Observational Study

Medicine®

OPEN

Changes in hemostatic factors after kidney transplantation

A retrospective cohort study

Kang Woong Jun, MD[a], Jinbeom Cho, MD, PhD[a], Mi Hyeong Kim, MD, PhD[b], Jeong Kye Hwang, MD, PhD[b], Sun Cheol Park, MD, PhD[c], In Sung Moon, MD, PhD[d], Ji Il Kim, MD, PhD[e,*]

Abstract

Chronic kidney disease affects hemostasis in complex ways, producing both thrombotic and hemorrhagic diatheses. These changes may impact patient morbidity and mortality pre-transplantation, as well as allograft survival after kidney transplantation (KT). This study was conducted to analyze changes in hemostatic factors in the early post-KT period.

We retrospectively analyzed 676 recipients of kidney allografts from December 2009 to December 2014. Patients receiving plasmapheresis pre- or post-KT, experiencing early allograft failure, or receiving anticoagulants or antiplatelet agents pre- or post-KT were excluded.

Of the 367 included patients, acute (≤1 month) rejection occurred in 4.1% and delayed graft function occurred in 3.3%. Postoperative bleeding complications occurred in 7.9% of patients and thrombotic complications in 3.3%. Pre-transplantation, recipients had below normal hemoglobin, above normal D-dimer and homocysteine levels, and elevated rates of antiphospholipid antibodies. Hemoglobin increased to almost normal by postoperative day (POD) 28 ($P < .001$). D-dimer increased on POD7, 14, and 28, although the values were not significantly different from pre-KT. The pattern of D-dimer changes suggested that they were a nonspecific consequence of major surgery. Homocysteine decreased to normal by POD7 ($P < .001$). The percentage of patients with ≥1 prothrombotic factor was 82.0% pre-KT and only 14.2% on POD28 ($P < .001$).

The most of patients exhibited prothrombotic tendencies, including increased D-dimer and homocysteine, and increased prevalence of antiphospholipid antibodies before transplantation. They also had pre-transplantation anemia, suggesting a concomitant bleeding diathesis. However, most of these abnormal hemostatic factors improved or resolved after KT.

Abbreviations: aCL = anticardiolipin, ATG = antithymocyte globulin, CKD = chronic kidney disease, ESRD = end stage renal disease, HD = hemodialysis, KT = kidney transplantation, LA = lupus anticoagulant, PD = peritoneal dialysis, POD = postoperative day, PS = protein S, RRT = renal replacement therapy.

Keywords: chronic kidney disease, end stage renal disease, hemostatic factors, kidney transplantation

Editor: Robert Chen.

Patient Consent: The consent is exempted, as study is retrospective cohort study.

The authors report no conflicts of interest.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Statistical consultation was supported by the Department of Biostatistics of the Catholic Research Coordinating Center, the Catholic University of Korea.

English editing was performed by BioScience Writers LCC., verified on the BioScience Writers website (https://www.biosciencewriters.com/verify) using the verification code 1F58E54E-ED68-4FDC-BDCD-5317BE9998D3

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study. All data generated or analyzed during this study are included in this published article [and its supplementary information files]. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] *Department of Surgery, Bucheon St, Mary's Hospital, College of Medicine, The Catholic University of Korea, Gyeonggi-do,* [b] *Department of Surgery, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Eunpyeong-gu,* [c] *Department of Surgery, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seocho-gu,* [d] *Department of Surgery, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Yeongdeungpo-gu, Seoul,* [e] *Department of Surgery, Uijeongbu St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Uijeongbu-si, Gyeonggi-do, Republic of Korea.*

[*] *Correspondence: Ji Il Kim, Department of Surgery, Uijeongbu St. Mary's Hospital, College of Medicine, The Catholic University of Korea. 271, Cheonbo-ro, Uijeongbu-si, Gyeonggi-do 11765, Republic of Korea (e-mail: cmckji@catholic.ac.kr).*

How to cite this article: Jun KW, Cho J, Kim MH, Hwang JK, Park SC, Moon IS, Kim JI. Changes in hemostatic factors after kidney transplantation: a retrospective cohort study. Medicine 2021;100:36(e27179).

Received: 29 March 2021 / Received in final form: 2 August 2021 / Accepted: 21 August 2021

http://dx.doi.org/10.1097/MD.0000000000027179

1. Introduction

Chronic kidney disease (CKD) affects hemostasis through various complex mechanisms, and in end-stage renal disease (ESRD), patients can experience both thrombotic complications and bleeding diathesis.[1] Hemorrhagic diathesis is attributed to the accumulation of protein degradation products, leading to reduced platelet production, platelet dysfunction, vessel wall damage, and deficiency of clotting factors II, V, IX, and X. ESRD-associated anemia also contributes to platelet dysfunction.[2] Hypercoagulability is attributed to changes in the coagulation cascade, with increased fibrinogen, plasma tissue factor, clotting factors XIIa and VIIa, activated protein C (PC), thrombin-antithrombin complexes, D-dimers, and prothrombin fragments, as well as reduced antithrombin III (AT III) activity.[3]

The effects of kidney transplantation (KT) on coagulation profiles and postoperative thrombotic complications are controversial. KT is a major operation, which can increase thromboembolic complications in CKD patients.[4] Deira et al[5] reported significantly decreased AT III and PC activity on the first postoperative day (POD), suggesting an increased thrombosis risk. Other studies reported correction of hypercoagulability after KT.[6,7]

This study was performed to characterize prothrombotic factor activity in patients with CKD before and after KT, and to analyze changes in these factors after KT.

2. Materials and methods

This retrospective single-center study was approved by the institutional review board of Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea (KC20RISI0792). From December 2009 to December 2014, 676 individuals with CKD underwent KT at our institute. We excluded 309 patients meeting these criteria: plasmapheresis before or after KT; early allograft failure ($\leq$1 month); or anticoagulant or antiplatelet agents $\leq$1 month before or after (eg, newly diagnosed coronary arterial disease (CAD), symptomatic venous thromboembolism (VTE), and so on after KT (Fig. 1). Thus, 367 recipients were included in the study.

2.1. Data collection

We collected the following information from electronic medical records: demographics, CKD etiology, type of renal replacement therapy (RRT), number of mismatched human leukocyte antigens, type of immunosuppressive agents, episodes of acute rejection, or delayed graft function (DGF); defined as an acute kidney injury, which necessitates a dialysis intervention in the first week of kidney transplantation; within a month post–KT, and bleeding/thrombotic events. Blood samples for coagulation factors were collected the day before transplantation and on POD7, 14, and 28. The following hemostatic parameters were prospectively analyzed (reference ranges in parentheses): hemoglobin (12–16 g/dL); platelet count (140–400 $\times 10^9$/L); prothrombin time (70%–125.7%); activated partial thromboplastin time (APTT; 21.9–36.7 seconds); international normalized ratio (0.89–1.2); D-dimer ($\leq$0.6 mg/dL); fibrinogen (160–350 mg/dL); protein S (PS) activity (60%–120%); PC activity (70%–130%); AT III activity (80%–120%); homocysteine (3–15 μmol/L); lupus anticoagulant (LA; $\leq$1:3 on screening test/confirmation test); anticardiolipin (aCL) IgG (<10 U/mL); aCL IgM and IgA (absent on qualitative test); clotting factor VIII (60%–150%); and clotting factor IX (60%–150%). Data regarding inherited disorders, such as factor V Leiden mutation and prothrombin G20210A mutations, and platelet adhesion-aggregation tests were too scarce to analyze in this study. Prothrombotic factors were defined as follows: decreased PS activity; decreased PC activity; decreased AT III activity; increased homocysteine; presence of LA; presence of aCL (IgG, IgA, or IgM); increased factor VIII level; or increased factor IX level.

