Nephrologia Urologia: Open Access (NUO)

Research Article

An Open Label Randomized Clinical Study Evaluating Impact of Nutritional Supplement in Malnourished Dialysis Patients (IMPROVES Trial) Protocol No PBL/PROS/07-11

Anita Saxena[1*], J. Kothari[2], M Gokulnath[3], Amit Gupta[1], Juan Jesus Carrero[4], Kam Kalantar Zadeh[5], CM Pandey[1]

[1] Department of Nephrology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India.

[2] Nephrology, Hinduja Hospital, Mumbai, India.

[3] Nephrology, St John's Medical College, Bangalore, India.

[4] Renal Medicine, Karolinska Institutet, Stockholm Sweden.

[5] University of California Irvine School of Medicine and UCLA School of Public Health.

Abstract

Background: Protein energy wasting (PEW) affects survival in patients on maintenance dialysis. Objective to evaluate effect of oral nutritional supplement on hypoalbuminemic dialysis patients.

Methods: Multicenter randomized intervention on maintenance dialysis (MD) patients with serum albumin <3.8g/dL. 180 patients were randomly assigned to 1:1 standard treatment (1.2 g/kg/d and 35 kcal/kg/d control) or standard treatment plus an oral nutritional supplement (ONS) for 6 months. The supplemented group received in addition 30 g/d of a renal-specific ONS (Proseventy©) containing 70% soya protein. At month 0, 3 and 6 routine biochemistry, subjective global assessment (SGA), dietary recalls, and skinfold thickness (SFT) were done.

Results: At inclusion, no difference was found in age, sex,dietary intake, SGA, CRP and biochemistry. Control group had significantly higher serum albumin (3.2±0.41 and 3.37±0.36 p 0.013) and subscapular SFT (14±6.0, 12.1±5.0 p 0.032) than supplemented group. At month 3, the supplemented group significantly increased their albumin (3.3 ±0.48 vs 3.4 ±0.43) and illiacSFT (15.5 ±8.5 and 18.1 ± 8.6 0.043). Protein intake was significantly higher in supplemented group compared to controls at 3 and 6 months (64± 21.5 54. ±1 16.3 p 0.004 and 69 ±28.4 and 53.5 ±15.1 p 0.000) respectively. In supplemented group subscapularSFT (16 ±5 12±5.1 p 0.000) was significantly high and albumin increased to 3.4± 0.049 versus 3.3 ±0.51 in controls at 6 months but difference in albumin was not significant. Serum phosphorus and lipid were not altered.

Conclusions: Addition of protein-rich renal specific ONS to standard nutritional counseling raised serum albumin and increased SFT in PEW patients undergoing dialysis. However, despite supplementation the serum albumin did not rise to ≥3.8 g/dL (ISRNM criteria). To correct PEW, ONS has to be given for longer period.

Keywords: *Protein Energy Wasting (PEW), Oral Nutritional Supplement, Hypoalbuminemia, Dialysis*

Introduction

Nutritional status in patients on hemodialysis is always a concern because of rampant morbidity and mortality due to malnutrition. Large scale dietary surveys of patients undergoing maintenance dialysis indicate that protein energy wasting (PEW) occurs in 17-85 percent of patients with chronic kidney disease (CKD) [1-3]. This in turn increases oxidative stress, inflammation, aggravates pre-existing heart failure and increases susceptibility to infections and mortality [4,5], hospitalization [6] and overall decreased quality of life (QOL) [7]. It is estimated that 50%-70% of PEW is related to inadequate dietary intake which is a consequence of uremia induced anorexia [8].

Given the poor dietary intake of energy and protein intake, renal specific dietary supplement is often the most effective measure to improve nutritional status of patients with CKD. National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) [9] best clinical practice guidelines for nutrition in chronic renal failure recommends a dietary protein intake of 1.2 g protein/kg body weight/day for patients on maintenance hemodialysis (MHD) and peritoneal dialysis and for clinically unstable chronic peritoneal dialysis (CPD) patients protein intake of 1.3 g/kg/day in clinically unstable PD patients. Fifty percent of protein should be of high biological value from poultry, dairy and soy products. Hypoalbuminemia is most likely the strongest predictor of mortality among maintenance dialysis patients. KDOQI guidelines recommend that individuals undergoing maintenance dialysis who are unable to meet their

***Corresponding author:** Anita Saxena, Department of Nephrology, Additional Professor, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India, Tel: 9453019812; Fax: 9453019812; E-mail: anitimmy@yahoo.com

Received: February 17, 2018; **Accepted:** March 08, 2018; **Published:** March 12, 2018

protein and energy requirements with food intake for an extended period of time should receive nutritional support. Clinical trials on oral nutrition supplements (ONS) for dialysis patients have shown that enteral therapy improves nutritional status which manifests as increase in serum albumin, prealbumin, and improvement in SGA scores [10-20].

Thus, early identification of patients with eating behaviour disturbances can potentially reduce the burden of malnutrition through appropriate intervention.

