Nephrol Dial Transplant (2000) 15: 1986–1992

Nephrology Dialysis Transplantation

Original Article

Low protein diets delay end-stage renal disease in non-diabetic adults with chronic renal failure

Denis Fouque[1,2], Ping Wang[2,3], Maurice Laville[1,2] and Jean-Pierre Boissel[2]

[1]Department of Nephrology, [2]Cochrane Renal Group, Hôpital Edouard Herriot, Lyon, France and [3]University of California, Irvine, CA, USA

Abstract

Background. The objective of this study was to determine the efficacy of low protein diets in delaying the need to start maintenance dialysis based on an analysis of published literature.

Methods. The search strategy involved a Medline and Embase search from January 1966 through to June 1999, congress abstracts (American Society of Nephrology since 1990, European Dialysis Transplant Association since 1985, International Society of Nephrology since 1987) and direct contacts with investigators. The selection criteria included randomized trials comparing two different levels of protein intake in adult patients suffering from moderate to severe renal failure, followed for at least 1 year. Patients with diabetic nephropathy were excluded. Seven trials were selected from 40 studies since 1975. A total of 1494 patients were analysed: 753 had received reduced protein intake and 741 a higher protein intake. The numbers of 'renal deaths' (defined as the need for starting dialysis, the death of a patient or kidney transplant during the trial) were collected.

Results. 242 renal deaths were recorded, 101 in the low protein diet and 141 in the higher protein diet group, giving an odds ratio of 0.61 with a 95% confidence interval of 0.46 to 0.83 ($P=0.006$).

Conclusion. Reducing protein intake in patients with chronic renal failure reduces the occurrence of renal death by about 40% as compared with larger or unrestricted protein intake. The optimal level of protein intake cannot be confirmed from these studies.

Keywords: Cochrane Collaboration; chronic renal failure; end-stage renal failure; low protein diet; meta-analysis; nutrition; systematic review

Introduction

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 renal disease. 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 renal failure. 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. Although a few trials 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.

Correspondence and offprint requests to: Denis Fouque, MD, PhD, Department of Nephrology, Hôpital Edouard Herriot, F-69437 Lyon cedex 03, France.

Methods

The objective of this review was to determine the efficacy of low protein diets in preventing the natural progression of chronic renal failure towards end-stage renal disease and therefore delaying the need for starting maintenance dialysis. For this purpose, we defined the 'renal death' outcome, i.e. the number of deaths or number of patients who will start dialysis or will receive a kidney transplant during the observation period according to their protein intake level.

Criteria for considering studies for this review

Types of studies

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

Types of participants

All patients were suffering from moderate to severe chronic renal failure, as estimated by either serum creatinine, creatinine clearance or a GFR measurement. Because of the difficulty in controlling confounding factors, trials including diabetic patients or children with renal failure were excluded from analysis.

Types of interventions

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

Types of outcome measures

Renal death was defined as:
death during follow-up, due to any cause;
need to start haemodialysis or peritoneal dialysis during follow-up;
kidney transplant during the study.

Search strategy for identification of studies

The search for studies was performed by one of the authors (DF) using to the Cochrane Renal Group search strategy. The Renal Group Trials Register was searched by Sandrine Dury, Trials Search Coordinator. Medline and Embase were searched from January 1966 through June 1999. 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.

Methods of the review

Two reviewers (DF, JPB) independently selected trials for inclusion in the review. Disagreements were resolved by discussion. For each trial, 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 trial included study 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), and time to the start of dialysis, if available. The nature of renal 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 randomization processes were obtained directly from the investigators. Heterogeneity between trials was tested using appropriate statistical analyses.

Description of studies

Seven randomized studies were identified and retained for this review (Table 1), with 1494 patients, 753 in the restricted protein intake groups and 741 in the unrestricted or higher protein intake groups. The number of patients in each study varied from 19 [1] to 585 [3]. The collection of events was done after the longest observation time obtained in each study. Data obtained during follow-up after completion of studies, if present, were not considered for analysis.

