Dietary Protein Requirements for Pre-Dialysis and Chronic Peritoneal Dialysis Patients

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A

Topics to be Discussed

1. Can LPDs and ketoacid/essential amino acid (KA/EAA) supplemented very low protein diets delay the need for renal replacement therapy (RRT)?

2. Do KA/SVLPDs retard the rate of GFR loss in chronic kidney disease (CKD)?

3. Can these diets reduce the needed dose of dialysis?

Do Low Protein Diets Retard Progression of CKD in Patients?

MDRD Study Overview (1)

1. The MDRD Study was a randomized controlled trial conducted from 1989 to 1993 to study the effect of dietary protein & phosphorus restriction & strict blood pressure control on the progression of kidney disease.

2. Eligibility criteria included age 18 to 70 years, serum creatinine 1.2 to 7.0 mg/dL in women and 1.4 to 7.0 mg/dL in men, and mean arterial BP of 125 mm Hg or less. Exclusion criteria were insulin-requiring diabetes, class III or IV heart failure, urine protein >10 g/d, kidney transplant, frequent hospitalizations.

3. Participants with true GFR of 25 to 55 mL/min/1.73 m2 entered study A and participants with true GFR of 13 to 24 mL/min/1.73 m2 entered study B.

MDRD Study Overview (2)

4. The 255 participants in study B were randomly assigned to either a low-protein diet (LPD, 0.58 g/kg/d) or a very LPD (0.28 g/kg/d) supplemented with a mixture of **keto-acids and amino acids** (0.28 g/kg/d). Participants also were randomly assigned to either a low or usual BP target.

5. Participants in study A were randomly assigned to either a usual-protein diet (1.3 g/kg/d) or LPD (0.58 g/kg/d), with approximately 65% of dietary protein of high biological value (from animal sources). GFR was measured by using iothalamate clearance.

Klahr et al
NEJM 1994;
330:877-884

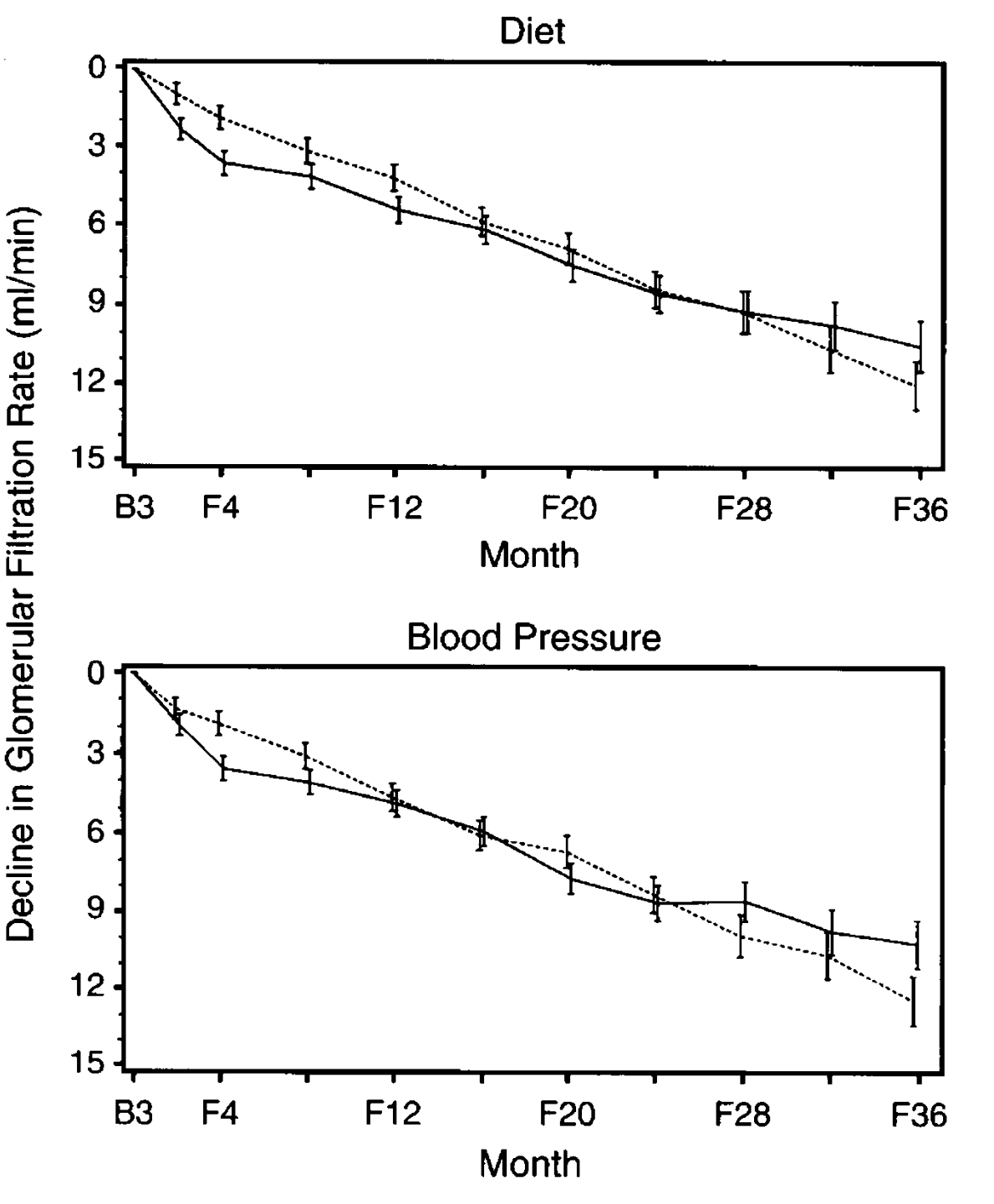


Table 4. Mean Rate of Decline in the Glomerular Filtration Rate from Base Line to the End of the Study in Study 2.*

DIET	DECLINE IN GLOMERULAR FILTRATION RATE		
	USUAL PRESSURE	LOW PRESSURE	BOTH
	milliliters per minute per year (95% confidence interval)		
Low protein	4.9 (3.8–5.9)	3.9 (3.2–4.7)	4.4 (3.7–5.1)
Very low protein	3.6 (2.8–4.4)	3.5 (2.6–4.5)	3.6 (2.9–4.2)
Both	4.2 (3.6–4.9)	3.7 (3.1–4.3)	4.0 (3.5–4.4)

*The mean rates of decline in the glomerular filtration rate, which were estimated according to the single-slope informative censoring model, did not differ significantly between the diet groups ($P = 0.07$) or between the blood-pressure groups ($P = 0.28$).