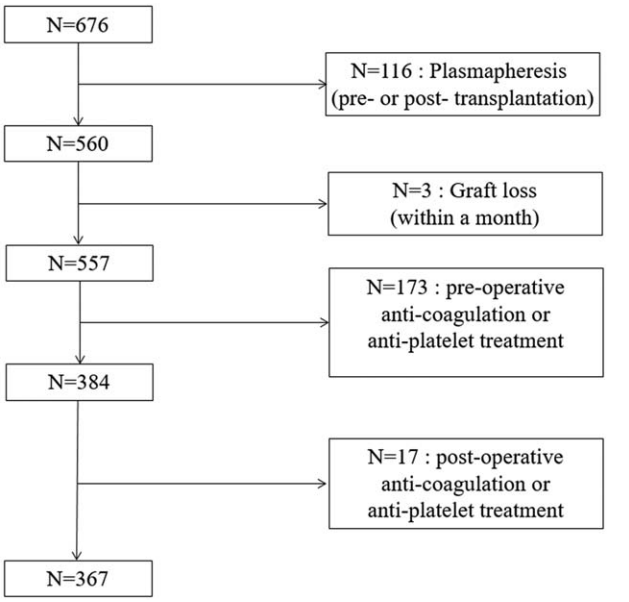

Figure 1. Flow sheet of patients' selection.

2.2. Postoperative imaging

Patients at our institute routinely undergo color duplex ultrasound on POD1, 7, 14, and 28 and magnetic resonance angiography on POD7 or 14 to evaluate the condition of the graft kidney (perfusion and renal artery resistive index) and the presence of peri-graft fluid (hematoma or lymphocele) or hydronephrosis. Magnetic resonance angiography is performed on POD7 in cases with multiple donor renal arteries or suboptimal environments of the donor renal artery or recipient iliac artery, such as heavy calcifications or atheroma of the artery. To detect lower extremity deep DVT, we perform bilateral, whole-leg color duplex ultrasound on POD7, 14, and 28, or at any time when clinically indicated.[8] When bleeding is suspected (eg, suddenly decreased blood pressure and hemoglobin or bloody discharge in the Jackson-Pratt drains [Cardinal Health, Waukegan, IL]), we perform nonenhanced abdominal computed tomography to assess hematoma around the allograft kidney.

2.3. Immunosuppressive regimen

The typical immunosuppressive regimen at our institute was described previously.[9] All kidney recipients receive basiliximab (Simulect, Novartis Pharmaceuticals Co., Basel, Switzerland) 20 mg on POD0 and 4 or antithymocyte globulin (ATG) (Thymoglobulin, Sanofi Genzyme, Cambridge, MA) 1.25 mg/kg from POD0 to 4 as induction immunosuppressants (in case of

highly sensitized patients or expanded criteria deceased donor). Maintenance immunosuppression consists of tacrolimus (Tacrobell, Chong Kun Dang Pharmaceuticals Co., Seoul, Korea; Prograf, Astellas Pharma Inc., Toyama, Japan), corticosteroid, and either mycophenolate mofetil (Cellcept, Hoffmann-La Roche Inc., Nutley, NJ) or mycophenolate sodium (Myfortic, Novartis Pharmaceuticals Co.).

2.4. Surgery

Recipient surgery was performed through an extraperitoneal "hockey stick" incision with creation of standard vascular anastomoses and extravesical ureteroneocystostomy. JP drains remained in the extraperitoneal space until drainage was <50 mL/day for 2 consecutive days.

2.5. Statistical analysis

Summary statistics are presented as frequency (percentage) for categorical variables and median (range) for continuous variables. χ^2 and Fisher exact test were used to compare categorical variables. Kruskal-Wallis test was used to compare continuous variables because the normality assumption was not satisfied with the Kolmogorov-Smirnov test. Repeated measures data were analyzed using a generalized linear mixed model to compensate for missing data, and distribution conditions for each variable are expressed as mean ± standard error. Bonferroni correction was used because of multiple comparisons. Two-sided P values <.05 were considered statistically significant. All analyses were performed using SAS 9.4 software (SAS Institute, Inc., Cary, NC).

3. Results

Table 1 summarizes demographics and short-term (≤1 month) outcomes post-KT of the 367 patients in this study. Deceased-donor KT accounted for 36.8% (135/367) of transplants, acute rejection occurred in 4.1% (15/367) of patients, and DGF occurred in 3.3% (12/367) of patients. All patients with DGF received kidneys from deceased donors.

Table 2 shows prothrombotic factors pre- and post-KT in each RRT subgroup (hemodialysis [HD], peritoneal dialysis [PD], and preemptive). Pre-transplantation, hemoglobin was below normal and D-dimer and homocysteine levels were above normal in all subgroups. Fibrinogen was within normal range, except in PD which was above normal. Platelet counts, prothrombin time, APTT, fibrinogen, PS activity, and PC activity were normal. The following factors significantly differed according to dialysis modality pre-transplantation: hemoglobin, and D-dimer were higher in HD patients than PD patients; and fibrinogen, PS activity, PC activity, AT III, and homocysteine were higher in PD patients than HD patients ($P < .05$). After KT, most prothrombotic factors differed significantly from pre-KT values (Table 2). Hemoglobin decreased from 10.5 ± 1.7 g/dL pre-KT to 9.5 ± 1.3 mg/dL and 9.6 ± 1.2 g/dL on POD7 and 14, but rose to almost normal on POD28 (11.4 ± 1.3 g/dL) ($P < 0.05$). D-dimer was increased pre-KT (1.3 ± 1.4 mg/dL) and remained above normal on POD7, 14, and 28 (2.7 ± 2.1, 2.0 ± 1.9, and 1.7 ± 1.5 mg/dL, respectively), with no significant differences from pre-KT. Homocysteine decreased from 21.9 ± 14.5 μmol/L pre-KT to normal on POD7, 14, and 28 (12.4 ± 7.8, 12.4 ± 6.8, and 14.5 ± 6.0 μmol/L, respectively) ($P < .05$). For the entire group, fibrinogen remained in the normal range pre- and post-KT. However, in

Table 1

Demographic characteristics and surgical outcomes according to pre-operative renal replacement therapy.

	Total (n = 367)	HD (n = 209)	PD (n = 90)	None (n = 68)	*P*
Age, y	44.0 (32.3–55.8)	43.8 (31.9–55.7)	45.9 (35.2–55.7)	42.5 (39.0–46.0)	.13
Sex (male/female)	220/147	127/82	56/34	37/31	.57
History of smoking (n)	35 (9.5)	20 (9.6)	9 (10)	6 (8.8)	.97
BMI, kg/m^2	23.0 (19.5–26.5)	22.4 (19.2–28.6)	22.8 (21.7–26.7)	22.7 (19.0–26.4)	*<.05*
Cause of ESRD (n)					*<.05*
CGN	137 (37.3)	74 (35.4)	33 (36.7)	30 (44.1)	
DM	42 (11.4)	26 (12.4)	12 (13.3)	4 (5.9)	
Hypertension	74 (20.2)	45 (21.4)	26 (28.9)	3 (4.4)	
Others	114 (31.1)	64 (30.6)	19 (21.1)	31 (45.6)	
Type of donor (n)					*< .05*
Living	232 (63.2)	128 (61.2)	37 (41.1)	67 (98.5)	
Deceased	135 (36.8)	81 (38.8)	53 (58.9)	1 (1.5)	
No. of KT (n)					*<.05*
1st	330 (89.92)	185 (88.52)	87 (96.67)	58 (85.29)	
2nd <	37 (10.08)	24 (11.48)	3 (3.33)	10 (14.71)	
Mismatch no. of HLA (n)					.41
0	34 (9.3)	20 (9.6)	6 (6.7)	8 (11.8)	
1	12 (3.3)	7 (3.4)	0	5 (7.4)	
2	65 (17.7)	37 (17.7)	16 (17.8)	12 (17.7)	
3	95 (26)	51 (24.4)	25 (27.8)	19 (27.9)	
4	67 (18.3)	43 (20.6)	17 (18.9)	7 (10.3)	
5	65 (17.7)	35 (16.8)	19 (21.1)	11 (16.2)	
6	29 (7.9%)	16 (7.7)	7 (7.8%)	6 (8.8%)	
Acute rejection within a month (n)	15 (4.1%)	13 (6.2%)	1 (1.1%)	1 (1.5%)	.07
Delayed graft function (n)	12 (3.3%)	7 (3.3%)	5 (5.6%)	0 (0)	.15

Values are presented as number (%) for categorical variables, and median (interquartile range) for continuous variables.

*P values are calculated by Kruskal–Wallis test for continuous variables and χ^2 or fisher test for categorical variables.