Randomization was performed using: (i) envelopes after stratification by age, gender and renal function [2]; (ii) after stratification by renal function and blood pressure levels, (iii) by centre and study and by block permutation [3]; (iv) after allocating envelopes without stratification [1,4,5], (v) by random number table and a telephone call [6] (vi) and by random number table [7].

The level of renal insufficiency was moderate [3,6] [2; study A1–B] or severe [1,4,7] [3; study 2] [2; study A2–C). Mean age of patients was: 48 years (range 15–73) [2], 62 (32–79) [1], 49 (18–65) [6], 55 (15–75) [7], 44 (15–70) [5] and 52 years [3].

The type of kidney disease was available for all studies. Glomerulopathies of included patients represented 36% [2], 26% [1], 29% [6], 28% [7], 47% [4], 23% [5] and 25% [3]. Polycystic kidney disease was present in 6% of patients [2], 21% [1], 16% [6], 30% [7], 18% [4], 17% [5] and 24% [3]. Interstitial nephritis was present in 24% of patients [2], 16% [1], 34% [6], 14% [7], 26% [4], 17% [5] but was not reported in one study [3]. Importantly, these nephropathies were equally distributed between groups within studies.

Gender (Male/Female) was as follows: 0.54 [2], 0.37 [1], 0.54 [6], 0.58 [7], 0.67 [4], 0.63 [5] and 0.60 [3], reflecting well the higher male prevalence of renal disease. Again, no difference between treated and control groups was observed.

All other studies were excluded from analysis (Table 2).

Methodological quality of included studies

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

Statistical methods

We conducted an 'intention to treat' analysis, and used standard statistical analyses (odds ratio, percentage difference, Peto, Mantel-Haenszel) [8]. As they all gave similar *P* values for the difference between control and treated groups, we only provide here the results from the analysis of the logarithm of odds ratio. Number needed to treat (NNT) was calculated for each trial as the inverse of the difference in absolute risks between treated and control groups [9]. The absolute risk in the treated group of a given trial was obtained by multiplying the overall odds ratio by the absolute risk in the control group of the corresponding trial. All data were adjusted for a 1-year period, in order to compare treatment efficiency in trials of different durations.

Results

From more than 40 clinical trials published between 1975 and 1999, there were only seven randomized controlled trials in non-diabetic adult patients. They were all published as full length articles, including the last study from France, published in 1999 [7].

The overall unadjusted incidence of renal death in the control groups was 19%, and ranged from 9% [3] to 78% [1]. All but one study [5] showed a trend for a beneficial effect of a restricted protein intake compared with an unrestricted intake, and one study

Table 1. Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes
Malvy 1999	Estimated GFR as (urea clearance + creatinine clearance)/2 as reported by Lubowitz *et al.* (1967).	Serum creatinine between 300 and 900 μmol/l at inclusion	LPD: 0.3 g protein per kg per day plus oral ketoacid supplement (Ketosteril 1 tab/6 kg BW/day); control diet: 0.65 g protein per kg per day	Dialysis or death on survival curve; renal death (death or start of dialysis during study) observed at 2 years	Analysis from individual data events recorded at 18 months from the start of study
Ihle 1989	GFR measured by plasma clearance of Cr-EDTA	Serum creatinine between 350 and 1000 μmol/l at inclusion	LPD: 0.4 g protein per kg per day; free diet: greater than 0.75 g per kg per day	Decline in GFR over time	Data obtained from 72 included patients (not from data on 64 patients of the final report)
Jungers 1987	Serum creatinine	Serum creatinine between 500 and 900 μmol/l at inclusion	LPD: 0.4 g protein per kg per day plus oral supplement with ketoacids (1 tab Ketosteril/kg BW/day) control: 0.6 g protein per kg per day	Increase in serum creatinine during study	Small effective ($n = 19$)
Klahr 1994	GFR measurement by plasma clearance of iothalamate	Patients with a GFR between 25 and 55 ml/min/1.73 m^2 (study 1) and between 13 and 24 ml/min/1.73 m^2 (study 2); all patients with a mean arterial blood pressure < 125 mmHg	Study 1: usual protein intake (1.3 g/kg/day) *versus* low protein intake (0.58 g/kg/day); study 2: low protein intake (0.58 g/kg/day) *versus* very low protein intake (0.28 g/kg/day) plus oral ketoacid supplement	Slope of GFR decline over time during 2.2 years	Data were obtained only for study 1; event number differs from publication since the publication included events observed during follow-up.
Locatelli 1991	Serum creatinine Number of patients starting dialysis during study	Serum creatinine between 130 and 620 μmol/l at inclusion	LPD: 0.6 g protein per kg per day; control: 1.0 g protein per kg per day	Renal survival curve (including start of dialysis or a doubling of baseline serum creatinine during study)	True difference in protein intake less than 0.4 g protein per kg per day, estimated to be 0.16 g/kg/day based on urinary analysis and 0.3 g/kg/d based on diet records; events recorded at 24 months from the start of study