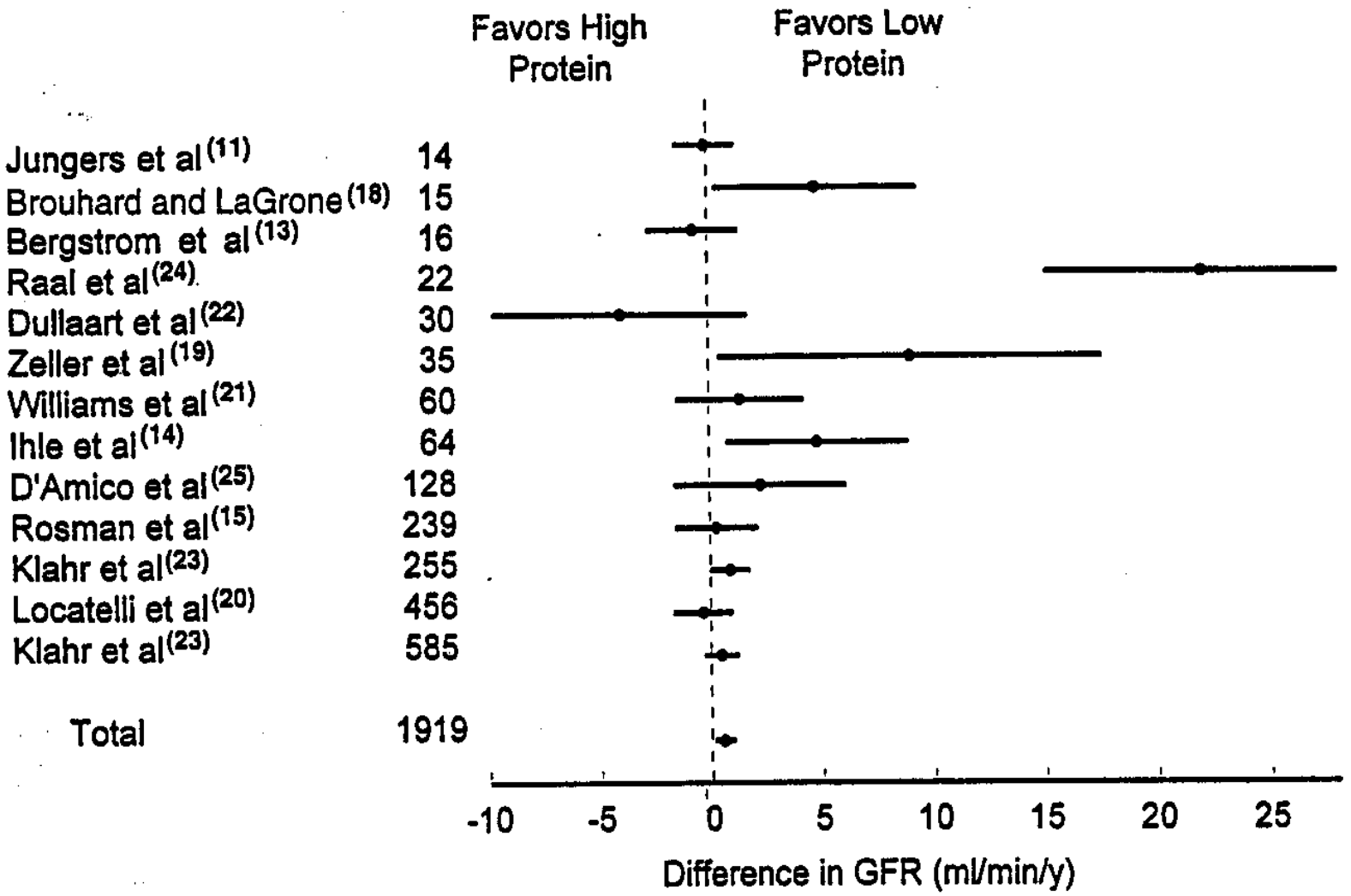
Klahr et al NEJM 1994;330:877-884

Methodological Problems with the MDRD Study (1)

1. **Follow-up period was too short (2.2 years)**
2. **A large proportion (25%) of patients had polycystic kidney disease which is probably poorly responsive or unresponsive to low protein diets .**
3. **The ketoacid supplemented diet was not compared to a normal diet or to no dietary protein restriction.**

Methodological Problems with the MDRD Study (2)

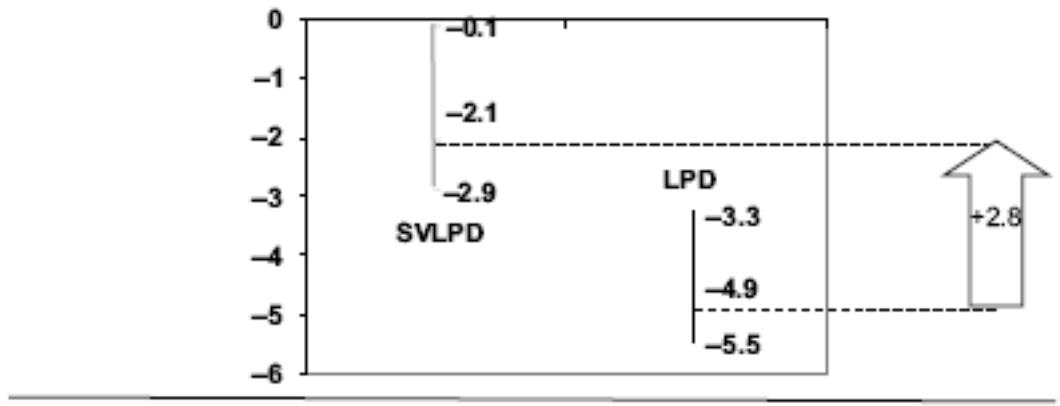
4. **Some patients did not have progressive loss of renal function.**
5. **The MDRD Study ketoacid diet may have had excessive tryptophan, which engenders at least one metabolite (indoxyl sulfate) that appears to be nephrotoxic.**



Kasiske et al. AJKD 31:954-961, 1998.

Controlled Trial in 207 non-Diabetic Stage 4-5 CKD Patients Randomized to Receive 0.3 g Prot/kg/day plus KA/EAA 1Tablet/ 5 kg/day or 0.6 g Prot/kg/day. Patients were Followed for 48 Weeks. >50% eGFR Decrease or Need for RRT were Endpoints

Figure 1. Decline in estimated glomerular filtration rate (GFR) (mean, 95% confidence interval [CI], mL/min/1.73 m^2/year) seen in comparison between treatment groups. LPD, low-protein diet; SVLP-LPD, supplemented very low-protein–low-protein diet; SVLPD, (keto acid) supplemented very low-protein diet.



Group	Estimated GFR decline (mL/min per year)	
	Mean	95% CI
SVLPD (n = 90)	−2.1	(−2.9,−0.1)
LPD (n = 69)	−4.9	(−6.5,−3.3)
SVLP-LPD	+2.8	(+2.6, +3.2)