BMI = body mass index, CGN = chronic glomerular nephritis, DM = diabetes mellitus, HD = hemodialysis, HLA = human leukocyte antigen, KT = kidney transplantation, PD = peritoneal dialysis.

Table 2

Comparison of the prothrombotic factors before and after kidney transplantation in each patient group.

		Pre-transplantation	7th POD	14th POD	28th POD	*P*
Hemoglobin, g/dL	Total	10.5±1.7	9.5±1.3	9.6±1.2	11.4±1.3	*<.05*
	HD	10.9±1.8	9.6±1.3	9.5±1.3	11.3±1.3	*<.05*
	PD	10.3±1.7	9.3±1.2	9.7±1.3	11.4±1.3	*<.05*
	None	9.8±1.3	9.3±1.1	9.4±1.1	11.4±1.3	*<.05*
		P<.05	*P*=.29	*P*=.55	*P*=.74	
Platelet ($\times 10^9$/L)	Total	185.6±59	161.6±57	183.2±60.9	214.5±72.6	*<.05*
	HD	179.7±56.4	162.9±61.4	183.5±64.5	211.8±75.4	*<.05*
	PD	195.6±65.3	155.7±56.6	182.7±62.3	214.3±74.3	*<.05*
	None	190.5±56.3	165.1±41.5	182.9±47.1	223.4±61.2	*<.05*
		P=.10	*P*=.24	*P*=.95	*P*=.23	
PT (%)	Total	91.6±13.2	84.6±15.4	96.7±13.6	110.4±17.1	*< .05*
	HD	92.4±12.6	84.3±15.6	96.9±13.4	111.7±16.7	*<.05*
	PD	93.2±14.9	85±15.8	95.3±15.3	106±20.3	*<.05*
	None	87.2±11.5	85±14.3	97.8±11.7	112.2±11.8	*<.05*
		P<.05	*P*=.70	*P*=.77	*P*=.09	
APTT, s	Total	26.9±5.9	25.8±5.8	23.9±5	22.5±6.1	*<.05*
	HD	27.3±6.8	26.4±6.3	23.9±4.2	22.4±4	*<.05*
	PD	26±4.3	25.1±5.3	24.4±7.2	23.5±10.2	*<.05*
	None	27±4.4	25.1±4.8	23.2±3.9	21.5±2.8	*<.05*
		P=.07	*P*<*.05*	*P*=.51	*P*=.38	
D-dimer, mg/dL	Total	1.3±1.4	2.7±2.1	2±1.9	1.7±1.5	.24
	HD	1.1±0.8	2.7±2	2.1±2.2	1.6±1.6	.24
	PD	1.0±0.9	2.4±2.4	1.8±1.4	1.7±1.3	.06
	None	1.3±1	3.1±1.8	2±1.2	1.6±1.1	.31
		P<.05	*P*<*.05*	*P*=.25	*P*=.30	
Fibrinogen, mg/dL	Total	322.4±89.3	215.3±70.3	241.3±92.2	264±84.2	*< .05*
	HD	295.9±80.6	207.4±65.9	230.9±86.3	266.2±85.4	*<.05*
	PD	386.5±78.7	242.7±72.7	286.3±93.9	283.1±80.5	*<.05*
	None	325.3±88.1	205.4±72	218.5±90.4	234.9±80.3	*<.05*
		P<.05	*P*<.05	*P*<.05	*P*=*.05*	
PS activity (%)	Total	90.9±32.1	66.2±22.4	76.5±26.2	93.8±37	.89
	HD	86.9±30.7	65.2±22	76.2±25.2	93.4±46.3	.37
	PD	98.3±33.1	65.6±23.8	76.7±27.7	95.5±22.9	.28
	None	93.4±33.5	69.4±22.1	76.8±27.4	92.8±21.1	.76
		P<.05	*P*=.57	*P*=.98	*P*=.67	
PC activity (%)	Total	100.6±22.7	102.4±24.8	119.6±26	127.6±23.1	*<.05*
	HD	99.2±21.4	101±24.3	119.1±26.9	124.3±25.5	*<.05*
	PD	108.2±24.5	102.7±27.9	119±23.6	129.3±20.9	*<.05*
	None	94.7±21.6	105.8±22.6	121.7±26.6	134.2±17.5	*<.05*
		P<.05	*P*=.45	*P*=.57	*P*=.21	
ATIII activity	Total	87±13.9	88.1±14	101.4±14.8	109.9±13.5	*<.05*
(%)	HD	84.2±13.7	88.5±13	101.8±14.6	110.5±10.1	*<.05*
	PD	91.9±13.3	88.1±15.1	99±16.6	105.5±20.7	*<.05*
	None	89.2±13.1	87±15.5	103±13.2	113.8±7.8	*<.05*
		P=.49	*P*=.80	*P*=.41	*P*=.33	
Homocystein, μmol/L	Total	21.9±14.5	12.4±7.8	12.4±6.8	14.5±6	*<.05*
	HD	19.6±13	12.3±8.7	12.6±7.8	14.1±4.8	*<.05*
	PD	23.3±12	12.7±6.4	11.3±5.5	14.4±7.9	*<.05*
	None	27.2±19.7	12.4±6.7	13.1±5.4	15.7±6.2	*<.05*
		P<*.05*	*P*=.27	*P*=.11	*P*=.45	
LA* (%)	Total	7.1	2.1	0.4	0.8	*<.05*
	HD	7.3	1.2	0	0	*<.05*
	PD	9	4.4	1.5	3.3	.18
	None	4.4	1.7	0	0	.07
		P=.54	*P*=.28	*P*=.45	*P*=.45	
aCL* (%)	Total	13.6	10.0	8.0	4.0	*<.05*
	HD	15.5	12.4	10.8	2.9	*<.05*
	PD	11.9	5.8	5.7	6.7	.24
	None	10.3	8.5	3.3	3.9	.12
		P=.49	*P*=.29	*P*=.14	*P*=.83	
Factor VIII†	Total	34.4	50	61.8	33.3	.06
	HD	25	33.3	66.7	50	.13

(*continued*)

Table 2
(continued).

		Pre-transplantation	7th POD	14th POD	28th POD	P
	PD	50	80	66.7	0	.42
	None	30	40	50	0	.54
		P=.53	P=.07	P=.74	P=.99	
Factor IX†	Total	6.3	9.4	35.3	33.3	< .05
	HD	0	0	33.3	50	<.05
	PD	10	10%	25	0	.37
	None	10	20%	50	0	.07
		P=.51	P=.27	P=.55	P=.99	

Values are presented as mean ± standard error for continuous variables, and percentages for categorical variables.
* Prevalence of cases of positive result.
† Prevalence of cases of increased result.
P values are calculated by longitudinal data analysis for the comparison of each operative stage, and calculated by Kruskal–Wallis test for continuous variables and χ^2 or Fisher test for categorical variables in the comparison of each patient group.
aCL = anticardiolipin, APTT = activated partial thromboplastin time, ATIII = antithrombin III, HD = hemodialysis, LA = lupus anticoagulant, PC = protein C, PD = peritoneal dialysis, POD = postoperative day, PS = protein S, PT = prothrombin time.

the PD subgroup, fibrinogen was increased pre-KT (386.5 ± 78.7 mg/dL) and decreased on POD7, 14, and 28 (242.7 ± 72.7, 286.3 ± 93.9, and 283.1 ± 80.5 mg/dL, respectively) ($P < .05$). PC activity was higher post-KT than pre-KT but remained in the normal range throughout the study in all subgroups ($P < .05$). LA and aCL rates were lower at POD28 than pre-KT (7.1% vs 0.8% and 13.6% vs 4.0%, respectively) ($P < .05$). Elevated factor VIII rates did not differ throughout the study. Prevalence of increased factor IX was significantly higher on POD7, 14, and 28 than pre-KT ($P < .05$).

