

Protein requirement in adult kidney transplant recipients

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Author: Steven Chadban, Maria Chan, Karen Fry, Aditi Patwardhan, Catherine Ryan, Paul Trevillian, Fidy Westgarth

GUIDELINES

No recommendations possible based on Level I or II evidence.

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- In the first 4 weeks after transplant, a diet providing at least 1.4 g protein/kg body weight may reverse negative nitrogen balance and lead to increased muscle mass in kidney transplant recipients. (Level III)
- Until there is stronger evidence to suggest otherwise, low protein intake (i.e. 0.55 g/kg) in kidney transplant recipients with chronic graft rejection should be avoided, as this may be associated with negative nitrogen balance. (Level III)
- Restricting dietary protein in kidney transplant recipients with chronic allograft nephropathy or chronic rejection may be beneficial with respect to kidney function, however, the magnitude of the benefit and a safe level of intake has yet to be identified. (Level III and IV)
- In the absence of supporting evidence, when treatment with high doses of prednisone is required (for example during episodes of acute rejection), it is reasonable to assume that protein requirement may be elevated to a level similar to that of the early post-transplant period.
- There is currently no evidence available regarding the long-term protein requirements of stable kidney transplant recipients. Stable kidney transplant recipients on a maintenance immunosuppression regimen, irrespective of renal function, should not exceed the NHMRC recommended daily intake of protein for the general population of 0.75 g protein/kg body weight for females and 0.84 g protein/kg body weight for males.¹
- Regular review by a dietitian is desirable in the long term to ensure that protein requirements are neither exceeded (potentially placing unnecessary pressure on the kidney graft) nor inadequate (possible in periods of acute rejection when prednisone dose may be increased).

BACKGROUND

Kidney transplant recipients require high dose glucocorticoids in the early post-transplant period. Such high doses are associated with a higher protein catabolic rate and

greater risk of a state of negative nitrogen balance. Unless protein intake is increased to match protein catabolism, poor wound healing, muscle mass loss and other morbidities may result.²

Chronic renal insufficiency in kidney transplant recipients is caused by chronic graft rejection, recurrence of the original renal disease or chronic cyclosporine toxicity.³ In non-transplant patients with chronic kidney disease, low protein diets have been shown to be effective in delaying end-stage kidney disease.⁴

This review set out to determine how much dietary protein is required by adult kidney transplant recipients to maintain lean body mass and achieve neutral or positive nitrogen balance; and to determine what level of protein intake might effectively and safely reverse or decelerate the progression of kidney disease with chronic renal insufficiency.

SEARCH STRATEGY

Relevant reviews and studies were obtained from the sources below and reference lists of nephrology textbooks, review articles and relevant trials were also used to locate studies. Searches were limited to human studies on adult transplant recipients and to studies published in English.

Databases searched: MeSH terms and text words for kidney transplantation were combined with MeSH terms and text words for dietary protein. MEDLINE – 1966 to week 1, September 2006; EMBASE – 1980 to week 1, September 2006; the Cochrane Renal Group Specialised Register of Randomised Controlled Trials.

Date of searches: 22 September 2006.

WHAT IS THE EVIDENCE?

Protein requirement in the immediate post-transplant period

In a pseudo-randomized controlled study, Whittier *et al.*,⁵ looked at the effect of two levels of protein intake in adult kidney transplant recipients ($n = 12$) in the first 4 weeks after transplantation. The patients were similar in age and

did not have pre-existing diabetes. The patients received prednisone at a dosage of 1 mg/kg per day for the first 14 days post-transplant, tapered to 0.5–0.7 mg/kg per day at the end of the 28 day study. In the first 3 days post-transplant, all of the patients received standard care, which involved intravenous fluids and the introduction of food as tolerated. On the fourth day, the patients were randomized to the control group, which received a low protein, high carbohydrate diet (providing 70 g protein and 210 g carbohydrate per day) or to the experimental group which received a high protein, low carbohydrate diet (providing 210 g protein and 70 g carbohydrate per day). Each diet provided 2100 kcal per day. Uneaten food was weighed and subtracted from the daily total intake. Any additional items were reported to the researchers.

In the analysis of the results, the researchers excluded one patient (from the control group) due to their high protein intake (133 g protein/d) and carbohydrate intake (348 g carbohydrate/d).