With this background, a multicentre study, sponsored by Panacea Biotech Ltd. was designed to see the effectiveness of high protein supplementation in improving nutritional status of patients and the overall QOL in dialysis patient. The primary end points for efficacy and safety were to evaluate the efficacy of ONS on the nutritional status of hypo-albuminemic malnourished patients on maintenance dialysis as increase in serum albumin from baseline to the end of the study. Other additional clinical parameters for efficacy were increase in body mass index (BMI), anthropometric measurement like skin folds thickness of biceps, triceps, suprailliac, and subscapular, mid upper arm circumference, subjective global assessment (SGA) and quality of life (QOL).

Material and Methods

Patients and Methods

Study Design: It was an open label, comparative, multicentric study of 6 months duration. The study product and the study (Protocol No PBL/PROS/07-11) was approved by the Drugs Controller General Of India (DCGI) and was later approved by the ethics committees of all the three participating centers.

In addition to screening visit, there were three visits, visit 1 was baseline, visit 2 was at 3 months and visit 3 was at 6 months and end of the study. **Safety endpoint** were assessed by biochemical parameters, adverse events and tolerability.

For diagnosis of PEW recommendation of the expert panel international society of renal nutrition and metabolism (ISRNM) was used [7].

Study product: ProSeventy is an artificial food supplement containing 70% soy protein, hence the name. The quality of this protein is high and contains all the essential amino acids.

Selection of Patients:

Inclusion criteria: Those patients who were willing to sign informed consent form, were above the age of 18 years, had clinical PEW as per ISRNM criteria [7], serum albumin < 3.8g/100 ml, were on maintenance dialysis for at least 3 months and adequately dialyzed as per investigator, with no uremic symptoms, and were from middle to high socioeconomic group were included in the study. Exclusion criteria included patients with no clinical PEW as per ISRNM criteria [7], patients with systemic infection like tuberculosis or malaria, patients who were on oral nutritional supplement (ONS) or had discontinued use of ONS, or patients planned for kidney transplantation within study period, pregnant or breast-feeding females, patient whose life expectancy was less than 6 month and patients who had switched over from hemodialysis to peritoneal dialysis.

A total of 180 patients on maintenance dialysis (haemodialysis and peritoneal dialysis), matched for age, sex and income were recruited for the study from 3 centers (Figure 1). Out of 180 patients, 90 patients were in group 1 and 90 were in group 2 but later there were 2 drop outs from group 1. On visit 2 there were 141 patients, 70 in group 1 and 71 in group 2; 128 patients completed visit 3, 39 were in group 1 and 89 were in controls.

The groups were randomized equally and divided into two groups: group 1: treatment group and group 2: control group. The treatment group was given 30 g of Proseventy in two divide doses along with standard 1.2g/kg/d protein and 35 kcal/kg/d energy diet for a period of 6 months while the control group received standard 1.2g/kg/d protein and 35 kcal/kg/d energy diet with no ONS. To assess compliance with the nutritional supplements, patients were asked to return empty cans of the ONS and a ONS dispensing log was maintained.

Dietary Record and Food Intake: Dietary intake was taken by a renal dietician on dialysis day, non-dialysis day and weekend day. Three days food diaries were maintained for all the patients. The amounts were recorded in household measures using standardized bowls, cups, spoons and glasses. Patients were taught to complete diaries using household measures and food models. Complete dietary record included the day and time when meals, snacks and beverages were taken, a description of the food or drink, methods of food preparations, missed meals, amount consumed in restaurants and the amount of consumed convenience and processed foods. For identifying sizes of bread (chapatti/paratha/bhakri) etc., food models of dough were used as also cardboard cut-outs. The cooked amount was converted to raw weight in grams [21-23]. Nutrients were calculated based on nutritive values published by ICMR [24]. Figure 2

Observation of Efficacy and Safety With Physical And

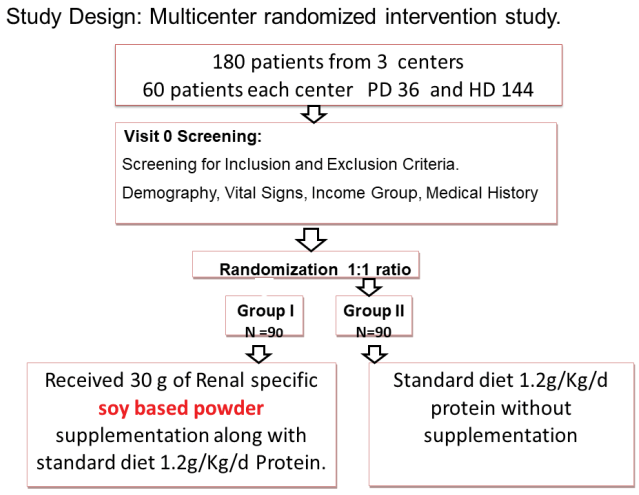

Figure 1: Schematic presentation of patient groups.

