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Controlled low protein diets in chronic renal insufficiency: meta-analysis

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Abstract

Objective—To determine whether low protein diets retard the development of end stage renal disease.

Design—Meta-analysis of 46 trials since 1975, from which six randomised controlled trials were selected.

Setting—Five trials in Europe and one in Australia between 1982 and 1991.

Subjects—890 patients with mild to severe chronic renal failure who were followed up for at least one year. 450 patients received a low protein diet and 440 a control diet.

Intervention—Difference in protein intake between control and treated groups of at least 0.2 g protein/kg/day.

Main outcome measure—Number of renal deaths (the necessity to start dialysis or death of patient during study).

Results—156 renal deaths were recorded, 61 in the low protein diet group and 95 in the control group, leading to an odds ratio of low protein to control of 0.54 with a 95% confidence interval of 0.37 to 0.79.

Conclusions—This result, obtained on a large population of patients suffering from chronic renal insufficiency, strongly supports the effectiveness of low protein diets in delaying the onset of end stage renal disease.

Introduction

During the past 10 years a lot of experimental data have suggested that dietary protein restriction may retard or even halt the development of non-specific glomerular lesions and hence the progression of end stage renal disease. Despite the many studies on dietary interventions that were performed a few decades ago, some questions have re-emerged¹—What kind of proteins? What degree of restriction? Is a supplement with essential amino acids or keto-analogues of amino acids required? When is the most appropriate moment to start the diet?²⁻⁴ These questions have been poorly answered by numerous studies showing that low protein diets reduce the time related increase in plasma creatinine concentration. However, the validity of plasma creatinine concentration as an estimate of renal function,⁵ especially during reduced protein intake, has not really been investigated in terms of extrarenal creatinine metabolism and the tubular secretion of creatinine, which is dependent on protein intake.⁶ The physician's main goal is to maintain clinical improvement in patients who wish to delay starting dialysis for as long as possible, and so we have reanalysed research data to determine the number of patients reaching end stage renal disease during follow up. This meta-analysis, should enable the strength of the association between low protein diet and reduction in end stage

renal failure to be assessed, taking into consideration the bias due to the various confounding factors (such as regression to the mean) and avoiding the use of intermediate criteria (such as the slope of the time course for the reciprocal values of serum creatinine concentration and the rate of decay of creatinine clearance).

Methods

The principle of meta-analysis entails the adjusted analysis of results in a collection of studies, with a unique criterion for all studies. Meta-analysis is particularly suitable for studies of rare events in, for example, ponderous or longlasting trials that do not include many patients.⁷⁻⁹ The quality and impact of a meta-analysis depends on the selection process for the criterion, which must be well defined at the beginning of the meta-analysis, and easily collected by non-specialist observers.

Definition of a common event—We defined renal death as either the necessity to begin dialysis or the death of patients during the study. Patients receiving grafts before starting dialysis were counted as having had renal death. Patients who were lost to follow up or who stopped taking the diet were not counted as having had renal death. These criteria were applied independently of the randomised treatment by the authors on the basis of published data or complementary data kindly provided by the investigators.

Collection of data and study selection—To avoid omission of results from less well known studies we scanned research reports with a computer search of Medline files and abstract books from the International Society of Nephrology and the American Society of Nephrology. We also asked many investigators for complete or incomplete, published or unpublished randomised studies. We restricted the review to randomised trials because without randomisation lack of bias cannot be guaranteed. Trials that used other methods of allocating treatments (such as retrospective controls and non-randomised, crossover, or prospective uncontrolled protocols) were therefore not included. Trials studying only diabetic nephropathy were not selected, because the equilibrium of diabetes is of major importance in the progression of renal failure and cannot be adequately measured between control and treated groups. Table I summarises 46 studies on protein restriction and its effects on the progression of chronic renal insufficiency. Individual data and extra details if not mentioned in the original papers, were collected from investigators who kindly agreed to send us their raw data.

