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Live kidney donors

Assessment and follow up

Background
Live kidney donation has increased steadily over the past decade, both in Australia and internationally. In some centres more than 50% of patients receiving a kidney transplant do so from a living related or unrelated donor. Live nondirected or altruistic donation has become more popular, as have paired exchange programs. General practitioners may be involved in pre-donation counselling and the assessment and follow up of otherwise healthy kidney donors.

Objective
This overview outlines the clinical pathway and considerations required pre- and post-live kidney donation and highlights some of the uncertainties of donor nephrectomy.

Discussion
Live donation requires comprehensive physical, psychological and immunological assessment of the donor-recipient pair. Assessment requires an integrated approach that incorporates the skills of a number of clinicians and allied health practitioners. General practitioners have a crucial role in the counselling, assessment and follow up of live kidney donors.

General practitioners routinely manage patients approaching end stage renal failure (ESRF), dialysed patients and renal transplant recipients. The impact of chronic renal failure on families is unquestionable and transplantation affords recipients improved survival rates, reduction of cardiac risk and greater social and financial prospects.

Kidney donation in Australia

Immediate family members commonly volunteer to donate, so called 'living related donors'. Unrelated donation has expanded donor programs and can be grouped into 'spousal donation' and 'unrelated' donation. These living unrelated donors have partly addressed the significant shortfall of donor kidneys in Australia (*Figure 1*). Live, nondirected donation or 'altruistic' donation in Australia is under constant review and is not common, although such donations have been made. Kidney 'exchange' cannot take place in Australia, except for another kidney. Exchange programs have been ratified by some Australian state governments and are aptly named 'paired exchange programs'. Paired exchange programs take place when more than one donor-recipient pair cannot proceed to transplantation, usually due to an immunological barrier. In such cases, by 'swapping' the donor kidneys, the immunological barrier is overcome and transplantation can proceed.

Who can receive a kidney?

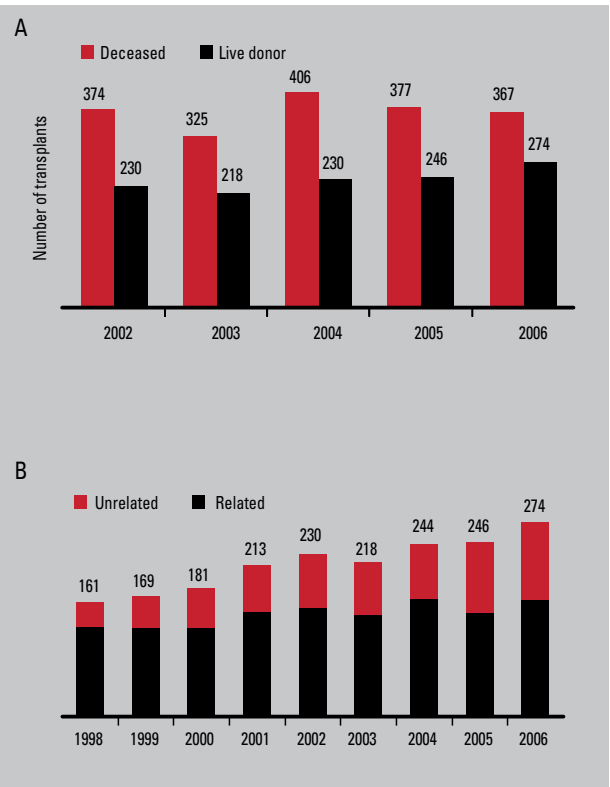
Live kidney donor recipients must be deemed physically and psychosocially suitable for transplantation in advance of potential donor assessment. Waitlisting on the 'deceased donor list' requires a patient to be established on dialysis and thoroughly assessed. Before embarking on donor screening it is important to clarify the recipient's 'transplant status'. Most waitlisted patients are aware of their status and associated requirements. Suitability is less obvious if pre-emptive transplantation is proposed. It is essential to establish transplant status in advance to avoid unnecessary psychological strain on the donor-recipient pair.

Who can donate a kidney?

Physical, emotional, social and immunological constraints dictate the suitability of a potential donor and recipient pair. Each of these areas is evaluated by a multidisciplinary team comprised of: surgeons, physicians, psychiatrists, nursing staff, anaesthetists, immunologists, social workers and pastoral care workers. Pre-emptive transplantation (transplantation before dialysis) is possible, and is broadly promoted by renal physicians as it is associated with better graft outcomes.

