

Donor renal function

Date written: August 2009

Final submission: June 2009

Author: Solomon Cohny, John Kanellis, Martin Howell

GUIDELINES

No recommendations possible based on Level I or II evidence

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based primarily on Level III and IV evidence)

- An accurate assessment of the glomerular filtration rate (GFR) should be undertaken in all potential donors. The benefit of obtaining a directly measured GFR (thought to be more accurate) over an estimated GFR, has not been proven in live donors (refer to CARI guidelines titled 'Use of estimated glomerular filtration rate to assess level of kidney function' and 'Direct measurement of glomerular filtration rate').
- When the GFR is estimated it is recommended that this be on the basis of serum creatinine using, for example, the Cockcroft-Gault (CG) formula or the Modified Diet in Renal Disease (MDRD). Measurement of creatinine clearance calculated from a 24 h urine collection is also acceptable, if collected accurately. The estimated glomerular filtration rate (eGFR) should be confirmed on at least two separate occasions.
- If there is doubt regarding the GFR from estimated methods, further techniques can be used to assess or clarify this. Acceptable methods include a direct evaluation of the GFR by methods such as Cr-EDTA (nuclear GFR), iohexol or inulin clearance.
- It is preferable not to accept kidneys from donors with GFR < 80 mL/min per 1.73 m².

IMPLEMENTATION AND AUDIT

1. Ensure all donors are followed and results submitted to the Donor Registry.
2. Monitor outcomes in the Donor Registry.

BACKGROUND

The aim of this guideline is to provide an indication as to the acceptable lower limit of renal function for living donors prior to donation. This is primarily with a view to providing sufficient residual (donor) renal function post-donation. A separate consideration is that the donated

kidney needs to provide sufficient function for the transplant recipient.

While long-term outcomes of renal donors reported in the literature have generally been good, these reports are from an era when more stringent criteria for organ donors were used, and selection criteria generally ensured healthy donors with normal renal function. Studies of donors with reduced renal function are limited.¹

The increasing success and safety of transplantation (including for marginal recipients), the associated widening gap between transplant and dialysis outcomes, and the lengthening waiting lists for cadaveric kidneys have led to a greater demand for donors. In turn, this has led to a greater willingness to consider and accept donors with isolated medical abnormalities (IMA) (e.g. hypertension, obesity and lower GFR) and older age.²

Concerns with respect to living donors with lower GFR are the following:

- (i) Outcome for the recipient: Transplant GFR is an important determinant of graft and patient outcome post kidney transplantation.^{3–5} Lower GFR is likely to be associated with poorer outcome but is still almost always superior to outcome on dialysis.
- (ii) Risk of renal insufficiency in the donor: The risk of end-stage kidney disease (ESKD) in donors is in the order of 0.04–0.5%. In comparison, the prevalence of patients undergoing treatment for ESKD in Australia at the end of 2006 was 0.08%.⁶
- (iii) Consequences of reduced GFR for the donor in light of the current knowledge of the association between reduced GFR and cardiovascular risk*: The clinical significance of a reduced GFR may not be the same for an individual with a single healthy kidney compared with an individual with disease and/or diseased kidneys and the same level of renal function.⁷

*There may be additional considerations in relation to reduced renal mass such as mineral/bone metabolism and anaemia.

The following factors also warrant consideration:

- (i) GFR normally decreases with age.
- (ii) After donation, there is an initial decline in GFR of 25–35%, followed by a small increase, and then maintenance of GFR at 60–75% of pre-nephrectomy GFR.

(iii) The amount of reserve required post-nephrectomy needs to consider the number of years of life remaining – therefore, lower GFR may be acceptable in an older donor.⁸

(iv) Dialysis dependency after donor nephrectomy is almost always due to *de novo* renal disease.⁹

Renal function is most widely assessed by GFR, either measured or estimated. An accurate measure of GFR can be undertaken using low molecular weight markers of kidney function such as inulin, iohexol, technetium (labelled DTPA) or labelled EDTA, however, the methods are time-consuming, expensive and generally not available.¹⁰ In addition to the direct measurement of GFR, there are several methods for estimating GFR. The measurement of 24 h creatinine clearance tends to underestimate hyperfiltration and overestimate low GFR levels and is subject to errors in urine collection unless great care is taken. The regular measurement of serum creatinine levels is easy to perform and is currently the most common method. However, because creatinine is invariably reabsorbed by the renal tubules, serum creatinine and creatinine clearance measurements tend to underestimate the GFR in the context of hyperfiltration and overestimate the GFR in the context of hypofiltration.¹¹

Estimation of GFR by serum creatinine-based equations such as the CG or MDRD equations are commonly used for chronic kidney disease (CKD) screening, however, the application in healthy populations and for the screening of potential living kidney donors is less clear. For example, the Australasian Creatinine Consensus Working Group currently recommend that eGFR values greater than 90 mL/min per 1.73 m², estimated using the MDRD equation, only be reported as >90 mL/min per 1.73 m².¹²

SEARCH STRATEGY

Databases searched: MeSH terms and text words for kidney transplantation were combined with MeSH terms and text words for living donor, and combined with MeSH terms and text words for renal function. The search was carried out in Medline (1950–January Week 2, 2009). The Cochrane Renal Group, Trials Register was also searched for trials not indexed in Medline.

