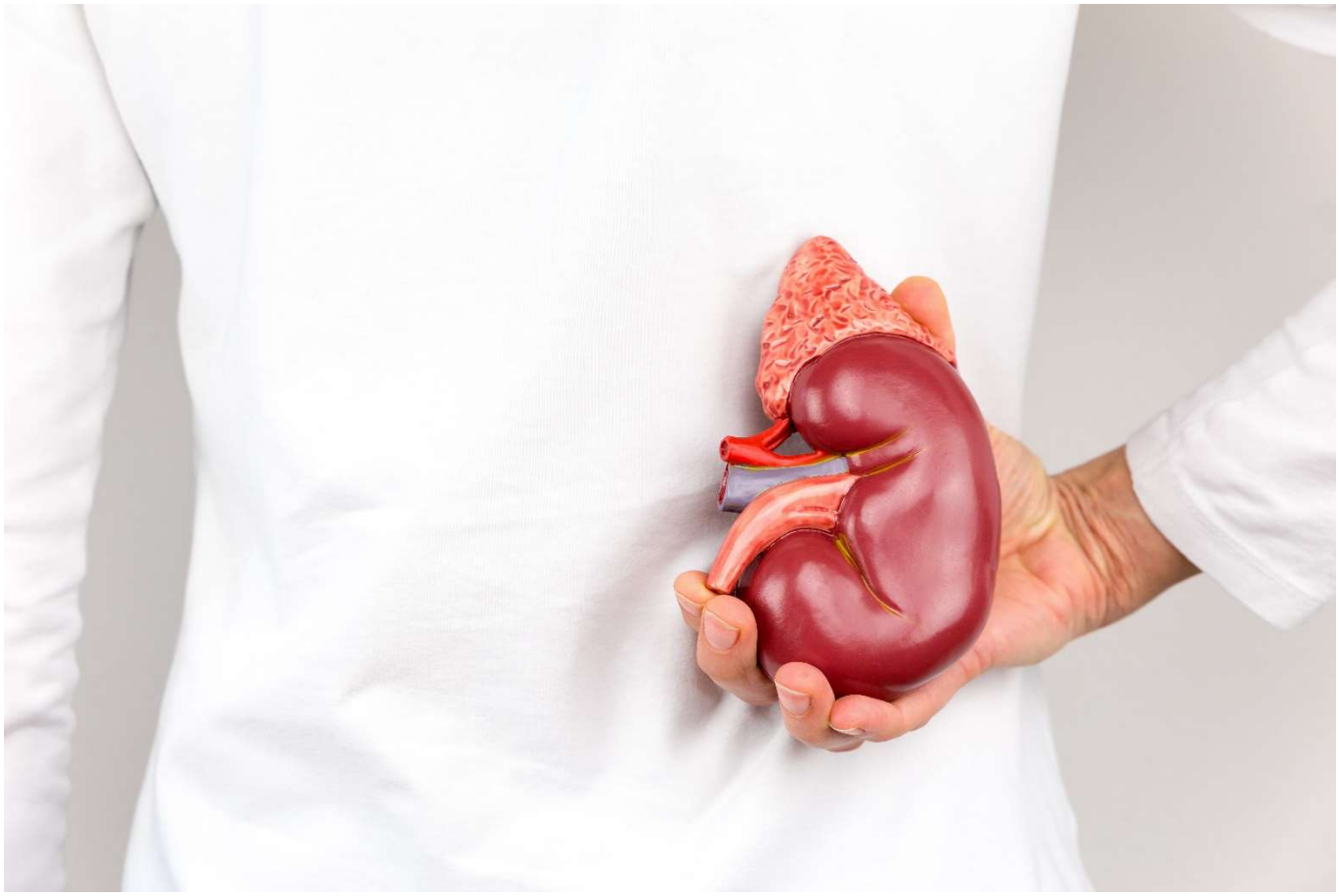

PREDICTIVE FACTORS OF IMMEDIATE GRAFT FUNCTION FOR LIVING-DONOR KIDNEY TRANSPLANT

Magdalena Kwapisz, Rafal Kieszek, Kalina Jedrzejko, Monika Bieniasz, Andrzej Chmura, Artur Kwiatkowski

Department of General and Transplantation Surgery, Orlowski Transplantation Institute, Medical University of Warsaw, Warsaw, Poland