Ideally, potential donors will have completed their own family, have a normal body mass index (BMI) and be able to give informed consent. Donors should be free of overt metabolic and cardiovascular risk factors and comprehensive screening is essential. Although ideally a donor should be free of comorbidities, the criterion for acceptance is often unit and physician specific. Uniform acceptance policies are not available, although excellent guidelines exist (see *Resources*). Clinicians and donors must consider and balance the overt and covert risks when discussing donation. Family history of diabetes, hypertension, vascular disease, emotional relationship and donor age need to be considered. Occasionally, a less than pristine donor will be knowingly accepted due to compelling psychosocial reasons that must be thoroughly explored before donation.

Figure 1. Trends in deceased and live kidney transplants in Australia 2002–2006



A) Numbers of deceased donors versus live donors

B) Source of live donors: related versus unrelated

Data obtained and used with permission: ANZdata registry. Available at www.anzdata.org.au/

The role of the GP

The general practitioner may be approached by a potential donor about 'donor suitability', the practicalities of donation, and/or with a list of screening tests to be performed. The donor may have already attended an education seminar at the potential recipient's hospital, attended a clinical appointment with the recipient, or liaised with a donor coordinator. Occasionally GPs will be the first point of contact. Most transplanting units have a donor coordinator available during working hours that can be contacted regarding the logistics of live donation.

Preliminary screening

Currently in Australia, all screening testing, inpatient services and follow up costs related to live kidney donation are financially recompensed by Medicare. Preliminary screening must be preceded by a thorough physical examination, confirmation of a normal blood pressure and BMI. Screening ensures unsuitable donors can be identified without significant resource expenditure.

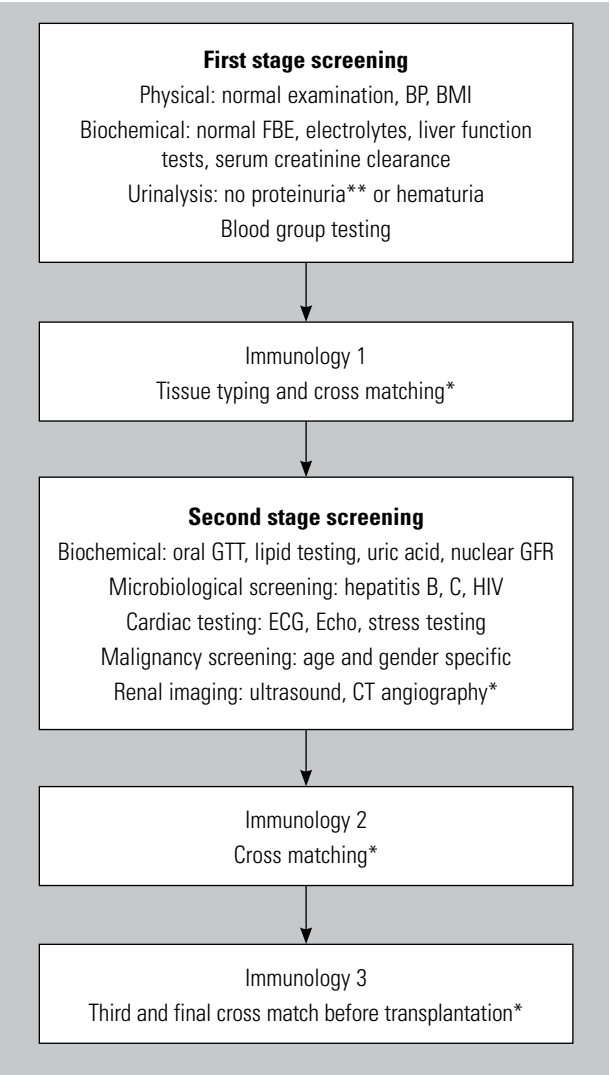
Potential donors are extensively assessed for renal disease, cardiovascular disease and metabolic risk factors. Renal disease is excluded by ensuring two midstream urine (MSU) samples are free of haematuria and proteinuria; a 24 hour urine collection is performed as the gold standard to exclude proteinuria. The utility of an albumin to creatinine ratio (ACR) remains undetermined, however most units exclude albuminuria using ACR. Immunological matching of the recipient and donor pair is assessed. Some immunological barriers, such as ABO incompatibility, previously perceived unsurpassable, have now been reconsidered with the advent of improved immunomodulating agents and regimens. Related donors must have inheritable renal diseases excluded where possible. Beyond single point gene mutations, the epigenetic influence of a shared environment and the polygenetic risks for cardiovascular disease, hypertension and diabetes must be considered. A thorough family history is essential. Screening for donors is outlined in *Figure 2*.

