Cochrane Library

Cochrane Database of Systematic Reviews

Low protein diets for chronic kidney disease in non diabetic adults (Review)

Fouque D, Laville M

Fouque D, Laville M.
Low protein diets for chronic kidney disease in non diabetic adults.
Cochrane Database of Systematic Reviews 2009, Issue 3. Art. No.: CD001892.
DOI: 10.1002/14651858.CD001892.pub3.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Low protein diets for chronic kidney disease in non diabetic adults

Denis Fouque[1], Maurice Laville[2]

[1]Département de Néphrologie, U870 INSERM-Université Claude Bernard Lyon 11, Lyon Cedex 03, France. [2]Service de Néphrologie, Hôpital Edouard Herriot, Lyon Cedex 03, France

Contact address: Denis Fouque, Département de Néphrologie, U870 INSERM-Université Claude Bernard Lyon 11, Hôpital Edouard Herriot, Lyon Cedex 03, 69437, France. denis.fouque@chu-lyon.fr.

Editorial group: Cochrane Kidney and Transplant Group
Publication status and date: Edited (no change to conclusions), published in Issue 3, 2009.

Citation: Fouque D, Laville M. Low protein diets for chronic kidney disease in non diabetic adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. Art. No.: CD001892. DOI: 10.1002/14651858.CD001892.pub3.

ABSTRACT

Background

For more than fifty years, low protein diets have been proposed to patients with kidney failure. However, the effects of these diets in preventing severe kidney failure and the need for maintenance dialysis have not been resolved.

Objectives

To determine the efficacy of low protein diets in delaying the need to start maintenance dialysis.

Search methods

Cochrane Renal Group studies register, the Cochrane Central Register of Controlled studies, MEDLINE, and EMBASE. Congress abstracts (American Society of Nephrology since 1990, European Dialysis Transplant Association since 1985, International Society of Nephrology since 1987). Direct contacts with investigators.

Selection criteria

Randomised studies comparing two different levels of protein intake in adult patients suffering from moderate to severe kidney failure, followed for at least one year.

Data collection and analysis

Two authors independently selected studies and extracted data. Statistical analyses were performed using the random effects model and the results expressed as risk ratio (RR) for dichotomous outcomes with 95% confidence intervals (CI). Collection of the number of "renal deaths" defined as the need for starting dialysis, the death of a patient or a kidney transplant during the study.

Main results

Ten studies were identified from over 40 studies. A total of 2000 patients were analysed, 1002 had received reduced protein intake and 998 a higher protein intake. There were 281 renal deaths recorded, 113 in the low protein diet and 168 in the higher protein diet group (RR 0.68, 95% CI 0.55 to 0.84, P = 0.0002). To avoid one renal death, 2 to 56 patients need to be treated with a low protein diet during one year.

Authors' conclusions

Reducing protein intake in patients with chronic kidney disease reduces the occurrence of renal death by 32% as compared with higher or unrestricted protein intake. The optimal level of protein intake cannot be confirmed from these studies.

PLAIN LANGUAGE SUMMARY

Low protein diets can delay kidney failure in people with kidney disease (diabetic kidney disease excluded)

Kidney disease (nephropathy) can lead to kidney failure (end-stage kidney disease). A diet low in protein is sometimes recommended to try to slow the progression of kidney disease. Monitoring compliance with a protein-restricted diet is possible by determining urea production since urea is a byproduct of the degradation of all proteins. If urea production is reduced then the accumulation of toxins will be limited.The review of studies for people with kidney disease (diabetic kidney disease excluded) found that low protein diets can delay end-stage kidney disease.

BACKGROUND

During the past years, numerous experimental and clinical studies have addressed the question of reducing protein intake to retard or even halt the development of non-specific glomerular or interstitial lesions, and hence the progression of patients towards end-stage kidney disease (ESKD). Despite the large number of studies on dietary interventions that were performed a few decades ago, it is still unclear if patients should limit their protein intake and if so, to what extent nutritional behaviour should be changed during chronic kidney disease (CKD). Most of the clinical studies were designed to test the efficacy of reducing protein intake on surrogate renal function outcomes, such as serum creatinine increase or creatinine clearance decrease over time. Unfortunately, changing protein intake will modify all creatinine markers and therefore no valid conclusions can be drawn from these studies. Reducing protein intake decreases creatinine production, reduces renal function (glomerular filtration as well as creatinine clearance) by unidentified mechanisms. Although a few studies used what are considered as gold standard renal function assessments such as glomerular filtration rate (GFR) the results from these studies have been conflicting. Moreover, GFR is not a clinical outcome.

OBJECTIVES

To determine the efficacy of low protein diets in preventing the natural progression of CKD towards ESKD and retard the need for starting maintenance dialysis.

METHODS

Criteria for considering studies for this review

Types of studies

Studies in which participants have been randomly allocated to receive either their usual intake of protein or were asked to limit their protein intake for at least 12 months. Cross-over studies were considered if the starting period of intervention was randomly allocated.

Types of participants

- All patients suffering from moderate to severe CKD, as estimated by either serum creatinine, creatinine clearance or GFR measurement.
- Because of difficulty to control for confounding factors, studies including diabetic patients or children with CKD were excluded from analysis.

Types of interventions

Standard protein intake (0.8 g/kg/d) or greater versus a moderate (0.6 g/kg/d) to severe protein restriction (0.3 g/kg/d) regardless of supplementation with essential amino acids or ketoacids.

Types of outcome measures

Renal death as defined by:

1. Death during follow-up, due to any cause
2. Need to start haemodialysis or peritoneal dialysis during follow-up
3. Kidney transplant during the study

Search methods for identification of studies

Initial search

The initial search for studies was performed by one of the authors (DF) using the Cochrane Renal Group search strategy. The Renal Group studies Register was searched by Sandrine Dury, studies Search Coordinator. MEDLINE and EMBASE were searched from January 1966 through to June 1999. (Appendix 1 - *Electronic search strategies).*

Congress abstracts (American Society of Nephrology since 1990, European Dialysis Transplant Association since 1985, International Society of Nephrology since 1987) were handsearched. Authors of published work were contacted to ask if they were aware of any unpublished studies.

Review update

For review updates the Cochrane Renal Group's specialised register and The Cochrane Central Register of Controlled studies (CENTRAL, in *The Cochrane Library*) was searched. CENTRAL and the Renal Group's specialised register contain the handsearched results of conference proceedings from general and speciality meetings. This is an ongoing activity across the Cochrane Collaboration and is both retrospective and prospective (http://www.cochrane.us/masterlist.asp). Please refer to The Cochrane Renal Review Group's Module in *The Cochrane Library* for the complete lis of nephrology conference proceedings searched.

Data collection and analysis

Two authors independently selected studies for inclusion in the review. Disagreements were resolved by discussion. For each study, the number of patients originally allocated to each treatment group was noted and an intention-to-treat analysis was performed. Data were obtained directly from investigators when not available in the published report.

Data collected for each study included inclusion and exclusion criteria, patient details (age, gender), type of diet prescribed (level of proposed protein intake, nature of proteins, supplementation in energy or amino-acids), time to the start of dialysis if available. The nature of kidney disease was recorded to verify that the distribution of prognostic factors was balanced between the groups.

No quality assessment of the studies was performed. Details of the randomisation processes were obtained directly from the investigators.

Heterogeneity was analysed using a chi-squared test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test (Higgins 2003). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

RESULTS

Description of studies

Ten RCTs were identified and retained for this review, with 2000 patients, 1002 in the restricted protein intake groups and 998 in the unrestricted or higher protein intake groups. The number of patients in each study varied from 19 (Jungers 1987) to 585 (MDRD 1994). The collection of events was done after the longest

observation time obtained in each study. Data obtained during follow-up but after completion of studies, if present, were not considered for analysis.

Randomisation and allocation concealment was done using a computer and kept concealed using numbered, opaque sealed envelopes (Cianciaruso 2008), envelopes after stratification by age, gender and renal function (Rosman 1989), after stratification by renal function and blood pressure levels, by centre and study and by block permutation (MDRD 1994), after allocating envelopes without stratification (Ihle 1989; Jungers 1987; Williams 1991), by random number table and a telephone call (Locatelli 1991), random number table (Malvy 1999). The method of randomisation was not stated in di Iorio 2003 and Mirescu 2007.

The level of renal insufficiency as assessed by CKD stage was moderate (MDRD 1994 study 1 (CKD 3-4); Locatelli 1991 (CKD 3-4), Rosman 1989 study A1-B (CKD 3)) or severe (Cianciaruso 2008 (CKD 4-5); di Iorio 2003 (CKD 4-5); Ihle 1989 (CKD 4-5); Jungers 1987 (CKD 5); MDRD 1994 study 2 (CKD 4); Malvy 1999 (CKD 4-5); Mirescu 2007 (CKD 4); Rosman 1989 study A2-C (CKD 4-5) and Williams 1991 (CKD 4-5).

Mean age of patients was: 48 years (range 15-73) (Rosman 1989), 62 (32-79) (Jungers 1987), 49 (18-65) (Locatelli 1991), 55 (15-75) (Malvy 1999), 44 (15-70) (Williams 1991), 61 (± 18) (Cianciaruso 2008), 52 (MDRD 1994) and 55 (di Iorio 2003; Mirescu 2007).

