Prevention of Progression of Kidney Disease

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Dietary protein restriction

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GUIDELINES

a. A protein-controlled diet consisting of 0.75–1.0 g/kg/day, is recommended for adults with chronic renal disease (CKD). The administration of a low protein diet (£ 0.6 g/kg/day) to slow renal failure progression is not justified when the reported clinically modest benefit on glomerular filtration rate (GFR) decline is weighed against the concomitant significant declines in clinical and biochemical parameters of nutrition. (Level I evidence)

b. For children, reduction of dietary protein intake to the lowest safe amounts recommended by the World Health Organisation (0.8–1.1 g/kg/day depending on age) has not been shown in a small randomised controlled trial (RCT) to decrease the progression of CKD and is therefore not currently recommended. (Level II evidence)

Background

Low protein diets have been recommended as a treatment for retarding renal failure progression for over 50 years. The objective of the current guideline was to evaluate the available clinical evidence pertaining to the effect of protein-restricted diets on the progression of CKD.

Search strategy

Databases searched: Medline (1999 to November Week 2, 2003). MeSH terms for kidney diseases were combined with MeSH terms and text words for dietary protein restriction. The results were then combined with the Cochrane highly sensitive search strategy for randomised controlled trials and MeSH terms and text words for identifying meta-analyses and systematic reviews. The Cochrane Renal Group Specialised Register of Randomised Controlled Trials was also searched for relevant trials not indexed by Medline.

Date of search: 16 December 2003.

What is the evidence?

The relationship between dietary protein restriction and non-diabetic renal failure progression has been examined by 4 meta-analyses (Kasiske et al 1998, Pedrini et al 1996, Fouque et al 1992, Fouque et al 2000), 11 randomised controlled trials (RCTs) (Klahr et al 1994, Rosman 1989, Jungers et al 1987, Locatelli et al 1991, D'Amico et al 1994, Ihle et al 1989, Williams et al 1991, Bergstrom et al 1989), 1 prospective double-blind cross-over study (Hecking et al 1980), 8 prospective controlled trials (Frohling et al 1980, Maschio et al 1982, Gretz et al 1983, Oldrizzi et al 1985, Di Landro et al 1986, Schmicker et al 1986, Frohling et al 1989, Walser 1975) ,13 prospective non-controlled trials (Mallick 1994, Burns et al 1978, Kampf et al 1980, Attman et al 1983, Frohling et al 1983, El Nahas et al 1984, Mitch et al 1984, Lucas et al 1986, Walser et al 1987, Ciardella et al 1988, Barsotti et al 1988, Levine et al 1989, Zeller et al 1991) and 7 retrospective observational cohort studies (Alvestrand et al 1980, Barsotti et al 1981, Alvestrand et al 1983, Bennett et al 1983, Attman 1986, Hannedouche et al 1989). In view of the potential for serious bias in the non-randomised studies, this review will be restricted to the RCTs and meta-analyses.

The Modification of Diet in Renal Disease (MDRD) study by Klahr et al (1994), is the largest and best-designed prospective RCT to date. Patients were included in the study if their GFR was 25–55 mL/min/1.73 m^2 (Study A) or 13–24 mL/min/1.73 m^2 (Study B), their mean arterial pressure was less than 125 mmHg and their dietary protein intake was greater than or equal to 0.9 g/kg body weight/day (Study A only). Patients with body weight extremes (< 80% or > 160% of standard body weight), dubious compliance, insulin-dependent diabetes mellitus or heavy proteinuria (> 10 g/day) were excluded.

Study A patients (n = 585) were randomly assigned (with adequate allocation concealment) to a usual protein diet (1.3 g /kg/day) or a low protein diet (0.58 g/kg/day), while Study B patients (n = 255) were randomised to a low protein diet (0.58 g/kg/day) or a very low protein diet (0.28 g/kg/day). An open-label design was used. The groups were similar at the start of the trial. Only 3% of the patients had non-insulin–dependent diabetes mellitus and 24% of the patients had polycystic kidney disease. ACE inhibitors were permitted and used by 32–44% of patients in each of the randomisation groups. Mean follow-up was 2.2 years (range 0–3.7 years) and the drop-out rate was very low (Study A = 1.9%, Study B = 1.2%). Compliance was reasonable, but the actual dietary intakes of the normal and low protein groups were 1.1 and 0.7 g/kg/day, respectively.