Second stage screening

Presuming medical (first stage) and psychological screening organised by the transplanting unit are not prohibitive, donors should be referred to a renal physician for consultation. (Due to an obvious conflict of interest, the potential donor's renal physician should not be the recipient's treating physician.) The renal physician organises an initial 'cross match' to assess the 'immunological risk' of the donor-recipient pair. Cross matching in Australia is performed by the central blood bank. The recipient-donor pair must have blood samples collected on the same day. Samples cannot be collected in regional centres.

Second stage testing includes screening for transmissible infectious diseases such as hepatitis B, C and human immunodeficiency virus (HIV), evaluation of renal vessels and parenchymal anatomy (renal ultrasound, computerised tomography [CT] angiography), exclusion of indolent cardiac disease (electrocardiogram

Figure 2. The stages involved in assessment for kidney donation suitability



* Specialised testing performed by the transplant unit

** Exclusion of proteinuria is usually performed by a 24 hour urine collection

[ECG], echocardiogram [Echo] and where appropriate, cardiac stress testing), metabolic screening (glucose tolerance test [GTT], lipids, uric acid) and nuclear glomerular filtration rate (GFR) testing to estimate split renal function. All results and their implications are discussed with potential donors. Routine screening for age and gender specific malignancies is also required. Automated testing can be performed by any accredited laboratory. Structural and functional renal testing is normally performed at the transplanting centre due to specific image requirements. Geographically remote donors will need to travel to the transplanting unit for immunological testing, renal structural and functional testing and surgical and medical reviews.

Donor suitability after testing is variable. Occult renal and nonrenal diseases are often diagnosed. Follow up of occult disease must be facilitated. If medical and psychiatric assessments do not preclude donation, cross matching is repeated and if negative, surgery organised.

Kidney donation

Operative procedures and risks

Traditionally an open procedure was used to perform donor nephrectomy. Over the past decade most centres have offered laparoscopic donor nephrectomy. Laparoscopic surgery advantages include donor acceptance, improved postoperative recovery, reduction in hospitalisation time, and surgical incision minimisation. Surgical complications include: haemorrhage, wound infection, deep vein thrombosis (DVT), postoperative chest infection and, rarely, pneumothorax. Postoperative risks can be minimised by donors ceasing smoking and hormone therapies known to increase postoperative DVT risk. A history of cigarette usage by deceased donors is associated with poorer graft outcomes.[1] Therefore, live donor cigarette usage may be a factor associated with inferior graft outcomes, although this has not been confirmed. Most donors can return to normal activities within 6 weeks after donation.

Outcomes after live kidney donation

Observational outcomes

Most live kidney donors are highly selected and by virtue of this process deemed to have no cardiac risks. Renal donor survival bias has been suggested by some investigators,[2] however, postoperatively, donors acquire one identified risk – renal function impairment. Live donors acquire renal impairment because of the kidney donation, and its significance has not been properly evaluated. Donor follow up studies have reported variable outcomes, in part due to inconsistent end points, assessment and follow up methodologies (*Table 1*).

Donors develop microalbuminuria at a faster rate than age and cardiovascular risk matched controls.[3,4] The aetiology of this new onset proteinuria or albuminuria is presumed to be related to glomerular changes rather than generalised endothelial dysfunction, although this has not been confirmed. Predictors of a postdonation GFR <60 mL include older age (47 ± 12 years), hypertension and proteinuria at the time of donation.[5]

Recent evidence suggests that 12% of living donors have a GFR <60 mL and 0.2% a GFR <30 mL after a mean follow up of 7 years,[6] however, there are issues about the accuracy of GFR estimations. Wan et al[7] reported that 75% of live donors have a mean GFR of 54.7 ± 9.26 mL/mn/1.73m^2 using the Modification of Diet in Renal Disease 4 point estimation equation; this estimated GFR (eGFR) is equivalent to stage 3 chronic kidney disease.

Literature examining the impact of renal impairment on cardiac outcomes has consistently confirmed that a low GFR correlates with adverse cardiac outcomes.[8,9] However, many of these studies have been in patients with other associated comorbidities and known cardiovascular risk factors.