Date of searches: 20 January 2009.

WHAT IS THE EVIDENCE?

Defining normal renal function

Grewal and Blake report GFR reference data (measured by ⁵¹Cr-EDTA clearance) in a population of 428 potential living donors (50.9% women) aged 19–72 years.¹³ The reference data indicated a mean GFR until the age of 40 years of 103.4 mL/min per 1.73 m² after which the GFR declined at a mean rate of 9.1 mL/min per 1.73 m² per decade. There were no significant gender differences either in the mean or the rate of decline of GFR. These reference data have been used as the basis for defining minimal age dependent GFRs in living donors by the British Transplantation Society (refer to later section in this document). An earlier evalu-

ation of GFR reference values based on ⁵¹Cr-EDTA clearance values obtained from eight studies of healthy individuals, reported GFR to decline at all ages¹⁴ with a greater rate at ages after 50 years. The average rate of GFR decline with age prior to 50 was 4 mL/min per 1.73 m² per decade and 10 mL/min per 1.73 m² per decade thereafter. No significant differences between sexes were noted.

A significant ($P = 0.0002$) annual decline of 1.05 mL/min per 1.73 m² in GFR (iohexol) with age was also reported by Fehrman-Ekholm and Skeppholm in 52 healthy individuals aged 70–110 years.¹⁵ In this group, the CG equation was found to underestimate the average GFR by approximately 30% (46.2 ± 11.3 mL/min per 1.73 m² compared with 67.7 mL/min per 1.73 m²) and there was no correlation between serum creatinine and age.

Rule *et al.* examined the performance of creatinine-based equations in a population of healthy living kidney donors older than 18 years.¹⁶ A total of 365 patients (56.2% women) aged from 18 to 71 years (mean 41.1 years) had their GFR measured using non-radiolabelled iothalamate and GFR estimated using the CG and MDRD equations. The measured GFR declined by 4.6 mL/min per 1.73 m² per decade in men and 7.1 mL/min per 1.73 m² per decade in women, however, the difference between sexes was not significant. Regression analysis was significant for age but not sex with an all patient decline of GFR of 4.9 mL/min per 1.73 m² per decade for all age groups. This is in contrast to earlier studies where age-related GFR decline increased after the age of 40¹³ or 50 years.¹⁴

Assessment of MDRD and CG equations was undertaken by Rule *et al.* after exclusion of 67 non-white and non-African-American individuals (for MDRD) and 24 individuals for whom no body weight data were available (for CG).¹⁶ In the healthy population, both equations appeared to underestimate GFR by 29 mL/min per 1.73 m² and 14 mL/min per 1.73 m² for the MDRD and CG equations, respectively. A large cause of the difference can be attributed to laboratory calibration bias, however, even when corrected, correlation between estimated and measured GFR remained weak.¹⁶

Modelled estimates by Douville *et al.*¹⁷ of decline in GFR by age, based on creatinine clearance measurements in 7551 outpatients (aged 18–90 years) with normal serum creatinine, suggest a decline in GFR from approximately 120 mL/min per 1.73 m² in early adulthood down to approximately 60 mL/min per 1.73 m² when people are in their 80s. There was a continuous downward trend over 50 years of age and no significant differences between males and females.

In contrast to the above, the study by Berg of 112 potential kidney donors (55% female) aged 21–67 years indicated a significant decline in GFR with age in males but not in females, over the age range of 20–50 years.¹⁸ The mean GFR (measured by inulin clearance) at 20–30 years was 119 (± 12) mL/min per 1.73 m² and 102 (± 15) mL/min per 1.73 m² in males and females, respectively, and were significantly different. The mean GFR at 40–50 years was 100 (± 11) mL/min per 1.73 m² and 105 (± 11) mL/min per 1.73 m² in males and females, respectively, and the differences were not significant. The data suggested to the author

that women seem to be protected in the pre-menopausal period. The apparent decline in males 20–50 years of age was consistent with the data reported by Rule *et al.*¹⁶

Donor outcomes

A critical analysis of studies on long-term medical outcomes (including renal function) in living kidney donors by Ommen and colleagues¹⁹ identified the following issues that limit the ability to assess medical risks:

- virtually all studies are retrospective and commonly have large losses to follow up,
- studies commonly have small sample sizes,
- a lack of suitably matched controls, and
- a lack of consideration of potential risk factors for development of hypertension and renal dysfunction in donor groups.