The type of kidney disease was available for all studies. Glomerulopathies represented 36% of included patients (Rosman 1989), 26% (Jungers 1987), 29% (Locatelli 1991), 28% (Malvy 1999), 47% (Ihle 1989), 23% (Williams 1991), 25% (MDRD 1994); 58% (Mirescu 2007)' 35% (di Iorio 2003) and 24% (Cianciaruso 2008). Polycystic kidney disease was present in 6% of patients (Rosman 1989), 21% (Jungers 1987), 16% (Locatelli 1991), 30% (Malvy 1999), 18% (Ihle 1989), 17% (Williams 1991), 24% (MDRD 1994) and 8% (Cianciaruso 2008). Interstitial nephritis was present in 24% of patients (Rosman 1989), 16% (Jungers 1987), 34% (Locatelli 1991), 14% (Malvy 1999), 26% (Ihle 1989), 17% (Williams 1991), 15% (di Iorio 2003), 28% (Mirescu 2007), 26% (Cianciaruso 2008) and was not reported (MDRD 1994). Importantly, these nephropathies were equally distributed between groups within studies. Six diabetic nephropathy patients were included in di Iorio 2003 (30%). There were three patients in each group.

Gender (M/F) was as follows: 0.56 (Cianciaruso 2008), 0.54 (Rosman 1989), 0.37 (Jungers 1987), 0.54 (Locatelli 1991), 0.58 (Malvy 1999), 0.67 (Ihle 1989), 0.63 (Williams 1991), 0.61 (Mirescu 2007) and 0.60 (MDRD 1994; di Iorio 2003), reflecting the higher male prevalence of kidney disease. Again, no difference between treated and control groups was observed.

Risk of bias in included studies

There was no follow-up of treatment, because of the nature of the nutritional intervention. All studies appeared to use adequate randomisation processes.

Effects of interventions

Low protein diets versus free or higher protein diets

The overall unadjusted incidence of renal death in the control groups was 17%, and ranged from 6% (Cianciaruso 2008) to 78% (Jungers 1987). All but one study (Williams 1991) showed a trend for a beneficial effect of a restricted protein intake compared with an unrestricted intake, and one study showed a statistically significant difference (Ihle 1989). There was no heterogeneity between studies (χ^2 = 8.20, df = 9, P = 0.51; I^2 = 0%). The overall effect was found to be highly significant, with 113 renal deaths observed with restricted protein intake compared with 168 events in the unrestricted protein intake (RR 0.68, 95% CI 0.55 to 0.84). There was a 32% relative risk reduction in renal death (P = 0.0002) in favour of a restricted protein intake. Of importance, due to randomisation, there was a similar percentage in categories of kidney disease (glomerulopathy, interstitial nephritis, nephroangiosclerosis, polycystic disease) in both restricted and unrestricted protein intake groups.

The number of patients needed to be treated (NNT) during one year to avoid one renal death ranged from 2 (di Iorio 2003), 4 (Jungers 1987), 5 (Mirescu 2007) 8 (Malvy 1999), 11 (Ihle 1989), 11 (Williams 1991), 14 (Rosman 1989), 37 (Locatelli 1991), 50 (Cianciaruso 2008) and 56 (MDRD 1994). To estimate the overall benefit of a restricted protein intake longer than one year, these results should be divided by the number of years during which the low protein diet is prescribed.

There was some heterogeneity between diets. This reflects the absence of homogenous experimental hypotheses and the historical background of these treatments. Theoretically, the mean difference in protein intake between higher and restricted protein intake groups was approximately 0.35 g/kg/d in all studies except 0.2 g/kg/d (Jungers 1987; Williams 1991) and 0.7 g/kg/d (MDRD 1994). However, based on urinary collection of protein waste products, the actual reduction in protein intake between groups in each study was less than expected and close to 0.2 g/kg/d (Locatelli 1991), 0.25 g/kg/d (Cianciaruso 2008; Ihle 1989; Williams 1991), 0.3 g/kg/d (Mirescu 2007; Rosman 1989) and 0.35 g/kg/d (MDRD 1994, in (Kopple 1997)). This value should be considered to be the true therapeutic intervention estimated by the present review.

The sub-analysis (Analysis 1.1.1) according to a more liberal intake (0.6 g/kg/d versus higher protein intake, three studies) showed little effect on renal death (RR 0.76, 95% CI 0.54 to 1.05, P = 0.10) whereas for the analysis of more reduced protein intakes (Analysis 1.1.2, 0.3 to 0.6 g/kg/d versus higher/free protein intake, 7 studies), the difference in renal deaths was strongly significant (RR 0.63, 95% CI 0.48 to 0.83, P = 0.0009).

DISCUSSION

Updating two previous meta-analyses (Fouque 1992; Pedrini 1996), this review shows that reducing the protein intake of patients with CKD significantly reduces the number of patients entering ESKD by about 32% (P = 0.0002).

For many decades, reducing protein intake has been proposed for patients suffering from kidney disease for metabolic purposes. Urea production, and hence, serum urea can be reduced by a low protein diet. More recently experimental studies have suggested that a low protein intake may prevent the natural progression of CKD towards ESKD thus delaying the start of maintenance dialysis treatment (Klahr 1989). Reducing protein intake modifies creatinine concentration, and since this was used as an intermediary outcome in many reports published since 1975, it is not possible to use these data to reliably assess the effects of low protein diets. To avoid problems raised by the use of

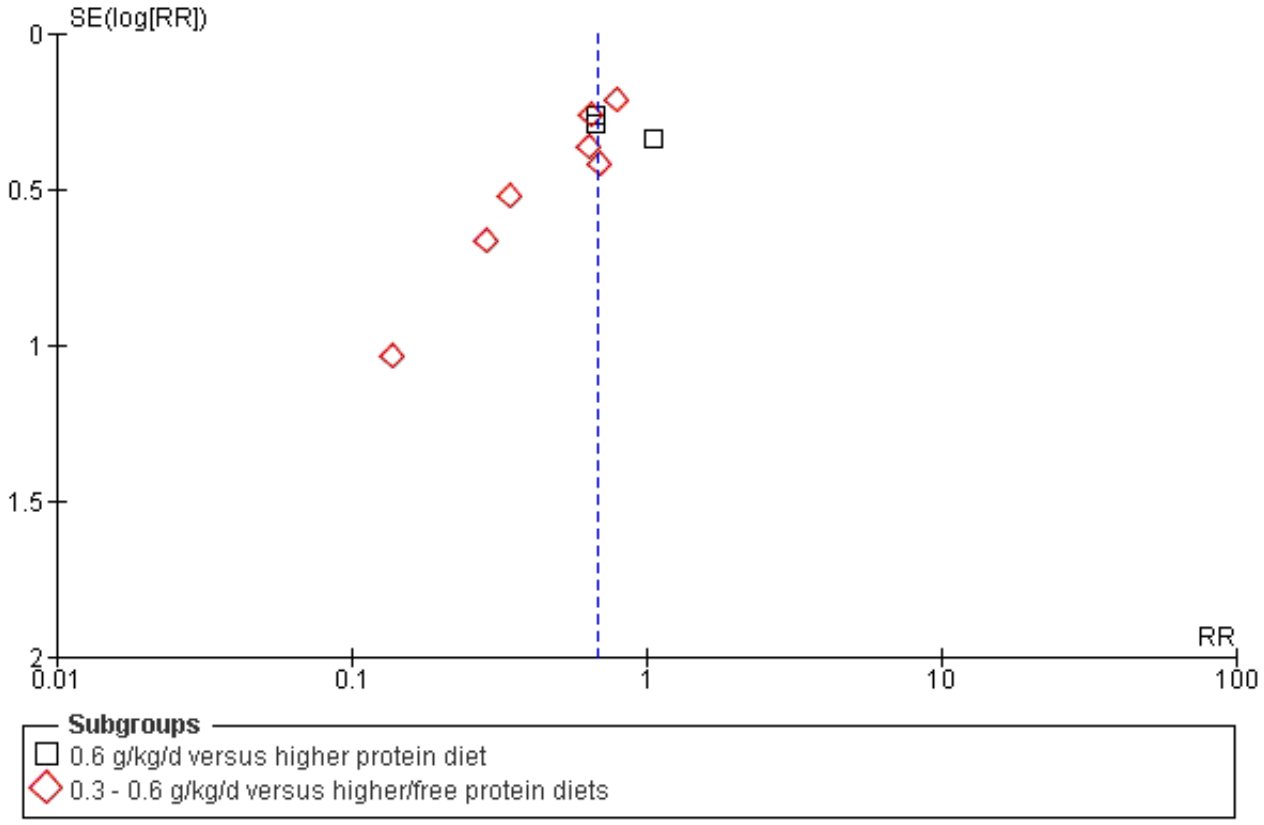
intermediary outcomes, we chose a robust clinical end-point, renal death. This end-point was easily observed for all patients, i.e., the date of first dialysis session, kidney transplant or the death of a patient during the study. Since in some studies, patients were transplanted before starting dialysis, we also counted them as renal death. These results were obtained accurately from each paper or by direct contact with the investigators.

