Gender imbalance among donors in living kidney transplantation: the Norwegian experience

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Abstract

Background. In living donor (LD) kidney transplantation, a predominance of female-to-male donations has been observed. Gender demographics of living donors and outcomes of LD kidney transplantations in Norway were assessed, as this has not been explored previously.

Methods. Data from the Norwegian Renal Registry of first LD kidney transplantations (n = 1319) in the period 1985–2002 were used.

Results. The majority of all LD was female (57.8%; P < 0.001), while 62.7% of the recipients were men (P < 0.001). Females dominated as donors in the spousal group and the parental group (P < 0.0001). However, no gender difference was observed in the parental group when the recipients were <30 years old (P = 0.65). In opposite-sex pairs, female-to-male donations were as expected based on the incidence of end-stage renal disease. Donor sex affected neither the incidence of acute rejections nor graft survival. Serum creatinine was higher in renal allografts from female donors to male recipients in the first 4 years after transplantation. Donor age also had significant impact on graft function measured as serum creatinine.

Conclusions. Gender disparities in LD transplantation result from a higher proportion of female-to-female and a lower proportion of male-to-male donations than expected. Both donor age and donor sex influence graft function during the first years. Graft survival and acute rejection episodes appear not to be affected by donor sex in LD kidney transplantation.

Keywords: gender; graft function; graft survival; kidney transplantation; living donor

Introduction

Since renal transplantation was established as a routine procedure in Norway in 1969, living donor (LD) kidney transplantation has constituted ~40% of all renal transplantations [1]. After the introduction of cyclosporin in 1984, living unrelated donors (LURD) and living related donors (LRD) mismatched for both human lymphocyte antigen (HLA) haplotypes were included in the programme. Graft survival after LURD transplantation in Norway is similar to that of LRD transplantation [2]. From 1983, one transplant centre has served the Norwegian population of 4.55 million. Furthermore, there is a national consensus regarding liberal indications for renal replacement therapy regardless of age and socio-economic factors. The National Health System covers the costs of dialysis and transplantation for all citizens.

Men are in the majority among kidney transplant recipients. Previous studies have shown a gender imbalance regarding kidney donation in LD transplantation as well [3–5]. In India, where LRD constitute the predominant source of renal allografts, ~55% of the donors were women but only 6% of the recipients were women [5]. It is may be more remarkable that a gender imbalance in the kidney transplantation population is observed in the US and Canada. Women were 10% less likely to receive a LRD kidney transplant than men and 28% more likely to donate a kidney in the US [4]. A predominance of female-to-male donation of kidneys among spouses has also been found [6,7] and even observed for all LRD transplantations based on data submitted to the Organ Procurement and Transplantation Network in the US [7]. To account for these gender differences, many explanations have been suggested, such as a gender difference in the incidence of end-stage renal disease (ESRD), greater incidence of cardiovascular disease among males, socio-economic reasons,
immunological dissimilarities and differences in health attitudes.

Superior kidney graft survival in recipients of male donor kidneys has been observed [7–9]. Furthermore, a greater incidence of acute rejection episodes during the first 3 months after transplantation has also been claimed in grafts from female donors [8,9].

Given this background, the aim of this study was to assess donor–recipient gender combinations in first kidney transplantsations with LD. Secondly, we investigated the impact of donor sex on the incidence of early acute rejection episodes, graft function and graft survival.

Subjects and methods

All renal transplantations in Norway take place at Rikshospitalet University Hospital. Data from renal transplant recipients and donors are transferred to the Norwegian Renal Registry, a national database. Gender and age of the recipients are recorded, as well as the relationship between donor and recipient. A total of 1419 LD kidney transplantations were performed in the period from 1985 to 2002. Only first transplantations were used in this analysis (n=1319). The incidence of acute rejection episodes during the first 3 months has been recorded since 1989. Data on acute rejection episodes, graft function and graft survival were collected from the same registry.

The study was approved by the regional ethical committee. Concession for data collection from the Norwegian Renal Registry was obtained from the Norwegian Data Inspectorate.