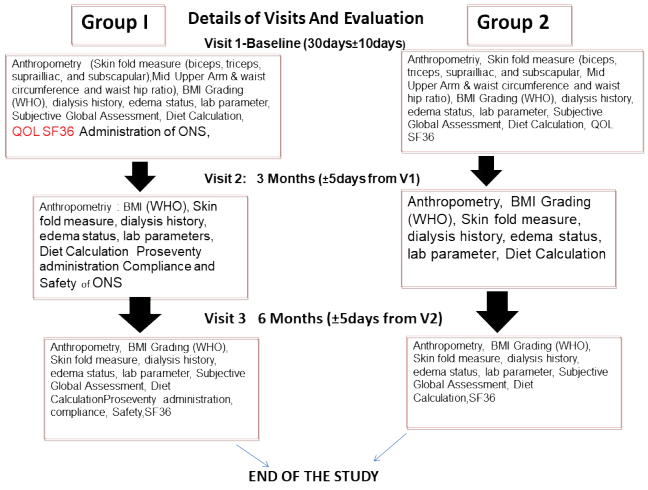

Figure 2: Visit wise schematic presentation of groups and parameters assessed.

Table 1: Visit Wise Biochemical Profile of Patients.

Parameters	Visit 1		Visit 2		Visit 3	
	N= 91	N = 87	N= 77	N= 69	N= 70	N=58
Hemoglobin g/dL	9.8±1.8	9.6±0.7	9.8±1.71	9.6±1.8	10.0±1.6	9.5±1.56
BUN	67±35.8	74±39.6	74.2±42..4	79.0±42.	59.94±23*	87.4±.49
Serum Albumin g/dL*	3.2 ±0.41	3.37±0.35	3.3±0.47	3.4±0.4	3.9±0.48	3.3±0.51
CRP * p .016	4.2 ±6.01	8.7±8.1	4.1±9.9	4.6±7.1	4.5±6.2	6.4±14.0
HbA1c visit 1 and 3	6.0±1.21	7.1±1.41	NR	N R	6.5±1.55	7.1±1.2
Serum LDL VLDL HDL	 84.9±28.1 26.4±16.8 41.2±12.6	 89.6±28.1 16.8±12.5 40.6±12.1	 85.2±28.3 27.9±16.4 39.4±13	 88.2±28 25.1±15 39±10.3	 91±31.5 30.4±19.2 37±11.8	 83.1±27 24.±15.7 36.4±11
Potassium	4.8±0.84	6.6±14.3	4.9±.89	5.3±.96	4.7±0.8	5.2±0.9
Phosphorus	4.6±1.17	4.7±1.5	4.5±1.2	4.7±1.6	4.76±1.51	4.6±1.55
Serum Calcium	8.1±1.27	8.2±1.2	8.3±0.85	8.4±0.68	8.2±1.3	8.3±0.75
Coagulation PT aPPT	12.8±2.1 34.2±10.5	12.8±2.5 34.0±6.9	12.7±1.8 34.5±9.9	12.4±1.9 35.5±8.0	13.4±2.02 34.8±35.8	12.7±1.8 35.8±.94
PTH	375±392	385±362	NR	NR	411.6±69	424±45

Biochemical Investigation

Patients were screened for inclusion in the study. At the onset, baseline data pertaining to personal information, medical history and treatment, biochemical parameters such as hemoglobin, serum albumin serum cholesterol-LDL, VLDL or HDL, HbAa1c (at baseline for all patients and at all the visits for diabetics), serum sodium, potassium, phosphorous, C reactive protein, PTH (at baseline and 6 months) serum calcium, blood urea nitrogen, coagulation profile: partial thromboplastin (PT) activated APTT were taken. Anthropometric measurements were taken using standard equipment and techniques [24-26]. BMI, skin folds thickness of biceps, triceps, suprailliac, and subscapular, mid upper arm and waist circumference and waist hip ratio were taken [24-26]. Subjective global assessment (SGA) was done at baseline and after 6 months. SF36 (baseline and after 6 month) and dietary intakes was recorded using a validated questionnaire and assessment. Following initiation of the study protocol, anthropometric, biochemical and dietary intake data as

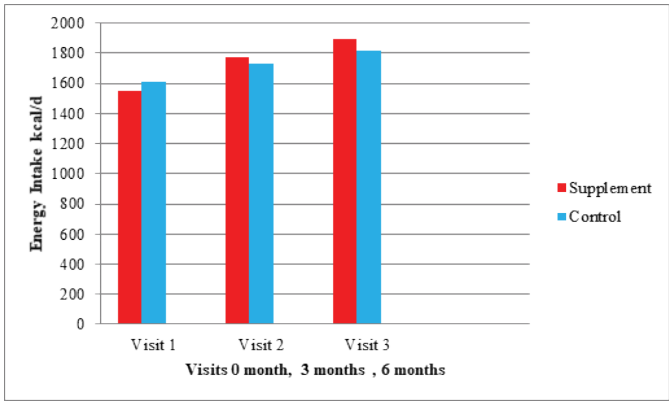

Figure 3a: Non-Dialysis Day Energy Intake Repeated Measures ANOVA (Wilk's Lambda) Sign. Difference between groups p 0.000.