The protein intake in the control group averaged 66 ± 7 g (1 ± 0.05 g/kg per day, ranging from 0.8 to 1.1 g/kg per day). In the experimental group protein intake averaged 157 ± 19 g (2 ± 0.3 g/kg per day, ranging from 1.4 to 3.0 g/kg per day). There was no significant difference in average energy intake.

During the 28 day study period, patients in the control group remained in negative nitrogen balance and lost an average of 1.3 kg muscle mass. In the experimental group, there was a conversion from negative to positive nitrogen balance over the 28 day study period and an average muscle mass gain of 3.2 kg ($P < 0.005$).

The results indicate that a protein intake of less than 1 g/kg in the early post-transplant period may lead to negative nitrogen balance and muscle mass loss.

The key limitation of this study is the small sample size as well as the difficulties associated with dietary studies, for instance the questionable reliability on subject reports of dietary intake. In this study measures were taken to obtain as accurate as possible an assessment of energy and protein intake, such as providing the nutrient-assessed meals to the patients and assessing any food left on the tray after meals.

On the basis of this study, until evidence suggests otherwise, kidney transplant recipients should be advised to consume at least 1.4 g/kg per day protein to prevent negative nitrogen balance in the early post-transplant period.

In a prospective, non-randomized study, Cogan *et al.*,⁶ examined the effect of a high *versus* low protein diet in adult kidney transplant recipients ($n = 15$) with acute tubular necrosis being treated with haemodialysis (three times per week) and daily prednisone (120 mg per day, tapered to 70–90 mg per day) over a period of 10–14 days. The patients had received their kidney transplants at least 10 days prior to the study.

Seven patients were offered a low protein diet (0.8 g/kg per day protein) and eight patients were offered a high protein diet (1.5 g/kg per day). The diets were intended to be isocaloric (30–35 kcal/kg per day). The patients on the low protein diet consumed an average of 0.73 ± 0.03 g/kg per day protein and 22 ± 2 kcal/kg per day. This differed significantly

from the average intake of the patients offered the high protein diet who were found to consume an average of 1.3 ± 0.06 g/kg per day protein and 33 ± 3 kcal/kg per day ($P < 0.025$).

The patients receiving the lower protein diet were in a stable state of negative nitrogen balance. The group receiving the higher protein diet achieved neutral nitrogen balance.

The key limitation of this study is the small sample size and short study period of 10–14 days. However, the study provides level IV evidence that a diet providing 1.3 ± 0.06 g/kg per day protein may enable neutral nitrogen balance to be achieved in kidney transplant recipients on high dose prednisone.

Although the evidence on dietary protein requirements in the early post-transplant period is scant and study quality poor, the results from the two studies described above suggests that at least 1.3–1.4 g/kg per day protein is required to prevent loss of lean body mass and achieve neutral or positive nitrogen balance in kidney transplant recipients requiring high dose prednisone. Multi-centre trials are needed to confirm the dietary protein requirement of kidney transplant recipients in the early post-transplant period receiving lower doses of prednisone.

Dietary protein and chronic allograft nephropathy

Rosenberg *et al.*⁷ compared low *versus* high protein intake with respect to the effect on glomerular perm-selectivity in kidney transplant recipients with biopsy-proven chronic graft rejection, who were on a stable immunosuppressive regimen.

In this randomized cross-over study, the patients ($n = 14$) received each diet for 11 days. The low protein diet (LP) provided 0.55 g protein per kg body weight. The high protein diet (HP) provided 2 g protein per kg body weight and both diets provided 35 kcal per kg body weight. After 11 days on LP, the fractional clearance of albumin and IgG was consistent with improved glomerular perm-selectivity. On both diets, nitrogen balance remained positive ($+0.13 \pm 0.45$ g on LP; $+5.94 \pm 1.78$ g on HP), however, serum total protein, albumin and transferrin were significantly lower after 11 days on LP compared with HP.

The authors conclude that changes in dietary protein intake are associated with alterations in glomerular perm-selectivity; however, they suggest that a protein restriction of 0.55 g per kg body weight may be insufficient in kidney transplant recipients. Until there is stronger evidence to suggest otherwise, a low protein diet should be avoided as it may lead to negative nitrogen balance.

In a prospective, observational study, Bernardi *et al.*⁸ compared a number of parameters, including serum creatinine, glomerular filtration rate (GFR) and 24 h urinary protein excretion, in two groups of kidney transplant recipients with chronic rejection. The patients were stratified into two groups based on dietary protein intake, calculated from 24 urinary urea measurement and dietary history. Group 1 patients consumed an average daily dietary protein intake of

0.73 ± 0.11 g/kg body weight (n = 30). Group 2 those with a daily protein intake of 1.4 ± 0.23 g/kg body weight (n = 13). The observation period was 12 years.

