Changes in hemostatic factors after kidney transplantation
A retrospective cohort study

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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

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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 (≤1 month); or anticoagulant or antiplatelet agents ≤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, 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.

2.2. 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) 20mg 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

| N=676 | N=560 | N=557 | N=384 | N=367 |
|-------|-------|-------|-------|-------|
| N=116: Plasmapheresis (pre- or post- transplantation) |
| N=3: Graft loss (within a month) |
| N=173: pre-operative anti-coagulation or anti-platelet treatment |
| N=17: post-operative anti-coagulation or anti-platelet treatment |

Figure 1. Flow sheet of patients’ selection.
highly sensitized patients or expanded criteria deceased donor). Maintenance immunosuppression consists of tacrolimus (Protopic, 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 <0.5 mL/day for 2 consecutive days.

2.5. Statistical analysis
Summary statistics are presented as frequency (percentage) for categorical variables, and median (interquartile range) for continuous variables. The normality assumption was tested 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).

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: hemoglobin, fibrinogen, D-dimer, and PS activity 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 mg/dL pre-KT to 9.5 ± 1.3 mg/dL and 9.6 ± 1.2 mg/dL on POD7 and 14, but rose to almost normal on POD28 (11.4 ± 1.3 mg/dL) (P<.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 2
Comparison of the prothrombotic factors before and after kidney transplantation in each patient group.

| Factor                  | 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     | <.05     | <.05     | <.05   |
| Platelet (×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 | 157.5 ± 66.7 | 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*                 | <.05     | <.05     | <.05     | <.05   |
| 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                  | 93.3 ± 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     | <.05     | <.05     | <.05   |
| PT (%)                  | Total               | 7.3 ± 1.4 | 2.7 ± 2.1 | 2 ± 1.9 | 1.7 ± 1.5 | .24   |
|                         | HD                  | 11.1 ± 0.8 | 2.7 ± 2.1 | 2 ± 1.2 | 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     | <.05     | <.05     | <.05   |
| Fibrinogen, mg/dL       | Total               | 322.4 ± 89.3 | 215.3 ± 70.3 | 241.3 ± 92.2 | 264.2 ± 84.2 | <.05   |
|                         | HD                  | 295.9 ± 80.6 | 207.4 ± 65.9 | 230.9 ± 86.3 | 262.6 ± 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     | <.05     | <.05     | <.05   |
| PS activity (%)         | Total               | 90.8 ± 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                | 90.4 ± 33.5 | 69.4 ± 22.1 | 76.8 ± 27.4 | 92.8 ± 21.1 | .76   |
|                         | *P*                 | <.05     | <.05     | <.05     | <.05   |
| 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     | <.05     | <.05     | <.05   |
| 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 | 99.6 ± 16.6 | 105.5 ± 20.7 | <.05   |
|                         | None                | 89.2 ± 13.1 | 87 ± 15.5 | 103 ± 13.2 | 113.8 ± 7.8 | <.05   |
|                         | *P*                 | <.05     | <.05     | <.05     | <.05   |
| Homocystein, µmol/L     | Total               | 21.5 ± 14.5 | 12.4 ± 7.8 | 12.6 ± 8.8 | 14.6 ± 8.6 | <.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     | <.05     | <.05     | <.05   |
| 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*                 | <.05     | <.05     | <.05     | <.05   |
| 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*                 | <.05     | <.05     | <.05     | <.05   |
| Factor VIII (%)         | Total               | 34.4 | 50 | 61.8 | 33.3 | .06   |
|                         | HD                  | 25 | 33.3 | 66.7 | 50 | .13   |
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 2 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 post-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 < .05). Platelet counts decreased from 186.3 ± 59.5 (×109/L) versus 180.3 ± 54.8 (×109/L) pre-KT (P < .05) to 166.4 ± 55.8 (×109/L) versus 126.3 ± 53.9 (×109/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 compared 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 (×109/L) versus 166.4 ± 55.8 (×109/L) POD7; 157.8 ± 53.2 (×109/L) versus 186.7 ± 61.2 (×109/L) POD14; 187.7 ± 80.0 (×109/L) versus 218.2 ± 70.9 (×109/L) POD28, respectively) (P < .05). d-dimer was increased in both basiliximab and ATG 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. As CKD advances, platelet dysfunction and hemorrhagic complications appear, with mucocutaneous bleeding, gastrointestinal bleeding, and, less frequently, hemotherax, hemoperitoneum, and intracranial or retroperitoneal bleeding. It is unclear why bleeding problems predominate in one patient, whereas thrombotic complications occur in others.

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.

Patients with CKD exhibit abnormalities of various proteins and amino acids, including homocysteine. Plasma homocysteine levels are inversely related to glomerular filtration rate, with hyperhomocysteinemia observed in up to 85% to 100% of people with ESRD. Elevated homocysteine levels are associated with increased risk of venous and arterial thrombosis. In our study, d-dimer and homocysteine were increased above
Comparison of the prothrombotic factors before and after kidney transplantation between basiliximab and ATG induction group.

