Recipient and Donor Body Mass Index as Important Risk Factors for Delayed Kidney Graft Function

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Background. Obesity is increasingly impacting the overall health status and the global costs for health care. The increase in body mass index (BMI) is also observed in kidney allograft recipients and deceased organ donors.
Methods. In a retrospective single-center study, we analyzed 1132 deceased donor kidney grafts, transplanted at our institution between 2000 and 2009 for recipient and donor BMI and its correlation with delayed graft function (DGF). Recipients/donors were classified according to their BMI (<18.5, 18.5–24.9, 25–29.9, and >30 kg/m^2). DGF was defined as requirement for one dialysis within the first week after transplantation.
Results. Overall DGF rate was 32.4%, mean recipient BMI was 23.64±3.75 kg/m^2, and mean donor BMI was 24.69±3.44 kg/m^2. DGF rate was 25.2%, 29.8%, 40.9%, and 52.6% in recipients with BMI less than 18.5, 18.5 to 24.9, 25 to 29.9, and more than 30 kg/m^2, respectively ($P<0.0001$). Donor BMI less than 18.5, 18.5 to 24.9, 25 to 29.9, more than 30 kg/m^2 resulted in a DGF rate of 22.5%, 31.0%, 37.3%, and 51.2% ($P<0.0001$). Multivariate analysis revealed recipient BMI and dialysis duration as independent risk factors for DGF. DGF results in inferior 1- and 5-year graft and patient survival.
Conclusion. Recipient and donor BMI correlate with the incidence of DGF. Awareness thereof should have an impact on peri- and posttransplant measures in renal transplant recipients.

Keywords: Delayed graft function (DGF), Renal transplantation, Body mass index (BMI), Overweight, Recipient evaluation.

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Delayed graft function (DGF) is defined as the need for dialysis within the first 7 days posttransplantation and has been shown to increase allograft immunogenicity and the risk for acute rejection (*1*). It occurs in 2% to 50% of kidney transplants in standard criteria brain-dead donors (*1*, *2*) and more than 50% of transplants from extended criteria donors (*3*). DGF results in longer hospitalization, higher costs, and a greater risk of cardiovascular complications (*4–6*). In addition, DGF is associated with a decreased long-term graft survival (*7*). Several risk factors for DGF related to donor, recipient, and the surgical procedure have been identified and stratified in risk quantification scores (*8*, *9*). Factors most closely correlated with early outcome after deceased donor kidney transplantation are cold ischemia time (CIT), retransplantation, human leukocyte antigen (HLA)-match, warm ischemia time, donor creatinine, gender age, recipient age, and diabetes mellitus (*3*, *4*, *8–11*).

Overweight, defined as a body mass index (BMI) of 25 to 29.9 kg/m^2 and obesity (BMI≥30 kg/m^2), are increasing in prevalence at an alarming rate in developed and developing countries throughout the world (*12*, *13*). Similarly, the incidence of overweight and obesity has been increasing in kidney transplant candidates on the waiting list during the last years (*14*, *15*).

Although the recipient BMI has previously been associated with inferior outcome and higher complication rates after kidney transplantation (*16*), no data are available regarding the impact of donor BMI on initial kidney graft function. In the current study, we investigated donor and recipient BMI as risk factors for DGF in brain-dead deceased donor kidney transplantation.

RESULTS

Eight kidney grafts did not develop any function, three grafts were from donors deceased after cardiac death and, for eight patients, data were not complete. These 19 cases were excluded from the analysis.