Donors

The consulting nephrologists convey information to potential donors and recipients about advantages and risks of LD transplantation, preferably before the need of renal replacement therapy is imminent. When blood group compatibility has been ensured and tissue typing undertaken, the nephrologists evaluate the suitability of the donor. Specific psychological testing is not done. Thereafter, potential donors undergo an extensive medical examination at the local hospital. Donors must be >18 years of age, but there is no upper age limit. The medical criteria are strict. Kidney function must be normal with creatinine clearance >80 ml/min and the urine specimen must be normal. Blood pressure should be in the normotensive range (<140/90 mmHg). X-ray of the chest as well as exercise echocardiogram in donors >40 years of age have to be normal. Body mass index >30 kg/m² and elevated fasting blood glucose are exclusion criteria. The final examination includes renal angiography with excretory urography. When all medical examinations are completed for donor and recipient, the results are presented to a team of nephrologists, transplantation surgeons and clinical immunologists at the transplant centre. Few potential donors are rejected at this stage.

After nephrectomy, the donors are given the option of free clinical examinations in their local hospital at 3, 6 and 12 months and then annually. Data on perioperative complications and clinical data of relevance for kidney function in donors at 1 and 5 years after the nephrectomy have been prospectively reported to the transplant centre since 1997.

Recipient follow-up

All transplantations included in the current analysis were performed after the introduction of cyclosporin in the standard immunosuppressive protocol. From 1984 to 1999 a triple therapy consisting of corticosteroids, cyclosporin and azathioprine was used. Induction therapy with basiliximab and maintenance with cyclosporin and corticosteroids was used in 2000. The standard immunosuppressive protocol from 2001 consisted of corticosteroids, cyclosporin and mycophenolate mofetil. The diagnosis of acute rejection episodes was based on an elevation of ≥20% of serum creatinine, excluding other causes. In later years, all rejections were biopsy-verified. During the first period after transplantation, nephrologists at the transplantation centre followed the patients. Control intervals were gradually increased and the patients transferred to their local hospitals after 3 months. After 6–12 months, transplantation controls were undertaken every third month, unless the clinical condition of the patients required more frequent controls.

Statistical analysis

The analyses were carried out with SPSS software, version 11.0. Results are given as means±SD for continuous variables or as a percentage when appropriate. Differences between groups are given as means and 95% confidence interval (CI). Descriptive and comparative statistics based on donor source and relationship, gender, age and donor-to-recipient gender pairing were done. Two-sided t-tests and analysis of variance (ANOVA) were used for comparison of continuous variables. Contingency tables and chi-square analysis were used to compare categorical variables. The 18-year time period for the present study was categorized in tertiles assessing spousal, LRD and LURD kidney donation and the number of male and female donations. Analyses by the Cox proportional hazard model, adjusting for the impact of HLA match, was used to assess the effect of donor sex on the incidence of early acute rejection episodes. Graft survival for the period 1989–2002 was estimated with Kaplan–Meier methods and survival curves compared with the Mantel–Haentzel log rank test. Patients who died with functioning grafts were counted as graft failures. Graft function was assessed by serum creatinine measurements 1–5 years after transplantation. Box plots were used to describe 1 year serum creatinine values according to quartiles of donor age. Statistical significance was identified by a two-sided P-value of <0.05.

Analyses comparing observed and expected proportions of gender combinations were performed, as described previously by Kayler et al. [7]. Expected recipient proportions were calculated based on the published incidence of ESRD for males and females for 1998–2002 (66.3% male and 33.7% female [http://www.nephro.no/registry.html (22.2.04)]). As the potential donor pool constitutes the entire Norwegian population between 20 and 80 years of age, expected proportions of donation were assumed to mirror this general
population (50.1% female, 49.9% men [http://www.ssb.no/emner/02/01/10/folkemengde/tab-2003-03-17-01.html]). Thus, expected proportions of the donor–recipient gender pairings among non-spousal pairs were 33% (0.499 x 0.663 x 100%) male to male, 33% (0.501 x 0.663 x 100%) female to male, 17% (0.499 x 0.337 x 100%) male to female and 17% (0.501 x 0.337 x 100%) female to female. When comparing only opposite-sex pairs (male to female and female to male), the published incidence for ESRD was used as the standard for expected recipients; thus, expecting 66.3% male recipients and 33.7% female recipients. Comparisons of actual and expected proportions of donation were performed by chi-square tests for 2 x 4 and 2 x 2 contingency tables.