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

(continued)
normal pre-transplant, suggesting a hypercoagulable state. Anti-phospholipid antibodies (APLAs), including aCL, anti-β2GPI-1 antibody, and LA, also promote thrombosis. LA is more strongly associated with increased thrombotic risk than aCL or anti-B2GPI-1 antibody, and a “triple positive” profile (all 3 APLAs) confers the highest risk. In one study, the prevalence of LA, IgG aCL, IgM aCL, and polyclonal aCL in a healthy population was 3.6%, 4.6%, 4.6%, and 5.5%, respectively. In a general population study, positive LA, aCL, and anti-B2GPI-1 antibody rates were 7%, 15%, and 11%, respectively, at initial testing and 5%, 9%, and 13% at 12-week retesting. Our pre-KT rates were 7.1% for LA and 11%, respectively, at initial testing and 5%, 9%, and 13% at 14th POD and 28th POD, 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. Inversely, HD appears to activate the coagulation cascade by reducing coagulation inhibitors, such as PC, PS, and AT III. 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.

Table 3

|            | 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) | <0.05 | 44 | 0 (0) | — | — |
| 14th POD   | 246 | 1 (0.4) | <0.05 | 43 | 0 (0) | — | — |
| 28th POD   | 86 | 1 (1.2) | 0.08 | 36 | 0 (0) | — | — |
| P for time within group | <0.05 | — | — |
| aCL (%)    | 308 | 37 (12.0) | — | 44 | 11 (25.0) | — | <0.05 (d) |
| 7th POD    | 246 | 25 (10.2) | 0.203 | 44 | 4 (9.1) | <0.05 | 0.97 (d) |
| 14th POD   | 245 | 21 (8.6) | <0.05 | 43 | 2 (4.7) | <0.05 | 0.53 (d) |
| 28th POD   | 89 | 3 (3.4) | <0.05 | 36 | 2 (5.6) | <0.05 | 0.33 (d) |
| P for time within group | <0.05 | — | — |
| Factor VIII (%) | 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) | <0.05 | 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 (%) | 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) | <0.05 | 8 | 2 (25.0) | 0.832 | 0.50 (d) |
| 28th POD   | 3 | 1 (33.3) | 0.273 | 0 | 0 (0) | — | — |
| P for time within group | <0.05 | 0.62 |
Table 4
Comparison of the prothrombotic factors before and after kidney transplantation between LDKT and DDKT group.