Garneata and Mircescu J Renal Nutrition 2013;23:210-213

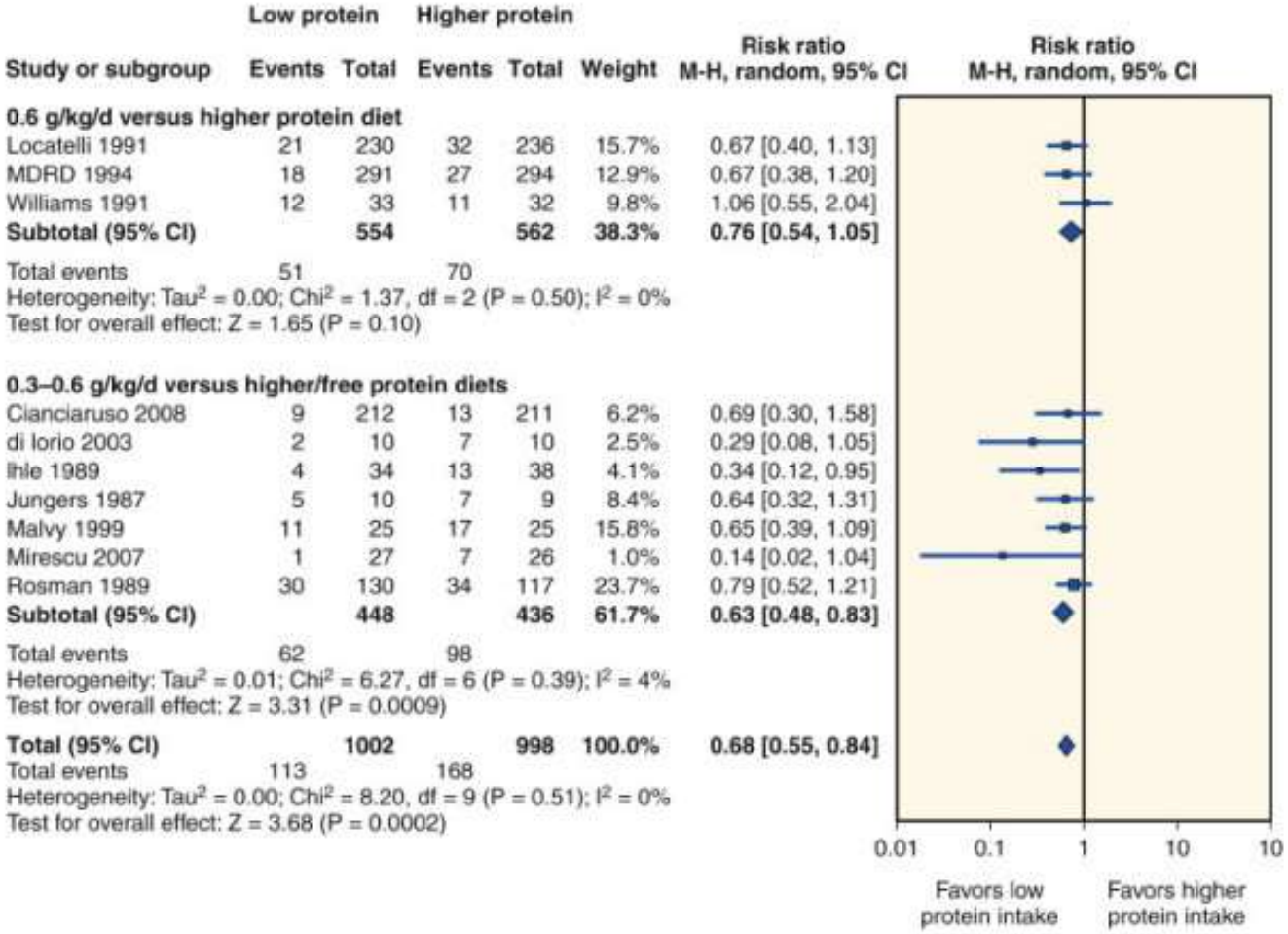


FIGURE 60-11 A meta-analysis of results from randomized controlled studies of the influence of low-protein diets (LPDs) in delaying progression of chronic kidney disease (CKD). A square denotes the odds ratio (treatment/control) for each trial, and the diamond indicates the combined results of all the trials; 95% confidence intervals are represented by horizontal lines. The designation, 1.1.1, is from three studies including a moderately reduced protein intake diet (0.6 g protein/kg/day) and a higher protein diet compared with self-selected diets. The designation, 1.1.2, is the result of seven studies that included a more reduced protein intake (0.3-0.6 g protein/kg/day compared with a greater amount of dietary protein or a free diet). Overall, the *common* odds ratio equals 0.68 (95% CI: 0.55, 0.84), $P = 0.0002$.
(From Fouque D, Laville M: Low protein diets for chronic kidney disease in non diabetic adults, Cochrane Database Syst Rev CD001892, 2009, with permission).

Some New Questions Regarding LPDs for Advanced CKD

1. How Beneficial are LPDs Providing about 0.6 g Protein/kg/day Supplemented with Ketoacids/Essential Amino Acids?
2. Can SVLPDs Safely Delay the Need for Chronic Dialysis Therapy?
3. Is There a Role for LPDs Supplemented with Ketoacids/Essential Amino Acids for Patients Undergoing Chronic Dialysis?

Table 2. Differences between CKD-5 groups intensively treated in tertiary nephrology clinics with (s-VLPD) or without (TNC) a very low-protein diet supplemented with ketoacids at the last visit prior (≤3 months) to dialysis start

	s-VLPD ($n = 184$)	TNC ($n = 334$)	P-value
GFR (mL/min)	5.4 ± 2.3	10.6 ± 3.8	<0.001
Weight (kg)	65.9 ± 13.1	70.7 ± 14.1	0.001
BMI (kg/m^2)	24.3 ± 3.5	26.4 ± 4.6	<0.001
SBP (mmHg)	149 ± 20	140 ± 19	<0.001
DBP (mmHg)	81 ± 11	81 ± 10	0.601
Haemoglobin (g/dL)	10.9 ± 1.1	11.5 ± 1.8	0.001
Protein intake (g/kg/die)	0.58 ± 0.18	0.83 ± 27	<0.001

GFR, glomerular filtration rate; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Bellizzi et al. Nephrol Dial Transplant 2015;30:71-77

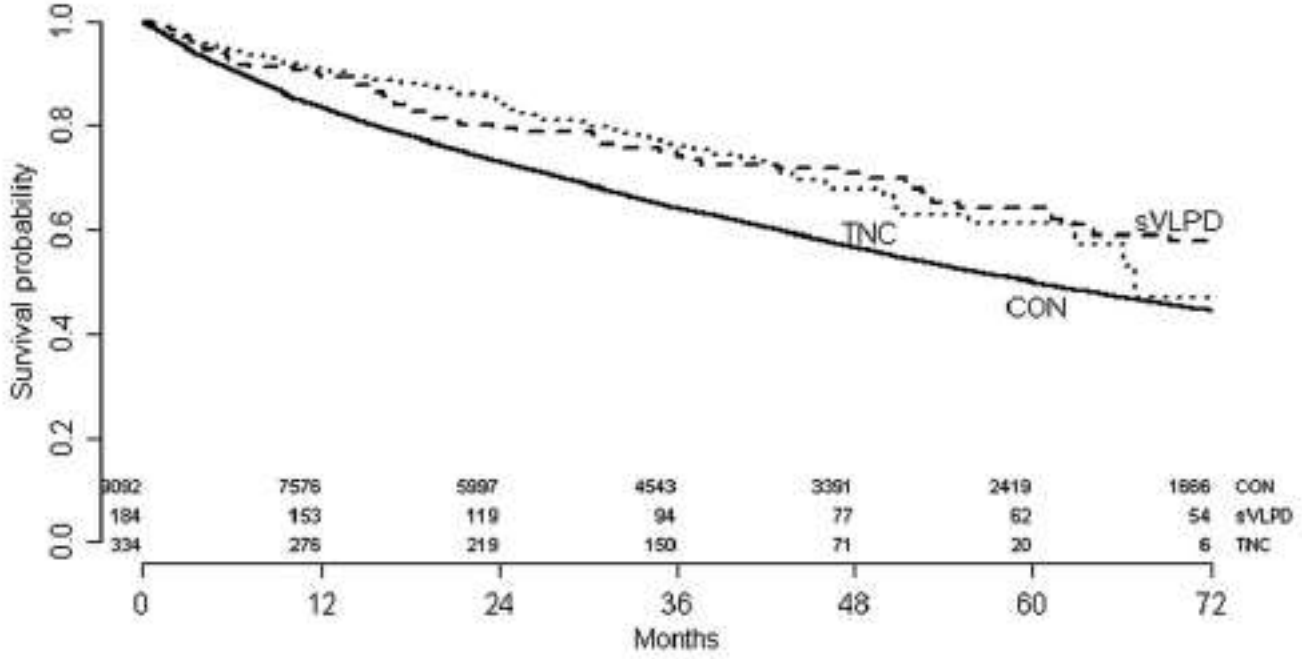


FIGURE 1: Survival of adult CKD-5 patients during RRT according to nephrology care characteristics during the previous CKD-4/5 period. Patients intensively treated in the tertiary nephrology clinic with (- - - - - - - s-VLPD, $n = 184$) and without (.....TNC, $n = 334$) very low-protein diet and ketoacids; unselected subjects (_____CON, $n = 9.092$).

Bellizzi et al. Nephrol Dial Transplant 2015;30:71-77

Table 4. Risk of all-cause death during RRT in CKD-5 patients; Cox regression model

	HR (95% CI)	P-value
s-VLPD versus matched-CON[a]	0.59 (0.45–0.78)	<0.001
s-VLPD versus TNC[b]	0.82 (0.56–1.19)	0.300
s-VLPD versus TNC[c]	0.84 (0.51–1.39)	0.496
s-VLPD versus TNC[d]	0.76 (0.45–1.28)	0.305

s-VLPD, group intensively treated in tertiary nephrology clinics with very low-protein diet supplemented with ketoacids; matched-CON, matched unselected controls (reference group); TNC, group intensively treated without s-VLPD.

[a]Results of matched propensity score (see statistical methods).

[b]HR adjusted for age, sex, diabetes, previous CVD and renal disease.

[c]HR adjusted for the previous covariates and for SBP, BMI, haemoglobin, GFR and time on CKD care.

[d]HR adjusted for all the previous covariates from model and fitted only in haemodialysis patients.

Bellizzi et al. Nephrol Dial Transplant 2015;30:71-77

Use of Ketoacid/EAA Supplemented Diets in Chronic Dialysis Patients

Ketoacid/EAA (KA) Supplemented Diets for CPD Patients (2)

Study 1: Nitrogen balance studies in CPD patients fed 1.2, 0.9, and 0.6 g protein/kg/day; ~50% of protein was of high biological value.

5. On CPD≥ 1 month; stable; no wasting illnesses.
6. Balance only measured at baseline and days 7 and 10 and measured dialysate urea and estimated fecal N and non-urea N losses.
7. 30 patients received one of the 3 protein intakes: (9 Pts, 1.2g; 12 Pts, 0.9 g; 9 Pts, 0.6 g/kg/day)

Jiang et al. NDT 2009;24:2551-2558

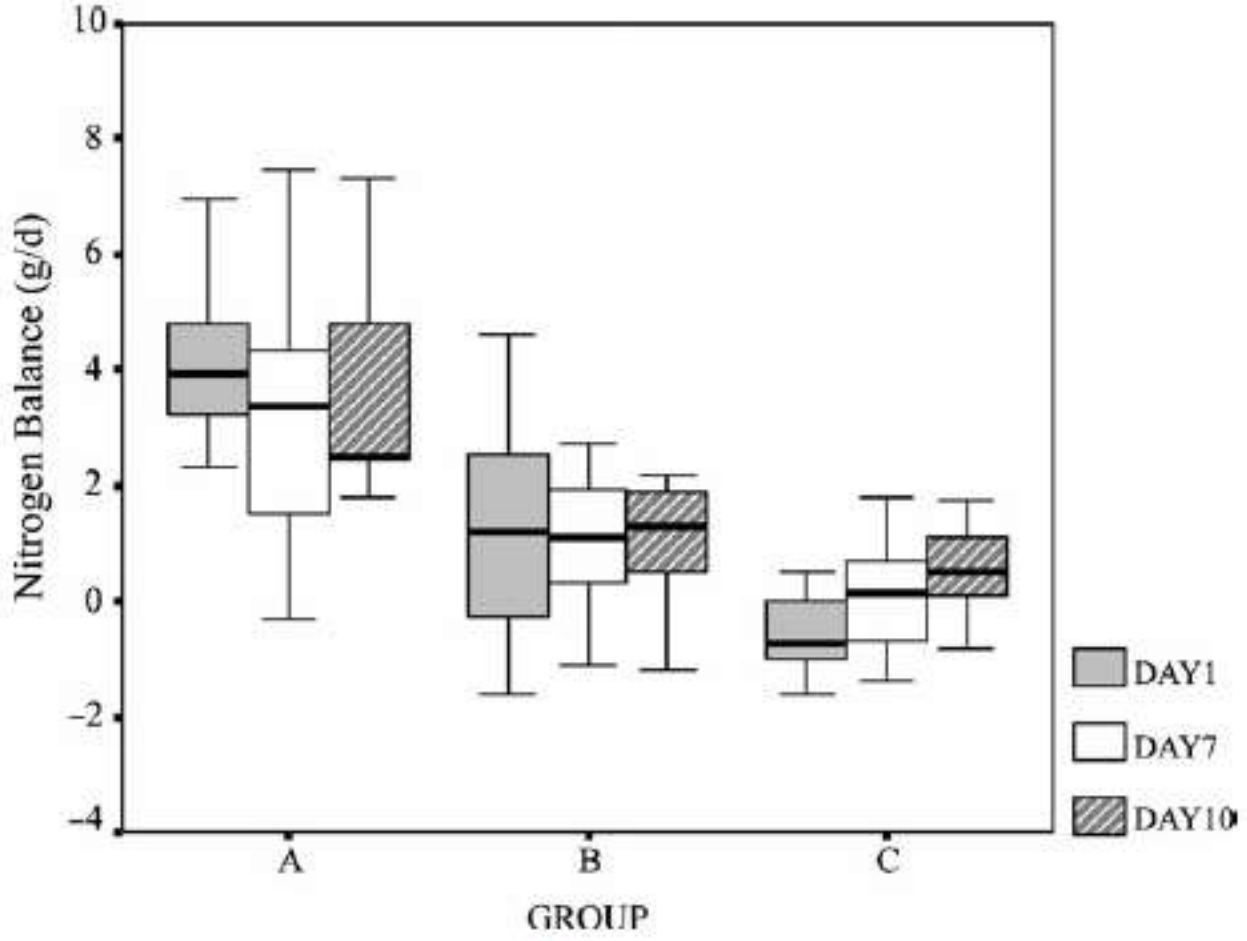
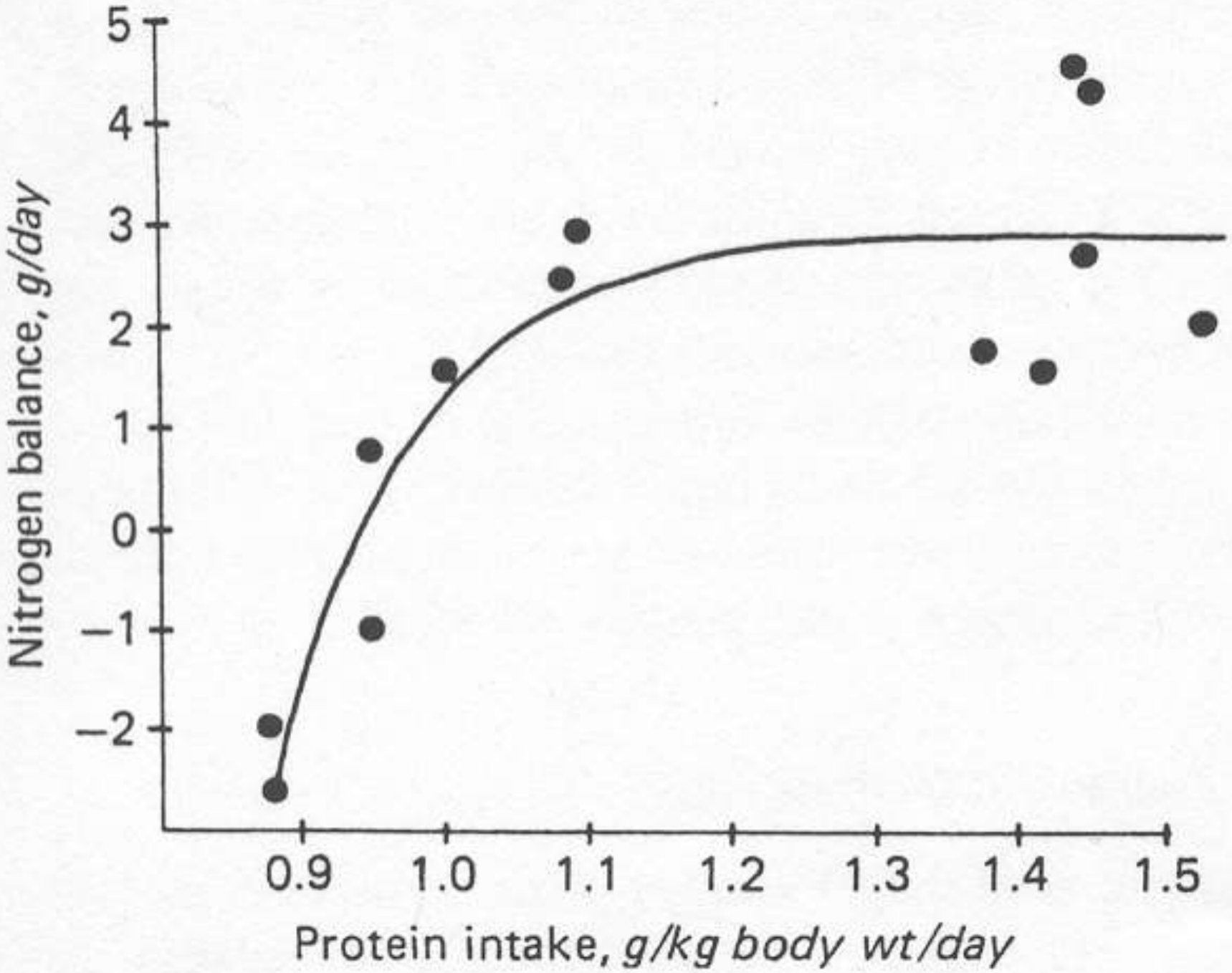


Fig. 3. Nitrogen balance of the three groups during the 10-day in-hospital follow-up. Positive nitrogen balance was found in group A, and neutral nitrogen balance was found in group B and C on both the 7th and 10th days of the study.

Jiang et al. NDT 2009;24:2551-2558


5
4
3
2
1
0
−1
−2
Nitrogen balance, g/day
0.9
1.0
1.1
1.2
1.3
1.4
1.5
Protein intake, g/kg body wt/day

Ketoacid/EAA (KA) Supplemented Diets for CPD Patients (3)

Outpatient Study 2: Clinically stable CPD patients prescribed 0.6-0.8 g protein/kg IBW/day (LP); 0.6-0.8 g protein/kg IBW/day plus 0.12 g KA/kg IBW/day (sLP) or 1.0-1.2 g protein/kg IBW/day (HP); ~50% of protein was high biological value. Energy intake was as above.

1. On CPD≥ 1 month. No wasting illnesses.
2. Urine output ≥800 mL/ or eGFR (mean of 24 h creatinine & urea clearances)≥2mL/min/1.73m^2

Jiang et al. NDT 2009;24:2551-2558

Table 3. Temporal changes of selected parameters of the 60 PD patients randomized to group LP (0.6–0.8 g/kg IBW/day), sLP (0.6–0.8 g/kg IBW/day) or HP (1.0–1.2 g/kg IBW/day), respectively, who underwent residual renal function study

		Follow-up duration (months)			
		0 month ($n = 60$)	4 months ($n = 55$)	8 months ($n = 54$)	12 months ($n = 53$)
SGA[a] (%)	LP	10.0	21.0	27.8	11.8
	sLP	15.0	11.1	16.7	0.0
	HP	10.0	26.3	16.7	20.0
BMI (kg/m^2)	LP	21.0 ± 2.0	21.4 ± 1.9	21.3 ± 2.1	21.7 ± 2.2
	sLP	22.4 ± 3.0	22.6 ± 3.2	22.3 ± 3.1	23.1 ± 3.7
	HP	22.1 ± 3.0	22.3 ± 2.9	22.6 ± 2.3	22.7 ± 3.3
LBM (kg)	LP	23.5 ± 5.3	24.9 ± 5.8	28.0 ± 7.4*	29.0 ± 6.2*
	sLP	25.4 ± 4.8	26.3 ± 6.7	27.6 ± 6.5*	29.8 ± 6.6*
	HP	25.1 ± 5.4	26.7 ± 6.9	28.2 ± 8.4*	30.3 ± 8.7*
Albumin (g/l)	LP	35.9 ± 3.3	35.3 ± 4.2	36.2 ± 3.0	36.9 ± 3.5
	sLP	37.4 ± 4.4	36.5 ± 3.8	37.1 ± 4.6	38.9 ± 4.4
	HP	38.1 ± 2.8	35.8 ± 3.6*	37.9 ± 3.4	39.2 ± 4.0
MAP (mmHg)	LP	101 ± 16	103 ± 11	101 ± 21	106 ± 11
	sLP	101 ± 11	101 ± 10	98 ± 13	105 ± 16
	HP	105 ± 14	106 ± 16	105 ± 14	108 ± 16
CRP (mg/l)	LP	2.97 (1.00–3.92)	3.12 (2.97–5.08)	3.00 (1.56–3.24)	3.12 (3.00–3.17)
	sLP	7.77 (3.00–13.90)#	3.00 (1.00–5.29)	3.12 (2.99–4.09)	3.12 (3.09–3.89)
	HP	3.17 (2.78–6.03)	2.97 (1.00–4.60)	3.12 (2.98–4.44)	3.16 (3.06–6.35)
Calcium (mmol/l)	LP	2.46 ± 0.17	2.38 ± 0.18	2.36 ± 0.17*	2.30 ± 0.16*
	sLP	2.46 ± 0.28	2.54 ± 0.24#	2.40 ± 0.15##	2.46 ± 0.28
	HP	2.33 ± 0.18	2.36 ± 0.16	2.27 ± 0.15*	2.35 ± 0.26
Phosphorus (mmol/l)	LP	1.46 ± 0.35	1.59 ± 0.44	1.70 ± 0.38*	1.54 ± 0.30
	sLP	1.48 ± 0.36	1.42 ± 0.23	1.42 ± 0.26	1.49 ± 0.21
	HP	1.28 ± 0.32	1.59 ± 0.39*	1.61 ± 0.41*	1.71 ± 0.50*
iPTH (pg/ml)	LP	133.5 (76.7–406.2)	215.5 (117.2–275.0)	219.5 (106.6–305.0)	232.0 (100.5–284.2)
	sLP	149.0 (36.7–411.0)	125.0 (34.8–229.5)	67.3 (36.4–207.5)##	64.4 (35.6–234.2)##
	HP	203.5 (115.5–609.6)	197.5 (84.8–324.5)	256.0 (70.8–472.8)	215.0 (131.8–444.2)

SGA, subjective global assessment of nutrition; BMI, body mass index; MAP, mean artery pressure; iPTH, intact parathyroid hormone.
[a]Percentage with malnutrition.
*$P < 0.05$, compared with 0 month, #$P < 0.05$, compared with the other two groups, ##$P < 0.05$, compared with group HP.

Jiang et al. NDT 2009;24:2551-2558

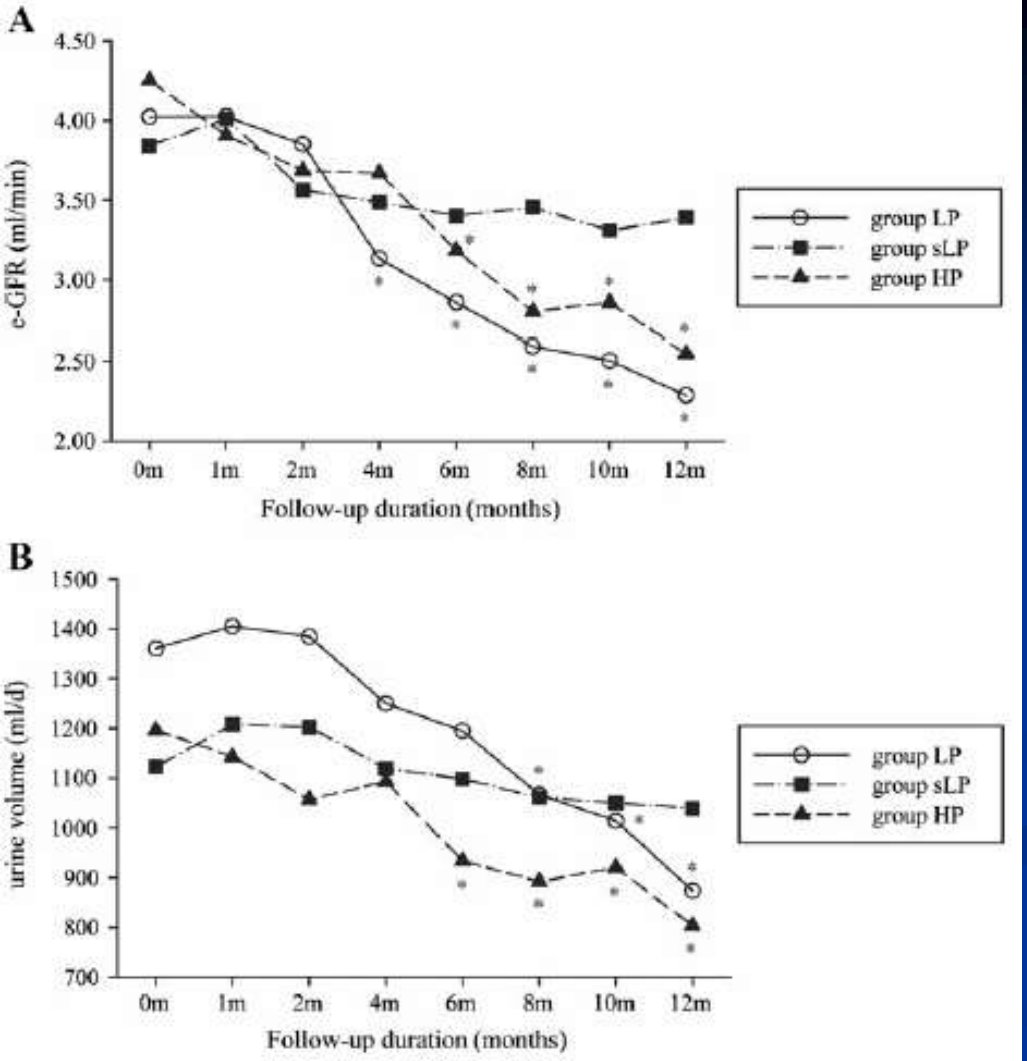
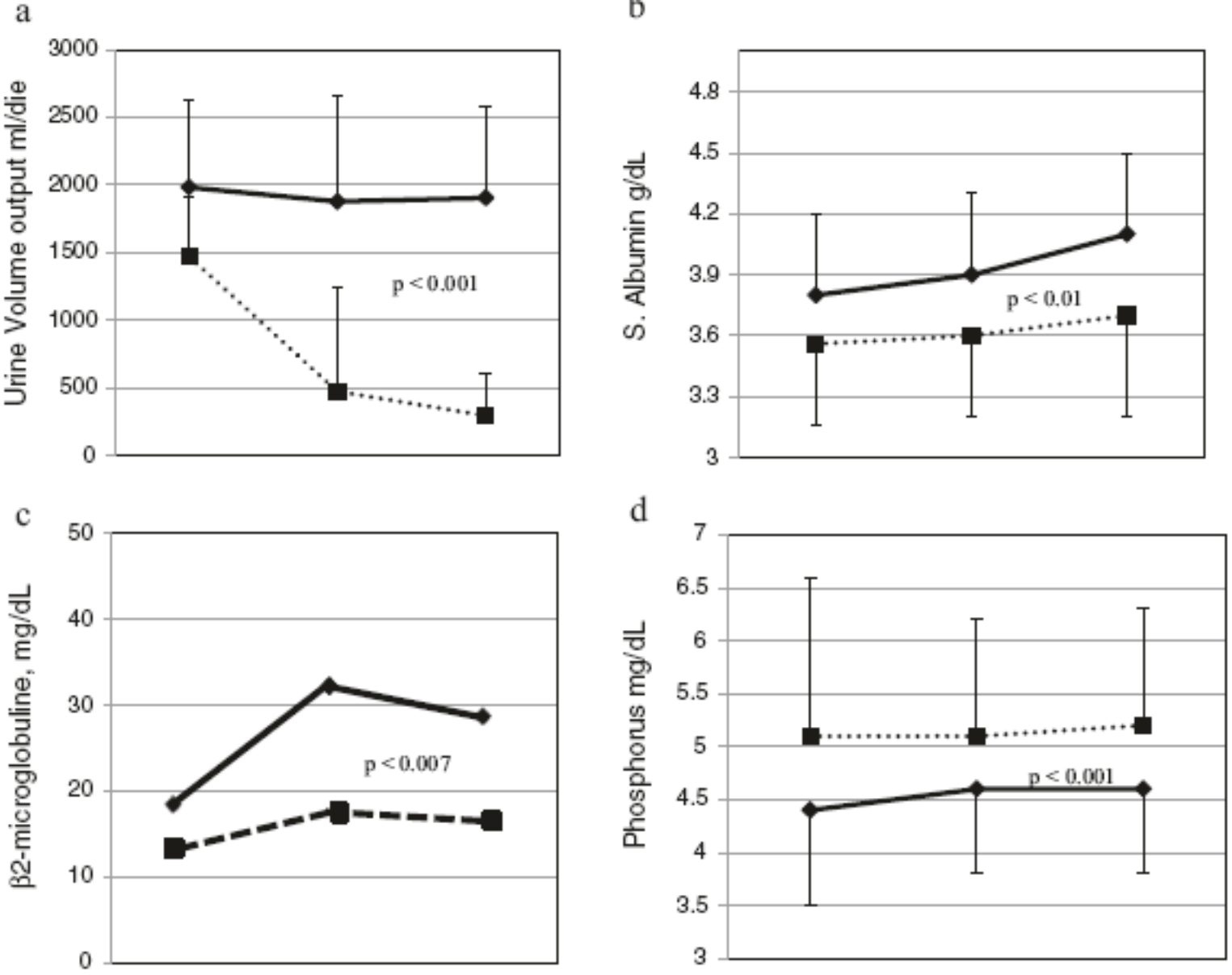


Fig. 5. Changes of renal function during the 12 months of the study in the three groups, LP (0.6–0.8 g/kg/day), sLP (0.6–0.8 g/kg/day + tx) and HP (1.0–1.2 g/kg/day). Panel **A** shows eGFR (estimated glomerular filtration rate, calculated as an average of the creatinine and urea clearances by 24-h urine). Panel **B** shows daily urine volume. Using repeated measures ANOVA, there was significant time effect for group LP and HP ($P < 0.01$ for both eGFR and urine volume), but no significant group effect ($P > 0.05$ for both eGFR and urine volume). $^*P < 0.05$, compared with 0 month.

Caria et al. BMC Nephrology 2014:15:172



Values at Baseline, 6 mos and 12 Mos in 34 CKD Patients Treated with Diet (0.6 g protein/kg/day)and HD 1x/wk or HD 3x/wk (29 patients, Broken Lines). GFR at onset: 5-10 mL/min.

n Value	LPD & 1HD /Wk MHD 3x/ Wk 38 Base-line	38 6 Mos	34 12 Mos	30 Base-line	30 6 Mos	29 12 Mos	ANOVA P*
BMI, kg/m2	65	63.9	63.4	66.2	64.9	65.5	0.07
SUN, mg/dL	68	68	70	84.4	77	77	0.003
GFR, mL/min	7.8	6.7	6.3[1]	9.2	_____	_____	_____
Serum K mmol/L	4.4	4.3	4.3	4.3	4.7	4.8[3]	0.07
EPO Resis-tance Index	10	6	5[3]	19	15	19	<0.001

Diet (0.6 g prot/kg/day) and HD1x/Wk

1. This was not a randomized study.
2. It is likely that the LPD and infrequent HD patients were more motivated, more compliant, and possibly more sophisticated.
3. Nonetheless, these findings support the thesis that motivated stage 5 CKD patients who comply with an 0.6 g protein/ kg/day diet may do well for ≥12 months with 1x/week HD.

Caria et al. BMC Nephrology 2014:15:172

Low Protein Diets and Infrequent or No Dialysis

1. Other studies support the possibility to delay or even, presumably temporarily, discontinue chronic dialysis in patients with advanced CKD (Piccoli et al. Hemodialysis Int. 2014;18:590-595).

2. In all such cases, patients had substantial residual renal function (GFR ≥~ 5 mL/min), urine output ≥500 -1000 mL/day, and were adherent to LPDs (~0.6 g protein/kg/day with about 50 % HBV protein or ~0.3-0.4 g protein/kg/day supplemented with ketoacids and EAAS).

Per Protocol Analyses: Brunori et al. AJKD 2007; 49: 569-580

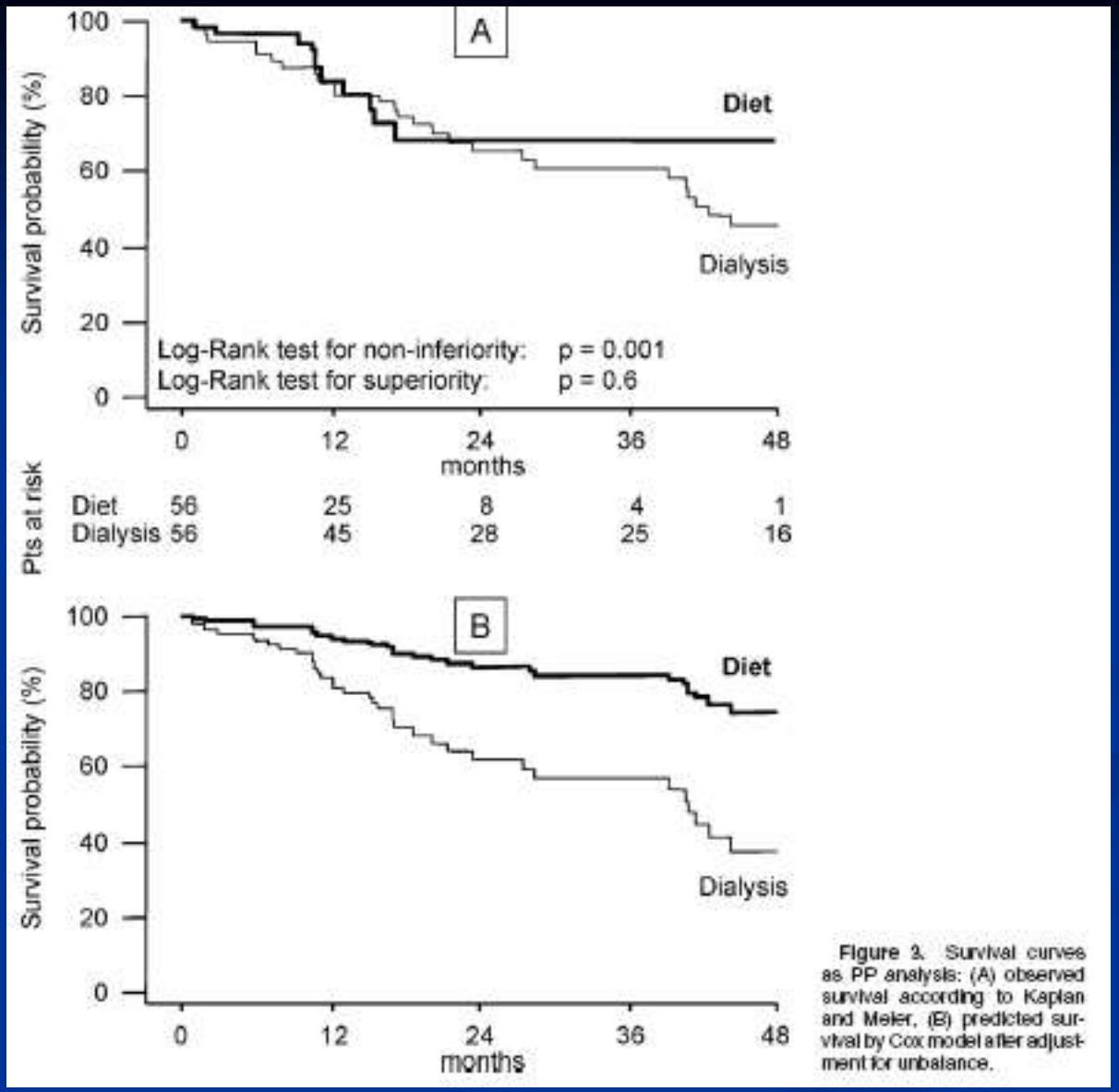


Figure 3. Survival curves as PP analysis: (A) observed survival according to Kaplan and Meier, (B) predicted survival by Cox model after adjustment for unbalance.

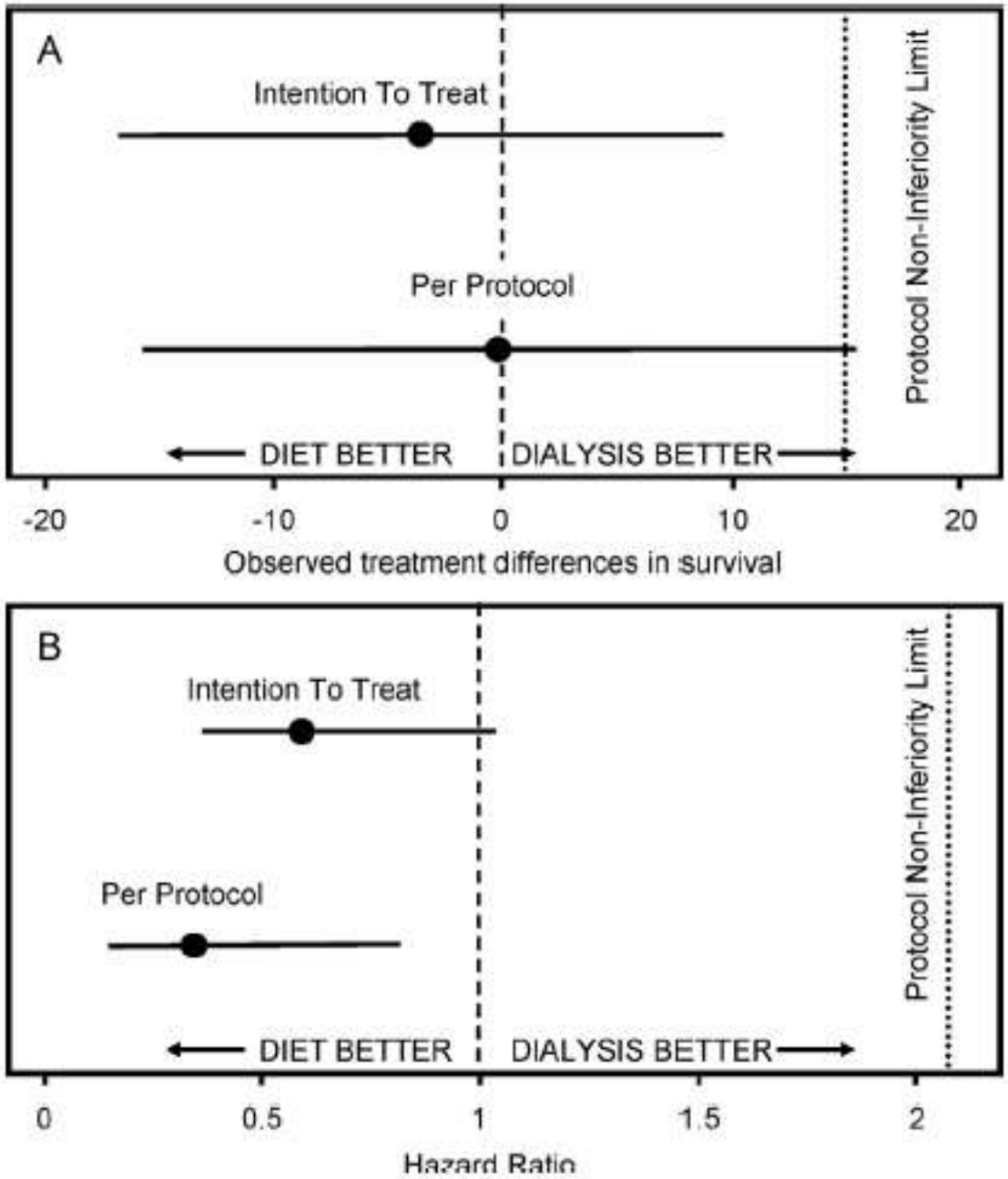


Figure 4. (A) Observed treatment differences in survival (percent survival) in PP and ITT analyses (2-sided 95% CI) and (B) HRs for survival at PP and ITT analyses after adjustment for unbalance (2-sided 95% CI).

Brunori et al. AJKD 2007;49:569-580

LPDs Allow Time for Vascular Access or PD Catheter to be Placed and Mature

1. 21 patients; 9 M/12F; 10 diabetics; 59.2 yrs
2. Prescribed 0. 3 g prot./kg/day plus KA/EAA

	Initial Value	Day 15	Day 30	P
Creatinine Cl ml/min/1.73m²	12.1 ±SD3.9	12.0 ±3.5	12.0 ±3.6	0.99
SUN[1], mg/dl	81.7 ±22.5	57.6 ±14.9	50.9 ±12.0	<0.001
Serum P[2], mg/dl	4.7 ±0.6	4.2 ±0.8	3.9 ±1.0	0.007
S. Albumin, g/dl	3.9±0.4	3.9±0.3	3.9±0.3	0.86

[1]P<0.001 Day 15 vs. Day 0; P=0.043 Day 30 vs Day15

[2]P=0.008 Day 15 vs. Day 0.

Duenas et al. Clinical Nephrol. 2013;79: 387-93

What Proportion of CKD Patients Will Adhere to a LPD/SVLPD

- Michel Aparicio (Bordeaux, France): About 15%
- Joel Kopple (Brentwood, California): About 15%
- Lilliana Garneata About 14% (Bucharest, Romania) J Renal Nutrit 2013
- Possibly Higher Proportion if Chronic Dialysis Treatment is imminent

Possible Anti-inflammatory Effects of KA/EAAs with CPD

1.100 CPD patients prescribed 0.8-1.2 g protein/kg/day diets were randomized to receive KA/EAAs 12 tablets/day or no KAA/EAAs.

2. After 6 months, serum hs-CRP rose and the leptin/adiponectin ratio fell in controls, whereas these values remained stable in the KA/EAA group (Between group comparisons: $p=0.02$ and $p<0.001$, respectively) . There was no change in HOMA-IR within or between groups.

Dong et al. Perit Dialy Int Sept 15, 2015(in press)

Summary and Conclusions

1.Data indicate that LPDs and KA/EAA supplemented VLPDs may retard CKD progression .

2. Evidence clearly indicates these diets may delay the need for chronic dialysis therapy or for standard dialysis treatment.

3. More data are needed to determine the GFR at which LPDs and sVLPDs are no longer safe and what proportion of patients will adhere to these diets.

End