

Original Article

Use of a renal-specific oral supplement by haemodialysis patients with low protein intake does not increase the need for phosphate binders and may prevent a decline in nutritional status and quality of life

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Abstract

Background. Protein-energy wasting is a frequent and debilitating condition in maintenance dialysis. We randomly tested if an energy-dense, phosphate-restricted, renal-specific oral supplement could maintain adequate nutritional intake and prevent malnutrition in maintenance haemodialysis patients with insufficient intake.

Methods. Eighty-six patients were assigned to a standard care (CTRL) group or were prescribed two 125-ml packs of Renilon 7.5[®] daily for 3 months (SUPP). Dietary intake, serum (S) albumin, prealbumin, protein nitrogen appearance (nPNA), C-reactive protein, subjective global assessment (SGA) and quality of life (QOL) were recorded at baseline and after 3 months.

Results. While *intention to treat analysis* (ITT) did not reveal strong statistically significant changes in dietary intake between groups, *per protocol* (PP) analysis showed that the SUPP group increased protein ($P < 0.01$) and energy ($P < 0.01$) intakes. In contrast, protein and energy intakes further deteriorated in the CTRL group (PP). Although there was no difference in serum albumin and prealbumin changes between groups, in the total population serum albumin and prealbumin changes were positively associated with the increment in protein intake ($r = 0.29$, $P = 0.01$ and $r = 0.27$, $P = 0.02$, respectively). The SUPP group did not increase phosphate intake, phosphataemia remained unaffected, and the use of phosphate binders remained stable or decreased. The SUPP group exhibited improved SGA and QOL ($P < 0.05$).

Conclusion. This study shows that providing maintenance haemodialysis patients with insufficient intake with a renal-

specific oral supplement may prevent deterioration in nutritional indices and QOL without increasing the need for phosphate binders.

Keywords: albumin; compliance; haemodialysis; malnutrition; oral supplement

Introduction

A significant number of individuals with chronic renal failure, particularly those on maintenance haemodialysis (MHD), have a poor nutritional status [1–6] and the impact of this on patient health has been extensively documented [7–10]. Several studies have linked biochemical and clinical indicators of poor nutritional status to an increased risk of morbidity and mortality in MHD patients [11–14]. In particular, low measurements of serum albumin [12,13,15–17], normalized protein nitrogen appearance (nPNA) [15,18], body mass index (BMI) [12,16], subjective global assessment (SGA) [16], serum prealbumin [19,20], serum creatinine [16,20], low protein [15] and low energy intake [7] have been reported to correlate with an increased risk of mortality. Low serum albumin levels and reduced nPNA have also been associated with increased time of hospitalization, indicating immediate effects of poor nutritional status on patient health [15,18,21,22].

Chronic malnutrition associated with maintenance haemodialysis is primarily characterized by protein and energy wasting. Several investigators have shown that MHD patients consume less energy and protein than recommended [23,24]. Dietary restrictions can also make the diet relatively unpalatable and attainment of adequate protein intake quite challenging. In response to the evidence

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indicating the importance of maintaining nutritional status, guidelines provide recommendations for the intakes of energy, protein and phosphate during maintenance dialysis [25–27]. However, the impact of disease and the haemodialytic therapy make attainment of recommended intakes difficult [2].

Evidence indicating the potential value of nutritional supplementation in preventing malnutrition and improving quality of life in MHD patients is limited and inconsistent. While a recent systematic review showed that supplemental nutrition improves nutritional intake and serum albumin [28], insufficient data are available to determine the effect of this on clinical outcomes. The only randomized controlled trial comparing oral nutritional supplementation versus routine care that could be included in the meta-analysis provided supplemental nutrition to malnourished patients for just 1 month [29].

The aim of this multicentre, randomized, open-label controlled trial was to study the effect of an energy-dense renal-specific oral nutritional supplement (Renilon 7.5[®], N.V. Nutricia, Zoetermeer, The Netherlands), on nutritional intake and status in haemodialysis patients over a 3-month period. Renilon 7.5 has been developed in line with current official European and American guidelines for dialysis patients [26,27]. It provides supplemental energy, protein and vitamins to match the specific requirements of patients undergoing dialysis: low in vitamin C, vitamin A, vitamin D, phosphate and potassium to avoid excess intakes and compromise mineral status. The protein source used is a demineralized whey, which contains very low minerals. In order to optimize compliance and limit fluid intake, the supplement that provides 2 kcal/mL is packaged into 125 mL tetra packs. The supplement is available in two different flavours (caramel and apricot) and has previously been shown to be accepted by patients [30]. This study was designed to test the hypothesis that daily supplementation with a specific oral supplement could prevent or reduce deterioration of nutritional status of mildly malnourished MHD patients. The primary parameter for this trial was the nutritional status. An improved nutritional status was defined as a significant change from baseline after 3 months of supplementation in any of the following parameters: nPNA, serum albumin, pre-albumin, dry body weight and/or serum creatinine. The effect of the nutritional supplement was compared to standard care, which in most cases does not include nutritional support.