No significant differences in GFR decline, measured by ^{125}I-iothalamate clearance every 4 months, were found between the diet groups in either study. In Study A, a biphasic response of GFR to the low protein diet was noted, with a greater decline in the first 4 months (3.4 versus 1.8 mL/min/4 months), followed by a significantly slower rate of decline (2.8 versus 3.9 mL/min/year), which only resulted in a small absolute benefit of 1.1 mL/min/year. This effect of dietary intervention was unrelated to baseline GFR or urinary protein excretion. The time to occurrence of a rapid decline in GFR (> 50% or ≥ 20 mL/min/1.73 m^2) or end-stage kidney disease (ESKD) did not differ significantly between the diet groups in either study, although these were secondary end-points for which the study was not adequately powered.

In Study A, the low protein diet group had significantly lower energy intakes (males = 3.6 kcal/kg/day, females = 2.8 kcal/kg/day), body weight (males = 5.3 kg, females = 2.9 kg) and biochemical nutritional markers (transferrin, percent body fat, biceps skinfold thickness, triceps skinfold thickness, subscapular skinfold thickness and arm muscle area were all 5-10% lower than in the usual protein group) (Kopple et al 1997). A 15–20% decline in urinary creatinine excretion was also observed in the lower protein diet groups and was attributed to a reduction in dietary creatine and creatinine intake. However, the significant reductions in arm muscle area also suggests that there was an additional component due to reduced skeletal muscle mass.

The limitations of this study included: (a) overall GFR decline was relatively slow compared with that of other studies and roughly 25% of patients did not experience progressive renal function decline; (b) the study design may not have provided sufficient statistical power to find a positive result, particularly in view of the erratic GFR decline in Study A patients and the relatively high proportion of polycystic kidney disease patients (who may be less amenable to therapy); and (c) the separation of GFR decline into 2 phases represented a post hoc analysis.

Levey et al (1996) subsequently reported a secondary analysis of the MDRD Study B in order to determine the relationship between achieved dietary protein intake (estimated from urinary urea nitrogen excretion) and renal failure progression. Total protein intake was slightly, but significantly, lower for the very low protein diet group (0.66 g/kg/day) compared with the low protein diet group (0.73 g/kg/day). Each 0.2 g/kg/day decrease in protein intake was associated with a slower mean GFR decline of 1.15 mL/min/year and an approximate halving of the risk of renal failure or death. Moreover, protein intake was directly correlated with final GFR prior to dialysis.

This study has serious limitations, which include: (a) the use of a secondary analysis rather than an intention-to-treat analysis is less valid for the clinical question of whether prescription of a low protein diet is an effective method of slowing renal failure progression; (b) the estimation of achieved protein intake assumes that patients are in a steady state of nitrogen balance but may have been affected by various factors such as acidosis, diuretics, acute illness or collection problems; (c) correlation analyses are limited by potential confounding effects from variables that are not controlled for in the regression model (this may be particularly relevant to post hoc secondary analyses which were not initially considered at the study inception); (d) the analysis may have been limited by the possible confounding effects of the presumed dependent variable (in other words, the association may have been explained by an effect of renal function on protein intake rather than vice versa); and (e) correlation analyses only detect an association and do not prove cause and effect. In short, extreme caution should be exercised with post hoc secondary analyses of initially negative studies.

