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Living Kidney Donor Evaluation and Rejection: A Danish Single-Centre Experience

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Abstract

Background: The purpose of this study was to evaluate our3-day living kidney donor work-up. To identify the potential kidney donors that either accepted for donation, or rejected in a 5-year period.

Methods: Retrospective study, all potential living kidney donors who attended our 3-day donor work-up programme in the department of Nephrology at Odense University Hospital in Denmark from 2005 to 2009 were included. A potential kidney donor was referred by the transplant nephrologist to the work-up if the candidate had normal screening tests, a life history without significant disease, a genuine interest in becoming a kidney donor and the donor/recipient couple had an acceptable immunological assessment.

Results: 153 potential living kidney donors completed the 3-day work-up. Thirty-four potential donors (22.2%) were declined. Nine of the 34 donor candidates (26.4%) had to low renal function based on measured glomerular filtration rate, and eight (23.5%) had an abnormal Oral Glucose Tolerance Test (OGTT). Nine (26.4%) were rejected by the transplant surgeons due to kidney anatomy.114 out of 119 approved candidates donated a kidney (74.5% of evaluated candidates).

Conclusions: It was possible to approve 77.8% as suitable donor candidates and 95.8% of them donated a kidney.

Keywords: Donor evaluation; Kidney transplantation; Living kidney donor; Donor assessment

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Introduction

Renal transplantation is the best treatment for selected patients with end-stage renal disease as it provides a better quality of life and survival advantages compared to patients on dialysis [1]. Living Kidney Donors (LKD) play a critical role in renal transplantation as the demand for organs exceeds the number of available deceased donors. Living kidney donation allows pre-emptive transplantation and provides better long-term patient and graft survival when compared with deceased-donor transplantations [2]. Consequently, the number of LKD is increasing in many countries. 27% of kidney transplants came from living donors in Scandinavia in 2016, while living kidney donation amounted to 41% of the total kidney transplant activity in Denmark in 2016, compared to 32% in 2006 [3]. An increase in living kidney donation must be balanced against the safety of the donors. Per-operative donor mortality has been reported to be in the range of 0-0.03% and major and minor per-operative complications to occur in 0.2 and 8% of donors, respectively [4,5,6]. Two recent matched cohort studies from the US and Norway published in 2014 have raised some concerns related to the long-term safety of kidney living donation [7,8]. Thus it is important trying to identify donors at risk of developing 'de novo' kidney diseases during life post-donation [9]. Lifetime risk may be difficult to assess in young donors, especially in those having first-degree relatives with End Stage Renal Disease (ESRD). Younger potential donors may have longer cumulative lifetime risk all diseases including those predisposing to ESRD [10]. Optimal risk-benefit assessment and proper information to the prospective donor is import as well as recommendations on health-promoting behaviour post-donation [9]. In Denmark, we have no national guidelines for donor evaluation to ensure donor safety, but compel with international guidelines [11]. AUS survey of LKD evaluation in 2007 and a French study in 2001 showed significant variability in practice for LKD assessment [12,13]. The United Kingdom (UK) is one of the few countries to have established donor evaluation guidelines and a recent study demonstrated considerable variability in accepting living kidney donors, particularly regarding age, BMI, and hypertension, and it remain sun clear