A blood pressure (BP) increase of 5–6 mmHg 5–10 years after donation, beyond that expected with increasing age, was reported in a

Table 1. Screening recommendations and medical complications postkidney donation[6,8,10,11,13]

Medical	Observation	Recommendations
Long term BP change	• 5–10 mmHg at 5–10 years postkidney donation	Annual BP check
Risk of microalbuminuria	• Pooled analysis 3.9%	Annual urinalysis
Incidence of proteinuria (>300 mg/day)	• 5–20% • Pooled analysis 10%	Annual urinalysis
End stage renal failure	• 1 in 1000	Annual biochemistry
GFR <60 mL	• 12% at 7 years	Annual biochemistry
Cardiovascular risk assessment	• Increased cardiac risk in those with renal impairment	• Annual – lipids – fasting glucose – check BMI
Metabolic bone disease	• Vitamin abnormalities • Elevated PTH	• Question annual vitamin D intake • PTH check if eGFR <30 mL

recent meta-analysis[10] and up to one in 1000 live donors will develop ESRF.[11] Occasionally, implantation biopsies confirm histological abnormalities suggesting incidental and occult renal disease of note in donors with an increased BMI, and such abnormalities are known to be associated with hypertension.[12]

If donors develop hypertension and/or albuminuria there may be some merit in commencing an angiotensin converting enzyme inhibitor or angiotensin receptor blocker as the first line agent, although this is not based on any current robust evidence.

Nontraditional biochemical markers

Biochemical markers of increased cardiac risk have been extensively investigated in dialysed and transplanted patients and c-reactive protein (CRP), B-type natriuretic peptide (BNP) and troponin have been positively correlated with adverse outcomes. All biomarker studies in kidney donors have involved small cohorts and short postnephrectomy intervals, hence little can be concluded. To date, routine donor follow up does not usually involve biomarker assessments and currently there is no rationale for screening.

A low GFR is known to be associated with abnormal bone and mineral metabolism. Gossman et al[13] confirmed that in donors at 10 years, 56% had proteinuria (>150 mg/day), 19% an increased parathyroid hormone (PTH), and 30% had decreased tubular phosphate reabsorption. Vitamin D abnormalities have been linked to adverse cardiac outcomes in patients with renal impairment. A low GFR is associated with abnormal vitamin D tubular reabsorption and vitamin D deficiency. This suggests live donors need careful follow up beyond renal function and cardiovascular risk factor assessment. Broad recommendations based on robust evidence cannot be currently made with respect to screening for metabolic bone disease in this population. Testing for vitamin D sufficiency would seem prudent, and if the eGFR is <30 mL/mn/1.73 m^2, PTH levels should also be tested.

Psychological satisfaction

Kidney donation can be associated with medical and surgical complications. It is important to be aware that unsuccessful recipient outcomes can be associated with donor physical and mental difficulties. All donors should be counselled in advance about the risk of unsuccessful recipient outcomes.[14] A survey of Australian donors confirmed de novo psychological difficulties in up to 30% of donors postoperatively.[15] Psychosocial assessment of donors postnephrectomy is not mandated. General practitioners should be formally contacted at the time of clinic discharge regarding any perceived psychosocial concerns or risks.

Current screening recommendations

The uncertainties for donors and clinicians are many. There is little prospective data to help clinicians identify at the time of donation, which patients may progress to renal, metabolic and/or cardiac dysfunction. The implantation biopsy is helpful in excluding occult renal disease.

Twelve months after donation, all donors should have an annual physical, metabolic and biochemical assessment of their renal function and cardiovascular risk factors (*Table 1*). Follow up is life long. Where practical, assessment of donors should be performed by a renal physician in conjunction with a GP and, with consent, relevant data provided for outcome analysis in Australia and New Zealand by the ANZdata registry (see *Resources*). If the measured eGFR is <30 mL/mn/1.73m^2, the role of the renal physician becomes paramount, and screening for bone, mineral and haematological complications, commenced.

Currently, there is no system for screening donors postnephrectomy in Australia. Follow up primarily remains the responsibility of the donor. It is therefore important that GPs are aware of the potential risks and screening recommendations,

given they are likely to see such patients. Follow up appointments are always offered to live donors by the renal specialist at the time of discharge.

Conclusion

Live kidney donation is increasingly used to enable those with kidney chronic kidney disease to remain dialysis free. Donation should only take place after the donor is deemed physically and psychologically fit. All donors must have life long follow up and prompt management as required for cardiovascular and metabolic diseases.

Resources

- Caring for Australasians with Renal Impairment (CARI) guidelines. Available at www.cari.org.au
- British Transplantation Society. Available at www.bts.org.uk/
- ANZdata registry. Available at www.anzdata.org.au.

Conflict of interest: none declared.

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