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The Medically Complex Living Kidney Donor: Glucose Metabolism as Principal Cause of Donor Declination

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Background: Transplant centers are increasingly confronted with medically complex living kidney donor candidates. Considerable differences exist among centers regarding handling of these patients and little data is available on characteristics, evaluation outcome and declination criteria. We now demonstrate impaired glucose metabolism to be the largest single cause of donor declination.

Material/Methods: Follow-up of 133 donor-recipient pairs, presenting to our transplant center between 03/2007 and 06/2012 was included in the analysis. Evaluation outcome of donor-recipient pairs was assessed and declinations stratified into donor or recipient reasons and underlying conditions.

Results: 65 donor-recipient pairs (49%) were accepted for transplantation, 68 (51%) were declined upon first evaluation. 77% of declinations were for donor- and 23% for recipient reasons. Almost half of donor declinations resulted from increased cardiovascular risk with the presence of diabetes mellitus or prediabetes as the largest single cause of declination.

Conclusions: Glucose metabolism is key in donor risk assessment and precludes kidney donation if abnormal. The high prevalence emphasizes the need for prevention. Prediabetes defines a cohort at risk and response to lifestyle intervention allows for individual risk stratification, thereby potentially increasing the number of persons eligible for kidney donation. Unification of evaluation criteria, as well as prospective long-term follow-up is required to account for increasingly complex living kidney donors.

MeSH Keywords: Diabetes Mellitus • Donor Selection • Glucose Metabolism Disorders • Kidney Transplantation • Living Donors • Prediabetic State

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Background

The active waiting list for kidney transplantation comprises more than 96,000 patients in the United States and 11,000 patients in the Eurotransplant area. Around 11,400 and 3,300 deceased donor kidney transplants were performed in the respective areas in 2013 (US) and 2014 (Europe) [1,2]. This results in substantial waiting time and mortality on the waiting list.

As a consequence of organ shortage, living donor kidney transplantation is an increasingly important option [1,2]. Graft survival is superior to deceased donor kidney transplantation and early or even preemptive transplantation further improves patient prognosis [3–5].

Much controversy regarding donor safety has arisen over the past year. Overall mortality and lifetime risk of end-stage renal disease (ESRD) for the healthy donor is comparable to the general population [6–9], however, for adequate risk evaluation, comparison to healthy non-donors is essential. Two recently published studies show a slightly increased risk of ESRD for kidney donors, as compared to healthy non-donors [10,11]. Also, an increased long-term risk of diabetes mellitus has recently been reported in living kidney donors, as compared to matched healthy controls [12]. Albeit these studies having some limitations, they underline the need for careful and critical donor selection prior to living donation.

The task of donor selection is complicated by an increasing number of medically complex living kidney donors presenting to transplant centers, reflecting demographic and socio-economic changes. The term "complex living donor" was originally coined by Reese and coworkers [13] for donors with potential risk factors concerning kidney donation. However, there is insufficient consensus of what constitutes a relevant risk factor and a paucity of data on decision criteria, evaluation outcome and long-term follow up of complex living donors. The 2004 Amsterdam Forum [14] provided a first framework, yet considerable differences exist among current international and national guidelines as well as individual transplant center practice [15–19].

In view of this, we assess the outcome of donor-recipient pair evaluation for living kidney donation of a large university hospital transplant program. We for the first time demonstrate donor metabolic disorders as the principal cause of declination, discuss its impact on donor safety, and provide an approach for individual risk stratification.

Material and Methods

In the present analysis, outcome of donor-recipient evaluation for living donor kidney transplantation was investigated. As a retrospective chart analysis, the institutional review board waived the need for approval and written informed consent of investigated patients. All consecutive potential donor-recipient pairs presenting to the Tübingen Collaborative Transplant Center between 03/2007 and 06/2012 were included. Donor and recipient evaluations had been performed according to center protocol assessing individual immunologic, medical and psychosocial status. Protocols remained unchanged throughout the period of observation.

