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Improving outcomes for kidney transplantation

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Improving outcomes for kidney transplantation

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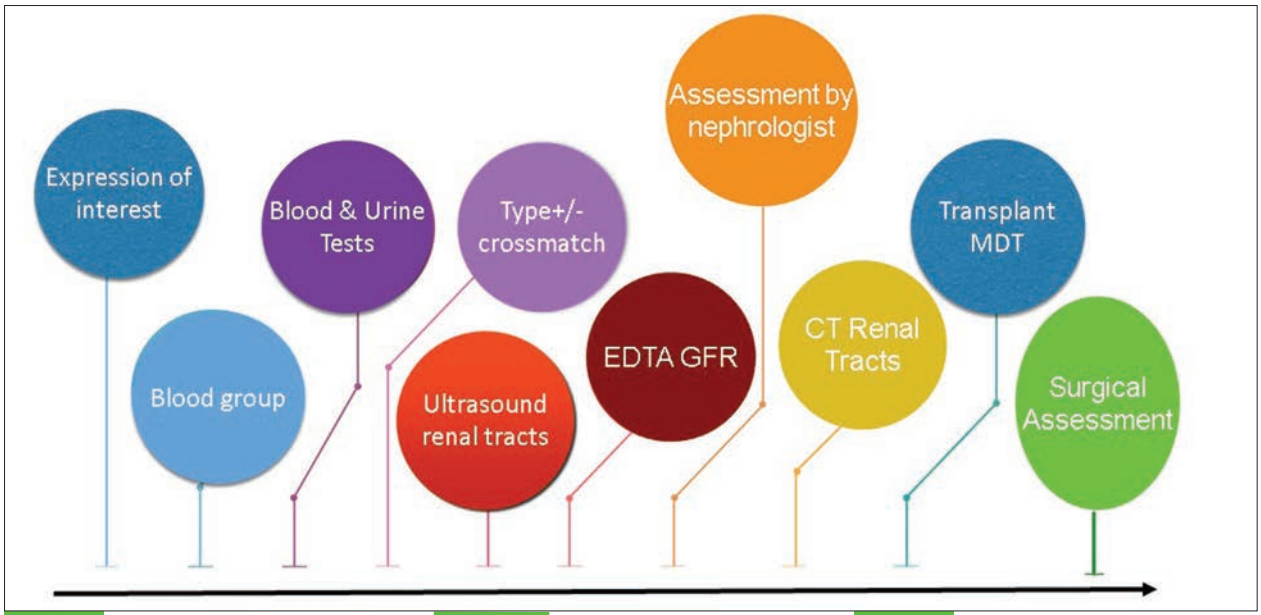

FIGURE 1
Assessment of potential living kidney donors

How should potential donors and recipients be assessed?

KIDNEY TRANSPLANTATION IS THE OPTIMUM FORM OF RENAL REPLACEMENT THERAPY FOR SUITABLE patients with end-stage renal disease (ESRD).[1,2] The benefits compared with maintenance dialysis therapy, in terms of patient survival and quality of life, are universally accepted.

Despite advances in haemodialysis over the past decades, with better molecular clearance, shorter hours, less stringent dietary restriction and the use of recombinant erythropoietin, it remains non-physiological and suboptimal compared with normal renal function.

A successful kidney transplant represents a much closer approximation to true renal replacement with excretion of waste products, regulation of electrolytes and other substances, and synthesis of important hormones; it therefore offers substantial benefits compared with dialysis, see box 1, right. Although it cannot be considered curative, (with the possible exception of transplantation between identical twins), it offers hope of a life expectancy that can approach normal.

What are the risks and possible complications?

SUITABILITY FOR TRANSPLANTATION

Not all patients with ESRD are suitable for transplantation. Assessment centres on the suitability of the patient for:

- General anaesthesia and surgery
- Renal transplant surgery
- Long-term immunosuppression

Table 1, p20, summarises the most common areas that require consideration. The demographic of chronic dialysis patients has changed dramatically in recent decades with increasing age, comorbidity, and prevalence of diabetes. Those with diabetic nephropathy inevitably have a constellation of other complications.

Age per se is not a contraindication to transplantation. There are some patients in good health in their 70s for whom this offers an important advantage in terms of quality of life. In contrast, there are patients with lifelong illness who are unsuitable for transplantation despite being decades younger.

