Impact of kidney donor hemostasis on risk of complications after transplantation – preliminary outcomes

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Background: This study analyzes the influence the of kidney donor hemostasis on the risk of complications in the kidney recipient after transplantation.

Material/Methods: We enrolled 38 deceased kidney donors, of whom 14 donors died from a physical injury and the others died from ischemic or bleeding central nervous system stroke. The donors were categorized into 2 subgroups. If the recipient's postoperative period proceeded smoothly, the kidney donor was assigned to the uncomplicated donors (UD) group. If the recipient's postoperative period was complicated, the donor was assigned to the complicated (CD) Group. The CD group of consisted of 9 donors who died from strokes or bleedings and 2 who died from physical injury. We examined the antithrombin (AT) protein C (PC), complexes of thrombin/antithrombin (TAT), fragments F_{1+2} of prothrombin (F_{1+2}), plasminogen (Pl), complexes of plasmin/antiplasmin (PAP), and D-dimers (D-d).

Results: In the CD group had decreased activity of AT, PC, and Pl and increased activity of F_{1+2}, TAT, and D-d. The UD group had a higher level of PAP. The CD group had evidence of intensive blood coagulation, but the UD group had evidence of fibrinolysis. Fisher's exact test revealed an increased risk in recipients who received a kidney from the CD group.

Conclusions: The hemostasis of the kidney donors had a correlation with the occurrence of some complications in the kidney recipients, especially complications connected with activation of blood coagulation. It seems that the activation of fibrinolysis could be positive prognostic factor, but this requires further investigations.

Key words: kidney transplantation • hemostasis • donors • death

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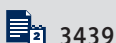
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Background

Despite recently discovered potent immunosuppressive agents, long-term allograft survival has not significantly changed in the last 2 decades [1]. Although various immunological factors seem to be very important, there are many different non-immunological factors that also affect the outcomes of transplantation. It is believed that one of factors could be a hemostatic process. Increased activity of blood coagulation may lead to thrombosis of blood vessels, including the blood vessels of the kidney, and could be a cause of postoperative complications in recipients. Some authors even regard the disturbances of hemostasis as the main cause of co-morbidity and co-mortality among kidney recipients [2–9]. But recognizing all aspects of blood coagulation, not only in recipients, appears to be crucial for improving the results of transplantation. The role of recipient hemostatic process in improving outcomes of kidney transplantation is no longer in question, but the role of hemostasis of the kidney donors still remains unclear. In a cadaveric transplantation, the donors and their graft have already been subjected to various circulatory and metabolic perturbations during intensive care; many of these perturbations have an influence on hemostasis, particularly towards an increased activity of blood coagulation, and can lead to endothelial injury of blood vessels of the kidney. This may be very important in prolongation of the prothrombotic reactions of the endothelium of the kidney's blood vessels in recipients after an operation. The cold preservation of the kidney and warm ischemia have negative effects on kidney endothelium, which may further contribute to its thrombogenicity and promote activation of blood coagulation. It now becomes clearer that the coagulation cascades both donors and recipients could be intimately connected with some early complications after transplantation, including delayed graft function. The micro-thrombi in the blood vessels may be the cause of low tissue organ perfusion, which ultimately leads to kidney failure [2–6]. Long cold ischemic time is an independent risk factor for renal graft thrombosis, but other factors remain still undiscovered [9,10]. The recent reports of kidney transplantation outcomes indicate interactions between hemostasis of kidney donors and the risk of complications after transplantation. Many cadaver kidney donors die because of disturbances of hemostasis. It seems reasonable to suspect an implication for the risk of complications after kidney transplantation [2–5].

To our knowledge, no data are available on the influence of the nature of hemostasis of kidney donors on outcomes of kidney transplantation. This is the first attempt to explore the interactions between hemostasis of the cadaver kidney donors and the occurrence of some complications after kidney transplantation. This could also determine whether thrombosis of the kidney donors influences the function of their kidney after transplantation [2].