Table 3 presents the comparison between basiliximab and ATG induction group. Hemoglobin decreased from 10.5 ± 1.7 g/dL versus 10.8 ± 1.6 g/dL pre-KT to 9.5 ± 1.3 g/dL versus 8.9 ± 1.4 g/dL POD7 ($P < .05$), 9.6 ± 1.2 g/dL versus 9.1 ± 1.6 g/dL on POD14 ($P < .05$) and return to normal after POD28 ($P < 0.05$). Platelet counts decreased from 186.3 ± 59.5 (x10^9/L) versus 180.3 ± 54.8 (×10^9/L) pre-KT ($P < .05$) to 166.4 ± 55.8 (×10^9/L) versus 126.3 ± 53.9 (×10^9/L) on POD7 ($P < .05$) and return to normal after POD14, respectively ($P < .05$). These decrements in hemoglobin and platelet counts were more pronounced in ATG groups comparing with basiliximab ones, and platelet counts were lower in ATG groups throughout the study period compared to basiliximab ones after KT (126.3 ± 53.9 (×10^9/L) versus 166.4 ± 55.8 (×10^9/L) POD7; 157.8 ± 53.2 (10^9/L) versus 186.7 ± 61.2 (×10^9/L) POD14; 187.7 ± 80.0 (×10^9/L) versus 218.2 ± 70.9 (×10^9/L) POD28, respectively) ($P < .05$). D-dimer was increased in both basiliximab and ATG groups after KT; however, there was no significant difference (3.0 ± 3.0 mg/dL vs 2.6 ± 1.9 mg/dL POD7 [$P > .05$], 2.5 ± 2.7 mg/dL vs 2.0 ± 1.7 mg/dL POD14 [$P > .05$], 1.7 ± 1.5 mg/dL vs 1.4 ± 1.3 mg/dL POD28 [$P > .05$]).

Table 4 presents the comparison between LDKT and DDKT groups. Hemoglobin and platelet counts were lower in DDKT group throughout the study period compared to LDKT group. Hemoglobin decreased from 10.1 ± 1.6 g/dL versus 11.3 ± 1.8 g/dL pre-KT to 9.7 ± 1.3 g/dL versus 9.1 ± 1.2 g/dL POD7, 9.7 ± 1.2 g/dL versus 9.3 ± 1.2 g/dL on POD14 and recovered normal range in both groups after POD28 ($P < .05$). Platelet counts decreased from 185.0 ± 61.8 (×10^9/L) vs 185.0 ± 61.8 (×10^9/L) pre-KT to 173.3 ± 56.4 (×10^9/L) and 141.4 ± 52.5 (10^9/L) on POD7 ($P < .05$) and were restored after POD14, respectively. These decrements in hemoglobin and platelet were steeper in DDKT group ($P < .05$). D-dimer was increased in both LDKT and DDKT groups after KT, and except for POD7 when the LDKT groups showed higher level of D-dimer (2.9 ± 2.1 mg/dL vs 2.2 ± 1.9 mg/dL, $P < .05$), there was no significant difference between 2 groups during the study period.

Table 5 shows patients with ≥1 positive prothrombotic factor pre- and post-KT in each RRT subgroup. Pre-transplant, the prevalence of ≥1 positive prothrombotic factor was 82.0%. The prevalence decreased on POD7, 14, and 28 to 55.3%, 29.7%, and 14.2%, respectively ($P < .05$). The same trend occurred in all RRT subgroups, although the differences were not statistically significant. The number of positive (abnormal) prothrombotic factors per patient was 1.4 ± 0.9 pre-KT and decreased significantly post-KT to 0.9 ± 0.1 on POD7, 0.4 ± 0.6 on POD14, and 0.2 ± 0.6 on POD28 ($P < .05$). Similar changes were noted in each RRT subgroup, which was statistically significant on multiple comparison analysis ($P < .05$) (Table 6).

4. Discussion

Patients with CKD have an increased risk of both thrombosis and bleeding. The main reported hemostatic abnormalities in CKD are increased tissue factor, von Willebrand factor, factor XIIa, factor VIIa, activated PC, fibrinogen, and plasminogen activator inhibitor-1, and reduced tissue plasminogen activator.[10] As CKD advances, platelet dysfunction and hemorrhagic complications appear, with mucocutaneous bleeding, gastrointestinal bleeding, and, less frequently, hemothorax, hemoperitoneum, and intracranial or retroperitoneal bleeding.[11] It is unclear why bleeding problems predominate in one patient, whereas thrombotic complications occur in others.[3]

Previous reports of hypercoagulability in patients with CKD have reported varying mechanisms. We examined eight hemostatic factors previously reported as possible contributors to thrombosis after KT. At least one of these prothrombotic factors was present in 82.0% of our study population pre-KT, with 1.4 ± 0.9 factors per patient.[12]

Patients with CKD exhibit abnormalities of various proteins and amino acids, including homocysteine.[13] Plasma homocysteine levels are inversely related to glomerular filtration rate, with hyperhomocysteinemia observed in up to 85% to 100% of people with ESRD.[13] Elevated homocysteine levels are associated with increased risk of venous and arterial thrombosis.[14] In our study, D-dimer and homocysteine were increased above

Table 3

Comparison of the prothrombotic factors before and after kidney transplantation between basiliximab and ATG induction group.

	Basiliximab (N = 323)			ATG (N = 44)			
	n	Mean ± SD or n (%)	*P for within group (a)*	n	Mean ± SD or n (%)	*P for within group (a)*	*P for between group*
Hemoglobin, g/dL							0.07 (c)
Pre	322	10.5 ± 1.7	—	44	10.8 ± 1.6	—	0.31 (d)
7th POD	323	9.5 ± 1.3	<.05	44	8.9 ± 1.4	<.05	<0.05 (d)
14th POD	323	9.6 ± 1.2	<.05	44	9.1 ± 1.6	<.05	<0.05 (d)
28th POD	323	11.4 ± 1.3	<.05	44	11.0 ± 1.5	0.42	0.06 (d)
P for time within group (b)		<.05			<.05		
Platelet ($\times 10^9$/L)							<.05 (c)
Pre	323	186.3 ± 59.5	—	44	180.3 ± 54.8	—	0.53 (d)
7th POD	323	166.4 ± 55.8	<.05	44	126.3 ± 53.9	<.05	<.05 (d)
14th POD	323	186.7 ± 61.2	0.91	44	157.8 ± 53.2	<.05	<.05 (d)
28th POD	323	218.2 ± 70.9	<.05	44	187.7 ± 80.0	0.45	<.05 (d)
P for time within group		<.05			<.05		
PT (%)							0.06 (c)
Pre	323	91.2 ± 13.2	—	44	94.8 ± 12.9	—	0.53 (d)
7th POD	318	84.9 ± 15.0	<.05	44	82.7 ± 18.2	<.05	<.05 (d)
14th POD	299	96.9 ± 13.3	<.05	44	95.0 ± 15.3	0.96	<.05 (d)
28th POD	268	110.7 ± 16.5	<.05	44	108.6 ± 20.3	<.05	<.05 (d)
P for time within group		<.05			<.05		
APTT, s							<.05 (c)
Pre	323	26.9 ± 6.0	—	44	26.9 ± 5.3	—	0.99 (d)
7th POD	318	25.7 ± 6.0	<.05	44	26.7 ± 4.8	0.80	0.33 (d)
14th POD	298	23.7 ± 4.1	<.05	44	25.3 ± 9.1	0.13	<.05 (d)
28th POD	268	22.1 ± 3.8	<.05	44	25.2 ± 12.9	0.15	<.05 (d)
P for time within group		<.001			0.318		
D-dimer, mg/dL							<.05 (c)
Pre	319	1.4 ± 1.4	—	44	0.9 ± 0.8	—	<.05 (d)
7th POD	319	2.6 ± 1.9	<.05	44	3.0 ± 3.0	<.05	0.28 (d)
14th POD	316	2.0 ± 1.7	<.05	44	2.5 ± 2.7	<.05	0.10 (d)
28th POD	302	1.7 ± 1.5	<.05	41	1.4 ± 1.3	<.05	0.37 (d)
P for time within group		<.05			<.05		
Fibrinogen, mg/dL							0.47 (c)
Pre	220	321.9 ± 91.1	—	43	324.9 ± 80.5	—	0.98 (d)
7th POD	249	218.3 ± 72.5	<.05	44	198.4 ± 53.1	<.05	0.09 (d)
14th POD	251	242.6 ± 94.7	<.05	44	234.2 ± 76.8	<.05	0.56 (d)
28th POD	93	266.6 ± 86.4	<.05	37	257.6 ± 79.1	<.05	0.70 (d)
P for time within group		<.05			<.05		
PS activity (%)							0.90 (c)
Pre	320	91.3 ± 32.9	—	43	87.9 ± 25.5	—	0.48 (d)
7th POD	247	67.2 ± 22.7	<.05	44	60.5 ± 20.2	<.05	0.09 (d)
14th POD	251	77.4 ± 26.1	<.05	44	71.1 ± 26.1	<.05	0.16 (d)
28th POD	92	93.8 ± 26.1	0.43	35	93.7 ± 57.1	0.49	0.80 (d)
P for time within group		<.05			<.05		
PC activity (%)							0.70 (c)
Pre	317	101.1 ± 23.0	—	43	96.7 ± 19.9	—	0.23 (d)
7th POD	247	103.0 ± 24.6	0.07	43	98.9 ± 26.3	0.56	0.211 (d)
14th POD	251	120.9 ± 25.9	<.05	44	112.2 ± 25.8	<.05	0.029 (d)
28th POD	92	129.2 ± 23.8	<.05	35	123.4 ± 21.0	<.05	0.040 (d)
P for time within group		<.05			<.05		
ATIII activity (%)							<0.05 (c)
Pre	320	87.2 ± 14.1	—	43	85.6 ± 12.2	—	0.472 (d)
7th POD	248	87.8 ± 14.1	0.832	44	89.4 ± 13.5	0.117	0.411 (d)
14th POD	252	101.9 ± 14.6	<.05	44	98.4 ± 16.0	<.05	0.218 (d)
28th POD	94	110.6 ± 12.8	<.05	37	108.0 ± 15.2	<.05	0.117 (d)
P for time within group		<.05			<.05		
Homocystein, μmol/L							0.607 (c)
Pre	320	22.2 ± 14.9	—	44	20.3 ± 11.7	—	0.42 (d)
7th POD	246	12.3 ± 7.9	<.05	44	13.1 ± 6.9	<.05	0.51 (d)
14th POD	247	12.3 ± 6.9	<.05	43	13.0 ± 6.5	<.05	0.57 (d)
28th POD	88	14.2 ± 5.1	<.05	35	15.2 ± 7.8	<.05	0.58 (d)
P for time within group		<.05			<.05		
LA* (%)							—