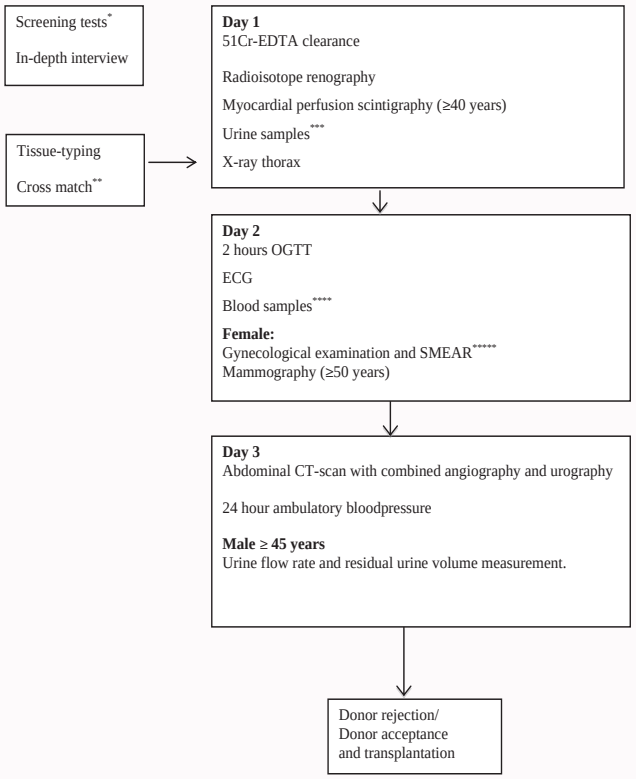

Figure 1:
*__Screening tests:__ Blood type, Blood pressure, urine dipstick, blood glucose, creatinine, hemoglobin, electrolytes and BMI.These tests/measurements were performed by the family doctor.
** __Cross match:__ Standard CDC can be expand with luminex and flow cytometric cross match.
***__Urine samples:__ albumin, creatinine, albumin/creatinine ratio, erythrocytes, culture, 24-hours urine sampling.
**** __Blood samples:__ lipid profile, Cytomegalovirus, Epstein-Barr virus, hepatitis serology B +C, HIV, metabolic panel.
***** __SMEAR__: cytopathological test of the cervix.

why nephrologists do not adhere to established guidelines [14].

At our transplant centre, we have established a 3-day evaluation programme. The aim of this retrospective study is to evaluate our donor work-up in a 5-year study period with emphasis on the reasons why potential donors did not proceed to kidney donation.

Material and Methods

Retrospective single centre study of all potential living kidney donors who underwent a donor work-up in the department of Nephrology at Odense University Hospital in DK over a 5-year period from 2005 to 2009. Permission from the regional data Protection Agency was given. Included in this study was 153 potential donors, almost exclusively Caucasians. The medical files were evaluated and demographic, clinical and laboratory data were collected. The donor workup was conducted according to the flow chart in (Figure 1). The potential donors were invited to stay at the hospital hotel during the work-up. The Danish healthcare system and the social system covered all costs related to the donor work-up, the hospitalization related to the kidney donation and subsequent sick leave. There was no provision for live kidney donation in DK.

The recipient and potential donor(s) were invited to an interview, where a transplant nephrologist carefully provided information on living kidney donation, including benefits and risks for both the recipient and the donor. Following each interview, the patient and potential donor(s) were encouraged to reconsider their thoughts about kidney donation and if still interested the potential donor should visit their general practitioner, who should check, plasma creatinine, urinary albumin/creatinine ratio, blood pressure, blood type, body mass index and return the results to us with information about medication and previously health problems. Our transplant centre do not contact a potential donor after the first consultation, we want the potential donor to demonstrate, that they really are interested in potential donation by taking the next step. Use of a psychological or psychiatric donor assessment may take place in a few selected cases. The transplant candidate was not signed upon the kidney waiting list from a deceased donor, as long as they have a potential live donor.

Our absolute contraindications to donation in the study period included known kidney disease, uncontrolled hypertension (>140/90) on 1-2 antihypertensive agent, major cardio-respiratory disease, abnormal 2-hour Oral Glucose Tolerance Test (OGTT) or diabetes mellitus, prior history of kidney stones, HIV infection, active hepatitis B or C infection, malignancy, a bleeding disorder, a not well controlled psychiatric disease, ongoing abuse of alcohol or drugs, younger women with a fertility desire, a BMI >30-35kg/m^2 or age<21 years old [11]. An upper age limit for donation is not specified in our department as findings may suggest that older age alone should not preclude donation.

If a potential donor with a genuine interest in donating a kidney had normal blood screening tests the candidate was then immunologically examined by Human Leukocyte Antigen (HLA) tissue typing with assessment of Donor-Specific Antibodies (DSA), Complement-Dependent Cytotoxic (CDC) cross-match and flow cytometric cross match when needed. AB0 incompatibilities between donor and recipient have been done since 2007 in our department, as well as desensitization procedures have been used in selected patients. In cases where the intended recipient had several donors, the best immunologically compatible candidate was selected. We never worked-up two or more donor candidates in the same time.