The aim of this study was to analyze the influence of the hemostasis of the kidney donors on the occurrence of some complications after transplantation.

Material and Methods

The group of kidney donors (KD) was composed of 38 consecutive deceased donors (11 women and 27 men) with an average age of 37±12 years. The follow-up included 1 year of observations. The cadaver kidney donors group included 14 donors (41%) who died from a physical injury (mainly motor vehicle injuries) and 24 donors (59%) whose death resulted from ischemic or bleeding strokes to the central nervous system (CNS). The donors were divided in 2 subgroups according to the recipients. If in the postoperative period some complications were encountered in the recipients, the donor of such kidney was assigned to the first sub-group – named as complicated donors (CD). The other donors were in the second sub-group, named uncomplicated donors (UD). The first subgroup (CD) included 11 donors (29% of all), with an average age of 43±12 years (2 died in road accidents and 9 of strokes and bleedings to CNS). The second subgroup (UD) comprised of 27 other donors (71% of all), with an average age of 35±11 years. The group of kidney recipients consisted of 61 patients with end-stage renal disease (27 women and 34 men), with an average age of 27±14 years. All cadaver kidney donors were managed routinely during intensive care with intravenous infusion of protective antibiotics, various types of vasoactive circulatory agents, or intravenous fluids to maintain their arterial pressure and outflow of urine in normal range.

Table 1 shows the causes of kidney failure of the recipients. Inflammatory diseases were the most frequent cause of renal failure, accounting for almost a half of all causes (45%). The second cause was diabetes (35% of all). Malformation of the urinary tract and ADPKD syndrome were 7% and 13%, respectively. The preliminary outcomes were set up after 2 years of observation.

We also measured some hemostatic parameters in 25 healthy volunteers (mean age 36±16 years, range 19–64 years) to obtain normal ranges. This group was described as the reference group. They denied taking any medical agents that could interfere with the hemostatic process at least 2 weeks before the study.

The blood samples of cadaver kidney donors were drawn from the renal vein during the organ retrieval procedure, just before an infusion of heparin and other preserving fluids. These samples were obtained by a direct intraluminal needle aspiration to disposable pyrogen-free plastic syringes and immediately collected into pyrogen-free plastic tubes with 3.8%

Table 1. The causes of renal failure and the type of postoperative complications in recipients.

The cause of renal failure	Number of recipients and percentage of recipients (n/%)	Type of complications (number and percentage of all recipients)					
		Thrombosis	Rupture of kidney	Necrosis of ureter	Lymphocele	Perineal haematoma	D G F
Diabetes	21/35%	1		1	1	1	1
Glomerulitis	27/45%	2			2	1	1
Pyelonephritis				1	1	2	2
Malformation of urinary tract	4/7%	1		1	2	2	1
ADPDK syndrom	8/13%	1	1			2	1
Total	61/100%	5/8%	1/2%	3/5%	6/10%	8/13%	6/10%

sodium citrate in a 9:1 volume ratio. Platelet-poor plasma was prepared by centrifugation at 1900 G for 10 min at room temperature. The sample tubes were aliquoted and stored at –70°C before being assayed.