As a consequence, assessment of the significance of findings of long-term renal function including the incidence of ESKD among donors is limited. Overall, in relation to renal outcomes, Ommen *et al.* consider that the available studies indicate no large decreases in GFR or increases in ESKD among donors. However, some studies suggest the potential for an increased risk of renal dysfunction in certain donors and given the limitations of the evidence, this suggests a cautionary approach should be taken in relation to 'marginal living donors'.¹⁹

The systematic review by Garg *et al.*²⁰ considered the following two questions for kidney donors:

- What proportion of kidney donors develop proteinuria or a GFR < 60 mL/min?
- Do kidney donors compared with controls have an accelerated loss of GFR after the initial decrement following nephrectomy?

The systematic review considered any study where 10 or more healthy adults donated a kidney and where proteinuria or GFR was assessed at least 1 year later. Studies that did not separate healthy donors from those with overt proteinuria or GFR < 80 mL/min per 1.73 m² were excluded. Forty-eight studies from 27 countries that followed a total of 5048 donors were identified. Eleven studies collected data on suitable non-donor controls, which allowed assessment of the risk of proteinuria and reduced kidney function following nephrectomy. Overall, studies with internal controls were limited and loss to follow up was high.

The average decrement in GFR (22 studies) in donors with normal renal function after donation was 26 mL/min per 1.73 m² (range 8–50). After 10 years (8 studies), 40% (range 23–52%) of donors had a GFR between 60 and 80 mL/min per 1.73 m², 12% (range 0–28%) had a GFR between 30 and 59 mL/min per 1.73 m² and 0.2% (range 0–2.2%) had a GFR less than 30 mL/min per 1.73 m². In the 6 controlled studies where average follow up was at least 5 years, the post-donation weighted mean difference in GFR among the donors compared with controls was –10 mL/min per 1.73 m² (95% CI: 6–15). Garg and colleagues note no evidence of an accelerated loss of GFR over that anticipated with normal ageing with the lower absolute

GFR being attributable to the decrement occurring as a result of nephrectomy. However, they also note that the prognostic significance of the reduced GFR in healthy donors is unknown given the mechanism of reduction is different to that which occurs in CKD.

The evidence with respect to the outcome of living kidney donors who have reduced GFR at the time of donation is limited. A systematic review and meta analysis of health outcomes for living donors with isolated medical abnormalities including age, obesity, hypertension or anti-hypertensive medication, haematuria, proteinuria, nephrolithiasis and reduced GFR (defined as ≤80 mL/min) has been recently completed by Young *et al.*¹ Only one study was identified that compared donors with a reduced GFR ($n = 16$) with those having normal GFR ($n = 75$).²¹ This was also the only study identified that considered proteinuria as an IMA. Although this was a prospective study, the proportion lost to follow up was not reported. One year after donation, the GFR was lower in the IMA group (51.7 ± 11 mL/min) compared with the control (68.0 ± 15 mL/min). At follow up 8 years after nephrectomy, the donor with the lowest GFR at 1 year (44 mL/min) had a GFR of 63 mL/min.

Young and colleagues also note that there are very few studies documenting important health outcomes among living kidney donors with IMAs. Across all IMA groups, longer term assessments (≥1 year) of blood pressure, proteinuria and renal function have been reported in only 3, 2 and 10 studies, respectively. Only 17 of the 37 studies included prospective data. A limited number provided loss to follow up and the studies were small. Overall, the ability of the primary studies to identify significant differences in long-term medical risks, including long-term renal function is limited.¹

In the study by Rook *et al.* examining the predictive capacity of pre-donation GFR, 31 of 125 donors had a post-donation GFR < 60 mL/min per 1.73 m².⁷ In this group, the mean pre-donation GFR measured by iothalamate was 99 mL/min ± 12 mL/min (88 ± 10 mL/min per 1.73 m²), while the pre-donation CG GFR was 83 ± 21 mL/min and the pre-donation GFR by simplified MDRD was 69 ± 8 mL/min. Follow up beyond 1 year (mean duration 161 months) was available for 63 donors. No significant deterioration in renal function occurred from <1 year to >1 year after nephrectomy as indicated by mean eGFR. Some studies have suggested that greater losses of GFR are seen in patients with low GFR,²⁰ while other studies have found that larger reductions in GFR occur in patients with higher pre-donation GFR.²²

Ramcharan and Matas²³ conducted a follow up of 773 living donor transplants 20–37 years after nephrectomy. Information was able to be obtained from 464 (60%) of the donors, of these, 380 were living at the time of the study and responses were obtained for 256. Serum creatinine levels and proteinuria assessments were available for 74 and 92 donors, respectively. The authors conclude that the long-term retrospective analysis indicates minimal deterioration in average serum creatinine levels and little proteinuria, but a few donors developed kidney dysfunction and ESKD. As

laboratory data were only available for 16% of the original donors, it is not possible to determine whether the incidence of kidney dysfunction was increased compared with non-donors.

