

Donors at risk: proteinuria

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GUIDELINES

No recommendations possible based on Level I or II evidence

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- Potential living donors should have their urinary protein excretion measured using either a 24-hour urine collection (daily excretion) or a spot urine sample (protein/creatinine ratio).
- A urine protein excretion of >300 mg/day (24 hour collection) or of >30 mg/mmol (spot urine protein/creatinine ratio) is usually a contraindication to live donation.
- Further investigations are warranted when urine protein excretion is >150 mg/day but less than <300 mg/day (corresponds approximately with spot urinary protein/creatinine of >15 mg/mmol but <30 mg/mmol). Repeat urinary protein estimation, as well as measurement of urinary albumin excretion may help in further assessing potential living donors.
- Although overt proteinuria may be absent, the presence of microalbuminuria (urinary albumin excretion of >30 mg/day or >20 µg/min; albumin/creatinine ratio >2.5 mg/mmol) should be considered a relative contraindication to live donation.
- Microalbuminuria or mild proteinuria (<300 mg/day) occurring in the presence of another associated clinical or laboratory abnormality (e.g. hypertension, obesity, glucose intolerance, glomerular haematuria) should be considered a relative contraindication to live donation.
- In potential living donors with minor degrees of proteinuria or albuminuria, a renal biopsy may help in further assessing the donor's risk of developing progressive renal disease following donation (Opinion).
- Donors should have their urinary protein excretion measured as part of their routine, follow-up care. It is recommended that this be performed at least once a year along with blood pressure and serum creatinine measurement (Opinion).

IMPLEMENTATION AND AUDIT

Short- and long-term living kidney donor outcomes need to be closely monitored.

BACKGROUND

The aim of this guideline is to review the available literature on the potential long-term risks of donating a kidney in the presence of pre-donation proteinuria and to develop suggestions for management of these potential donors.

The justification for performing living kidney donation is based on the benefits of the procedure on the recipient's health and on the psyche of the donor through the act of altruism, outweighing the short- and long-term adverse outcomes on the donor. In the medical assessment of the potential donor, a critical estimation is made of their future risk of kidney failure and cardiovascular disease. If the risk is predicted to be too great then the living kidney donation does not proceed.

A normal amount of urinary protein excretion is dependent on the local laboratory but is typically <150 mg/24 hours or a spot urine protein to creatinine ratio of <15 mg/mmol. In some laboratories, the upper limit of normal may be as high as 300 mg/24 hours. Increased levels of proteinuria are a sensitive marker in the general population of an increased risk of kidney failure and cardiovascular disease.^{1–6} The theoretical incremental increase in the risk of future kidney failure with the combination of proteinuria and a nephrectomy has resulted in this factor being examined critically in all potential donors.

In living kidney donors who had a normal amount of proteinuria prior to the nephrectomy, studies to date have consistently demonstrated the development of proteinuria post-nephrectomy in up to 41% of donors.⁷ In a meta-analysis, the pooled incidence of proteinuria was 10% after 7 years post-nephrectomy.⁷ One of the difficulties in interpreting adverse long-term outcomes in living kidney donors is teasing apart the relative contribution of the nephrectomy to the adverse event from the ageing process and the development of other comorbidities in the donor. In all 3 studies that compared the development of proteinuria in healthy donors to control patients, the incidence of proteinuria was increased in the donors.^{8–10} A meta-analysis of these studies demonstrated that donors had a statistically significant 66 mg/24 hour increase in proteinuria compared with non-donor controls, an average of 11 years post-nephrectomy.⁷ However, none of these

studies meet strict methodological criteria to accurately assess the long-term risk of proteinuria in healthy living kidney donors.^{7,11}

To date, there has only been one publication that assesses the long-term risk for donors who already have increased levels of proteinuria pre-donation.¹² The results of this study are inconclusive however, due to its small sample size, short follow-up and lack of non-donor controls. As such, it is not possible to directly estimate the effect of proteinuria pre-donation on the long-term outcomes of a living kidney donor. Estimates must therefore be made through extrapolation of results from the general population and the assumption that it will be at least as great as that seen in healthy donors.

The mechanism through which a living donor develops proteinuria is different to that for members of the general population who have proteinuria. As such, the relative significance of the degree of proteinuria in donors' post-nephrectomy compared to that seen in the general population is also uncertain.

Measurement of urinary albumin excretion, through a 24-hour urine collection or a spot urine albumin to creatinine ratio has been shown to be a sensitive and specific marker of proteinuria.¹³ Elevated levels of urinary albumin excretion are a risk factor in diabetic and non-diabetic patients of kidney failure and cardiovascular disease.¹⁻⁴ The relative strengths of albuminuria versus proteinuria are uncertain in the general population. Studies in living kidney donors to date are lacking, and so the interpretation of the effect of the degree of urinary albumin excretion on long-term outcomes in addition to the determination of a well-accepted cut-off level is uncertain.