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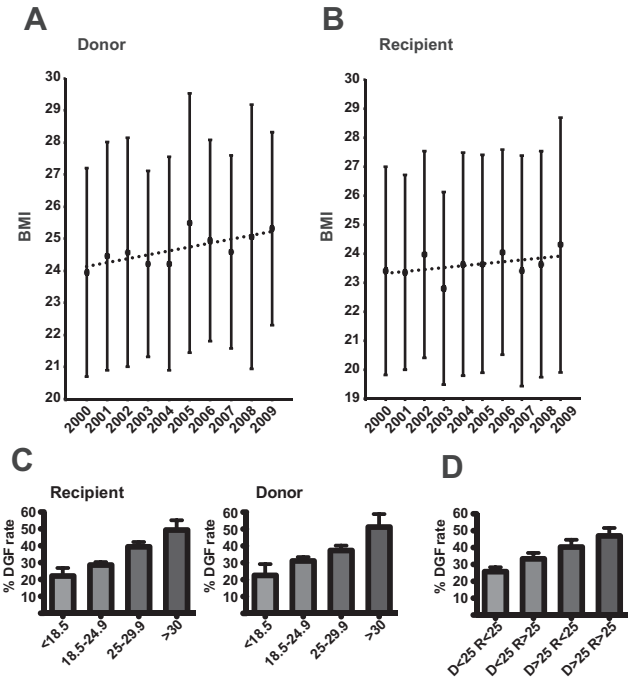

FIGURE 1. (A-D) Values are represented as mean±SD. Donor (A) and recipient (B) body mass index (BMI) steadily increased during the 10-year observational period. The mean donor BMI increased from 23.9 to 25.3 kg/m^2 (P=0.0084); the mean recipient BMI rose steadily from 23.41 to 24.30 kg/m^2 (P=0.202). (C) Increase of the delayed graft function (DGF) rate related to the recipient and donor BMI. (D) Analysis of combined donor and recipient BMI. DGF rates: R<25, D<25, 24.3% vs. R>25, D>25, 43.67% (P<0.0001); R>25, D<25, 39.52% vs. R>25, D>25, 43.67% (P<0.0001); R<25, D<25, 24.3% vs. R<25, D>25, 33.93% (P=0.0045); R<25, D>25, 33.93% vs. R>25, D<25, 39.52% (P=0.2033).

TABLE 1. Characteristics of 1113 deceased donor kidneys and recipients between 2000 and 2009

Characteristic	
Donor male gender, n (%)	662 (59.5)
Donor age (mean±SD) (yr)	44.15±16.59
Donor BMI (mean±SD) (kg/m^2)	24.69±3.44
Cause of death, n (%)	
Cerebrovascular accident	455 (40.88)
Trauma	430 (38.63)
Anoxia	65 (5.84)
Other	163 (14.65)
Serum creatinine (mean±SD) (mg/dL)	0.93±0.56
Serum urea (mean±SD) (mg/dL)	32.53±19.15
Recipient male gender, n (%)	740 (66.5)
Recipient age (mean±SD) (yr)	49.54±13.55
Recipient BMI (mean±SD) (kg/m^2)	23.64±3.75
Duration of dialysis (mean±SD) (mo)	38.03±30.96
Peritoneal dialysis, n (%)	99 (8.89)
Cause of renal failure, n (%)	
Immune-mediated disease	337 (30.28)
Diabetes mellitus	288 (25.88)
Polycystic kidney disease	107 (9.61)
Others	381 (34.23)
Previous kidney transplantation, n (%)	175 (15.72)
PRA+ recipients, n (%)	159 (14.29)
PRA (mean±SD) (%)	46.48±34.22
HLA A/B mismatch, n (%)	772 (69.36)
HLA DR mismatch, n (%)	870 (78)
Cold ischemia time (mean±SD) (hr)	15.09±5.01
Anastomoses time (mean±SD) (min)	31.28±9.811

BMI, body mass index; PRA, panel reactive antibody; HLA, human leukocyte antigen.

Donor Characteristics

Among 1113 deceased donor kidneys from 912 deceased donors with a mean age of 44.15±16.59 years, 59.5% were male. The causes of death were cerebrovascular incident (40.88%), trauma (38.63%), anoxia (5.84%), and others (14.65%). Mean donor serum creatinine and serum urea were 0.93±0.56 mg/dL and 32.53±19.15 mg/dL, respectively. According to the United Network for Organ Sharing (UNOS) definition, 261 donors were extended criteria donors (23.45%). Mean donor BMI was 24.69±3.44 kg/m^2 and continuously increased from year 2000 (23.95±3.26 kg/m^2) until 2009 significantly (25.32±3.02 kg/m^2, P=0.0084; Fig. 1A). More than one third of all donor kidneys (39.3%) were from a donor with a BMI more than 25 kg/m^2 (Table 1).