The retrospective study by Gossman *et al.*²² achieved a 93% follow up of 152 living donors aged 45 ± 11 years at the time of donation and an average of 11 years (range 1–28 years) from the time of nephrectomy. The average eGFR (MDRD) showed a significant ($P < 0.001$) decrease from 92 ± 20 mL/min per 1.73 m^2 to 71 ± 15 mL/min per 1.73 m^2 at the time of evaluation. There was no significant correlation between the magnitude of loss of eGFR and duration since nephrectomy. No significant risk factors for the percentage loss of eGFR were identified (e.g. age, sex, smoking status, body mass index and blood pressure) other than the magnitude of the eGFR before donation.

A retrospective study of 1112 consecutive living kidney donors found an incidence of ESKD of 0.5%, occurring 14–27 years post donation (beginning 36 years after the start of the living donor program).²⁴ The age at the time of ESKD was 73–89 years, except for one younger donor who had developed renal cell carcinoma. The other renal diagnoses were nephrosclerosis in four patients, and obstructive uropathy in the other.

In an attempt to examine the cardiovascular risk of donor nephrectomy and the associated reduced GFR, Seyahi and colleagues used multidetector spiral computed tomography to examine coronary artery calcification (CAC) in 101 living kidney donors and 99 age- and sex-matched healthy controls without diabetes and a history of coronary artery disease.²⁵ GFR was calculated using the abbreviated MDRD formula. The frequency of risk factors for coronary artery disease was compared in kidney donors and controls, and the relation between kidney donors' clinical characteristics and the presence or absence of CAC was examined. The authors wished to examine the effect of the reduced GFR in the absence of other cardiovascular risk factors and used the following exclusion criteria: age older than 65 years, history of coronary artery disease (myocardial infarction, coronary artery angioplasty or bypass grafting surgery), stroke, diabetes mellitus, documented hypertension before nephrectomy or malignancy. Hypertension that developed after nephrectomy was not an exclusion criterion. Of 282 patients who donated between 1986 and 2000, 69 donors could not be contacted. Sixty-nine donors were older than 65 years, 6 had diabetes mellitus, 1 had a history of coronary artery disease, 4 had malignancy and 5 had documented hypertension before nephrectomy, leaving 101 patients for comparison with the control group. Patients had to be at least 12 months post-nephrectomy and the median time post-donation was 5 years. The mean GFR of kidney donors was 75 mL/min, which was approximately 25 mL/min per 1.73 m^2 (0.42 mL/min per 1.73 m^2) less than that of controls.

The frequency of CAC and mean calcification scores were similar for kidney donors (13.9%; 4.5 ± 22.6) and controls (17.2%; 13.2 ± 89.2). CAC was not associated with decreased GFR, and the correlation between CAC and GFR was not statistically significant. Kidney donors with calcifi-

cation were more likely to be older ($P = 0.003$) and male ($P = 0.001$). Age- and sex-adjusted analysis showed an association between greater parathyroid hormone (PTH) levels (odds ratio 1.023; 95% CI: 1.001–1.045; $P = 0.037$) and CAC in kidney donors.²⁵

Recognizing that a fixed lower limit of GFR does not adequately define donor acceptability (probably too low for young donors and too high for older donors), Thiel and colleagues developed calculations taking into account the life expectancy of the donor – the Minimum Creatinine Clearance.⁸ Discussions with nephrologists and gerontologists in Switzerland led them to define a creatinine clearance (CrCl) of 40 mL/min at age 80 years as adequate to maintain fluid and electrolyte homeostasis in the donor as well as maintaining adequate levels of erythropoietin and active Vitamin D. A second calculation was made targeting a CrCl of at least 30 mL/min per 1.73 m^2 at age 80 years as the absolute minimum acceptable for an elderly person (but possibly requiring some intervention to maintain normal, age-related quality of life). Using such a formula, a 30-year-old donor may require a CrCl of 123 mL/min per 1.73 m^2 while the level for a 70-year-old may be of the order of 68 mL/min per 1.73 m^2 .

SUMMARY OF THE EVIDENCE

Most of the evidence relating to renal function in living donors comes from retrospective cohort studies commonly of small size and with poor follow up (see Table 1). There is a lack of prospective long-term data regarding live donor renal function following donation, particularly in relation to consequences of donation in certain donor subgroups such as those with reduced GFR. There are few studies that include appropriately matched control groups to allow assessment of the significance of long-term changes in renal outcomes, in particular, the small incidence of ESKD following live kidney donation.

The available data in healthy populations (i.e. with normal renal function) indicate GFR declines with age. The rate of decline appears to be greater after the age of 40 or 50 years and may be constant or close to constant at younger ages (i.e. less than 40 years). The rate of decline in GFR after 40 or 50 years is in the order of 1 mL/min per 1.73 m^2 per year and the average GFR for young adults is in the order of 100–110 mL/min per 1.73 m^2 .