The serum creatinine levels differed between the two groups of patients – stable in those in Group 1; increasing in Group 2 ($P < 0.001$). The GFR over the 12-year period was stable in Group 1, but was observed to progressively decline in Group 2 ($P < 0.0001$). Twenty-four h urinary protein excretion was significantly reduced in Group 1 ($P < 0.002$) but not significantly in Group 2.

The key limitation to this study is its small sample size. Furthermore, the authors do not present demographic data for the patients post-stratification. However, the follow-up period of 12 months enabled long-term trends to be elucidated and an association between protein intake and GFR to be made.

Until there is stronger evidence that suggests otherwise, adult kidney transplant recipients with chronic rejection should limit protein intake to 0.73 ± 0.11 g/kg body weight as this may safely stabilize glomerular filtration rate and slow the progression to kidney failure. Multi-centre trials are needed to establish the safe level of dietary protein restriction and to assess the long-term efficacy and safety of protein restriction on the progression of allograft nephropathy.

SUMMARY OF THE EVIDENCE

The evidence examining the dietary protein requirement in kidney transplant recipients is sparse and of low quality being small and generally of short duration.

High protein intake in the period after transplant is required to prevent loss of body mass and achieve neutral or positive nitrogen balance. This would appear to be applicable to kidney transplant recipients on high dose prednisone, however, there is a need for trials to confirm the dietary protein requirement of kidney transplant recipients receiving lower doses of prednisone.

There is limited evidence that suggests restricting protein intake in transplant recipients with chronic allograft nephropathy may be beneficial in terms of kidney function however, low protein intake may lead to negative nitrogen balance. Based on the available evidence, it is not possible to identify a safe lower level of protein restriction.

There is no evidence in relation to the long-term protein requirements of stable kidney transplant recipients.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: No recommendation.

International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendations.

SUGGESTIONS FOR FUTURE RESEARCH

The evidence related to protein requirements in the early post-transplant period is limited to small studies on patients receiving prednisone at levels which may be higher than currently used. Multi-centre trials are needed to confirm the dietary protein requirement of kidney transplant recipients in the early post-transplant period receiving lower doses of prednisone. There is also limited research on the effects of a moderate dietary protein restriction, though the evidence to date suggests that such a restriction may improve glomerular perm-selectivity in adult kidney transplant recipients with chronic allograft nephropathy. Multi-centre trials are needed to establish the safe level of dietary protein restriction and to assess the long-term efficacy and safety of protein restriction on the progression of allograft nephropathy.

CONFLICT OF INTEREST

All 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

Table A1 Characteristics of included studies

Study ID (author, year)	n	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Rosenberg <i>et al.</i> 1995	14	Randomized cross over clinical trial	US	Kidney transplant recipients with biopsy-proven chronic rejection, proteinuria, elevated serum creatinine, stable immuno-suppressive regimen, no ACE inhibitor for 2 months prior to study	Low protein diet	High protein diet	Until completion of second diet	
Whittier <i>et al.</i> 1985	12	Randomized controlled clinical trial	US	Non diabetic kidney transplant recipients	2100 kcal, 70 g protein, 210 g CHO, 109 g fat	2100 kcal, 210 g protein, 70 g CHO, 109 g fat	4 weeks	

Table A2 Quality of randomized trials

Study ID (author, year)	Method of allocation concealment*	Blinding			Intention-to-treat analysis†	Loss to follow up (%)
		Participants	Investigators	Outcome assessors		
Rosenberg <i>et al.</i> 1995	Not specified	No	No	No	Not stated	0.0
Whittier <i>et al.</i> 1985	Not specified	No	No	No	No stated	0.0

*Choose between: central; third party (e.g. pharmacy); sequentially labelled opaque sealed envelopes; alternation; not specified.

†Choose between: yes; no; unclear.

Table A3a Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Whittier <i>et al.</i> 1985	Cushingoid appearance	0/6	4/6	0.67 (95% CI: 0.04, 11.07)	-0.67 (-1.07, -0.26)

Table A3b Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean (SD))	Control group (mean (SD))	Difference in means [95% CI]
Rosenberg <i>et al.</i> 1995	Nitrogen balance (g)	0.13 (0.45)	5.94 (1.78)	-5.81 (95% CI: -6.77, -4.85)