All coagulation parameters were worked-up using commercial kits. The parameters describing an activity of blood coagulation cascade included: antithrombin (AT), Protein C (PC), complexes of thrombin/antithrombin (TAT) and fragments F_{1+2} of prothrombin (F_{1+2}). The activity of antithrombin was measured using chromogenic substrates (Chromogenic Bioksel, Poland). The reference value for antithrombin was 80–120%. The activity of Protein C was examined using chromogenic substrates (Asserachrom Protein C, Roche Diagnostics, Poland). The reference range for Protein C is 70–140%. The blood plasma concentration of complexes of thrombin/antithrombin (TAT) was measured using enzyme immunoassay (IMUBIND TAT-ELISA American Diagnostica GmbH, Germany). The reference range for thrombin/antithrombin is 1–4.1 μg/l. The blood plasma level of fragments F_{1+2} of prothrombin (F_{1+2}) was measured using enzyme immunoassay (Enzygnost F_{1+2} micro Dade Behring, Germany). According to the manufacturer's reference, the range for F_{1+2} is 0.4–1.1 nmol/l. The following fibrinolytic parameters were examined: plasminogen (Pl), complexes of plasmin/antiplasmin (PAP) and D-dimers (D-d). The activity of plasminogen was measured using chromogenic substrates (Chromogenic Bioksel, Poland). The reference value for plasminogen is 70–140%. The blood plasma concentration of complexes of plasmin/antiplasmin (PAP) was measured using enzyme immunoassay (PAP Complexes, Roche Diagnostics, Poland). The reference range for complexes of plasmin/antiplasmin is 50–800 ng/ml. The blood plasma concentration of D-dimers (D-d) was measured using chromogenic substrates (Asserachrom D-dimer, Roche Diagnostics, Poland). The reference range for D-dimers is 0–450 ng/ml. According to the manufacturers' suggestions, each laboratory should determine its own reference range,

so we performed our own reference range for each assay, both in controls and in cadaver kidney donors (CKD). Delayed graft function (DGF) was defined as described by Halloran et al: plasma creatinine concentration higher than 500 mmol/l throughout the first post-transplantation week, or the need of more than 1 dialysis session in the first week, or oliguria of less than 1L/24 h for more than 2 days. In our observations, the need for dialysis during the first postoperative week was considered as DGF [11].

All data were analyzed using Statistica 6.0 computer software (Statistica 6.0 StatSoft, Poland). Normality of continuous variables was assessed by normal probability plots. Variables following normal distribution are presented as the mean ± standard error of the mean (SEM); the non-normally distributed data are presented as median. The comparisons between the 2 examined groups were made using the appropriate tests. The Mann-Whitney U test was used for non-normally distributed data, but for normal distribution of variables we used the t test. The value of $p < 0.05$ was considered as statistically significant. The statistical differences of occurrence of complications between donors were evaluated using Fisher's exact test. The local ethics committee approved the study protocol.

Results

Table 1 shows the outcomes of kidney transplantation after 2 years of follow-up. In 29 kidney recipients (47% of all), the following postoperative complications were observed: 6 patients with thrombosis of renal vessels (10% of all) including 1 patient with kidney rupture (2% of all), 3 patients with urinary fistula caused by necrosis of the distal ureter (5% of all), 6 patients with perirenal lymph collection – so-called lymphocele (10% of all), and 8 patients with perirenal hematoma (13% of all). Delayed graft function (DGF) was observed in 16 patients

Table 2. The category of cadaver kidney donors according to the nature of death and the complications after transplantation.

| Follow-up | The nature of a death of cadaver kidney donors | | | Statistical significance |
| | Physical injury | Stroke to Central Nervous System (CNS) | Total | |
	n (%)	n (%)	n (%)	p
Complicated donors	2 (5%)	9 (24%)	11 (29%)	
Uncomplicated donors	12 (32%)	15 (39%)	27 (71%)	p<0.046
Total	614 (37%)	24 (63%)	38 (100%)	

n – number; % – percentage; statistical significance according to Fisher exact test (p).