The examinations in the donor work-up programme included the measurement of Glomerular Filtration Rate (GFR) by 51-Chrome -EDTA clearance normalized for surface area. International guidelines have advised that acceptable donors should have GFR either above 80 mL/min or within two standard deviations of the normal GFR range for their age and gender [11,15]. Other investigations in the work-up include dremography using the radionuclide Tc-99m-MAG3 (Technetium-Mercapto Acetyl tri Glycine) and Computed Tomography (CT) with combined angiography and urography to assess detailed information on vascular, renal and extra renal anatomy. Myocardial perfusion scintigraphy using the radiotracer Tc-99m-Tetrofosmin under dipyridamol and exercise stress test was used to examine for coronary artery disease. If needed, 24-h blood pressure test was conducted. The OGTT was evaluated according to the WHO definitions of diabetes [16]. Gynaecological examination and cervical screening test was done in all women and flow and residual measurement in all men over forty-five years old. If the transplant surgeons and nephrologists approved the donor work-up results, the donor candidate entered the final stage of the assessment with a new CDC cross-match within one week prior to the scheduled transplantation.

Table 1a: Demographic data as mean ± Standard Deviation (SD).

Demographics of the prospective donors	(%)	
Number	153	
Gender [m/f]	[64/89]	(42/58)
(number)		
Age (years)	49.7±11.2	
BMI (kg/m^2)	26.5 ± 3.9	
Smoking (number)	71	-46
Systolicblood pressure (mmHg)	133 ± 18	
Diastolic blood pressure (mmHg)	80 ± 11	
In treatment with blood pressure medication (number)	12	-8

Table 1b: Data of the relationship of potential donor with the recipient.

Relationship of potential donor to recipient	Number	(%)
Parent	49	-32
Sibling	31	-20
Grandparent	6	-4
Another genetically related family member	7	-5
Spouse	38	-25
Another non-genetically related family member	15	-10
Friend or acquaintance	7	-4

Statistical Test

Data was evaluated by using Student's t-test. Results were considered of statistical significance when P<0.05. Data are given as mean ± Standard Deviation (SD).

Results

The demographics of the 153 prospective donors of this study are presented in (Table 1A and B). There was a predominance of female volunteers (59%). The candidates ranged in age from 23 years to 75 years and had a BMI between 18kg/m^2 and 40kg/m^2 at the time of investigation. Almost half were smokers. Twelve (8%) used antihypertensive medication, a maximum of two drugs. Ninety-three (61%) were genetically related to the recipient, and most often it was a parent (32%) or a sibling (20%). No off-spring was among the potential candidates. Among non-genetically related prospective donors, it was typical a spouse (25%) who was assessed. Only 4% were friends or acquaintances to the potential recipient.

153 completed our 3-day donor assessment program and 119 (77.8%) were accepted for kidney donation. 114 of the 119 approved candidates (95.8%) donated a kidney to a recipient. Donation rate was 74.5%. Two approved donors withdraw their consent regarding donation and two others did not donate because the recipient died before planned transplantation. One did not donate because transplantation was cancelled during surgery, as the donor kidney was severely arteriosclerotic.

Thirty-four potential donors (22.2%) were rejected due to investigations. None of the rejected volunteers asked for a second opinion in another transplant centre. Sixty-two% of the potential donors was not approved because of a single cause. The others were not suitable because of two or more causes. In this study, we report only the main reasons for rejecting donors, see (Table 2B).

A medical contraindication was the reason why 24 out of 34 (70.6%) potential donors were rejected by the donor work-up. Suboptimal renal function based on GFR was the most frequent medical cause to reject a donor candidate (N=9). The second most common reason for disqualifying a potential donor was an abnormal OGTT (N=8), and more than half of these candidates had a BMI over 30. Two were excluded due to uncontrolled hypertension treated by two drugs and both had a BMI close to 35. One was rejected due to malignant melanoma within the last 5 years (not mentioned at the initial interview). Nine of 34 donors (26.5%) were rejected by the transplant surgeons. Two candidates were rejected because of infravesical obstruction and seven were excluded by an abnormal abdominal CT scan with combined angiography and urography. One candidate was rejected for unknown reason.

