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Nutrition in Chronic Renal failure

Low protein diet and ketoanalogues

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ketoanalogues
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Introduction

- Several guidelines recommend the prescription of a planned low-protein diet in non-dialyzed patients with chronic kidney failure :
 - to ameliorate metabolic complications and related symptoms
 - to retard kidney disease progression
 - to preserve nutritional status

Protein intake and nitrogen balance

- The reduction in protein intake is limited by the necessity to maintain a positive or at least a neutral nitrogen balance
- An amount of 0.6g/kg/day is the minimal protein requirement for patients with uncomplicated CRF to achieve nitrogen balance, as do normal adults.
- If a supplement of essential amino acids and/or their nitrogen-free analogues (ketoacids) is used, a neutral nitrogen balance can be maintained with a lower protein intake

K/DOQI Recommendations for Nutrition in Chronic Renal Failure

Am.J.Kidney Dis.2000

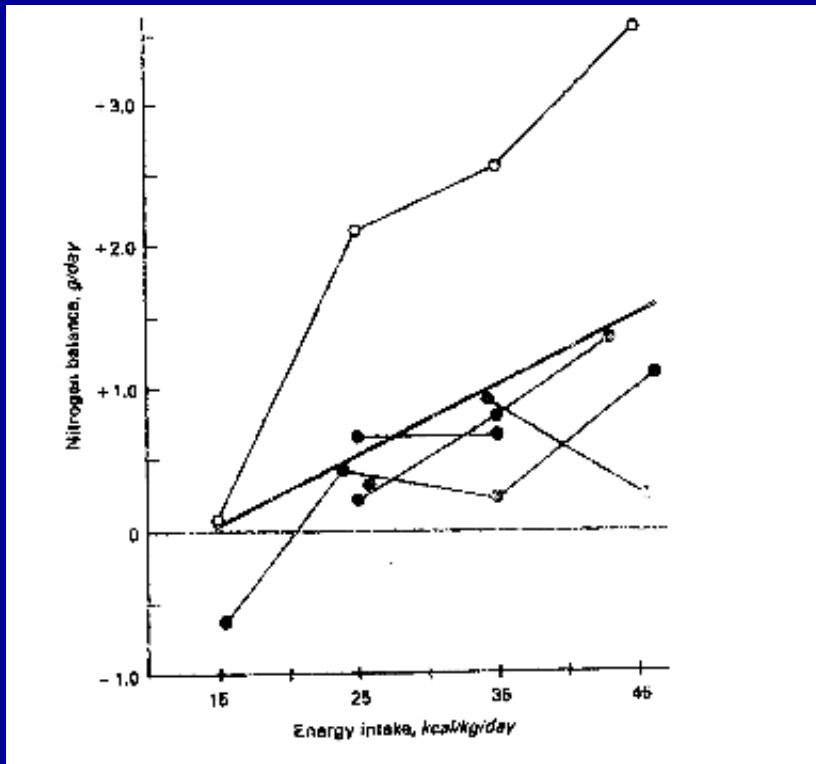
- | Stages CKD | Daily protein intake |
|--|---|
| • Stages I-II :
- > 60mL/min/1.73m ² | normal (<1.0 g/kg IBW) |
| • Stage III :
- 30-59mL/min/1.73m ² | 0.6-0.8g/kg IBW (2/3 of HBV) |
| • Stages IV-V :
- < 30mL/min/1.73m ² | 0.6-0.8g/kg IBW (2/3 of HBV)
or 0.3-0.4g of vegetable
origin/kg IBW
supplemented with EAA
and/or KA |

Principles of ketoacids (KAs)