(26% of all). DGF was accompanying all the above-mentioned complications, but additionally in 6 recipients was encountered as the lone complication (10% of all). During 24 months of follow-up, no recipients died. The urgent operations on blood vessels of the kidney had to be performed in 7 recipients (11% of all), in 4 patients with renal vein thrombosis, and in three patients because of necrosis of the distal ureter. In 1 patient with kidney rupture the operation was undertaken because of a life-threatening hemorrhage. Unfortunately, the operation failed and the kidney had to be removed. Similarly, in 3 patients with renal vein thrombosis, an attempt at restoration of blood outflow failed and the kidneys had to be removed (5% of all). Two remaining recipients with thrombosis of small branches of the renal vessels were qualified for an antithrombotic therapy, with good results for inflow and outflow of the blood of the kidney. It was confirmed by color Doppler ultrasound examination. In 3 patients the operation was done because of ureter necrosis followed by urinary fistula (5% of all). The results were excellent and the function of the graft was restored completely. Other complications were treated, with good results for preserving and restoring the function of the kidney. Table 1 shows the causes of renal failure and the complications after an operation. None of listed diseases was correlated with increased incidence of complications after surgery. Reviewing the list of complications, we found that more often complications were encountered in recipients when their kidney was retrieved from a donor who died from an ischemic or bleeding stroke to the CNS. In consideration of the above, we decided to establish the causes of these complications. It is well known that in immunosuppressive treatment of the recipients, the nature of their renal failure may increase the risk of some complications after transplantation, but the role of the kidney donors on the risk of postoperative complications still requires further investigation. If we manage to find other pathomechanisms of an increased risk of some complications, we will be able to prevent them and improve the outcomes of kidney transplantation. The importance of a hemostatic process in the pathomechanism of many complications is indisputable. In our study many complications had a strong relation with hemostasis, but it is still an open question which haemostatic process – the recipients or

maybe also the donors. The impetus for our study was the observation of an increased rate of complications in recipients who received a kidney from a donor who died as a result of stroke or bleeding into the CNS. There are many factors that interfere with the hemostatic balance of the kidney donors; recognition of them could be crucial for the improvement of outcomes. It is intriguing to ask whether the hemostasis of kidney donors has a potent impact on increased risk of complications in recipients after transplantation. And the next question is whether the nature of a death has an impact on the hemostatic process of the kidney donors. The cadaver kidney donors can be divided into many categories, such as young and old donors or optimal and marginal donors. Among of the cadaver kidney donors, are the donors who died as a result of physical injury like the road accidents and the ones who died from complications of stroke to the CNS. Therefore, we also divided our donors according to the nature of their deaths. Table 2 presents the categorized group of cadaver kidney donors. The group of complicated donors consisted of 11 deceased donors (29% of all donors), including 2 donors (5%) who died because of physical injury and 9 donors (24%) who died from stroke to the CNS. The group of uncomplicated donors consisted of deceased donors (71% of all donors), including 12 donors who died because of physical injury (32%) and 15 donors (39%) who died from stroke to the CNS. According to Fisher's exact test, we calculated that the risk of complications is significantly higher in recipients who received kidneys from donors whose death was the result of stroke to the CNS ($p < 0.046$). To explore this phenomenon, we decided to evaluate the hemostasis of kidney donors, focusing on the nature of their death. Table 3 presents the examined parameters in the group of complicated donors (CD), uncomplicated donors (UD), and the controls. It is interesting that in the group of complicated donors (CD) the activity of antithrombin was significantly lower than in the uncomplicated donors (UD). The activity of plasminogen in blood plasma of both groups of donors did not differ significantly. The activity of Protein C in both groups of donors was statistically lower than in the controls ($p < 0.002$ and $p < 0.05$, respectively) but the lowest activity was noticed in the group of complicated donors ($p < 0.05$ in comparison with UD). Table 4 shows

Table 3. The coagulative parameters in both subgroups of cadaver kidney donors with normalized distribution: complicated (CD) and uncomplicated donors (UD).

Coagulative parameter	Complicated cadaver kidney donors (CD)		Uncomplicated cadaver kidney donors (UD)		Control group	Statistical significance (between donors)
	X±SD		X±SD		X±SD	
	n=11		n=27		n=25	
Antithrombin [%]	80±31	$p_1 < 0.05$	114±41	$p_1 < 0.06$	99±134	$p < 0.05$
Plasminogen [%]	78±18	$p_1 < 0.0005$	84±19	$p_1 < 0.0005$	122±17	$p < 0.98$
Protein C [%]	58±23	$p_1 < 0.002$	73±33	$p_1 < 0.05$	106±16	$p < 0.05$

X – mean; SD – standard deviation. Statistical significance according to t-Student's test (p) (p – between subgroups of donors; p_1 – to the control).