Results

The total number of first LD transplantations has been stable in the study period (P = 0.4), although there has been an increase in LURD transplantations (P = 0.02; Figure 1). The study population consisted mainly of ethnic Norwegians and <1% of the donors were of non-Caucasian origin. Females constituted the majority of the donors (57.8%; P < 0.001) and men the majority of the recipients (62.7%, P < 0.001; Table 1). The numerical difference between male and female donors has remained constant in the study period (P = 0.5; Figure 2). Female donors were older than male donors (49.3±12.3 vs 46.4±12.9 years, P < 0.001; Table 1). Spousal recipients were the oldest, being on average 12.8 (95% CI: 10.3–15.2) years older than non-spousal recipients (53.4±10.9 vs 40.7±17.1 years, P < 0.001; Table 1).

The majority of donors were related [n = 1099 (83.3%)] and only 220 donors (16.7%) were unrelated to the recipient, i.e. 15.1% spouses and 1.6% unrelated non-spousal donors.

Living related donors

Female gender dominated among the LRD, while males were more often recipients (Table 1); the relationships to the recipients are given in Table 2. Mothers were more often donors than fathers (P < 0.0001). However, a difference in gender was only apparent when recipients were >30 years old, with mothers more frequently being donors (P < 0.001; Figure 3). Parental female donors were slightly older than fathers (54.0±11.8 vs 51.5±11.8 years; P = 0.035). More sons than daughters (241 vs 169; P = 0.001) were recipients, but mothers and fathers donated to sons and daughters with the same frequency (P = 0.80).

Siblings constituted the largest group of LRD. Sisters were more frequent donors than brothers, but the difference was not statistically significant (272 vs 234, P = 0.09; Table 2). Female siblings were older

| Table 1. Distribution of gender and age of donors and recipients in 1319 first living kidney transplantations in Norway, 1985–2002 |
|-----------------|-------|----------------|-------|
| All             |       |                 |       |
| Recipient       |       |                 |       |
| Male            | 827   | 62.7%           | 43.3±16.9 |
| Female          | 492   | 37.3%           | 41.5±17.0 | 0.07 |
| Donor           |       |                 |       |
| Male            | 556   | 42.2%           | 46.4±12.9 |
| Female          | 763   | 57.8%           | 49.3±12.3 | <0.001 |
| Living related  |       |                 |       |
| Recipient       |       |                 |       |
| Male            | 683   | 62.1%           | 41.0±17.0 |
| Female          | 416   | 37.9%           | 40.2±17.4 | 0.46 |
| Donor           |       |                 |       |
| Male            | 478   | 43.5%           | 45.8±12.8 |
| Female          | 621   | 56.5%           | 48.8±12.8 | <0.001 |
| Spousal pairs   |       |                 |       |
| Recipient       |       |                 |       |
| Male            | 131   | 65.8%           | 55.5±9.8 |
| Female          | 68    | 34.2%           | 49.5±12.0 | <0.001 |
| Donor           |       |                 |       |
| Male            | 68    | 34.2%           | 50.9±12.1 |
| Female          | 131   | 65.8%           | 52.0±9.9  | 0.49 |

*aP-value for difference in gender.  
bP-value for difference in age.
than male siblings (47.1±11.9 vs 44.8±12.4 years; P = 0.03). More males than females received a kidney transplant (339 vs 167; P<0.0001), but siblings donated to siblings regardless of gender (P = 0.42).

The proportion of child-to-parent kidney donation was 10.6% of all LD transplantations. Considering all recipients >40 years of age, 18.8% of the donations were from child to parent. There were no gender differences when children donated to parents (Table 2) and sons and daughters donated to fathers and mothers with similar frequency (P = 0.78).