Table 1. Tübingen multistep donor evaluation program.

Immunology	• Blood group, HLA typing, CDC x-match, antibody screen (luminex, ELISA)
Screen for major diseases	• Medical history, physical examination, routine laboratory test, abdominal ultrasound
Metabolic	• BMI, laboratory testing (HbA1c, blood lipids), oral glucose tolerance test
Renal assessment	• Laboratory testing (creatinine, eGFR, BUN, creatinine clearance), urinalysis, renal ultrasound, DTPA scintigraphy (side ratio), MR angiography (vascular anatomy)
Cardiovascular	• ECG, ergometry, echocardiography, 24h blood pressure monitoring, chest x-ray, spirometry
Infectious disease	• Screen for urinary tract infection, toxoplasmosis, virology (VZV, CMV, EBV, HIV, HAV, HBV, HCV, HEV)
Malignancy	• Gastrointestinal, urologic, gynecologic screen
Psychosocial	• Medical history, psychiatric or psychosomatic evaluation

CDC x-match – complement-dependent lymphocytotoxic cross match; HLA – human leukocyte antigen; ELISA – enzyme-linked immunosorbent assay; MR – magnetic resonance; eGFR – estimated glomerular filtration rate, calculated according to the abbreviated MDRD formula [20]; BUN – blood urea nitrogen; DTPA – diethylentriaminpentaacetate; ECG – electro-cardiography; HbA1c – glycated hemoglobin A1c; VZV – varizella zoster virus; CMV – cytomegalovirus; EBV – Epstein-Barr virus; HIV – human immundeficiency virus; HAV – hepatitis A virus; HBV – hepatitis B virus; HCV – hepatitis C virus; HEV – hepatitis E virus.

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Table 2. Patient characteristics.

	Donor		Recipient	
Gender (f/m)	76/57		49/84	
Age (yrs)	52	[24–78]	46	[4–77]
BMI (kg/m^2)	26.4	[19.3–38.5]	25.0	[15.4–38.6]
FPG (mmol/l)	5.4	[3.8–10.7]		
HbA1c (%)	5.6	[4.7–7.5]		
HbA1c mmol/mol	38	[28–58]		
Total cholesterol (mmol/l)	5.5	[2.9–8.1]		
LDL cholesterol (mmol/l)	3.4	[1.4–6.6]		
Serum creatinine (µmol/l)	71	[35–159]		
eGFR (ml/min/1.73 m^2)	89	[38–173]		
Creatinine clearance (ml/min)	120	[58–265]		
# of transplantation				
1 st			124	
2 nd or more			9	

Data are given as median [range]. BMI – body mass index; FPG – fasting plasma glucose; HbA1c – glycated hemoglobin A1c; LDL – low density lipoprotein; eGFR – estimated glomerular filtration rate.

Routinely, multistep donor evaluation is performed in the onsite outpatient clinic as listed in detail in Table 1. Special emphasis is laid on renal assessment as well as cardiovascular and metabolic risk. Renal function is determined by multiple laboratory and imaging techniques. Metabolic assessment includes a standard oral glucose tolerance test. Diabetes and prediabetes are defined according to criteria of the American Diabetes Association [21]; definition of obesity is according to World Health Organisation criteria [22]. Psychosocial evaluation is performed by an independent psychiatrist or psychosomatic expert in the field of living organ donation. In case of pathological results, further investigation is initiated on a patient specific basis. Recipient evaluation follows standard protocol as for regular kidney transplant waiting list. Results of donor-recipient pair evaluation are discussed in a multidisciplinary transplantation grand round, deciding upon medical acceptance or declination of donor and recipient. All decisions are protocolized. Accepted donors are seen by an independent Living Donor Committee prior to donation.