#Corresponding author: Rafal Kieszek, email: rafal.kieszek@gmail.com, Department of General and Transplantation Surgery, Orlowski Transplantation Institute, Medical University of Warsaw, Infant Jesus Teaching Hospital, ul. Nowogrodzka 59, 02-006 Warsaw, phone number +48 22 5021470

RUNNING TITLE	Predictors of immediate graft function
KEYWORDS	immediate graft function; predictive factors; predictors of IGF; kidney transplant; living kidney donor
WORD COUNT	2200
CONFLICT OF INTERESTS	no conflicts of interest

ABSTRACT

Favorable outcome of kidney transplantation is particularly expected in the case of living donation. Satisfactory result can be referred as immediate graft function, defined by fast postoperative recovery of renal function with satisfactory diuresis and no further need for dialysis. Prospective analysis of 40 living-donor renal transplants was performed to assess whether there are any predictive factor of immediate graft function. Patients were compared in two groups in accordance with their initial graft function (immediate vs. slow or delayed). Clinical data relevant to the recipients, their donors and harvested organs (kidney weight and dimension) were assessed. No statistically significant differences were found between the groups. Further long-sampled studies are required to investigate the predictors of successful outcome of living-donor kidney transplantation.

BACKGROUND

Nephroureterectomy for living kidney donation is an unique procedure, seeing that highly invasive surgical intervention is performed on a totally healthy person who does not receive any direct benefits to itself. It should be noted that an altruistic sense of accomplishment is the only reward for a donor, while the risk of postoperative ailments and complications, although determined as being marginal, exists. That is the reason, inter alia, that the successful outcome of living donor transplantation is generally expected. Three groups of kidney transplant recipients can be specified in accordance with the initial graft function. Those requiring dialysis therapy within the first week after transplant form the delayed graft function (DGF) group. The others, who are nondialyzed and show a fast recovery of renal function with satisfactory diuresis, can be determined as immediate graft function (IGF) group. An intermediate ones, defined as a slow graft function (SGF) group, do not have IGF, but their graft dysfunction is not sufficient to be classified as DGF. Risk factors of SGF and DGF for deceased-donor (DD) grafts are well known. The purpose of our study was to investigate the predictive factors for IGF after living-donor (LD) kidney transplantation, which have not been well defined yet in the literature.

MATERIAL AND METHODS

The assessment of adult kidney transplants from living donor performed between August 20, 2014 and December 01, 2016 included 40 cases. The subjects with inadequate data or graft loss during the first week after transplant (caused by vascular thrombosis or other) were excluded. Also those with surgical complications, that may affect the initial graft function (e.g. urinary leakage, artery stenosis, folding of the artery), have not been admitted to evaluate. Both donation and transplantation procedures were held at the Department of General and Transplant Surgery, Medical University of Warsaw. Recipients were compared in two groups based on their initial graft function. IGF group was defined as the serum creatinine concentration level (SCr) lower than 3 mg/dl by 5th postoperative day (POD). SGF/DGF group included slow graft function patients defined as SCr above 3 mg/dl on 5th POD with no need for dialysis and those referred as delayed graft function, meaning first-week dialyzed or preemptively transplanted with 2th POD SCr higher than 0.9 of its pretransplant value. Maintenance immunosuppression included steroids, mycophenolate mofetil (2g/day initially) and tacrolimus (0.1 mg/kg/day) for all subjects. Induction treatment was delivered in all cases using basiliximab or thymoglobulin. Data of harvested kidney's weight and dimensions (pole-to-pole length, thickness and width measured through the middle of the hilum) after its cold preparation and perfusion were prospectively collected. Clinical evidence of age, sex, body mass index (BMI) and body surface area (BSA) were also gathered, in reference both to the donors and the recipients. Variables were compared between groups using t-Student, Cochran's C, Mann-Whitney and Chi-Square Pearson tests. A p value of 0.05 was considered significant. The analysis was specified at predictors for IGF, as compared with factors for SGF or DGF. All analyses were performed using StatSoft, Inc. (2014). STATISTICA (data analysis software system), version 12. www.statsoft.com.