In the subgroup that constituted second-degree relatives, the majority of the donors was female (28 female vs 15 males; P = 0.05).

Living unrelated donors

The LURD group was dominated by spousal pairs [n = 199 (90.5%)], while 21 (9.5%) pairs were friends or family members by law. Of the spousal donors the majority (65.8%) were females (Table 1). In the non-spousal donor group no gender difference was observed (11 females vs 10 males; P = NS). Spousal transplantations have increased slightly during the 18-year period of our study (P = 0.04). Male and female donors were of the same age at donation, while male recipients were 6.0 (95% CI: 2.8–9.1) years older than female recipients (P<0.0001; Table 1).

Gender pairing and opposite-sex pairs

Females received a kidney from male and female donors with the same frequency (248 vs 244; P = 0.86). Overall, male recipients had predominantly female donors (515 females vs 312 males; P<0.0001). The majority of donors >45 years of age were females (486 vs 278; P<0.0001) and donated predominantly to men (P<0.0001; Table 3).

In the LRD group, women were as likely to donate to male and female recipients and there were similar findings among male donors (P = 0.26; Table 4).

When assessing donor–recipient gender pairing, one would expect that the donor pool should mirror the general population and the expected sex distribution of recipients would be similar to that of patients with ESRD in the population. Thus, one would expect 33% female-to-male, 33% male-to-male, 17% female-to-female and 17% male-to-female donations. Given these premises, a difference between the observed and expected proportions appeared, with a lower than expected male-to-male donation rate and a higher than expected female-to-female donation rate (P<0.0001; Table 5). An additional analysis was done
in which same-sex pairs were excluded from the LRD group to allow comparison with the spousal transplant pairs. The gender distribution of recipients was expected to be equal to the incidence of ESRD in men and women in the population. In this analysis the male-to-female and female-to-male donations were as expected in both groups (Table 6).

**Table 6.** Comparison of opposite-sex pairs (female to male, male to female) among living related and spousal transplants

<table>
<thead>
<tr>
<th></th>
<th>Living related (n = 1099)</th>
<th>Expected proportions*</th>
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<tbody>
<tr>
<td>Female to male</td>
<td>377 (34.3%)</td>
<td>363 (33%)</td>
</tr>
<tr>
<td>Male to female</td>
<td>306 (27.8%)</td>
<td>363 (33%)</td>
</tr>
<tr>
<td>Female to female</td>
<td>244 (22.2%)</td>
<td>187 (17%)</td>
</tr>
<tr>
<td>Male to female</td>
<td>172 (15.7%)</td>
<td>187 (17%)</td>
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</tbody>
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Observed vs expected
Chi-square (df = 3) = 28.02
P < 0.0001

*Expected proportion of donation is based on the incidence rates for ESRD by gender in Norway [http://www.nephro.no/registry.html (22.2.04)] and donor gender ratio corresponding to the general population of 20–80 years of age in Norway in 2002 [http://www.ssb.no/emner/02/01/10/folkemengde/tab-2003-03-17-01.html].

Graft survival and function

Overall, survival of grafts from female and male donors was similar (Figure 4). As serum creatinine 1 year after the kidney transplantation was higher in male than female recipients (146.5 vs 119.2 μmol/l; P < 0.0001), a separate analysis was performed to look at the impact of donor gender. As shown in Table 7, the proportion of patients who had serum creatinine concentrations <130 μmol/l was significantly lower in male recipients with grafts from female donors compared with the other groups. After 5 years this difference was lost (Table 7). Donor sex had no predictive impact on acute rejection episodes during the first 3 months (P = 0.81).

**Discussion**

Women compose the majority of LD and men the majority of kidney transplant recipients in our study. We also report novel and unexplored gender differences in subgroups of the donor population, namely, that fathers were as likely as mothers to donate to children <30 years of age. This is in contrast to the claim that females dominate as donors among parents to young recipients [4].

