Han Ro, Department of Internal Medicine, Gachon University Gil Medical Center, ADD 21, Namdong-daero 774 beon-gil, Inchon, 21565, Republic of Korea. Tel: +82-10-6316-0848; Fax: +82-32-460-2622. E-mail: godad@hilhospital.com

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Table 1. Baseline Characteristics of Patients

	Patients Included (N = 786)	Patients Excluded (N = 184)	*P* Value
Recipient's age at KT, mean (SD), y	45.17 (12.07)	45.90 (13.19)	.46
Recipient's sex, male, %	63.4	58.7	.24
Comorbidity, %			
Diabetes mellitus	26.8	24.0	.46
Hypertension	95.6	95.9	.87
Pre-emptive transplant, %	22.3	22.8	.87
Retransplant, %	7.5	1.1	.001
Body mass index at KT, mean (SD)	22.77 (3.49)	23.16 (3.43)	.17
Hemoglobin at KT, mean (SD), g/dL	10.53 (1.63)	10.52 (1.49)	.95
Albumin at KT, mean (SD), mg/dL	3.99 (0.50)	4.00 (0.48)	.74
Ferritin at KT, mean (SD), ng/mL	190.63 (217.43)	238.02 (224.33)	.02
Transferrin saturation at KT, mean (SD), %	33.89 (18.73)	34.04 (17.97)	.93
Deceased donor, %	16.2	25.5	.003
Donor's age at KT, mean (SD), y	44.07 (12.07)	44.21 (12.24)	.89
Donor's sex, male, %	49.9	55.4	.17
Donor's hemoglobin, mean (SD), g/dL	13.40 (2.07)	13.07 (2.31)	.06

Body mass index calculated as weight in kilograms divided by height in meters squared.
KT, kidney transplant.

persistence and development of anemia after KT is an important topic. However, there is little study on how iron deficiency changes after KT and how hemoglobin levels respond accordingly. This study was undertaken to identify changes in iron levels after KT and to determine the effect of iron on post-transplant anemia.

METHODS

The Korean cohort study for outcome in patients with KT is a multicenter prospective cohort study for Korean KT patients. A total of 1080 KT recipients enrolled in a multicenter observational cohort study between July 2012 and August 2018. Among them, 970 patients completed 1 year of follow-up at the time of analysis. A total of 786 patients with transferrin saturation and ferritin at pretransplant and 1 year after KT were reviewed. There was no significant difference in the baseline characteristics of the patients included in the analysis and those not included in the analysis except serum ferritin level, retransplant, and deceased donor transplant (Table 1). This study was approved by the Institutional Review Board, and informed consent was taken from all participants.

Anemia was defined as hemoglobin (Hb) < 13 g/dL (male) or <12 g/dL (female). Transferrin saturation (TSAT [%]) was calculated as 100 × serum iron (μg/dL)/total iron-binding capacity (μg/dL). Iron deficiency was defined as TSAT <20% and ferritin <200 ng/mL. Body mass index is calculated by dividing a person's body weight in kilograms by their height in meters squared.

All analyses were performed using SPSS software version 20 (IBM, Armonk, NY, United States). The results are shown as mean (SD) for continuous variables and as proportions for categorical variables. Proportions were compared by χ^2 tests or Fisher exact tests. Continuous variables were compared using the *t* test, paired *t* test, and analysis of variance. Multivariate linear regression analysis was used to identify significant factors associated with post-transplant anemia. A *P* value less than .05 was considered statistically significant.

RESULTS

The mean age of patients was 45 years; male patients comprised 63.4% (Table 1). A total of 7.5% of patients received deceased donor transplant. Hemoglobin at 1 year after KT was higher than Hb at KT (13.64 [SD, 1.87] g/dL vs 10.53 [SD, 1.63] g/dL; *P* < .001). The TSAT decreased from baseline at 1 year after KT (33.89% [SD, 18.73%] vs 29.09% [SD, 14.54%]; *P* < .001), and ferritin level decreased from baseline at 1 year (190.63 [SD, 217.43] ng/mL vs 141.39 [SD, 194.25] ng/mL; *P* < .001).

