Transpl Int (2002) 15: 10–16
DOI 10.1007/s00147-001-0368-7

ORIGINAL ARTICLE

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Risk factors for delayed graft function after renal transplantation and their significance for long-term clinical outcome

Received: 5 December 2000
Revised: 25 May 2001
Accepted: 28 June 2001
Published online: 2 February 2002

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Abstract Delayed graft function (DGF) remains a grieving complication after renal transplantation. In this study, we examined various factors related to organ donation, transport, and transplantation for their influence on the incidence of DGF and on long-term prognosis. The incidence of DGF, renal function after 5 years, and allograft survival were analyzed in 200 kidneys transplanted in Düsseldorf as well as in 193 partner kidneys transplanted at 43 other centers. The main risk factors for DGF were donor age, cold ischemia time (CIT) and organ shipment. DGF itself, as well as donor age, influenced the long term prognosis. A significant relationship between the partner organs regarding clinical outcome was demonstrated. Non-immunological factors strongly influence the clinical results after renal transplantation. Organs of older donors have a limited long-term prognosis. To minimize additional risks, prevention of DGF, especially by reducing CIT, should be regarded as of paramount importance.

Keywords Renal transplantation · Delayed graft function · Donor age · Non immunological risk factors · Long term allograft survival

Introduction

In the last two decades, the introduction of new drugs for immunosuppressive therapy after renal transplantation has led to a marked reduction in the number of acute rejection episodes and to an improvement of the clinical results after transplantation [8, 21]. Nevertheless, progressive deterioration of graft function in the long-term continues to be a major clinical problem. Epidemiological data show that grafts from living donors, even from unrelated living donors with poor HLA compatibility, have a better short- and long-term prognosis than cadaveric grafts, even with good HLA compatibility [28]. The reasons for the evidently poorer quality of organs from brain-dead donors are not yet fully understood. Accordingly, decisions to transplant organs from donors whose suitability appears borderline, e.g. on account of their age or critical circulatory situation, tend to be subjective.

In the clinical setting, it is frequently unclear which factors of organ donation are particularly relevant for the prognosis of transplants. In the present study comprising a total of 393 renal transplantations, we therefore investigated various factors related to organ donation, organ transport and organ transplantation and exam-

ined their influence on the incidence of delayed graft function and on the long-term prognosis.

Patients and methods

200 consecutive cadaveric renal allograft transplantations were performed at the Düsseldorf center between 1.1.1990 and 1.5.1992. The organs came from 198 different donors. Apart from the 200 kidneys transplanted in Düsseldorf, 193 kidneys from the above donors were transplanted at 43 European centers. Three organs could not be used for technical reasons.

For each of the 198 organ donors and for the 393 transplantations, the following parameters were documented and categorized for statistical analysis: Donor age: (< 40 years/40–60 years/ > 60 years); recipient age: (< 40 years/40–60 years/ > 60 years); multi-organ donation (yes/no); locally retrieved organ (yes/no); catecholamine treatment of the organ donor (yes/no); perfusion solution: (Eurocollins/Custodiol/UW); cold ischemic time (CIT) (< 24 h/ > 24 h); 2nd warm ischemic time (< 30 min/ > 30 min).

On the basis of our own documentation and with the support of the other 43 transplantation centers, Professor Dr. Opelz, Head of the Collaborative Transplant Study Group, Heidelberg, and the Eurotransplant Foundation, we were able to establish the incidence of delayed graft function after renal transplantation (defined as the need for dialysis within 72 h after transplantation or as diuresis in the first 24 h, which was less than the residual diuresis before transplantation) for 383 of 393 (97%) patients, the 5-year data after transplantation for 377 of 393 patients (96%), and the 7-year data after transplantation for 367 of 393 patients (93%).

Statistics

The univariate analyses were done with respect to the influence of individual parameters on the incidence of DGF, on the quality of allograft function after 5 years, and on the long-term allograft survival rate. The analyses to determine the significance of individual parameters for the incidence of DGF were performed using the Mantel-Haenszel test for ordinal- and the Chi-Square-test for nominal parameters.