Table 2a: Comparison of demographic data of accepted and rejected donor candidates.

	Accepted as donor	Rejected as donor	Level of significance
Gender [m/f] (number)	53/66	23-Nov	-
Age (years)	49.6 ±11.2	49.2±10.8	0.42
BMI(kg/m^2)	26.3±3.5	27.2±5.2	0.14
Smoking (number)	54	17	-
In treatment with blood pressure medication (number/average per person)	0.07	0.28	0.01

Table 2b: Causes for rejection of potential donors.

Medical cause for rejection of donor	Number	(%)	Surgical cause for rejection of donor	Number	(%)
Low measured GFR	9	(26.5)	Double ureters to one kidney	2	(5.9)
Abnormal OGTTand/or BMI > 35	8	(23.5)		1	(2.9)
Lateralization of renal function measured by renography	1	(2.9)	An aneurysm of a renal artery in one kidney	1	(2.9)
Uncontrolled hypertension treated by 2 drugs	2	(5.9)	A renal arteriovenous malformation in one kidney	1	(2.9)
Malignantmelanoma	1	(2.9)	A fibromuscular dysplasia in a renal artery in one kidney	1	(2.9)
NSAID abuse	1	(2.9)	Fourrenal arteries bilateral	1	(2.9)
Psychosocial problems	1	(2.9)		1	(2.9)
Positive crossmatch measured just before transplantation	1	(2.9)	Nephrolithiasis	1	(2.9)
Unknowncause	1	(5.9)	Infravesical obstruction	2	(5.9)

Discussion

This review of our 3-day donor assessment programme showed that our multidisciplinary donor work-up only rejected 22% of the prospective donors. Almost 78% of 152 potential donors were accepted for kidney donation and nearly 96% of the accepted candidates donated a kidney. We believe that the high donor yield was likely to be a result of the active role of our transplant nephrologists in an early stage evaluation of the potential donor found by the patient. Studies have shown that early support in the donor assessment process may lead to increased commitment and reduced risk of early drop out [17]. In centres where physicians had an active role in finding a live kidney donor, higher levels of positive attitudes toward live donation were observed. The transplant nephrologists in our department have been involved in providing information about transplantation and recruitment of both donors and recipients. Such a situation demands ethical responsibility as the health care professionals have a great responsibility to understand how potential kidney donors experience the situation and how mixed their feelings may be [18]. It is difficult to compare the share of potential donors in various studies that ultimately continued to donate, due to variability in the overall assessment process and in the manner in which it is reported. Saunders et al. [19]. reported that the donor yield was low from their donor work-up as 87% of potential donors failed to proceed to organ donation. In a study from another Danish transplant department, Larsen et al. found that 48% of 133 prospective donors were unsuited for donation and about 28% of these dropped out already after receiving general information regarding kidney donation or after a positive cross-match [20]. In our study, we did not have data on the dropout rate at the initial stage of assessment, after providing general information on kidney donation or after the first immunological assessment, as we only registered the candidates who subsequently underwent the 3-day donor-work-up. Recently, Connaughton et al. [17]. Reported on Irish living kidney donor programme and found that 18.4% of donors ultimately proceeded to live kidney donation. The donor dropout rate at the initial stage of assessment was 64.2%, after a telephone conversation about donation or after an immunological assessment, where AB0 incompatibility was not allowed. The remaining donor candidates in the Irish study were subsequently assessed by a multidisciplinary team, and about 35% were rejected, which was a higher proportion of rejected candidates than in our multidisciplinary donor work-up. Calder et al. [21]. Demonstrated an 18% live donation rate and McCurdie et al. [22] Found that 17% of their donors assessed were ultimately used, and in both studies it was stated that a considerable time and effort was required to conduct the donor investigations.

Connaughton et al. [17]. Found that surgical contraindications accounted for 13% of donors declined, with the majority having complex vasculature making them unsuitable candidates. We found that 26.5% of the rejected volunteers were turned down by the transplant surgeons while Larsen et al. [20]. Found that abdominal CT-scan with angiography and urography ruled out 34% of the rejected candidates. We found that suboptimal renal function based on GFR was the most common medical reason for rejection as predicted GFR should remain satisfactory after donation within the expected lifetime of the donor.

