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RENAL TRANSPLANTATION

REVIEW

Controversies related to living kidney donors

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KEYWORDS

Kidney;
Donor;
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Abnormality

ABBREVIATIONS

BP, blood pressure; BMI, body-mass index; CKD, chronic kidney disease; DM, diabetes mellitus; ESKD, end-stage kidney disease; eGFR, estimated GFR; IMA, isolated medical abnormality; RBC, red blood cell; TBMN, thin basement-membrane nephropathy

Abstract ***Background:*** Increasing the living-donor pool by accepting donors with an isolated medical abnormality (IMA) can significantly decrease the huge gap between limited supply and rising demand for organs. There is a wide range of variation among different centres in dealing with these categories of donors. We reviewed studies discussing living kidney donors with IMA, including greater age, obesity, hypertension, microscopic haematuria and nephrolithiasis, to highlight the effect of these abnormalities on both donor and recipient sides from medical and surgical perspectives.

Methods: We systematically searched MEDLINE, ISI Science Citation Index expanded, and Google scholar, from the inception of each source to January 2011, using the terms 'kidney transplant', 'renal', 'graft', 'living donor', 'old', 'obesity', 'nephrolithiasis', 'haematuria' and 'hypertension'. In all, 58 studies were found to be relevant and were reviewed comprehensively.

Results: Most of the reviewed studies confirmed the safety of using elderly, moderately obese and well-controlled hypertensive donors. Also, under specific circumstances, donors with nephrolithiasis can be accepted. However, persistent microscopic haematuria should be considered seriously and renal biopsy is indicated to exclude underlying renal disease.

Conclusion: Extensive examination and cautious selection with tailored immunosuppressive protocols for these groups can provide a satisfactory short- and medium-term outcome. Highly motivated elderly, obese, controlled hypertensive and the donor with a unilateral small stone (< 1.5 cm, with normal metabolic evaluation) could be accepted. Donors with dysmorphic and persistent haematuria should not be accepted. A close follow-up after donation is crucial, especially for obese donors who developed microalbuminuria.

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Introduction

Currently, kidney transplantation is the treatment of choice for the increasing number of patients with end-stage kidney disease (ESKD), with the best survival, better quality of life and lower cost than other replacement therapies [1–3]. However, there is a wide gap between the number of patients with ESKD and available grafts, despite the increased frequency of living donation, which raises the issue of using more donors with an isolated medical abnormality (IMA) including those who are older, or obese, and those with well-controlled hypertension, or renal calculi and asymptomatic haematuria [4]. For some groups of these donors the acceptable thresholds for pre-donation factors such as blood pressure (BP), donor age and body-mass index (BMI), remain unclear, which reflects the wide diversity of the eligibility standards for living kidney donation among institutions [5]. Similarly, for abnormal urine analysis, there are no clear established thresholds [6,7].

In Middle East and South-east Asia, 95% of kidney transplants is from living donors, most probably for religious reasons, legislative issues and due to lack of resources and infrastructure to establish a deceased donation and procurement programme [1,8,9]. It is very important to remain cognisant of this increasing demand for living kidney donation, and yet still maintain stringent and evidence-based standards for the selection and eligibility of the donors [10]. To date, in Egypt and many developing countries, it is the only source of grafts. Moreover, living kidney donation is increasing also in the developed countries.

Many studies have reported the long-term outcomes and guidelines for donor selection in healthy living kidney donors, but there is still a need for more studies to evaluate the long-term outcome among donors with IMA, to clearly justify the decision to accept them. In this review we discuss the results of studies concentrating on the outcome of donors with IMA, by assessing both the donor and recipient.

Methods

We comprehensively reviewed all available reports discussing the outcome and complications of living kidney donors with IMA, including those having one of the following isolated medical abnormalities before transplantation:

1. Older donors (age >50 years, varying in different studies; Table 1 [2–9,11–31].
2. Obesity, i.e. a BMI of $\geqslant 30$ kg/m^2 [26–43].
3. Hypertension $>140/90$ mmHg, or controlled with medication [16,25,26,28,44–46].
4. Donors with nephrolithiasis [45,47–53].
5. Asymptomatic microscopic haematuria [54–57].