Locatelli et al (1991) conducted a prospective, multi-centre, open-label, RCT of 456 patients randomised to a low protein diet (0.4 g/kg/day) or a normal controlled-protein diet (1 g/kg/day). Patients were included if their creatinine clearance was less than 60 mL/min, 24-hour protein excretion was less than 3 g/day and body weight was between 45 and 90 kg. ACE inhibitors were avoided as much as possible. Allocation concealment was adequate. Baseline demographic, clinical and laboratory characteristics of each group were not provided. Patients were followed-up for 2 years or until an end-point (doubling of baseline plasma creatinine or dialysis) was reached. Seventeen percent of patients were withdrawn from the study (non-compliance 13%, intolerance of low protein diet 1%, concomitant disease

1%, death 1%, other causes 1%). No differences in actuarial renal survival rate, creatinine clearance decline or slope of plasma creatinine reciprocal were noted between the two diet groups. No correlation was found between the progression of renal failure and protein catabolic rate. The potentially significant pitfalls of the study included: (a) indirect measurement of GFR by creatinine clearance (which is often inaccurate and significantly affected by diet); (b) a moderately high drop-out rate (17%); (c) non-compliance with protein restriction minimised the difference in dietary intake between control and treated groups (0.16 g/kg/day versus intended 0.4 g/kg/day); and (d) the clinically important outcome of effect of diet on nutritional status was not considered.

Rosman (1989) conducted a prospective, single centre, open-label RCT of 228 patients with creatinine clearances between 10 and 60 mL/min/1.73 m^2. Patients were stratified for sex, age and renal function and then randomly allocated to receive either a low protein diet (0.4 g/kg/day if creatinine clearance 10–30 mL/min/1.73 m^2 [Group C] or 0.6 g/kg/day if creatinine clearance 31–60 mL/min/1.73 m^2 [Group B]) or their usual diet (averaging 55 g/day for A2 and 70 g/day for A1). Allocation concealment was adequate (sealed envelopes). ACE inhibitors were not prescribed.

The groups were comparable at baseline but 23 (10%) patients (A1 n = 4, A2 n = 7, B n = 1, C n = 7) were subsequently removed from the study due either to death, transplantation or dialysis. The initial results published in 1984 were favourable with protein restriction reducing the median rate of progression of renal insufficiency, determined by reciprocals of median plasma creatinine, by a factor of 3 (group C) to 5 (group B). However, after another 4 years of follow-up, no significant differences were found between the groups (except for the subset of patients with chronic glomerulonephritis). The authors concluded that protein restriction is of limited value and should only be used in selected patient groups. Patient dissatisfaction with the low protein diets was very high, especially in the early stages. The major pitfall of the study was the use of reciprocal plasma creatinine as a marker of GFR.

Ihle et al (1989) conducted a prospective, single centre, randomised study of 72 patients with serum creatinine concentrations between 0.35 and 1.0 mmol/L. Diabetics and patients receiving angiotensin converting enzyme inhibitors (ACE) were excluded. Patients were randomly allocated to receive either a regular diet (at least 0.75 g/kg/day) or a protein-restricted diet (0.4 g/kg/day). Allocation concealment was adequate. GFR was assessed every 6 months by ^{51}Cr-EDTA clearance. The study lasted 18 months, during which time 3 patients (4%) withdrew voluntarily and 5 patients (6%) were withdrawn because of non-compliance. Compliance in the remaining patients was reasonable. A significantly higher proportion of control patients reached ESKD compared with the protein-restricted group (27% versus 6%, $p < 0.05$). This, however, is a misleading end-point since this may have reflected differences in the development of uraemic symptoms rather than progression of renal impairment *per se*. Moreover, given the lack of blinding, it is conceivable that clinicians caring for patients on a low protein diet may have been more prone to delay initiation of dialysis. Nevertheless, mean ^{51}Cr-EDTA clearance did not change in the low protein group, but significantly decreased by 60% in the control group. Of major concern were the significant falls in body weight, serum albumin, serum transferrin and lymphocyte counts in the protein-restricted group suggesting an adverse effect of the dietary intervention on nutrition. The limitations of the study were (a) its small numbers and short follow-up; (b) the exclusion of diabetics; (c) the withdrawal of non-compliant patients rather than analysing on an intention-to-treat basis; and (d) the disallowance of ACE inhibitors.