For analysis of donor-recipient evaluation outcomes, causes for declination were collected and stratified into recipient or donor reason and underlying conditions. In case of multiple causes for declination, the principal cause was entered into analysis. Immunologic issues, *i.e.* the presence of donor-specific antibodies (DSA), were counted as recipient reasons.

Donor declinations were stratified into the following subgroups: (i) (pre)diabetes: presence of prediabetes or diabetes mellitus according to ADA criteria (fasting plasma glucose ≥5.6 mmol/l or 7.0 mmol/l, respectively; 2 h glucose in OGTT ≥7.8 mmol/l or 11.1 mmol/l, respectively); (ii) obesity: BMI >35 kg/m^2; (iii) arterial hypertension: uncontrolled hypertension (RR ≥140/90 mmHg) and/or hypertensive end organ damage; (iv) CAD: presence of coronary artery disease or structural heart disease; (v) anatomy: presence of more than two renal arteries or renal artery stenosis; (vi) CKD: eGFR <80 ml/min/1.73 m^2, albuminuria or unexplained microhematuria; (vii) other: i.e. nephrolithiasis, incidental renal cell carcinoma, psychosocial reasons.

Starting in 2010, donor candidates with prediabetes were prospectively guided to lifestyle intervention. To date, nine potential donors have been enrolled in a structured lifestyle intervention program at our university hospital.

Results

In the period of observation, 133 donor-recipient pairs completed pre-transplant evaluation. Patient characteristics are given in Table 2. All potential donors were adults, whereas the recipient cohort included a small number of children. 124 recipients (93.2%) presented for first kidney transplantation and 9 (6.8%) for second or higher transplantation. 20 evaluations (22.2%) were in a preemptive setting.

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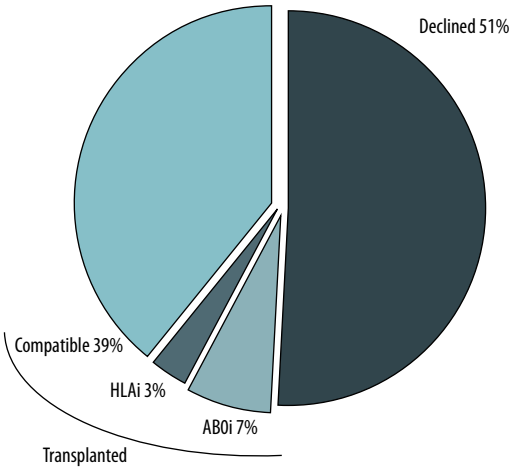

Figure 1. Outcome of donor-recipient pair evaluation. Percentage of pairs declined or transplanted in a compatible, blood group- (ABOi) or HLA-incompatible (HLAi) setting.

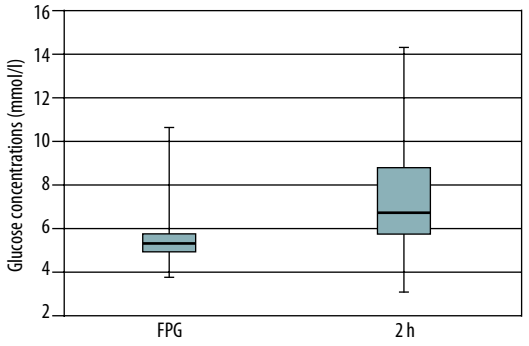

Figure 3. Results of the OGTT of all donors evaluated. FPG – fasting plasma glucose; 2-h – plasma glucose after 2 h in OGTT.

Sixty-five donor-recipient pairs (49%) were accepted for transplantation, among them one-fifth in a blood group- or HLA-incompatible setting; 68 of evaluated pairs (51%) were declined upon first evaluation (Figure 1). Among donor-recipient pairs declined, 16 (23%) were for recipient reasons, with the recipient either not eligible for transplantation or due to immunological reasons, and 52 declinations (77%) were for donor reasons (Figure 2). Among donors, more than half were declined for increased cardiovascular risk (see below). Other reasons included renal vascular anatomy, chronic kidney disease, or other (nephrolithiasis, incidental renal cell carcinoma or psychosocial reasons) (Figure 2).