Table 1. *(Cont.)*

Study	Methods	Participants	Interventions	Outcomes	Notes
Rosman 1989	Serum creatinine	Patients with creatinine clearance between: 10 and 30 ml/min (groups A2 and C) or 30 and 60 ml/min (groups A1 and B)	LPD: 0.6 g protein per kg per day (group B) and 0.4 g protein per kg per day (group C); control: free diet (groups A1 and A2)	Slope of reciprocal serum creatinine (1/S creatinine) over time	Updated report (1989) from previous paper (*Lancet* 1984;ii:1291–1296) Eight patients received a renal transplant in the LPD group and four in the control group and were counted as renal death event
Williams 1991	Serum creatinine	Serum creatinine between 200 and 600 µmol/l at inclusion	LPD: 0.6 g protein per kg per day; control: greater than 0.8 g protein per kg per day	Slope of reciprocal serum creatinine (1/S creatinine) over time	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

showed a statistically significant difference [4]. There was no heterogeneity between studies (χ^2 heterogeneity test 4.62, degrees of freedom = 6, $P=0.59$). The overall effect was found to be highly significant, with 101 renal deaths observed with restricted protein intake compared with 141 events in the unrestricted protein intake. There was a 39% relative risk reduction in renal death ($P=0.006$, odds ratio) in favour of a restricted protein intake. Of importance, due to randomization, there was a similar percentage in categories of renal disease (glomerulopathy, interstitial nephritis, nephroangiosclerosis, polycystic disease) in both restricted and unrestricted protein intake groups. A subgroup analysis of the 'start of dialysis' event was also highly significant, with an odds ratio of 0.56 in favour of a restricted protein intake, $P<0.01$.

The number of patients needed to be treated (NNT) during 1 year to avoid one renal death ranged from four [1], eight [7], 11 [4], 11 [5], 14 [2], 37 [6] and 56 [3]. To estimate the overall benefit of a restricted protein intake longer than 1 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/day in all studies except 0.2 g/kg/day in studies by Jungers [1] and Williams [5] and 0.7 g/kg/day in Klahr [3]. 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/day [6], 0.25 g/kg/day [4,5], 0.3 g/kg/day [2] and 0.35 g/kg/day [3,10]. These values should be considered to be the true therapeutic intervention estimated by the present review.

Although we report a limited number of trials, a publication bias may be discussed as there is a trend for a funnel plot on the graphical representation (Fig. 1 [11]).

Discussion

Updating two previous meta-analyses [12,13], this systematic review shows that reducing the protein intake of patients with chronic renal failure significantly reduces the number of patients entering end-stage renal disease by about 40% ($P=0.006$). In addition to a positive trial [4], a favourable but not significant trend was already present in five of the seven studies (individual odds ratio <1; Fig. 1), but on limited size or inadequate duration. In response to a more appropriate number of patients obtained through the meta-analysis, the overall result was strongly positive and thus confirmed the beneficial effect of low protein diets in a cohort of almost 1500 patients.