A number of comments should be made (Sacks 1987; Boissel 1989). First, although the populations studied were clinically heterogeneous in age, gender, types of nephropathy and the level of protein restriction, the effects of treatments were not statistically different (heterogeneity test, P = 0.51; I^2 = 0%). Secondly, although the protein intakes were quite different between studies, the fact that a common effect was found indicates that the gradient in protein intake is the therapeutic factor. In fact, due to a well described spontaneous increase in protein intake during a diet (Kopple 2000), it was not surprising that the true protein intake gradient between groups was less than expected. Thus, the effect of the diet might have been even more pronounced if the diet was better adhered to. Thirdly, because the decision to start dialysis is often based on serum urea levels (but not only), and since low protein diets decrease these urea levels, it can be expected that patients with a reduced protein intake will have a more reduced serum urea levels and, hence, will start dialysis later than patients with higher protein intake. Only studies measuring GFR and reporting a decrease in renal function over time may give this information. In the present report, two studies used these markers: (Ihle 1989) showed a beneficial effect and (MDRD 1994) reported a nearly significant beneficial effect (P = 0.07). Interestingly, Kasiske 1998 performed a meta-analysis on the renal function deterioration (not on the renal death) and showed a moderate but significant protection by low protein diets (0.5 mL/min/y less loss for restricted protein intakes than for higher protein intakes). Even if this represents a renal protective effect of low protein diets, it is moderate and not responsible for the greater reduction in renal death we have observed in the present review. Thus, it is probably a combination of renal protection and better metabolic control offered by the low protein diets that may explain the benefit we report here.

The NNT is a tool recently introduced to better compare the strength of a treatment between studies and to homogenise these effects when absolute even risks are quite different between studies (Altman 1999). In the present review, NNT during one year for each study varied from 2 to 56. These variations mainly depend on the basal risk for renal death at inclusion and correspond to the impairment in renal function, since the absolute risk of renal death during the study is greater when renal function is more impaired (Jungers 1987; Malvy 1999). However, the amplitude of NNTs among studies is not very large (2 to 56) and thus appears to be very acceptable in primo-secondary prevention for a treatment that is not expensive and whose potential side-effects can be avoided by routine dietary survey. Moreover, these results compare favourably with the well-accepted mortality reduction obtained by prescribing statins in the 4S study (NNT = 30) or in the WOSCOPS study (NNT = 111) (Skolbekken 1998).

The funnel plot represents the individual risk ratio (RR) corresponding to the study patients number (Egger 1997). The funnel plot representation (Figure 1) shows that the RR from the four largest studies (Cianciaruso 2008; Locatelli 1991; MDRD 1994; Rosman 1989) are closer to the common RR (i.e. 0.68), whereas the smaller studies (Ihle 1989; Malvy 1999; Mirescu 2007) provide smaller RRs (0.14 to 0.34), suggesting a stronger beneficial effect of reducing protein intake. The fact that only one small size study provided an RR greater than 0.61 (Williams 1991) suggests that a publication bias might have occurred. Indeed, if investigators found negative or less robust conclusions on small effects (e.g. 20 to 100 patients), they might have censored themselves and were reluctant to report their findings. Also, medical journals might have refused to publish negative studies due to inadequate size.

Figure 1. Funnel plot of comparison: 1 Low protein versus higher protein diets, outcome: 1.1 Renal death.



Although the sub-analysis based on the degree of protein restriction led to a stronger benefit for more restricted protein intake, there are some nutritional risks to a more restricted protein intake in CKD patients. In this review, sparse nutritional data could not allow a reliable assessment of nutritional consequences of such diets. Thus, a combined analysis of survival data in one hand and nutritional requirements in another hand should recommend a protein intake closer to 0.6 rather than 0.3 g/kg/d.

Attention should be focused on the potential additive protective effect of a reduction in protein intake and the renoprotective drugs ACE inhibitors as reported by Gansevoort 1995.

AUTHORS' CONCLUSIONS

Implications for practice

A nutritional intervention should be proposed to patients with moderate CRF, including a reduction in protein intake. The optimal level of protein intake cannot be deduced from the present review. The fact that the actual patient protein intake was greater than prescribed in all studies suggests that a skilled and regular dietary survey should be proposed (NKF-KDOQI Guideline #23, in (DOQI 2000)). Moreover, it has been demonstrated that patients with CRF left without dietetic survey will express a progressive decline in protein and energy intakes, potentially contributing to the decline in nutritional markers (Kopple 2000). By contrast, feasibility of low protein diets has been shown in large studies with convincing results (Aparicio 2000), highlighting the fact that interested teams can motivate patients to the point of excellent compliance and optimal nutritional benefit, a goal that should be reached for most patients in all renal units. Thus, based on physician enthusiasm and dietary survey, the patient may eventually make his personal treatment choice. Factors other than diet therapy have demonstrated a renal protective effect and have been shown to be able to delay ESKD (Locatelli 1999). These include angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, blood pressure control, optimal glucose monitoring in diabetic patients. Even if it is more difficult to modify dietary habits than taking blood pressure treatment, a restricted protein intake should be proposed to the patients in addition to other current and future renoprotective treatments.

Implications for research

Further nutritional studies may be necessary to characterise the optimal level of protein restriction and duration of intervention. Additional studies should test a potential additive effect of a low protein diet in combination with angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists or other antiproteinuric medications.

ACKNOWLEDGEMENTS

We are grateful to Prof Jean-Pierre Boissel who contributed to the original iteration of this review (Fouque 2000b; Fouque 2006), contributing to the design, quality assessment, data collection, entry, analysis and interpretation, and writing.

We thank the authors of each included study for providing additional data and are particularly indebted to Michel Cucherat MD PhD, Margaret Haugh PhD and the Centre Cochrane Français for statistical and methodological assistance. Prof Bert Kasiske and Prof Teut Risler should be acknowledged for critically reviewing the manuscript.

REFERENCES

References to studies included in this review

Cianciaruso 2008 *{published data only}*

Cianciaruso B, Pota A, Pisani A, Torraca S, Annecchini R, Lombardi P, et al. Metabolic effects of two low protein diets in chronic kidney disease stage 4-5--a randomized controlled trial. *Nephrology Dialysis Transplantation* 2008;**23**(2):636-44.

Cianciaruso B, Pota A, Torraca S, Somma G, Nazzaro P, Annecchini R, et al. Comparison of two different protein intakes (0.3-0.6 vs 0.7-0.9 g/kg/day) on the metabolic control of advanced renal failure [abstract]. ERA - EDTA Congress; 2004; May 15-18; Lisbon (Portugal). 2004:295.

di Iorio 2003 *{published data only}*

Di Iorio BR, Minutolo R, De Nicola L, Bellizzi V, Catapano F, Iodice C, et al. Supplemented very low protein diet ameliorates responsiveness to erythropoietin in chronic renal failure. *Kidney International* 2003;**64**(5):1822-8. [MEDLINE: 14717953]

Ihle 1989 *{published data only}*

Ihle BU, Becker G, Whithworth JA, Charlwood RA, Kincaid-Smith PS. The effect of protein restriction on the progression of renal insufficiency. *New England Journal of Medicine* 1989;**321**(26):1773-7. [MEDLINE: 2512486]

Jungers 1987 *{published data only}*

Jungers P, Chauveau P, Ployard F, Lebkiri B, Ciancioni C, Man NK. Comparison of ketoacids and low protein diet on advanced chronic renal failure progression. *Kidney International - Supplement* 1987;**22**:67-71. [MEDLINE: 3323621]

Locatelli 1991 *{published data only}*

* Locatelli F, Alberti D, Graziani G, Buccianti G, Redaelli B, Giangrande A. Prospective, randomised, multicentre trial of effect of protein restriction on progression of chronic renal insufficiency. Northern Italian Cooperative Study Group. *Lancet* 1991;**337**(8753):1299-304. [MEDLINE: 1674294]

Tentori F, Marai P, Marcelli D, Ponti R, La Milla V, Locatelli F. Monocentric prospective randomised controlled study on the progression rate of chronic renal failure with two different protein intakes [abstract]. *Nephrology Dialysis Transplantation* 1987;**2**(5):400.

Malvy 1999 *{published data only}*

Malvy D, Maingourd C, Pengloan J, Bagros P, Nivet H. Effects of severe protein restriction with ketoanalogues in advanced renal failure. *Journal of the American College of Nutrition* 1999;**18**(5):481-6. [MEDLINE: 10511331]

Nivet H, Maingourd C, Malvy D, Pengloan J, Bagros PH. Effects of severe protein-restriction with ketoanalogues in advanced renal failure [abstract]. *Journal of the American Society of Nephrology* 1992;**3**(3):286. [CENTRAL: CN-00461412]

MDRD 1994 *{published data only}*

* Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, et al. The effects of dietary protein restriction and blood pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *New England Journal of Medicine* 1994;**330**(13):877-84. [MEDLINE: 8114857]

MDRD Study Group, Hunsicker LG, Adler S, Caggiula AW, England B, Greene T, et al. Relationship among baseline proteinuria (p), mean arterial blood pressure (map) during follow-up, and decline in glomerular filtration rate (agfr) in the modification of diet in renal disease study [abstract]. *Journal of the American Society of Nephrology* 1993;**4**(Program & Abstracts):254. [CENTRAL: CN-00485053]

MDRD Study Group, Kusek JW, Agodoa L, Greene T, Jones C. Comparison of decline of gfr in blacks versus non-blacks in the mdrd study [abstract]. *Journal of the American Society of Nephrology* 1993;**4**(Program & Abstracts):253. [CENTRAL: CN-00485054]

MDRD Study Group, Levey AS, Beck GJ, Caggiula AW, Greene T, Hunsicker LG, et al. A hypothesis for the results of the modification of diet in renal disease (mdrd) study. [abstract]. *Journal of the American Society of Nephrology* 1993;**4**(Program & Abstracts):253. [CENTRAL: CN-00485055]

MDRD Study Group, Levey AS, Bosch JP, Coggins CH, Greene T, Mitch WE, et al. Effects of diet and blood pressure on creatinine clearance (ccr) and serum creatinine (pcr) in the mdrd study. [abstract]. *Journal of the American Society of Nephrology* 1993;**4**(Program & Abstracts):253. [CENTRAL: CN-00485056]