The recent NICE guideline on renal replacement therapy[3] recommends that patients should not be precluded from consideration for transplantation based on BMI alone. However, there are increasing challenges and risks of complications in obese individuals, and few centres will consider transplanting the morbidly obese. In regions without bariatric services, the options for these patients to achieve an 'acceptable' BMI are limited, and some transplant units will accept such patients for transplantation, considering obesity as part of an overall risk assessment on a case by case basis.

If a patient is deemed suitable for a general anaesthetic and surgical procedure, then specific consideration to the requirements for renal transplant »

Box 1

Survival of patients with end-stage renal disease

Patients live longer if they have a:

- Transplant compared with dialysis
- Living donor compared with a deceased donor transplant
- Transplant before requiring dialysis (pre-emptive)

How should donors and recipients be followed up?

Table 1

Assessing suitability for renal transplantation

General anaesthesia/ intermediate surgery	**Comorbidity**		**Frailty**		**Obesity**	
	Cardiovascular disease is common in patients with ESRD		Age per se is not a contraindication Some young/middle-aged patients have had lifelong disease and are unsuitable		Some transplant centres have an absolute cut-off BMI, others do not	
Transplant surgery	**Vascular**		**Urological**		**Space**	
	Vascular calcification	Vascular stenosis	Adequate bladder or alternative drainage		≥ 2 previous transplants	Polycystic kidneys
Immunosuppression	**Malignancy**		**Infection**		**Adherence**	
	Previous malignancy with potential obligatory delay		Chronic infection	Recurrent infections	Psychiatric illness	Previous non adherence

surgery must be considered. Many patients with ESRD, particularly if they have been on dialysis for a long time, have extensive vascular calcification. It may be impossible to clamp the vessels successfully and achieve vascular anastomoses.

In patients with previous transplants or multiple femoral venous catheters for central access, there may be previous vascular disruption limiting the options for implantation of a transplant.

An important minority of patients have renal failure because of urological problems such as obstruction or abnormal bladder function. In such cases it is important to ensure there can be appropriate drainage from a transplanted kidney, or inevitably it will have the same fate as the native kidneys.

For patients who have had two or more transplants already or have very large polycystic kidneys that extend into the pelvis, consideration has to be given to nephrectomy to allow space for transplantation.

Finally, the risks of immunosuppression are evaluated. Antirejection drugs reduce the body's normal immunosurveillance function thereby increasing the risk of malignancy. For those patients with treated malignancy the risk of (potentially aggressive) recurrent disease must be considered. International guidelines advise on obligatory waiting periods following treatment for different types of cancer before solid organ transplantation.

Those with chronic infection e.g. osteomyelitis in dialysis patients with concurrent vascular disease, are also precluded from transplantation until they are infection free. Patients with recurrent infections must have careful consideration of the risk-benefit ratio with transplantation, and all steps to minimise the risk of sepsis taken.

Those who have been non adherent with immunosuppression previously, particularly if it has resulted in the loss of a transplanted organ, must be very carefully assessed before a further transplant can be considered.

The only additional consideration is the risk of recurrent disease in the new kidney. There are a tiny number of cases where the original (typically glomerular) disease returns so rapidly and aggressively that a transplant is not a feasible option.

LIVING VS DECEASED DONATION OUTCOMES

Transplantation from a living donor is associated with better graft and patient survival than that from a deceased donor.[4,5] This persists despite adjustment in analysis for the other factors known to influence outcomes, and is consistently reported in different countries and healthcare settings. In the latest reported outcomes in the UK, five-year patient survival rates following deceased and live kidney donation were 87% and 94% respectively.[6]

'Patients live longer if they have a living donor compared with a deceased donor transplant'

The reasons for the better outcomes associated with living donor transplantation can be categorised into donor and recipient factors.

Donor factors

Injury to a deceased donor kidney can be sustained in the premortal period, at time of death, and in the post-donation stage.

The demography of donors has changed substantially from the early years of transplantation, when the typical donor was young and male. Road safety and drink-driving campaigns have contributed to a great reduction in this cohort of donors, (in the UK in 2017-18 only 3% of deceased donors died because of trauma[7] compared with 25% in 1999,[8] and the average age of donors has risen substantially. In 1992 only 5% of donors were over 65 years old,[8] while 33% in 2017/18 were over 60 years old.[7]

Donors often have preexisting comorbidities such as hypertension or diabetes. Many kidneys now available for transplantation from deceased donors have established chronic damage.

A physiological calamity has occurred in all deceased donors, so inevitably there is a degree of insult to renal function at the time of death. The extent of this is impossible to establish definitively, a substantial proportion of kidneys that are offered for donation are declined as the clinical impression is that there may be irreversible damage. Despite this careful consideration some transplanted kidneys never work.