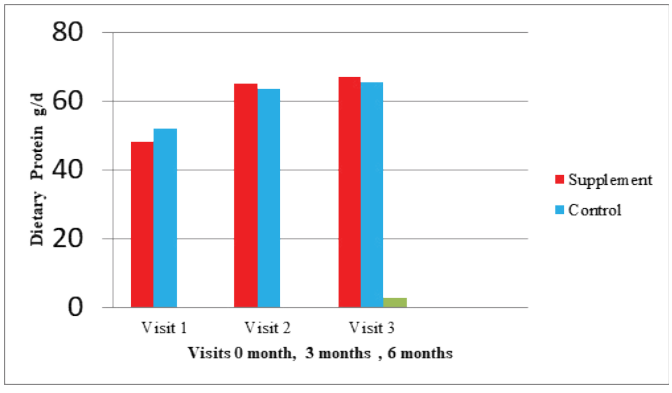

Figure 3b: Non-Dialysis Day Protein Intake Repeated Measures ANOVA (Wilk's Lambda) Sign. Difference between groups p 0.000.

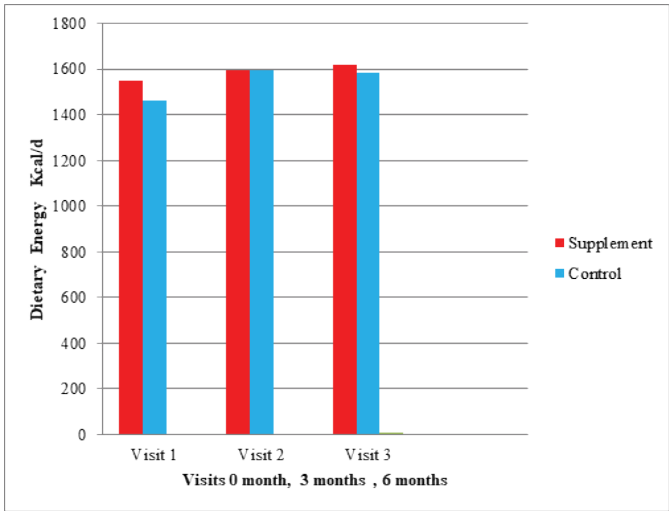

Figure 4 a: Dialysis Day Energy Intake Repeated Measures ANOVA Sign. Difference between groups p 0.000.

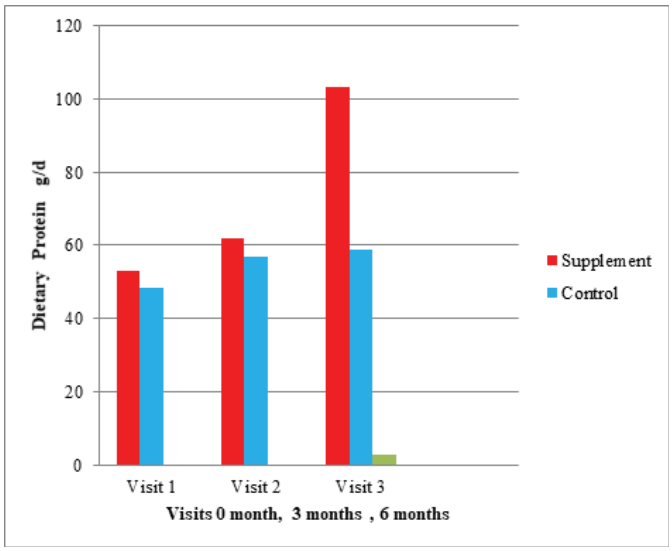

Figure 4 b: Dialysis Day Protein Intake Repeated Measures ANOVA Sign. Difference between groups p 0.000.

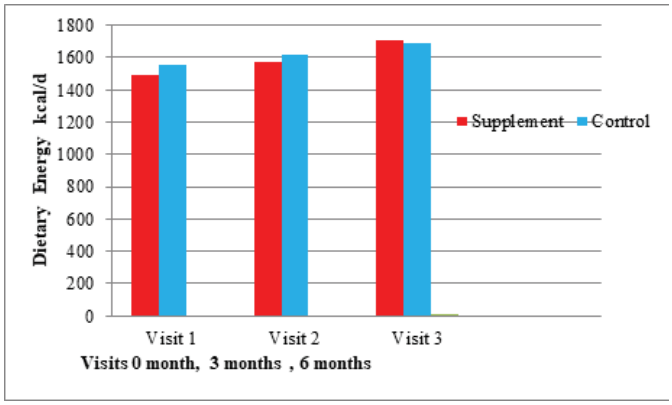

Figure 5 a: 24 Hour Dietary Recall - Energy Intake Repeated Measures ANOVA Sign. Difference Between Groups p 0.000.