Methods

Patients

Mildly malnourished MHD patients at screening were selected for inclusion in the study. A total of 88 patients were recruited for the study from the 45 dialysis centres belonging to the ‘Groupe de Recherche en Nutrition et Hémodialyse’ [1]. These patients were selected from a total of 2398 subjects, aged >18 years and on MHD for at least 3 months. Mildly malnourished patients (defined as both serum albumin <40 g/L and BMI <30 kg/m²) were selected for inclusion if they had a low protein intake, indicated by an nPNA <1.0 g/kg/day, as this was considered a high risk for developing malnutrition. Patients with a C-reactive protein (CrP) level >20 mg/L at inclusion were excluded. Other exclusion criteria were as follows: nutritional supplementation within the last 2 months or the requirement for complete enteral nutrition, inadequate dialysis (Kt/V <1.2), peritoneal dialysis in the past 3 months or the use of any investigational drug. Baseline characteristics of the patient population are described in Table 1. The study protocol was approved by relevant ethics review committees in each of the countries involved (‘Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale de Lyon A’, France; ‘Ethikkommission, Ärztekammer Sachsen-Anhalt’, Germany; ‘Commission d’Éthique de la Recherche Clinique’, Lausanne, Switzerland) and the study was conducted in accordance with the ‘Declaration of Helsinki’. Informed and signed consent was obtained from all study participants.

Study design

The study was a randomized, open-label controlled trial in which the efficacy of an oral renal-specific nutritional supplement was compared with standard care. Patients were recruited from 18 centres in France, Germany and Switzerland, and were stratified according to the study centre and the presence of diabetes mellitus. Having fulfilled the recruitment criteria, a baseline consultation was scheduled, usually within 3 weeks, where baseline measures were taken. Patients were then randomly assigned to either the standard treatment group (CTRL) or the supplement group (SUPP). Patients in the SUPP group were instructed to take two 125 ml/day servings of a renal nutritional supplement (Renilon 7.5[®], N.V. Nutricia, Zoetermeer, The

Table 1. Baseline characteristics for patients receiving standard care (CTRL) or dietary supplementation (SUPP) of the intention to treat (ITT, all patients) and per protocol (PP, patients that fulfilled the criteria for compliance, see the Methods section) groups of patients

	ITT		PP	
	CTRL (n = 40)	SUPP (n = 46)	CTRL (n = 37)	SUPP (n = 29)
Number of males (%)	23 (50)	23 (43)	21 (57)	15 (52)
Age (years)	76.0 (38–90)	71.4 (21–90)	76.3 (38–90)	74.2 (41–90)
Years on dialysis (years)	3.4 (0.3–27.3)	2.7 (0.4–25.2)	3.3 (0.3–27.3)	2.8 (0.4–25.2)
Diabetes (n)	4	11	4	7

Data are expressed as median and range (lowest and highest value).

Netherlands) for 3 months. Dietary advice was similarly provided to both groups by the facility dietician, whereas no nutritional supplementation was given to the CTRL group. In the SUPP group, the prescribed nutritional supplementation provided an additional 500 kcal, 18.75 g protein, and 15 mg phosphorus per day. Throughout the 3-month study period, patients were followed on a monthly basis at baseline (BL), Month 1 (M1), Month 2 (M2) and Month 3 (M3). Dietary intake was assessed using a 2-day diet record at baseline and after 3 months, under the supervision of the dialysis facility dietician, and included intakes on both a dialysis and a non-dialysis day. All patients recorded their drug therapy on a daily basis, and those in the SUPP group also recorded their intake of the nutritional supplement alongside. Subjects with an average supplement intake of <1250 ml/week (10 packs) for 3 consecutive weeks were considered as non-compliers. Product tolerance and any adverse events were also recorded.

Blood samples were taken at baseline and after 3 months, immediately prior to haemodialysis and were analysed by the respective dialysis centre. Biochemical measurements included serum albumin, prealbumin, creatinine, phosphate, calcium, haemoglobin, haematocrit, ferritin, glycosylated haemoglobin (HbA1c) and C-reactive protein (CRP). Normalized protein nitrogen appearance (nPNA) and dialysis adequacy (Kt/V) were calculated according to Garred *et al.* [31]. Serum lipids (triglycerides, cholesterol, VLDL, LDL and HDL) and serum sodium, serum potassium and bicarbonate were all measured at baseline and after 3 months. In addition, measurements of body mass index (BMI), dry body weight and mid-arm muscle circumference (MAMC) were taken at baseline and after 3 months. Patients served as their own controls for the calculations of the differences between baseline and Month 3.