(*continued*)

Table 3

(continued).

	Basiliximab (N = 323)			ATG (N = 44)			
	n	Mean ± SD or n (%)	*P* for within group (a)	n	Mean ± SD or n (%)	*P* for within group (a)	*P* for between group
Pre	321	21 (6.5)	—	43	5 (11.6)	—	0.21 (f)
7th POD	245	6 (2.5)	<.05	44	0 (0)	—	—
14th POD	246	1 (0.4)	<.05	43	0 (0)	—	—
28th POD	86	1 (1.2)	0.08	36	0 (0)	—	—
P for time within group		<.05			—		
aCL* (%)							0.11 (c)
Pre	308	37 (12.0)	—	44	11 (25.0)	—	<.05 (d)
7th POD	246	25 (10.2)	0.203	44	4 (9.1)	<.05	0.97 (d)
14th POD	245	21 (8.6)	<.05	43	2 (4.7)	<.05	0.53 (d)
28th POD	89	3 (3.4)	<.05	36	2 (5.6)	<.05	0.33 (d)
P for time within group		<.05			<.05		
Factor VIII† (%)							0.68 (c)
Pre	25	8 (32.0)	–	7	3 (42.9)	—	0.59 (d)
7th POD	25	13 (52.0)	0.077	7	3 (42.9)	0.957	0.69 (d)
14th POD	26	16 (61.5)	<.05	8	5 (62.5)	0.161	0.98 (d)
28th POD	3	1 (33.3)	0.996	0	0 (0)	—	—
P for time within group		0.08			0.38		
Factor IX† (%)							0.49 (c)
Pre	25	1 (4.0)	—	7	1 (14.3)	—	0.37 (d)
7th POD	25	2 (8.0)	0.379	7	1 (14.3)	0.973	0.64 (d)
14th POD	26	10 (38.5)	<.05	8	2 (25.0)	0.632	0.50 (d)
28th POD	3	1 (33.3)	0.273	0	0 (0)	—	—
P for time within group		<.05			0.62		

P value by mixed model for repeated measurement (MMRM) for continuous variables and generalized estimating equation (GEE) method for binary outcomes.

(a) *P* for comparison between pre-transplantation and each POD value within group.

(b) *P* for time within group.

(c) *P* for interaction between group and time.

(d) *P* for comparison between groups within each time point.

Values are presented as mean ± standard error for continuous variables, and percentages for categorical variables.

* Prevalence of cases of positive result.

† Prevalence of cases of increased result.

P values are calculated by longitudinal data analysis for the comparison of each operative stage, and calculated by Kruskal–Wallis test for continuous variables and χ^2 or fisher test for categorical variables in the comparison of each patient group.

aCL = anticardiolipin, APTT = activated partial thromboplastin time, ATG = antithyomocyte globulin, ATIII = antithrombin III, HD = hemodialysis, LA = lupus anticoagulant, PC = protein C, PD = peritoneal dialysis, POD = postoperative day, PS = protein S, PT = prothrombin time.

normal pre-transplant, suggesting a hypercoagulable state. Antiphospholipid antibodies (APLAs), including aCL, anti-β2GP-1 antibody, and LA, also promote thrombosis. LA is more strongly associated with increased thrombotic risk than aCL or anti-B2GP-1 antibody, and a "triple positive" profile (all 3 APLAs) confers the highest risk.[15] In one study, the prevalence of LA, IgG aCL, IgM aCL, and polyvalent aCL in a healthy population was 3.6%, 4.6%, 4.6%, and 5.5%, respectively.[16] In a general population study, positive LA, aCL, and anti-β2GP-1 antibody rates were 7%, 15%, and 11%, respectively, at initial testing and 5%, 9%, and 13% at 12-week retesting.[17] Our pre-KT rates were 7.1% for LA and 10.5% for aCL, which were higher than in the healthy population. Although false-positive LA may occur with oral anticoagulants, we excluded patients receiving this therapy.[18] Our pre-KT prevalence of elevated factor VIII was 34.4%, which was likewise higher than the 11% rate reported in a normal population.[19]

Uremia is strongly associated with platelet dysfunction, increasing the risk of hemorrhagic events. The pathogenesis of platelet dysfunction in uremia is multifactorial: platelet-platelet (aggregation) and platelet-vessel wall (adhesion) interactions appear crucial.[20] In this study, platelet counts decreased from 185.6 ± 59 ($\times 10^9$/L) pre-transplant to nadir (161.6 ± 57 [$\times 10^9$/L]) at POD7, then recovered to normal at POD28 as uremia and anemia improved. Anemia plays a role in platelet dysfunction, as platelets are more dispersed, impairing their adherence to endothelium. Furthermore, red blood cells enhance platelet function by releasing adenosine diphosphate, inactivating prostacyclin, and scavenging nitric oxide; thus, their reduced number in anemia contributes to platelet dysfunction.[21] Erythropoietin to correct anemia in CKD reduces the risk of uremic bleeding.[10] In this study, pre-KT hemoglobin was decreased below normal in all RRT subgroups suggesting an increased hemorrhagic risk in ESRD patients. Several reports have suggested that RRT might promote hypercoagulability in patients with CKD. As compared to HD, PD is known to increase the thrombotic tendency via increased levels of platelets, fibrinogen, clotting factor VII, and plasminogen activator inhibitor-1.[22–26] Inversely, HD appears to activate the coagulation cascade by reducing coagulation inhibitors, such as PC, PS, and AT III.[6,27] In the present study, the HD group had elevated D-dimer and decreased PS, PC, and AT III activity levels compared to the PD group, which might indicate a decline in the circulating levels of coagulation inhibitors. By contrast, the PD group had higher levels of homocysteine and fibrinogen than the HD group. The increased levels of fibrinogen observed in PD patients compared to those in HD patients or nondialyzed patients. These results might be explained by the chronic peritoneal irritation that can occur during dialysis, as fibrinogen can act as an acute-phase protein.[13]

Table 4

Comparison of the prothrombotic factors before and after kidney transplantation between LDKT and DDKT group.