RESULTS

Recipient characteristics

Of the 40 renal transplant recipients, IGF was observed in 24 cases (60%; with a male-to-female ratio of 13:11, [n.s.]) at the mean age of 34.9, ranged 20 – 60.3 years old. 16 patients (40%; with a male-to-female ratio of 12:4, [n.s.]) at the mean age of 36.6, ranged 22.3 – 65.7 years old were classified as SGF (12 cases in all) or DGF (4 cases). The difference noticed in average age value between the groups revealed no statistical significance (Mann – Whitney U=183, p=0.81). Mean recipient BMI was 22.37 kg/m^2 in IGF group, whilst 23.82 kg/m^2 in SGF/DGF group (Mann-Whitney U=149, p=0.235, [n.s.]). Average BSA (based on the Moesteller formula) was estimated on 1.78 m^2 vs. 1.85 m^2 consecutively for IGF and SGF/DGF (t-Student test, t(38)= -0.96, p=0.36, [n.s.]). Demographic characteristics of the recipients are shown in Table 1. 37 patients received left-sided organ (23 vs. 14 for IGF and SGF/DGF, respectively, [n.s.]). Right-sided organ was transplanted in 3 cases only (1 vs. 2 for IGF and SGF/DGF, respectively [n.s.]). No significant differences were observed in human leukocyte antigen (HLA) matching between the groups (Mann-Whitney U=137.5, p=0.13 [n.s.]). More than 3 HLA mismatches were found in 14 cases (58.3%) in IGF group, while in 5 cases (31.3%) in SGF/DGF group.

Donor characteristics

Renal transplantations were performed from 12 unrelated (7 vs. 5 for IGF vs. SGF/DGF) and 28 related (with the IGF-to-SGF/DGF ratio of 17:11) living donors. There were no significant difference observed in IGF vs. SGF/DGF cases between patients who received organ from related vs. genetically unrelated living donor (Chi-squared Pearson =0.020, p=0.89, [n.s.]). Mean donor age reached 44.96 y.o. (from 24.84 up to 72.49) and mean donor BMI was 24.23 kg/m^2 (ranged 19.16 - 32.63) for the recipients of IGF group. Similarly, donor age averaged 48.16 y.o. (in the range of 31.36 - 59.79) and mean donor BMI was 24.13 (ranged 20.57 - 29.04) for SGF/DGF recipients. No significant differences between groups were observed in terms of donors age (t-Student test, t(38)= -0.981, p=0.378) and donors BMI (t-Student test, t(27)= 0.095, p=0.93) as well.

Transplant characteristics

The analysis of impact of the organ-related factors for initial graft function was specially performed. The results are summarized in the Table 2. Mean cold ischemia time (CIT) was 48.4 minutes for IGF recipients vs. 66.8 minutes for SGF/DGF recipients (Mann-Whitney U=7.0, p=0.296, [n.s.]) and mean anastomosis time (AT) was 33.3 minutes vs. 36.88 minutes for IGF and SGF/DGF group consecutively (t-Student test, t(14)= -0.69, p=0.5, [n.s.]). There were no notable differences in terms of harvested organ's dimensions between compared groups. Mean length of the kidney transplanted with the IGF result was 115.2 mm and its averaged width and thickness were 58.3 mm and 41.9 mm, respectively. At

the same time, organs donated for SGF/DGF group were on mean 111.1mm-length, 56.3mm-width and they had an average of 42.3 mm of thick. It means that average volume of the donated organ (based on ellipsoid to approximate) was estimated at 145.8 cm^3 for IGF and 138.2 cm^3 for SGF/DGF consecutively (t-Student test, t(38)=0.60, p=0.55, [n.s.]). All harvested kidneys were weighed after their preparation and perfusion on the cold table, just before being transplanted. The accuracy of mensuration was 0.001 kg. Although the mean weight in IGF group was determined on 0.163 kg (in the range of 0.112 – 0.228) vs. 0.153 kg (in the range of 0.120 – 0.242) for SGF/DGF, no statistical significance was observed (Mann-Whitney, U =139, p=0.242). As it follows, the mass of 1cm3 of transplanted kidney is estimated at 1.17g in average for IGF recipient, while it is 1.16g for SGF/DGF group (Mann-Whitney, U=175, p=0.90, [n.s.]).

We also compared the impact of Kidney Weight/Recipient Weight Ratio (Kw/Rw), Kidney Weight/Recipient BMI Ratio (Kw/BMI) and Kidney Weight/Recipient BSA Ratio (Kw/BSA) on initial graft function in both recipient subgroups, as multiple prior studies have described this direction of association [1–3]. No significant differences were observed between the groups compared in current study (Table 3).