Nutritional status was measured monthly with the 7-point subjective global assessment (SGA), a modification of the SGA originally described by Detsky *et al.* [32]. In this modification, objective and subjective information about recent weight change, appetite and dietary intake, symptoms of gastrointestinal distress and a visual assessment of body composition are combined into a summary score of 1–7 [33,34]. The physician completed a SGA at each monthly review. SGA was scored according to McCann [35] where a score of 1–2 indicates severe risk of malnutrition, 3–5 indicates a mild-to-moderate risk and 6–7 indicates no risk of malnutrition. Quality of life scores were obtained at baseline and after 3 months using the Medical Outcomes Study (MOS) 36-item short form health survey (SF36) [36,37] suitable for use in chronic renal failure [38].

Statistical analysis

Outcomes of this study were changes in nutritional and biochemical parameters over the course of the 3-month intervention period, as outlined in Table 3. The primary parameter for this trial was the nutritional status. An improved nutritional status was defined as a significant change from baseline after 3 months of supplementation in any of the following parameters: nPNA, serum albumin, pre-albumin, dry body weight and/or serum creatinine.

Sample size calculation was based on the albumin concentrations collected in a large database of HD patients in France [1]. Taking into account a maximum variation of albumin assay of 5%, it is possible to detect a mean difference in albumin levels of 2.5 g/L or greater with a probability of 80% at the predetermined level of $\alpha = 0.05$ with a sample size of 42 patients per group. Data were analysed on an *intention to treat* (ITT) and *per protocol* (PP) basis. The ITT analysis included all recruited subjects providing baseline measurements, whereas the PP analysis excluded all subjects with protocol violations. Data were analysed using ANOVA after confirming normality by Shapiro–Wilk tests and equal variances by Levene tests. ANOVA included the factors treatment (CTRL or SUPP), centre, and diabetes for each time point and the differences from baseline values. In addition, interactions were tested and where no interaction was observed this was removed from the model. Data that did not meet the criteria for ANOVA were transformed, where possible, to ensure normality or were analysed using the Mann–Whitney test. Quality of life data were also analysed using the same ANOVA procedure. The outcomes of SGA were compared between treatment groups using Fisher's exact test per visit and the change from baseline. As proposed in clinical research, differences were considered statistically significant when the *P*-value was <0.10. Data are expressed as mean \pm SD or as median (lowest–highest value) for normally distributed or not normally distributed data, as appropriate.

Results

Compliance

Seventeen patients were excluded in the PP analysis (SUPP group) due to non-compliance with the required intake of supplements (12 patients stopped taking the supplement within the first week of the study, 3 took less than the required amount for a period of 3 consecutive weeks and 2 consistently took less than the required amount throughout the study period). Reasons for non-compliance included dislike of the supplement and satiety. For the patients who were able to comply with the supplementation (63%), the average consumption was 93% of the two packs prescribed daily. There were 15 subjects with diabetes in ITT (4 STD, 11 SUPP), and 11 were kept in the PP analysis (4 STD, 7 SUPP).

Dietary intake

Table 2 shows the differences in dietary intake from food between baseline and after 3 months, as recorded by the patients' dietician. Dietary records of 8 patients were uninterpretable, while the dietary intakes of another 11 patients were recorded outside the predetermined window of -21 or $+7$ days from baseline and -7 or $+7$ days from Month 3 measurements. These records were excluded from the ITT as well as the PP analysis. Significant differences were observed neither in the CTRL nor in the SUPP group in the actual intakes of energy, protein, carbohydrate, fat, phosphate at baseline, or after 3 months, in the changes in intake over the study period. The only exception was a significant

Table 2. Changes from baseline in nutrient intakes from food alone, based on food report analysis, after 3 months of standard care (CTRL) or dietary supplementation (SUPP) of the intention to treat (ITT, all patients) and per protocol (PP, compliant patients only) groups of patients