A prospective, single-centre, open-label, RCT of a severe (0.30 g/kg/day) protein-restricted diet supplemented with a preparation of ketoanalogues, hydroxyanalogues of amino acids and amino acids (Group A) vs a moderate protein-restricted diet (0.65 g/kg/day, Group B) was conducted in 50 patients with a GFR < 19 mL/min/1.73 m^2 (Malvy et al 1999). Follow-up ranged between 3 months and 3 years. There were no statistically significant differences between the two dietary regimens with respect to renal survival, although a Type 2 statistical error could not be excluded.

Pijls et al (2002) conducted a prospective, single-centre, open-label RCT of protein restriction (0.8 g/kg/day) vs usual dietary advice in 131 patients with Type 2 diabetes mellitus and microalbuminuria or known diabetes duration in excess of 5 years. Patients were followed for at least 12 months. No significant differences were seen between the two groups with respect to decline in cimetidine creatinine clearance. However, the difference in dietary protein intake between the two groups at 6 months was only 0.08 g/kg/day and disappeared over time.

Several small RCTs (Fouque et al 1992, Jungers et al 1987, Williams et al 1991) have all reported essentially negative results with respect to the effects of protein restriction. Protein intakes ranged from 0.3–0.6 g/kg/day in the treated groups and 0.6 to > 0.8 g/kg/day in the control group. These studies have all been significantly limited by their small numbers, short follow-up times (12–18 months) and the use of inappropriate measures of GFR (plasma creatinine, reciprocal plasma creatinine or arithmetic mean of urinary urea and creatinine clearance).

A more recent small, prospective, randomised trial of 128 non-diabetic patients with CKD by D'Amico et al (1994), suggested that dietary protein restriction conferred a modest benefit. Over a 2.3 year follow-up, a 50% reduction in creatinine clearance was observed in 40% of the control group (mean protein intake 1.06 g/kg/day) compared with 29% in the low protein diet group (mean protein intake 0.8 g/kg/day). The major limitation of this study was the use of creatinine clearance as a marker of GFR.

Fouque et al (1992) published a meta-analysis of 6 RCTs (Rosman 1989, Jungers et al 1987, Locatelli et al 1991, Ihle et al 1989, Williams et al 1991) in 1992, prior to the publication of the results of the MDRD study. The criteria and methods used to select articles for inclusion were appropriate and it is unlikely that important relevant studies were missed. Although of limited sensitivity, the chi-squared heterogeneity test between odds ratios was not significant. A total of 890 patients with mild to severe CKD were followed-up for at least 1 year. Sixty-one renal deaths, defined as the commencement of dialysis or patient death, were recorded in the low protein diet group and 95 in the control group, leading to an odds ratio of 0.54 (95% CI 0.37–0.79) in favour of protein restriction. The authors concluded that low protein diets are effective in delaying the onset of ESKD, but it is impossible to tell from this analysis whether or not the reduction in renal death was the consequence of a reduction in uraemic symptoms (thereby delaying the need for dialysis) or a reduction in the progression of renal insufficiency. Another limitation of the meta-analysis was the heterogeneity of the studies with respect to treatments (for example, the protein intake in the control group of 1 study was the same as that in the treatment group of another study). Furthermore, not all clinically important outcomes were considered, since the effect of treatment on nutritional status was not evaluated.

Finally, the validity of meta-analyses may be threatened by publication bias, which may be suggested, among other things, by an inverse association between trial size and treatment. Such an analysis was not performed in Fouque's meta-analysis. However, a funnel plot of odds ratio vs trial size does raise the possibility of a positive publication bias. Fouque et al

(2001) have subsequently published a systematic review of only 7 RCTs since 1975, which concluded that low protein diets are associated with a significantly lower incidence of renal death compared with higher protein diets (odds ratio 0.62, 95% CI: 0.46–0.83, P = 0.006). This Cochrane review suffered the same limitations as the 1992 meta-analysis and did not include all available RCTs.