MDRD Study Group, Peterson JC, Burkart J, Greene T, Hebert L, King A, et al. The effect of blood pressure control on progression of renal disease depends on level of proteinuria (p) at baseline evaluation [abstract]. *Journal of the American Society of Nephrology* 1993;**4**(Program & Abstracts):254. [CENTRAL: CN-00485057]

MDRD Study Group, Porush JG, Lazarus JM, Bourgoignie JJ, Buckalew VM, Greene T, et al. Efficacy of anti-hypertensive interventions in reducing blood pressure in the mdrd study [abstract]. *Journal of the American Society of Nephrology* 1995;**6**(3):400. [CENTRAL: CN-00485058]

MDRD Study Group, Rocco MV, Coyne T, Eastin S, Faubert J, Gassman JJ, et al. Patient symptoms and quality of life in the mdrd study at enrollment-correlation with gfr [abstract]. *Journal of the American Society of Nephrology* 1993;**4**(Program & Abstracts):254. [CENTRAL: CN-00485060]

MDRD Study Group, prepared by Levey AS, Beck GJ, Bosch JP, Caggiula AW, Greene T, et al. Short-term effects of protein intake, blood pressure, and antihypertensive therapy on gfr in the mdrd study. [abstract]. *Journal of the American Society of Nephrology* 1995;**6**(3):395. [CENTRAL: CN-00487729]

Yamamoto ME, Olson MB, Stollar C, MDRD Study Group. Effects of weight and na+ change on blood pressures of hypertensive mdrd study patients [abstract]. *Journal of the American Society of Nephrology* 1995;**6**(3):408. [CENTRAL: CN-00486522]

Mirescu 2007 *{published data only}*

Mircescu G, Garneata L, Stancu SH, Capusa C. Effects of a supplemented hypoproteic diet in chronic kidney disease. *Journal of Renal Nutrition* 2007;**17**(3):179-88.

Rosman 1989 *{published data only}*

Donker AJ, Piers-Becht TP. Four-years Follow-up of Patients with Chronic Renal Insufficiency Randomly allocated to a Protein-restricted Diet and a Control Group [abstract]. *Nephrology Dialysis Transplantation* 1989;**4**(5):455.

Donker AJ, Rosman JB, Piers-Becht TP, Sluiter WJ. Effect of protein restriction in chronic renal insufficiency: a prospective randomized trial [abstract]. *Kidney International* 1985;**27**:137.

Rosman JB, Donker AJ. The Response to a Low-protein Diet to Retard the Progression of Renal Failure is Sex-Dependent [abstract]. *Nephrology Dialysis Transplantation* 1989;**4**(5):457.

Rosman JB, Donker AJ, Meijer S, Sluiter WJ, Piers-Becht TP, van der Hem GK. Two years' experience with protein restriction in chronic renal failure. *Contributions to Nephrology* 1986;**53**:109-20. [CENTRAL: CN-00420852]

* Rosman JB, Langer K, Brandl M, Piers-Becht TP, Van der Hem GK, Ter Wee PM, et al. Protein-restricted diets in chronic renal failure: A four year follow-up shows limited indications. *Kidney International - Supplement* 1989;**27**:96-102. [MEDLINE: 2636680]

Rosman JB, ter Wee PM, Meijer S, Piers-Becht TP, Sluiter WJ, Donker AJ. Prospective randomised trial of early dietary protein restriction in chronic renal failure. *Lancet* 1984;**324**(8415):1291-6.

Rosman JB, ter Wee PM, Piers-Becht GP, Sluiter WJ, van der Woude FJ, Meijer S, et al. Early protein restriction in chronic renal failure. *Proceedings of the European Dialysis & Transplant Association - European Renal Association* 1985;**21**:567-73.

Williams 1991 *{published data only}*

Williams PS, Stevens M, Irons L, Fass G, Bone JM. Failure of Dietary Protein/Phosphate Restriction to Slow the Progression of Chronic Renal Failure; A Prospective Randomised Controlled Trial [abstract]. *Nephrology Dialysis Transplantation* 1990;**5**(8):674.

Williams PS, Stevens ME. A Randomised Trial of the Effect of Protein and Phosphate Restriction on the Progression of Chronic Renal Failure [abstract]. *Nephrology Dialysis Transplantation* 1987;**2**(5):401.

Williams PS, Stevens ME, Fass G, Irons L, Bone JM. Failure of dietary protein and phosphate restriction to retard the rate of progression of chronic renal failure: a prospective, randomized, controlled trial. *Quarterly Journal of Medicine* 1991;**81**(294):837-55. [MEDLINE: 1801057]

References to studies excluded from this review

Alvestrand 1980 *{published data only}*

Alvestrand A, Ahlberg M, Furst P, Bergstrom J. Clinical experience with amino acid and keto acid diets. *American Journal of Clinical Nutrition* 1980;**33**(7):1654-9. [MEDLINE: 7395786]

Alvestrand 1983 *{published data only}*

Alvestrand A, Ahlberg M, Bergstrom J. Retardation of the progression of renal insufficiency in patients treated with low-protein diets. *Kidney International - Supplement* 1983;**16**:268-72. [MEDLINE: 6588263]

Attman 1983 *{published data only}*

Attman PO, Bucht H, Larsson O, Uddebom G. Protein-reduced diet in diabetic renal failure. *Clinical Nephrology* 1983;**19**(5):217-20. [MEDLINE: 6851260]

Attman 1986 *{published data only}*

Attman PO. Long term treatment with low protein diet in uremia. *Contributions to Nephrology* 1986;**53**:128-36. [MEDLINE: 3802819]

Barsotti 1981 *{published data only}*

Barsotti G, Guiducci A, Ciardella F, Giovanetti S. Effects on renal function of a low nitrogen diet supplemented with essential amino acids and ketoanalogues and of hemodialysis and free protein supply in patients with chronic renal failure. *Nephron* 1981;**27**(3):113-7. [MEDLINE: 7219640]

Barsotti G, Morelli E, Giannoni A, Guiducci A, Lupetti S, Giovannetti S. Restricted phosphorus and nitrogen intake to slow the progression of chronic renal failure, a controlled trial. *Kidney International - Supplement* 1983;**16**:278-84. [MEDLINE: 6376918]

Barsotti 1984 *{published data only}*

Barsotti G, Giannoni A, Morelli E, Lazzeri M, Vlamis I, Baldi R, et al. The decline of renal function slowed by very low phosphorus intake in chronic renal patients following a low nitrogen diet. *Clinical Nephrology* 1984;**21**(1):54-9. [MEDLINE: 6705274]

Barsotti 1988 *{published data only}*

Barsotti G, Ciardella F, Morelli E, Cupisti A, Mantovanelli A, Giovanetti S. Nutritional treatment of renal failure in type 1 diabetic nephropathy. *Clinical Nephrology* 1988;**29**(6):280-7. [MEDLINE: 3396230]

Bellizzi 2007 *{published data only}*

Bellizzi V, Di Iorio BR, De Nicola L, Minutolo R, Zamboli P, Trucillo P, et al. Very low protein diet supplemented with ketoanalogs improves blood pressure control in chronic kidney disease.[see comment]. *Kidney International* 2007;**71**(3):245-51.

Bennett 1983 *{published data only}*

Bennett SE, Russell GI, Walls J. Low protein diets in uraemia. *British Medical Journal Clinical Research Ed* 1983;**287**(6402):1344-5. [MEDLINE: 6416404]

Bergstrom 1989 *{published data only}*

Bergstrom J, Alvestrand A, Bucht H, Gutierrez A. Stockholm clinical study on progression of chronic renal failure--an interim report. *Kidney International - Supplement* 1989;**36**(Suppl 27):S110-4.

Bernhard 2001 *{published data only}*

Bernhard J, Beaufrere B, Laville M, Fouque D. Adaptive response to a low-protein diet in predialysis chronic renal failure patients. *Journal of the American Society of Nephrology* 2001;**12**(6):1249-54.

Brunori 2003 *{published data only}*

Brunori G, Viola F, Zubani R, de Biase V, Franco V, Cuoma D, et al. The DODE Study (diet or dialysis in elderly): interim analysis [abstract]. *Nephrology Dialysis Transplantation* 2003;**18 Suppl**(4):440.

Burns 1978 *{published data only}*

Burns J, Cresswell E, Ell S, Fynn M, Jackson MA, Lee HA, et al. Comparison of the effects of keto acid analogues and essential amino acids on nitrogen homeostasis in uremic patients on moderately protein-restricted diets. *American Journal of Clinical Nutrition* 1978;**31**(10):1767-75. [MEDLINE: 707331]

Coresh 1994 *{published data only}*

Coresh J, Walser M, Hill S. Long-term outcome of treatment of chronic renal failure with a supplemented low protein diet [abstract]. *Journal of the American Society of Nephrology* 1994;**5**(3):489.

D'Amico 1994 *{published data only}*

D'Amico G, Gentile MG, Fellin G, Manna G, Cofano F. Effect of dietary protein restriction on the progression of renal failure: a prospective randomized trial. *Nephrology Dialysis Transplantation* 1994;**9**(11):1590-4. [MEDLINE: 7870348]

Dek 1998 *{published data only}*

Dek K, Gullulu M, Yavuz M, Ersoy A, Karakoc Y, Dalk E, Yurtkuran M. The effects of low dose proteinaceous diet and essential amino acid ketoanologue therapy on the metabolism of lipid and insulin resistance in predialysis patients [abstract]. XXXV ERA-EDTA; 1998; Jun 6-9; Rimini (Italy). 1998:161.

