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 studies on humans; adult kidney transplant recipients; single organ transplants and to studies published in English. Unpublished studies were not reviewed.

Databases searched: MeSH terms and text words for kidney transplantation were combined with MeSH terms and text words for both hypertension and dietary interventions. 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?

There are few published studies on the nutritional management of hypertension in kidney transplant recipients.

Level I/II: There are no randomized controlled trials investigating the efficacy of nutritional interventions for treating hypertension in adult kidney transplant recipients.

Level III: There is one pseudo-randomized controlled study examining the efficacy of a sodium-restricted diet[20] and one non-randomized prospective study, which compared the efficacy of a dietary sodium restriction in patients treated with cyclosporine and those treated with azathioprine.[20] There is one randomized crossover study[21] examining the effect of L-arginine supplementation on blood pressure in kidney transplant recipients.

Level IV: Cross-sectional studies[22,23] are of poor quality.

Dietary sodium restriction and hypertension

In a pseudo-randomized study, Keven *et al.*[24] investigated the effect of a sodium restriction on blood pressure levels. Thirty-two kidney transplant recipients with stable kidney function were randomly assigned to either the intervention group, who followed a 3-month sodium-restricted diet (80–100 mmol/day), arranged by a dietitian, or to the control group. The characteristics of patients in each group were similar with respect to age, time since transplantation and mean systolic and diastolic blood pressure. Compliance was assessed by the dietitian every 4 weeks and 24 h urinary sodium excretion was measured at baseline and at 3 months.

Both systolic and diastolic blood pressure levels decreased significantly ($P < 0.0001$) in the intervention group compared with those in the control group. Seven of the 18 in the intervention group needed lower doses or fewer antihypertensive medications. The investigators noted that while there was no correlation between urinary sodium excretion and blood pressure at baseline, after 3 months there was a correlation ($P < 0.0001$, $r = 0.626$).

The limitations of the study were:

- Small numbers in each group.
- No sub-group analysis with respect to type of immunosuppressive regimen.

This study provides satisfactory level III evidence that the use of a sodium-restricted diet, in combination with antihypertensive medications, helps to lower blood pressure in kidney transplant recipients.

A prospective study by Curtis *et al.*[20] compared the effect of a sodium-restricted diet on hypertensive adult kidney transplant recipients taking cyclosporine with those taking azathioprine.

Subjects were selected sequentially on the basis of hypertension and stable graft function and treatment with cyclosporine and prednisone. Azathioprine-treated subjects were selected to match each cyclosporine-treated subject. There were five females and 10 males in each group. To study the effect of sodium on blood pressure, subjects in both groups were placed on a 'normal salt diet' (150 mmol/day sodium) diet for 3 days, followed by a dose of captopril, followed by 4 days on a low sodium (9 mmol/day), then a high sodium diet of 3.8 mmol *per kilogram body weight* per day for 5 days.

The researchers found that while a sodium restriction significantly lowered blood pressure in cyclosporine-treated patients ($P < 0.01$), it had no effect on azathioprine-treated patients. In contrast, captopril lowered blood pressure in azathioprine-treated patients ($P < 0.01$) but not in cyclosporine-treated patients.

While a sodium restriction of 9 mmol/day is unfeasible and unrealistic in the long term, it allowed the researchers to clearly demonstrate the existence of a difference between patients treated with cyclosporine and those treated with azathioprine with respect to the mechanisms underlying hypertension.

The study provides level III evidence that a sodium-restricted diet is more likely to lower blood pressure in hypertensive kidney transplant recipients treated with cyclosporine than in those treated with azathioprine.

In addition to the prospective studies described above, cross-sectional studies have also been conducted to examine the association between sodium intake and blood pressure in kidney transplant recipients.[22,23] In these studies, no correlation was found between urinary sodium excretion (surrogate marker of sodium intake) and blood pressure.

The limitations of these studies included:

- No sub-group analysis according to medications.
- Cross-sectional design does not permit an assessment of change over time for example, the effect of a sodium restriction on the efficacy of anti-hypertensive medications to be assessed or whether a reduction in sodium intake might lower blood pressure levels.
- Compliance was poor in the study in which subjects had been advised on a dietary sodium restriction of less than 100 mmol/day.[22]

Overall, these cross-sectional studies are inadequate to answer whether or not a sodium-restricted diet can lower blood pressure in hypertensive kidney transplant recipients.