Another meta-analysis which included the MDRD study (making up 40% of its patients) was subsequently published by Pedrini et al (1996). Only full-length published studies were included in the analysis, raising the possibility that important relevant studies were missed. As an example of this, Pedrini et al (1996) only included 4 of the 6 studies used in the meta-analysis of Fouque et al (1992), even though the latter was published 4 years earlier. Assessments of the reproducibility of study inclusion between the 2 investigators were not made, although there must have been some disparity as the paper states that differences were resolved in a conference. The analysis included 5 RCTs (Klahr et al 1994, Rosman 1989, Locatelli et al 1991, Ihle et al 1989, Williams et al 1991) and found that a low protein diet significantly reduced the risk of renal failure or death (RR 0.67, 95% CI: 0.50–0.89). Significant heterogeneity of treatment effects was unlikely as the results were similar using both random-effects and fixed-effects models. However, this meta-analysis suffered the same serious limitations as that of Fouque and co-workers (Foque et al 1992).

The most recent meta-analysis of the effects of dietary protein restriction on the rate of decline of renal function was reported by Kasiske et al (1998). The meta-analysis only considered published studies between 1980 and 1996 using Medline and bibliographies found in published reviews. The results of 13 RCTs (including 4 trials in purely diabetic populations) were pooled (n = 1919) and found that dietary protein restriction reduced the rate of decline in estimated GFR by a meagre 0.53 ml/min/year (95% CI: 0.08–0.98 mL/min/year). The unweighted mean dietary protein content was 0.68 ± 0.11 g/kg/day in the low protein groups and 1.01 ± 0.32 g/kg/day in the control groups. Interestingly, the magnitude and variability of the treatment effects were inversely proportional to the size of the studies, indicating a possible publication bias in favour of low-protein diets. A weighted regression analysis of 13 RCTs compared with 11 other non-randomised trials demonstrated that the effect of dietary protein restriction was significantly less in the former and relatively greater among diabetic vs non-diabetic patients. The impact of restricted protein diets on nutrition was not considered in this meta-analysis, but is clearly crucial given the very modest beneficial effect on GFR decline.

Another concern regarding dietary protein restriction in patients with CKD is the spontaneous reduction in dietary protein intake with declining GFR. Ikizler et al (1995) noted that mean spontaneous dietary intakes averaged 1.1 g/kg/day for patients with creatinine clearances > 50 mL/min, 0.85 g/kg/day at 25–50 mL/min, 0.70 g/kg/day at 10–25 mL/min and 0.54 g/kg/day at <10 mL/min. These changes presumably reflect uraemic anorexia and raise questions regarding the safety of further restricting protein intake.

What is the evidence in children?

In a recent, multicentre trial by Wingen et al (1997), 191 children with CKD were randomly allocated to the lowest safe protein intake recommended by the World Health Organisation (1.1 g/kg/day in infants to 0.8 g/kg/day in adolescents) or to a regular diet. ACE inhibitors were allowed. Over the 2-year follow-up, no benefit was noted with respect to decline in creatinine clearance. The actual mean protein intakes of the two groups were 125% and 181% of the WHO recommendations, respectively. Calculation of protein intake by urinary

urea nitrogen excretion found that patients in the diet group under-reported their protein intake (141% of WHO recommendations) whereas controls did not (181%). One hundred and twelve patients completed an optional third year of the study with still no significant difference apparent between the two groups with respect to decline in creatinine clearance. Growth was also comparable between the two groups. The main limitations of the study were the use of creatinine clearance as a GFR marker and the fact that the study was probably under-powered.