DISCUSSION

Delayed graft function is a common complication after kidney transplantation, that affects the allograft in the immediate post-transplant period and impacts on the long-term results of the procedure. IGF patients are observed to have a better long-term outcome of organ transplantation than SGF or DGF patients [4, 5]. SGF and DGF recipients have a lower renal function with serum creatinine concentration significantly worse at 12 months and higher rate of acute rejection (AR) episodes than IGF group [4]. Also worse graft survival for SGF and DGF is showed by some authors [4, 6]. However, studies on graft survival among recipients with SGF in comparison to DGF are conflicting, as Zeraati et al. observed in their study a similar impact of IGF and SGF on kidney graft survival and showed it being better than those of DGF [5]. At the same time, there is no differences observed in the incidence of AR among the SGF and DGF patients [4]. It means that kidney transplant recipients with SGF show a worse outcome than those with IGF, similar to DGF patients, despite not needing dialysis [4]. Narayanan et al. reported in their study consisted of 44630 adult US living transplant recipients, that death with graft function is more prevalent in patients classified as DGF [7]. DGF also has negative implications in terms of economic, because of additional costs related with prolonged hospitalization after surgery and possibly needed hemodialysis [6,8].

The reported frequency of DGF after DD kidney transplantation are extremely variable worldwide [6, 9, 10]. According to UNOS data, 23% of DD renal transplants in US, and even up to 30% in some centers in Europe, manifest an early dysfunction leading to the clinical syndrome of DGF [5]. At the same time, an average annual rate of DGF for LD kidney transplantations is estimated at about 3.5% in United States [11, 12]. Although the enumeration of its incidence suggests that the occurrence of DGF is statistically much less frequent after LD transplantation, its impact for the long-term outcome of the procedure is severe enough to warrant a strict monitoring to reduce a risk for individuals. Recognizing, a patients with higher risk of worse initial graft function is justified due to possibility of suitable and timely posttransplant intervention. It should be emphasized that any negative outcomes of living kidney donation affects not only the recipient, but may also be associated with psychological and emotional distress in the donor. And this may further tends to discourage other potential altruists from kidney donation.

The risk factors of slow or delayed graft function in deceased-donor kidney transplants are well-understood as a result of the large amount of evidence focused on this aspect. Also an effects of DGF and SGF on health outcomes for DD graft recipients have been well reported. Unfortunately, the same cannot be said for the living kidney transplants. There is a lack of evidence on this clinical issue and it seems to be a lack of awareness about it. Despite the lack of a large-scale studies on initial graft function factors in LD kidney transplants, those currently available studies show clearly the negative impact of DGF in terms of acute rejection and patient or graft survival in them likewise [5, 7, 11]. Some demographical and clinical risk factors for DGF in LD kidney recipients have been already described by Otaibi et al. [11]. Older donor age was assessed to be associated with initial DGF in LD transplantation by Lee et al. [13], however Lan et al. reported, that there were no significant difference in the incidence of DGF in patients who undergone LD kidney transplant from donors older than 60 y.o. in comparison to those with younger donor. However, it should be noted that a small size of older donor group in their study limits the interpretation of statistical significance [14]. Some other studies have also obtained the female gender of donor, allograft multiple arteries, previous transplantation as a DGF risk factors upon univariate analysis models, but it has been not confirmed by multivariate analysis yet [11, 15]. Molnar et al. reported in their study that recipient higher body weight and higher body mass index are associated with a higher risk of DGF [16]. Also an inflammatory markers, diabetes mellitus, ischemia and vascular anastomosis time, donor-recipient relatedness, duration of dialysis treatment, HLA mismatch and AB0 compatibility have been already investigated for possible association with the incidence of DGF after LD kidney transplantation [10, 11]. Factors mostly considered to impact the early outcome after DD renal transplantation are cold ischemia time (CIT), retransplantation, warm ischemia time (WIT), donor creatinine, recipient age and HLA-match. Transplantation of LD organ generally provides closer immunological match than DD grafts [11]. The incidence of DGF among DD transplants remains high due to the expansion of acceptable donors criteria (more frequent accepting marginal and older donors) in order to reduce the organ shortage [8]. It can be also caused by the qualification of recipients with greater predispositions to the development of DGF. As Redfield et al. identified, that LD kidney recipient with DGF were more often male,

diabetic, more HLA mismatched, highly sensitized and had higher BMI and longer CIT, what remains similar to DD kidney recipients [12]. Determination of the importance of specific factors in current study groups requires further research. However, planning a large-sample study is timely-limited, as annual total number of LD kidney transplantation in Poland still remains about 50 – 60 [17].