Recipient Characteristics

Mean recipient age was 49.45±13.55 years, 66.5% were male. The mean BMI was 23.64±3.75 kg/m^2 (Table 1). A total of 367 (32.97%) recipients showed a BMI higher than 25 kg/m^2. Recipient BMI constantly increased during the investigated period between 2000 (23.41±3.60 kg/m^2) and 2009 (24.3±4.39 kg/m^2), but this was not statistically significant (P=0.202; Fig. 1B).

Most common causes of renal failure were glomerulonephritis (30.28%), diabetes mellitus (25.88%), and polycystic kidney disease (9.61%). Mean duration of dialysis was 38.03±30.96 months. Peritoneal dialysis was used for renal replacement therapy in 8.89% of the recipients. One hundred fifty-nine (14.29%) patients had panel reactive antibodies (PRAs) before transplantation with peak PRA levels ranging from 2% to 98%; mean±SD: 46.48%±34.22%. Retransplantation comprised 15.72% of the cases. Induction therapy was administered in 64.42% of the patients (interleukin-2 receptor antagonist 41.8%, alemtuzumab 31.4%, and anti-thymocyte globulin 26.8%). For maintenance immunosuppression tacrolimus, cyclosporine, mycophenolate mofetil (MMF), and azathioprine (AZA) were used in 71.6%, 28.4%, 95.4%, and 4.6%. There were no significant differences in the occurrence of DGF between the calcineurin inhibitors, MMF, and AZA.

Transplant Characteristics

In 111 (9.97%) cases, the HLA-match was 6 of 6; 65 (5.84%) had one HLA mismatch; 162 (14.56%) had two HLA mismatches; 314 (28.21%) had three HLA mismatches; 248 (22.28%) had four HLA mismatches; 148 (13.30%) had five

TABLE 2. Univariate comparison of possible predictive parameters associated with DGF

Characteristic	DGF (n=361)	No DGF (n=752)	*P*
Donor BMI (kg/m^2)	25.16±0.18	24.47±0.12	0.0012
Recipient BMI (kg/m^2)	24.53±0.21	23.21±0.13	<0.0001
Donor age (yr)	47.03±0.86	42.77±0.60	<0.0001
Recipient age (yr)	52.50±0.66	48.11±0.50	<0.0001
Donor male gender	217 (60.11)	445 (59.17)	0.6690
Recipient male gender	251 (69.53)	489 (65.03)	0.1043
Duration of dialysis	46.06±40	33.93±24.3	<0.0001
Donor creatinine	0.96±0.024	0.91±0.022	0.2148
Donor urea	34.64±1.127	31.51±0.66	0.0113
AT (min)	33.08±0.57	30.41±0.34	<0.0001
CIT (hr)	16.12±0.27	14.6±0.18	<0.0001
Previous kidney transplantation	80 (22.16)	95 (12.63)	0.0062
PRA+ recipients	62 (17.17)	97 (12.9)	0.056
HLA A/B mismatch	249 (68.98)	523 (69.55)	0.517
HLA DR mismatch	287 (79.50)	583 (77.53)	0.328

Values are expressed as mean±SD or n (%).

BMI, body mass index; AT, anastomosis time; CIT, cold ischemia time; PRA, panel reactive antibody; HLA, human leukocyte antigen.

HLA mismatches; and 65 (5.84%) had six HLA mismatches. Mean CIT was 15.09±5.01 hr and anastomosis time (AT) was 31.2±9.8 min (Table 1).

Evaluation of Predictors for Delayed Graft Function

Univariate analysis of the parameters analyzed for their association with DGF is displayed in Table 2. One hundred (8.3%) patients received one dialysis due to hyperkalemia or volume overload. Overall DGF rate was 32.4%. In recipients with a BMI less than 18.5, 18.5 to 24.9, 25 to 29.9, and more than 30 kg/m^2, the DGF rate was 25.2%, 29.8%, 40.9%, and 52.6%, respectively ($P<0.0001$) (Fig. 1C). Donor BMI less than 18.5, 18.5 to 24.9, 25 to 29.9, and more than 30 kg/m^2 resulted in DGF rates of 22.5%, 31.0%, 37.3%, and 51.2% ($P<0.0001$) (Fig. 1C). During the observational period, the DGF rate increased significantly from 22.69% in the year 2000 up to 31.57% in 2009 ($P=0.0157$).