	ITT		PP	
	CTRL	SUPP	CTRL	SUPP
Energy (kcal/day)	-188.6 ± 334.2 n = 25	-21.7 ± 427.9 n = 34	-196.4 ± 344.9 n = 22	-15.3 ± 435.7 n = 23
Protein (g/day)	-2.8 ± 20.2 n = 25	1.5 ± 16.9 n = 34	-4.6 ± 19.0 n = 22	0.6 ± 16.7 n = 23
Carbohydrate (g/day)	-29.8 ± 51.3 n = 25	-4.1 ± 61.0 n = 34	-27.9 ± 54.2 n = 22	-8.5 ± 59.1 n = 23
Fat (g/day)	-6.5 ± 17.3 n = 25	-1.2 ± 20.8 n = 34	-7.4 ± 17.3 n = 22	1.8 ± 21.3* n = 23
Phosphorus (mg/day)	-80.2 (-404-1378) n = 23	39 (-545-563) n = 33	-38.8 ± 283.4 n = 20	36.5 ± 264.7 n = 22
Calcium (mg/day)	-0.5 (-570-950) n = 23	-8 (-348-534) n = 33	-51.4 ± 218.3 n = 20	18.5 ± 204.4 n = 22

*Significant difference between groups ($P = 0.03$).

Data are expressed as mean ± SD, or as median and range (lowest and highest value), as appropriate.

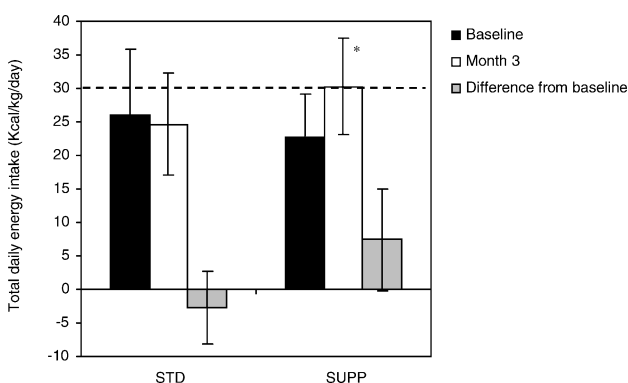


Fig. 1. Total energy intake per kg body weight per day (mean ± SD) at baseline (BL) and after 3 months (M3), and the difference in intake from baseline. Energy intake at M3 was significantly greater in the SUPP group ($P < 0.001$) and the difference in energy intake from baseline showed a significant increase for the SUPP group ($P = 0.03$) after 3 months (PP analysis).

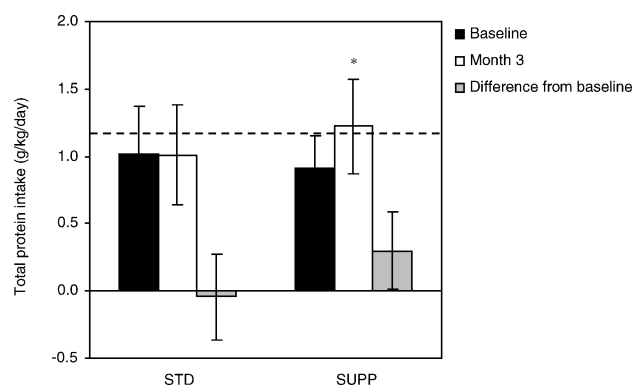


Fig. 2. Total protein intake per kg body weight per day (mean ± SD) at baseline (BL) and after 3 months (M3), and the difference in intake from baseline. The difference in protein intake from baseline showed a significant increase for the SUPP group ($P < 0.01$) after 3 months (PP analysis).

increase in fat intake in the SUPP group in the PP analysis ($P = 0.03$). When expressed per kg body weight, the addition of the nutritional supplement to the diet increased intake of energy and protein by 7.4 kcal/kg/day and 0.3 g protein/kg/day, respectively, in the SUPP group, as shown in Figures 1 and 2. Patients receiving the nutritional supplement were consequently able to achieve intakes of 30.3 ± 7.2 kcal/kg/day and 1.22 ± 0.4 g protein/kg/day (mean ± SD). Interestingly, phosphate intake did not differ between groups or from baseline throughout the study period, as shown in Figure 3. As a result, mean intakes of phosphorus remained below the recommended upper limit of 1000 mg/day, despite the net increase in protein from the nutritional supplement [26].

Biochemistry and anthropometry

Biochemical and anthropometric measurements at baseline and the change from baseline at 3 months are presented in Table 3. Changes after 3 months of supplementation showed consistent improvements in the SUPP group in compari-

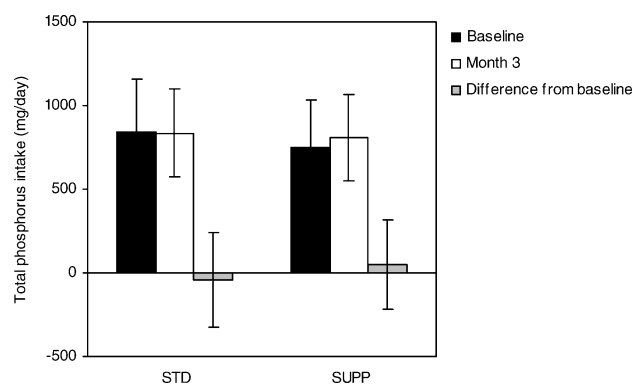


Fig. 3. Total phosphorus intake in mg per day (mean ± SD) at baseline (BL) and after 3 months (M3), and the difference in intake from baseline. Phosphorus intake did not differ between groups at baseline or 3 months. Changes from BL were not significantly different between groups after 3 months (PP analysis).

son to the CTRL group for which all parameters, except nPNA, deteriorated, although statistical significance was not achieved. (Table 3).

