Evaluation of 84 elderly donors in renal transplantation


Abstract: Background: The use of elderly donors (ED) and dual kidney transplantation (DKT) procedures have become common in clinical practice. A correct evaluation of kidneys from ED is crucial to avoid unsuccessful transplantation or the use of DKT when a single transplant (ST) would be equally successful. The aim of this investigation was to assess the role of renal biopsy (RB) in the assessment of kidneys from ED.

Patients and methods: A total of 84 ED aged ≥ 60 yr were evaluated. In 19 cases, the kidneys were not used, mainly because of atherosclerotic vascular lesions. A histological score (HS) from 0 to 12 was awarded, considering the proportion of glomerulosclerosis, tubular atrophy, interstitial fibrosis, and arterial and arteriolar narrowing. On the basis of the HS, 37 donors were selected for 40 ST and 21 for DKT, three were discarded. All recipients received triple-drug therapy based on calcineurin inhibitors, mycophenolate mofetil and steroids.

Results: Primary non-function was observed in three of 40 ST and one of 21 DKT. Acute tubular necrosis occurred in 22/40 ST and in 11/21 DKT. Acute rejection occurred in 16/40 ST and four of 21 DKT. Renal function was satisfactory in both groups, with 1-yr S-Cr = 171 umol/L and 137 umol/L, respectively in the ST and DKT groups. One-year patient survival was 92% in ST and 100% in DKT; 1-yr graft function was 87% in ST and 95% in DKT.

Conclusion: The histological assessment of kidneys from ED enables a correct selection of kidneys for ST or DKT and prevents the transplantation of high-risk kidneys.

In recent years there has been a shift in age distribution toward a larger percentage of older donors in organ transplantation worldwide. UNOS data show that the percentage of donors over 50 has doubled in the last 10 years (1). In Italy, according to the National Transplant Organization, 25% of the kidneys transplanted between 2000 and 2001 were from cadaveric donors over 60 yr old, and the percentage was as high as 36% in our own programme at the University of Padua (2).

The two reasons for this trend are the decrease in fatal traumatic closed-head injuries as a consequence of laws making crash helmets, seatbelts and airbags mandatory, and – more important – the more flexible donor selection criteria adopted in order to increase the number of organs available.

Unfortunately, this situation has a negative impact on transplant results. In fact, several reports have shown that donor age significantly affects kidney graft survival (3, 4). The reduction in nephron mass and functional reserve of the elderly kidney makes it more susceptible to immunological assault, ischemic insult and drug toxicity.

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To increase the transplanted nephron mass in the case of older donors, the procedure of transplanting two kidneys into the same recipient, or dual kidney transplantation (DKT), has been adopted by several centers with satisfactory results (5–9). However, if DKT is performed without clear indications, it could lead to a reduction in the total number of transplanted patients, as two kidneys are used for one recipient. Selection is consequently crucial in the case of elderly donors, in order to ensure the optimal use of kidneys, which means maximizing the number of transplants without a negative fallout on outcome.

Donor evaluation is based on several parameters, including age, concomitant disease (e.g. hypertension), renal function and renal morphology, but clear guidelines on this matter have yet to be established (10, 11).

This study reports on our experience with a group of elderly donors, comparing the discarded kidneys with those transplanted both as single transplants (ST) and as DKT, examining the relationship between donor characteristics and recipient outcome, and emphasizing the importance of renal biopsy in donor evaluation.

Material and methods

Between January 2000 and September 2002 a total of 84 cadaveric donors aged ≥ 60 yr were observed at our Center.

Donor evaluation protocol

The following donor parameters were analyzed: age, sex, body weight, cause of death, concomitant disease, renal function (serum creatinine and creatinine clearance calculated according to the Cockroft formula), macroscopic evaluation and renal histology. Renal biopsy was performed in all kidneys after harvesting using a 16-gauge trucut needle. The specimens were processed as follows: formalin fixation, microwave paraffin embedding, 5µ thick sectioning, staining with hematoxylin and eosin, PAS, Masson’s trichrome, elastic Van Gieson. The whole procedure took 3 h.

Renal tissue alterations were quantified according to a scale previously described by Remuzzi (12). In short, a score from 0 to 12 was attributed, considering the percentage of glomerulosclerosis, tubular atrophy, interstitial fibrosis, arterial and arteriolar narrowing. Kidneys with a score between 0 and 3 were used for ST, those scoring between 4 and 6 were used for DKT, those scoring over 6 were discarded.

Recipient inclusion criteria

Patients were informed during the pre-transplant work-up about the current post-transplant outcome with ST and DKT from elderly donors.

Recipients were aged > 55 yr, donor ABO compatible, with PRA (Panel Reactive Antibody) < 50%. Surgical contraindications to DKT were large polycystic kidneys, previous transplants, previous major urological pelvic surgery.