When the patients were divided into 4 groups (persistent anemia, improved anemia, developed anemia, persistent normal Hb) according to the change of anemia between baseline and 1 year of follow-up, serum ferritin decreased (200.39 [SD, 225.87] ng/mL vs 133.30 [SD, 190.89] ng/mL; *P* < .001), and TSAT also decreased slightly (32.65% [SD, 17.30%] vs 30.17% [SD, 13.93%]; *P* = .008) in the improved anemia group (Table 2). However, serum ferritin did not decrease (175.20 [SD, 173.39] ng/mL vs 163.15 [SD, 204.39] ng/mL; *P* = .38), and TSAT decreased (36.70% [SD, 21.44%] vs 26.36% [SD, 15.43%]; *P* < .001) in the persistent anemia group. There was no statistical significance because of the small number of patients in the group, but ferritin tended to increase (*P* = .26) and TSAT tended to decrease (*P* = .06) in the developed anemia group. Both ferritin (*P* = .05) and TSAT (*P* = .05) tended to decrease in the persistent normal Hb group.

In multivariate linear regression analysis, low ferritin at KT, low TSAT at 1 year, and high ferritin at 1 year were the risk factors for low Hb level at 1 year after adjusting multiple variables (Table 3).

Table 2. Characteristics of Patients According to Change of Hemoglobin

	Developed Anemia (n = 22)	Persistent Anemia (n = 192)	Improved Anemia (n = 500)	Both Normal Hb (n = 72)	*P* Value
Recipient's age at KT, mean (SD), y	41.64 (12.80)	45.85 (12.79)	45.06 (11.72)	45.15 (12.36)	.47
Recipient's sex, male, %	36.4	57.3	68.8	50.0	<.001
Comorbidity, %					
Diabetes mellitus	9.5	29.2	27.0	24.3	.27
Hypertension	90.5	95.5	95.9	95.7	.70
Pre-emptive transplant, %	0.0	22.4	24.8	11.1	.004
Retransplant, %	4.5	6.8	8.2	5.6	.76
Body mass index at KT, mean (SD)	20.75 (3.19)	22.51 (3.39)	23.03 (3.53)	22.26 (3.28)	.005
Albumin at KT, mean (SD) mg/dL	4.43 (0.52)	3.95 (0.50)	3.94 (0.47)	4.31 (0.48)	<.001
Deceased donor, %	31.8	16.7	14.2	23.6	.04
Donor's age at KT, mean (SD), y	51.55 (12.21)	45.98 (11.98)	43.06 (11.74)	43.69 (13.34)	.001
Donor's sex, male, %	45.5	55.7	46.4	59.7	.046
Donor's hemoglobin, mean (SD) g/dL	12.18 (1.93)	13.36 (2.01)	13.46 (2.05)	13.46 (2.37)	.04
Donor's eGFR, mean (SD), mL/min/1.73m^2	82.66 (35.05)	99.04 (57.54)	101.55 (34.18)	99.80 (46.73)	.22
Recipient's eGFR at discharge, mean (SD), mL/min/1.73m^2	58.44 (24.72)	62.79 (21.48)	67.65 (19.12)	69.12 (21.96)	.005
Recipient's eGFR at 1 y, mean (SD), mL/min/1.73m^2	54.72 (27.47)	58.17 (18.76)	67.15 (16.21)	66.60 (17.52)	<.001
Hemoglobin at KT, mean (SD), g/dL	13.05 (0.98)	10.15 (1.32)	10.17 (1.35)	13.27 (0.86)	<.001
Hemoglobin at 1 y, mean (SD), g/dL	11.03 (1.24)	11.51 (1.02)	14.50 (1.37)	14.17 (1.53)	<.001
Ferritin at KT, mean (SD), ng/mL	108.40 (73.30)	175.20 (173.39)	200.39 (225.87)	189.12 (279.76)	.163
Ferritin at 1 y, mean (SD), ng/mL	177.35 (293.24)	163.15 (204.39)	133.30 (190.89)	128.57 (144.84)	.23
Transferrin saturation at KT, mean (SD), %	33.01 (17.96)	36.70 (21.44)	32.65 (17.30)	33.01 (35.31)	.07
Transferrin saturation at 1 y, mean (SD), %	25.30 (17.72)	26.36 (15.43)	30.17 (13.93)	30.04 (14.46)	.01

Abbreviations: eGFR, estimated glomerular filtration rate; Hb, hemoglobin; KT, kidney transplant.