Table 2. Studies excluded from the meta-analysis and reasons for exclusion

Authors	Reference	Reason for exclusion
Alvestrand *et al.*	*Kidney Int* Suppl 1983; 16: 268–272	retrospective
Alvestrand *et al.*	*Am J Clin Nutr* 1980; 33: 1654–1659	retrospective
Attman *et al.*	*Clin Nephrol* 1983; 19:217–220	not controlled
Attman *et al.*	*Contrib Nephrol* 1986; 53: pp 128–136	retrospective
Barsotti *et al.*	*Clin Nephrol* 1988; 29: 280–287	not controlled
Barsotti *et al.*	*Clin Nephrol* 1984; 21: 54–59	not controlled
Barsotti *et al.*	*Nephron* 1981; 27: 113–117	retrospective
Barsotti *et al.*	*Kidney Int* Suppl 1983; 16: 278– 284	retrospective
Bennett *et al.*	*Br Med J* 1983; 287: 1344–1345	retrospective
Burns *et al.*	*Am J Clin Nutr* 1978; 31: 1767–1775	not controlled
D'Amico *et al.*	*Nephrol Dial Transplant* 1994; 9: 1590–1594	*
Di Landro *et al.*	*Contrib Nephrol* 1986; 53: 137–143	not randomized
El Nahas *et al.*	*Br Med J* 1984; 289: 1337–1341	not controlled
Frohling *et al.*	*Clin Nephrol* 1983; 20: 212–215	not controlled
Frohling *et al.*	*Blood Purif* 1989; 7: 28–32	not randomized
Frohling *et al.*	*Am J Clin Nutr* 1980; 33: 1667–1672	not randomized
Gretz *et al.*	*Kidney Int* Suppl 1983; 16: 263–267	not randomized
Gretz *et al.*	*Blood Purif* 1989; 7: 33–38	not randomized
Gretz *et al.*	*Infusionstherapie* 1987; 14 Suppl 5: 21–25	not randomized
Gretz *et al.*	*Contrib Nephrol* 1986; 53: 92–101	not randomized
Gretz *et al.*	*Contrib Nephrol* 1985; 49: 78–86	not randomized
Heckling *et al.*	*Am J Clin Nutr* 1980; 33: 1678–1681	short duration
Kampf *et al.*	*Am J Clin Nutr* 1980; 33: 1673–1677	not controlled
Levine *et al.*	*Nephron* 1989; 52: 55–61	not controlled
Lucas *et al.*	*Kidney Int* 1986; 29: 995–1003	not controlled
Maschio *et al.*	*Kidney Int* 1982; 22: 371–376	not randomized
Meisinger *et al.*	*Kidney Int* 1987; 22: 170–173	not randomized
Mitch *et al.*	*N Engl J Med* 1984; 6: 623–629	not controlled
Oldrizzi *et al.*	*Kidney Int* 1985; 27: 553–557	not randomized
Schmicker *et al.*	*Contrib Nephrol* 1986; 53: 121–127	not randomized
Schmicker *et al.*	*Infusionstherapy* 1987; 14: 34–38	not randomized
Walser *et al.*	*Clin Nephrol* 1975; 3: 180–186	not controlled
Walser *et al.*	*Infusionstherapie* 1987; Suppl. 14 5: 17–20	not controlled
Wingen *et al.*	*Lancet* 1997; 349: 1117–1123	paediatric study
Zakar *et al.*	*Proc EDTA-ERA* 1984. Pitman, London 1985	not randomized
Zeller *et al.*	*N Engl J Med* 1991; 324: 78–84	diabetic patients

*To avoid double counting of patients, this study was not selected since some patients were included in a larger study kept for analysis [6].