The influence of the parameters investigated on the quality of graft function in the long-term course was evaluated on the basis of the 5-year data, as data on the creatinine ranges in patients with functioning grafts were available for a large proportion of the patients (367 of 377, 97%). The 5-year graft function was divided into the following categories: Group A: creatinine $\leq$ 1.5 mg/dl; Group B: creatinine > 1.5 mg/dl and $\leq$ 2.5 mg/dl; Group C: creatinine > 2.5 mg/dl and $\leq$ 3.5 mg/dl; Group D: creatinine > 3.5 mg/dl with functioning graft; Group E: dialysis. Since it was our aim to analyze the quality of graft function in this part of the investigation, patients who had died were not included in the statistical analysis. Again, the statistical calculation was performed using the Mantel-Haenszel test for ordinal and Chi-Square-test for nominal parameters.

The influence of the factors on the long-term graft survival rate was examined with the Log Rank procedure. In these analyses, the death of a patient was evaluated as graft loss, as previously described in the literature [12, 17, 18, 21].

All partner kidneys from the 198 organ donors were compared with regard to 5-year function, again dividing them into the groups A–E. The agreement of both kidneys regarding quality level was measured by Cohen's Kappa. It was tested whether these statistics indicated a significant agreement. This test uses the asymptotic normal distribution of Cohen's Kappa. The asymptotic standard deviation was estimated under assumption of the null hypothesis of no agreement.

In addition to the univariate analyses, the factors were also examined by multivariate analysis with simultaneous logistic regression (DGF and 5-year function) and simultaneous Cox regression (cumulative long-term graft survival). P values less than 0.05 were regarded as statistically significant in all analyses.

Results

In the 7-year period following transplantation, of the 367 patients documented over the entire period, 76(21%) died with functioning grafts. Of the 291 patients still living after 7 years, 206(71%) had functioning grafts. Thus, at the end of the observation period, 206 of the 367(56%) patients were living with functioning renal allografts.

Univariate analyses

Table 1 shows the results of the univariate analyses of the influence of the investigated parameters on the development of DGF and on long-term graft function. For greater clarity, the 5-year graft function was divided into two groups (groups A and B, i.e. grafts with good function, versus groups C, D, and E, i.e. grafts with unsatisfactory function and non-functioning grafts). The statistical results are thus slightly different from those given below with individual consideration of the different groups.

Factors influencing the incidence of DGF

Data on postoperative graft function immediately after transplantation were available for 383 transplantations. DGF occurred in 168 cases (44%). There was no difference between the transplantations performed at the Düsseldorf center (incidence 45%) and those carried out at the partner centers (incidence 42%). In the univariate analysis, donor age, origin of donor kidney, and CIT were identified as risk factors. A long CIT, in particular, showed a considerable influence on post-operative graft function. The rate of DGF in grafts with a CIT > 24 h was 20% higher than in grafts with a shorter ischemic time (60% versus 39%, $P = 0.001$).

Factors influencing the quality of graft function after 5 years

Apart from DGF, the only factor with a significant influence on the quality of graft function after 5 years was donor age. Thus, organs from young donors under 40 years showed good function (Groups A, B) after 5 years in 79% of the cases, while organs from donors over 60 years only showed good organ

Table 1 Univariate analysis of the influence of individual parameters on the incidence of DGF and on long term allograft function

