Proteinuria and reduced kidney function in living kidney donors: a systematic review, meta-analysis, and meta-regression


CRD summary
The authors conclude that live kidney donation is safe. However, it causes a small rise in urinary protein which increases over time, as well as an initial decrease in the glomerular filtration rate which does not worsen over time except when due to normal ageing. Despite limitations associated with poor-quality primary studies, these conclusions appear well supported by the data.

Authors' objectives
To determine the long-term effects of donating a kidney on the donor's kidney function.

Searching
MEDLINE, EMBASE and the Science Citation Index were searched to November 2005; the search terms were reported. Citations provided by primary study authors, articles retrieved by the 'Related Articles' feature on PubMed, and the reference lists of previous reviews and the included studies were also checked.

Study selection
Study designs of evaluations included in the review
Studies of any design with at least 10 participants were eligible for inclusion.

Specific interventions included in the review
Eligible studies included donation of kidneys by living adult donors.

Participants included in the review
Studies of healthy normotensive adult kidney donors were eligible for inclusion. Studies that included participants with hypertension, overt proteinuria or a glomerular filtration rate (GFR) of less than 80 mL/minute were excluded, unless they analysed healthy donors separately. The participants in the included studies had a mean pre-surgery age of 41 years (range: 26 to 59). The controls (where included) comprised healthy volunteers or potential donors of similar age, gender, race and/or height.

Outcomes assessed in the review
Studies were eligible if they assessed either proteinuria or GFR at least a year after kidney donation. The outcomes in the included studies were assessed for a mean of 7 years' follow-up (range: 1 to 25). In most studies urine protein was quantified via a timed (24 hourly) collection or random urine sampling. Clinical proteinuria in the included studies was defined by levels on a urinary dipstick or thresholds varying from greater than 100 mg to greater than 600 mg of protein daily. In most cases the GFR was estimated via a timed urine creatinine clearance and was standardised to 1.73 square metres of body surface area. The other outcomes reported were serum creatinine, death and/or kidney failure during follow-up, and pre-donation prognostic features of higher proteinuria or lower GFR post-donation.

How were decisions on the relevance of primary studies made?
Pairs of reviewers working independently determined the eligibility of English language studies, with any disagreements resolved by a third reviewer. A single reviewer assessed the eligibility of non-English language articles, with the help of a translator.

Assessment of study quality
The following features were assessed: whether the study was prospective; whether the outcomes were collected at fixed intervals; the duration of follow-up; whether renal function measures were clearly defined; whether the participation rate of eligible donors was reported; rates of loss to follow-up; and whether details about losses to follow-up were reported. Two reviewers assessed validity independently, with any disagreements resolved by a third reviewer.
Data extraction
Pairs of reviewers working independently extracted the data from English language studies, with any disagreements resolved by a third reviewer. A single reviewer abstracted the data from non-English language articles, with the help of a translator. Attempts were made to contact the authors of primary studies, to check data and supply missing information: 31 authors responded.

For binary outcomes, the percentage of participants with each outcome and the 95% confidence interval (CI) were reported; for continuous outcomes, the mean and standard deviation were reported. Where measures of variance for pre-donation and post-donation GFR were not reported by the primary study, estimates were calculated from t-statistics or imputed from correlations between pre- and post-donation data. Creatinine clearance was used as a proxy for GFR in the meta-analysis, and GFR was reported as mL/minute per 1.73 m², whether or not the GFR was standardised to body surface area. Where studies provided a range of donor follow-up, the mean follow-up time was estimated as the midpoint of the provided range.

Methods of synthesis
How were the studies combined?
The study results were tabulated and/or were pooled in meta-analyses, using random-effects models, weighted according to study variance.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Q statistic (p<0.05 considered significant). The I-squared statistic was also used to quantify heterogeneity, with 30%, 50% and greater than 50% representing the thresholds for mild, moderate and notable heterogeneity, respectively.

Differences between study findings were explored using univariate and multivariate meta-regression mixed models for continuous outcomes, and logistic normal random-effects models for dichotomous outcomes. Meta-regression was used to test whether methodological differences between the studies predicted reduced kidney function (increased proteinuria or lower GFR) post-donation, or whether selected donor variables (older age, higher pre-donation blood pressure, lower pre-donation GFR) were prognostic. A two-tailed p-value of less than or equal to 0.05 was considered statistically significant for dichotomous variables; for continuous variables, statistical significance was inferred by the degree to which each variable accounted for overall variability and the size of residual variance. Sensitivity analyses were performed to investigate the effect of the choice of correlation between pre- and post-donation data.

Results of the review
Forty-eight observational studies (n=5,048 donors) were included, of which ten were prospective (n=1,330) and the remainder were retrospective (n=3,718). Eleven studies had control groups.