Overall, the evidence indicates that renal function, as measured by GFR, declines between 65% and 75% following donation with a long-term GFR around 10 mL/min per 1.73 m^2 less than would be expected without nephrectomy. There is no evidence of an accelerated decline compared with age-matched controls. The absolute decrement in GFR appears to remain constant with ageing. The prognostic implication of the reduced GFR in living kidney donors is unknown.

It is commonly acknowledged that there is a need for more precise information regarding long-term risks faced by donors. This would ideally be obtained from prospectively collected live donor registry data.

WHAT DO THE OTHER GUIDELINES SAY?

British Transplant Society (2005)²⁶

The potential kidney donor must have sufficient kidney function prior to donation to have an effective GFR at the age of 80 years independent of the age at which he/she donated. Acceptable GFR by donor age have been derived based on the reference data reported by Grewal and Blake¹³ and therefore assumes a constant GFR up until age 40. The acceptable GFR prior to donation have been established so as to achieve a predicted GFR at 80 greater than 37.5 mL/min per 1.73 m² which is equal to the population mean at 80 minus 2 standard deviations. The acceptable GFR by donor age are as listed in the table below:

Donor age (years)	Acceptable corrected GFR prior to donation (mL/min per 1.73 m ²)
Up to 40	86
50	77
60	68
70	59
80	50

GFR should be measured using an isotopic marker in all potential donors as alternate methods based on serum creatinine are not sufficiently accurate in this context and measured creatinine clearance, using timed urine collections, is susceptible to considerable inaccuracy. When renal function is normal but there is a significant difference in function between the two kidneys, the kidney with lower function should be used for transplantation.

European Renal Association-European Dialysis and Transplant Association (2000)²⁷

It is recommended that donor renal function be assessed by 24 h urine for creatinine clearance or a direct evaluation of the GFR by Cr-EDTA or iothexol or inulin clearance. As an optional assessment radionuclide determination of GFR as a separate evaluation of the function of the two kidneys. Donors with a reduced GFR in comparison to the normal range for age should be excluded.

The Amsterdam Forum on The Care of the Live Kidney Donor (2005)²⁸

Adopted the following consensus guideline regarding acceptable renal function:

- A GFR < 80 mL/min or 2 standard deviations below normal (based on age, gender and body surface area corrected to 1.73 m²) generally precludes donation.
- Kidneys from live donors with GFR ≤ 80 mL/min are associated with a relative risk of graft loss of 2.28 compared with those with greater pre-nephrectomy GFR.⁵
- However, successful transplantation was noted from some, usually elderly living donors, with GFR as low as 65–70 mL/min, indicating a need for individualization and careful follow up of donors with GFR of <80 mL/min per 1.73 m².

The Canadian Council for Donation and Transplantation (2006)²⁹

It is recommended that in the absence of higher quality evidence, it is reasonable to refer to existing guidelines regarding the assessment and eligibility of potential living kidney donors (e.g. Amsterdam Forum). However, it is recommended that these guidelines not be used as absolute criteria where risk is poorly quantified or uncertain.

American Society of Transplantation Position Statement on the Medical Evaluation of Living Kidney Donors (2007)³⁰

Renal focused evaluation to determine the presence of underlying kidney disease in the potential donor should include measurement of GFR (method not specified).

CKD Stage 3 or less (defined as 30–59 mL/min per 1.73 m²) will typically exclude a living donor candidate from donating based upon scientific data of medical risk.

The Organ Procurement and Transplantation Network (2008)³¹

Medical evaluation of potential donors should include:

- measurement of GFR by 24 h urine collection or equivalent testing. Possible exclusion criteria that may make an individual unsuitable for living donation includes:
- creatinine clearance < 80 mL/min per 1.73 m², or projected GFR with removal of one kidney at 80 years old of <40 mL/min per 1.73 m².

SUGGESTIONS FOR FUTURE RESEARCH

Perform a prospective assessment of donors with respect to the relationship between pre-donation GFR and:

- mortality
- cardiovascular system complications
- long-term renal function
- pre-donation GFR
- haemoglobin
- vitamin D/calcium, PTH
- renal function (isotopic GFR) and graft outcome of recipients.

CONFLICT OF INTEREST

Solomon Cohny has a Level IIb conflict of interest while John Kanellis and Martin Howell have no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

REFERENCES

1. Young A, Storsley L, Garg A *et al*. Health outcomes for living kidney donors with isolated medical abnormalities: A systematic review. *Am. J. Transplant.* 2008; **8**: 1878–90.
2. Davis CL, Delmonico FL. Living-donor kidney transplantation: A review of the current practices for the live donor. *J. Am. Soc. Nephrol.* 2005; **16**: 2098–110.