	*n**	Donor age 40 years	Donor age 40–60 years	Donor age 60 years	*P*
Incidence of DGF	383	38%	48%	53%	0.03
Creatinine after 5 years ≤ 2.5 mg/dl	302	79%	66%	55%	0.001
Creatinine after 5 years > 2.5 mg/dl or graft failure		21%	34%	45%	
Cumulative allograft survival after 7 years	377	63%	54%	44%	0.04
	*n**	Cold ischaemia ≤ 24 h	Cold ischaemia > 24 h		*P*
Incidence of DGF	379	39%	60%		0.001
Creatinine after 5 years ≤ 2.5 mg/dl	297	71%	67%		n.s.
Creatinine after 5 years > 2.5 mg/dl or graft failure		29%	33%		
Cumulative allograft survival after 7 years	365	58%	55%		n.s.
	*n**	2nd warm ischaemia ≤ 30 min	2nd warm ischaemia > 30 min		*P*
Incidence of DGF	334	43%	45%		n.s.
Creatinine after 5 years ≤ 2.5 mg/dl	264	70%	71%		n.s.
Creatinine after 5 years > 2.5 mg/dl or graft failure		30%	28%		
Cumulative allograft survival after 7 years	327	55%	58%		n.s.
	*n**	Use of catecholamines yes	Use of catecholamines no		*P*
Incidence of DGF	383	53%	43%		n.s.
Creatinine after 5 years ≤ 2.5 mg/dl	304	69%	71%		n.s.
Creatinine after 5 years > 2.5 mg/dl or graft failure		31%	29%		
Cumulative allograft survival after 7 years	377	58%	54%		n.s.
	*n**	Multi-organ donation	Kidney donation		*P*
Incidence of DGF	383	41%	46%		n.s.
Creatinine after 5 years ≤ 2.5 mg/dl	304	72%	69%		n.s.
Creatinine after 5 years > 2.5 mg/dl or graft failure		28%	31%		
Cumulative allograft survival after 7 years	377	59%	56%		n.s.
	*n**	Perfusion solution EC	Perfusion solution HTK	Perfusion solution UW	*P*
Incidence of DGF	383	49%	44%	38%	n.s.
Creatinine after 5 years ≤ 2.5 mg/dl	304	69%	67%	74%	n.s.
Creatinine after 5 years > 2.5 mg/dl or graft failure		31%	33%	26%	
Cumulative allograft survival after 7 years	377	55%	55%	61%	n.s.
	*n**	Organ donation: local center	Organ donation: foreign center		*P*
Incidence of DGF	378	36%	49%		0.02
Creatinine after 5 years ≤ 2.5 mg/dl	304	70%	70%		n.s.
Creatinine after 5 years > 2.5 mg/dl or graft failure		30%	30%		
Cumulative allograft survival after 7 years	377	52%	60%		n.s.

*Number of organs with completely available data. Patient death was excluded from the analysis of 5-year allograft function

function in 55% of the cases (Mantel-Haenszel test, $P = 0.001$).

Factors influencing graft survival after 7 years

The long-term graft outcome was influenced significantly by the factors donor age, recipient age and, as shown above, postoperative DGF. Comparison of organs from younger donors (under 40 years) with those of older donors (over 60 years) showed a difference of 19% with regard to graft outcome after 7 years (65% for organs from younger donors versus 44% for organs from older donors, $P = 0.03$). Figure 1 shows the cumulative graft survival as a function of donor age.

As already mentioned, for the statistical analysis of graft survival, the death of a patient was evaluated as graft loss. In a subanalysis in which patients who had died were censored, the results were still significant (7-year graft survival for organs with versus those without DGF: 69% versus 79%, $P=0.02$; 7-year graft survival for organs from younger donors <40 years versus organs from older donors $>$ 60 years: 82%, versus 58%; $P=0.004$). The recipient age no longer had a significant influence, so that an association between this factor and patient survival can be postulated. This was clearly confirmed by a separate analysis of patient survival after 7 years (7-year survival for patients <40 years: 91%; for patients aged 40–60 years: 79%; for patients $>$ 60 years: 58%; $P<0.0001$).

Influence of DGF on the long-term function of the renal transplant

Figure 1 shows the influence of DGF on cumulative long term allograft survival. After 7 years, graft survival was 50% for organs with DGF, versus 63% for organs with immediate postoperative function ($P=0.005$). The quality of organ function after 5 years on the basis of categorization into the groups A–E was also significantly impaired in organs with DGF (Mantel-Haenszel test, $P=0.02$).