CONCLUSIONS

Conventionally, the perception of DGF predominant association with deceased-donor kidney transplant causes the scarcity of studies focused on DGF in living-donor kidney transplants. With an increasing number of LD kidney transplantations, detailed understanding of determinants of posttransplant results seems to be essential. Although there were a slight differences, leading toward those being reported worldwide, noticed between compared groups in our current analysis, no statistical significance was observed. The influence of a small sample cannot be excluded. Further studies, with a greater number of cases included, investigating a predictors of LD kidney transplant immediate function are urgently needed. Minimizing the risks associated with negative outcomes after living-donor graft transplantation will not only improve the direct recipient results, but will also have a positive impact on an incentive for other altruists to living kidney donation.

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MEDtube Science Jun, 2018, Vol. VI (2), 29 – 34

ABBREVIATIONS

AT – Anastomosis time
BMI – Body mass index
BSA – Body surface area
CIT – Cold ischemia time
DD – Deceased donor
DGF – Delayed graft function
HLA – Human leukocyte antigen
IGF – Immediate graft function
LD – Living donor
POD – Postoperative day
SCr – Serum creatinine level
SGF – Slow graft function

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LIST OF TABLES

TAB. 1. CLINICAL FEATURES OF STUDY GROUPS.

	IGF Group	SGF/DGF Group	P value
No. of patients	24	16	-
Sex Male Female	 13 11	 12 4	0.182 [n.s.]
Mean age [years]	34.9 (20.0 – 60.3)	36.6 (22.3 – 65.7)	0.81 [n.s.]
Mean BMI [kg/m^2]	22.37	23.82	0.235 [n.s.]
Mean BSA [m^2]	1.78	1.85	0.36 [n.s.]
Donors characteristics			
Donor-recipient relatedness Related Unrelated	 17 7	 11 5	0.89 [n.s.]
HLA mismatches: average no.	3.0	2.13	0.13 [n.s.]
0 of 6	1	3	
1 of 6	3	0	
2 of 6	6	8	
3 of 6	8	3	
4 of 6	1	1	
5 of 6	1	1	
6 of 6	4	0	
Mean donor age [years]	44.96 (24.84 – 72.49)	48.16 (31.36 – 59.79)	0.378 [n.s.]
Mean donor BMI [kg/m^2]	24.23	24.13	0.93 [n.s.]

n.s. – non-significant

TAB. 2. CLINICAL DETAILS OF TRANSPLANTED ORGANS.

	IGF Group	SGF/DGF Group	P value
Mean length [mm]	115.2 (95.0-135.0)	111.1 (95.0-130.0)	0.233 [n.s.]
Mean width [mm]	58.3 (30.0 – 75.0)	56.3 (40.0 – 75.0)	0.57 [n.s.]
Mean thickness [mm]	41.9 (30.0 – 60.0)	42.3 (30.0 – 55.0)	0.90 [n.s.]
Mean volume [cm^3]	145.8 (83.65 – 238.1)	138.2 (78.5 – 197.2)	0.55 [n.s.]
Mean weight [kg]	0.163 (0.112 – 0.228)	0.153 (0.120 – 0.242)	0.242 [n.s.]
Mass of $1cm^3$ [g]	1.17 (0.76 – 1.95)	1.16 (0.78 – 1.73)	0.9 [n.s.]
Mean CIT [min]	48.4 (27.0 – 75.0)	66.8 (45.0 – 120.0)	0.296 [n.s.]
Mean AT [min]	33.3 (23.0 – 45.0)	36.88 (23.0 – 58.0)	0.5 [n.s.]

n.s. – non-significant

TAB. 3. COMPARISON OF THE ANALYSIS RESULTS BETWEEN STUDY GROUPS.

	IGF Group	SGF/DGF Group	P value
Mean Kidney Weight/Recipient Weight Ratio (Kw/Rw), g/kg	2.5 (1.64 – 4.3)	2.3 (1.35 – 4.2)	0.116 [n.s.]
Mean Kidney Weight/Recipient BMI Ratio (Kw/BMI), gm2/kg	7.4 (4.65 – 10.5)	6.7 (4.1 – 14.0)	0.145 [n.s.]
Mean Kidney Weight/Recipient BSA Ratio (Kw/BSA) g/m2	93.0 (66.4 – 141.0)	85.5 (57.4 – 140.9)	0.137 [n.s.]

n.s. – non-significant


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