DISCUSSION

In this study, similar to previous studies [3,4], most of the patients experienced an improvement in anemia after KT, but in some patients the anemia persisted or worsened. In addition, this study showed that ferritin and TSAT were reduced after transplant in most patients. It is difficult to distinguish the depletion of iron store due to the improvement of anemia or the decrease in iron supplementation compared with the time of renal replacement therapy [5]. Ferritin was significantly decreased in the improved anemia

Table 3. Multivariate Linear Regression Analysis for Hemoglobin at 1 Year after Kidney Transplant

	Univariate			Multivariate		
	B	95% CI	*P* Value	B	95% CI	*P* Value
Recipient's female sex	−1.608	−1.856 ~ −1.360	<.001	−1.232	−1.493 ~ −0.972	<.001
Retransplant	−0.159	−0.657 ~ 0.338	.53	−0.138	−0.589 ~ 0.312	.55
Pre-emptive transplant	−0.112	−0.427 ~ 0.203	.49	−0.043	−0.336 ~ 0.251	.78
Deceased donor	−0.164	−0.520 ~ 0.192	.37	0.674	0.173 ~ 1.175	.008
Donor's female sex	0.402	0.141 ~ 0.662	.003	0.534	0.228 ~ 0.840	.001
Donor's Hb, g/dL	0.033	−0.030 ~ 0.096	.308	0.187	0.095 ~ 0.278	<.001
Donor's eGFR, mL/min/1.73m^2	0.002	−0.001 ~ 0.005	.308	0.001	−0.002 ~ 0.003	.69
BMI at KT	0.092	0.055 ~ 0.129	<.001	0.043	−0.017 ~ 0.104	.16
Hb at KT, g/dL	0.063	−0.017 ~ 0.144	.124	0.116	0.035 ~ 0.198	.005
Ferritin at KT, ng/mL	0.001	0.000 ~ 0.002	.001	0.001	0.001 ~ 0.002	<.001
TSAT at KT, %	−0.001	−0.008 ~ 0.006	.696	−0.003	−0.009 ~ 0.003	.35
Albumin at KT, mg/dL	0.050	−0.215 ~ 0.314	.713	−0.297	−0.577 ~ −0.016	.04
CRP at KT	0.091	−0.075 ~ 0.257	.280	−0.019	−0.162 ~ 0.124	.792
eGFR at 1 y, mL/min/1.73m^2	0.021	0.013 ~ 0.028	<.001	0.025	0.018 ~ 0.031	<.001
BMI at 1 y	0.086	0.044 ~ 0.128	<.001	0.025	−0.040 ~ 0.089	.45
Ferritin at 1 y, ng/mL	−0.001	−0.001 ~ 0.000	.027	−0.001	−0.002 ~ −−0.001	<.001
TSAT at 1 y, %	0.025	0.016 ~ 0.034	<.001	0.024	0.015 ~ 0.032	<.001
Albumin at 1 y, mg/dL	1.136	0.721~1.551	<.001	1.065	0.680 ~ 1.451	<.001
CRP at 1 y, mg/L	−0.279	−0.441 ~ −−0.117	.001	−0.202	−0.340 ~ −−0.063	.004

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; KT, kidney transplant; TSAT, transferrin saturation.

group, but ferritin was not decreased in the group with persistent anemia. On the contrary, TSAT severely decreased in the persistent anemia group. It is represented that insufficient iron storage is a cause of post-transplant anemia. Conversely, although it is small number of patients, an increase in ferritin as opposed to a decrease in TSAT in the developed anemia group is observed, suggesting that chronic inflammatory status has a negative effect on the correction of anemia like the previous time with chronic kidney disease [6]. Ultimately, it is not appropriate to evaluate iron storage with ferritin, which is also an acute phase reactant. It is necessary to evaluate the iron deficiency pattern in TSAT and to identify the chronic inflammatory condition through indicators such as C-reactive protein and ferritin [5].

Although this study has the advantage of prospective study, it has a disadvantage in that it cannot compare the indexes such as Hb and TSAT sequentially because of short follow-up duration. It is a disadvantage that there was no short-term result in comparing the patterns of short-term anemia and long-term anemia. It is necessary to conduct long-term study with indicators for anemia and iron storage through continuous follow-up and to add additional biomarkers to identify the cause of iron deficiency.

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