Diabetes mellitus is a contraindication to donation while impaired glucose tolerance is not an absolute contraindication to donation according to ERBP [24]. However, abnormal OGTT increases the risk of future development of diabetes and thus nephropathy [25]. We found that an abnormal OGTT was the second most frequent medical reason for rejecting a potential donor. Almost 24% of our rejected donors had an abnormal OGTT, and these candidates had an average BMI of 31.5 kg/m^2 compared with 26.5 kg/m^2 for all prospective donors. Amsterdam Forum guidelines dictate that individuals should be excluded from donating a kidney if they have2-h OGTT glucose>11.1 mmol/L while the majority of US transplant centres excluded potential donors with 2-h OGTT glucose>7.8 mmol/L [12]. BMI above 35 kg/m^2 is an absolute contraindication to donation in international guidelines, while moderately obese volunteers (BMI 30-35 kg/m^2) should be counselled carefully about the increased risk of perioperative complications and about the long-term risk of kidney disease [23,24,26]. Long-term outcomes in moderately obese donors are not well described, but the negative impact of obesity on renal outcomes in the general population has been studied [25]. In addition, obesity has been shown to worsen outcomes after unilateral native nephrectomy in obese non-donors as ten years post-nephrectomy data described a probability of noproteinuria and normal renal function as only 40% and 70%, respectively [27]. Overt proteinuria is a contra-indication for living donation while persistent micro-albuminuria is considered a high risk for donation [24]. None of the potential donors in our work-up had proteinuria since urinalysis for protein is included in the routine screening, but a few had micro-albuminuria and other disqualifying morbidity at the same time. Hypertensive donor candidates with evidence of target organ damage should be rejected while well-controlled hypertension (<130/85 mmHg) under treatment with maximum two anti-hypertensive drugs is not considered a contraindication to donation [24]. Eight percent of our potential donors were in treatment with antihypertensive medication and 5.9% of the rejected donors were excluded due to uncontrolled hypertension despite treatment. Hypertension is a common reason for declaring a potential donor medically unsuitable and the concerns are that hypertension presents a risk for per-operative morbidity and mortality and pre-existing hypertension in the donor may be worsened by unilateral nephrectomy and associated with an increase in long-term cardiovascular risk [23]. There is, however, a paucity of evidence on what level of blood pressure control is acceptable in a live donor and it is difficult to draw definite conclusions whether mild hypertension controlled non-pharmacologically or with1 or 2 antihypertensive agents presents an increased risk for renal function post-donation.

We advised smoking cessation prior to donation and treatment of hyperlipidaemia consistent with recommendations from the Amsterdam Forum, but smoking or hyperlipidaemia itself was not a contraindication to kidney donation in this study [11]. Almost 46% of our potential candidates were smoking before donor assessment.

Potential donors can be pushed for donation by the recipient or family, and if such ambivalence is detected, medical or surgical unsuitability may be used as the reason for rejecting a donor. In our study, one candidate was rejected without a contraindication clearly stated. Some dropouts from a live donor program may be due to recipient issues, of which some recipients receive a transplant from the deceased donor pool despite having a suitable donor and some recipients are not cleared for transplantation. We found that three approved donors did not donate due to the recipient. A Swedish study has shown that the strongest motives to become a donor were a wish to help the recipient, self-benefit from the recipient's improved health and identification with the recipient [28].

This retrospective study has limitations as the results are influenced by practices inherent to the study design and our transplant centre and it may affect its external validity. In addition, a direct comparison to other studies about donor evaluation is difficult. As decisions to accept or reject a given donor rely on a combination of scientific decision-making and individual provider judgment. However, despite these limitations we think that this study is important because it reflects our real experience evaluating potential donors. By making the donation process more transparent, we hope that this can be a resource for other departments doing donor assessments.

In conclusion, we benefited greatly from our 3-day work-up programme, as the kidney donation rate was high. We recommend that the nephrologist meets and talks with the potential donor candidate at an early stage of the investigation process.

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