When assigning increased cardiovascular risk to underlying disorders (Figure 2, blue bars), 28% of donor-recipient pair declinations were for donors with newly diagnosed prediabetes or diabetes mellitus, thereby presenting the largest single cause of donor declination. Of these, 9/19 had manifest diabetes mellitus and 10/19 we declined for prediabetes. The results of the OGTT of all investigated donors are displayed in Figure 3. In 10% of presenting pairs declined, donor obesity without impairment of glucose metabolism was the reason

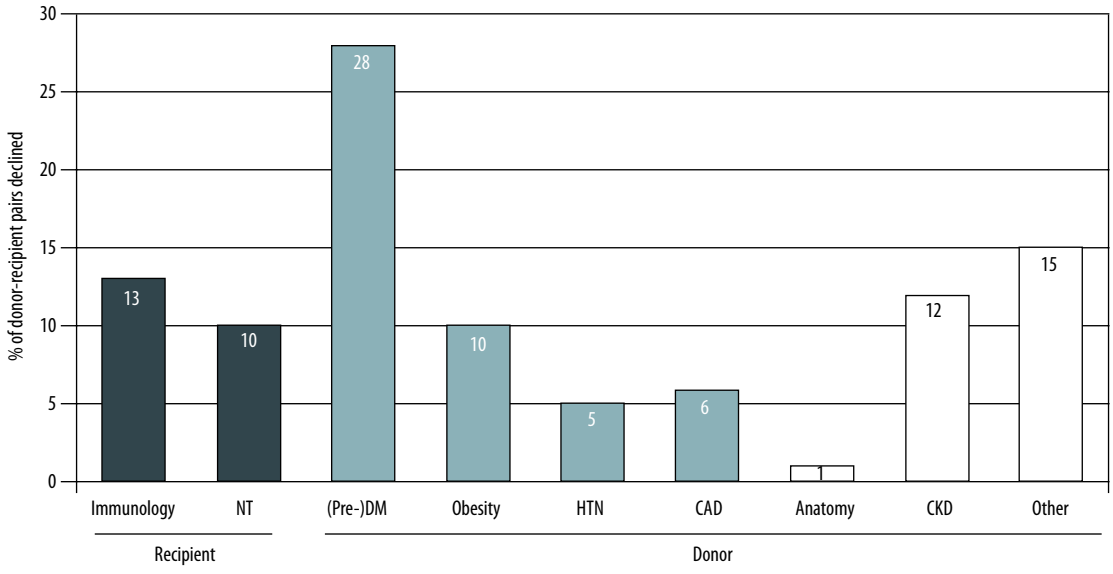

Figure 2. Donor and recipient reasons resulting in declination: 77% of declinations were for donor reasons, 23% for recipient reasons. Bars display percentage of evaluated donor-recipient pairs declined for the respective reason. Blue bars indicate declination for cardiovascular risk. NT – not eligible for transplantation; DM – diabetes mellitus; HTN – arterial hypertension; CAD – coronary artery disease; CKD – chronic kidney disease.

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Table 3. Characteristics and outcomes of the donor lifestyle intervention program.