In comparison to living donor transplants, deceased donor organs have a prolonged period of ischaemia given the obvious inability to organise the transplant in advance. This adds further to the injury to a deceased donor kidney.

Recipient factors

The longer a recipient has been dialysis dependent before transplantation the poorer the outcome. Length of time on dialysis is the strongest independent modifiable risk factor for renal transplant outcome. Having an available living donor provides the opportunity for a pre-emptive transplant (i.e. avoidance of dialysis altogether). This offers a distinct

advantage, acknowledged in the NICE guideline, especially for patients with diabetic nephropathy (who typically have limited survival on dialysis), multiple comorbid potential recipients, and older individuals all of whom will particularly benefit from minimisation of time on dialysis. In the UK, 40% of living donor transplants in 2017-18 were pre-emptive, compared with 16% of transplants from deceased donation.[6]

'The longer a recipient has been dialysis dependent before transplantation the poorer the outcome'

A small but important exception to the premise of a healthier recipient cohort in living donor transplantation is the group with such complexity that they are considered unsuitable for an emergency surgical procedure (i.e. a deceased donor transplant). With a carefully planned elective transplant from a living donor, they can potentially benefit from transplantation, without this option the risks are prohibitive. Careful counselling of both the potential donor and recipient is imperative.

RISKS AND COMPLICATIONS OF LIVING KIDNEY DONATION

The risks of donating and living with one kidney are categorised according to the temporal association with donation.

Short-term risks

These are complications related to:

- **General anaesthesia**
- **Any surgical procedure** i.e. pain, nausea, infection, thrombosis, nerve injury
- **Nephrectomy** i.e. vascular, bowel, splenic, or thoracic injury

Almost all centres now offer minimally invasive laparoscopic surgery for donors. The risk of a major complication, including conversion to open surgery is 1-2%.[9] The risk of death is typically quoted as 1 in 3,000, based on data on more than 6,000 living donors in the USA.[10]

Medium-term risks

Following the initial recovery period after nephrectomy, few living donors have any persistent problems. For the minority that do, one of the most common for men who have had a left kidney removed is testicular discomfort. The venous drainage of the left testis is conventionally into the left renal vein, the disruption to this can result in venous engorgement, manifest as swelling and tenderness of the testis. This typically settles over a few weeks or months as collateral drainage develops, with supportive treatment only required.

Persistent pain and symptoms of irritable bowel can also occur in a small minority of donors, and as with any surgery, an incisional hernia may complicate recovery. While not sinister, the added morbidity of these medium-term complications is unwelcome for previously healthy donors.

Long-term risks

Hypertension, renal failure, and premature death are potential long-term risks. The challenge in drawing conclusions about the magnitude of any additional risk is the observational nature of many reports, and the validity of comparison with the general population is limited by the inclusion in the latter group of people who, by virtue of comorbidities or lifestyle, would not have been considered suitable donors.

More recently several large studies have made efforts to recruit healthy non donors as controls. This year a systematic review and meta-analysis, which included approximately 118,000 donors and a similar number of non donors has concluded that, despite higher diastolic blood pressure (BP) readings, lower eGFR, increased relative risk for ESRD, and pre-eclampsia, the absolute risks for such adverse outcomes in a living donor is low.[11]

The distinction between relative and absolute risk is important; if an individual's lifetime risk of renal failure is 0.05%, then even a ten-fold increase in relative risk means that the absolute risk of ESRD is still only 0.5%. While it is accepted that there is an increased long-term risk of ESRD in living donors crucially the absolute risk in studies remains very low at $\leq$ 0.5%.

Similarly, although the relative risk of pre-eclampsia is considered two fold higher than in a healthy non donor, there are good maternal and fetal outcomes reported in pregnancies after living donation. The evidence does not indicate an increased risk of low birthweight or prematurity.

It is postulated that the mechanism of pre-eclampsia in this setting is different (i.e. not related to placental insufficiency) and subsequently not deleterious to fetal outcome.

The applicability of historic studies to today's potential living donors is uncertain, as the demographic profile has evolved as donors now are older, and the potential donor population is increasingly more likely to be obese, have impaired glucose metabolism, and hypertension.

Risks of renal failure vary between ethnic groups, another factor for which long-term data are scarce.

Overall, despite an increased relative risk of long-term complications, there must be appreciation of the excellent outcomes for those who have donated after being assessed in accordance with national and internationally agreed guidelines.[12]

For the vast majority of living donors the experience is a positive one, often associated with improved physical and psychological wellbeing. There are definitely donors who have increased their life expectancy by modifying their lifestyle in order to become eligible to donate.