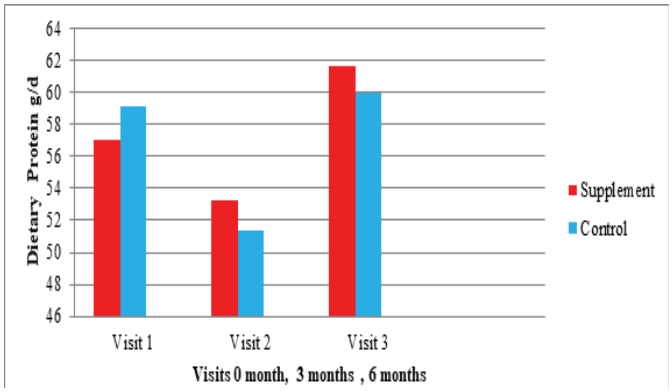

Figure 5 b: 24 Hour Dietary Recall - Protein Intake Repeated Measures ANOVA Sign. Difference Between Groups p 0.000.

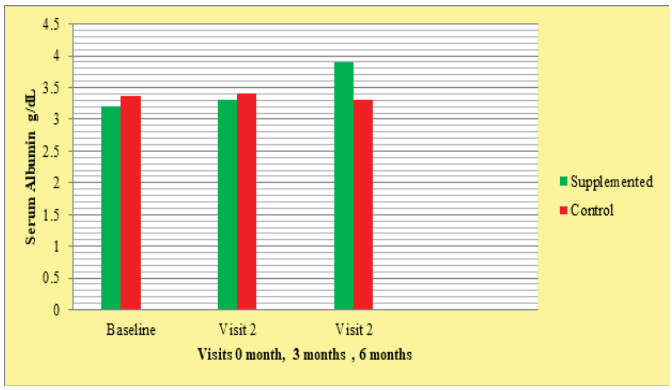

Figure 6a: Effect of ONS on Serum Albumin: Serum albumin significantly increased (3.3 ±0.48 vs 3.4 ±0.43) and at 6 months serum albumin was higher the controls p= 0.000.

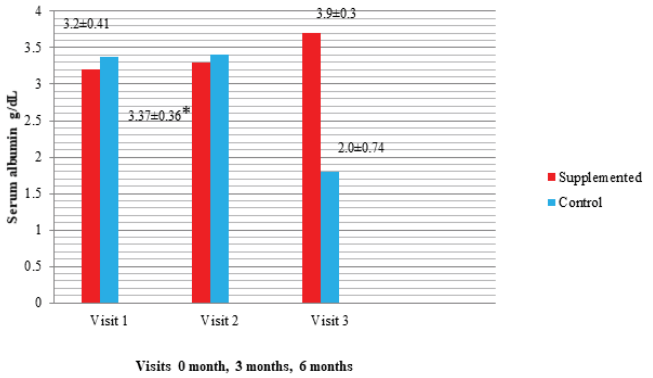

Figure 6b: Paired Comparison using Anova Analysis Significant Difference in Albumin level at 3 and 6 months p=0.000 Higher in supplemented group.

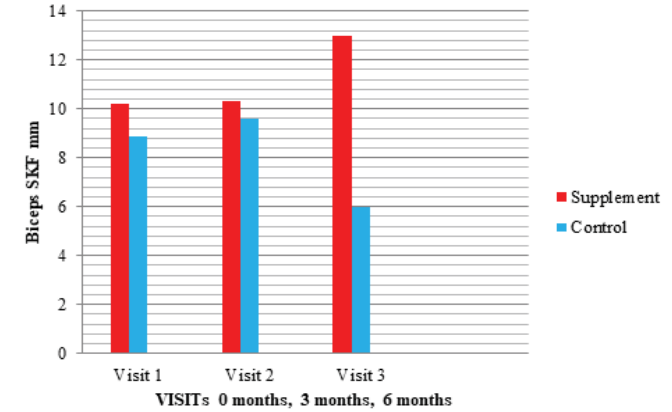

Figure 7 a: Effect of ONS on Biceps Skinfold Significant Difference in visit 2 and 3 p 0.000 Higher in Supplemented Group.

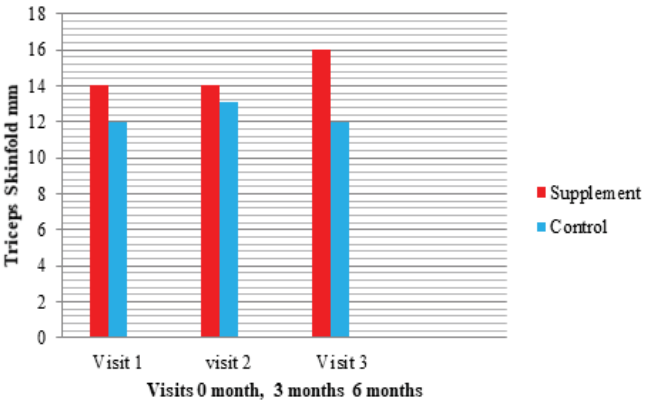

Figure 7 b: Effect of ONS on Triceps Skinfold Significant Difference in visit 2 and 3 p 0.000 Higher in Supplemented Group.