Influence of partner kidney function on the incidence of DGF and on the long-term function of the renal graft

Similarities between the partner kidneys were found both with regard to the incidence of DGF and with regard to long-term outcome (see Table 2). Fifty percent of the kidneys developed DGF in case of DGF of the partner kidney. In case of spontaneous graft function of the partner kidney, the incidence of DGF was reduced to 39% ($P=0.05$). There was also a significant association between the 5-year function of a graft and the long-term outcome of the partner kidney. Thus the 7-year survival rate in the case of a well-functioning partner kidney (groups A and B) was 64% compared with 46% in the case of unsatisfactory function of the partner kidney (group C-, D-, E- patients who died are not included); $P=0.007$. The comparison of the partner kidneys with regard to quality of graft function after 5 years was again performed after categorization of the kidney function into the groups A–E. On this basis, a significant correlation between the partner kidneys was found (Cohen's kappa; $r=0.13$, $P=0.029$).

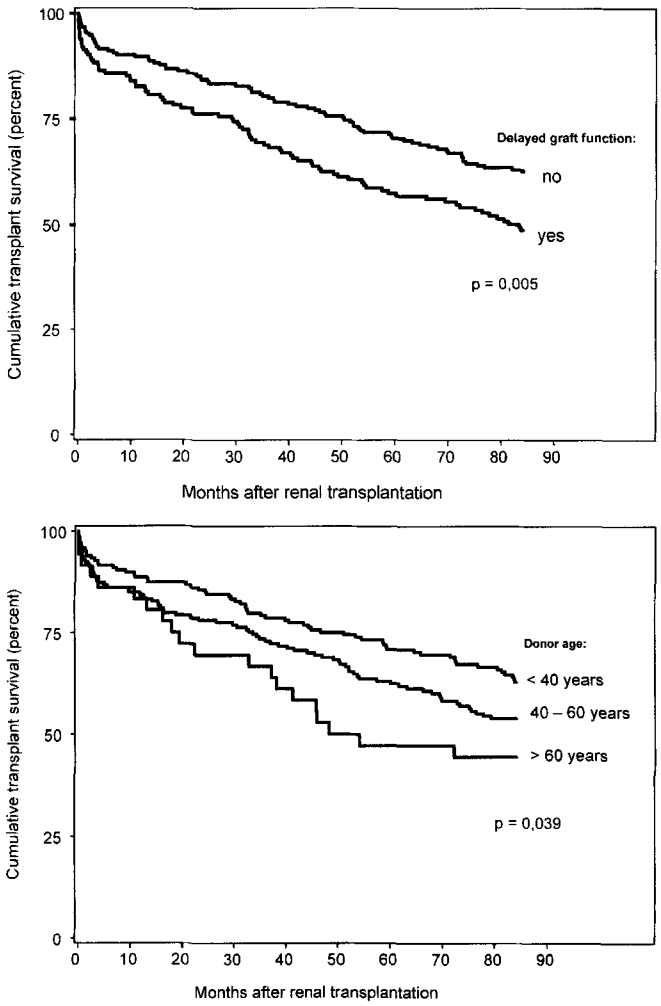

Fig. 1 Cumulative long term allograft survival in relation to donor age and occurrence of delayed graft function

Multivariate analyses

The multivariate analysis (simultaneous logistic regression) also showed the cold ischemic time to be the main risk factor for postoperative DGF ($P=0.004$, odds ratio 1,92, 95% confidence interval 1,24–2,98). The factors donor age ($P=0.08$) and origin of the organ ($P=0.10$), which were identified as relevant factors in the univariate analysis, were not significant in the multivariate analysis.