Table 4. The coagulative parameters in both subgroups of cadaver kidney donors without normal distribution: complicated (CD) and uncomplicated donors (UD).

Examined parameter	Complicated donors (CD)				Uncomplicated donors (UD)				Control group	Statistical significance
	n=11				n=27				n=25	
	Me		I Q	III Q	Me		I Q	III Q	X ± SD	
TAT [µg/l]	27	$p_1 < 0.001$	17.1	37	11	$p_1 < 0.001$	14.1	37	2.7±0.9	$p < 0.016$
F_{1+2} [nmol/l]	1357	$p_1 < 0.01$	916	1662	930	$p_1 < 0.01$	606	1233	515±268	$p < 0.046$
D-d [ng/ml]	1286	$p_1 < 0.001$	1012	1359	1010	$p_1 < 0.001$	1095	1283	102±44	$p < 0.05$
PAP [ng/ml]	1702	$p_1 < 0.001$	1185	2513	1927	$p_1 < 0.001$	1382	2316	258±177	$p < 0.046$

X – mean; Me – median; SD – standard deviation; I Q – I Quartile; III Q – III Quartile. Statistical significance according to Mann-Whitney test (p) (p – between donors; p_1 – to the control).

results of further analysis of the selected parameters of hemostasis in the examined groups. In blood plasma of both groups of donors, the concentrations of all examined parameters (including complexes of thrombin/antithrombin, fragments F_{1+2} of prothrombin, D-dimers, and complexes of plasmin/antiplasmin) were considerably higher than in the controls (p<0.001, p<0.01, p<0.001, and p<0.001, respectively). The comparative analysis among groups of donors revealed much more intensive activation of blood coagulation in the group of complicated donors. This was supported by a higher concentration of complexes of thrombin/antithrombin (TAT), fragments F_{1+2} of prothrombin, and D-dimers (p<0.016, p<0.046, and p<0.005, respectively). However, the concentration of complexes of plasmin/antiplasmin (PAP) was higher in the UD group. We would like to emphasize that during follow-up, no kidney recipients died.

Discussion

The analysis of hemostatic parameters revealed symptoms for an activation of blood coagulation and fibrinolysis in both groups of donors. The activation of blood coagulation was confirmed by a statistically significant higher concentration of the complexes thrombin/antithrombin (TAT) and fragments F_{1+2} of prothrombin and D-dimers. Additionally, strong proof is provided by the lower activity of antithrombin and Protein C. The increased concentrations of D-dimers and complexes of plasmin / antiplasmin (PAP) with the lower activity of plasminogen are evidence of activation of the fibrinolysis process. Comparative analysis of hemostatic parameters revealed signs of intense activation of blood coagulation in the group of complicated donors, while in the group of uncomplicated donors we observed symptoms for a slightly more intensive activation of fibrinolysis.

In summary, disturbances of blood coagulation increase the risk of complications post-transplantation and fibrinolysis has protective properties. The type of disturbances of hemostasis of kidney donors has been associated to the cause of their death. Deeper abnormalities of the blood coagulation process were connected with strokes or bleedings to the CNS. This seems reasonable because their death was often associated with

atherosclerosis or diabetes, in which abnormalities of the hemostatic process often accompany these diseases. Interestingly, there was a slightly higher activity of fibrinolysis in the group of uncomplicated donors, which is difficult to explain. This group included both types of donors: those who died from strokes and those who died from physical injury. Interestingly, there was a slightly higher activity of fibrinolysis in the group of uncomplicated donors, which is difficult to explain clearly. This group included donors who died from strokes and donors who died from physical injury. This may be partially explained by reports that a dominant component of the blood plasma of young people is fibrinolysis [12]. Indeed, in our study many uncomplicated donors were younger than the complicated donors. Another explanation may be found in the reports of other authors who observed an intense fibrinolysis in the case of sudden death syndrome [13,14]. Among our uncomplicated donors, almost half died from physical head injury.