In a single study of donors who had a 24-hour urine protein excretion between 150 mg and 300 mg, the simultaneous estimation of urinary albumin excretion was normal in all individuals.¹⁴ No follow-up, however, was provided to determine which factor proved to be the superior risk marker.

The effect of the addition of proteinuria with other renal and cardiovascular risk factors is uncertain. There is limited literature on this topic but it is assumed that there would be an incremental rise in the adverse long-term outcome of living kidney donors with every additional risk factor. The size of this incremental rise is unknown.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for kidney transplantation were combined with MeSH terms and text words for living donor and with MeSH terms and text words for hematuria, proteinuria, and albuminuria, combined with the Cochrane highly sensitive search strategy for prognosis questions. The search was carried out in Medline (1966 – January Week 2, 2008). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

Date of search/es: 15 January 2008.

WHAT IS THE EVIDENCE?

Due to the limited information on the outcome in living kidney donors with pre-donation proteinuria, we commenced our review by examining the effect of donation on proteinuria in healthy living kidney donors (i.e. normal blood pressure, GFR > 80 mL/min and normal amount of proteinuria pre-donation). There are more than 40 studies that describe the development of proteinuria following living kidney donation in donors who had 'normal' levels of proteinuria pre-operatively.⁷ The key studies include a study that followed 70, out of a possible 180 donors, over 20 years following nephrectomy.¹⁵ These authors discovered 19% of donors had a protein excretion of over 150 mg/24 hours and 7% had greater than 800 mg/24 hours.

Fehrman-Ekholm *et al.* described 348 Swedish living kidney donors a mean of 12 years post-donation.¹⁶ They detected 'slight' proteinuria (<1.0 g/L) in 9% and 'significant' proteinuria (≥1.0 g/L) in 3% of donors. There was a significant association between proteinuria and increased blood pressure ($P < 0.01$) and lower glomerular filtration rate ($P < 0.05$).

There are 3 published articles that examined the long-term outcome of proteinuria in donors compared with controls.⁸⁻¹⁰ They compared a total of 129 donors with 83 control subjects, with a mean follow-up of 11 years after donation. Two of the 3 papers detected a statistically significant increase in proteinuria in the donors compared with the control. On pooling the results, the weighted average increase in proteinuria in living kidney donors was 66 mg/24 hours compared with controls (95% CI: 24 mg/24 hours, 108 mg/24 hours).⁷

Four studies measured 24-hour urine albumin excretion in donors compared with controls^{8-10,17}. In 2 of the 4 studies, there was a statistically significant increase in albuminuria of about 50 mg/24 hours compared with controls, at a mean of 14 years post-donation.^{10,17} In the 2 studies that examined the risk of developing microalbuminuria in a total of 67 donors and 51 controls, there was a 3.9-fold increased relative risk of microalbuminuria with donation.^{7,17,18}

There is only one study that has been published (in abstract form only) that examines the long-term outcomes of living kidney donors with elevated levels of proteinuria prior to donation.¹² This study prospectively examined 8 donors who pre-donation had a spot urine albumin to creatinine concentration over 10 mg/mmol and/or a spot urine protein to creatinine ratio over 20 mg/mmol. At 1 year post-donation, there was no significant difference in creatinine, blood pressure and inulin clearance compared with 'normal' living kidney donors.

SUMMARY OF THE EVIDENCE

Studies to date in healthy donors suggest that there is an increased risk of developing proteinuria following living kidney donation. However, the literature is limited by the lack of appropriate control groups, retrospective nature of most published articles, large loss to follow-up of donors,

and small sample sizes. The external validity of their findings is therefore questionable.

There is only one study that examined the outcomes of living kidney donors who had elevated levels of proteinuria pre-donation. This study included a small sample size and had a follow-up of only 1 year. In addition, the controls they used were healthy donors rather than healthy non-donors.

The suggestions for clinical care are therefore based on the assumption that a potential donor who has proteinuria prior to donating their kidney is likely to develop an increase in the level of proteinuria at least equal to that seen in healthy donors. We also know that proteinuria is a risk factor for the development of kidney failure in the general population and assume that it represents a similar risk in this patient group.

As the degree of pre-donation proteinuria that is a risk factor is unknown, we have limited our recommendations to any abnormal amount of proteinuria but have opted to take the upper limit of normal (i.e. 300 mg/24 hours).

WHAT DO THE OTHER GUIDELINES SAY?

INTERNATIONAL GUIDELINES:

The Amsterdam Forum on the Care of the Living Kidney Donor (2006):

A 24 hour urine protein of >300 mg is a contraindication to donation.

Microalbuminuria determination may be a more reliable marker of renal disease, but its value as an international standard of evaluation for kidney donors has not been determined.

The Canadian Council for Donation and Transplantation (2006):

We recommend . . . to refer to existing guidelines regarding the assessment and eligibility of potential living kidney donors (e.g. Amsterdam Forum).

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

Exclusion criteria of donor proteinuria >300 mg/day.

UK Guidelines for Living Donor Kidney Transplantation (2005):

The presence of proteinuria is a strong independent predictor of future end stage renal disease in the general population.