3. Hawley CM, Kearsley J, Campbell SB *et al.* Estimated donor glomerular filtration rate is the most important donor characteristic predicting graft function in recipients of kidneys from live donors. *Transplant. Int.* 2007; **20**: 64–72.
4. Issa N, Stephany B, Fatica R *et al.* Donor factors influencing graft outcomes in live donor kidney transplantation. *Transplantation* 2007; **83**: 593–9.
5. Norden G, Lennerling A, Nyberg G. Low absolute glomerular filtration rate in the living kidney donor: A risk factor for graft loss. *Transplantation* 2000; **70**: 1360–62.
6. Australian and New Zealand Dialysis and Transplant Registry. ANZDATA Registry Report 2007. p. 30.
7. Rook M, Hofker HS, van Son WJ *et al.* Predictive capacity of pre-donation GFR and renal reserve capacity for donor renal function after living kidney donation. *Am. J. Transplant.* 2006; **6**: 1653–59.
8. Thiel G, Nolte C, Tsinalis D. Living kidney donors with isolated medical abnormalities: The SOL-DHR experience. In: Gaston RS, Wadstrom J (eds). *Living Donor Kidney Transplantation*. London: Taylor & Francis, 2005; 55–73.
9. Hartmann A, Fauchald P, Westlie L *et al.* The risk of living kidney donation. *Nephrol. Dial. Transplant.* 2003; **18**: 871–73.
10. Mathew TH, Australasian Creatinine Consensus Working Group. Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: A position statement. *Med. J. Aust.* 2005; **183**: 138–41.
11. Shemesh O, Golbetz H, Kriss JP *et al.* Limitations of creatinine as a filtration marker in glomerulopathic patients. *Kidney Int.* 1985; **28**: 830–38.
12. Mathew TH, Johnson DW, Jones RD. Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: Revised recommendations. *Med. J. Aust.* 2007; **187**: 459–63.
13. Grewal GS, Blake GM. Reference data for 51Cr-EDTA measurements of the glomerular filtration rate derived from live kidney donors. *Nucl. Med. Comm.* 2005; **26**: 61–5.
14. Granerus G, Aurell M. Reference values for 51Cr-EDTA clearance as a measure of glomerular filtration rate. *Scand. J. Clin. Lab. Invest.* 1981; **41**: 611–16.
15. Fehrman-Ekholm I, Skeppholm L. Renal function in the elderly (>70 years old) measured by means of iohexol clearance, serum creatinine, serum urea and estimated clearance. *Scand. J. Urol. Nephrol.* 2004; **38**: 73–7.
16. Rule AD, Gussak HM, Pond GR *et al.* Measured and estimated GFR in healthy potential kidney donors. *Am. J. Kidney Dis.* 2004; **43**: 112–19.
17. Douville P, Martel AR, Talbot J *et al.* Impact of age on glomerular filtration estimates. *Nephrol. Dial. Transplant.* 2009; **24**: 97–103.
18. Berg UB. Differences in decline in GFR with age between males and females. Reference data on clearances of inulin and PAH in potential kidney donors. *Nephrol. Dial. Transplant.* 2006; **21**: 2577–82.
19. Ommen ES, Winston JA, Murphy B. Medical risks in living kidney donors: Absence of proof is not proof of absence. *Clin. J. Am. Soc. Nephrol.* 2006; **1**: 885–95.
20. Garg AX, Muirhead N, Knoll G *et al.* Proteinuria and reduced kidney function in living kidney donors: A systematic review, meta-analysis, and meta-regression. *Kidney Int.* 2006; **70**: 1801–10.
21. Tsinalis D, Binet I, Steiger J *et al.* Can 'borderline' living kidney donors (BLKD) be used safely for transplantation? *Kidney Blood Press. Res.* 1999; **22**: 388–89.
22. Gossman J, Wilhelm A, Kachel HG *et al.* Long-term consequences of live kidney donation follow-up in 93% of living kidney donors in a single transplant center. *Am. J. Transplant.* 2005; **5**: 2417–24.
23. Ramcharan T, Matas AJ. Long-term (20–37 years) follow-up of living kidney donors. *Am. J. Transplant.* 2002; **2**: 959–64.
24. Fehrman-Ekholm I, Norden G, Lennerling A *et al.* Incidence of end-stage renal disease among live kidney donors. *Transplantation* 2006; **82**: 1646–48.
25. Seyahi N, Kahveci A, Bolayirli M *et al.* Coronary artery calcification and chronically decreased GFR in living kidney donors. *Am. J. Kidney Dis.* 2007; **49**: 143–52.
26. British Transplant Society and the Renal Association. *United Kingdom Guidelines for Living Donor Kidney Transplantation*, 2nd edn. British Transplant Society and the Renal Association, 2005.
27. European Renal Association and European Dialysis and Transplant Association. European Best Practice Guidelines for Renal Transplantation (Part 1). II.3 Living kidney donors. *Nephrol. Dial. Transplant.* 2000; **15** (Suppl 7): 47.
28. Delmonico F. Council of the Transplantation Society. A Report of the Amsterdam Forum on the Care of the Live Kidney Donor: Data and Medical Guidelines. *Transplantation* 2005; **79** (6 Suppl): S53–S66.
29. The Canadian Council for Donation and Transplantation. *Enhancing Living Donation: A Canadian Forum*. February 9–12 2006 Vancouver [Cited July 2009.] Available from URL: <http://www.ccdt.ca/>.
30. AST Position Statement on the Medical Evaluation of Living Kidney Donors. *American Society Transplantation* 2007. [Cited July 2009.] Available from URL: http://www.a-s-t.org/files/pdf/public_policy/key_position/EvalLivingKidney.pdf
31. The Organ Procurement and Transplantation Network. *Guidance for the Development of Program-Specific Living Kidney Donor Medical Evaluation Protocols* 2008. [Cited July 2009.] Available from URL: <http://optn.transplant.hrsa.gov/>