We systematically searched MEDLINE, ISI Science Citation Index expanded and Google scholar from their inception to January 2011. Our search included, but was not limited to, the terms 'kidney transplant', 'renal', 'graft', 'living donor', 'old', 'obesity', 'nephrolithiasis', 'haematuria', and 'hypertension'. To include all narrow subheadings, we exploded the selected subject headings. The search was tailored for each database.

Results

In all, 58 articles were retrieved. Meta-analyses and prospective studies with evidence-based levels I and II were included, together with retrospective studies containing many patients.

Older donors

In an attempt to decrease the shortfall in organs the use of aged donors has grown, raising the question of the clinical effects of donor age on graft outcome and donor safety [1]. The perceived increased risk of perioperative surgical or medical complications and age-related decline in GFR for donors of advanced age make the acceptance of them as a donor a point of controversy [2]. We extensively reviewed all studies related to older donors for surgical aspects, effect of donation on the elderly donor, and the graft outcome for the recipient. We found 29 studies, nine prospective and 20 retrospective, which included 1614 older donors. The age above which the donor was considered 'old' differed among the studies; 13 defined it as >60 years, seven as $\geqslant 65$ years, six as >50 years and only three as >55 years. Seventeen studies discussed the graft outcome only, eight reported the outcome for both donor and recipient, three concentrated on donor follow-up only, and seven studied the surgical issues (Table 1).

Donors

We found 12 studies including 551 donors, five prospective and seven retrospective that documented outcome of the old donor from medical and surgical perspectives (Table 1). Textor et al. [3], in a prospective study, followed 65 old donors ($\geqslant 50$ years). They recommended that patients with higher BPs only on clinic measurements, and which cannot be detected by ambulatory BP monitoring or measurements by a trained nurse, should be accepted as donors, with meticulous BP monitoring by different means. Also Jacob et al. [9] prospectively followed 42 old donors, comparing them with donors aged <40 years, and they found no greater increase serum creatinine levels in the older group in the follow-up.

Recently, in our centre, El-Agroudy et al. [4] retrospectively followed 73 donors aged >50 years at the time of donation. They found that 24 (31%) became hypertensive (62% of them controlled by one drug), five became diabetic; the mean (SD) serum creatinine level was 1 (0.9) mg/dL and five developed proteinuria of <2 mg/day. The rates of diabetes mellitus (DM) and hypertension were the same as in an age-matched population and they recommended the acceptance of healthy older donors.

Surgical outcome of older donors

Eight studies concentrated on the surgical aspects of the older donors, comprising five retrospective and three prospective, with a total of 182 donors [2,9,12,15,19–22]. Johnson et al. [2] investigated complications and risks associated with open living-related donor nephrectomy. They found that donor age >50 years was not an independent risk factor for complications in a multivariate analysis, but it was an independent risk factor for prolonged hospital stay. This was the largest study to report the surgical outcome in older donors (for 42

Table 1 The reports assessed for the various categories of donor.