Statistical methods—Intention to treat analysis was made on the selected populations, randomly assigned to control or treated groups (a restricted protein diet). Standard statistical methods were used (percentage

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TABLE 1—Summary of different trials studying the impact of protein restriction on renal function since 1975 and reasons for exclusion from analysis

First author and reference No	Year	Reason for exclusion	No of patients
Walser ¹¹	1975	Prospective non-controlled	7
Burns ¹²	1978	Prospective non-controlled	7
Alvestrand ¹³	1980	Retrospective	68
Frohling ¹⁴	1980	Prospective controlled	26
Hecking ¹⁵	1980	Prospective, double blind crossover, six week study	15
Kampf ¹⁶	1980	Prospective non-controlled	20
Barsotti ¹⁷	1981	Retrospective	56
Maschio ¹⁸	1982	Prospective controlled	75
Alvestrand ¹⁹	1983	Retrospective	17
Attman ²⁰	1983	Prospective non-controlled	21
Barsotti ²¹	1983	Same patients as Barsotti ¹⁷	
Bennett ²²	1983	Retrospective	96
Frohling ²³	1983	Prospective non-controlled	46
Gretz ²⁴	1983	Prospective controlled	161
Barsotti ²⁵	1984	Prospective controlled	55
El Nahas ²⁶	1984	Prospective non-controlled	34
Mitch ²⁷	1984	Prospective non-controlled	24
Rosman ²⁸	1984	—†	228
Gretz ²⁹	1985	Same patients as Gretz ²⁴	
Oldrizzi ³⁰	1985	Prospective controlled	100
Rosman ³¹	1985	Same patients as Rosman ²⁸	
Williams ³²	1985	Same patients as Bennett ²²	
Zakar ³³	1985	Prospective controlled	60
Attman ³⁴	1986	Retrospective	119
Chauveau ³⁵	1986	Same patients as Jungers ⁴¹	
Di Landro ³⁶	1986	Prospective controlled	68
Gentile ³⁷	1986	Same patients as Locatelli ⁴⁴	
Gretz ³⁸	1986	Same patients as Gretz ²⁴	
Lucas ³⁹	1986	Prospective non-controlled	12
Rosman ⁴⁰	1986	Same patients as Rosman ²⁸	
Schmicker ⁴¹	1986	Prospective controlled	119
Gretz ⁴²	1987	Same patients as Gretz ²⁴	
Jungers ⁴¹	1987	—†	19
Meisinger ⁴⁴	1987	Prospective controlled	38
Schmicker ⁴⁵	1987	Same patients as Schmicker ⁴¹	
Walser ⁴⁶	1987	Prospective non-controlled	12
Williams ⁴⁷	1987	—†	65
Barsotti ⁴⁸	1988	Prospective non-controlled	8
Gentile ⁴⁹	1988	Same patients as Locatelli ⁴⁴	
Bagros ⁵⁰	1989	—†	50
Frohling ⁵⁰	1989	Prospective controlled	81
Gretz ⁵¹	1989	Same patients as Gretz ²⁴	
Ihle ⁵²	1989	—†	72
Levine ⁵³	1989	Prospective non-controlled	7
Locatelli ⁵⁴	1991	—†	456
Zeller ⁵⁵	1991	Diabetic patients only	35

*Unpublished. †Selected for meta-analysis.

TABLE II—Summary of data from six randomised controlled studies selected for meta-analysis

Study No	Place, reference No	Year of publication	No of patients	Mean age (years) (range)	Follow up (months)	No with dialysis	No of deaths	No of grafts	No of renal deaths
1	Groningen, Rosman ³⁸	1984	228	48 (15-73)	18	14	6	3	23
2	Paris, Jungers ⁴¹	1987	19	62 (32-79)	12	12	0	0	12
3	Northern Italy, Locatelli ⁴⁴	1991	456	49 (18-65)	24	47	6	0	53
4	Tours, Bagros	Unpublished	50	55 (15-75)	18	25	3	0	28
5	Victoria, Ihle ⁵²	1989	72	—	18	17	0	0	17
6	Liverpool, Williams ⁴⁷	1987	65	44 (15-70)	18	22	1	0	23
All		890				137	16	3	156

TABLE III—Details of populations and renal deaths in control and treated groups of each trial and summary of results