Di Landro 1986 *{published data only}*

Di Landro D, Perin N, Bertoli M, Gasparotti ML, Ruffatti A, Naso A, et al. Clinical effects of a low protein diet supplemented with essential amino acids and keto analogues in uremic patients. *Contributions to Nephrology* 1986;**53**:137-43. [MEDLINE: 3802820]

DODE Study 2007 *{published data only}*

Brunori G, Viola BF, Parrinello G, De B, Como G, Franco V, et al. Efficacy and safety of a very-low-protein diet when postponing dialysis in the elderly: a prospective randomized multicenter controlled study.[see comment]. *American Journal of Kidney Diseases* 2007;**49**(5):569-80.

Maiorca R, Brunori G, Viola BF, Zubani R, Cancarini G, Parrinello G, et al. Diet or dialysis in the elderly? The DODE study: a prospective randomized multicenter trial. *Journal of Nephrology* 2000;**13**(4):267-70.

El Nahas 1984 *{published data only}*

El Nahas AM, Masters-Thomas A, Brady SA, Farrington K, Wilkinson V, Hilson AJ, et al. Selective effect of low protein diets in chronic renal diseases. *British Medical Journal Clinical Research Ed* 1984;**289**(6455):1337-41. [MEDLINE: 6437539]

Esaian 2002 *{published data only}*

Esaian AM, Kucher AG, Kaiukov IG, Ermakov I, Nikogosian I, Riabov SI. Effect of protein load on kidney functions in patients with chronic glomerulonephritis. *Terapevticheskii Arkhiv* 2002;**74**(6):19-24. [MEDLINE: 12136476]

Frohling 1980 *{published data only}*

Frohling PT, Schmicker R, Vetter K, Kaschube I, Gotz KH, Jacopian M, et al. Conservative treatment with ketoacid and amino acid supplemented low-protein diets in chronic renal failure. *American Journal of Clinical Nutrition* 1980;**33**(7):1667-72. [MEDLINE: 7395787]

Frohling 1983 *{published data only}*

Frohling PT, Kokot F, Schmicker R, Kaschube I, Lindenau K, Vetter K. Influence of keto acids on serum parathyroid hormone levels in patients with chronic renal failure. *Clinical Nephrology* 1983;**20**(4):212-5. [MEDLINE: 6641029]

Frohling 1989 *{published data only}*

Frohling PT, Lindenau K, Vetter K, Krupki F, Schmicker R. What can be safely said about predialysis treatment?. *Blood Purification* 1989;**7**(1):28-32. [MEDLINE: 2920099]

Fuessl 2006 *{published data only}*

Fuessl HS. [Egg white-poor diet in kidney failure: annoyance or meaningful measure?]. [German]. *MMW Fortschritte der Medizin* 2006;**148**(26):4-6.

Gretz 1983 *{published data only}*

Gretz N, Korb E, Strauch M. Low-protein diet supplemented by keto acids in chronic renal failure, a prospective controlled study. *Kidney International - Supplement* 1983;**16**:263-7. [MEDLINE: 6376916]

Gretz N, Korb E, Strauch M. Protein restricted diet supplemented by keto-acids in chronic renal failure: a prospective controlled study [abstract]. 19th Annual Scientific Meeting of the Australasian Society of Nephrology. 1983:30.

Gretz N, Meisinger E, Strauch M. Does a low protein diet really slow down the rate of progression of chronic renal failure?. *Blood Purification* 1989;**7**(1):33-8. [MEDLINE: 2645923]

Gretz N, Meisinger E, Strauch M. Influence of diet and underlying renal disease on the rate of progression of chronic renal failure. *Infusionstherapie Und Klinische Ernahrung* 1987;**14 Suppl**(5):21-5. [MEDLINE: 3436665]

Gretz N, Meisinger E, Strauch M. Influence of the underlying renal disease on the rate of progression. *Contributions to Nephrology* 1986;**53**:92-101. [MEDLINE: 3542381]

Gretz N, Strauch M. Delayed progression of chronic renal failure, a prospective controlled trial with a low protein diet supplemented by keto acids. *Contributions to Nephrology* 1985;**49**:78-86. [MEDLINE: 3830572]

Hecking 1980 *{published data only}*

Hecking E, Andrzejewski L, Prellwitz W, Opferkuch W, Muller D. Double-blind cross-over study with oral alpha-ketoacids in patients with chronic renal failure. *American Journal of Clinical Nutrition* 1980;**33**(7):1678-81. [MEDLINE: 6994475]

IRCCA Study 1988 *{published data only}*

Forget D, Caranhac G, Quillot MJ. French multicentric trial (IRCCA) for testing a new ketoanalog and essential amino acid mixture in patients with chronic renal failure. [abstract]. *Kidney International* 1988;**36**(Suppl 27):S300.

Forget D, Caranhac G, Quillot MJ, Besnier MO. Compliance with very low protein diet and ketoanalogues in chronic renal failure. The French Multicentric Trial IRCCA. *Contributions to Nephrology* 1990;**81**:79-86.

Ivarsen 1995 *{published data only}*

Ivarsen P, Pedersen EB. Effect of protein supplement on nutritional status in hemodialysis patients [abstract]. *Journal of the American Society of Nephrology* 1995;**6**(3):579.

Kampf 1980 *{published data only}*

Kampf D, Fischer HC, Kessel M. Efficacy of an unselected protein diet (25 g) with minor oral supply of essential amino acids and keto analogues compared with a selective protein diet (40 g) in chronic renal failure. *American Journal of Clinical Nutrition* 1980;**33**(7):1673-77. [MEDLINE: 7395788]

Levine 1989 *{published data only}*

Levine SE, D'Elia JA, Bistrian B, Smith-Ossman S, Gleason R, Mitch WE, et al. Protein restricted diets in diabetic nephropathy. *Nephron* 1989;**52**(1):55-61. [MEDLINE: 2710267]

Lim 2000 *{published data only}*

Lim CS, Norashikin AB, Noor Aini MY, Zahara AM, Angl BB, Aparicio M, et al. The effect of very low protein supplemented by ketoamino acid versus low protein diet on progression of chronic renal failure. 13th Asian Colloquium in Nephrology; 2000 Nov 23-25; Bali (Indonesia). 2000:68.

Noor Aini MY, Zahara AM, Norashikin AB, Lim CS, Ang BB, Aparicio M, et al. Dietary changes and nutritional status of chronic renal failure patients on very low protein diet supplemented by ketoamino acid versus low protein diet. 13th Asian Colloquium in Nephrology; 2000 Nov 23-25; Bali (Indonesia). 2000:140.

Lucas 1986 *{published data only}*

Lucas PA, Meadows JH, Roberts DE, Coles GA. The risks and benefits of a low protein-essential amino acid-keto acid diet. *Kidney International* 1986;**29**(5):995-1003. [MEDLINE: 3723930]

Maksic 2004 *{published data only}*

Maksic D, Pavlovic G, Kostic-Milosavljevic M, Mijuskovic Z, Radjen S, Bokonjic D, et al. Comparison of effects of low protein diet (lpd) and very low protein diet (vlpd) supplemented with essential and ketoanalogue amino acids on the progression of predialysis chronic renal failure [abstract]. ERA - EDTA Congress; 2004; May 15-18; Lisbon (Portugal). 2004:296.

Maroni 1997 *{published data only}*

Maroni BJ, Staffeld C, Young VR, Manatunga A, Tom K. Mechanisms permitting nephrotic patients to achieve nitrogen equilibrium with a protein-restricted diet. *Journal of Clinical Investigation* 1997;**99**(10):2479-87.

Tom K, Young VR, Umeakunne K, Maroni BJ. Anabolic responses activated in nephrotic patients fed a protein-restricted diet [abstract]. *Journal of the American Society of Nephrology* 1994;**5**(3):343.

Maschio 1982 *{published data only}*

Maschio G, Oldrizzi L, Tessitore N, D'Angelo A, Valvo E, Lupo A, et al. Effects of dietary protein and phosphorus restriction on the progression of early renal failure. *Kidney International* 1982;**22**(4):371-6. [MEDLINE: 7176336]

Masud 1992 *{published data only}*

Masud T, Young VR, Maroni BJ. Metabolic responses to protein restriction: the first comparison of ketoacids (ka) with essential amino acids (eaa) [abstract]. *Journal of the American Society of Nephrology* 1992;**3**(3):286.

Meisinger 1987 *{published data only}*

Meisinger E, Strauch M. Controlled trial of two keto acid supplements on renal function, nutritional status, and bone metabolism in uremic patients. *Kidney International - Supplement* 1987;**22**:170-3. [MEDLINE: 3323611]

Mitch 1984 *{published data only}*

Mitch WE, Walser M, Steinman TI, Hill S, Zeger S, Tungsanga K. The effect of a keto acid-amino acid supplement to a restricted diet on the progression of chronic renal failure. *New England Journal of Medicine* 1984;**6**(10):623-9. [MEDLINE: 6472341]

Moreira 2007 *{published data only}*

Moreira AC, Gaspar A, Serra MA, Simoes J, Lopes da Cruz, Freitas do Amaral T. Effect of a sardine supplement on C-reactive protein in patients receiving hemodialysis. *Journal of Renal Nutrition* 2007;**17**(3):205-13.