#	Age (yrs.)	Gender	Weight (kg)	BMI (kg/m²)	FPG (mmol/l)	2 h (mmol/l)	HbA1c (%)	Δ time (months)	Δ weight (kg)	FPG_2 (mmol/l)	2 h_2 (mmol/l)	Donation
1	65	F	93	27.0	6.0	9.2	5.9	1.7	8	4.5	6.3	Yes
2	53	M	92	28.1	7.2	7.7	5.3	5.0	5	5.3	4.3	Yes
3	62	F	78	26.4	5.8	9.0	5.9	5.3	5	5.6	5.8	Yes
4	69	F	72	27.1	6.6	9.2	5.6	2.6	7	4.6	6.4	Yes
5	46	M	106	31.7	6.1	7.3	5.8	8.1	5	5.9	6.1	No
6	44	F	77.5	28.1	5.6	10.8	5.4	6.3	3.5	4.8	5.4	Yes
7	54	F	84	30.9	5.6	9.4	6.1	11.8	7	4.7	7.0	Yes
8	44	F	85	30.8	5.9	6.0	5.3	4.7	14	5.3	5.2	Yes
9	54	M	104	29.7	5.8	4.0	6.0	4.1	10	4.6	6.8	Yes
Median	54		85	28.0	5.9	9.0	6.0	5.0	7	4.8	6.1	
Range	44-69		72–106	26.0–32.0	5.6–7.2	4.0–10.8	5.0–6.0	1.7–11.8	3.5–14.0	4.5–5.9	4.3–7.0	

BMI – body mass index; FPG – fasting plasma glucose; 2 h – plasma glucose after 2 h in OGTT.

for declination. These donors (n=7) all had a BMI ≥35 kg/m². Other reasons of declination for increased cardiovascular risk were uncontrolled arterial hypertension (5.0%) and coronary artery disease (6.0%) of the donor.

Of the nine donor candidates enrolled in our structured lifestyle intervention program, eight succeeded in losing weight and regained normalization of glucose metabolism. All were subsequently accepted for kidney donation. One potential donor (#5) is still in the program. Detailed characteristics and outcomes of the patients enrolled are displayed in Table 3.

Discussion

The present data reveal a more than 50% overall declination rate among donor-recipient pairs upon first evaluation for living donor kidney transplantation. This is in accord with published data from two transplant centers in the United States, reporting declination rates of 47% and 54%, respectively [23,24] and reflects the heterogeneity of patients presenting to a university hospital transplant center. Of note, a vast majority (77%) of declinations was for donor reasons, reflecting the increasingly complex living donor cohort.

Previously undiagnosed prediabetes or diabetes mellitus was the largest single cause of donor declination. The prevalence of disturbances in glucose metabolism among all 133 potential donors was 14%, in accordance with currently published data on the combined prevalence of prediabetes and diabetes mellitus in Europe [25,26]. Of note, the prevalence has markedly increased over the last decades, not only in the general population, but also in accepted kidney donors. In a large retrospective analysis of 8951 donors, the prevalence of impaired fasting glucose at timepoint of donation increased from 9% in 1963 to 25% in 2007 [27]. In light of donor safety, eligibility of these patients has to be questioned and uniform decision criteria need to be established.

To date, considerable differences among individual transplant centers exist. For manifest diabetes mellitus, the 2004 Amsterdam Forum consensus guidelines exclude these patients as potential donors [14], as do most international and national guidelines [19] and individual transplant centers [15,16,18]. Lifetime risk of developing nephropathy in type 2 diabetes mellitus is approximately 30% [28]. Furthermore, data from patients with renal malignancy undergoing unilateral nephrectomy indicates a higher loss of GFR within the first year in diabetic patients, as compared to non-diabetic patients, irrespective of baseline renal function [29]. In established diabetic nephropathy, evidence from both animal and human studies demonstrates unilateral nephrectomy to result in progression of renal injury [30,31]. Therefore, kidney donation will result in a substantial increase in donor risk and it is common sense not to accept these patients as donors. A small Japanese trial, investigating 71 donors with IGT or diabetes mellitus, found no difference in post-donation overall survival and rate of ESRD, when compared to 373 healthy donors over a median follow-up of approximately 10 years [32]. However, the rate of renal dysfunction was significantly higher in diabetic patients, as compared to healthy donors, and a follow-up of ten years is not enough to detect all long-term effects of kidney donation in these donors.