Only 21% of the studies were prospective (10 out of 48) and only 15% (7 out of 48) had donor outcomes measured at fixed years post-donation. Few studies (23%) were controlled, and those that had controls assembled them at the time of follow-up assessment in the intervention group. Most studies (67 to 91%) defined the outcome measures, but there was limited consistency across studies in terms of the methods used, few used up-to-date methods of assessing renal function, and it was unclear whether donors who developed a low GFR also had proteinuria. The majority of studies described the total number of donors from which the participating sample was drawn. A mean of 30% of surviving eligible donors were lost to follow-up (range: 0 to 78%) and few studies (8%) provided details about losses to follow up.

Proteinuria.

The incidence of proteinuria was reported in 42 studies (n=4,793) with a mean follow-up of 7 years (range: 2 to 25). Incidence ranged from less than 5% to more than 20%, with significant heterogeneity between the studies (p<0.0001). The pooled incidence was 12% (95% CI: 8, 16). A supplementary analysis of 9 studies (n=1,799), with a mean follow-up of 7 years and a common definition of proteinuria, found a pooled incidence of 10% (95% CI: 7, 12).

Three studies compared 24-hour urine protein in donors (n=129) versus controls (n=59) at a mean of 11 years' follow
up. There was a significantly higher risk among donors (weighted mean difference 66 mg/day, 95% CI: 24, 108), with no heterogeneity. The difference increased with the time from donation (p<0.001). Four studies compared 24-hour urine albumin between 146 donors and 105 controls. The results were not pooled because of heterogeneity (p<0.00001). Three out of 4 studies showed significantly higher urine albumin in the donor groups at 7 to 15 mean years' follow-up. Two studies that measured micro-albuminuria in 67 donors and 51 controls reported a significantly higher rate among donors (relative risk 3.9, 95% CI: 1.2, 12.6). However, there was notable heterogeneity in this result (p=0.13; I-squared 56%).

GFR.

Thirty-six studies (n=3,529) reported a post-donation serum creatinine of 98 micromol/L (range: 58 to 119) and an average GFR of 86 mL/minute (range: 64 to 117) at a mean follow-up of 6 years. The average reduction in GFR post-donation was 26 mL/minute in the 22 studies that reported this outcome. Nine studies reported post-donation GFR in categories: a mean of 10 years post-donation, the GFR was 60 to 80 mL/minute in 40% of donors, 30 to 59 mL/minute in 12% of donors and less than 30 mL/minute in 0.2% of donors.

Among 239 donors and 189 controls in 6 studies that compared GFR over a mean of at least 5 years, the pooled GFR was significantly lower in donors (weighted mean difference 10 mL/minute, 95% CI: 6,15) The difference was similar across studies, irrespective of the time from donation (p=0.2).

Prognostic features.

Mean age at donation, gender and mean pre-donation blood pressure were not significantly associated with proteinuria post-donation (p=0.22 to p=0.69). The only methodological features associated with post-donation kidney function were loss to follow-up (higher losses were associated with a somewhat larger decrease in GFR) and mean follow-up time post-donation (longer time associated with a higher rate of clinical proteinuria) (range of p values: 0.09 to 0.68).

Death, kidney failure and cardiovascular disease.

Deaths ranged from 0 to 16% in the 33 studies that reported this outcome. Ten donors (0.2%) were reported to have developed kidney failure requiring dialysis during follow-up. However, kidney failure and cardiovascular disease were not systematically assessed in the included studies.

Sensitivity analyses did not change the statistical significance of any of the results.

Authors' conclusions

Live kidney donation is safe. However, it associated with small increases in urinary protein, which become more pronounced over time. It is also associated with an initial decrement in GFR, but this does not become more pronounced over time beyond changes associated with normal ageing.

CRD commentary

This review addressed a clear objective with defined inclusion criteria. Several relevant sources and strategies were used in the literature search, the quality of the included studies was assessed in detail, and adequate steps were taken to minimise potential error and bias during the review process. Suitable meta-analytic techniques appear to have been used to pool the main results, and heterogeneity was assessed and (where present) investigated. Sensitivity analyses were used to investigate the effect of review methodology. Although the review was limited by the poor quality of the primary studies, the authors' conclusions appear well supported by the data.

Implications of the review for practice and research

Practice: The authors stated that live kidney donation is safe but that donors should have their serum creatinine clearance and urine protein screened annually for life, until the implications of low-grade proteinuria or reduced GFR in some donors is better understood. All donors should be advised about the prevention of future renal and cardiovascular disease.

Research: The authors stated that a large prospective multicentre cohort study with long-term follow-up is needed, with
representative numbers of donors and appropriate controls followed for extended periods. A diverse range of participants should be included to ascertain the differential effects of donation in different groups, and definitive outcomes such as death and cardiovascular disease should be measured.

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