Transplant procedure

ST were performed in the standard fashion with anastomosis of the renal vessels to the external iliac vessels and an extravescical uretero-neocystostomy. DKT were performed as two ST on each side with two separate extraperitoneal incisions.

Immunosuppressive therapy

Immunosuppression was based on a triple drug therapy with cyclosporine or tacrolimus, mycophenolate mofetil and steroids. Some patients also received induction therapy with antithymocyte globulin (ATG, Thymoglobuline® – Sangstat) 1–2 mg/kg for 3–5 d, or two 20 mg doses of basiliximab. Rejection treatment consisted in steroid pulses of 500 mg of methylprednisolone for 3 d; steroid-resistant rejections were treated with ATG.

Variables analyzed

Incidence of primary non-function, delayed graft function, acute rejection, surgical complications, serum creatinine at 1, 3, 6 and 12 months, patient and graft survival, causes of graft loss and death were the analyzed variables.

Statistical analysis

The results obtained from the quantitative variables were expressed as means ± SD and those of the qualitative variables as proportions. Student’s t-test and the chi-squared or Kruskal–Wallis test were used to test the differences between the quantitative and qualitative variables respectively. Graft and patient survival rates were calculated by Kaplan Meier analysis. Comparison between groups was performed with the log rank test.
Results

Donor utilization

Of the 84 donors ≥ 60 yr of age evaluated, 26 were not used for transplantation: 15 because of severe atherosclerotic lesions involving the renal arteries, four because of voluminous cysts and seven following the outcome of renal biopsy. At histological evaluation, three kidneys were discarded with scores > 6, two because of renal neoplastic nodules, one for pyelonephritis and one for diabetic nephropathy. The kidneys from the remaining 58 donors were used for 40 ST and 21 DKT performed at our institution, while 34 kidneys were transplanted as ST at other centers and were not considered in this study. Nine ST were performed despite the HS being > 3 because the kidneys were shipped from other centers and the results of renal biopsy became available only after the transplant.

Donor demographics

The characteristics of the donors are shown in Table 1. Donors are divided into three groups according to the usage of their kidneys, i.e. ST, DKT and discarded kidneys.

Age proved lower in the ST group than in the DKT group (Fig. 1). Vascular events were the main cause of death in all three groups; ST kidneys had a significantly lower incidence of diabetes than discarded kidneys. Creatinine clearance was lower in DKT than in ST, and was even lower in discarded kidneys, though the difference lacked statistical significance.

Renal histology

The average number of glomeruli per specimen was 18.

Table 1. Donor demographics

<table>
<thead>
<tr>
<th></th>
<th>Single transplant</th>
<th>Dual transplant</th>
<th>Not used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>40</td>
<td>21</td>
<td>26</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>65.7* †</td>
<td>72.7*</td>
<td>71.6†</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>21/19</td>
<td>10/11</td>
<td>12/4</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>73.4</td>
<td>68.9</td>
<td>70.9</td>
</tr>
<tr>
<td>Cause of death (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebro-vascular</td>
<td>75</td>
<td>76.2</td>
<td>64</td>
</tr>
<tr>
<td>Traumatic</td>
<td>22.5</td>
<td>23.8</td>
<td>32</td>
</tr>
<tr>
<td>Anoxia</td>
<td>2.5</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>History of hypertension (%)</td>
<td>58</td>
<td>76</td>
<td>53</td>
</tr>
<tr>
<td>History of diabetes (%)</td>
<td>6†</td>
<td>19</td>
<td>24‡</td>
</tr>
<tr>
<td>Serum creatinine (μmol/L)</td>
<td>92.8</td>
<td>86.6</td>
<td>101.6</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>79.7</td>
<td>65.9</td>
<td>59.9</td>
</tr>
</tbody>
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* p = 0.0001, † p = 0.0005, ‡ p = 0.05.

Figures 2 and 3 compare the renal biopsy assessments in the kidneys used for ST and DKT. Only 8% of ST kidneys had grade 2 glomerulosclerosis.

Fig. 1. Distribution of donor ages in ST and DKT.

Fig. 2. Donor renal biopsy evaluations in the kidneys used for ST and DKT.
(20–50% of sclerotic glomeruli) as opposed to 38% (plus 6% grade 3) for DKT kidneys. No significant differences were observed for tubular atrophy. Interstitial fibrosis was absent in 43% of ST kidneys and only in 6% of DKT organs. Arterial and arteriolar wall thickness grade 1 (less than the lumen) was recorded in 42% of ST kidneys and in 56% (plus 6% grade 2) in DKT kidneys.

Recipient demographics and immunosuppressive treatment

Recipient characteristics are shown in Table 2, divided according to type of transplant, ST or DKT. The two groups differ only in age, which was higher in the DKT group. Induction therapy with monoclonal or polyclonal antibodies was used in about 75% of both groups. All DKT patients were treated with cyclosporine A (CyA), mycophenolate mofetil (MMF) and steroids for maintenance immunosuppression, whereas 10 ST patients received tacrolimus (TAC), MMF and steroids, four CyA, rapamycin and steroids.