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More controversy exists regarding potential donors with prediabetes. In our cohort, more than 50% of potential donors declined for disturbances in glucose metabolism were in a prediabetic state. Prediabetes is defined as a state when glucose metabolism is disturbed but criteria for manifest diabetes mellitus are not yet present, and summarizes impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and an HbA1c of 5.7–6.4% [21]. Patients with prediabetes are at high risk of developing diabetes mellitus over time [33–35]. Gerstein and coworkers, in a meta-analysis comprising 29.475 patients, estimated the relative risk of progression to manifest diabetes mellitus as 4.66 (95% confidence interval 2.47–6.85) for IFG, 6.35 (4.87–7.82) for IGT and 12.13 (4.27–20.0) for the combination of both [36]. The individual risk is further determined by a family history of diabetes in first degree relatives or a history of gestational diabetes [37,38]. Current observations suggest that up to 70% of individuals with prediabetes eventually develop diabetes mellitus [34].

Donation of a kidney modulates glucose metabolism. Unilateral nephrectomy has been shown to impair insulin sensitivity [39]. The effect of kidney donation on glucose homeostasis is clinically underlined by a recent analysis of 1074 kidney donors and a matched control cohort from population based observational studies, which demonstrated a lower cumulative incidence of diabetes in living donors early after donation but a substantially higher incidence beyond 10 years post-donation (incidence rate >10 yrs. 2.10 [95% CI 1.46–3.04] *vs.* 0.55 [95% CI 0.48–0.62] in matched controls) [12]. Donation of a kidney, therefore, in patients most at risk for diabetes will further impair glucose metabolism.

In addition, prediabetes may be associated with alterations in renal function. Glomerular hyperfiltration, if present, is a hallmark of incipient diabetic nephropathy and will be aggravated by any reduction in nephron mass [40]. Also, microvascular injury and microalbuminuria may be present in prediabetes as a consequence of altered glucose metabolism [41]. Albeit considered functional changes, these have been shown to precede structural injury by years and be of prognostic relevance, if unaltered.

Taken together, the presence of prediabetes implies a substantial risk for the donor and should preclude kidney donation.

Nonetheless, prediabetes is a modifiable state, especially in obese patients. In our cohort, patients with prediabetes were mainly overweight or obese with a median body mass index of 28.1 [26.4–32.0] kg/m^2. The efficacy of structured lifestyle intervention programs to reduce associated risk is established: In a large cohort of subjects with prediabetes, lifestyle intervention reduced the incidence of diabetes by 58%, as compared to placebo [42], and regression to a state of normal glucose metabolism led to a sustained risk reduction, even if this state was transient [43]. Clearly, individual responses and adherence vary. Potential kidney donors are a group of highly motivated individuals and willing to comply with lifestyle intervention. In 2010, we started a structured donor lifestyle intervention program. To date, nine donor candidates with prediabetes were enrolled, of which eight attained sustained normalization of glucose metabolism, as confirmed by oral glucose tolerance test and remained normoglycemic in follow-up. Considering such patients as kidney donors may be feasible. In a risk stratification approach, a number of aspects will have to be taken into account. Based on current knowledge, sustained response to lifestyle intervention reduces future diabetes and associated risk. Also, individual medical history as well as age and lifetime risk will guide this decision [44]. Results from our donor lifestyle invention program are encouraging and pave the way for a prospective donor lifestyle intervention trial, aiming to increase the number of persons eligible for kidney donation.

Conclusions

In summary, donor selection inevitably has to be strict regarding diabetes mellitus and prediabetes. We demonstrate alterations in glucose metabolism to account for the largest single cause of donor declination. Response to lifestyle intervention may allow for stratification of future diabetes risk and donor eligibility in patients with prediabetes. Unification of evaluation criteria, as well as prospective long-term follow-up, is necessary to account for the increasingly complex living donors in kidney transplantation.

Conflict of interest

The authors declare that there is no conflict of interest associated with this manuscript.

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