Summary of the evidence

In summary, there is no convincing or conclusive evidence that long-term protein restriction delays the progression of CKD. The longest lasting, largest and best-designed RCT (MDRD study) argues against an important benefit. Four meta-analyses have demonstrated either a modest or substantial benefit of protein-restricted diets, but three of these used an inappropriate outcome measure (renal survival), which does not allow distinction between delay of dialysis due to suppression of uraemic symptoms vs slowing renal failure progression. The only meta-analysis which used estimated GFR as an outcome measure found only a very weak benefit of dietary protein restriction. It also found evidence of possible publication bias favouring a beneficial effect of low protein diets. The trials showed some heterogeneity and cannot substitute for properly conducted RCTs. Moreover, the possibility of a modest benefit of low-protein diets on renal failure progression must be weighed against the risk of a concomitant decline in nutritional parameters. Only three of the 11 RCTs in non-diabetics have addressed the effect of restricted protein diets on nutrition (Klahr et al 1994, Ihle et al 1989, Malvy et al 1999) and two have found statistically important reductions in nutritional parameters (the other observed neither a benefit nor adverse effect of dietary protein restriction).

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative: For individuals with chronic renal failure (GFR < 25 mL/min) who are not undergoing maintenance dialysis, the institution of a planned low-protein diet providing 0.6 g protein/kg/d should be considered. For individuals who will not accept such a diet or who are unable to maintain adequate dietary energy intake with such a diet, an intake of up to 0.75 g protein/kg/d may be prescribed (Evidence and Opinion).

When properly implemented and monitored, low-protein, high-energy diets maintain nutritional status while limiting the generation of potentially toxic nitrogenous metabolites, the development of uraemic symptoms, and the occurrence of other metabolic complications

Evidence suggests that low protein diets may retard the progression of renal failure or delay the need for dialysis therapy.

When patients with chronic renal failure consume uncontrolled diets, a decline in protein intake and indices of nutritional status is often observed.

British Dietetic Association Renal Nutrition Group: Recommends 0.6–1.0 g protein/kg/day.

European Dialysis and Transplant Nurses Association - European Renal Care Association: Recommends 0.6–1.0 g protein/kg/day.

European Society of Parenteral and Enteral Nutrition: Recommends 0.55–0.6 g protein/kg/day.

Implementation and audit

No recommendation

Suggestions for future research

No recommendation

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Appendices

Table 1 – Characteristics of included studies

Study ID (author, year)	N	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Malvy et al, 1999	50	Prospective randomised controlled study	Single centre	50 uremic outpatients with GFR < 19 mL/min/1.73m^2	Severe protein restriction diet (0.3 g/kg/day) with a supplement of ketoanalogues and hydroxyanalogues of amino acids (0.17 g/kg/day)	0.65 g/kg/day protein intake	Min. 3	
Pijls et al, 2002	160	Randomised single-blind controlled study	Single centre	160 patients with type II diabetes and micro-albuminuria or detectable albuminuria aged < 79 yrs	Dietary counselling on protein restriction (to reduce protein intake to 0.8 g/kg/day) + normal dietary advice	Normal dietary advice about restriction of saturated fat intake	28 ± 7	
Wingen et al, 1997	191	Randomised prospective controlled study	Multicentre	191 children (aged 2–18yrs) with creatinine clearances between 15 and 60 mL/min per 1.73m^2	Patients were advised to decrease their protein intake to 0.8–1.1 g/kg	No restrictions on protein intake	24–36	
D'Amica et al, 1994	128	Prospective randomised controlled study	Single centre (outpatient clinic)	128 adult patients with chronic renal failure (creatinine clearance between 70 and 15 mL/min 1.73m^2).	Low protein diet (0.6 g protein/kg with an energy supplement of 35kcal/kg daily)	Control diet (1.0 g protein/kg with an energy supplement of 30 kcal/kg daily).	27.1 ± 21.8	