Oldrizzi 1985 *{published data only}*

Oldrizzi L, Rugiu C, Valvo E, Lupo A, Loschiavo C, Gammaro L, et al. Progression of renal failure in patients with renal disease of diverse etiology on protein-restricted diet. *Kidney International* 1985;**27**(3):553-57. [MEDLINE: 3999543]

Patel 2000 *{published data only}*

Patel Z, Bhattacharjee LI, Shah BV. The role of dietary protein restriction in Indian patients with chronic renal failure. *Journal of the Association of Physicians of India* 2000;**48**(11):1078-81. [MEDLINE: 21205533]

Prakash 2003 *{published data only}*

Prakash S, Pande D, Suresh K, Kulkarni H. Randomized double blind placebo controlled trial of ketoanalogues in retardation

of chronic renal failure in tropics [abstract]. *Nephrology Dialysis Transplantation* 2003;**18 Suppl**(4):130. [CENTRAL: CN-00447278]

Prakash S, Pande DP, Sharma S, Sharma D, Bal CS, Kulkarni H. Randomized, double-blind, placebo-controlled trial to evaluate efficacy of ketodiet in predialytic chronic renal failure. *Journal of Renal Nutrition* 2004;**14**(2):89-96. [MEDLINE: 15060873]

Riabov 2001 *{published data only}*

Riabov SI, Kucher AG, Grigor'eva ND, Kaiukov IG, Ermakov I. Effects of different variants of low-protein diet on progression of chronic renal failure and indices of nutritional status in predialysis stage. *Terapevticheskii Arkhiv* 2001;**73**(6):10-5. [MEDLINE: 11521513]

Sanfelippo 1978 *{published data only}*

Sanfelippo ML, Swenson RS, Reaven GM. Plasma triglyceride (TG) and insulin responses to diet in dialyzed subjects with end stage renal failure. [abstract]. *Kidney International* 1976;**10**:525.

Sanfelippo ML, Swenson RS, Reaven GM. Response of plasma triglycerides to dietary change in patients on hemodialysis. *Kidney International* 1978;**14**(2):180-6.

Schmicker 1986 *{published data only}*

Schmicker R, Frohling PT, Goetz KH, Kaschube I, Rakette I, Vetter K. Influence of low protein diet supplemented with amino acids and keto acids on the progression of chronic renal failure. *Contributions to Nephrology* 1986;**53**:121-7. [MEDLINE: 3542378]

Schmicker R, Vetter K, Lindenau K, Frohling PT, Kobot F. Conservative long-term treatment of chronic renal failure with keto acid and amino acid supplementation. *Infusionstherapie und Klinische Ernahrung* 1987;**14 Suppl**(5):34-8. [MEDLINE: 3125108]

Teplan 2003 *{published data only}*

Teplan V, Schuck O, Knotek A, Hajny J, Horackova M. Ketoacids and recombinant human erythro-poietin may in fluence progression of chronic renal incufficiency: czech multicentre study [abstract]. XXXVIII ERA-EDTA; 2001 Jun 24-27; Vienna (Austria). 2001:145.

Teplan V, Schuck O, Knotek A, Hajny J, Horackova M, Kvapil M. Enhanced metabolic effect of erythropoietin and keto acids in CRF patients on low-protein diet: Czech multicenter study. *American Journal of Kidney Diseases* 2003;**41**(3 Suppl 2):26-30. [MEDLINE: 22498947; CN-00413403]

Teplan 2006 *{published data only}*

Teplan V, Schuck O, Hanzal V, Hajny J, Horackova M, Ryba M, et al. [Obesity and progression of chronic renal insufficiency: a Czech long term prospective double-blind randomised multicentre study]. [Czech]. *Vnitrni Lekarstvi* 2006;**52**(6):571-6.

Terzi 1995 *{published data only}*

Terzi F, Dartois AM, Broyer M, Niaudet P, Claris-Appiani C, Dechaux M, et al. Growth in uremia: an unsolved enigma. Study with two low protein diets in infancy [abstract]. *Journal of the American Society of Nephrology* 1995;**6**(3):404.

Walser 1975 *{published data only}*

Walser M. Ketoacids in the treatment of uremia. *Clinical Nephrology* 1975;**3**(5):180-6. [MEDLINE: 1149342]

Walser 1987 *{published data only}*

Walser M, LaFrance N, Ward L, Van Duyn MA. Progression of chronic renal failure in patients given keto acids following amino acids. *Infusionstherapie und Klinische Ernahrung* 1987;**14 Suppl**(5):17-20. [MEDLINE: 3436664]

Wingen 1997 *{published data only}*

Wingen AM, Fabian-Bach C, Schafer F, Mehls O. Randomised multicentre study of a low-protein diet on the progression of chronic renal failure in children. *Lancet* 1997;**349**(9059):1117-23. [MEDLINE: 9113009]

Younes 2006 *{published data only}*

Younes H, Egret N, Hadj-Abdelkader M, Remesy C, Demigne C, Gueret C, et al. Fermentable carbohydrate supplementation alters nitrogen excretion in chronic renal failure. *Journal of Renal Nutrition* 2006;**16**(1):67-74.

Zakar 1984 *{published data only}*

Zakar G. Effects of dietary protein restriction on the course of early renal failure. *Proceedings of the European Dialysis & Transplant Association - European Renal Association* 1984;**21**:600-3. [MEDLINE: 3991551]

Zeller 1991 *{published data only}*

Zeller K, Whittaker E, Sullivan L, Raskin P, Jacobson HR. Effect of restricting dietary protein on the progression of renal failure in patients with insulin-dependent diabetes mellitus. *New England Journal of Medicine* 1991;**324**(2):78-84. [MEDLINE: 1984187]

Additional references

Altman 1999

Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. *BMJ* 1999;**319**(7223):1492-5. [MEDLINE: 10582940]

Aparicio 2000

Aparicio M, Chauveau P, De Precigout V, Bouchet JL, Lasseur C, Combe C. Nutrition and outcome on renal replacement therapy of patients with chronic renal failure treated by a supplemented very low protein diet. *Journal of the American Society of Nephrology* 2000;**11**(4):708-16. [MEDLINE: 10752530]

Boissel 1989

Boissel JP, Blanchard J, Panak E, Peyrieux JC, Sacks H. Considerations for the meta-analysis of randomized clinical trials, summary of a panel discussion. *Controlled Clinical Trials* 1989;**10**(3):254-81. [MEDLINE: 2791560]

DOQI 2000

Anonymous. Clinical practice guidelines for nutrition in chronic renal failure. K/DOQI, National Kidney Foundation. *American Journal of Kidney Diseases* 2000;**35**(6 Suppl 2):1-140. [MEDLINE: 10895784]

Egger 1997

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629-34. [MEDLINE: 9310563]

Fouque 1992

Fouque D, Laville M, Boissel JP, Chifflet R, Labeeuw M, Zech PY. Controlled low protein diets in chronic renal insufficiency: meta-analysis. *BMJ* 1992;**304**(6821):216-20. [MEDLINE: 1531426]

Gansevoort 1995

Gansevoort RT, de Zeeuw D, de Jong PE. Additive antiproteinuric effect of ACE inhibition and a low-protein diet in human renal disease. *Nephrology Dialysis Transplantation* 1995;**10**(4):497-504. [MEDLINE: 7623991]

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60. [MEDLINE: 12958120]

Kasiske 1998

Kasiske BL, Lakatua JDA, Ma JZ, Louis TA. A meta-analysis of the effects of dietary protein restriction on the rate of decline in renal function. *American Journal of Kidney Diseases* 1998;**31**(6):954-61. [MEDLINE: 9631839]

Klahr 1989

Klahr S. The modification of diet in renal disease study. *New England Journal of Medicine* 1989;**320**(13):864-6. [MEDLINE: 2494456]

Kopple 1997

Kopple JD, Levey AS, Greene T, Chumlea WC, Gassman JJ, Hollinger DL, et al. Effect of dietary protein restriction on nutritional status in the modification of diet in Renal Disease study. *Kidney International* 1997;**52**(3):778-91. [MEDLINE: 9291200]

Kopple 2000

Kopple JD, Greene T, Chumlea WC, Hollinger D, Maroni BJ, Merrill D, et al. Relationship between nutritional status and the glomerular filtration rate: results from the MDRD study. *Kidney International* 2000;**57**(4):1688-703. [MEDLINE: 10760105]

Locatelli 1999

Locatelli F, Del Vecchio L. How long can dialysis be postponed by low protein diet and ACE inhibitors?. *Nephrology Dialysis Transplantation* 1999;**14**(6):1360-4. [MEDLINE: 10382993]

Pedrini 1996

Pedrini MT, Levey AS, Lau J, Chalmers TC, Wang PH. The effect of dietary protein restriction on the progression of diabetic and nondiabetic renal diseases: a meta-analysis. *Annals of Internal Medicine* 1996;**124**(7):627-32. [MEDLINE: 96201235]

Sacks 1987

Sacks HS, Berrier J, Reitman D, Ancona-Berk VA, Chalmers TC. Meta-analyses of randomized controlled trials. *New England Journal of Medicine* 1987;**316**(8):450-55. [MEDLINE: 3807986]

Skolbekken 1998

Skolbekken JA. Communicating the risk reduction achieved by cholesterol reducing drugs. *BMJ* 1998;**316**(7149):1956-8. [MEDLINE: 9641937]

References to other published versions of this review

Fouque 2000a

Fouque D, Wang P, Laville M, Boissel JP. Low protein diets delay end-stage renal disease in non-diabetic adults with chronic renal failure. *Nephrology Dialysis Transplantation* 2000;**15**(12):1986-92. [MEDLINE: 11096144]