	LDKT (N = 232)			DDKT (N = 135)			
	n	Mean ± SD or n (%)	*P for within group (a)*	n	Mean ± SD or n (%)	*P for within group (a)*	*P for between group*
Hemoglobin, g/dL							<.05 (c)
Pre	232	10.1 ± 1.6	—	134	11.3 ± 1.8	—	<.05 (d)
7th POD	232	9.7 ± 1.3	<.05	135	9.1 ± 1.2	<.05	<.05 (d)
14th POD	232	9.7 ± 1.2	<.05	135	9.3 ± 1.2	<.05	<.05 (d)
28th POD	232	11.5 ± 1.3	<.05	135	11.2 ± 1.4	0.68	0.06 (d)
P for time within group (b)		<.05			<.05		
Platelet ($\times 10^9$/L)							<.05 (c)
Pre	232	185.0 ± 61.8	—	135	186.6 ± 54.0	—	0.80 (d)
7th POD	232	173.3 ± 56.4	<.05	135	141.4 ± 52.5	<.05	<.05 (d)
14th POD	232	185.9 ± 61.5	0.81	135	178.5 ± 59.9	0.09	0.26 (d)
28th POD	232	224.3 ± 71.0	<.05	135	197.8 ± 72.5	<.05	<.05 (d)
P for time within group		<.05			<.05		
PT (%)							<.05 (c)
Pre	232	90.8 ± 13.0	—	135	93.1 ± 13.4	—	0.11 (d)
7th POD	227	86.9 ± 13.1	<.05	135	80.8 ± 18.1	<.05	<.05 (d)
14th POD	215	98.3 ± 13.8	<.05	128	94.0 ± 12.8	0.41	<.05 (d)
28th POD	191	113.8 ± 14.7	<.05	121	105.0 ± 19.1	<.05	<.05 (d)
P for time within group		<.05			<.05		
APTT, s							<.05 (c)
Pre	232	27.4 ± 6.8	—	135	26.1 ± 3.9	—	<.05 (d)
7th POD	227	25.6 ± 4.6	<.05	135	26.2 ± 7.4	0.82	0.34 (d)
14th POD	215	23.5 ± 4.1	<.05	127	24.6 ± 6.2	<.05	0.06 (d)
28th POD	191	21.7 ± 3.7	<.05	121	23.8 ± 8.4	<.05	<.001 (d)
P for time within group		<.05			<.05		
D-dimer, mg/dL							<.05 (c)
Pre	230	1.4 ± 1.4	—	133	1.2 ± 1.2	—	0.19 (d)
7th POD	228	2.9 ± 2.1	<.05	135	2.2 ± 1.9	<.05	<.05 (d)
14th POD	227	2.0 ± 1.8	<.05	133	2.0 ± 2.0	<.05	0.92 (d)
28th POD	217	1.7 ± 1.6	<.05	126	1.6 ± 1.3	<.05	0.99 (d)
P for time within group		<.05			<.05		
Fibrinogen, mg/dL							<.05 (c)
Pre	171	323.2 ± 87.4	—	92	320.9 ± 93.1	—	0.90 (d)
7th POD	184	214.9 ± 72.5	<.05	109	216.0 ± 66.7	<.05	0.97 (d)
14th POD	185	230.1 ± 93.1	<.05	110	260.3 ± 87.8	<.05	<.05 (d)
28th POD	75	255.2 ± 84.2	<.05	55	276.1 ± 83.4	<.05	0.20 (d)
P for time within group		<.05			<.05		
PS activity (%)							0.25 (c)
Pre	230	89.3 ± 31.9	—	133	93.6 ± 32.2	—	0.20 (d)
7th POD	184	66.5 ± 21.9	<.05	107	65.6 ± 23.5	<.05	0.78 (d)
14th POD	185	77.0 ± 24.1	<.05	110	75.5 ± 29.4	<.05	0.63 (d)
28th POD	76	96.1 ± 41	0.071	51	90.3 ± 30.3	0.525	0.28 (d)
P for time within group		<.05			<.05		
PC activity (%)							0.11 (c)
Pre	230	99.9 ± 21.5	—	130	101.7 ± 24.7	—	0.46 (d)
7th POD	183	104.7 ± 23.8	<.05	107	98.4 ± 26.1	0.42	0.05 (d)
14th POD	185	121.0 ± 26.2	<.05	110	117.2 ± 25.7	<.05	0.27 (d)
28th POD	76	129.0 ± 24.4	<.05	51	125.6 ± 21.2	<.05	0.27 (d)
P for time within group		<.05			<.05		
ATIII activity (%)							0.26 (c)
Pre	230	88.2 ± 13.7	—	133	85.1 ± 13.9	—	<.05 (d)
7th POD	183	89.7 ± 14.1	0.27	109	85.3 ± 13.5	0.94	<.05 (d)
14th POD	186	103.5 ± 14.4	<.05	110	97.9 ± 14.9	<.05	<.05 (d)
28th POD	76	112.9 ± 8.5	<.05	55	105.7 ± 17.6	<.05	<.05 (d)
P for time within group		<.05			<.05		
Homocystein, μmol/L							0.05 (c)
Pre	230	21.9 ± 15.8	—	134	22.0 ± 12.1	–	0.973 (d)
7th POD	182	10.9 ± 7.5	<.05	108	15.0 ± 7.6	<.05	<.05 (d)
14t POD	183	11.2 ± 4.6	<.05	107	14.3 ± 9.3	<.05	<.05 (d)
28th POD	71	13.9 ± 5.3	<.05	52	15.3 ± 6.8	<.05	<.05 (d)
P for time within group		<.05			<.05		
LA* (%)							—

(*continued*)

Table 4

(continued).

	LDKT (N = 232)			DDKT (N = 135)			
	n	Mean ± SD or n (%)	*P* for within group (a)	n	Mean ± SD or n (%)	*P* for within group (a)	*P* for between group
Pre	231	12 (5.2)	—	133	14 (10.5)	—	0.06 (g)
7th POD	182	3 (1.7)	0.07	107	3 (2.8)	—	0.67 (f)
14th POD	183	1 (0.6)	<.05	106	0 (0)	—	—
28th POD	71	1 (1.4)	0.20	51	0 (0)	—	—
P for time within group		<.05			—		
aCL* (%)							0.110 (c)
Pre	225	30 (13.3)	—	127	18 (14.2)	—	<.05 (d)
7th POD	182	23 (12.6)	0.20	108	6 (5.6)	0.019	0.97 (d)
14th POD	182	18 (9.9)	0.10	106	5 (4.7)	0.004	0.53 (d)
28th POD	73	3 (4.1)	<.05	52	2 (3.9)	0.018	0.33 (d)
p for time within group		<.05			<.05		
Factor VIII† (%)							0.117 (c)
Pre	21	7 (33.3)	—	11	4 (36.4)	—	0.83 (d)
7th POD	21	10 (47.6)	0.492	11	4 (54.6)	0.019	0.08 (d)
14th POD	20	10 (50.0)	0.17	14	11 (78.6)	0.012	0.17 (d)
28th POD	1	0 (0)	<.05	2	1 (50.0)	0.042	0.70 (d)
P for time within group		0.08			<.05		
Factor IX† (%)							—
Pre	21	1 (4.8)	—	11	1 (9.1)	—	>.99 (f)
7th POD	21	2 (9.5)	—	11	1 (9.1)	>.99	>.99 (f)
14th POD	20	7 (35.0)	—	14	5 (35.7)	0.19	>.99 (f)
28th POD	1	0 (0)	–	2	1 (50.0)	0.19	—
P for time within group		—			0.39		

P value by mixed model for repeated measurement (MMRM) for continuous variables and generalized estimating equation (GEE) method for binary outcomes.

(a) *P* for comparison between pre-transplantation and each POD value within group.

(b) *P* for time within group.

(c) *P* for interaction between group and time.

(d) *P* for comparison between groups within each time point.

Values are presented as mean ± standard error for continuous variables, and percentages for categorical variables.

* Prevalence of cases of positive result.

† Prevalence of cases of increased result.