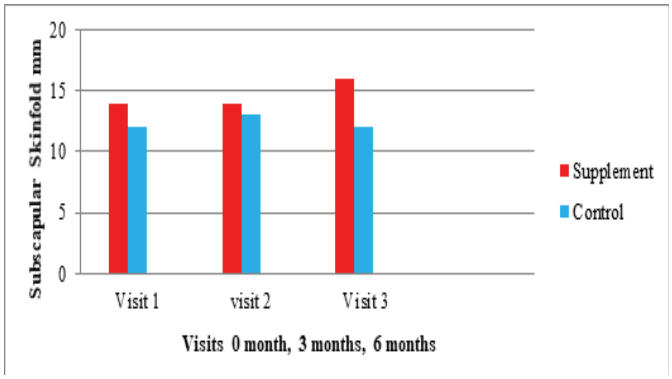

Figure 7 c: Effect of ONS On Subscapular Skinfold Significant difference at visit 2 and 3 p=0.000 Higher in supplemented group.

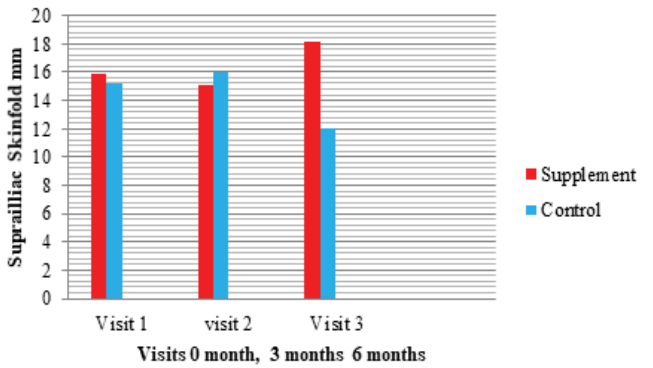

Figure 7 d: Effect of ONS On suprailliac Skinfold Significant difference at visit 2 and 3 p=0.000 Higher in supplemented group.

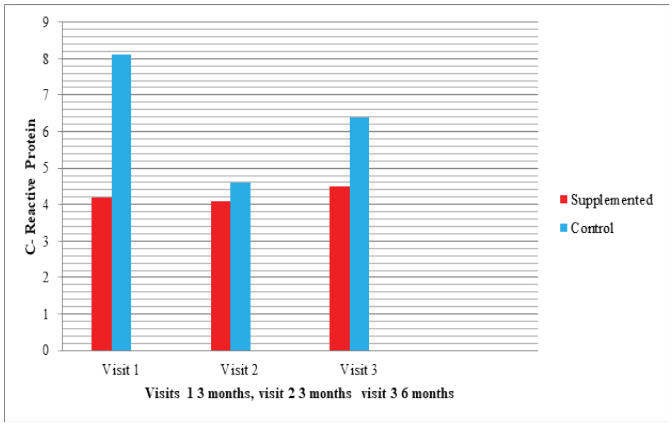

Figure 8: Lower CRP levels In Supplemented Group compared to Controls.

well as compliance to nutritional supplement use was recorded at 0, 3 and 6 months of the supplementation period. Illness, if any, was documented.

Assessment of Quality of Life (QOL): The SF-36 (Medical Outcomes Trust, Boston, MA), a multipurpose, short-form health survey with only 36 questions was used for assessing QOL. The SF-36 consists of eight scaled scores. Each scale is directly transformed into a 0-100 scale. The lower the score, the more the disability. The eight sections are vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health [30].

Statistical Methodology Data were normalized and analyzed for mean standard deviation, correlation and repeated measure anova for paired comparison using SPSS for windows version 17.0 version.

Results

At visit 1, there was no statistically significant difference in the two groups in age, sex, dietary intake, SGA, and lipid profile, serum sodium, potassium, phosphorus, calcium, PTH, coagulation profile except serum albumin level which was 3.2 ±0.41g /dL in group 1 and 3. 37±0.35 g /dL in group 2 (Table 1). In the control group the serum albumin level declined. At baseline the dietary energy and protein intake were higher in the control group but with intervention, the energy and protein intake increased significantly in the intervention group compared to control group (Figures 3-5(a,b)). By the end of the study the serum albumin increased above 3.8 g/dL in the intervention group (Figure 6(a,b)). CRP levels though were high in both the groups, but they were significantly higher in the control group compared to the intervention group (Figure 7(a,b,c,d), Figure 8). The quality of life in terms of regular daily activities, social role, mental health significantly improved intervention group compared to control group (Table 2,3).

Discussion

Malnutrition is common in patients on maintenance hemodialysis, affecting 40-70% patients [1]. Uremic toxins lower appetite and contribute to decline in nutrition once the patient is on maintenance hemodialysis (HD) [3]. Malnutrition leads to increased morbidity and mortality with increased hospitalization rates, increased susceptibility to infections, wound healing impairment, fatigue and poor rehabilitation [12]. It is known that enteral multinutrient support

Table 2: Three Days and 24 Hour Dietary Energy and Protein Intake of Patient Groups.