Transplantation outcome

The results of ST and DKT are given in Table 3. In the ST group, two patients died with non-functioning kidneys on post-operative days 11 and 37 as a result of vasculo-cerebral hemorrhage and aspergillosis, one died of sepsis 3 months after transplantation and one died of leukemia 15 months after transplantation. All patients in the DKT group are alive.

There were two graft losses in the ST group (one primary non-function and one acute rejection) and three in the DKT group (one primary non-function with kidneys from an 85-year-old donor, one acute rejection and one chronic allograft nephropathy).

Acute tubular necrosis occurred in 22/40 ST and in 11/21 DKT. One ST patient developed a post-operative hematoma; one DKT patient had ureteral necrosis. The incidence of acute rejection was higher in the ST group (16/40 ST vs. 4/21 DKT cases). Renal function was satisfactory in both groups, with 1-yr serum creatinine = 171 umol/L and 137 umol/L, respectively in the ST and DKT groups. The 1-yr patient survival was
Discussion

Elderly kidneys develop well-known morphological and functional alterations: the weight, volume and number of glomeruli decrease, arteries and arterioles develop intimal thickening, the glomerular filtration rate decreases by approximately 1 ml/min/year in people over 40 (13, 14). So, when more than a third of the kidneys used in a transplant programme are harvested from donors over 60, it is reasonable for this to raise concern as to the efficacy of such transplantations.

It has been convincingly demonstrated in experimental animal models that adequate nephron mass is a major determinant for kidney allograft outcome (15). Transplanting two kidneys undoubtedly doubles the transplanted nephron mass and thus compensates for the decrease in the function of elderly kidneys.

Indeed, the 95% 1-yr graft survival obtained with DKT in our study is remarkable, particularly if we consider that it was obtained in recipients with an average age of 62 and with kidneys from 72 yr-old donors. Moreover, DKT seems to offer results at least as good as those obtained with ST, as we found that despite DKT donors being older, having a higher incidence of hypertension and a lower Cr clearance, DKT recipients had a graft survival and renal function at discharge similar to ST recipients. Furthermore, two potential risks of DKT (i.e. a higher incidence of surgical complications because of the double surgical procedure and a higher incidence of acute rejections because of the greater antigen load) did not occur in our experience. These results are confirmed by several other reports (5–8, 12), showing that DKT is a safe procedure and produces optimal results with elderly kidneys, though the lack of a randomized clinical trial does not permit a final comparison to be drawn between single transplants and double kidney transplants.

The results of DKT are therefore no longer open to question, in our opinion, but donor selection for this procedure remains a crucial issue. Some authors only perform DKT on the basis of donor age (> 60) and renal function (Cr cl < 90) (6), others add histology to clinical and functional parameters (7, 12). The routine use of renal biopsy for donor evaluation demands a proper technique for adequate sampling, rapid processing (as the cold ischemia time must not be too long and frozen processing is not useful), the availability of a histotechnologist and pathologist round the clock, and an objective evaluation method.

Some studies (7, 16) have focused on the histological evaluation on the percentage of glomerulosclerosis, setting a cutoff for DKT between 10 and 50%. In other studies, different alterations, such as fibrosis or intimal thickening, have been correlated with graft function (10, 17). That is why we prefer a more extensive semiquantitative evaluation, as proposed by Remuzzi (12). In our experience, the two changes that discriminate best between kidneys suitable for DKT vs. ST are glomerulosclerosis grade 1 (20–50%), recorded in 38 and 8% of kidneys respectively, and the absence of fibrosis (6% vs 43%). The importance of the histological evaluation is confirmed by the fact that results were unsatisfactory in the group who received kidneys having a score > 3 in ST procedures, with only three of nine patients achieving good renal function.

In our experience, renal biopsy was also useful in identifying untransplantable kidneys. Among the 26 discarded donors, seven were rejected on the strength of the renal biopsy: three scored > 6 and four had incidentally-detected pathological alterations including neoplastic disease. We also considered the histological finding of diabetic nephropathy among our exclusion criteria, whereas donor diabetes was not per se a reason for exclusion.

A donor rejection rate of 30% might seem high, although other experiences with elderly donors have reported discard rates approaching 50% (17). In this study, the main reason for not using certain kidneys was the presence of atherosclerotic lesions involving the renal arteries. We believe that such lesions increase the risk of renal artery thrombosis, a complication that did not occur in our series. Identifying such potential donor organs prior to harvesting is currently impossible, but cost-effectiveness will have to be considered in the future.

In conclusion, DKT is a procedure that enables the use of elderly donors with remarkably good results, but well-established guidelines for donor selection are needed and we believe that renal
biopsy is a fundamental step in the donor evaluation process. It is important to increase the number of kidneys available for transplantation, but it is even more important to provide our patients with good functional transplants.

References