Urine protein excretion should be quantified by analysis of a 24-hour urine collection or spot urine protein : creatinine ratio. Increased urine protein excretion usually excludes further consideration as a kidney donor.

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

The following reasons will typically exclude a living donor candidate from donating . . . ≥ 300 mg/day of proteinuria.

SUGGESTIONS FOR FUTURE RESEARCH

1. Conduct prospective, controlled studies on long-term living kidney donor outcomes. Include an assessment of the

utility of urinary protein excretion compared with urinary albumin excretion; and outcomes of donors with isolated medical abnormalities.

2. Set up a registry for living kidney donors. Include practice patterns of living kidney donors.

CONFLICT OF INTEREST

Both of the authors have no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

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APPENDIX

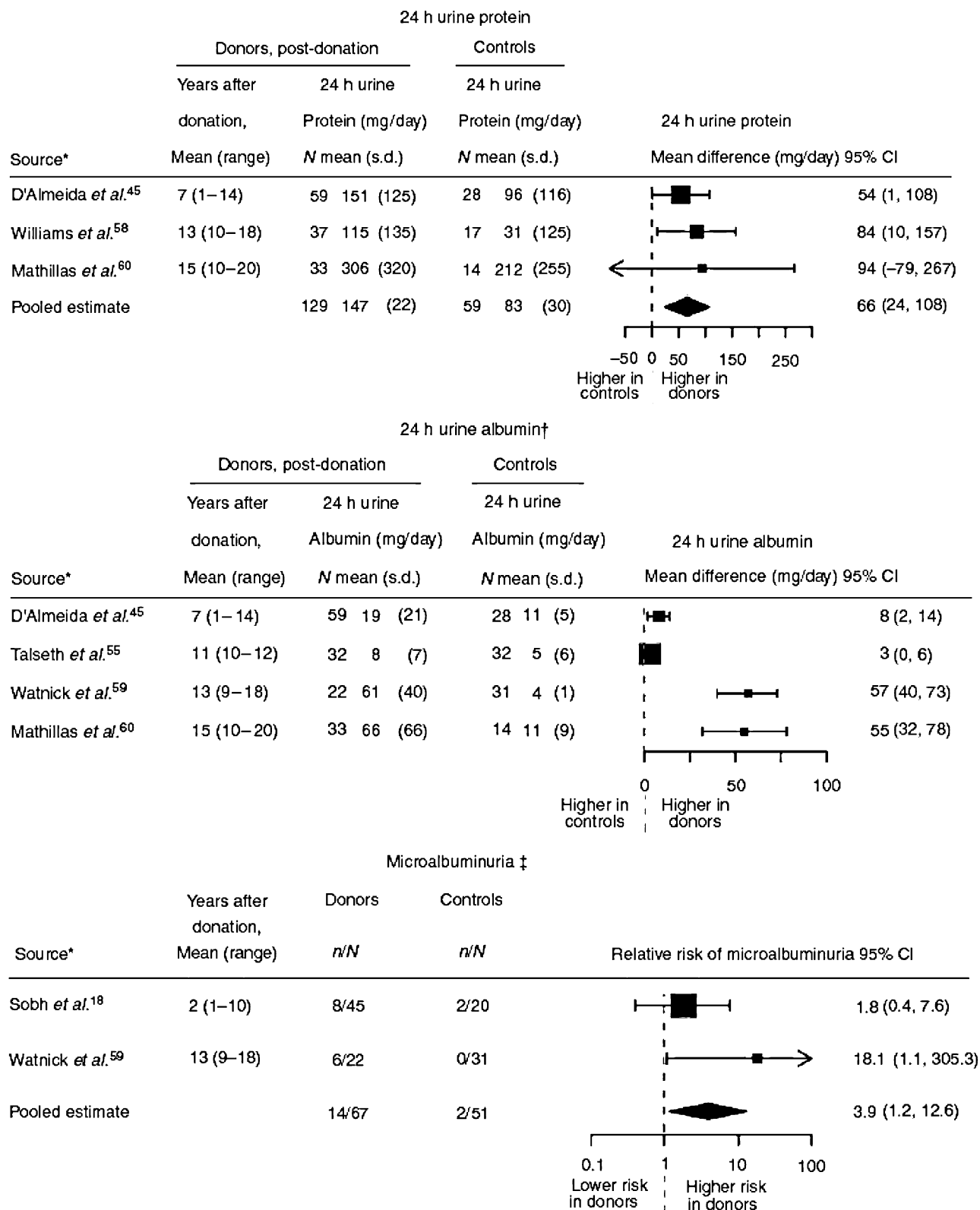


Fig. 1 Controlled studies of proteinuria after kidney donation. The size of each square is inversely proportional to the variability of the study estimate. *Studies are arranged by the average number of years after donation. †Microalbuminuria was assessed by 24 h urine. Reprinted with permission from Macmillan Publishers Ltd. 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 International*. 2006; 70: 1801–10.