Table 3. Levels of nPNA, serum albumin, serum prealbumin, CRP, BMI and dry body weight measured at baseline (BL), and the change from baseline after 3 months of standard care (CTRL) or dietary supplementation (SUPP) of the intention to treat (ITT, all patients) and per protocol (PP, compliant patients only) populations

	CTRL		SUPP	
	BL	Change from BL at M3	BL	Change from BL at M3
ITT				
nPNA (g/kg/day)	0.93 ± 0.2 <i>n</i> = 35	0.03 (−0.5–0.6) <i>n</i> = 33	0.87 ± 0.3 <i>n</i> = 46	0.07 (−0.5–1.87) <i>n</i> = 44
Serum albumin (g/L)	35.2 ± 6.4 <i>n</i> = 40	−0.7 (−8.4–14.9) <i>n</i> = 38	35.2 ± 4.3 <i>n</i> = 46	0 (−9.7–7.4) <i>n</i> = 46
Serum prealbumin (mg/L)	300 (110.0–638.0) <i>n</i> = 40	0 (−200.0–220.0) <i>n</i> = 39	286 (150.0–530.0) <i>n</i> = 46	15 (−160.0–110.0) <i>n</i> = 45
Serum CRP (mg/L)	6 (2.0–68.5) <i>n</i> = 39	−0.4 (−67.8–136.0) <i>n</i> = 39	4.9 (0.5–91.0) <i>n</i> = 46	0 (−81.0–59.0) <i>n</i> = 44
BMI (kg/m ²)	23.2 ± 3.9 <i>n</i> = 40	−0.09 ± 0.5 <i>n</i> = 40	23.6 ± 3.8 <i>n</i> = 46	0.01 ± 0.9 <i>n</i> = 45
Dry body weight (kg)	63.9 ± 14.8 <i>n</i> = 40	−0.4 ± 1.5 <i>n</i> = 40	62.4 ± 12.6 <i>n</i> = 46	0.01 ± 2.2 <i>n</i> = 46
PP				
nPNA (g/kg/day)	0.91 ± 0.2 <i>n</i> = 33	0.03 (−0.5–0.6) <i>n</i> = 31	0.87 ± 0.3 <i>n</i> = 29	0.1 (−0.3–1.9) <i>n</i> = 27
Serum albumin (g/L)	35.0 ± 6.5 <i>n</i> = 37	0 (−8.4–14.9) <i>n</i> = 35	34.8 ± 4.7 <i>n</i> = 29	0 (−5.0–7.4) <i>n</i> = 29
Serum prealbumin (mg/L)	300 (110.0–638.0) <i>n</i> = 37	0 (−200.0–220.0) <i>n</i> = 36	282 (150.0–530.0) <i>n</i> = 29	18 (−100.0–110.0) <i>n</i> = 29
Serum CRP (mg/L)	5.6 (2.0–68.5) <i>n</i> = 36	−0.5 (−67.8–136.0) <i>n</i> = 36	5 (0.5–21.0) <i>n</i> = 29	0 (−13.0–33.7) <i>n</i> = 29
BMI (kg/m ²)	23.1 ± 3.7 <i>n</i> = 37	−0.09 ± 0.5 <i>n</i> = 37	23.5 ± 3.5 <i>n</i> = 29	0.06 ± 0.7 <i>n</i> = 28
Dry body weight (kg)	63.0 ± 13.7 <i>n</i> = 37	−0.36 ± 1.5 <i>n</i> = 37	61.7 ± 11.7 <i>n</i> = 29	0.24 ± 1.9 <i>n</i> = 29

No significant differences were observed between the CTRL and SUPP groups or over time within each group. Data are expressed as mean ± SD, or as median and range (lowest–highest value), as appropriate.

Mean values for nPNA in the SUPP group after 1 and 2 months (1.14 ± 0.4 and 1.07 ± 0.4 , respectively) exceeded 1.0 g/kg/day. The analysis of nPNA at each monthly interval also indicated significant differences between groups. The change in nPNA from baseline was significantly greater for the SUPP group in both the ITT ($P = 0.03$) and PP ($P = 0.01$) analyses after 1 month, and in the PP analysis ($P = 0.03$) after 2 months; however, no significant changes were seen after 3 months.