Analysis of recipient and donor combinations regarding DGF rate, stratified for BMI less than 25 vs. more than 25 kg/m^2 is shown in Figure 1D. DGF rate was significantly higher in combinations of obese kidneys with obese recipients when compared with a BMI less than 25 kg/m^2 in both, $P<0.0001$ (Fig. 1D); however, no additive effect in transplanting a kidney from an overweight donor to an overweight recipient was seen.

The duration of dialysis was significantly longer in the DGF group than in the no DGF group, 46.06±40 months vs. 33.93±24.3 months ($P<0.0001$). The type of dialysis did not have any influence on the occurrence of DGF ($P=0.547$).

In the DGF group, mean donor and recipient age were higher (47.0±0.8 years vs. 42.7±0.6 years and 52.5±0.6 years vs. 48.1±0.5 years, respectively; $P<0.0001$ for both). Donor ($P=0.669$) and recipient ($P=0.104$) gender did not have an impact on the incidence of DGF. Donor serum urea was significantly higher in the DGF group (34.64±1.13 mg/dL vs. 31.51±0.66 mg/dL; $P=0.0113$). Similarly, donor serum creatinine was higher in the DGF group (0.96 mg/dL vs. 0.91 mg/dL) but the difference was not statistically significant ($P=0.21$).

AT and CIT were significantly longer in the DGF group with an AT of 33.08±0.57 min vs. 30.41±0.34 min and a CIT of 16.12±0.27 hr vs. 14.6±0.18 hr in kidneys, which did not develop a DGF ($P<0.0001$ for both).

PRA levels did not show any significant impact on DGF rate in the univariate analysis ($P=0.056$). The underlying renal diseases and the use of induction therapy did not correlate with DGF. For HLA-A/B and HLA-DR mismatches, no significant influence on the initial organ function could be detected. Patients who underwent retransplantation had a significantly higher DGF rate than patients having received their first kidney allograft, 45.71% vs. 29.85% ($P<0.0062$).

Acute Rejection

Acute rejection defined as biopsy-proven or clinically suspected occurred in 163 (14.65%) recipients with a significantly higher incidence in patients after retransplantation (20.57% vs. 13.54%; $P=0.016$). In 93 patients, acute rejection of the allograft was clinically suspected. Percutaneous kidney biopsies revealed Banff I in 18 kidneys, Banff II in 45 kidneys, and Banff III rejections in 7 kidneys. One-way ANOVA analysis showed a significantly higher mean recipient BMI (26.51±4.5 kg/m^2) in Banff III rejections than in grade II (24.44±3.94 kg/m^2), grade I (23.18±3.17 kg/m^2), and presumed (23.04±3.92 kg/m^2) acute kidney rejections. Acute rejection grades did not show any correlation with the donor BMI.

In the DGF group, significantly more acute rejections were found when compared with the no DGF-group (24.9% vs. 9.71%; $P<0.0001$). The mean BMI of patients, which developed acute rejection, was 24.72±0.395 kg/m^2 vs. 22.41±0.421 kg/m^2 in nonrejecting patients ($P=0.0001$).

Acute rejection occurred in 12.97% of patients after receiving induction treatment. This was significantly lower than in 17.68% of patients without any induction therapy; $P=0.0335$. There were no significant differences in the occurrence of acute rejection episodes in patients receiving tacrolimus (71.6%, acute rejection [AR] 15.24%), cyclosporine A (28.4%, AR 13.58%), MMF (95.4%, AR 16.83%), and AZA (4.6%, AR 13.92%) in our kidney allograft recipients.

Multivariate Analysis

The multivariate logistic regression analysis is summarized in Table 3. Recipient BMI (odds ratio [OR] 1.087, 95% confidence interval [CI] 1.043–1.132, $P<0.0001$) was independently associated with DGF. Further, also duration of dialysis (OR 1.012, 95% CI 1.007–1.017, $P<0.0001$), retransplantation (OR 1.908, 95% CI 1.315–2.769, $P=0.001$), CIT (OR 1.001, 95% CI 1.000–1.001, $P=0.001$), AT (OR 1.024, 95% CI 1.009–1.038, $P=0.001$), and recipient age (OR 1.013, 95% CI 1.001–1.026, $P=0.03$) were independent predictors for DGF although donor criteria (BMI, age, and serum urea) failed to show statistical significance in the multivariate analysis.