P values are calculated by longitudinal data analysis for the comparison of each operative stage and calculated by Kruskal–Wallis test for continuous variables and χ^2 or Fisher test for categorical variables in the comparison of each patient group.

aCL = anticardiolipin, APTT = activated partial thromboplastin time, ATIII = antithrombin III, DDKT = deceased donor kidney transplantation, HD = hemodialysis, LA = lupus anticoagulant, LDKT = living donor kidney transplantation, PC = protein C, PD = peritoneal dialysis, POD = postoperative day, PS = protein S, PT = prothrombin time.

The percentage of patients with ≥1 positive prothrombotic factor decreased from 82.0% pre-KT to 14.2% by POD28. In patients with ≥1 positive prothrombotic factor before transplantation, 9.0% developed bleeding complications and 3.3% had thrombotic complications post-transplantation. However, these rates were not significantly different from those in patients without these factors. However, we analyzed the number of positive prothrombotic factors at each clinical course. The number of prothrombotic decreased from 1.4 ± 0.9 pre KT to 0.2 ± 0.4 by POD28 which was significant. These results also support improvement in hemostatic status after KT.

Plasma homocysteine levels, which were above normal pre-KT, normalized by POD7 and remained within the normal range through POD28. These changes were expected because homocysteine levels are highly dependent on glomerular filtration rate. As increased plasma homocysteine levels are an independent risk factor for cardiovascular disease and thromboembolic events,[28] our results suggest that the risk of these events would decrease after KT.

Table 5

Patients with ≥1 positive prothrombotic factors before and after kidney transplantation in each patients group.

	Pre-transplantation	7th POD	14th POD	28th POD	*P**
Total (n = 367)	301 (82)	203 (55.3)	109 (29.7)	52 (14.2)	*<.05*
HD (n = 209)	163 (78)	114 (54.6)	63 (30.1)	24 (11.5)	*<.05*
PD (n = 90)	78 (86.7)	48 (53.3)	23 (25.6)	15 (16.7)	*<.05*
None (n = 68)	60 (88.2)	41 (60.3)	23 (33.8)	13 (19.1)	*<.05*
P†	.067	.646	.518	.215	

Values are presented as numbers (%).

* *P* values are calculated by longitudinal data analysis.

† *P* values are calculated by χ^2.

HD = hemodialysis, PD = peritoneal dialysis, POD = postoperative day.

Table 6

Number of positive prothrombophilic factors per each patient before and after kidney transplantation in each patients group.

	Pre-transplantation	7th POD	14th POD	28th POD	P*
Total (n=367)	1.4±0.9	0.9±1	0.4±0.6	0.2±0.4	<.05
HD (n=209)	1.4±1	0.8±0.9	0.4±0.6	0.1±0.4	<.05
PD (n=90)	1.4±0.8	1±1.1	0.3±0.6	0.2±0.5	<.05
None (n=68)	1.3±0.8	1±1.1	0.4±0.7	0.2±0.4	<.05
P†	.89	.58	.58	.21	

Values are presented as mean±standard deviation and median (IQR).

* *P* values are calculated by longitudinal data analysis.

† *P* values are calculated by kruskal wallis test.

HD=hemodialysis, PD=peritoneal dialysis, POD=postoperative day.

Over the first month postoperatively, the prevalence of APLAs decreased to rates found in the general population.[16,17] Conversely, D-dimer was elevated throughout this period. D-dimer, the smallest fibrinolysis-specific degradation product in the circulation,[29] is detected within 2 hours of intravascular thrombus formation and circulates with a half-life of approximately 6 hours.[30,31] After general surgery, D-dimer levels peak at approximately 1 week and then decrease 5% to 10% per day, remaining above normal for up to 1 month.[32] In the present study, D-dimer levels similarly peaked on POD7 and remained elevated on POD28, suggesting that they reflected nonspecific findings of any major operation.

ATG, along with basiliximab, is one of the most widely used induction immunosuppressant agents in KT. ATG, targets a broad range of T-cell surface antigens, including CD2, 3, 5, 8, 28, 45, the T-cell receptor, CD154 which are activate in primary antigenic signaling. And ATG also contains antibodies against natural killer cell marker and antibodies against CD20; a B-cell surface marker.[33,34] As a result, ATG interacts with large range of antigens on immune and nonimmune cell type, inducing apoptosis of B-cells, peripheral T-cells and NK cells, and plasma cells (CD138+).[33–36]

There are many comparative studies between ATG and basiliximab, and it is well known that ATG presents more hematologic side effect, such as anemia, lymphocytopenia, and thrombocytopenia. [33,37,38] de Nattes et al[38] reported that thrombocytopenia and hemolytic anemia occurring after ATG inductions probably might be heteroimmune origin via an interaction with a common Fc-receptor epitope in the different cell lines. In this study, 44 patients (12%) received ATG induction and others received basiliximab (323 patients, 88%) for induction therapy. Anemia was observed in both ATG group and basiliximab group at POD7 and 14; however, hemoglobin was significantly lower in ATG group ($P < 0.5$). Moreover, thrombocytopenia was observed at POD7 and recovered to normal range after POD14 in ATG group. In previously reported studies, anemia after KT occurred about 40% of patients, which was usually caused by or aggravated by blood losses during the surgery or hemodilution due massive fluid therapy in perioperative periods.[38,39] Anemia in both groups might be multifactorial, however, thrombocytopenia presented in ATG group, especially at POD7, might the side effect of ATG.

Comparative analyses were also performed between LDKT and DDKT groups. Hemoglobin and platelet count were lower in DDKT groups throughout the study period compared to LDKT groups after KT. Decrements in hemoglobin and platelet counts were steeper in DDKT group ($P < 0.05$). In DDKT groups, APTT was prolonged and fibrinogen was increased within normal limit range DDKT group ($P < 0.05$); D-dimer was slightly increased in LDKT after transplantation ($P < 0.05$). These results might be related to the special condition DDKT, i) emergent surgery, ii) longer total ischemic time is longer which results in longer surgery time, increased bleeding risk, and a more required massive fluid resuscitation, iii) relatively high rate of DGF and rejection, and iv) ATG induction for those with expanded criteria donor.

A main strength of this study was the exclusion of patients receiving pre- or postoperative antiplatelet agents or anticoagulants; thus, the study cohort was more hematologically "pure" than that of our previous study.[12] We also evaluated the number of prothrombotic factors per patient and demonstrated that this number decreased post-KT. The study has some drawbacks. We did not analyze various confounders that may affect hemostatic factors, such as type of immunosuppressive agent,[40] presence of cytomegalovirus infection,[41] donor factors, or ischemic time.[14] The follow-up duration was only 28 days, limiting our results to short-term outcomes.

However, this study focused on overall characteristics of hemostatic factors before and after KT and produced results that validated previous findings and hypotheses and provide a basis for future studies.

5. Conclusions

Before KT, most recipients exhibited prothrombotic tendencies, in terms of decreased hemoglobin, increased D-dimer and homocysteine, and increased prevalence of LA and aCL. By POD28, most of these abnormalities had improved or resolved. This improvement in thrombotic factors after KT may decrease the risk of cardiovascular disease, thromboembolic events, and mortality in recipients. These results are considered to be the major pathophysiologic effects on the hemostatic factors following KT. Based on this study, we suggest that improvement of renal function after KT might play an important role in recovery of hemostatic parameters in CKD patients, who simultaneously suffered from thrombosis and bleeding tendency. Finally, in order to identify the mechanism of hemostatic problems not only in CKD patients but also long-term effects of KT, further investigations, and longer follow up durations are warranted.

Author contributions

Conceptualization: Ji Il Kim, Jinbeom Cho.

Data curation: Jinbeom Cho, Kang Woong Jun, Mihyeong Kim, Jeong Kye Hwang

Formal analysis: Jinbeom Cho, Kang Woong Jun, Sun Cheol Park

Funding acquisition: Ji Il Kim
Investigation: Jinbeom Cho, Kang Woong Jun, Mihyeong Kim
Methodology: In Sung Moon, Kang Woong Jun
Project administration: Jinbeom Cho, Ji Il Kim
Resources: Kang Woong Jun, Ji Il Kim, Sun Cheol Park.
Software: Kang Woong Jun, Mihyeong Kim, Jeong Kye Hwang
Supervision: Kang Woong Jun, Mihyeong Kim, Jeong Kye Hwang
Validation: Jinbeom Cho, Kang Woong Jun, Mihyeong Kim
Visualization: Jinbeom Cho, Kang Woong Jun, Mihyeong Kim
Writing – original draft: Kang Woong Jun, Jinbeom Cho.
Writing – review & editing: Kang Woong Jun, Ji Il Kim, Jinbeom Cho.