The analysis of the correlation between the change in nPNA and the change in serum albumin (Figure 4) or prealbumin (not shown) for both groups indicated a significant positive relationship: an increase in nPNA corresponded to a significant increase in serum albumin ($P = 0.01$) and prealbumin ($P = 0.02$). This suggests that compliance with the nutritional therapy should improve serum albumin (Figure 4).

Dry body weight slightly increased after 3 months in the SUPP group in comparison with the CTRL group in the PP analysis ($P = 0.07$). No significant changes in MAMC were observed between groups at baseline or following the 3-month study period. Serum potassium, bicarbonate and creatinine levels did not change significantly between groups from baseline throughout the study period (data not shown). There were no significant differences in serum levels of CRP at baseline, nor there was a change from baseline after 3 months significantly different between treatments (Table 3). Similarly, no differences were observed in

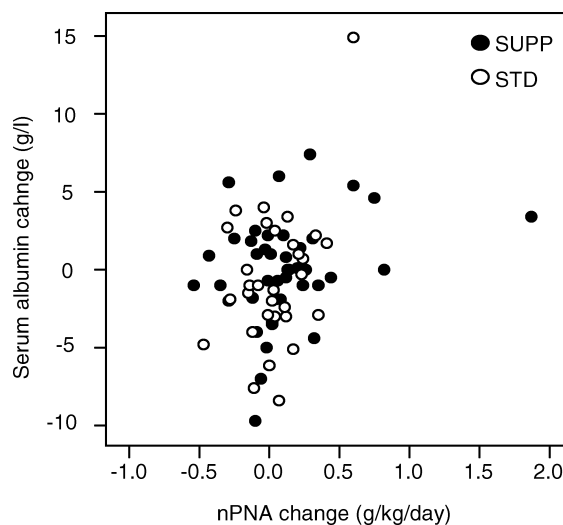


Fig. 4. The relationship between the individual variation in protein intake (g/kg/day as assessed by nPNA) and serum albumin (g/l) during the 3-month period (ITT, $n = 75$; $r = 0.293$, $P = 0.01$), indicating that the nutritional response was greater in patients with increased protein intake. Of nine patients either the serum albumin or nPNA data were incomplete.

serum lipid levels (data not shown). Serum haemoglobin, HbA1c, serum haematocrit and ferritin all remained stable throughout the study period, indicating no differences between groups.

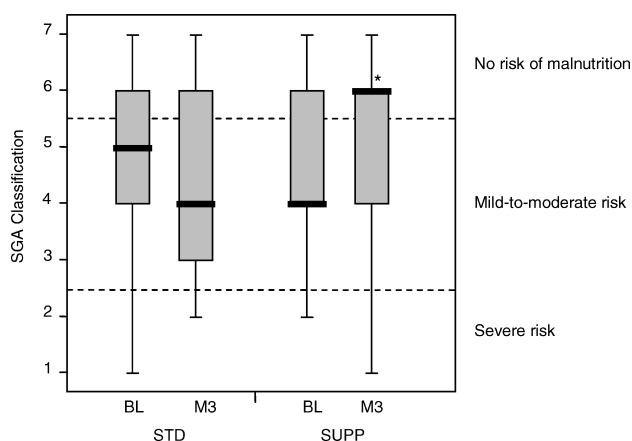


Fig. 5. Median SGA at baseline (BL) and after 3 months (M3) for the CTRL and SUPP groups; * between group change from baseline, $P < 0.05$ (PP analysis). Solid lines indicate median results, with the block representing the interquartile range and the whiskers indicating the results range.

Serum phosphate levels did not differ from baseline or between groups throughout the study period. At baseline, phosphate binders were prescribed to 48 subjects (73%) included in the PP analysis (27 STD, 21 SUPP). Throughout the study period only eight patients (3 STD, 5 SUPP) indicated a change in prescription, all of whom recorded a decrease in phosphate binder use.

Subjective global assessment (SGA)

The results for the SGA for the ITT and PP groups are presented in Figure 5. For the SUPP group, there was an increase in median classification from 4, indicating a mild-to-moderate risk, to 6, indicating no risk of malnutrition. In the CTRL group, the median classification decreased, consistently indicating a mild-to-moderate risk of malnutrition.