| Factor                        | LDKT (N = 232) |     |          | DDKT (N = 135) |     |          |
|-------------------------------|----------------|-----|----------|----------------|-----|----------|
| Hemoglobin, g/dL              |                |     |          |                |     |          |
| Pre                           | 232            | 10.1±1.6 | —        | 134            | 11.3±1.8 | —        |
| 7th POD                       | 232            | 9.7±1.3  | <.05     | 135            | 9.1±1.2  | <.05     |
| 14th POD                      | 232            | 9.7±1.2  | <.05     | 135            | 9.3±1.2  | <.05     |
| 28th POD                      | 232            | 11.5±1.3 | <.05     | 135            | 11.2±1.4 | 0.68     |
| P for time within group (a)   | <.05           | <.05 |          | <.05           | <.05 |          |
| Platelet (×10^9/L)            |                |     |          |                |     |          |
| Pre                           | 232            | 185.0±61.8 | —        | 135            | 186.6±54.0 | —        |
| 7th POD                       | 232            | 173.3±56.4 | <.05     | 135            | 141.4±62.5 | <.05     |
| 14th POD                      | 232            | 185.9±61.5 | 0.81     | 135            | 178.5±59.9 | 0.09     |
| 28th POD                      | 232            | 224.3±71.0 | <.05     | 135            | 197.8±72.5 | <.05     |
| P for time within group (a)   | <.05           | <.05 |          | <.05           | <.05 |          |
| APTT (s)                      |                |     |          |                |     |          |
| Pre                           | 232            | 27.4±6.8  | —        | 135            | 26.1±3.9  | —        |
| 7th POD                       | 227            | 25.6±4.6  | <.05     | 135            | 26.2±7.4  | 0.82     |
| 14th POD                      | 215            | 23.5±4.1  | <.05     | 127            | 24.6±6.2  | <.05     |
| 28th POD                      | 191            | 21.7±3.7  | <.05     | 121            | 23.8±8.4  | <.05     |
| P for time within group (a)   | <.05           | <.05 |          | <.05           | <.05 |          |
| D-dimer, mg/dL                |                |     |          |                |     |          |
| Pre                           | 230            | 1.4±1.4   | —        | 133            | 1.2±1.2   | —        |
| 7th POD                       | 228            | 2.9±2.1   | <.05     | 135            | 2.2±1.9   | <.05     |
| 14th POD                      | 227            | 2.0±1.8   | <.05     | 133            | 2.0±2.0   | <.05     |
| 28th POD                      | 217            | 1.7±1.6   | <.05     | 126            | 1.6±1.3   | <.05     |
| P for time within group (a)   | <.05           | <.05 |          | <.05           | <.05 |          |
| Fibrinogen, mg/dL             |                |     |          |                |     |          |
| Pre                           | 171            | 323.2±87.4 | —        | 92             | 320.9±93.1 | —        |
| 7th POD                       | 184            | 214.9±72.5 | <.05     | 109            | 216.0±66.7 | <.05     |
| 14th POD                      | 185            | 230.1±93.1 | <.05     | 110            | 260.3±87.8 | <.05     |
| 28th POD                      | 75             | 255.2±84.2 | <.05     | 55             | 276.1±83.4 | <.05     |
| P for time within group (a)   | <.05           | <.05 |          | <.05           | <.05 |          |
| PS activity (%)               |                |     |          |                |     |          |
| Pre                           | 230            | 89.3±31.9  | —        | 133            | 93.6±32.2  | —        |
| 7th POD                       | 184            | 66.5±21.9  | <.05     | 107            | 65.6±23.5  | <.05     |
| 14th POD                      | 185            | 77.0±24.1  | <.05     | 110            | 75.5±29.4  | <.05     |
| 28th POD                      | 76             | 96.1±41.0  | 0.071    | 51             | 90.3±30.3  | 0.525    |
| P for time within group (a)   | <.05           | <.05 |          | <.05           | <.05 |          |
| PC activity (%)               |                |     |          |                |     |          |
| Pre                           | 230            | 99.9±21.5  | —        | 130            | 101.7±24.7 | —        |
| 7th POD                       | 183            | 104.7±23.8 | <.05     | 107            | 98.4±26.1  | 0.42     |
| 14th POD                      | 185            | 121.0±26.2 | <.05     | 110            | 117.2±25.7 | <.05     |
| 28th POD                      | 76             | 129.0±24.4 | <.05     | 51             | 125.6±21.2 | <.05     |
| P for time within group (a)   | <.05           | <.05 |          | <.05           | <.05 |          |
| ATIII activity (%)            |                |     |          |                |     |          |
| Pre                           | 230            | 88.2±13.7  | —        | 133            | 85.1±13.9  | —        |
| 7th POD                       | 183            | 89.7±14.1  | 0.27     | 109            | 85.3±13.5  | 0.94     |
| 14th POD                      | 186            | 103.5±14.4 | <.05     | 110            | 97.9±14.9  | <.05     |
| 28th POD                      | 76             | 112.9±8.5  | <.05     | 55             | 106.7±17.6 | <.05     |
| P for time within group (a)   | <.05           | <.05 |          | <.05           | <.05 |          |
| Homocystein, μmol/L           |                |     |          |                |     |          |
| Pre                           | 230            | 21.9±15.8  | —        | 134            | 22.0±12.1  | —        |
| 7th POD                       | 182            | 10.9±7.5   | <.05     | 108            | 15.0±7.6   | <.05     |
| 14th POD                      | 183            | 11.2±4.6   | <.05     | 107            | 14.3±9.3   | <.05     |
| 28th POD                      | 71             | 13.9±5.3   | <.05     | 52             | 15.3±6.8   | <.05     |
| P for time within group (a)   | <.05           | <.05 |          | <.05           | <.05 |          |

LA^% (continued)
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, our results suggest that the risk of these events would decrease after KT.

### Table 4
(continued)

| LDKT (N = 232) | DDKT (N = 135) |
|----------------|----------------|
|                | P for within group (a) | P for between group |
|                | n | Mean ± SD or n (%) |                  | n | Mean ± SD or n (%) |                  |
| Pre            | 231 | 12 (5.2) | —                  | 133 | 14 (10.5) | —                  |
| 7th POD        | 182 | 3 (1.7)  | 0.07               | 107 | 3 (2.8)  | —                  |
| 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 (%)       | 225 | 30 (13.3) | —                  | 127 | 18 (14.2) | —                  |
| Factor VIII (%)| 21  | 7 (33.3) | —                  | 11  | 4 (36.4) | —                  |
| Factor IX (%)  | 21  | 1 (4.8)  | —                  | 11  | 1 (8.1)  | —                  |
| P for time within group | — | — | <.05 |

*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.

‡Values are calculated by longitudinal data analysis for the comparison of each operative stage and calculated by Kruskal–Wallis test for continuous variables and Χ² or Fisher test for categorical variables in the comparison of each patient group.

### 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 (86.2)           | 41 (60.3) | 23 (33.8) | 13 (19.1) | <.05 |
| *P*              | .087                | .646     | .518      | .215      |

Values are presented as numbers (%).

*P* values are calculated by longitudinal data analysis.

†*P* values are calculated by Χ².

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. Conversely, D-dimer was elevated throughout this period. D-dimer, the smallest fibrinolysis-specific degradation product in the circulation, is detected within 2 hours of intravascular thrombosis formation and circulates with a half-life of approximately 6 hours. 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. 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. 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+).

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. de Nattes et al reported that thrombocytopenia and hemolytic anemia occurring after ATG inductions probably might be heteroimmune origin via an antigenic signaling. And ATG also contains antibodies against the T-cell receptor, CD154 which are activate in primary immunosuppressive agent, presence of cytomegalovirus infection, donor factors, or ischemic time. 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.

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