Study ID (author, year)	N	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Jungers et al, 1987	19	Randomised controlled trial	Single centre	19 adult patients with advanced chronic renal failure with a creatine clearance of 5–15 mL/min/1.73m^2	0.4g/kg/day of mixed quality proteins with a phosphate intake < 600 mg/day + keto acids administered as a calcium salt (1 tablet/6kg/day divided into 3 equal doses taken with meals)	0.6 g/kg/day proteins with a phosphate intake < 750 mg/day. Caloric intake was maintained at between 35–40 kcal/kg/day	18	
Bergstrom et al, 1989	57	Prospective randomised controlled trial	Single centre	57 adult patients with chronic renal disease and an approximately linear progression of renal failure with a creatinine clearance of < 70 mL/min/1.73m^2	0.4 g/kg bwt/day protein, 0.1 g/kg bwt/day essential amino acids	Unrestricted protein intake	12–24	
Locatelli et al, 1991	456	Prospective randomised controlled trial	Multicentre (Northern Italian Cooperative Study Group)	456 adult outpatients with chronic renal insufficiency as defined by a creatine clearance level below 60 mL/min.	Low protein diet (0.6 g/kg bwt/day + energy supplement of 35 kcal/kg/day)	Normal controlled-protein diet (1.0 g/kg bwt/day + energy supplement of 30 kcal/kg/day)	24	
Klahr et al, 1994	840	Randomised controlled trial	Multicentre	840 adult patients with various chronic renal diseases/insufficiencies	Low protein diet (0.58 g/kg/day) or very low protein diet (0.28 g/kg/day)	Normal protein diet (1.3 g/kg/day)	18–45 Mean = 26 months	2 simultaneous studies stratified by GFR
Ihle et al, 1989	64	Prospective randomised controlled study	Single centre	72 adult patients with chronic renal insufficiency (serum creatinine concentrations between 350–1000 μmol/L	Protein-restricted diet (0.4 g/kg/day protein)	Regular diet – at least 0.75 g/kg/day protein	18	

Study ID (author, year)	N	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Williams et al, 1991	95	Prospective randomised controlled trial	Multicentre (2 nephrology clinic units)	95 adult patients with chronic renal failure (plasma creatinine < 900 µmol/L)	Dietary protein and phosphate restriction: 0.6 g/kg/day protein, 800 mg phosphate, energy intake ≥ 30 kCal/kg/day	Dietary phosphate restriction only: 1000 mg/day + oral phosphate binders with each meal	3	3 arm study: 3rd group had no protein or phosphate restriction
Rosman, 1989	228	Prospective open-label randomised controlled trial	Single centre	Adult patients with chronic renal insufficiency (serum creatinine clearance between 10–60 mL/min/1.73m^2	Low protein diet of 0.4 g/kg/day if Cr 10–30 mL/min/1.73m^2 or 0.6 g/kg/day if Cr 31–60 mL/min/173m^2	Normal diet: 55 g/day (group 1) or 70 g/day (group 2)	48	
Levey et al, 1996	255	Randomised controlled trial	Multicentre (15 university hospital outpatient nephrology practices)	Adult patients with chronic renal insufficiency and baseline GFR between 13–24 mL/min/1.73m^2	Very low protein diet (0.28 g/kg/day) supplemented with keto acids and amino acids (0.28 g/kg/day)	Low protein diet (0.58 g/kg/day)	Av. = 26	

Table 2 – Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis †	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Levey et al, 1996	Not specified	No	Blinded to GFR measurements only	No	No	Unclear
Rosman, 1989	Sealed envelopes	No	No blinding	No	Unclear	Unclear
Williams et al, 1991	Pack of numbered cards and random numbers table	No	No blinding	No	Unclear	0
Ihle et al, 1989	Not specified	No	No blinding	No	Unclear	0
Klahr et al, 1994	Not specified	No	No blinding	No	Yes	1.7 (14/840)
Locatelli et al, 1991	Central	No	No blinding	No	Yes	31.8 (145/456)
Bergstrom et al, 1989	Not specified	No	No blinding	No	Unclear	0
Jungers et al, 1987	Not specified	No	No blinding	No	Unclear	21.1 (4/19)
Pijls et al, 2002	Randomisation by computer software	No	Blinded	No	Yes	18 (29/160)
Malvy et al, 1999	Not specified	No	No blinding	No	Unclear	0
D'Amico et al, 1994	Not specified	No	No blinding	No	Unclear	0
Wingen et al, 1997	Computerised randomisation	No	No blinding	No	No	15.5 (35/226)