Quality of life

The SF36 Quality of Life questionnaire comprises eight different parameters representing different components of quality of life and their summaries (Table 4). A significant difference between the changes in scores for the general health and bodily pain components was identified in the PP analysis ($P = 0.01$), indicating improvement in the patients who effectively took the supplement. This difference was not seen in the ITT analysis, which included non-compliant subjects. Overall, for the PP analysis, the SUPP group showed consistent improvements in all individual and summary component scores, except the score for vitality. In contrast, the CTRL group showed deterioration in seven of the eight individual component scores and also for the physical component summary score. Results for the ITT analysis showed a similar pattern of consistency.

Adverse events

Forty-three adverse events were reported 21 of which were considered serious (stroke, myocardial infarction, fistula

Table 4. Mean changes from baseline in Quality of Life SF36 scores after 3 months of standard care (CTRL) or dietary supplementation (SUPP) of the intention to treat (ITT, all patients) and per protocol (PP, compliant patients only) groups of patients

Estimated marginal mean (EMM)	ITT		PP	
	CTRL	SUPP	CTRL	SUPP
Physical functioning	-2.49	2.47	-5.19	6.28
Physical role	-14.92	-6.46	-13.02	2.50
Vitality	-0.93	-5.57	-4.30	-2.02
Social functioning	-0.14	0.53	0.75	7.46
Emotional role	4.49	6.89	-3.49	14.66
Mental health	-0.74	2.73	-2.26	4.77
General health	-2.64	3.30	-7.06	5.69*
Bodily pain	-15.05	-0.93	-20.54	2.83*
Physical component summary	-2.49	-0.69	-3.92	1.44
Mental component summary	3.89	2.75	0.839	2.94

*Changes from baseline were significantly different between groups ($P = 0.01$).

thrombosis, lower limb ischaemia and sepsis). None of the serious adverse events were considered to be related to the intake of the supplement, and there was no difference in the distribution between treatment groups. Six non-serious adverse events were identified to be potentially related to the intake of Renilon 7.5[®]: hyperglycaemia ($n = 1$), vomiting ($n = 2$), mild abdominal pain ($n = 2$) and soft stools ($n = 1$).

Discussion

This is the first open-label randomized controlled study showing the effects of a renal-specific oral supplement in MHD patients. The hypothesis was tested whether MHD patients at risk of malnutrition would maintain an adequate nutritional status by taking a daily oral supplement as compared to patients receiving standard care. The results showed that use of this oral supplement partially prevented impairment of nutritional parameters and increased energy and protein intake without increasing the use of phosphate binders. Moreover, patients who complied with the supplementation improved SGA and quality of life scores.

Based on biochemical indexes, the per protocol nutritional response to supplementation was modest, with no change in serum albumin and a non-significant increase in prealbumin of 18 mg/L between the CTRL and SUPPL groups. This could be explained by a number of factors. Firstly, at the start of the study, the patients nutritional status was only slightly impaired as compared to patients involved in most previous studies in the field [28,39,40], indicating that they were at risk of, rather than exhibiting, overt malnutrition. Secondly, there was a large baseline variance in serum albumin, which may indicate some heterogeneity in the nutritional status of patients. The analysis of biochemical parameters by the subsequent dialysis centres might have introduced additional variations in the results, although patients served as their own controls for the calculations of the differences between baseline and Month 3. Another potential drawback of using serum albumin as a

marker of nutritional status is the influence of inflammation on this marker [41]. Therefore, for this trial, patients were selected with normal or moderately increased CRP levels at the start of the trial. Moreover, the CRP levels hardly changed during the 3-month period (median -0.5 and 0.0 , respectively) and no significant correlations were found between changes in CRP and changes in serum albumin. Whether these results apply to more inflamed patients cannot be inferred from the present study and deserve further research.

The albumin and prealbumin responses observed in this study were limited in some patients (Figure 4), which might be related to their higher values than those reported in previous nutritional studies [39,40,42,43], probably indicating that these patients were in an early stage of malnourishment, having been selected only on the basis of insufficient dietary intakes. It is therefore conceivable that an albumin response may have been greater in more malnourished patients [42,43].

The total amount of supplemental energy and protein effectively taken from supplements in chronic disease is generally lower than prescribed by physicians. In CKD, most studies report supplemental energy intakes totalling 200–500 kcal/day [28,44]. It is important to note that IDPN, which is administered just three times a week, cannot provide more energy/nutrients than oral supplements: in the FineS study, the equivalent nutritional support from IDPN was 420 kcal and 18 g protein per day [40]. In another IDPN study over a 3-month period, patients actually received 30% less than prescribed [43]. Oral essential or branched chain amino acid supplements have been suggested to reduce anorexia and/or improve appetite, as for instance shown by Hiroshige *et al.* [45] or Eustace and coll. [46]. In another short-term pilot study, Kalantar-Zadeh and colleagues reported an improvement in serum albumin from 34.4 to 36.8 g/L ($P < 0.01$) in 20 malnourished MHD patients taking a daily combination of supplements (Nepro[®] + Oxepa[™]) containing fish oil [47]. In a more recent trial, Majchrzak *et al.* improved the anabolic effects of an oral supplement by adding a short resistance exercise during the haemodialysis session [48]. In the present study, there was a clear trend for the CTRL group to spontaneously reduce energy and protein intakes, whereas the SUPP group maintained their nutritional intake over the 3 months (Table 2). An extended survey might have shown significant worsening in the non-supplemented group over time.