TABLE 3. Results of the multivariate logistic regression analysis to evaluate independent predictors for DGF

Characteristic	Wald	OR	95% CI	*P*
Recipient BMI (kg/m^2)	16.055	1.087	1.043–1.132	<0.0001
Donor BMI (kg/m^2)	1.086	1.024	0.979–1.071	0.297
Recipient age (yr)	4.725	1.013	1.001–1.026	0.030
Donor age (yr)	0.990	1.005	0.995–1.015	0.320
Duration of dialysis	20.369	1.012	1.007–1.017	<0.0001
Previous kidney transplantation	11.563	1.908	1.315–2.769	0.001
Donor urea (mg %)	3.214	1.006	0.999–1.013	0.073
AT (min)	10.637	1.024	1.009–1.038	0.001
CIT (hr)	11.485	1.001	1.000–1.001	0.001

BMI, body mass index; AT, anastomosis time; CIT, cold ischemia time.

Influence of BMI on AT and CIT

When stratified for donor and recipient BMI, AT was significantly longer in recipients with a BMI more than 25 kg/m^2 (33.01±0.52 min) than in patients with a BMI less than 25 kg/m^2 (30.43±0.36 min) ($P<0.0001$). The duration of CIT was longer in recipients with a BMI more than 25 kg/m^2 (15.35±0.26 hr vs. 14.87±0.19 hr), although this did not reach statistical significance ($P=0.07$).

AT and CIT did not differ significantly in kidneys retrieved from donors with a BMI more than 25 kg/m^2 compared with less than 25 kg/m^2 (31.43±0.39 min vs. 31.18±0.46 min, $P=0.689$; 14.98±0.19 hr vs. 14.93±0.25 hr, $P=0.859$).

These results were confirmed by a nonparametric correlation of AT, CIT, donor BMI, and recipient BMI, showing that the recipient BMI had the highest impact on the duration of AT ($P<0.001$).

Overall Graft Function

Overall 1- and 5-year patient survival was 95.4% and 87.5%, overall 1- and 5-year graft survival was 91.6% and 79.0% (Fig. 2A). As our study focused on the correlation of recipient and donor BMI with DGF, we analyzed whether the occurrence of DGF has an impact on long-term patient and graft survival. In the DGF group, 1- and 5-year patient survival was 93.0% and 80.5% in contrast to 96.5% and 90.9% in the no DGF group ($P<0.0001$; Fig. 2B). Similarly, 1- and 5-year graft survival was inferior in the DGF group (84.0% and 69.3%) when compared with 95.2% and 83.7% in the no DGF group ($P<0.0001$; Fig. 2C).