The recommendation to limit sodium to 80–100 mmol/day is in line with current guidelines for the general population,[25] however, clinicians should emphasize adequate

fluid intake over sodium restriction in the immediate post-transplant period. The suggestion to lower sodium intake further to 65–70 mmol/day is in line with the Suggested Dietary Target for chronic disease prevention set by the National Health and Medical Research Council and the New Zealand Ministry for Health[25] and recently adopted by the National Heart Foundation of Australia.[26]

Adverse effects of restricted sodium intake

There is no evidence from human studies that a sodium intake of 80–100 mmol has an adverse effect on the health of kidney transplant recipients. Animal studies[27–29] have concluded that a low sodium intake may amplify the nephrotoxic effect of cyclosporine. However, these studies examined the effect of sodium depletion rather than a moderate sodium restriction and cannot be applied to human low sodium diets.

L-Arginine and hypertension

L-arginine is the precursor of nitric oxide, which promotes vasodilation thus lowering blood pressure. In a randomized crossover study, Kelly *et al.*[21] investigated the effect of L-arginine supplementation (at a dose of 4.5 g consumed twice per day) over a period of 2 months on blood pressure. The study suggests that the supplement is well-tolerated and effective in significantly reducing systolic blood pressure (SBP) ($P = 0.03$) and that SBP remained significantly lower than baseline after a 1-month washout period and after a further 2 months of supplementation. While diastolic blood pressure (DBP) did not decrease significantly in the first 2 months, it was significantly lower than baseline after the 1-month washout and the following 2 months. After supplementation was ceased both SBP and DBP increased significantly.

The key problems with this study were:

- Small number of subjects (27 with only 20 completing the study).
- Any changes to diet or lifestyle habits were not assessed or described thus there may have been confounding factors.
- Cross-over design did not include a separate control group.

Because of the problems associated with the design, it is not possible to state definitively whether or not L-arginine supplementation is an effective adjunct therapy for blood pressure control.

Weight loss and hypertension

There are no published studies exploring the effect of weight loss on blood pressure among kidney transplant recipients. However, weight loss in the general population is known to significantly decrease blood pressure.[14]

Evidence from research in the general population

There is strong evidence from studies on the general population that particular lifestyle and dietary measures assist in the management of hypertension.[10–16,30] Guidelines have been produced on the basis of this evidence.[17–19,31]

The Dietary Approaches to Stop Hypertension (DASH) and DASH-sodium trials[13,32] were controlled feeding dietary trials that lowered blood pressure in the absence of weight loss. The characteristics of the DASH diet, which appear to be beneficial, include low saturated fat content (<7%); an emphasis on plant-based food – vegetables, fruit and wholegrains – and an adequate intake of calcium, potassium and magnesium. Sodium restriction added additional blood pressure lowering to the DASH diet. Sodium restriction was more effective with increasing age and more effective than increasing fruit and vegetable content. The DASH diet is recognized as one of the most important non-pharmacological measures for managing blood pressure.

The PREMIER study[33] was a multicentre randomized trial, involving 810 adults with hypertension but not taking antihypertensive medications, which provided level II evidence that lifestyle changes, including weight loss, increased physical activity, a sodium-restricted diet and limited alcohol consumption, can lead to significant reductions in blood pressure, with or without adherence to the DASH diet (described above). This study found that once a sodium restriction is achieved and exercise and weight loss goals are reached, adding the DASH diet had additional benefit with respect to blood pressure but, in contrast to the DASH study findings, this was only the case for those over 50 years of age. Nevertheless, those who followed the DASH diet had significantly higher intakes of fibre, folate and certain minerals.