With regard to the quality of renal function after 5 years, simultaneous logistic regression showed a significant influence of donor age ($P=0.02$, odds ratio 2,98, 95% confidence interval 1,23–7,21). None of the other parameters examined were statistically significant. On account of the association between recipient age and long-term patient survival shown above, the factor recipient age was not included in the multi-

Table 2 Influence of partner kidney function on the incidence of DGF and on the long-term function of the renal allograft

	*n**	Partner kidney with DGF	Partner kidney without DGF	*P*
Incidence of DGF	366	50%	39%	0.05
	*n**	Partner kidney with a creatinine ≤ 2.5 mg/dl after 5 years	Partner kidney with a creatinine > 2.5 mg/dl after 5 years or graft failure	*P*
Creatinine after 5 years ≤ 2.5 mg/dl Creatinine after 5 years > 2.5 mg/dl or graft failure	287	74% 26%	69% 31%	n.s.
	*n**	Partner kidney with a creatinine ≤ 2.5 mg/dl after 5 years	Partner kidney with a creatinine > 2.5 mg/dl after 5 years or graft failure	*P*
Cumulative allograft survival after 7 years	287	64%	46%	0.007

*Number of organs with completely available data. Patient death was excluded from the analysis of 5-years allograft function

variate analysis of 7-year graft outcome. The unfavourable influence of postoperative DGF on 7-year graft survival and the trend towards an influence of donor age shown in the univariate analysis were also confirmed in the multivariate analysis (DGF, $P = 0.008$, hazard ratio 1.55, 95% confidence interval 1.12–2.14; donor age, $P = 0.05$, hazard ratio 1.74, 95% confidence interval 1.00–3.02).

Discussion

The results of our study underline the importance of non-immunological factors for the long-term prognosis of renal transplants. With regard to the 5-year function, we found a significant correlation between the partner kidneys from 198 organ donors, even though these organs were transplanted almost without exception at different centers. In the univariate analysis, graft outcome after 7 years was significantly better for kidneys with a well-functioning partner organ than for the remaining organs. These relationships suggest that the long-term prognosis of a renal transplant is already determined at the time of organ acquisition and transplantation.

The incidence of DGF in 383 patients was 44%. It should be mentioned that the definition of DGF was quite liberal, including not only the need for dialysis but also an initial 24 h diuresis below the residual diuresis prior to transplantation. Several definitions of DGF are applied in the current literature, thus influencing the reported incidences. Many studies define DGF as the need for any or more than one dialysis session in a specified postoperative period [12, 16, 17, 25, 26], a definition that is easy to apply especially for aquisition of data in large registries. However, there are undoubtedly forms of early impairment of allograft function that do not require postoperative dialysis. Therefore many authors use additional parameters such as oliguria or the failure of serum creatinine to fall within a specified postoperative period, either in epidemiologic or in interventional studies [2, 4, 14, 22, 23]. It was demonstrated recently that allografts after DGF, defined as the need for dialysis or a serum creatinine > 150 mol/l at day 8 (a definition leading to an incidence of 49%), had an increased risk for chronic histological changes according to the Banff criteria in a subsequent routine biopsy after 3 months [19]. Therefore, extending the definition of DGF beyond the need for dialysis appears to be appropriate in order to reflect the pre- and perioperative renal allograft damage.

Delayed graft function after transplantation had a significant influence on the clinical outcome after 5 and 7 years in both the univariate and the multivariate analysis. After 7 years, a difference in the graft survival rate of 14% was found between grafts with postoperative DGF and those without. Therefore, the 43% incidence of DGF leads to considerable consequences for a large percentage of patients undergoing transplantation. In view of the usually prolonged hospitalization after transplantation and the earlier resumption of dialysis in the long-term course, it is also of economic relevance. Other authors have also drawn attention to the significance of DGF for long term graft survival [4, 12, 16, 26].

It should, however, be emphasized that the incidence of DGF is not a fixed value and that it is therefore important to try to minimize the relevant risk factors. In this connection we found a significant relationship between the duration of cold ischemia and the incidence of DGF. With an average cold ischemic time at our own center of 25.23 + 6.3 h, there is definitely room for improvement. We saw no direct effect

of the ischemic times on long-term graft survival, although this has been described by other authors [18, 26]. It is plausible that delayed graft function is a multifactorial occurrence. Therefore it is understandable that individual parameters may not show a statistically significant influence on later graft function [22]. Nevertheless, we believe that attempts to reduce the risk factor of cold ischemic time make sense, particularly as approaches to reduce ischemic- and reperfusion injury with measures like the addition of arginine or trimetazidine to the storage solution [6, 9], or treatment of the recipient with superoxide dismutase, prostaglandins, antisense oligonucleotides against ICAM-1 or bioflavonoids [5, 10, 11, 13] are still of experimental character.