Study No	Diet	No of patients	Sex ratio (M/F)	No of patients with:					Renal death
				Glomerulo-nephritis	Polycystic disease	Interstitial nephritis	Other nephropathies		
1	{Control	110	62/48	36	4	31	39	15	
	{Treated	118	62/56	43	10	23	42	8	
2	{Control	9	2/7	3	2	2	2	7	
	{Treated	10	5/5	2	2	1	5	5	
3	{Control	226	127/99	66	40	71	49	32	
	{Treated	230	120/110	66	34	85	45	21	
4	{Control	25	15/10	6	9	3	7	17	
	{Treated	25	14/11	8	6	4	7	11	
5	{Control	38	24/14	17	7	10	4	13	
	{Treated	34	24/10	17	6	9	2	4	
6	{Control	32	21/11	8	6	5	13	11	
	{Treated	33	20/13	7	5	6	15	12	
All	{Control	440	251/189	136	68	122	114	95	
	{Treated	450	245/205	143	63	128	116	61	

differences; logarithm of odds ratio; Cochran; Mantel-Haenszel; Peto).^{7,8} As they all gave similar p values for the difference between control and treated groups, only the results from the analysis of the logarithm of odds ratio are given. These results represent the ratios of the number of events in the treated group times the number of non-events in the control group to the number of events in the control group times the number of non-events in the treated group. For simplification it is useful to consider the odds ratio and its 95% confidence interval. An odds ratio of 0.60 corresponds to a reduction of 40% in the odds of experiencing an event. Heterogeneity between trials—that is, the interaction between trials and the effect of treatment—was tested by the appropriate χ^2 test.¹⁰ However, such tests of heterogeneity between many different trials have a limited value, partly because they are dominated by unstable contributions from the smaller studies that could obscure any real heterogeneity between the larger studies and, partly because of a low power.

Results

STUDY POPULATION

From 46 trials between 1975 and 1991 (table I), only six reports of randomised controlled trials were selected. Four were reported as full length articles (studies 1, 2, 3, and 5), one was presented as an oral communication and is not yet published (study 4, Bagros *et al*, personal communication), and the sixth was published as an abstract (study 6). Randomisation was from one centre in all six studies and by allocating an envelope after stratification by age, sex, and renal function in study 1, by allocating an envelope in studies 2, 5, and 6, by random number table and a telephone call in study 3, and by random number table in study 4.

DESCRIPTION OF PATIENTS STUDIED

The data on the patients studied are summarised in tables II and III. Patients varied between trials in age, sex ratio, and population size. The length of follow up was homogeneous, between 12 and 24 months. In study 1 not all the randomised patients were followed up for 18 months, but we considered the initial randomised population for intention to treat analysis. In study 5 we considered the initial 72 randomised patients and not the final 64 patients in the published results. In study 6 we considered two of the three randomised groups (control, low protein diet, and low phosphorus diet), rejecting the low phosphorus group because lowering phosphorus intake alone was not suitable for our analysis. The level of renal insufficiency was heterogeneous (table IV), from mild (study 3) to severe (study 2). The follow up criteria for renal function were also heterogeneous, with the use of serum creatinine concentration in studies 1, 2, and 6; renal survival (end point defined as the need for dialysis or the doubling of the plasma creatinine concentration) in study 3; estimation of glomerular filtration rate ((creatinine clearance+urea clearance)/2) according to Lubowitz *et al*⁵⁶ in study 4; and the clearance of ethylenediaminetetra-acetic acid labelled with chromium-51 in study 5.

The incidence of renal death in control groups was variable (0.14 in study 1 to 0.78 in study 2), which may be a result of renal insufficiency at inclusion. However, the heterogeneity test for the control groups was not significant.

TREATMENTS

A large heterogeneity was observed for the reduced protein intakes. It should be noted that the intake of protein in the control group in study 2 was about the

TABLE IV—Follow up, renal function at inclusion, and diets in six studies selected for meta-analysis

Study No	Follow up criterion of renal function	Renal function at inclusion	Diet	
			Treated group	Control group
1	Reciprocal of serum creatinine (all groups)	Creatinine clearance (A2, C $\leq$ 30 and >10 ml/min A1, B $\leq$ 60 and >30 ml/min)	B 0.6 g Protein/kg body weight/day C 0.4 g Protein/kg body weight/day	Free diet (A1, A2)
2	Increase in serum creatinine	Serum creatinine between 500 and 900 μ mol/l	0.4 g Protein/kg body weight/day with ketoacids supplementation Ketosteril 1 tablet/6 kg/day	0.6 g Protein/kg body weight/day
3	Renal survival curve (doubling of serum creatinine at inclusion or need for dialysis)	Serum creatinine between 130 and 620 μ mol/l	0.6 g Protein/kg body weight/day	1 g Protein/kg body weight/day
4	Estimated glomerular filtration ((creatinine clearance+urea clearance)/2)	Serum creatinine between 300 and 900 μ mol/l	0.3 g Protein/kg body weight/day with ketoacids supplementation (Ketosteril 1 tablet/6 kg/day)	0.65 g Protein/kg body weight/day
5	Plasma clearance of 51 Cr-EDTA	Serum creatinine between 350 and 1000 μ mol/l	0.4 g Protein/kg body weight/day	Free diet >0.75 g protein/kg body weight/day
6	Reciprocal of serum creatinine	Serum creatinine between 200 and 600 μ mol/l	0.6 g Protein/kg body weight/day	>0.8 g Protein/kg body weight/day

51 Cr-EDTA=ethylenediaminetetra-acetic acid labelled with chromium-51.

same as the degree of protein restriction in the treated group in study 3 (table IV). However, the mean difference in protein intake between control and treated groups was at least 0.35 g/kg/day in all studies except studies 2 and 6, when it was 0.2 g/kg/day. Interestingly, the treated groups in studies 2 and 4, which had the strictest restrictions received a ketoacid supplement.

HOMOGENEITY OF STUDIES

There was no qualitative interaction between effect and treatment. The χ^2 heterogeneity test between odds ratios was 4.05, with five degrees of freedom ($p=0.54$). Thus, the hypothesis that the effect of treatment in the different trials is heterogeneous is rejected.

EFFECTS OF DIETARY INTERVENTION ON INCIDENCE OF RENAL DEATH

Renal deaths are noted in tables II and III and the statistical results are shown in table V. In the six studies the number of renal deaths observed in treated and control groups were respectively 8 and 15 in study 1, 5 and 7 in study 2, 21 and 32 in study 3, 11 and 17 in study 4, 4 and 13 in study 5, and 12 and 11 in study 6. Five trials showed a reduction in renal death in treated groups and one a slight increase in renal death in the treated group (study 6). Only the results for study 5 were significant as the confidence interval of the odds ratio did not include 1. After summarising the data 156 renal deaths were recorded, 61 for the treated groups (450 patients) and 95 for the control groups (440 patients). This represents a highly significant reduction in renal death (odds ratio 0.54, 95% confidence interval 0.37 to 0.79; $p<0.002$) for subjects allocated to low protein diets.

Discussion

One of the problems in measuring the progression of renal insufficiency is the identification of aetiological or therapeutic factors that may improve renal function.^{6 57} Inadequate markers or protocols or confounding factors may mask the effects of low protein diets.^{6 57} Of the 46 trials analysed, only three used reference methods to measure glomerular filtration rate—that is 119 out of 2277 patients (5.2%).^{46 52 55} To avoid problems raised by surrogate criteria we chose a clearly defined clinical end point, renal death. This end point was easily observed for all patients retrospectively—that is, the date of the first dialysis session. These data were obtained accurately from each paper or by direct contact with the investigators.

In this review low protein diets were shown to reduce renal deaths significantly in the treated groups. The reduction of renal deaths occurred in five of the six trials (table V). In practical terms this reduction

represents a longer period before the start of dialysis, but it should not be taken to represent a reduction in the progression of renal disease.

This review has four potential limitations. Firstly, although the populations studied are clinically heterogeneous in age, sex ratio, level of renal insufficiency, and protein restriction, as seen in tables II, III, and IV, the effects of treatment are not statistically different. This heterogeneity of patients and degree of renal function is due, in part, to the small number of subjects. Interestingly, as observed for patients entering dialysis,⁵⁸ more male subjects were present in these trials (sex ratio (m/f) 1.26) and were identically distributed in both control and treated groups (table III). The different kinds of nephropathies were also equally distributed to avoid clustering of glomerulonephritides which are more sensitive to low protein diets.^{4 40} The limited number of patients presenting with stabilised renal insufficiency associated with the difficulty of dietary follow up may explain the individual trial sizes and the low significance of results.⁴ However, this heterogeneity may be viewed as an advantage for meta-analysis, because if it gives positive results it thus indicates a broader applicability of the treatment.⁷

Secondly, as the decision to begin dialysis varies locally, the definition of our criterion depends on physicians' opinions, the dialysis unit, and sometimes financial restrictions. The five countries involved (the Netherlands, France, Italy, Australia, and England) do not have dialysis restrictions and may start at similar degrees of renal insufficiency. Nevertheless, dialysis should be started at the same time for each trial in both treated and control groups according to clinical symptoms.

Thirdly, although the protein intake in the treatment and control diets varies, the fact that a common effect is found indicates that the gradient in protein content is the therapeutic factor. In fact, the widely observed drift during low protein diets is due to a regular increase in the protein intake with time for treated groups⁵⁹ and an underestimation of protein intake by the dietary reports.⁶⁰ These two facts tend to minimise the real gradient of protein intake between control and treated groups. Despite this, our meta-analysis is significant, and any factor that would minimise the difference in protein intake between control and treated groups—poor observance of protein restriction in the treated group or spontaneous restriction in the control group—would in fact enhance the significance of the meta-analysis. Thus, one reason why the individual studies gave weakly significant results could be that there was a too small protein gradient between treated and control groups at the start or during the trial (studies 2 and 6). The only significant study (study 5) showed a mean difference in protein intake of 13 g/day at six months (estimated by

TABLE V—Odds of renal death in six prospective randomised studies of protein restriction in chronic renal insufficiency

Study	Odds ratio (treatment/control)	95% Confidence interval
1	0.46	0.19 to 1.13
2	0.29	0.04 to 2.11
3	0.61	0.34 to 1.09
4	0.37	0.12 to 1.17
5	0.28	0.08 to 0.95
6	1.09	0.40 to 3.02
All	0.54	0.37 to 0.79

$\chi^2=4.05$, $df=5$, $p=0.54$ for test of heterogeneity between odds ratios.

urea nitrogen excretion; Maroni, *et al*'s correction is not useful in estimating a gradient of protein intake) in 50 patients.⁶¹ For a mean estimated weight of 60 kg (two thirds male patients, one third female) this represents a difference of 0.25 g/kg/day of protein. The significance of this meta-analysis could decrease if the treated groups ate less protein than prescribed and the control groups more. This would probably improve the effects of true protein restriction on renal function.

Fourthly, in the control groups (less or unrestricted protein intake) increased urea production may decrease clinical tolerance and hasten the decision to start dialysis, compared with the treated groups. This potential limitation has not been resolved, so clinical intolerance of urea is only one of many reasons for starting dialysis.

CONCLUSION

Finally, the heterogeneity does not limit the results from this meta-analysis. From this review low protein diets have clearly been found to delay end stage renal disease. However, no conclusion may be drawn about its effects on the rate of progression of renal insufficiency or on its nutritional risks or additional benefits on osteodystrophy, anaemia, and quality of life. Level of restriction and need for supplements could also not be measured. This meta-analysis should not be considered as definitive as renal death was not the end point used in the six studies. A new randomised controlled trial should be initiated with a sufficient number of patients. From the mean reduction of risk observed in our meta-analysis, it can be estimated that this trial should include at least 800 patients (control risk of event=0.21, odds ratio=0.54, two sided hypothesis, $\alpha=0.05$, $\beta=0.05$). Renal death should be closely monitored, as well as all other reasons for leaving the study. The modification of diet in renal disease study is suitable for this type of approach.^{57 60}

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Mortality and occupational exposure to radiation: first analysis of the National Registry for Radiation Workers

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Abstract

Objective—To study cause specific mortality of radiation workers with particular reference to associations between fatal neoplasms and level of exposure to radiation.

Design—Cohort study.

Setting—United Kingdom.

Subjects—95 217 radiation workers at major sites of the nuclear industry.

Main outcome measure—Cause of death.

Results—Most standardised mortality ratios were below 100: 83 unlagged, 85 with a 10 year lag for all causes; 84 unlagged, 86 lagged for all cancers; and 80 for all known other causes, indicating a "healthy worker effect." The deficit of lung cancer (75 unlagged, 76 lagged) was significant at the 0.1% level. Standardised mortality ratios were significantly raised (214 unlagged, 303 lagged) for thyroid cancer, but there was no evidence for any trend with external recorded radiation dose. Dose of external radiation and mortality from all cancers were weakly correlated ($p=0.10$), and multiple myeloma was more strongly correlated ($p=0.06$); for leukaemia, excluding chronic lymphatic, the trend was significant ($p=0.03$; all tests one tailed). The central estimates of lifetime risk derived from these data were 10.0% per Sv (90% confidence interval <0 to 24%) for all cancers and 0.76% per Sv (0.07 to 2.4%) for leukaemia (excluding chronic lymphatic leukaemia). These are, respectively, 2.5 times and 1.9 times the risk estimates recommended by the International Commission on Radiological Protection, but 90% confidence intervals are large and the commission's risk factors fall well within the range. The positive trend with dose for all cancers, from which the risk estimate was derived, was not significant. The positive association between leukaemia (except chronic lymphatic leukaemia) was significant and robust in subsidiary analyses. This study showed no association between radiation exposure and prostatic cancer.

Conclusion—There is evidence for an association between radiation exposure and mortality from cancer, in particular leukaemia (excluding chronic lymphatic leukaemia) and multiple myeloma, although mortality from these diseases in the study population overall was below that in the general population. The central estimates of risk from this study lie above the most recent estimates of the International Commission on Radiological Protection for leukaemia (excluding chronic lymphatic leukaemia) and for all malignancies. However, the commission's risk estimates are well within the 90% confidence intervals from this study. Analysis of combined cohorts of radiation workers in the United

States indicated lower risk estimates than the commission recommends, and when the American data are combined with our analysis the overall risks are close to those estimated by the commission. This first analysis of the National Registry for Radiation Workers does not provide sufficient evidence to justify a revision in risk estimates for radiological protection purposes.

Introduction

Estimates of the risks of ionising radiation rest mainly on evidence from Japanese atomic bomb survivors and from people exposed for medical reasons. These groups provide information on risks from exposure to high doses at high dose rates. There is little direct evidence of the effects of lower doses and dose rates typical of occupational exposures. To provide such direct evidence the National Radiological Protection Board, after extensive consultation with the nuclear industry and other interested groups, set up the National Registry for Radiation Workers in 1976 as the national study of radiation workers, following individuals through different employments.¹

The first analysis of the registry covers over 95 000 radiation workers whose collective dose from external radiation is about 3200 man Sv. The essentials of the study are described in this paper; more details can be found in a separate report.²

Methods

Although the study population for the National Registry for Radiation Workers is broadly defined,³ practical considerations have limited the first analysis to certain groups. Radiation workers were divided into four categories: (a) those in radiation work when the registry was set up; (b) those in employment at the inception of the study but no longer doing radiation work; (c) those who had left employment before the inception of the study; and (d) those starting radiation work after the inception of the study.

It was recognised that it would be easier to ensure that data were complete and accurate for those still in radiation work, and at the request of the participating organisations those in categories (a) and (d) were generally the first to be enrolled. The first analysis of the registry includes the following groups of workers: from British Nuclear Fuels, category (a) and (d) workers from 1 January 1976, with category (b) and (c) for Sellafield and Chapelcross; from the Ministry of Defence Atomic Weapons Establishment, workers in all categories; from the Ministry of Defence, Defence Radiological Protection Service, workers in categories (a) and (d) from 1 January 1977; from Nuclear Electric,

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