APPENDIX

Table 1 Characteristics of included studies

Study ID	N	Study design	Participants	Follow up	Comments and results
Defining normal renal function Grewal and Blake (2005) ¹³	428	Retrospective analysis. GFR measured by ⁵¹ Cr-EDTA.	Potential UK live kidney donors after screening and exclusion for non-renal contraindications for donation. 218 females, 210 males; age range 19–72 years.	NA	Pooled GFR for males and females was constant at 103.4 mL/min per 1.73 m ² until the age of 40 and then declined at a rate of 9.1 mL/min per 1.73 m ² per decade thereafter.
Granerus G and Aurell M (1981) ¹⁴	503	Combined analysis of 8 retrospective studies. GFR measured by inulin or ⁵¹ Cr-EDTA.	Healthy men and women of different ages. 145 females, 358 men; ages 17–75.	NA	No systematic difference between measured mean ⁵¹ Cr-EDTA clearance values and mean values calculated from inulin clearance. Decrease with increasing age of approximately 4 mL/min per decade at age less than 50 years and 10 mL/min per decade at age greater than 50 years. The mean (\pm standard deviations) was 105 \pm 26 mL/min at 30 years; 98 \pm 23 mL/min at 50 years; and 78 \pm 24 mL/min at 70 years.
Fehrman-Ekholm and Skeppholm (2004) ¹⁵	52	Cross-sectional. GFR measured by iohexol clearance and estimated from serum creatinine by a range of equations.	20 females, 32 males; ages 71–110	NA	GFR by iohexol clearance showed a linear correlation with age with a mean annual decline of 1.05 mL/min (i.e. approximately 11 mL/min per decade). GFR ranged from 113 to 38 mL/min per 1.73 m ² with a mean of 67.7 mL/min per 1.73 m ² . The CG formula underestimated GFR.
Rule <i>et al.</i> (2004) ¹⁶	365	Retrospective analysis. GFR measured using non-radiolabelled iothalamate clearance and estimated from serum creatinine using CG and MDRD equations.	Potential living donors. 205 females, 106 males; ages 18–71 years; predominantly white Americans	NA	Linear regression analysis significant for age but not gender with an overall decline of 4.9 mL/min per 1.73 m ² per decade. Mean GFR declined from 111 mL/min per 1.73 m ² at age 20 to 84 mL/min per 1.73 m ² at age 75. The rate of decline before and after 50 years was not significantly different. Both the CG and MDRD equations provided weak correlation with measured GFR.
Douville <i>et al.</i> (2009) ¹⁷	Group A – 773 Group B – 7551	Cross-sectional analysis. GFR estimated from serum creatinine (Group A and B) and creatinine clearance (Group A only). eGFR by MDRD, MAYO and CHUQ.	Group A outpatients with completed 24 h creatinine clearance (45% female; ages 18–90 years). No exclusion for chronic kidney disease. Group B non-hospitalized clinic patients with normal serum creatinine (56% female; ages 18–102)	NA	Relatively stable GFR up until age 30 followed by a slow decline. Modelling suggests a regular decrease in GFR from approximately 120 mL/min per 1.73 m ² in early adulthood to approximately 60 mL/min per 1.73 m ² in the 80s with a continuous trend over 50 years of age. Analysis did not include a gold standard for GFR.