The benefits of seeing a close relative or friend transformed by transplantation cannot be overstated, and the risk a potential donor considers acceptable is frequently different from that of the medical profession.

A person from one ethnic group can potentially donate to a friend or partner from another ethnic group. A genetic relationship with the recipient is not a prerequisite to being a living donor, and even an emotional association is no longer essential. In the past decade non directed altruistic living donors, those that do not have a particular person to donate to, known as Good Samaritan donors, have made an important contribution to transplantation with more than 80 donating annually in the UK. Each can trigger a chain of transplants by entry into the UK Kidney Sharing Scheme.[13]

More recently direct solicitation of a living donor using social media has resulted in directed altruistic donation, approximately a dozen times per annum in the UK.

ASSESSMENT OF POTENTIAL LIVING DONORS

The purpose of assessment is to ensure, as far as possible, that the risks for that individual in being a living donor are acceptably low. It is not essential to have perfect health in order to be a donor. Table 2, p22, summarises the key aspects of assessment.

Consideration of long-term risks to renal function is key. First, it must be established that there are two kidneys and no current concern in relation to »

Table 2

Assessing suitability for living kidney donation

General anaesthesia/ laparoscopic surgery	**Obesity**		**Smoking**		**Previous thrombosis**	
	Increased perioperative risks		Increased perioperative risks		Increased perioperative risks	
	Current renal function		**Risk for renal disease**			
Renal function after donation	Creatinine Isotopic GFR	Urinalysis	Obesity Blood pressure Diabetes	Familial disease	Stone disease	
	Technical		**Immunological**		**Disease transmission**	
Kidney for transplant into recipient	Vascular anatomy		Blood group	HLA type	Infective	Malignant

renal function. Second, there needs to be determination of any particular risks for this individual in terms of the development of renal disease in the long term, which means that the person should not be left with a single kidney.

One increasingly frequent concern is obese individuals. Persistent hyperfiltration in a single kidney, together with the concomitant higher risk of hypertension and diabetes will compromise long-term function. While some individuals are sufficiently motivated to lose a substantial quantity of weight to permit donation, maintaining such weight loss lifelong is crucial.

Occasionally, the risk of familial renal disease is of sufficient concern to preclude donation.

The final part of the assessment process mandates consideration of three areas:

- Technical feasibility of donation and implantation
- The risk of transmissible disease (malignancy or infection)
- The compatibility of blood group and HLA loci between donor and recipient.

Surgical teams rarely decline a donor on a technical basis as there are a number of reconstructive techniques and options to overcome vascular complexity. With the possibility of living donor exchange programmes in many countries, the finding of incompatibility no longer precludes donation, provided that the donor is willing for entry into such a sharing scheme.

Figure 1, p19, illustrates the typical minimal assessment process. How this is organised varies between centres, it is possible to have a streamlined donor journey which is popular with potential donors by adopting the ethos of making it as easy as possible to donate.[14] Additional investigations are required if initial screening reveals another potentially relevant pathology.

POTENTIAL COMPLICATIONS IN RECIPIENTS

There are a number of technical and immunological issues that can be problematic in the immediate post-transplant period, when the patient is still in hospital. The most common early complications following discharge are infection (most typically urine), wound dehiscence, and poor glycaemic control. Transplant recipients are under close review by the transplant team in this period, but primary care teams may be asked by medical staff to assist in care.

In the medium term the most common cause of death in transplant recipients is cardiovascular disease, and management of risk factors is an important aspect of GP care.

With time, avoidance of malignancy becomes the most likely determinant of survival. Minimisation of immuno-suppression is the remit of the transplant clinicians; encouraging adherence to screening protocols and having a high index of suspicion for potential neoplasia that of the primary care team.

Particular relevant practical care for transplant recipients relates to their ongoing immunosuppressed state: live vaccines should not be administered and infections must be treated swiftly and for longer as these patients can develop sepsis and become critically unwell quickly.

MONITORING OF DONORS AND RECIPIENTS

Living kidney donors are typically followed by the transplant centre in the early weeks after donation, and lifelong annual follow-up is recommended. The arrangements for this vary between regions. Historically, when there were very small numbers of living donors, this was often by clinic attendance at the transplant unit. With rising numbers, (there are now more than 1,000 living donors annually in the UK), and increasing time from donation, alternative processes are being put in place in some areas. The key aspects for donor follow-up are BP, urine protein estimation, and serum creatinine/eGFR.