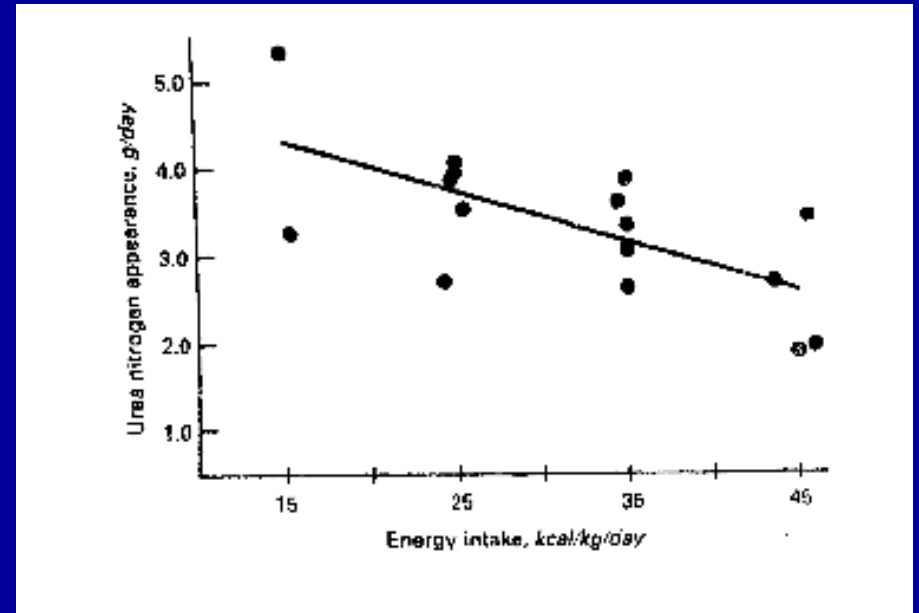
- KAs are transaminated to form the respective amino acid in the body.
- KAs allow the essential aminoacids requirements to be met with a lower nitrogen intake and with reduced nitrogenous waste products formation

Characteristics of SVLPD

- Caloric supply (kcal/kg/d) 35
 - % from carbohydrates 67
 - % from lipids 30
 - % from proteins 3
- Protein content (g/kg/d) 0.3-0.4
- Phosphorus content (mg/kg/d) 5-7
- Supplemented with :
 - EAA/KAA
 - Calcium 0.5 - 1 gram in salt form
 - Multivitamin preparation - iron



Nitrogen Balance vs Energy intake



UNA vs Energy intake

- J.Kopple, Kidney Int 1986

Monitoring of patients on low-protein diets

- When a protein-restricted diet is prescribed, a careful follow-up by a physician and a dietitian is necessary to monitor :
 - compliance with the dietary prescription
 - nutritional safety of the dietary prescription
 - potential efficacy of the dietary prescription on the course of kidney disease and other conditions

Common methods of survey of CRF patients on LPD diets

- Physical examination :
 - body weight and BMI
 - anthropometrics, hand grip muscle strength
- Biochemical parameters :
 - serum albumin, prealbumin, cholesterol
 - serum creatinine, BUN
 - glomerular isotopic clearances
- Dietary assessment :
 - 24h urinary urea nitrogen excretion
 - estimating calorie intake from 3-day food diaries/recall

MDRD-Study (Modification of Diet in Renal Disease)

DESIGN :

A multicentre, randomised, prospective trial of 840 patients with various chronic kidney diseases.

Study A : Patients (585) with a GFR of 25-55 mL/min
1.3g protein/kg/d vs 0.58g protein/kg/d

Study B : Patients (255) with a GFR of 13-24 mL/min
0.58g protein/kg/d vs 0.28g protein/kg/d

AIM OF THE STUDY :

Comparison of the rate of decline (slope) in GFR associated with different levels of protein intake

MDRD-Study : compliance

Prescribed and achieved protein intake

Study A:

Normal diet :

- Prescribed : 1.30 g/kg/j
- Achieved : 1.11 g/kg/j

Study B :

LPD :

- Prescribed : 0.58 g/kg/j
- Achieved : 0.73 g/kg/j

LPD :

- Prescribed : 0.58 g/kg/j
- Achieved : 0.77 g/kg/j

SVLPD :

- Prescribed : 0.28 g/kg/j
(+ ketoanalogues : 0.18g/kg/j)
- Achieved : 0.66 g/kg/j

Compliance to LPD

- In many other reports achieved protein intake averages 25 to 40% above prescribed protein intake.
- Although this is an imperfect compliance, it represents however a substantial reduction in protein intake.

Malnutrition and outcome of CRF patients

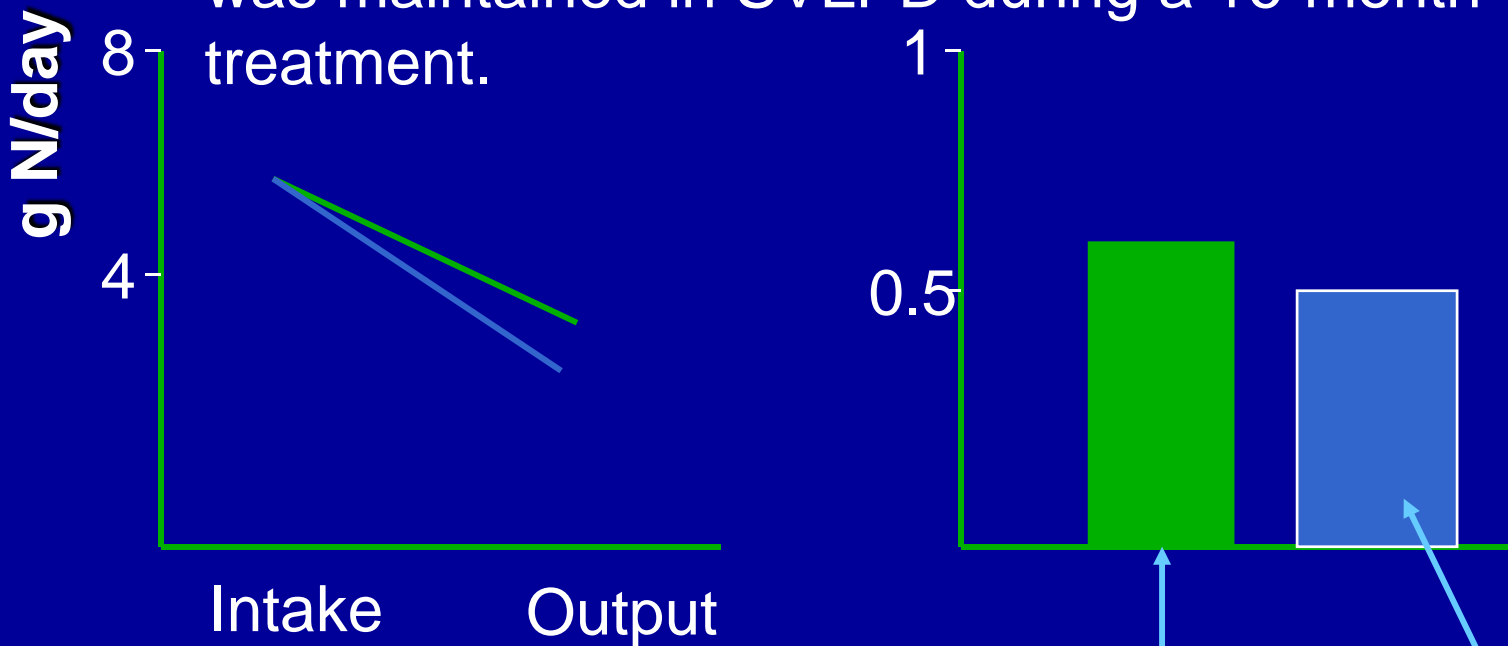
- It is essential to ascertain that the dietary prescription is not harmful for the patient and more especially that their nutritional status is well preserved
- The nutritional safety of protein-restricted diets and their long-term effects on body protein stores have been frequently questioned by non-users

Adaptation to a low-protein intake

- Uncomplicated CIRI patients and healthy adults activate similar adaptive metabolic responses to dietary protein restriction :
 - reduction in AA oxidation
 - post-prandial suppression of protein degradation
 - +/- stimulation of protein synthesis

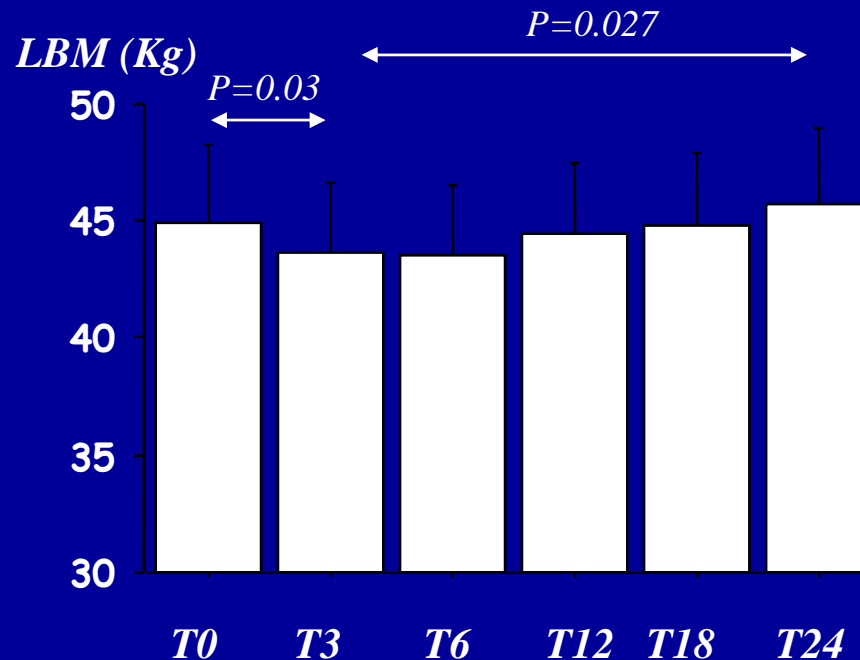
Adaptation to ketodiet in CRF patients

- Tom et al.(Am.J.Physiol. 1994) : nitrogen balance was maintained in SVLPD during a 16-month treatment.



N intake, output and N Balance 3 weeks and 16 months after initiation of SVLPD regimen

Evolution of lean body mass during 2 years on SVLPD



Ph.Chauveau et col. J.Ren.Nutr. 2003;13:282-287
Lean body mass measured by DEXA at start and 3,6,12,18, and 24 months (Mean \pm 1 SEM).

Outcome of patients in the MDRD study

- After 2.2 years follow-up, biochemical and anthropometric indices of nutritional status remained within normal limits in all diet groups.
- Most importantly, a lower protein intake was not associated with a higher rate of death, hospitalizations, or stop points.

Annual death rate of CRF patients on LPD or SVLPD

	diet	n	death rate
Klahr NEJM 1994	LPD/SVLPD	128	2.4%
Walser JASN 1999	SVLPD	76	2.5%
Aparicio JASN 2000	SVLPD	239	2.4%

Predialysis protein-restricted diet and outcome of patients on hemodialysis

- Concerns have also been raised about the outcome of patients, previously on a protein-restricted diet, once dialysis therapy has begun

GFR at initiation of dialysis

- In patients previously on ketodiet, GFR at the initiation of dialysis was lower than current NKF-DOQI guidelines (ie, GFR < 10.5 mL/min)

- Walser 5.6 +/- 1.9 ml/min
- Aparicio 5.8 +/- 1.5 ml/min
- Vendrely 6.3 +/- 1.6 ml/min

J.Am.Soc.Nephrol.1999

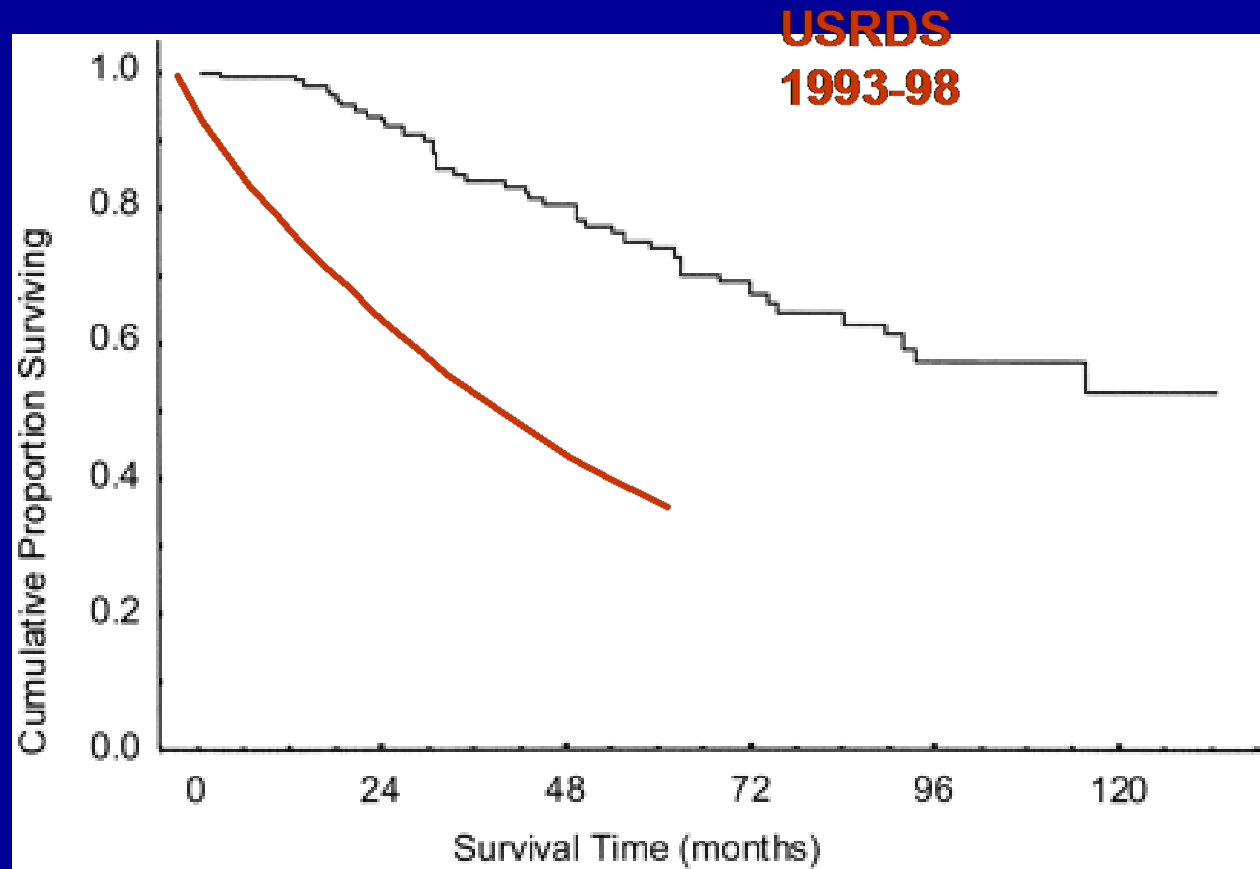
J.Am.Soc.Nephrol.2000

Walser

Aparicio

Vendrely Kidney Int.2003

Survival on hemodialysis after cessation of SVLPD

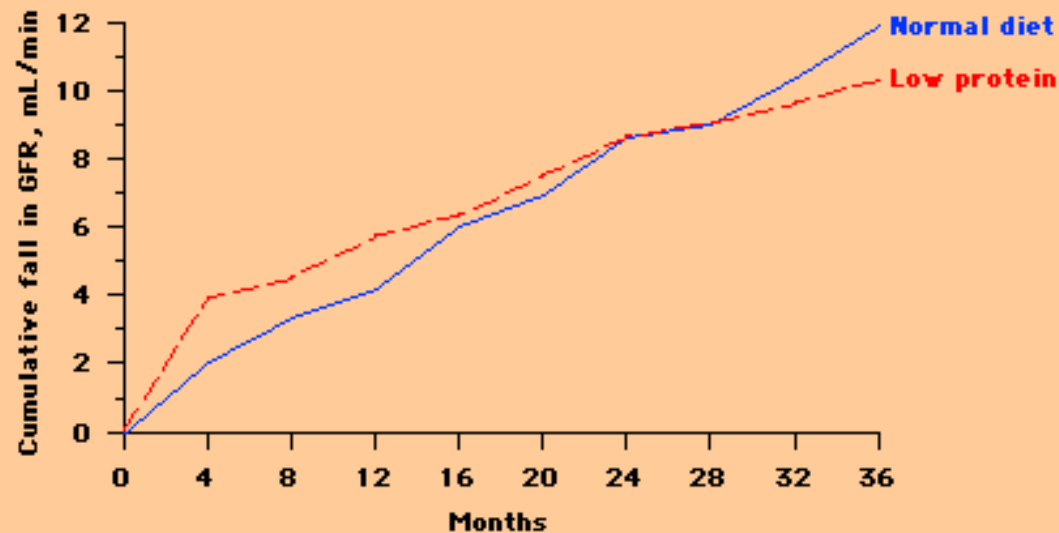


Effects of LPD on the QOL

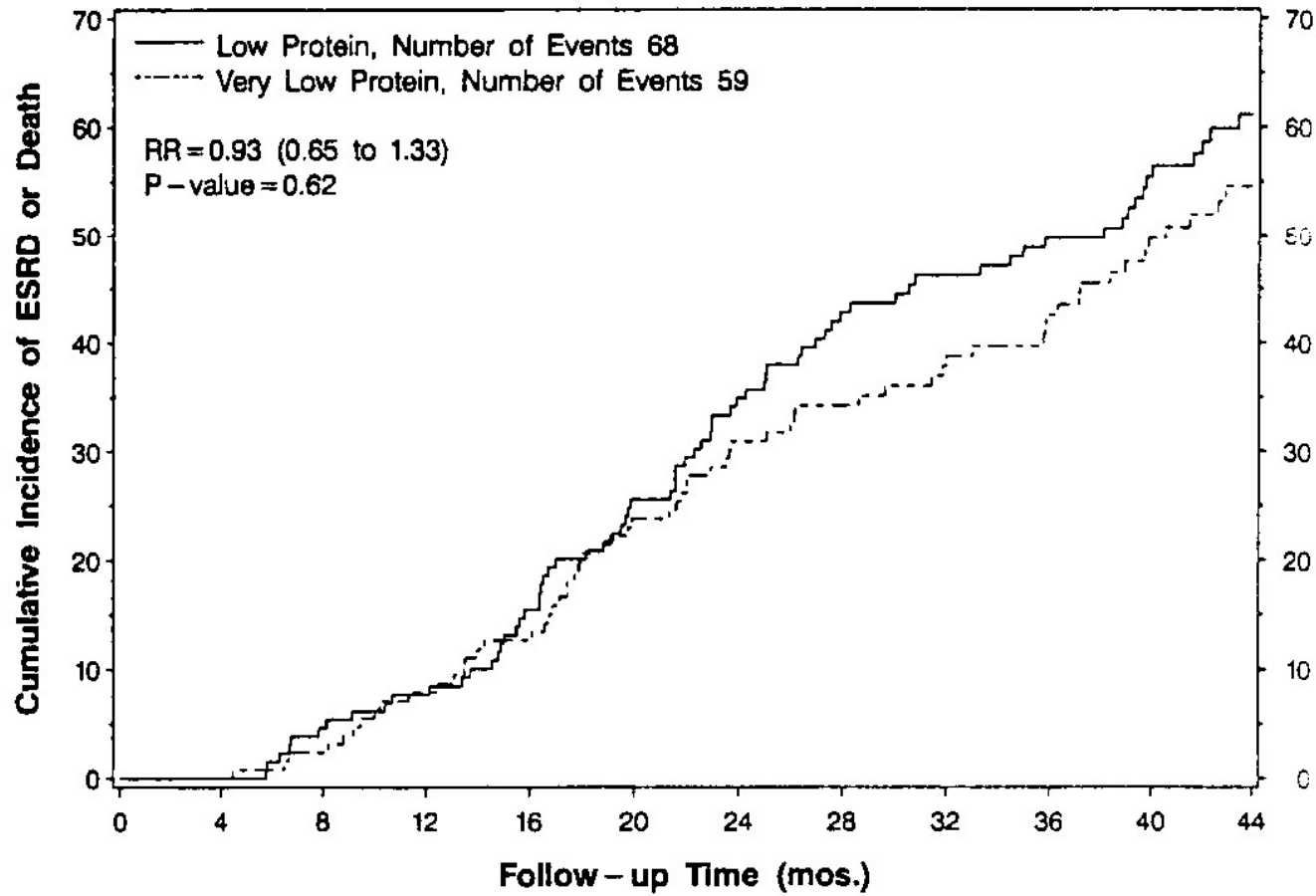
- Most of the patients acknowledged feeling a clear-cut amelioration of their general state of health with disappearance of tiredness
- In spite of the dietetic changes, appetite remained good, digestive and taste toleration were satisfactory in most cases

Beneficial effects of reduced protein intake on uremic signs and symptoms

- Reduced nitrogenous waste products :
 - peripheral neuropathy (Barsotti 1989)
 - insulin resistance (Gin 1991)
 - sodium pump (Aparicio 1991)
 - lipid peroxidation (Peuchant 1997)
- Low acidic ash :
 - metabolic acidosis (Aparicio 2000)
- Low phosphorus intake
 - secondary HPT (Lafage 1992)
 - EPO responsiveness (Di Iorio 2003)



Protein restriction has minimal protective effect in nondiabetic chronic renal failure Cumulative fall in glomerular filtration rate (GFR) over three years in patients with nondiabetic chronic renal failure (mean baseline GFR 39 mL/min) receiving a normal (solid line) and low protein (dashed line) diet. Protein restriction had little or no overall beneficial effect. There was a trend toward more rapid loss of GFR in the first four months followed by a modest slowing of progression during the last 32 months. (Data from Klahr, S, Levey, AS, Beck, GJ, et al, N Engl J Med 1994; 330:877.)



SVLPD and progression of CRF , MDRD study B

Klahr NEJM 1994

MDRD study : secondary analyses

Levey AJKD 1996, JASN 1999

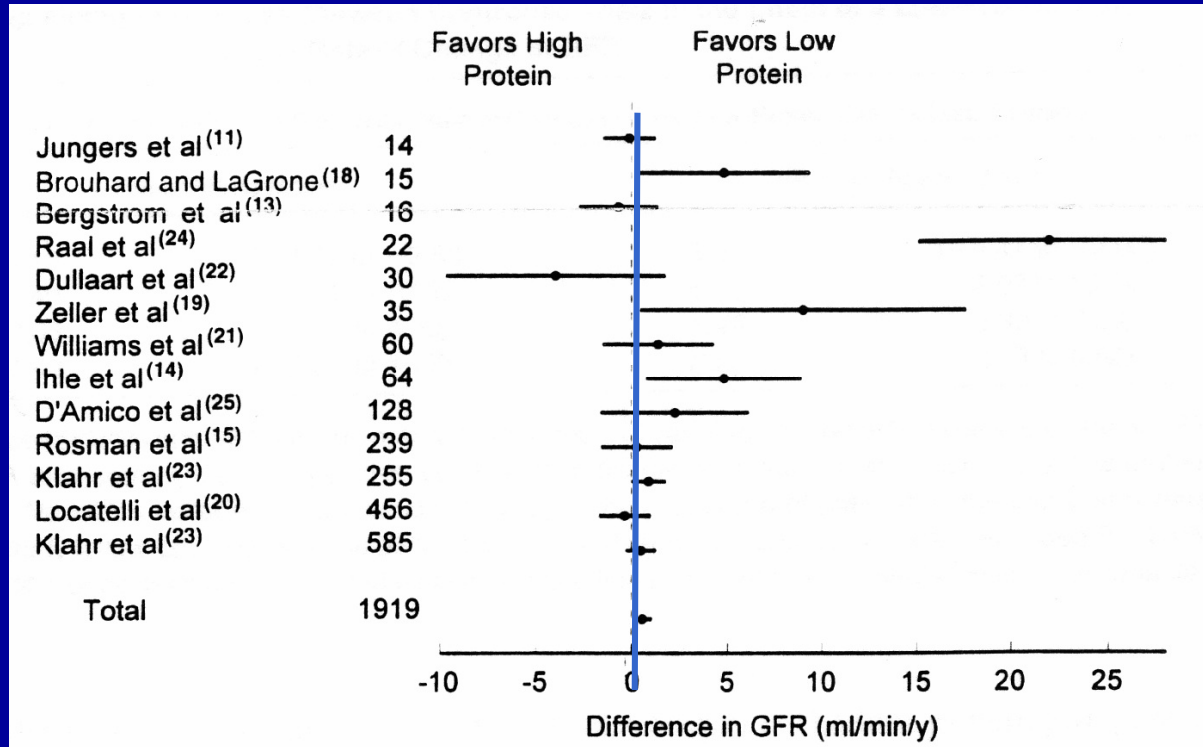
Study A :

Each 0.2 g/kg/d lower achieved protein intake was associated with a 10% slower mean GFR decline ($p=0.075$) and a 35% reduction in the risk of ESRD or death

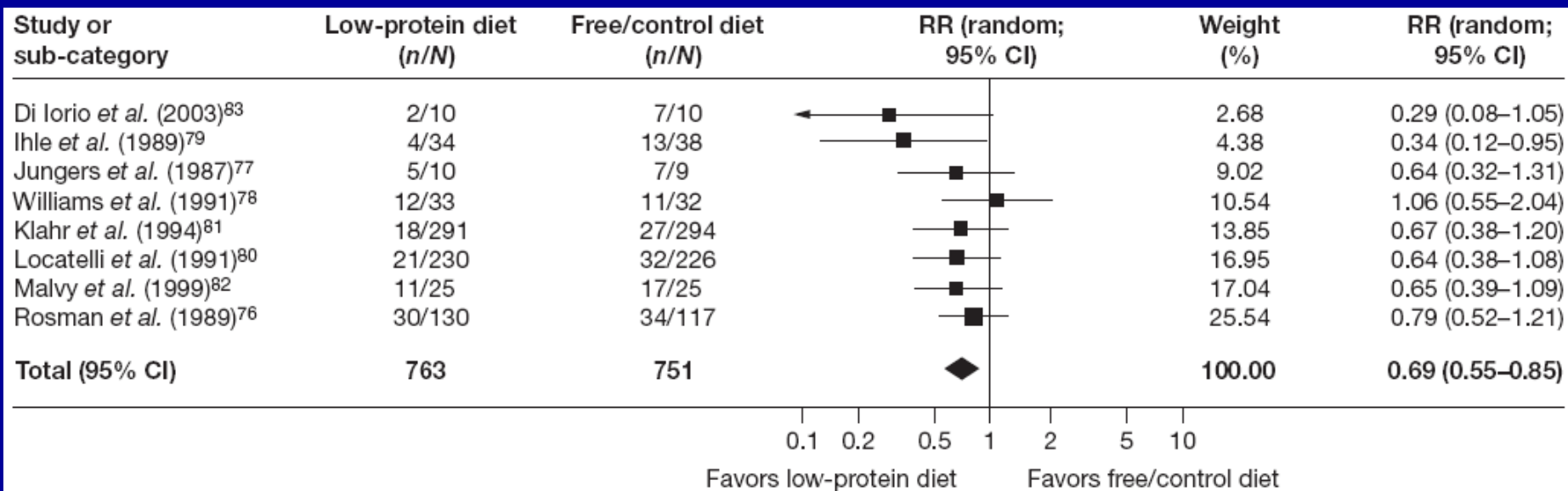
Study B :

Each 0.2 g/kg/d lower achieved protein intake was associated with a 30% slower mean GFR decline ($p=0.011$) and a 50% reduction in the risk of ESRD or death

Low protein diet and CRF : outcome of GFR



- 24 controlled clinical trials, 13 randomized
- main target: loss of GFR (ml/min/yr)
- total : 2248 patients (1919 in randomized studies)
- loss of GFR : 0.53 ml/min/yr lower (95%CI, 0.08-0.98) in the diet group (p<0.05)



Total events: 103 (low-protein diet), 148 (free/control diet)
 Test for heterogeneity: $\chi^2 = 5.78$, $df = 7$ ($P = 0.57$), $I^2 = 0\%$
 Test for overall effect: $Z = 3.45$ ($P = 0.0006$)

Figure 1 Results of a systematic review of the effect on 'renal death' of low-protein diets in people with chronic kidney disease. Squares denote the odds ratio (treatment:control) for each trial. The diamond represents the overall results of the eight trials combined. Horizontal lines represent 95% CIs. The overall odds ratio was 0.69 (95% CI 0.55–0.85; $P < 0.001$). Permission obtained from John Wiley & Sons Limited © Fouque D *et al.* *Cochrane Database Systematic Reviews* 2006, Issue 2. Art. No.: CD001892. DOI: 10.1002/14651858.CD001892.pub2. Abbreviations: df, degrees of freedom; n, number of 'renal deaths'; N, total number of subjects; RR, relative risk.

How much time can be gained ?

« In a patient with an initial GFR of 40 ml/min a decrease in total protein intake by 0.2 grams / Kg / day would lengthen the interval until ESRD from 7 1/4 yr to 10 yr »

Leavey et al. J Am Soc Nephrol 1999

« Patients following a very low protein diet for nearly 3 years could gain 15 months in comparison with those following a conventional low protein diet »

Locatelli et al. Nephrol Dial Transplant, 1999

Conclusion -I-

- When properly implemented, low protein diets preserve nutritional status in patients with CRF.
- The benefits include the amelioration of uremic symptoms and biochemical abnormalities, substantially delaying the time to dialysis and possibly the rate of progression of renal failure.

Conclusion -II-

- LPD brings a positive answer to the patient for whom the essential issue is not so much whether protein restriction actually slows the progression of CRF but how long he can remain free of dialysis by reducing its protein intake.
- This point of view is certainly shared by the economists.....

Suggested readings -I-

- Walser M., Mitch W.E., Maroni B.J., Kopple J.D. :
Should protein intake be restricted in predialysis patients ?
Kidney Int.1999 ; 55 :771-777
- Mehrotra R., Nolph K.D.: Treatment of advanced renal failure : low-protein diets or timely initiation of dialysis ? Kidney Int.2000 ; 58 :1381-1388
- Aparicio M., Chauveau Ph., Combe C. : Low-protein diets and outcome of renal patients
J.Nephrol.2001 ; 14 :433-439

Suggested readings -II-

- Mitch W.E., Remuzzi G. : Diets for patients with chronic kidney disease, still worth prescribing?
J.Am.Soc.Nephrol.2004 ;15 : 234-237
- Mich W.E. : Beneficial responses to modified diets in treating patients with chronic kidney disease
Kidney Int.2005; 67 (Suppl.94) S 133-S 135
- Fouque D., Aparicio M. : Eleven reasons to control the protein intake of patients with chronic kidney disease Nature Clin. Pract. Nephrol. 2007 ; 3:383-392

Suggested readings -III-

- Brunori G., Viola B.F., Parrinello G. et al : Efficacy and safety of a very-low-protein diet when postponing dialysis in the elderly : a prospective randomized multicenter controlled study
Am.J.Kidney Dis.2007 ; 49:569-590