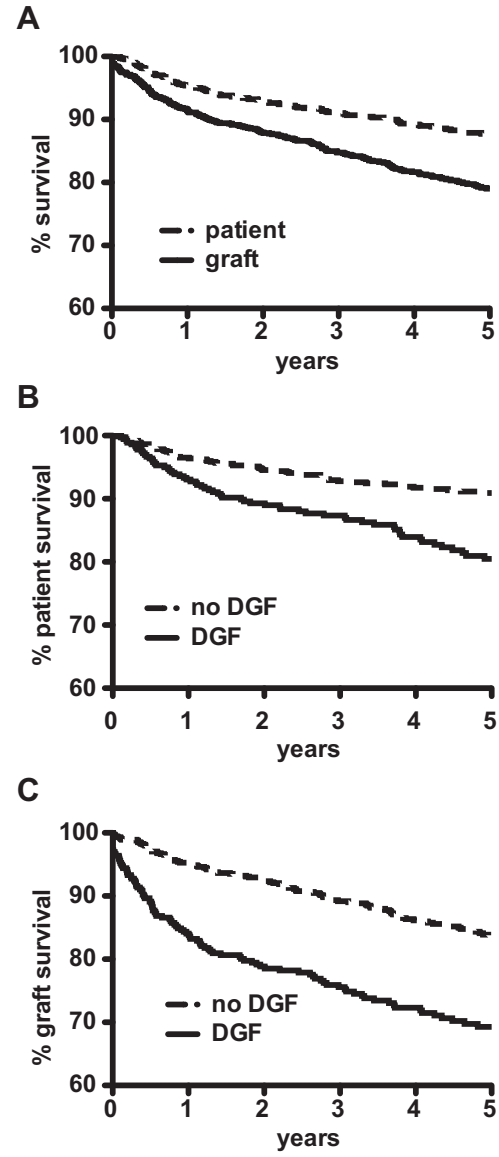

FIGURE 2. (A-C) Kaplan-Meier survival curves. (A) Overall patient and graft survival. One-year patient survival 95.4%; 5-year patient survival 87.5%; 1-year graft survival 91.6%; 5-year graft survival 79.0%. (B) Patient survival stratified for delayed graft function (DGF). One-year patient survival in DGF group 93% vs. 96.5% in no DGF group; 5-year patient survival in DGF group 80.5% vs. 90.9% in no DGF group; $P<0.0001$. (C) Graft survival stratified for DGF. One-year graft survival in DGF group 84% vs. 95.2% in no DGF group; 5-year graft survival in DGF group 69.3% vs. 83.7% in no DGF group; $P<0.0001$.

DISCUSSION

A large body of literature documents risk factors for DGF (*1*, *3*, *4*, *8*–*11*). Herein, we retrospectively analyzed the correlation of the BMI in the donor and in the recipient with initial graft function after deceased donor kidney transplantation in comparison with other, established risk factors for DGF. The BMI has been continuously increasing in the transplant and in the general population in the past decade (*17*). In our recipient population, we have also found an increase in BMI over a 10-year observational period similar to what has been described by others (*14*). Although measurements of waist circumference and waist-to-hip ratio might be a valuable addition or alternative, such data were not available in our cohort (*18*). The BMI in our deceased kidney donor population has increased significantly during the 10-year observational period.

Living donor kidneys transplanted during this period (n=166) were excluded ab initio as the DGF rate in living donor kidneys in the period observed was less than 2% (data

not shown) and for reasonable statistics more patients are needed.

DGF is a consequence of mostly but not exclusively ischemia-reperfusion–mediated immunological (*19*, *20*) and nonimmunological factors (e.g., hypoxia during cold ischemia, cooling of organ) (*1*, *7*, *21*). The overall DGF rate (32.4%) in kidneys from brain-dead donors was within the range published previously. In the clinic routine, DGF is defined by the need for dialysis and causes renal replacement therapy until the graft resumes adequate function (*9*, *22*, *23*). Further, DGF is closely related to reduced long-term graft survival (*7*, *9*, *24*) as also seen in our cohort, and creates significant costs, thus concepts to avoid/reduce DGF are needed.

Jindal and Zawada (*16*) described an association of obesity and DGF. Obesity in the recipient has a significant impact on posttransplant outcomes, resulting in a higher rate of wound infections (*25*) and DGF (*26–29*). As a consequence, recipient BMI has been included in donor risk indices (*8*, *9*). Our study confirms in uni- and multivariate analysis, the significant input of recipient BMI on the rate of DGF. Possible explanations for this effect may be immunological and nonimmunological.

CIT (due to longer time for vessel preparation) and AT (due to impaired vascular access) were longer in obese recipients and independent risk factors for DGF in our study (Table 3).

The association of BMI and ischemia-reperfusion injury has not been well studied; however, obesity is known to be associated with a proinflammatory environment and correlated with a lack of anti-inflammatory mediators that might counterbalance the ischemia-reperfusion injury–mediated immunological response (*30–32*).

Previous studies have shown an increased rate of acute rejections in obese kidney graft recipients (*26*). This may be related to the higher rate of DGF, and thus an initiation of the immune response toward the grafts, both was seen in our cohort.