Box 2

Renal function after living kidney donation

Reduced nephron mass
Serum creatinine will be substantially higher and eGFR substantially lower than previously

- A lower eGFR in this instance does NOT represent chronic kidney disease
- The remaining kidney is perfectly good, it has been carefully assessed
- The change in renal function simply reflects reduced nephron mass

There is a normal variability in serum creatinine (and hence eGFR) of at least 10% in all individuals, e.g. if creatinine is 130 μmol/L then values between 115 μmol/L and 145 μmol/L are essentially the same

- Additional investigation or referral is not required unless there is a progressive decline

A lower eGFR therefore should not cause alarm unless there are other health concerns or it continues to decline

key points

SELECTED BY

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Kidney transplantation is the optimum form of renal replacement therapy for suitable patients with end-stage renal disease. A successful transplant represents a much closer approximation to true renal replacement with excretion of waste products, regulation of electrolytes and other substances, than dialysis. The longer a recipient has been dialysis dependent before transplantation the poorer the outcome. Length of time on dialysis is the strongest independent modifiable risk factor for renal transplant outcome.

Post-transplant antirejection drugs reduce the body's normal immunosurveillance function thereby increasing the risk of de novo and recurrent malignancy. Also, patients with current or recurrent infections must have careful consideration of the risk-benefit ratio associated with transplantation. Live vaccines should not be administered. Infections must be treated swiftly and for longer as these patients can develop sepsis and become critically unwell quickly.

The demography of donors has changed substantially from the early years of transplantation, when the typical deceased donor was young and male. Today, many have preexisting comorbidities. Living donor transplantation on the other hand is associated with better graft and patient survival than transplantation from a deceased donor. A genetic relationship with the recipient is not a prerequisite to becoming a living donor.

Having a living donor offers the opportunity of pre-emptive transplant (i.e. avoidance of dialysis altogether). In the UK, 40% of living donor transplants in 2017-18 were pre-emptive, compared with 16% of transplants from deceased donors. Almost all centres now offer minimally invasive laparoscopic surgery for donors.

The risk of a major complication for donors is 1-2%, and risk of death is around 1 in 3,000. Following nephrectomy, few living donors have persistent problems. In the longer term, hypertension, renal failure, and premature death are potential risks. All donors should be followed up with BP, urine protein, and serum creatinine/eGFR testing.
Every living donor will have a lower eGFR after donation which is completely different from the same eGFR in someone with two kidneys. For the vast majority of living donors the experience is a positive one, often associated with improved physical and psychological wellbeing.

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Box 3

Essential information for patients about living kidney donation

- Living donor kidney transplantation is the very best treatment for end-stage renal disease
- It is possible to avoid dialysis completely if there is a suitable available donor
- A donor does not have to be genetically related to the recipient
- There are options for living donation even if the donor is a different blood group or ethnic group from the recipient
- All potential donors undergo a thorough assessment
- Nobody is permitted to donate unless their short- and long-term risks are low
- The absolute risk of a serious complication for living donors is small
- All donors are offered lifelong follow-up
- It is possible to donate a kidney to a stranger
- Typically the experience of being a living donor is positive

Every living donor will have a lower eGFR after donation. Substantial anxiety is caused when donors are told they have CKD. It is important to note that a lower eGFR in a donor, with one kidney, is completely different from the same eGFR in someone with two kidneys, as this will represent a disease process in the latter case but not in a donor.

Box 2, p22, summarises the advice given to primary care colleagues by one transplant unit. If the eGFR trend does cause concern, referral back to the nephrology/transplant team is appropriate and typically welcomed by both the donor and the nephrologist. Box 3, above, summarises information about living kidney donation.

Recipients attend nephrology services lifelong, not least as virtually all still have a below normal GFR. However, they require the expertise of primary care for the non-renal aspects of health.

CONCLUSION

There are significant advantages with kidney transplantation compared with dialysis, and importantly in graft and recipient survival with living compared with deceased donor transplantation. Outcomes for donors are good when suitability is determined in accordance with established guidelines.

Appreciation of the benefits of living donor transplantation and facilitation of the process will result in an increased number of living donors. It is typically a positive experience.

Competing interests: None

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Useful information

Kidney Research UK
www.kidneyresearchuk.org/health-information/kidney-transplantation

NHS Blood and Transplant information on living donation
www.organdonation.nhs.uk/about-donation/living-donation

Information on non-directed altruistic living kidney donation
www.giveakidney.org

Information on donation and transplantation
www.donatelife.co.uk