	Supplement N=91	**Control N=87**	**Supplement N=77**	**Control N=69**	**Supplement N=70**	**Control N=58**
Energy*	**1546.06± 397.24**	**1607.41±396.72**	**1774.73± 535.9**	**1730.49± 408.15**	**1891.31± 490.65**	**1813.26± 464.82**
Protein*	48.35±14.2	51.93±16.4	65.15±21.86	63.49±19.4	67.05±20.7	65.36±19.1
Dialysis Day Energy And Protein Intake Repeated Measures ANOVA Sign. Difference between groups p 0.000						
Energy	**1547.52± 432.75**	**1460.77±418.84**	**1596.68± 411.56**	**1597.14± 526.50**	**1615.59± 445.08**	**1585.83±425.93**
Protein	52.9± 17.34	48.36±14.1	61.88±15.97	56.77±15.9	103.09±363.9	58.98±15.9
Weekend Day Energy And Protein Intake Repeated Measures Anova Sign. Difference between groups p 0.000						
Energy	**1563.26± 434.8**	**1577.96± 459.45**	**1590.13± 456.60**	**1745.14± 538.42**	**1728.04± 523.31**	**1798.2± 501.30**
Protein	55.13±17.3	54.86±17.8	64.64±20.36	65.37±23.1	67.62±24.45	69.82±25.4
24 Hour Dietary Recall - Energy And Protein Intake Repeated Measures ANOVA Sign. Difference Between Groups p 0.000						
Energy	**1495.06± 429.40**	**1556.58± 428.06**	**1571.3± 449.69**	**1616.63± 552.42**	**1706.93± 490.41**	**1686.98± 520.73**
Protein	57±19.31	59.18±23.4	53.28±17.65	51.37±17.9	61.62±22.21	59.96±19.5

Table 3: SF36 Questionnaire: Comparison of Visit 1 and 3.

No	Questions	**P values**	
		Supplemented Group	**Control Group**
1	**In general, would you say your health**	**.026**	0.045
2	Compared to one year ago, your health now	**.010**	0.093
3	Vitality: limitation in movements	440	0.402
4	Problems with work or regular daily activities as a result of physical health	.001	142
5	Problems with work or other regular daily activities as a result of any emotional problems	.004	.243
6	Physical health or emotional problems interfered with normal social activities	.005	.081
7	Bodily pain	.199	.566
8	Social Role Functioning: Pain interference with work both outside the home and housework	.102	.024
9	Mental Health	.001	.242
10	General health perceptions	0.554	564
11	Final Score	0.001 Improved	.047 Poor

significantly increases serum albumin and improves total dietary intake which may improve clinical outcome [12] Oral nutritional supplementation given during hemodialysis improves nutritional markers in malnourished chronic hemodialysis patients [29].

A randomized crossover design evaluated impact of oral protein supplementation given during hemodialysis and peritoneal dialysis (n=49) showed increase in serum albumin, normalized protein catabolic rate (nPCR), and *reduction* total hospitalizations, and length of stay were compared in patients who received protein supplements with those who did not30-35. A randomized, controlled, nonblinded, parallel trial on 92 hemodialysis patients evaluated change in SGA score and malnutrition-inflammation score (MIS) with 3 treatment groups (23 patients each) received 220mL of fermented vitamin E-fortified whey beverage (15g of whey protein concentrate + 600IU of vitamin E) or 220mL of fermented whey beverage (15g of whey protein concentrate) or vitamin E (600IU) 3 times a week for 8 weeks. The control group (23 patients) received no intervention and concluded that whey protein in the form of a new fermented whey beverage and vitamin E supplementation may improve SGA score and MIS in the short term. The overall caloric intake and protein intake of patients on hemodialysis was found to be deficient. This has been found in Indian study previously also where malnutrition was found in 58% of patients on HD [30-37].