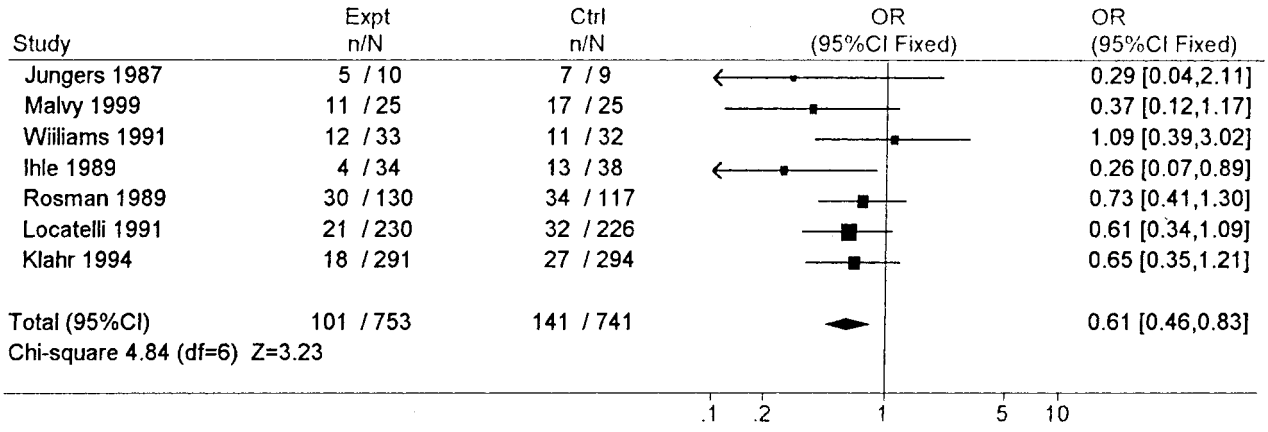

Fig. 1. Reduction in the odds of renal death in seven prospective randomized studies of protein restriction in chronic renal insufficiency. A square denotes the odds ratio (treatment/control) for each trial and the diamond for the overall results. 95% CIs are represented by the horizontal lines. Overall 'common' odds ratio = 0.61 (95% CI: 0.46, 0.83), $P = 0.006$. Test for heterogeneity between studies: $\chi^2 = 4.84$; degrees of freedom = 6, $P = 0.56$.

For many decades, reducing protein intake has been proposed for patients suffering from kidney disease for metabolic purpose. Urea production, and hence, serum urea can be reduced by a low protein diet. More recently, it was suggested that, from experimental studies, a low protein intake may prevent the natural progression of chronic renal insufficiency towards end-stage renal disease, thus delaying the start of mainten-

ance dialysis treatment [14]. However, inadequate markers or protocols may have masked the effects of low protein diets [15]. Reducing protein intake modifies creatinine concentrations and since this was used as a 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. Because 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 [16,17]. First, although the populations studied were clinically heterogeneous in age, gender, type of nephropathy, level of protein restriction, the effects of treatments were not statistically different since the heterogeneity test was not significant ($P=0.59$). Secondly, although the amounts of protein intake were quite different between studies (Table 1), 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 [18], 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 observed.

Thirdly, because the decision to start dialysis is often based on serum urea levels (but not only), and because 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. Hence they will start dialysis later than patients with higher protein intake. Therefore, it cannot be derived from our review that low protein diets reduce the progression of renal disease. 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: [4] showed a beneficial effect and [3] did report a nearly significant beneficial effect ($P=0.07$). Interestingly, Kasiske and colleagues [19] 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/year smaller loss for restricted protein intake than for higher protein intake). Even if this represents a protective renal 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. However, from a patient's point of view, there is no doubt that 'renal death' is a very clinical indicator of renal disease worsening.

The number needed to treat is a tool recently introduced to better compare the strength of a treatment between studies and to homogenize these effects when absolute event risks are quite different between studies [9]. In the present review, NNT during 1 year for each study varied from four 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 [1,7]. However, the amplitude of NNTs among trials is not very large (from four 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 dietician survey. Moreover, these results compare favourably with the well-accepted mortality reduction obtained by statins in the 4S trial (NNT = 30) or WOSCOPS study (NNT = 111) [20].

The funnel plot represents the individual odds ratio corresponding to the study patients number [11]. Figure 1 shows that the odds ratios from the three largest studies [2,3,6] are closer to the common odds ratio (i.e. 0.61), whereas the smaller trials [1,4,7] provide a smaller odds ratio (between 0.29 and 0.38) suggesting a stronger trend for a beneficial effect of a reduced protein intake. The fact that only one small size trial provided an odds ratio greater than 0.61 [5] suggests that a publication bias might have occurred. Indeed, if investigators did find negative or less robust conclusions on small effectives (e.g. 20–100 patients), they might have censored themselves and were eventually reluctant to report their findings. Also, medical journals might have refused to publish negative trials due to inadequate size. On the basis of the limited number of trials in the present review, funnel plot analysis may, however, not be very robust, and should be re-analysed when future trials are available.