A review of the evidence in the general population suggests that reducing dietary sodium and/or increasing dietary potassium is associated with a clinically significant fall in systolic blood pressure for both normotensive and hypertensive individuals. There is evidence that high sodium diets are associated with increased stroke incidence, and mortality from coronary heart disease and cardiovascular disease whereas high potassium diets are associated with decreased stroke and cardiovascular disease mortality. An upper limit of 6 g salt (2300 mg sodium)/day has been set by NHMRC but estimates suggest that reducing salt to as low as 3 g salt/day would confer benefits on blood pressure.[31]

An important finding of the PREMIER trial was that intensive behavioural interventions (14 group sessions and four individual sessions in the first 6 months, with monthly group sessions and three individual sessions during months 7–18) versus 'advice only' (two individual sessions at the start of the study and at 6 months) effected significantly greater changes to diet and physical activity, and a more significant decrease in weight and blood pressure.[33]

SUMMARY OF THE EVIDENCE

A sodium-restricted diet (80–100 mmol/day) has been shown to lower the blood pressure in kidney transplant recipients. There is evidence that the blood-pressure lowering effect of a sodium restriction is more likely to occur in cyclosporine-treated patients compared with those treated with azathioprine.

There are no studies that have examined the potential for adverse effects to be associated with restricted sodium intake in kidney transplant recipients.

Studies in the general population show that an initial consultation with a dietitian, identifying the most important dietary modifications for individual patients, and regular follow-up sessions at least every 6 weeks in the first 6 months and at least every 6 months thereafter are important in reinforcing appropriate dietary recommendations.

Studies in the general population show that lifestyle and dietary measures assist in the management of hypertension. In the general population, regular aerobic activity and weight reduction by as little as 5 kg reduces blood pressure in most people who are greater than 10% above their ideal body weight.[34] The recommendation to limit alcohol consumption is based on guidelines for reducing the lifetime risk of harm from drinking, from a chronic disease or through accident or injury In health men and women.[1]

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: Blood pressure control (<130/85 for kidney transplant recipients without proteinuria, <125/75 for proteinuric patients) is mandatory in these patients. General measures and pharmacological intervention are necessary in many cases.
International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

Evaluation is necessary to determine whether or not the guidelines have an effect on clinical practice and clinical outcomes. Patient blood pressure should be monitored with the goal of achieving <130/85 mmHb (no proteinuria) or <125/75 mmHb (with proteinuria >1 g/day).[35,36] Diet histories as well as 24 h urinary sodium should be used to assess dietary sodium intake and a patient's compliance to specific dietary sodium recommendations.

CONFLICT OF INTEREST

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

ACKNOWLEDGEMENT

These guidelines were developed under a project funded by the Greater Metropolitan Clinical Taskforce, New South Wales.

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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	Comments
Keven *et al*. 2006	32	Randomized controlled clinical trial	Turkey	Kidney transplant recipients with stable allograft function	80–100 mmol sodium/d	No restriction	12 months	Evidence of an effect on surrogate outcomes (blood pressure) known to be predictive of clinical outcomes (CVD events, mortality and graft function). No evidence of a positive or negative effect on patient-relevant outcomes (eg. quality of life)
Kelly *et al*. 2001	20	Randomized cross over study	US	Kidney transplant recipients with stable allograft function	Arginine + Canola Oil	Arginine	**7**	Sodium restriction resulted in significant drop on mean arterial pressure in cyclosporine group ($P < 0.01$) but had no significant effect on the blood pressure of the azathioprine-treated group. Decreased sodium intake led to decreased plasma volume in both groups. Cyclosporine group did not respond to captopril, whereas azathioprine group did.

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		
Keven *et al.* 2006	Not specified	No	No	No	No	0.0
Kelly *et al.* 2001	Not specified	No	No	No	No	35.0

*Choose between: central; third party (e.g. pharmacy); sequentially labelled opaque sealed envelopes; alternation; not specified.
†Choose between: yes; no; unclear.

Table A3 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean (SD))	Control group (mean (SD))	Difference in means [95% CI]
Keven *et al.* 2006	Urine Na (mEq/d)	106 (48)	237 (113)	−131 (95% CI: −194.21, −67.79)
	SBP (mmHg)	116 (11)	132 (13)	−16.00 (95% CI: −24.50, −7.50)
	DBP (mmHg)	72 (10)	80 (9)	−8.00 (95% CI: −14.60, −1.40)
	Serum creatinine (mg/dL)	1.34 (0.31)	1.46 (0.37)	−0.12 (95% CI: −0.36, 0.12)
	Serum sodium level (mEq/L)	138 (4)	140 (2)	−2.00 (95% CI: −3.95, −0.05)