Sibling donors constitute the largest subgroup in this material. Although numerically there were more sisters than brothers among the donors, the difference was not statistically significant. One could argue that as males are more likely to be recipients, females are more likely to be potential donors. However, for the
recipient, the probability of his/her sibling being male or female is 50%.

Sons and daughters donated to parents with the same frequency whether the recipient was female or male, but the group was small. In a recent American study exploring child-to-parent kidney donation, no gender difference was found [10]. Only recipients >40 years of age were included in that study and child-to-parent kidney donation constituted 44% of all living transplantations, a number that exceeds by far what we observed.

In contrast to a Canadian study [6], in which 90% of the spousal transplantations were from wife to husband, we observed that females constituted approximately two-thirds of the spousal donors. The female donor frequency mirrors the incidence of ESRD in Norway for >30 years. Female donors are older than male donors in our study and this could be a reflection of men being less suitable in older age because of cardiovascular morbidity. Scandinavian men have a higher age-adjusted coronary mortality and morbidity than women [17,18]. Although the gender difference in the risk of developing coronary artery disease has been attenuated in recent years, the risk was still twice that in men up to 75 years of age in a Swedish study [17]. In a Finnish report in 2004, the risk of developing coronary heart disease among middle-aged men was three times higher and the mortality five times higher than in age-matched women [18].

The system for reimbursement of lost income for donors is not optimal and 21% of the Norwegian donors experienced an economic loss [1]. This could affect the proportion of male donation as males are still the main breadwinners in many Norwegian families.

Graft survival was similar for kidneys from female and male donors in our study. On the other hand, we observed that male recipients of female grafts had higher serum creatinine compared with other recipients, the probability of his/her sibling being male or female is 50%.

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Graft survival was similar for kidneys from female and male donors in our study. On the other hand, we observed that male recipients of female grafts had higher serum creatinine compared with other
recipients. Nepron underdosing is a possible explanation for the poor outcome of renal grafts from female donors [8,9]. Our findings are not incompatible with that hypothesis. An increased risk of graft failure of kidneys from younger female donors has been reported, suggesting that the hormonal status in the donor could be of importance for graft survival [8]. The male recipients in our study received their grafts predominantly from female donors older than 45 years. This could provide, in part, an explanation as to why we do not find a difference in graft survival according to donor sex.

It has been claimed that male recipients of grafts from female donors have a higher incidence of acute rejection episodes [8,9] and reduced survival [7]. Our observations do not concur with these findings, as the incidence of acute rejection episodes was similar regardless of donor sex. This could also offer yet another explanation why graft survival was the same for kidneys from both genders, as it has been reported that long-term graft outcome correlates with early acute rejection episodes [9]. There is one major difference in the study populations, which also could, in part, explain the inconsistency regarding reported graft survival. Our study deals with first LD transplantations, whereas the other studies include only cadaveric donor source [9], mixed living and cadaveric donors [8] or deal with retransplantations as well [7].

Not surprisingly, we observed that the donor age affected graft function, with persistent lower serum creatinine in recipients of grafts from younger donors. On the other hand, although graft function from female donors to male recipients was lower than when males donated, this difference was lost after 5 years.

Our study features certain strengths, being population-based and from a national centre with a constant LD transplantation rate over two decades. On the other hand, there are limitations when using registry data because of the retrospective approach. Registry data may be useful for identifying trends and generating hypothesis, but they are limited by an inability to determine the reasons behind those trends.

In summary, our study has shown that more women than men are kidney donors. There are, however, important exceptions, namely fathers being as likely as mothers to be donors for younger children. There is no gender difference when siblings are donors or when children donate to parents. Furthermore, in opposite-sex pairs the observed rate is similar to what could be expected based on the gender composition in the incidence of ESRD. There was no difference in graft survival or in the rate of acute rejection episodes related to donor gender. The donor age influenced unequivocally the level of serum creatinine. Graft function measured as serum creatinine in male recipients was favoured by kidneys from male donors compared with allografts from females, while such differences could not be observed in female recipients.

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