Conclusion

Patients with moderate chronic renal failure should be proposed a nutritional intervention, which includes 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 dietitian survey should be proposed (NKF-DOQI Guideline #23 [21]). 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 [18]. In contrast, feasability of low protein diets has been shown in large studies with convincing results [22], 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 dietitian 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 delay end-stage renal disease [23]. These include angiotensin-converting enzyme inhibitors, blood pressure control, and 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.

Acknowledgements. We thank the authors of each included trial for providing additional data and are particularly indebted to Michel Cucherat, MD, PhD, and Margaret Haugh, PhD, Centre Cochrane Français, for statistical and methodological assistance.

References

1. 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 Int* 1987; 22: 67–71
2. Rosman JB, Langer K, Brandl M, Piers-Becht TP, van der Hem GK, ter Wee PM, Donker AJ. Protein-restricted diets in chronic renal failure: a four year follow-up shows limited indications. *Kidney Int* 1989; S-27: S96–102
3. Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, Striker G. 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. *N Engl J Med* 1994; 330: 877–884
4. Ihle BU, Becker G, Withworth JA, Charlwood RA, Kincaid-Smith PS. The effect of protein restriction on the progression of renal insufficiency. *N Engl J Med* 1989; 321: 1773–1777
5. 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. *Q J Med* 1991; 81: 837–855
6. 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. *Lancet* 1991; 337: 1299–1304
7. Malvy D, Maingourd C, Pengloan J, Bagros P, Nivet H. Effects of severe protein restriction with ketoanalogues in advanced renal failure. *J Am Coll Nutr* 1999; 18: 481–486
8. Whitehead A, Whitehead J. A general parametric approach to the meta-analysis of randomized clinical trials. *Stat Med* 1991; 10: 1665–1677
9. Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. *Br Med J* 1999; 319: 1492–1495
10. Kopple JD, Levey AS, Greene T *et al.* Effect of dietary protein restriction on nutritional status in the Modification of Diet in Renal Disease Study. *Kidney Int* 1997; 52: 778–791
11. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Br Med J* 1997; 315: 629–634
12. Fouque D, Laville M, Boissel JP, Chifflet R, Labeeuw M, Zech PY. Controlled low protein diets in chronic renal insufficiency: meta-analysis. *Br Med J* 1992; 304: 216–220
13. 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. *Ann Intern Med* 1996; 124: 627–632
14. Klahr S. The modification of diet in renal disease study. *N Engl J Med* 1989; 320: 864–866
15. Levey A. Nephrology forum: measuring renal function. *Kidney Int* 1990; 38: 167–184
16. 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: 254–281
17. Sacks HS, Berrier J, Reitman D, Ancona-Berk VA, Chalmers TC. Meta-analyses of randomized controlled trials. *N Engl J Med* 1987; 316: 450–455
18. Kopple JD, Greene T, Chumlea WC *et al.* Relationship between nutritional status and the glomerular filtration rate: results from the MDRD study. *Kidney Int* 2000; 57: 1688–1703
19. Kasiske BL, Lakatua JD, Ma JZ, Louis TA. A meta-analysis of the effects of dietary protein restriction on the rate of decline in renal function. *Am J Kidney Dis* 1998; 31: 954–961
20. Skolbekken JA. Communicating the risk reduction achieved by cholesterol reducing drugs. *Br Med J* 1998; 316: 1956–1958
21. DOQI guidelines in Nutrition. *Am J Kidney Dis* 2000; 35 [Suppl 2]: S9–133
22. 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. *J Am Soc Nephrol* 2000; 11: 708–716
23. Locatelli F, Del Vecchio L. How long can dialysis be postponed by low protein diet and ACE inhibitors? *Nephrol Dial Transplant* 1999; 14: 1360–1364

Received for publication: 30.11.99
Accepted in revised form: 11.7.00