References

[1] Pawlicki J, Cierpka L, Król R, Ziaja J. Analysis of coagulation parameters in the early period after kidney transplantation. Transplant Proc 2007;39:2754–5.
[2] Fellström B, Siegbahn A, Liljenberg G, et al. Primary haemostasis, plasmatic coagulation and fibrinolysis in renal transplantation. Thromb Res 1990;59:97–104.
[3] Lutz J, Menke J, Sollinger D, Schinzel H, Thurmel K. Haemostasis in chronic kidney disease. Nephrol Dial Transplant 2014;29:29–40.
[4] Clagett GP, Anderson FAJr, Levine MN, Salzman EW, Wheeler HB. Prevention of venous thromboembolism. Chest 1992;102:391S–407S.
[5] Deira J, Alberca I, Lerma JL, Martin B, Tabernero JM. Changes in coagulation and fibrinolysis in the postoperative period immediately after kidney transplantation in patients receiving OKT3 or cyclosporine A as induction therapy. Am J Kidney Dis 1998;32:575–81.
[6] Nampoory MR, Das KC, Johny KV, et al. Hypercoagulability, a serious problem in patients with ESRD on maintenance hemodialysis, and its correction after kidney transplantation. Am J Kidney Dis 2003;42: 797–805.
[7] Ghisdal L, Broeders N, Wissing KM, et al. Thrombophilic factors in Stage V chronic kidney disease patients are largely corrected by renal transplantation. Nephrol Dial Transplant 2011;26:2700–5.
[8] Jun KW, Park KM, Kim MH, et al. Mechanical thromboprophylaxis is sufficient to prevent the lower extremity deep vein thrombosis after kidney transplantation. Ann Surg Treat Res 2014;87:28–34.
[9] Hwang JK, Kim SI, Choi BS, et al. Short-term results of ABO-incompatible living donor kidney transplantation: comparison with ABO-compatible grafts. J Korean Surg Soc 2011;81:10–8.
[10] Jalal DI, Chonchol M, Targher G. Disorders of hemostasis associated with chronic kidney disease. Semin Thromb Hemost 2010;36:34–40.
[11] Kaw D, Malhotra D. Platelet dysfunction and end-stage renal disease. Semin Dial 2006;19:317–22.
[12] Cho J, Jun KW, Kim MH, Hwang JK, Moon IS, Kim JI. Coagulation profile in patients with chronic kidney disease before and after kidney transplantation: A retrospective cohort study. Clin Transplant 2017;31.
[13] van Guldener C. Why is homocysteine elevated in renal failure and what can be expected from homocysteine-lowering? Nephrol Dial Transplant 2006;21:1161–6.
[14] Parajuli S, Lockridge JB, Langewisch ED, Norman DJ, Kujovich JL. Hypercoagulability in kidney transplant recipients. Transplantation 2016;100:719–26.
[15] Pengo V, Ruffatti A, Legnani C, et al. Clinical course of high-risk patients diagnosed with antiphospholipid syndrome. J Thromb Haemost 2010;8: 237–42.
[16] Shi W, Krilis SA, Chong BH, Gordon S, Chesterman CN. Prevalence of lupus anticoagulant and anticardiolipin antibodies in a healthy population. Aust N Z J Med 1990;20:231–6.
[17] Egiziano G, Widdifield J, Rahman A, et al. Antiphospholipid antibody testing in a general population sample from the USA: An Administrative Database Study. Sci Rep 2020;10:3102.
[18] Seligsohn U, Lubetsky A. Genetic susceptibility to venous thrombosis. N Engl J Med 2001;344:1222–31.
[19] Rosendaal FR. Venous thrombosis: a multicausal disease. Lancet 1999;353:1167–73.
[20] Boccardo P, Remuzzi G, Galbusera M. Platelet dysfunction in renal failure. Semin Thromb Hemost 2004;30:579–89.
[21] Galbusera M, Remuzzi G, Boccardo P. Treatment of bleeding in dialysis patients. Semin Dial 2009;22:279–86.
[22] Irish A. Cardiovascular disease, fibrinogen and the acute phase response: associations with lipids and blood pressure in patients with chronic renal disease. Atherosclerosis 1998;137:133–9.
[23] Irish AB. Plasminogen activator inhibitor-1 activity in chronic renal disease and dialysis. Metabolism 1997;46:36–40.
[24] Irish AB, Green FR. Factor VII coagulant activity (VIIc) and hypercoagulability in chronic renal disease and dialysis: relationship with dyslipidaemia, inflammation, and factor VII genotype. Nephrol Dial Transplant 1998;13:679–84.
[25] Tomura S, Nakamura Y, Doi M, et al. Fibrinogen, coagulation factor VII, tissue plasminogen activator, plasminogen activator inhibitor-1, and lipid as cardiovascular risk factors in chronic hemodialysis and continuous ambulatory peritoneal dialysis patients. Am J Kidney Dis 1996;27:848–54.
[26] Vaziri ND, Gonzales EC, Wang J, Said S. Blood coagulation, fibrinolytic, and inhibitory proteins in end-stage renal disease: effect of hemodialysis. Am J Kidney Dis 1994;23:828–35.
[27] Lai KN, Yin JA, Yuen PM, Li PK. Effect of hemodialysis on protein C, protein S, and antithrombin III levels. Am J Kidney Dis 1991;17:38–42.
[28] Bostom AG, Carpenter MA, Kusek JW, et al. Homocysteine-lowering and cardiovascular disease outcomes in kidney transplant recipients: primary results from the Folic Acid for Vascular Outcome Reduction in Transplantation trial. Circulation 2011;123:1763–70.
[29] Olson JD. D-dimer: an overview of hemostasis and fibrinolysis, assays, and clinical applications. Adv Clin Chem 2015;69:1–46.
[30] Chandler WL, Velan T. Plasmin generation and D-dimer formation during cardiopulmonary bypass. Blood Coagul Fibrinolysis 2004;15:583–91.
[31] Mager JJ, Schutgens RE, Haas FJ, Westermann CJ, Biesma DH. The early course of D-dimer concentration following pulmonary artery embolisation. Thromb Haemost 2001;86:1578–9.
[32] Dindo D, Breitenstein S, Hahnloser D, et al. Kinetics of D-dimer after general surgery. Blood Coagul Fibrinolysis 2009;20:347–52.
[33] Hardinger KL. Rabbit antithymocyte globulin induction therapy in adult renal transplantation. Pharmacotherapy 2006;26:1771–83.
[34] Mohty M. Mechanisms of action of antithymocyte globulin: T-cell depletion and beyond. Leukemia 2007;21:1387–94.
[35] Pascual J, Zuckermann A, Djamali A, Hertig A, Naesens M. Rabbit antithymocyte globulin and donor-specific antibodies in kidney transplantation–A review. Transplant Rev (Orlando) 2016;30:85–91.
[36] Popow I, Leitner J, Grabmeier-Pfistershammer K, et al. A comprehensive and quantitative analysis of the major specificities in rabbit antithymocyte globulin preparations. Am J Transplant 2013;13:3103–13.
[37] Mourad G, Garrigue V, Squifflet JP, et al. Induction versus noninduction in renal transplant recipients with tacrolimus-based immunosuppression. Transplantation 2001;72:1050–5.
[38] de Nattes T, Lelandais L, Etienne I, Laurent C, Guerrot D, Bertrand D. Antithymocyte globulin-induced hemolytic anemia and thrombocytopenia after kidney transplantation. Immunotherapy 2018;10:737–42.
[39] Molnar MZ, Mucsi I, Macdougall IC, et al. Prevalence and management of anaemia in renal transplant recipients: data from ten European centres. Nephron Clin Pract 2011;117:c127–134.
[40] Naesens M, Kuypers DR, Sarwal M. Calcineurin inhibitor nephrotoxicity. Clin J Am Soc Nephrol 2009;4:481–508.
[41] Atzmony L, Halutz O, Avidor B, et al. Incidence of cytomegalovirus-associated thrombosis and its risk factors: a case-control study. Thromb Res 2010;126:e439–443.