Table 1 Continued

Study ID	N	Study design	Participants	Follow up	Comments and results
Berg (2006) ¹⁸	122	Cross-sectional analysis. GFR measured by inulin clearance.	Potential live kidney donors. 62 female, 60 male; ages 21–67 years.	NA	GFR not significantly different between men and women (105 and 106 mL/min per 1.73 m ² respectively). Significant mean decline with age of 5.1 mL/min per 1.73 m ² per decade. The rate of decline in males was 8.1 mL/min per 1.73 m ² which was significantly different to females (1.4 mL/min per 1.73 m ²).
Donor outcomes Ommen <i>et al.</i> (2006) ¹⁹	125 studies	Systematic review	Living donors.	NA	Studies are predominantly small, retrospective with a low participation rate and tend to lack suitable controls. Characteristically underpowered to detect clinically meaningful differences between donors and comparison groups. Given the difficulty in measuring renal function, studies may underestimate the impact of donation.
Garg <i>et al.</i> (2006) ²⁰	5048 donors	Systematic review, meta analysis and meta regression.	10 or more health kidney donors and either proteinuria or GFR assessed at 1 year or later. Total of 48 studies of which 36 (3529 donors) reported a post-donation serum creatinine or GFR.		Overall high loss to follow up of about one-third on average. In 22 studies the average decrement in GFR after donation was 26 mL/min per 1.73 m ² (range of 8–50). In nine studies after a mean of 10 years post-donation 40% had a GFR between 60 and 80 mL/min per 1.73 m ² , 12% between 30 and 59 mL/min per 1.73 m ² , and 0.2% less than 30 mL/min per 1.73 m ² . In six studies with controls the post-donation GFR was 10 mL/min per 1.73 m ² lower in donors compared with controls. The difference did not vary significantly with time from donation. No evidence of an accelerated loss in GFR over that anticipated with normal ageing.
Young <i>et al.</i> (2008) ¹	37 studies	Systematic review	Living kidney donors with isolated medical abnormalities. Greater than 1 year duration with three or more living kidney donors.	Minimum 1 year	Only one study was identified that included reduced GFR (defined as <70 mL/min by inulin clearance). Overall the ability of the studies to identify significant differences in long-term medical risks is limited.
Tsinalis <i>et al.</i> (1999) ²¹	180	Prospective cohort. GFR by inulin clearance measured before and 1 year after donation	'Normal' and 'Borderline' living kidney donors of whom 16 had GFR < 70 mL/min.	1 year	Normal group GFR declined from 101.8 mL/min to 68.0 mL/min 1 year after donation. No significant difference in abnormal group with low GFR prior to donation. Insufficient long term follow up to give a recommendation with respect to abnormally low GFR.

Rook <i>et al.</i> (2006) ⁷	125	Prospective analysis. GFR and dopamine stimulated GFR measured using ¹²⁵ I-iothalamate clearance	Consecutive donors (45 males; age 49 ± 11 years)	57 ± 16 days	The average baseline GFR was 104 ± 15 mL/min per 1.73 m ² . GFR fell to 64 ± 7% of the pre-donation value. eGFR by MDRD fell to 71 ± 7% of pre-donation eGFR. Renal function impairment (GFR < 60 mL/min per 1.73 m ²) occurred in 25% of donors after donation. Independent risk factors for low GFR post-donation were, low GFR pre-donation, age and body mass index.
Gossmann <i>et al.</i> (2005) ²²	152	Retrospective analysis. Pre-donation data taken from records. Post-donation from 24 h urine and blood samples. Abbreviated MDRD used to estimate GFR.	Live donors cohort from a single centre from the period 1973–2001 (96 females; age at donation 45 ± 11)	11 ± 1 years	Achieved 93% follow up of the 145 donors who were alive at follow up. Creatinine clearance declined from 119 ± 30 mL/min per 1.73 m ² to 99 ± 30 mL/min per 1.73 m ² after donation ($P < 0.001$) and eGFR from 92 ± 20 mL/min per 1.73 m ² to 71 ± 15 mL/min per 1.73 m ² ($P < 0.001$). No significant correlation between the loss of GFR with time after donation. The only significant risk factor for the percentage loss of GFR was a higher GFR at the time of donation.
Ramcharan and Matas (2002) ²³	464	Retrospective analysis	Laboratory results available for 125 living donors who donated over the period 1963–1979	20–37 years	Obtained information on 60% and laboratory results from 16% of the donors. Of the 84 donors known to have died three were known to have had kidney failure. Of the 380 alive, three had abnormal kidney function and two undergone transplantation. Remainder had normal kidney function. Most donors had normal kidney function 20–37 years after donation. The retrospective nature and the large loss to follow up limit the ability to assess the significance of the small number who developed renal dysfunction and renal failure.
Fehrman-Ekholm <i>et al.</i> (2006) ²⁴	1,112	Retrospective analysis of medical records	Consecutive living donors who donated over the period 1965–2005	1–40 years (median 14 years)	Six (0.5%) had developed ESKD. Majority were males, most common diagnosis was nephrosclerosis and the age at time of uraemia was 73–89 years. Time since donation was 14–27 years, median 20 years.
Seyahi <i>et al.</i> (2007) ²⁵	101 (donors) 99 (controls)	Cross-sectional analysis GFR estimated using MDRD	Live donors ≥ 1 year after nephrectomy. Exclusion criteria, age older than 65 years, history of coronary artery disease, stroke, diabetes, hypertension before donation and malignancy.		The mean eGFR of donors was significantly lower than the control group ($P < 0.001$) being 75 ± 16.0 mL/min per 1.73 m ² compared with 99.8 ± 20.7 mL/min per 1.73 m ² . The incidence of ESKD was in the same order as expected for the Swedish population taking age into account.

CG, Cockcroft-Gault; GFR, glomerular filtration rate; ESKD, end-stage kidney disease; MDRD, Modified Diet in Renal Disease.