Fouque 2000b

Fouque D, Wang PH, Laville M, Boissel JP. Low protein diets for chronic renal failure in non diabetic adults. *Cochrane Database of Systematic Reviews* 2000, Issue 4. [DOI: 10.1002/14651858.CD001892]

Fouque 2006

Fouque D, Laville M, Boissel J-P. Low protein diets for chronic kidney disease in non diabetic adults. *Cochrane Database of Systematic Reviews* 2006, Issue 1. [DOI: 10.1002/14651858.CD001892.pub2]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Cianciaruso 2008

Methods	**Randomisation method**: Computer generated **Blinding**: Yes **Intention-to-treat**: No **Country**: Italy **Setting**: University Hospital CKD clinic
Participants	**Inclusion criteria** • Number: 392 • Age: 61 ± 18 years

Cianciaruso 2008 *(Continued)*

- Gender (M/F): 220/172
- eGFR ≤ 30 mL/min/1.73 m^2
- Stable renal function

Treatment group

- Number: 200
- Age: 61 ± 16 years
- Gender (M/F):112/88

Control group

- Number: 192
- Age: 62 ± 18 years
- Gender (M/F): 110/82

Exclusion criteria

- Malignant disease
- Treatment with immunosuppressive drugs
- UPE > 5 g/24 h
- Pregnancy

Interventions	**Treatment group** • 0.55 g/kg/d **Control group** • 0.8 g/kg/d **Cointerventions** • Patients were prescribed at least 30 kcal/kg/d (25 kcal/kg/d for overweight patients or if hypertension or hyperlipidaemia present) • Daily multivitamin and mineral tablet • Dietary sodium intake restricted to 2.5 g/d • Calcium supplements to guarantee calcium intake of 1000-1500 mg/d • Iron supplementation (200 mg/d oral element iron) as required to maintain transferrin saturation ≥ 20%
Outcomes	• Urea nitrogen • Phosphate • PTH • Bicarbonate • Death • Commenced dialysis
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Numbered opaque sealed envelopes opened in sequence by administration staff personnel not involved in patient care.

di Iorio 2003

Methods	**Randomisation method**: NS **Blinding**: NS **Intention-to-treat**: NS **Setting**: Outpatient clinic, Italy
Participants	**Inclusion criteria** • CrCl ≤ 25 mL/min/1.73 m^2 • EPO for 6-12 months **Treatment group** • Number: 10 • Age: 57 ± 17 years • Gender (M/F): 6/4 **Control group** • Number: 10 • Age: 52 ± 15 years • Gender M/F: 6/4 3 patients in each group had diabetic kidney disease **Exclusion criteria** • Bleeding or diseases potentially affecting EPO response (i.e. neoplastic diseases, infectious diseases, severe malnutrition) • CKD stage: 4-5
Interventions	**Treatment group (VLP)** • 0.3 g protein/kg/d **Control group (LP)** • 0.6 g protein/kg/d
Outcomes	• CrCl • MAP • Urinary sodium mEq/d • Triglycerides mg/dL • Cholesterol mg/dL • Renal death: End point: CrCl ≤ 7 mL/min/1.73 m^2 or development of uraemic complications requiring haemodialysis
Notes	• 3 month run-in period before randomisation to verify stability of Hb coefficient • Follow-up: 24 months • All patients required to restrict dietary sodium intake • Treatment group diet was supplemented with a mixture of ketoanalogues and essential amino acids (Alfa Kappa) 1 tablet/5 kg BW.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Ihle 1989

Methods	**Study type**: Prospective randomised **Duration**: 18 months
Participants	**Inclusion criteria** • SCr 350-1000 µmol/L at enrolment • Gender ratio (M/F): 0.67 • CKD stage: 4-5
Interventions	**Treatment group (LPD)** • 0.4 g protein/kg/d **Control group (free diet)** • Greater than 0.75 g/kg/d
Outcomes	• Decline in GFR over time
Notes	Data obtained from 72 included patients (not from data on 64 patients of the final report)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Jungers 1987

Methods	**Study type**: Prospective randomised **Duration**: 12 months
Participants	**inclusion criteria** • SCr 500 and 900 µmol/L at inclusion • Age: 62 (32-79) years • M/F ratio: 0.37 • CKD stage: 5
Interventions	**Treatment group (LPD)** • 0.4 g protein/kg/d • Oral supplement with ketoacids (1 tab Ketosteril/kg BW/d) **Control group** • 0.6 g protein/kg//d
Outcomes	• Increase in SCr during study
Notes	Small effective (n = 19)

Risk of bias

Jungers 1987 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Locatelli 1991

Methods	**Study type**: Prospective randomised **Setting**: Multicentre **Duration**: 24 months
Participants	**Inclusion criteria** • SCR 130 - 620 µmol/L at enrolment • Age: 49 (18-65) years • M/F ratio: 0.54 • CKD stage: 3-4
Interventions	**Treatment group (LPD)** • 0.6 g protein/kg/d **Control group** • 1.0 g protein/kg/d
Outcomes	• Renal survival curve (including start of dialysis or a doubling of baseline SCr during study)
Notes	• True difference in protein intake less than 0.4 g protein/kg/d, estimated to be 0.16 g/kg/d based on urinary analysis and 0.3 g/kg/d based on diet records • Events recorded at 24 months from the start of study

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Malvy 1999

Methods	**Study type:** Prospective randomised **Duration** 18 months
Participants	**Inclusion criteria** • SCr 300-900 µmol/L at enrolment • Age: 55 (15-75) years • M/F ratio: 0.58 • CKD stage: 4-5
Interventions	**Treatment group (LPD)** • 0.3 g protein/kg/d • Oral ketoacid supplement (Ketosteril 1 tab/6 kg BW/d)

Malvy 1999 *(Continued)*

	Control group • 0.65 g protein/kg/d
Outcomes	• Dialysis or death on survival curve • Renal death (death or start of dialysis during study) observed at two years
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

MDRD 1994

Methods	**Study type:** Prospective randomised **Setting:** Multicentre **Duration**: 23 months

Participants	**Inclusion criteria**
	• Renal function
	  * Study 1: 25-55 mL/min/1.73 m^2
	  * Study 2: 13-24 mL/min/1.73m^2
	• MAP: < 125 mm Hg
	• Age: 52 years
	• M/F ratio: 0.60
	• CKD stage
	  * Study 1: 3-4
	  * Study 2: 4

Interventions	**Treatment group (study 1)** • 0.58 g protein/kg/d **Control group (study 1)** • 1.3 g protein /kg/d **Treatment group (study 2)** • 0.28 g protein/kg/d • Oral ketoacid supplement **Control group (study 2)** • 0.58 g protein/kg/d
Outcomes	• Slope of GFR decline over time during 2.2 years
Notes	• Data were obtained only for study 1 • Event number differs from publication since the publication included events observed during follow-up.

Risk of bias

MDRD 1994 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Mirescu 2007

Methods	**Country**: Romania **Setting**: Single centre, prospective, open label, parrallel RCT **Duration**: 60 weeks with a 12-week baseline phase **Time frame**: 15 Jan 2004 to 15 Feb 2005
Participants	**Inclusion criteria** • Adults • eGFR < 0.5 mL/s (30 mL/min/1.73 m^2, MDRD formula) • Stable renal function for at least 12 weeks before enrollment (reduction in eGFR ≤ 4 mL/min/y) • Well controlled arterial pressure • Proteinuria < 1 g/g urinary Cr • Good nutritional status (subjective Global Assessment score A/B; serum albumin > 35 g/L) • Anticipated good compliance with the prescribed diet **Treatment group** • Number: 27 • Age: 55 ± 12.7 years • Gender (males): 63% **Control group** • Number: 26 • Age: 53.6 ± 11.0 years • Gender (males): 58% **Exclusion criteria** • Poorly controlled arterial pressure (> 145/85 mm Hg) • Comorbid conditions: Diabetes mellitus, heart failure, active hepatic disease, digestive diseases with malabsorption, inflammation/anti-inflammatory therapy • Uremic complications: Pericarditis, polyneuropathy • Feeding inability: Anorexia, nausea

Interventions	**Treatment group**
	• Severe hypoproteic diet supplemented with ketoanalogues
	  * 0.3 g/kg/d vegetable protein
	• Ketoanalogues or essential amino acids (Ketosteril, Fresnius Kabi, Bad Homburg, Germany)
	  * 1 capsule/5 kg of ideal body weight/d
	• Total recommended energy intake: 30 kcal/kg/d
	Control group
	• Conventional low protein diet
	  * 0.6 g/kg/d (including high biological value proteins)
	• Total recommended energy intake: 30 kcal/kg/d
	Co-interventions

Mirescu 2007 *(Continued)*

	• All received calcium and water soluble vitamin supplementation as required.
	• Serum ferritin
	  * < 200 ng/mL: 100 mg IV iron sucrose weekly.
	  * 200-400 ng/mL: 100 mg IV iron sucrose every other week
	  * 400-500 ng/mL: 100 mg IV iron sucrose monthly
	  * > 500 ng/mL: Iron administration stopped

Outcomes	• Nitrogen waste products: serum urea and Cr • Calcium-phosphorus metabolism: serum calcium, serum phosphate, calcium-phosphorous product, alkaline phosphatase activity • Acid-base balance: serum bicarbonate • Death: patient or 'kidney' • Blood pressure • Drug therapy requirements for hypertension • Adverse events
Notes	• Dietary compliance was assessed weekly for the first month, every 4 weeks for the next 8 weeks and every 12 weeks thereafter