More intriguing, this is the first study describing an association of donor BMI and DGF in renal transplantation, whereas data indicating a negative impact of deceased organ donor obesity on the outcome of pancreas transplantation (*33*) and liver transplantation (*34*) have been published previously. We found that in univariate (but not multivariate) analysis, donor BMI is a significant risk factor for the occurrence of DGF. The immune system in the overweight/obese donor may play a prominent role in the context of the generalized inflammatory response known to appear with brain death (*35*). A more systematic animal study is warranted to substantiate this hypothesis. Further, insufficient cooling of organs taken from overweight/obese donors may have an impact because the perirenal fat is not always removed adequately.

Findings regarding other risk factors represented in the donor risk indices (CIT, AT, donor and recipient age, previous kidney transplant, and serum urea) were in line with what has been previously published. As a consequence of our findings and suggestion to counteract the impact of high donor and recipient BMI on DGF, we propose to remove the fatty capsule of the kidney immediately after organ retrieval to enable adequate cooling, to allocate kidneys of obese donors locally, for example, similarly as with kidneys from aged kidney donors since years in the Eurotransplant Senior Program (*36*), an adequate exposition of the recipient's iliac vessels before anastomosis to keep AT short and to take into account that induction therapy and calcineurin inhibitors sparing might be beneficial. Other measures include more general strategies aiming to improve organ quality, such as anti-inflammatory conditioning of the donor, local measures to improve graft preservation (e.g., machine perfusion) (*37*), virtual crossmatch to reduce CIT (*38*), and antioxidative/-inflammatory measures in the recipient.

In summary, our study identifies recipient and donor BMI as important risk factors for DGF in deceased donor kidney transplantation. Although the ability to counteract this development is limited, certain measures could be taken into consideration to improve results in kidneys from overweight/obese donors and in obese/overweight recipients.

MATERIALS AND METHODS

Patients and Data Collection

This is a single-center retrospective analysis of 1132 consecutive deceased donor renal transplants done between January 1, 2000, and December 31, 2009. Patients with primary nonfunction or receiving kidneys from donors deceased after cardiac death were excluded from the analysis due to the low numbers. According to UNOS criteria, extended criteria donors were defined as donors older than 60 years or donors with an age between 50 and 60 years with two of the three following risk factors: hypertension, serum creatinine more than 1.5 mg/dL, cerebrovascular accident. Delayed graft function (DGF) was defined according to the UNOS data collection convention as the need for at least 1 dialysis within the first week after transplantation. Cases with dialysis requirement for a different indication, such as hyperkalemia, more than 5 mmol/L potassium, or volume overload, clinically diagnosed by occurrence of pulmonary edema, were excluded from the DGF group. The study was approved by the Institutional Review Board of the Medical University of Innsbruck (UN4358; 300/4.19; April 14, 2011).

Immunosuppression

Induction therapy and maintenance immunosuppression was analyzed and evaluated for their correlation with acute rejection and DGF. Health information and demographic data for recipients, donors, and the surgical procedure were collected in a digital database. Recipient factors included BMI, age, gender, duration of dialysis, type of dialysis, history of previous transplant, percentage of PRAs, pretransplant serum creatinine, pretransplant serum urea, and the cause of renal failure. Donor factors included BMI, age, gender, cause of brain death, serum creatinine, and serum urea. Transplant factors included HLA A/B mismatch, HLA DR mismatch, CITs, and ATs. AT was defined as the time from the start of anastomosis until reperfusion.

Criteria for presumed rejection were as follows: rise in serum creatinine more than 0.5 mg/dL, reduced graft blood flow determined by Doppler ultrasonography, and discomfort of the recipient.

Statistical Analysis

Statistical analysis was performed with SPSS version 17.0 software (SPSS Inc., Chicago, IL) and GraphPad Prism version 4.0 (GraphPad Software, La Jolla, CA). To test for univariate differences in categorical variables, the Pearson chi square test or Fisher's exact test (when appropriate) was applied. Continuous variables were tested with the Student *t* test or Mann-Whitney *U* test (if assumption of Gaussian distribution was not fulfilled). Multivariate logistic regression analysis was performed to determine the OR and 95% CIs for potential predictors of DGF. Thereby, the selection of variables was based on univariate comparisons (entry criteria $P<0.05$) and clinical relevance. Values if not otherwise indicated are mean±SD.

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