Apart from DGF, donor age was shown by both univariate and multivariate analysis to have a significant influence both on graft survival and on the long-term quality of renal function. With regard to the 7-year outcome, a comparison between the organs of younger donors and those of older donors showed a difference in graft survival of 19%. In order to exclude the possibility of errors as a result of more frequent allocation of "older" organs to older donors with a poor life expectancy, a separate analysis was performed in which the death of a patient was not evaluated as graft loss, which leads to a statistical overestimation of graft survival. In this analysis there was also a difference of 22% in graft survival after 7 years, which was highly significant. This influence of donor age on the long-term prognosis of organs is undoubtedly of considerable significance for clinical transplantation. High donor age and delayed graft function may lead to an early reduction in the number of functioning nephrons. An imbalance between the nephron mass of the graft and the recipient's needs impairs the long-term prognosis of the organ. This is the case with kidneys from pediatric or female donors, for example, or with recipients of large body size. It has been postulated that in such constellations the more frequent incidence of late graft losses might be due to hyperfiltration damage [3, 29].

Of 50 organ recipients aged over 60 years, 58% were still alive 7 years after the transplantation, compared with 91% of the patients under 40 years of age ($n = 120$, $P < 0.001$). Whether this clearly poorer survival of older patients together with the unfavorable long-term prognosis of organs from older donors justifies deliberately combining these factors is open to debate, since an unfavorable influence of high donor age on long-term clinical outcome was also found in older organ recipients [1]. Nevertheless, the allocation of organs from older donors to older recipients is currently the chosen strategy of the Eurotransplant Senior Program [20]. Our data, as well as a recently published report [17] indicate that in view of the unclear long-term prognosis of these grafts, at least the additional risk factor of DGF and in turn, long cold ischemic times, should be avoided as far as possible. The Eurotransplant Program addresses this particular point with its recommendation that the cold ischemic time be less than 8 h. Although the initial results indicate an acceptable short-term prognosis of the patients receiving transplants in the context of the Senior Program [24], more extensive figures are required before such a policy can, in our opinion, be generally recommended.

The question of the relevance of catecholamine therapy of the organ donor for the occurrence of DGF and for the long-term prognosis of the graft recipient is controversial. Several authors came to the conclusion that catecholamine therapy of the donor substantially increases the risk of delayed graft function [7, 15]. However, results showing exactly the opposite have also been published [27]. We can definitely not confirm the results of a recently published study according to which treatment with dopamine or noradrenaline can reduce the risk of rejection and significantly improve the long-term prognosis [25]. Although our statistical analysis did not look separately at the individual catecholamines, we definitely did not see a positive effect. If anything, the univariate analysis of the catecholamine therapy suggests an unfavourable effect on the occurrence of DGF, although the difference compared with the organs from donors without catecholamine therapy was not statistically significant.

We were able to show in our study that, independently of the rate of graft survival, the quality of long-term organ function is influenced by non-immunological factors. These were found to include high donor age and possibly also postoperative DGF. This means that if we assume that the quality of graft function influences other events such as cardiovascular complications, the incidence of hyperparathyroidism or renal anaemia, these factors are also relevant in patients with permanently functioning transplants.

In summary, non-immunological factors play a substantial role in the long-term functioning of renal transplants. The prevention of postoperative DGF should be regarded as an important target. Apart from the avoidance of long cold ischemic times, it is to be hoped that pharmacological approaches will be developed to diminish the extent of the ischemic- or reperfusion injury in the future. With regard to donor selection, one should be aware that the organs of older- and possibly also of catecholamine-treated donors have a limited long-term prognosis. The question of whether these findings should be taken into account in organ allocation must remain open until further study results have been analyzed and discussed.

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