Ensuring compliance is a key target for effective nutritional therapy involving oral supplements. It is now well documented that in most malnourished patients, even if chronic inflammation occurs, increasing nutritional intake will improve body composition [39,40,49]. In this study, compliance was not as good as expected; 66% of patients complied with the nutritional supplementation, achieving an average additional intake of 7.4 kcal/kg/day and 0.3 g protein/kg/day. However, this issue is well established in MHD patients, compliance being close to 50% after 6 to 12 months of treatment in other studies [42,50]. Efforts should be focused on barriers to compliance in this particular patient group. While compliance could be inadequate due to (presumed) side effects (e.g. nausea and vomiting) associated with taking oral supplements, this was the case

for only two patients in this study. Two other patients refused to continue taking the supplement after the first day, describing a feeling of fear of being overhydrated rather than due to any direct problems with the supplement. In these cases, accurately informing the patient, temporarily decreasing the daily prescription or offering practical advice on how to successfully incorporate the supplement into the diet, seem all worthwhile efforts for successfully maintaining this support. In fact, the supplement used in this study is twice as concentrated (2 kcal/ml) as most supplements available, and this may be of interest in patients who fear of overhydration or who do not accept any modification of their regular fluid intake.

The results observed in the ITT analysis were hampered by the fact that non-compliant patients were included, which might have diluted the true efficacy of the supplement. When analysed per protocol (also called 'as treated'), the positive effects, although non-significant, were slightly improved (Table 3). Excluding any non-compliant patients reflects the true efficacy of the supplement. Figure 4 also confirms that the more the patients increased their intakes, the greater was their albumin increment after 3 months. Such a nutritional supplementation seems limited, but may be adequate to prevent a patient entering the protein-energy-wasting phase of CKD. Previous pilot studies in MHD have associated this magnitude of intake with clear positive anabolic responses [28,44].

An additional benefit of the present supplement is the very low phosphate content (15 mg/500 kcal), even though it contains 7.5 g protein/100 ml. As a consequence, serum phosphate did not increase in the SUPP group and it was not necessary to increase phosphate binders, which is of significant benefit to patients. In comparison, an equivalent amount of protein from diet (e.g. one 100-g piece of red meat) would have provided an additional 250 mg dietary phosphate. Although controlling hyperphosphataemia by reducing protein intake is not recommended anymore [51], many patients still avoid high protein foods in order to minimize the risk of hyperphosphataemia. Therefore, use of a supplement with negligible phosphate content overcomes this barrier.

Quality of life (QoL) is uncommonly reported in nutritional studies in MHD patients, although a non-neglectable issue [52,53]. Indeed, MHD patients experience a decreased quality of life and those who improve some of their quality of life parameters are likely to eat better and/or comply with nutritional support. Laws *et al.* [10] suggested an association between severe malnutrition and poor quality of life, and this was supported by Kalantar-Zadeh *et al.* [54] who reported a correlation between serum albumin and SF36 score. Low intakes of protein and several micronutrients correlated with poor quality of life scores in a study involving 60 MHD patients [55]. In the present study, all mean SF36 parameters, except vitality, improved in the SUPP group, and this increase was significant for general health and bodily pain by PP analysis, whereas it was not significant in the control group (Table 4). This indicates a true clinical improvement when patients successfully take their supplement. The dietary supplement (Renilon 7.5) had a beneficial effect on SGA and QoL scores, and this is of clinical relevance to patients. Thus, this improvement in

general status might have occurred at a very early stage of malnutrition, before any impairment in body composition and routine laboratory parameters could be detected.

In conclusion, this paper reports some beneficial effects of a renal-specific oral nutritional support in MHD patients who have a reduced nutritional intake and who are at risk of emerging malnutrition. Compliance was similar to other nutritional strategies and when patients complied, significant improvements in clinical status were observed. The use of this energy-dense very low phosphate nutritional supplement may prevent the development of malnutrition. Whether these effects may be sustained over time will require long-term studies, but ultimately could lead to significant cost benefits by reducing infectious complications and hospitalization.

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