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Not stated

Rosman 1989

Methods	**Study type:** Prospective randomised **Duration**: 18 months

Participants	**Inclusion criteria**
	• CrCl
	  * 10-30 mL/min (groups A2 and C)
	  * 30-60 mL/min (groups A1and B)
	• Age: 48 (15-73) years
	• M/F ratio: 0.54
	• CKD stage
	  * group A1: 3
	  * A2: 4-5
	  * B: 3
	  * C: 4-5

Interventions	**Treatment groups** • 0.6 g protein/kg/d (group B) • 0.4 g protein/kg/d (group C) **Control groups** • Free diet (groups A1 and A2)
Outcomes	• Slope of reciprocal SCr (1/SCr) over time
Notes	• Updated report (1989) from previous paper (Lancet 1984; ii:1291-1296)

Rosman 1989 *(Continued)*

- Eight patients received a renal transplant in the LPD group and four in the control group and were counted as renal death event

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Williams 1991

Methods	**Study type:** Prospective randomised **Duration**: 18 months
Participants	**Inclusion criteria** • SCr: 200-600 µmol/L at enrolment • Age: 44 (15-70) years • M/F ratio: 0.63 • CKD stage: 4-5
Interventions	**Treatment group** • 0.6 g protein/kg/d **Control group** • > 0.8 g protein/kg/d
Outcomes	• Slope of reciprocal SCr (1/SCr) over time
Notes	• A third group of patients (low phosphorus intake, n = 30) was not kept for analysis • Events recorded at 18 months from the start of study

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

CKD - chronic kidney disease; CrCl - creatinine clearance; eGFR - estimated glomerular filtration rate; LPD - low protein diet; MAP - mean arterial pressure mm Hg; NS - not stated; SCr - serum creatinine; UPE - urinary protein excretion

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alvestrand 1980	Retrospective
Alvestrand 1983	Retrospective
Attman 1983	Not controlled
Attman 1986	Retrospective

Study	Reason for exclusion
Barsotti 1981	Retrospective
Barsotti 1984	Not randomised
Barsotti 1988	Not controlled
Bellizzi 2007	Not RCT
Bennett 1983	Retrospective
Bergstrom 1989	RCT. Not the final report - 57 patients randomised but data on only 16 patients presented. Renal death not reported.
Bernhard 2001	RCT - randomised to ketoanalogue supplements not protein diet
Brunori 2003	No controlled protein intake
Burns 1978	Not controlled
Coresh 1994	RCT - randomised to keto acid supplements
D'Amico 1994	A number of patients included have been published in the larger Locatelli's study (Lancet 1991) kept for the meta-analysis
Dek 1998	Not randomised
Di Landro 1986	Not randomised
DODE Study 2007	RCT - randomised to diet or dialysis
El Nahas 1984	Not controlled
Esaian 2002	Not randomised
Frohling 1980	Not randomised
Frohling 1983	Not controlled
Frohling 1989	Not randomised
Fuessl 2006	Not randomised
Gretz 1983	Not randomised
Hecking 1980	Six weeks duration only
IRCCA Study 1988	RCT - randomised to keto acid supplements
Ivarsen 1995	RCT - haemodialysis patients
Kampf 1980	Not controlled
Levine 1989	Not controlled
Lim 2000	Six months duration only

Study	Reason for exclusion
Lucas 1986	Not controlled
Maksic 2004	RCT - six months duration
Maroni 1997	Not randomised
Maschio 1982	Not randomised
Masud 1992	Metabolic study, no relevant outcomes
Meisinger 1987	Not randomised
Mitch 1984	Not controlled
Moreira 2007	RCT - haemodialysis patients
Oldrizzi 1985	Not randomised
Patel 2000	Not randomised
Prakash 2003	Less than 12 months duration
Riabov 2001	Not randomised
Sanfelippo 1978	RCT - haemodialysis patients
Schmicker 1986	Not randomised
Teplan 2003	Intervention is EPO not protein
Teplan 2006	RCT - randomised to keto acids and placebo
Terzi 1995	Study performed in children
Walser 1975	Not controlled
Walser 1987	Not controlled
Wingen 1997	Paediatric study
Younes 2006	RCT - randomised to fermentable carbohydrate supplementation
Zakar 1984	Not randomised
Zeller 1991	Diabetic patients only

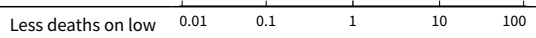
DATA AND ANALYSES

Comparison 1. Low protein versus higher protein diets

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Renal death	10	2000	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.55, 0.84]
1.1 0.6 g/kg/d versus higher protein diet	3	1116	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.54, 1.05]
1.2 0.3 - 0.6 g/kg/d versus higher/free protein diets	7	884	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.48, 0.83]

Analysis 1.1. Comparison 1 Low protein versus higher protein diets, Outcome 1 Renal death.

Study or subgroup	Low protein n/N	Higher protein n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 0.6 g/kg/d versus higher protein diet					
Locatelli 1991	21/230	32/236		15.69%	0.67[0.4,1.13]
MDRD 1994	18/291	27/294		12.86%	0.67[0.38,1.2]
Williams 1991	12/33	11/32		9.79%	1.06[0.55,2.04]
Subtotal (95% CI)	**554**	**562**		**38.34%**	**0.76[0.54,1.05]**
Total events: 51 (Low protein), 70 (Higher protein)					
Heterogeneity: Tau^2=0; Chi^2=1.37, df=2(P=0.5); I^2=0%					
Test for overall effect: Z=1.65(P=0.1)					
1.1.2 0.3 - 0.6 g/kg/d versus higher/free protein diets					
Cianciaruso 2008	9/212	13/211		6.18%	0.69[0.3,1.58]
di Iorio 2003	2/10	7/10		2.49%	0.29[0.08,1.05]
Ihle 1989	4/34	13/38		4.07%	0.34[0.12,0.95]
Jungers 1987	5/10	7/9		8.37%	0.64[0.32,1.31]
Malvy 1999	11/25	17/25		15.81%	0.65[0.39,1.09]
Mirescu 2007	1/27	7/26		1.03%	0.14[0.02,1.04]
Rosman 1989	30/130	34/117		23.71%	0.79[0.52,1.21]
Subtotal (95% CI)	**448**	**436**		**61.66%**	**0.63[0.48,0.83]**
Total events: 62 (Low protein), 98 (Higher protein)					
Heterogeneity: Tau^2=0.01; Chi^2=6.27, df=6(P=0.39); I^2=4.36%					
Test for overall effect: Z=3.31(P=0)					
Total (95% CI)	**1002**	**998**		**100%**	**0.68[0.55,0.84]**
Total events: 113 (Low protein), 168 (Higher protein)					
Heterogeneity: Tau^2=0; Chi^2=8.2, df=9(P=0.51); I^2=0%					
Test for overall effect: Z=3.68(P=0)					
Test for subgroup differences: Not applicable					



APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
MEDLINE	1. Randomized Clinical Trial.pt 2. Controlled Clinical Trial.pt 3. Clinical Trial.pt 4. Random 5. Double blind method 6. Single blind method 7. Placebo 8. OR 1-7 9. Animal not Human 10.8 not 9 11.Kidney disease OR Kidney failure 12.Nephropathy 13.Chronic renal disease 14.OR 11-13 15.10 AND 14 16.Dietary intervention OR nutritional intervention 17.Diet protein restricted 18.16 OR 17 19.15 AND 18 20.Adults NOT children 21.19 AND 20 22.Not Diabetic
CENTRAL	1. KIDNEY FAILURE 2. KIDNEY FAILURE CHRONIC 3. (end-stage next renal next failure) 4. (end-stage next kidney next failure) 5. (end next stage next renal next failure) 6. (end next stage next kidney next failure) 7. (end next stage next renal next disease) 8. (end next stage next kidney next disease) 9. (end-stage next renal next disease) 10.(end-stage next kidney next disease) 11.(chronic next renal next failure) 12.(chronic next renal next disease) 13.(chronic next kidney next disease) 14.(chronic next kidney next failure) 15.(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14) 16.DIET PROTEIN-RESTRICTED 17.DIET THERAPY 18.(low-protein next diet*) 19.(low next protein next diet*) 20.(protein next restrict*) 21.(protein next reduct*) 22.(diet* next restrict*)

(Continued)

23.(diet* next intervention*)
24.(nutrition* next intervention*)
25.(#16 or #17 or #18 or #19 or #20 or #21 or #22 or #24)
26.(#15 and #25)

WHAT'S NEW

Date	Event	Description
12 May 2009	New citation required but conclusions have not changed	Author list updated
31 March 2009	Amended	Two new studies added, no change to conclusions

HISTORY

Protocol first published: Issue 4, 2000
Review first published: Issue 4, 2000

Date	Event	Description
13 October 2008	Amended	Converted to new review format.
30 November 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

DF and JPB independently selected studies for inclusion in the review.
All authors contributed to the data analysis and writing of the review.

DECLARATIONS OF INTEREST

Prof Denis Fouque has received lecture fees for the topic "Nutrition and progression of chronic kidney disease".

SOURCES OF SUPPORT

Internal sources

- Hospices Civils de Lyon, France.
- University Claude Bernard Lyon 1, France.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Diet, Protein-Restricted; Chronic Disease; Disease Progression; Kidney Diseases [*diet therapy]; Kidney Failure, Chronic [*prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans