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Supplemented low-protein diets — are they superior in chronic renal failure?

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Twenty-two patients with chronic renal failure were randomly assigned to a conventional low-protein diet containing 0,6 g protein/kg/day or a very-low-protein diet containing 0,4 g protein/kg/day supplemented with essential amino acids; they were followed up for 9 months. There were no significant changes in body mass index, arm muscle area, percentage body fat, serum albumin and transferrin levels in any of the groups; neither was there any difference between the groups in respect of these parameters. Renal function, as measured by the reciprocal of serum creatinine over time, stabilised in both groups during intervention, with no significant difference between the groups. There was however no correlation between changes in renal function and changes in blood pressure, or dietary intake of protein, phosphorus, cholesterol, polyunsaturated and saturated fatty acids. There were also no significant changes and no significant differences between the groups in serum levels of parathyroid hormone and alkaline phosphatase, urine cyclic adenosine monophosphate, tubular reabsorption of phosphate, and the theoretical renal threshold for phosphate.

The results of this study suggest that the supplemented very-low-protein diet was not superior to the conventional low-protein diet in terms of its effect on protein-energy status, renal function and biochemical parameters of renal osteodystrophy.

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Research has shown substantial support for the thesis that dietary intervention slows the progression of chronic renal failure.[1-3] Although renal function in earlier studies was based on changes in serum creatinine (S_{cr}), the protective effect of a low-protein (LP) diet was confirmed by Ihle *et al.*[4] who used

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both $1/S_{cr}$ and ^{51}Cr-EDTA clearance as measures of this effect. It is not clear whether amino acid supplementation of a very-low-protein (VLP) diet is superior to the conventional LP diet. Di Landro *et al.*[5] reported that a VLP diet plus essential amino acids (EAAs) or keto acids can delay the rate of progression compared with the conventional LP diet, but this effect may have been due to a lower phosphorus intake, rather than a lower protein intake. Unfortunately phosphorus intake was not reported, but serum phosphate levels were significantly lower after treatment with the VLP diet. Barsotti *et al.*[6] also found a significant slowing in the decline of creatinine clearance on a VLP diet supplemented with EAAs or keto acids. The supplemented VLP diet was, however, compared with a diet high in protein and phosphorus. Therefore, the protective effect may have been the result of protein and/or phosphorus restrictions, and not EAAs or keto acids *per se*.

In practice there is very little difference between the total protein intake on the conventional LP diet and a VLP diet supplemented with EAAs; the main difference is the amino acid composition and the types of food included in the diet. Given the high cost of EAA supplements, the question arises as to whether EAA supplementation of the VLP diet in fact offers an advantage over the conventional LP diet. Kopple[7] argues that EAA supplementation offers potential advantages in the lowering of phosphate and potassium levels and normalisation of altered plasma and muscle amino acid profiles, but that the value of these changes have not been proven.

This study investigated the effect of the conventional LP diet and a VLP diet supplemented with EAAs in respect of the progression of chronic renal failure, nutritional status, and biochemical evidence of renal osteodystrophy over a period of 9 months.

Subjects and methods

Patients

The study protocol was approved by the Ethical Advisory Committee of the Faculty of Medicine, University of Stellenbosch. All predialysis outpatients at Tygerberg Hospital between 18 and 65 years of age were screened according to the following criteria: a history of confirmed chronic renal failure for at least 6 months; S_{cr} level 150 - 700 µmol/l; no evidence of diabetes mellitus, liver disease, alcoholism, underlying malignancy or psychiatric disorders; no prescription for corticosteroids, cyclophosphamide, angiotensin-converting enzyme inhibitors, calcium entry blockers or other bone toxic drugs. The 22 patients who qualified and gave informed consent were enrolled in the dietary training period of the study, during which time they maintained their usual diet. To ensure that all patients received the same standard of counselling, they all participated in the same educational programme as developed and tested by Herselman *et al.*[8] Each patient was supplied with food scales for the weighing of food, and was visited at home to optimise education. Following the training period of 8 weeks, patients were matched for underlying nephropathy, S_{cr}, creatinine clearance, known duration of disease, age, sex and dietary knowledge, and were then randomly assigned to either the LP diet or a VLP diet supplemented with EAAs. The normal treatment regimen of each patient was adhered to, and frequency of medical check-ups was not altered. The LP and VLP groups were similar at entry (Table I).

Table I. Patient characteristics at entry (mean (SD))

Group	Case	Diagnosis	Sex	Age (yrs)	Duration of CRF (mo.)	S_{cr} (µmol/l)	C_{cr} (ml/min/1,73m^2)	Slope of $1/S_{cr}$ x10^3	U_{prot} (g/d)	Dietary knowledge (%)
VLP	1	IgA	M	34	24	345	18	−4,43	00,9	81
(*N* = 11)	2	PCK	F	46	300	433	14	2,66	00,2	100
	3	IN	M	59	120	186	50	−0,83	00,1	92
	4	MCGN	F	26	48	230	31	−13,28	01,1	100
	5	MCGN	F	38	96	345	17	−7,08	00,0	53
	6	MGN	M	58	84	168	38	0,00	01,6	81
	7	ICGN	M	33	12	230	24	−0,89	03,3	64
	8	MCGN	M	36	60	318	34	−26,55	22,4	97
	9	IN	M	51	60	327	28	−3,54	00,3	94
	21	PGN	F	25	36	186	—	−5,31	—	36
	22	Unknown	M	61	12	389	17	−1,77	03,6	89
			7M 4F	42	77	287	27	−5,31	03,4	79
				(13)	(81)	(91)	(11)	(7,97)	(6,8)	(21)
LP	10	GN	M	21	24	230	52	15,93	01,5	89
(*N* = 11)	11	IN	F	42	18	141	56	0,00	00,2	94
	12	PCK	F	28	216	663	09	−4,43	00,4	64
	13	MGN	M	23	12	522	09	−97,35	12,6	81
	14	CN	M	59	24	239	38	−12,39	00,4	86
	15	CN	F	45	60	415	13	−6,20	00,2	80
	16	IN	F	56	36	194	44	−0,89	03,0	97
	17	MGN	M	65	24	469	17	−42,48	02,9	92
	18	IN	F	50	192	212	33	−0,89	00,0	100
	19	PCK	F	52	72	177	25	−7,08	00,0	86
	20	FSGN	M	35	36	221	30	−22,13	04,0	17
			5M 6F	43	65	317	30	−15,93	02,3	81
				(15)	(71)	(171)	(17)	(31,00)	(3,7)	(25)
P value*					0,9738	0,5302	0,9476	0,4904	0,8599	0,7905

*Comparison of the groups at entry (Wilcoxon 2-sample test).
IgA = immunoglobin A nephropathy; GN = glomerulonephritis; IN = interstitial nephropathy; PCK = polycystic kidneys; MGN = membraneous GN; CN = cortical necrosis; UTI = urinary tract infection; FSGN = focal segmental GN; MCGN = mesangiocapillary GN; ICGN = immune complex GN; PGN = proliferative GN.

Diet and medication

The LP and VLP diets are described in Table II. All patients received daily supplementation in the form of the water-soluble vitamins and glucose polymers. Calcium carbonate was prescribed in order to attain the recommended calcium intake. Aluminium hydroxide was used in only 3 patients with severe hyperphosphataemia (1 patient on the VLP diet and 2 patients on the LP diet). Dietary intake before and during the study was assessed by an experienced renal dietitian by means of a quantitative food frequency questionnaire (QFFQ), validated against urea nitrogen appearance[9,10] for protein intake.

Table II. Description of the LP and VLP dietary regimens, with intake before and during intervention as measured by the QFFQ, (mean (SD))

Nutrient	Group	Recommended intake	Intake before study	Intake during study	*P*-value
Energy*	LP	150† (35)	133 (47)	125 (34)	0,4772
(kJ/kg/d)	VLP	150† (35)	132 (51)	116 (34)	0,2664
Protein‡	LP	0,60	1,04 (0,41)	0,73 (0,25)	0,0244¶
(g/kg/d)		(70% HBV)			
	VLP	0,54 (0,40 g/kg, mixed quality, plus 0,14 g EAA§/kg)	0,98 (0,32)	0,63 (0,17)	0,0059¶
Calcium*	LP	500 - 750	930 (742)	808 (212)	0,6835
(mg/d)	VLP	500 - 750	871 (366)	730 (96)	0,3066
(mg/kg/d)	LP	—	14 (9)	13 (5)	
	VLP	—	11 (4)	9 (2)	
Phosphorus	LP	< 800	1135 (510)	741 (208)	0,0330¶
(mg/d)	VLP	< 800	1218 (453)	696 (262)	0,0039¶
(mg/kg/d)	LP	—	17 (7)	11 (4)	
	VLP	—	15 (5)	9 (3)	
Total fat	LP	—	89 (41)	62 (30)	0,0300¶
(g/d)	VLP	—	99 (45)	54 (19)	0,0039¶
PUFA	LP	—	15 (6)	13 (5)	0,1596
(g/d)	VLP	—	25 (8)	15 (6)	0,0059¶
SFA	LP	—	30 (17)	19 (9)	0,0378¶
(g/d)	VLP	—	38 (14)	18 (5)	0,0058¶
PUFA/SFA	LP	—	0,63 (0,27)	0,78 (0,17)	0,0905
Ratio	VLP	—	0,69 (0,17)	0,86 (0,41)	0,3032
CHOL	LP	—	303 (226)	136 (69)	0,0440¶
(mg/d)	VLP	—	327 (133)	148 (76)	0,0022¶

* Total intake from diet and supplements.
† All patients except for the obese received energy supplements in the form of Caloreen, supplied by Roussel Laboratories.
‡ Corrected for U_{prot}: for every gram U_{prot}, 1,2 g dietary protein was added.
¶ Significant lower intakes during intervention (Wilcoxon sign rank test).
§ Supplied by Kabi Vitrum AB.
HBV = high biological value; PUFA = polyunsaturated fatty acids; SFA = saturated fatty acids; CHOL = cholesterol.

Anthropometric findings

Body weight and arm muscle area were assessed at 3-monthly intervals by the same investigator according to internationally standardised methods.[11]

Biochemical parameters

Blood samples were obtained by venepuncture after a 12-hour fast and the following parameters were analysed: S_{cr} levels, total calcium, ionised calcium, phosphate, magnesium, alkaline phosphatase, C-terminal parathyroid hormone and albumin. All these were measured with a Technikon SMAC II Autoanalyzer, except for ionised calcium which was measured with the Nova 2 Analyzer, and parathyroid hormone by means of radio-immunoassay.[12] Serum levels of calcium were corrected for albumin.[13] Twenty-four-hour urine samples were collected every 3 months for assessment of proteinuria, which was determined turbidimetrically,[14] as well as creatinine clearance, urinary urea, phosphate and creatinine levels, all of which were measured with a Beckman Astra 8. Tubular reabsorption of phosphate and the theoretical renal threshold for phosphate were calculated from the data according to the formulae of Agus,[15] and Walton and Bijvoet,[16] respectively. Urinary creatinine was expressed as a function of body weight to assess completeness of 24-hour urine samples. The urinary urea level was used to determine dietary protein intake from urea nitrogen appearance[9] and to serve as an independent check on the QFFQ. Urinary calcium levels were measured with the Technikon SMAC II Autoanalyzer and expressed in µmol/100 ml glomerular filtrate. Cyclic adenosine monophosphate levels were determined from a hydrated random urine sample using Amersham's RIA kit, and expressed in nmol/100 ml glomerular filtrate.

Statistical analyses

Spearman's correlation coefficient was used on the combined data of the two groups to examine the correlations between variables. The Wilcoxon 2-sample test was used for comparisons between groups, while the Wilcoxon sign rank test and the Friedman test were used to test for significant differences between baseline and intervention data. Progression of chronic renal failure was assessed from changes in creatinine clearance and by plotting of $1/S_{cr}$ against time. Retrospective results for S_{cr} and blood pressure were obtained from medical files for a mean period of 21 months to assess changes in renal function and blood pressure. The repeated median procedure was used for regression analysis for $1/S_{cr}$ over time.[17]

Results

Renal function

Renal function, as measured by $1/S_{cr}$, deteriorated significantly in both groups before entry, and then stabilised during the study (Table III). There was no difference between the groups with regard to the rate of progression before (P = 0,4904) or during (P = 1,0000) the study. Creatinine clearance also remained stable during intervention (Table IV). No correlations were found between changes in $1/S_{cr}$ against time and changes in systolic/diastolic blood pressure (r = –0,2033/–0,1022; P = 0,3767/0,6594), and changes in dietary intake of protein (r = 0,0481; P = 0,8403), phosphorus (r = 0,3265; P = 0,1486), cholesterol (r = –0,1714; P = 0,4575), polyunsaturated fatty acids (r = 0,1743; P = 0,4623) and saturated fatty acids (r = –0,1936; P = 0,4003).

Table III. Changes in the slope of $1/S_{cr}$ and mean blood pressure before and during intervention (mean (SD))

Group	Slope of $1/S_{cr}$ ($\mu mol/l^{-1} \times 10^3$)		Mean BP (mmHg)	
	Before	During	Before	During
LP (N = 11)	–0,18 (0,35)	–0,05 (0,10)	140/87 (17/9)	144/89 (23/12)
P-value	0,0415*	0,2131†	0,1878/0,2034‡	
VLP (N = 11)	–0,06 (0,09)	–0,01 (0,12)	149/92 (18/9)	150/96 (14/8)
P-value	0,0191*	0,4755†	0,4471/0,1699‡	
LP+VLP (N = 22)	–0,12 (0,26)	–0,02 (0,11)	145/90 (18/9)	147/92 (18/10)
P-value	0,0021*	0,1474†	0,7779/0,1699‡	

* Significant deterioration before intervention.
† Stabilisation during intervention.
‡ No change in mean systolic/diastolic BP (Wilcoxon sign rank test).

Table IV. Changes in anthropometric and biochemical parameters at baseline and following intervention (mean (SD))

Parameter	LP diet		VLP diet	
	Baseline	9 months	Baseline	9 months
Anthropometry				
BMI (kg/m^2)	24 (5)	24 (5)	25 (4)	25 (4)
AMA (cm^2)	49 (14)	50 (14)	51 (12)	53 (13)
Body fat (%)	26 (11)	27 (12)	31 (7)	32 (7)
Blood				
S_{alb} (g/l)	39 (9)	43 (5)	39 (9)	41 (5)
S_{Trans} (g/l)	3,3 (0,9)	3,3 (0,6)	3,0 (1,1)	3,2 (0,8)
S_{cPTH} (pmol/l)	127 (150)	139 (143)	105 (46)	122 (75)
S_{ALP} (U/l)	131 (85)	123 (90)	105 (36)	101 (31)
S_P (mmol/l)	1,4 (0,6)	1,2 (0,5)	1,3 (0,3)	1,3 (0,2)
S_{Ca} (mmol/l)	2,3 (0,1)	2,3 (0,2)	2,3 (0,2)	2,3 (0,2)
S_{Ca++} (mmol/l)	1,2 (0,1)	1,2 (0,1)	1,2 (0,1)	1,2 (0,1)
S_{mg} (mmol/l)	0,8 (0,1)	0,8 (0,2)	0,8 (0,1)	0,8 (0,0)
Urine				
C_{cr} (ml/min/1,73 m^2)	30 (17)	32 (14)	27 (11)	28 (15)
U_{prot} (g/d)	2,3 (3,7)	0,7 (0,8)	3,4 (6,8)	2,2 (3,0)
U_{cr} (mmol/kg)	0,2 (0,1)	0,2 (0,0)	0,2 (0,0)	0,2 (0,1)
$U_{c\text{-}AMP}$ (nmol/100 ml GF)	5,9 (3,7)	5,4 (7,6)	4,5 (2,3)	5,5 (4,6)
U_{Ca} (µmol/100 ml GF)	8,6 (7,9)	5,8 (6,6)	3,5 (3,1)	3,9 (2,6)
TRP (%)	59 (18)	57 (12)	54 (16)	60 (13)
TmP/GFR	0,7 (0,2)	0,7 (0,2)	0,7 (0,2)	0,7 (0,2)

No significant changes.
BMI = Body mass index; AMA = arm muscle area; S_{alb} = serum albumin; S_{Trans} = serum transferrin; S_{cPTH} = serum parathyroid hormone; S_{ALP} = serum alkaline phosphatase; S_p = serum phosphate; S_{Ca} = serum total calcium; S_{Ca++} = serum ionised calcium; S_{mg} = serum magnesium; C_{cr} = creatinine clearance; U_{prot} = urinary protein; U_{cr} = urinary creatinine; $U_{c\text{-}AMP}$ = urinary cyclic adenosine monophosphate; GF = glomerular filtrate; TRP = tubular reabsorption of phosphate; TmP/GFR = theoretical renal threshold of phosphate.

Diet and anthropometric findings

There were significant reductions in the intakes of protein, phosphorus and dietary fats during intervention in both groups, but there were no differences between the groups in respect of these nutrients (Table II). There were also no significant differences between the groups in respect of serum protein levels and anthropometric readings (Table IV). Changes in protein intake were inversely correlated with changes in serum albumin levels (r = –0,49; P = 0,029), but not proteinuria (r = 0,1522; P = 0,5219).

Biochemical parameters of renal osteodystrophy

There were no significant changes in biochemical parameters of renal osteodystrophy and no difference between the groups (Table IV). The most marked abnormalities included increased serum levels of parathyroid hormone and alkaline phosphatase, increased urinary cyclic adenosine monophosphate, and decreased tubular reabsorption of phosphate and theoretical renal threshold for phosphate.

Discussion

In this study, on both diets the rates of deterioration of renal function were apparently slowed, indicating that some factors other than EAAs were primarily involved. Among the mechanisms previously suggested to explain a protective effect of a LP diet on renal function is the concept of hyperfiltration,[18] as well as the effect of protein intake on urine concentration[19] and the charge-selective properties of the glomerular basement membrane.[20] In addition to dietary protein, both dietary phosphorus[21] and fats[22] have been incriminated in the progression of renal disease. However, the lack of correlation between changes in renal function and dietary intake of protein, phosphorus, cholesterol and dietary fats in this study suggests that the stabilisation of $1/S_{cr}$ may have been a consequence of non-dietary factors. The change in $1/S_{cr}$ cannot be explained by a change in mean blood pressure either. It is, however, possible that better control of blood pressure may have played a role in individual patients. Bergstrom *et al.*[23] have shown that slowing of disease progression was at least partly due to better control of blood pressure — with a significant correlation between changes in mean blood pressure and the slope of creatinine clearance. The findings of our study therefore question the beneficial role of dietary treatment on renal function.

Protein and energy intakes were apparently sufficient to maintain protein and energy reserves in both groups over a period of 9 months. Vujic D'Djukanovic[24] also found that nutritional status was well preserved in patients treated with a LP diet and a VLP diet supplemented with EAAs, with no difference between the groups, and Guarnieri *et al.*[25] and Rosman *et al.*[26] reported that anthropometric values remained stable after more than 4 years of treatment with LP diets. Although the energy requirement for nitrogen balance may be somewhat higher, the level of energy required for prevention of weight loss on LP diets was found to be approximately 122 kJ/kg/d.[25,27] There was no significant difference in the energy intake between the LP and VLP groups in our study, but it was more difficult to reach the energy recommendations on the VLP diet — with the result that mean energy intake in this group was only 116 kJ/kg/d compared with the 125 kJ/kg/d on the LP diet. In the long term, VLP diets supplemented with EAAs may therefore suffer from energy deficiency, and have an adverse effect on protein metabolism and nitrogen balance, unless a practical method can be found to increase energy intake further. The negative correlation between changes in dietary protein and serum albumin levels found in this study supports the observations of Kaysen *et al.*[28] that LP diets are associated with a reduction in proteinuria and an increase in serum albumin. No association could, however, be demonstrated between changes in protein intake and urinary protein in our study. It is possible that urinary protein undergoes more acute changes in response to protein intake than could be detected by 3-monthly investigations of proteinuria and the assessment of mean protein intake over 9 months.

Renal osteodystrophy is a frequent complication of chronic renal failure, usually comprising hypocalcaemic secondary hyperparathyroidism and/or impaired skeletal mineralisation.[29] As in the case of nutritional status and renal function, there was no change in biochemical parameters of renal osteodystrophy and no difference between the groups in this regard. Although VLP diets supplemented with EAAs have the potential advantage of a lower intake of phosphorus and hence a beneficial effect on renal bone disease, in this study the intake was not significantly lower than on the conventional LP diet.

In conclusion, this study failed to prove a VLP diet supplemented with EAAs superior to the conventional LP diet over a period of 9 months. Furthermore, although nutritional status was preserved on both diets, a contributory role of dietary intervention in the stabilisation of renal function could not be confirmed. Interpretation of results must, however, take due cognisance of the limitations of the small sample size and the use of S_{cr} and creatinine clearance[30] as sole markers of renal function.

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Expenditure on health research in South Africa, 1991/1992

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Objective. To determine expenditure on health research in South Africa in 1991/1992.

Design. Data from the financial statements of large statutory councils conducting research in South Africa, as well as other relevant reports, particularly the Department of National Education's (NATED) survey of research institutions, were analysed.

Results. A total of R198,7 million was spent on health research in 1991/1992, 56,1% by the tertiary education sector and 20,7% by the Medical Research Council. Only 1,1% of expenditure on health was spent on research. Less than 9% of health research expenditure by tertiary educational institutions is classified within the category of 'comprehensive medicine' (which includes community health, epidemiology and nutrition), whereas 82% of expenditure by autonomous government institutions is so classified.

Conclusions. Given that expenditure on health research in South Africa is relatively low by international standards, an increase in expenditure by both the public and private sectors should be considered. Given the scarcity of research resources, there should be adequate planning, co-ordination, and particularly prioritisation of resource allocations, so that research can be directed towards addressing the country's health needs.

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