Ref.	Year	No. of subjects	Type of study	Subjects studied	Remarks
Old donors; last column, age in years					
[27]	1986	4	Retrospective	Recipient	> 60
[17]	1989	25	Retrospective	Recipient	> 66
[11]	1991	70	Prospective	Donors	> 60
[14]	1994	21	Retrospective	Recipient	> 60
[7]	1995	41	Retrospective	Recipient	> 65
[13]	1996	50	Retrospective	Recipient	⩾60
[18]	1997	161	Retrospective	Donor and recipient	> 60
[15]	1997	15	Retrospective	Donor and recipient	> 55
[28]	1999	13	Prospective	Recipient	⩾65
[5]	1999	74	Retrospective	Recipient	> 55
[24]	2001	28	Prospective	Recipient	⩾65
[19]	2002	6	Retrospective	Donor and recipient	> 65
[29]	2003	19	Retrospective	Recipient	> 60
[3]	2003	65	Prospective	Donor and recipient	> 50
[20]	2003	19	Prospective	Donor	> 61
[26]	2003	6	Prospective	Recipient	
[6]	2004	52	Retrospective	Recipient	> 50
[9]	2004	42	Prospective	Donor and recipient	> 60
[2]	2005	22	Retrospective	Donor and recipient	> 50
[16]	2005	46	Retrospective	Recipient	> 60
[21]	2006	35	Prospective	Donor and recipient	> 60
[30]	2006	25	Retrospective	Recipient	> 60
[25]	2006	44	Retrospective	Recipient	> 60
[12]	2006	14	Retrospective	Donor	⩾65
[23]	2007	521	Prospective	Recipient	50–60, 60–65 and ⩾65
[4]	2009	73	retrospective	Donor	> 50
[8]	2010	49	Retrospective	Recipient	> 60
[31]	2010	45	Retrospective	Recipient	> 50
[22]	2010	29	Retrospective	Donor and recipient	> 50
Obese donors: last column BMI (kg/m^2)					
[34]	2000	12	Retrospective	Donor	> 31
[33]	2000	41	Retrospective	Donor	⩾35
[32]	2002	34	Prospective	Donor	> 30
[37]	2002	23	Both	Donor	
[38]	2003	12	Prospective	Donor	⩾30
[26]	2003	81	Prospective	Donor	> 30
[36]	2005	172	Retrospective	Donor	⩾35
[42]	2005	23	Prospective	Donor	> 30
[39]	2006	49	Retrospective	Donor	⩾30
[43]	2006	37	Prospective	Recipient	⩾30
[40]	2009	32	Retrospective	Donor	
[35]	2009	1194	Retrospective	Donor and recipient	30 to < 35, ⩾35
[41]	2010	36	Retrospective	Donor	⩾30
Hypertensive donors					
[28]	1999	46	Prospective	Donor	ABP > 150/90
[25]	2000	20	Retrospective	Donor and recipient	
[26]	2003	16	Prospective	Donor	Controlled on one drug
[44]	2003	12	Retrospective	Donor and recipient	Controlled on one drug
[45]	2004	24	Prospective	Donor	ABP > 140/90
[16]	2005	18	Retrospective	Donor and recipient	Controlled on one drug
[46]	2011	17	Retrospective	Donor	
Donors with nephrolithiasis					
[52]	1995	2	Case reports + long-term	Recipient follow-up	
[53]	2002	4	Case reports + long-term	Recipient follow-up	
[51]	2003	5	Prospective	Recipient	
[44]	2003	8	Retrospective	Donor and recipient	
[49]	2004	10	Prospective	Donor and recipient	
[50]	2004	5	Prospective	Recipient	
[48]	2007	5	Prospective	Donor and recipient	
[47]	2007	9	Prospective	Donor and recipient	

(*continued on next page*)

Table 1 (*continued*)

Ref.	Year	No. of subjects	Type of study	Subjects studied	Remarks
Isolated microscopic haematuria					
[55]	1993	30	Prospective	Donor	
[56]	2005	14	Prospective	Donor and recipient	
[57]	2009	6	Prospective	Donor and recipient	
[54]	2010	20	Prospective	Donor and recipient	

ABP, ambulatory BP.

donors) and they showed a comparable outcome in both donor and recipient sides, with lower pain and postoperative stay also benefits of applicable laparoscopic donor nephrectomy in this older group of donors [9].

Recipients

We identified 25 studies (six prospective and 19 retrospective) that documented the outcome of the recipients receiving their grafts from older donors (Table 1). Recently, Berardinelli et al. [8] followed 49 recipients receiving their grafts from donors older aged >60 years, with a mean (SD) follow-up of 13.1 (6.1) years; they confirmed an excellent outcome in this long-term follow-up. Pena de la Vega et al. [6] followed 52 recipients of grafts from older donors for 2 years, and they reported comparable graft and patient survival despite a lower GFR in the older group, with a higher frequency of cytomegalovirus and polyomavirus infections, which suggested tailoring a more renoprotective protocol for these special subgroups.

Kerr et al. [5] included 74 donors aged >55 years, and they confirmed an excellent outcome at 10 years of follow-up only in the absence of acute rejection. Textor et al. [3] also reported an excellent outcome for recipients of older donor grafts. In the largest series discussing old donors, a prospective Norwegian study included 521 donors (age >50 years) divided into three groups (50–60, 60–65 and >65 years) with a median follow-up of 51.3 months. Their results encouraged the use of older donors, who are highly motivated and who can meet stringent medical criteria. In a multivariate analysis they only found that extreme age (>65 years) and steroid-resistant acute rejections during the first 5 years after transplantation were independent risk factors for graft loss [23].

Obese donor

Obesity has long been recognized as a cause of proteinuria and glomerular disease [58]. Studies also show a greater risk of chronic kidney disease (CKD) with obesity, even after adjustment of BP and DM [59–61]. Biopsies of obese patients commonly show glomerular changes such as glomerulomegaly and increased mesangial matrix [62]. Notably, after nephrectomy, live kidney donors are known to have compensatory hyperfiltration in the remaining kidney [63]. Therefore, preexisting obesity-related hyperfiltration might have a lower capacity to undergo further adaptive hyperfiltration after donor nephrectomy than in a normal-weight donor. Praga et al. [64] retrospectively studied 73 patients who had a unilateral nephrectomy for different causes, and they found that the obese patients were at higher risk of developing proteinuria and renal insufficiency, after a follow-up of 1 year.

As the use of obese-donor grafts in transplantation has increased recently, studying the outcome of donation in this group for both donor and recipient has become a more urgent and pressing point. We reviewed 13 studies comprising 1814 obese donors, including cohort, cross-sectional and case-control studies (Table 1). All patients were categorized according to their BMI into four groups, i.e. normal weight (<25 kg/m^2), overweight ($\geqslant 25$ to <30 kg/m^2), obese ($\geqslant 30$ to <35 kg/m^2) and very obese ($\geqslant 35$ kg/m^2), as defined by the WHO [65]. Most of these concentrated on obese donors (BMI $\geqslant 30$ kg/m^2) and three of them studied markedly overweight donors (very obese). Some of the studies concentrated on the surgical approach to the obese donors, comparing open and laparoscopic methods, and some documented the outcome of both donor and recipient.

Donors

Surgical outcome of obese donors: We identified seven studies reporting the surgical outcome of donor nephrectomy in obese donors [32–38]. Three of them included the very obese group in the study [33,35,36]. Chow et al. [32] compared the outcome of hand-assisted donor nephrectomy in two groups ($<$ and >30 kg/m^2) and they concluded that the laparoscopic approach is effective and safe for obese donors, with no increase in complication rate.

Jacobs et al. [33] studied the outcome of laparoscopic nephrectomy in very obese donors vs. donors with a BMI of <25 kg/m^2, and they found significantly longer operation times by a mean of 40 min, in the very obese donors. Also, conversion to open nephrectomy was more likely in obese donors (7.3% vs. 0%), with the same rate of postoperative complications. With these trivial differences they concluded that the laparoscopic donor nephrectomy appears to be a convenient approach for very obese donors. Moreover, Kuo et al. [34] assessed the intraoperative considerations and short-term postoperative outcome in obese donors, and they concluded that there were many advantages to laparoscopic nephrectomy, such as decreased pain, avoidance of loss of sensation, and a rapid return to work, apart from an improved cosmetic outcome.

Recently, Reese et al. [35] followed 2108 overweight donors (BMI 25 to <30), 944 obese donors (30 to <35), and 250 very obese donors ($\geqslant 35$). They assessed the rates of re-operation, re-admission within 6 weeks and conversion to open surgery, length of stay and vascular and nonvascular complications; they reported similar results across all donor categories.

Medical outcome of obese donors: We reviewed studies assessing the effect of donation on obese donors, and studies that evaluated the outcome of the graft from an obese donor for the recipient. It is reasonable to accept and follow-up obese

donors to determine whether decreasing donor renal mass will directly increase the incidence of cardiovascular problems, proteinuria and renal insufficiency, or if it is only related to the obesity, which is modifiable. We found seven studies that documented renal function and other medical aspects in obese kidney donors, with different follow-up periods [26,35,36,38–41]. One of these [39] assessed the pathological findings in obese and non-obese donors, and documented similar serum creatinine levels and microalbuminuria in both groups, with a median follow-up of 340 days. Also, they found that the corrected and uncorrected iothalamate clearance were significantly higher in the obese group, which can be explained by biopsy that confirmed a more prevalent glomerulomegaly in this group.

Garcida et al. [26] followed 81 obese living donors for a mean (SD) of 80.7 (32.58) months and concluded that obesity did not affect the outcome of these donors after ≈9 years of follow-up. Heimback et al. [36] assessed 114 obese donors (BMI 30–35 kg/m^2) and 58 very obese at 6 and 12 months; the data at this short-term outcome showed similar results for corrected iothalamate clearance, microalbuminuria and blood pressure.

Recently, Tavakol et al. [40] reported a long-term follow-up of 98 donors who donated 5–40 years ago, comparing the donors (obese and non-obese) with well-matched two-kidney control subjects. They concluded that obese donors have an equal risk to non-obese donors for long-term renal function. They also reported that the obesity itself is the cause of increased cardiovascular risk and hypertension, and was not exacerbated by donor nephrectomy. For BP, there was no difference between the obese and non-obese groups in mean systolic values, but increased total albumin excretion was detected in the obese group in a multivariate linear regression (coefficient 8.7; 95% CI 2.0–15.0; $P = 0.01$).

Reese et al. [35] compared the medical outcome in three categories, i.e. 2108 donors with a BMI of 25 to <30 kg/m^2, 944 obese and 250 very obese. Six months after donation they reported an insignificant but consistent increase in mean systolic and diastolic BP across all donor BMI categories, as reflected by the differences in baseline BP. The differences in estimated GFR (eGFR) were statistically significant across the groups but clinically were not important, and did not increase consistently across the BMI groups. Also, at 1 year the changes in eGFR, percentage increase in creatinine, systolic and diastolic BP values were not statistically different across the donor BMI categories. Lastly, Nogueira et al. [41] followed 36 obese donors for a mean (SD) of 6.8 (1.5) year after donation, and reported a greater risk of hypertension in this group and deteriorated renal function (using the Modification of Diet in Renal Disease equation to calculate eGFR) in obese donors who developed microalbuminuria.

Recipient

Two studies investigated the recipients who received their graft from obese donors. Espinosa et al. [43] followed 37 recipients who had grafts from obese donors for a mean (SD) follow-up of 50.8 (28.5) months; they concluded that grafts from obese donors had a lower GFRs of 71.7 mL/min vs. 80.1 mL/min for grafts from non-obese donors ($P = 0.002$). Surprisingly, they also noted a significantly greater rate of acute rejection episodes in recipients from obese donors. However, more recently, Reese et al. [35] reported similar rates in acute rejection, graft survival and patient mortality, and only showed an increased rate of primary non-functioning graft and delayed graft function, in recipients from very obese donors at 1 year.

Hypertensive donors

Hypertension is mostly defined as having a BP of >140/90 mmHg, and it is one of the most common causes of donor exclusion [66]. Over the last 20 years, the threshold for defining hypertension has decreased steadily [67], which caused more donors to be excluded as they were considered to be hypertensive. To provide a clearer decision about accepting this group of donors, we reviewed all the studies discussing the outcome of having a graft from a hypertensive donor, on both the donor and the recipient.

Donor

Seven studies described 142 hypertensive donors [16,25,26,28,44–46], three prospective [26,28,46] and the rest retrospective. Definitions of hypertension vary among the studies and two studies did not even give a specific definition [25,26]. BP was measured by health-profession members in only one study [45].

Textor et al. [45] prospectively followed 24 hypertensive donors before, and 6 months and 1 year after donation, by detailed measurements and monitoring of BP, iothalamate GFR, and assessed urinary protein and microalbuminuria. The hypertensive group was older (53.4 vs. 41.4 years, $P < 0.001$). They concluded that the hypertensive group had a mean (SD) lower GFR, of 61 (2) vs. 68 (1) mL/min/1.73 m^2 ($P < 0.01$) after donation. For BP, they found no change in the normotensive group after donation and surprisingly, BP decreased in hypertensive donors even in those who were maintained on antihypertensive drugs. No change in both proteinuria and albuminuria was detected in both groups after nephrectomy. Textor et al. [45] concluded that donors with moderate essential hypertension might be accepted for kidney donation if their kidney functions were normal. Srivastava et al. [16] studied 18 hypertensive donors for a median follow-up 30 months; the duration of hypertension treatment was 3.5 years, controlled by non-pharmacological management or by a single drug. The mean age was 46.2 years. Only two donors needed additional antihypertensive drugs at 2 and 3.5 years. None developed proteinuria and they reported an increase in their GFR by a mean (SD) of 18 (2.4) mL/min. They recommended extensive evaluation of BP before and after donation, using ambulatory monitoring.

Sahin et al. [25] examined 20 hypertensive donors and found no statistically significant difference in mean BP at 5 years of follow-up after donation. Kumar et al. [44] retrospectively studied 12 hypertensive donors who were controlled by one antihypertensive medication, and none of them needed any change in their antihypertensive treatment. Also, Gracida et al. [26] followed 628 donors for a mean (SD) of 80.7 (32.58) months; 16 of them were hypertensive and they reported equal short-term results but with significantly lower GFR values than in the control group at the end of the follow-up. Recently, Mjoen et al. [46] followed 17 donors with uncomplicated hypertension, and who were allowed to donate, at 1 and 5 years, and they found that six of the donors became normotensive after 1 year, though the rest were still hypertensive. At 5 years they reported follow-up data for only seven do-

nors; four were on one antihypertensive and two were on two drugs; the last one became normotensive.

Recipient

Three studies commented on the outcome of grafts from hypertensive donors [16,25,44]. Sahin et al. [25] reported a similar outcome in recipients who had their grafts from hypertensive donors compared to those who had their grafts from normotensive donors at 5 years of follow-up. Srivastava et al. [16] reported that 10 of 18 recipients had a serum creatinine level of <1.4 mg/dL at a median follow-up of 30 months, and the rest a value of <2.5 mg/dL within the same period. Kumar et al. [44] found no change in antihypertensive medications in the recipients of grafts from hypertensive donors up to the end of their study.

Donors with nephrolithiasis

Urinary lithiasis has been considered a relative contraindication to living-donor transplantation, due to the risk of future stone formation, not only in the recipient but more importantly in the donor. With the widespread use of screening CT angiography during renal donor evaluation the prevalence of asymptomatic solitary nephrolithiasis has increased [68]. Depending on the individual case, specific imaging, blood chemistry, hormonal and urine analyses are used to assess the current status and recurrence risk.

Donor

We found only four studies that followed donors with nephrolithiasis after donation [44,47–49]. Three of these studies were prospective [49–51] and the last was retrospective [44]. In all, 32 donors were included, with different follow-up periods. Strang et al. [47] followed nine donors who donated a stone-bearing graft for a mean follow-up of 11.2 months; the mean (range) stone diameter was 2.1 (1–8) mm and there was no stone recurrence reported. Martin et al. [48] assessed five donors with a mean (SD) follow-up of 16.9 (10.4) months; none of the donors had developed any symptoms consistent with the development of a renal stone.

Rashid et al. [49] prospectively followed 10 donors for 36.4 months and there was no new stone formation in any donor. Kumar et al. [44], in a retrospective study, included 1011 donors of whom only eight were confirmed to donate a stone-bearing graft, and only one with a renal stone was admitted as an emergency for anuria 2 years after surgery. A stone in the lower ureter was diagnosed and treated by ureteroscopic removal. There was no recurrence of stones in other donors.

Recipient

There were eight studies with 43 patients that assessed the outcome of receiving a stone-bearing graft [44,47–53], and concentrated on different methods used to treat these transplanted stones. All the available methods for treating stones in the native kidney were used successfully in the stone-bearing transplanted graft. Furthermore, Rashid et al. [49] reported the successful use of *ex vivo* ureteroscopic removal of nine solitary, small (<8 mm) and unobstructing stones of 10 found in eight recipients, with a mean (range) procedure time of 6.5 (3–28) min. The follow-up for 33.2 months showed no clinical or radiological evidence of stone recurrence.

Devasia et al. [50] followed five recipients for 24 months after treating two stones with lithotripsy, and three received the graft with the stone *in situ*; no recipients developed stone disease or functional deficit.

Martin et al. [48] evaluated five recipients with asymptomatic small stones (<4 mm). CT at a mean (SD) of 6.9 (10.4) months later showed spontaneous passage of the stones in three patients. In the remaining two patients the stones maintained nearly the same size, with no evidence of any other stones or complications. Kumar et al. [44] retrospectively analysed the outcome of eight recipients of a stone-bearing graft, and no complications were noted. None of the eight studies evaluating the outcome of receiving a stone-bearing graft reported stone recurrence or related morbidity for the silent stone left *in situ*.

The Amsterdam Forum on the Care of the Live Kidney Donor [69] outlined certain acceptance criteria for an asymptomatic potential donor with a history of a single stone, including: (1) no hypercalciuria, hyperuricaemia or metabolic acidosis; (2) no cystinuria or hyperoxaluria; (3) no UTI; and (4) multiple stones or nephrocalcinosis not evident on CT. An asymptomatic potential donor with a current single stone, if the described criteria are met, and if the current stone is <15 mm or potentially removable during transplantation, is acceptable for donation according the Amsterdam Forum recommendations. However, they acknowledged the importance of donor age, specifically highlighting the longer exposure of younger donors (aged 25–35 years) to the risk of recurrence.

Isolated microscopic haematuria

Although glomerular haematuria can be considered as a sign of CKD that might develop into overt nephropathy after donor nephrectomy, it remains an urgent question as to whether these donors should be excluded. Haematuria can be occasional or persistent, which is more important. Haematuria is considered persistent if the duration is >3 months, which is seen in up to 3% of the general population, and its association with pathological findings is more likely [70]. Also the origin of haematuria is extremely important; a glomerular source gives dysmorphic red blood cells (RBCs) while normomorphic RBCs indicate a non-glomerular origin.

From April 2001 to October 2007, Kido et al. [54] followed up 242 donors, using urine analysis on many occasions before and after donation, and estimating the renal function in these donors who had been followed for >2 years after donation. The association of annual changes in GFR with donor haematuria status and risk of progressive renal dysfunction after donation was carefully investigated. They reported that persistent haematuria after donation was a significant risk for the progression of kidney disease after donation, and for persistent proteinuria, which is a sign of chronic allograft glomerulopathy. In a multivariate analysis, persistent glomerular haematuria was significantly more prevalent in donors with persistent haematuria before donation ($P < 0.001$) or dysmorphic RBC before donation (odds ratio 15.2; 95% CI, 2.04–161; $P = 0.007$). However, they failed to confirm the direct relation between the persistent haematuria before and the deterioration in allograft function after donation. Interestingly, they found a

significant association between donors showing persistent haematuria after donation and those with a positive family history of IgA nephropathy or Alport syndrome ($P = 0.01$). They concluded that potential donors with persistent glomerular haematuria should be excluded, and that those with any haematuria be closely investigated, and might be accepted for donation, with caution.

Sobh et al. [55] evaluated 30 potential living-related kidney donors with asymptomatic microscopic haematuria by a thorough history, medical examination and laboratory tests, and finally renal biopsies were taken from all. Interestingly, an obscured cause of microscopic haematuria was found in all potential donors, and hereditary nephritis was the most common cause in 25; three were diagnosed with isolated C3 deposit disease, one with IgA nephropathy and the last with IgM nephropathy. Thus the authors concluded that isolated microscopic haematuria can be a misleading term, and mostly it is due to a hidden pathology. Hence the Amsterdam forum guidelines stated that patients with persistent microscopic haematuria should not be considered for kidney donation unless assessed by urine cytology and a complete urological evaluation. After excluding urological malignancy and stone disease, a kidney biopsy can be indicated to exclude glomerular pathology, such as IgA nephropathy [69].

In a recent study, Koushik et al. [56] assessed 512 prospective donors and they found 14 (2.7%) with persistent, asymptomatic, microscopic haematuria. The kidney biopsies from 10 elective donors were obtained; four were found to have thin basement-membrane nephropathy (TBMN), one had non-homogeneous basement-membrane abnormalities, with a thickness of 150–600 nm (normal 326–45 nm) and one had IgA nephropathy. Another woman with a positive family history for Schimke's syndrome had seven globally sclerosed glomeruli of 30. Another had TBMN with early hypertensive changes. Of the 10 prospective donors who had a kidney biopsy, only two had completely normal biopsy results and two had TBMN and were accepted as kidney donors. These four donors were permitted to donate and were followed for 15 months, with an excellent short-term outcome. Finally, Koushik et al. concluded that a renal biopsy is indicated before accepting a donor with unexplained persistent asymptomatic haematuria, as a large proportion of these donors can have abnormalities in their kidney biopsy which might render them unacceptable for donation.

Recently Gross et al. [57] investigated the safety of donation from the relatives of patients with Alport syndrome, as a special group with a mild urinary abnormality, and they concluded that living-donor kidney transplantation from heterozygous relatives is an acceptable option, with a satisfactory 1- and 5-year outcome in both donor and recipient. Also, careful donor evaluation, including a mandatory kidney biopsy before transplantation, close follow-up, early diagnosis and subsequent therapy of renal risk factors such as hypertension and microalbuminuria, are the mainstay to minimize the increased risk of renal failure in this donor group.

Conclusion

None of the reviewed studies reported medical or serious surgical age-related increased risks for donor nephrectomy, and confirmed the safety of the laparoscopic approach. Also, most of them confirmed the safety and applicability of using older donors, provided that they are cautiously selected and extensively examined. Using specific immunosuppressive protocols for this special donor subgroup to decrease the incidence of interstitial fibrosis and tubular atrophy, especially with calcineurin inhibitor-dependent protocols, and avoid over-immunosuppression to decrease viral infections like cytomegalovirus. Also, special attention should be given to early treatment of acute rejection episodes to guarantee a satisfactory outcome.

For obese donors, short- and medium-term studies that followed obese donors and their recipients gave encouraging results. However, a close follow-up is recommended for obese donors who develop microalbuminuria after donation, as this group is at higher risk of developing hypertension and a deteriorating GFR. Surgical approaches for obese donors, especially laparoscopic donor nephrectomy, do not carry an extra risk for these donors. Most studies showed acceptable short-term results of donation from well controlled, mild hypertensive donors, and a reasonable graft outcome, but more detailed results are required for more reassurance on the long-term outcome. As stated by the Amsterdam forum, asymptomatic small stones (< 1.5 cm) can be accepted after careful selection and exclusion of any metabolic abnormalities. Also, the stone can be treated conservatively, during surgery or with lithotripsy.

Persistent microscopic haematuria mostly indicates underlying occult renal disease, and a renal biopsy is indicated in that situation for clear decision making regarding acceptance, as recommended by the Amsterdam Forum group. Here we must stress on that donors with dysmorphic persistent haematuria should be excluded.

Finally, maintaining a high index of suspicion, extensive examination, cautious selection and a close follow-up is mandatory for all these donors with IMA, for assurance of, early diagnosis and intervention to minimize the complications. Long-term, prospective randomised trials are still required to more accurately describe their long-term outcome.

Conflict of Interest

The authors have no conflict of interest to declare.

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