This study was conducted to clarify the role of hemostasis of the kidney donors on the risk of early complications after renal transplantation. To our knowledge, this preliminary report is the first attempt to investigate the correlations between hemostasis of kidney donors and the risk of complications after transplantation. Our study especially focused on the exploration of thrombin and plasmin, and we showed that activation of thrombin had a negative aspect and increased the risk of post-transplantation complications. The opposite effect was accompanied by generation of plasmin, which had protective properties and reduced the risk.

Perturbations of the hemostatic process may participate in development of some complications after renal transplantation. Some of them have strong relations with blood coagulation and fibrinolysis, but the nature of many others, such as like delayed graft function, still remains unclear. Some scientific studies have shown that various disorders of blood-clotting are involved in the pathogenesis of some diseases of the donors. The thrombi that were involved in the pathogenesis of strokes to the CNS were the result of atherosclerosis, which involves all blood vessels of the donors, including the kidney donors. Arteriosclerosis of the blood vessels of the kidney has a negative effect on the function of the transplanted kidney, which could have a negative impact on the final results of transplantation [11,15]. In patients with stroke to the CNS, Cesarman-Maus et al noticed clinical symptoms of thrombosis with laboratory evidence for activation of blood coagulation. This is consistent with our observations. The authors also found that ischemic strokes were due to thrombotic complications [16]. Nina et al., in patients with subarachnoid bleedings, revealed an increased level of thrombin/antithrombin complexes and D-dimers. This is also consistent with our results [17]. The others also found laboratory symptoms for activation of blood coagulation in patients with clinical symptoms of ischemic strokes to the CNS. Similar to our observations, they also showed an increased concentration of complexes of plasmin/antiplasmin [16]. The deposition of fibrin in the microvasculature of traumatic patients is well documented [18,19]. However, not all traumatic patients presented an intense deposition of fibrin in their vasculature symptoms, especially in the patients with an increased activation of fibrinolysis [20–22]. Fluctuations of both processes blood coagulation and fibrinolysis are typical for disseminated intravascular coagulation (DIC) and can also be observed in patients with trauma [20–22]. If the balance is tilted in the direction of thrombosis, then we observe an intense deposition of fibrin in the blood vessels. Conversely, in the case of intense activation of fibrinolysis, this balance tilts to lysis of thrombi. Fortunately, it has a beneficial effect on the blood vessels of the kidney. Fibrinolysis clears deposits of fibrin from the blood vessels and minimizes the disturbances of inflow and outflow of blood to the kidney after transplantation. Basically, the reactions between fibrinolysis and blood coagulation have a negative effect on the endothelium. In unfavorable conditions like hypoxia or a cold preserve, these hemostatic reactions can move the cells of the endothelium towards a prothrombotic state that is clearly unfavorable for the kidney to be transplanted. The endothelium of the blood vessels seems to be the key for understanding the pathogenesis of some complications after kidney transplantation. The early function of the transplanted kidney could be an indicator of the balance between blood clotting and fibrinolysis.

Our results on the impact of the donors' hemostasis on the early complications after kidney transplantation indicate that its disturbances could be a prognostic factor and be considered to be a prognostic factor in kidney transplantation. Another prognostic factor in kidney transplantation could be the nature of the kidney donors' death, which is indirectly connected with blood clotting. Better understanding of these phenomena can contribute to improving the final outcomes of renal transplantation. There are still many unrecognized factors, and the possible connections between hemostasis and the risk of complications after kidney transplantation should be a challenge to further scientific research.

Conclusions

There is a higher risk of postoperative complications after transplantation in recipients who received a kidney from older donors, especially whose deaths were caused by cerebral ischemia or bleedings into the CNS. This is due to the kidney donors' increased activity of blood coagulation. Activation of fibrinolysis has some positive aspect for the outcomes of kidney transplantation. We realize that the number of enrolled recipients and donors is not sufficient for drawing definitive conclusions; this should encourage other research centers to resolve this problem.

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