The present study explored effect of renal specific nutritional supplement on hypoalbuminimic patients on maintenance dialysis [19,20] and found that intervention with renal specific oral nutritional supplements improves nutritional status as seen in improvement of serum albumin, and skinfold thickness. A similar study as ours was conducted on patients with CKD in which 3 daily servings of ONS given for 6 months improved serum albumin and anthropometric measures, as well as reduced EPO dose [12]. A recently published prospective controlled trial [34] showed that nutritional supplementation with renal specific nutrients during hemodialysis have significant positive impact on nutritional parameters, glycemic variability, hospitalization rate in malnourished hemodialysis patients. Among several factors that contribute to protein energy malnutrition, decrease protein and energy intake is one important factor that is treatable. Several reports indicated that protein and energy intake is usually low than recommended value in maintenance hemodialysis patients [18,19]. Decreased nutritional intake may be a function of uremia itself, leading to anorexia that may also be associated with disorders in taste, fatigue, and nausea and/or vomiting [20,21]. Dietary advice carried forth from predialysis days that may have advocated for a low-protein diet coupled with intake restrictions for potassium, sodium, and phosphorus also may have residual effects on the patient's will to eat even after initiation of dialysis therapy [22,23]. It is estimated that approximately 6-8 grams of amino acids (approximately 40 grams of protein) are lost into the dialysate and 200 Kcal of extra energy is utilized during hemodialysis [24-26]. In addition to that hemodialysis has been shown to result in a net catabolic state that predisposes to protein breakdown due to activation of inflammatory mediators [27-28]. Supplementing renal specific oral nutrition during hemodialysis session when amino acid loss is maximum and catabolism is at its peak, will compensate the dialysis associated catabolism. Another important aspect of oral nutritional supplementation is its financial advantages over intradialytic parental nutrition (IDPN). Moreover studies showed that IDPN when compared with oral nutritional supplement does not improve 2 year mortality event, hospitalization rate, BMI or laboratory markers of nutritional status in malnourished hemodialysis patients [29]. Hemodialysis patients are particularly at risk of developing protein energy malnutrition and use of oral nutritional supplements may have been responsible at least in part (in addition to focus on vascular access and other issues) for improved survival as reported in the Right Start Program Right Start program showed that consuming a meal enriched in protein and energy during hemodialysis treatments led to a positive protein balance to the same extent as on a nondialysis day. In a multicenter Right Start Program [30], a total of 918 CHD incident patients were prospectively enrolled and compared with a time-concurrent group of 1020 control patient from non-RightStart clinics. RightStart patients received 3 months of intervention in management of anemia, dosage of dialysis, nutrition, and dialysis access and a comprehensive educational program. At 3 months, RightStart patients had higher albumin and hematocrit values and after 12 months follow up mean hospitalization days per patient year were reduced with RightStart versus control subjects. Compared with baseline, Mental Composite Score for RightStart patients improved significantly as was observed in improvement of mental health and quality of life in our study using SF36 questionnaire. This study shows that supplementation with ONS significantly improved health, able to deal better with problems related to work or regular daily activities as a result of physical health, there was improvement in physical health or emotional problems which interfered with normal social activities and mental health.

Pupim et al [38] extended these observations by showing not only protein accumulation and skeletal muscle protein homeostasis during dialysis with intradialytic oral nutritional supplements, but also continued anabolic benefit for muscle protein metabolism in the postdialysis period. Although the inflammatory state adds complexity to the management and prognosis of malnourished maintenance hemodialysis patients, nutritional interventions in this patient population may still contribute to a net anabolic effect in the presence of inflammation.

Hypoalbuminemia is most likely the strongest predictor of mortality among MHD patients [19,30-39]. Seven randomized and nonrandomized trials with ONS reported significant improvements in serum albumin levels [6-10,12,14]. In our study population, a significant increase in serum albumin was observed only in the renal specific ONS group with serum albumin increasing to >3.8 g/dL at the end of the follow-up period. Therefore, it seems reasonable to consider the significant improvement in serum albumin as well as nutrition status in patients receiving ONS to result in lower inflammatory status [40,41]. It is worth noting that a significant increase in skinfold thickness was evident in the RS-ONS group, while the control group showed a significant decline as also observed in other studies.

Conclusion

This study shows that supplementation with ONS significantly improved health, and patients were able to deal better with problems related to work or regular daily activities as a result of physical health, there was improvement in physical health or emotional problems which interfered with normal social activities and mental health. Protein-rich renal specific nutritional supplement given daily along with standard nutritional diet of 1.2 g/kg/d raised serum albumin and increased skin fold thickness in patients with PEW undergoing dialysis. At the end of the study, patients in supplemented group showed improvement in nutritional status compared to controls. The functional capability as per SGA score improved significantly in supplemented group compared to control (p=0.001). There was significant improvement in Quality of life of supplemented group after 6 months in terms of vitality, emotional, mental and social health. Given the poor dietary intake of adequate energy and protein in dialysis patients, renal specific dietary supplements form the most effective measure to improve nutritional status and quality of life of patients on dialysis to correct PEW.

Future directions

Whether protein-energy-wasting(PEW) is causally related to adverse outcomes in CKD needs to be verified in randomized

controlled trials of nutritional interventions. The initiation of major clinical trials targeting nutritional interventions with the goal of improving survival in CKD offer the promise of extending the survival of this vulnerable patient population.

This work was presented at ASN Renal week 2016.

References

1. Kopple JD (1997) Protein-energy malnutrition in maintenance dialsis patients. *Am J Clin Nutr* 65: 1544-1557.
2. Mehrotra R, Kopple JD, Wolfson M (2003) Metabolic acidosis in maintenance dialysis patients: clinical considerations. *Kidney Int Suppl* : S13-25. [crossref]
3. Kalantar-Zadeh K, Ikizler TAA, Block G, Avram MM, Kopple JD, et al. (2003) Malnutrition-inflammation complex syndrome in dialysis patients: causes and consequences. *Am J Kidney Dis* 42: 864-881.
4. Bergström J, Lindholm B (1998) Malnutrition, cardiac disease, and mortality: an integrated point of view. *Am J Kidney Dis* 32: 834-841. [crossref]
5. Dong J, Wang T, Wang HY (2006) The impact of new comorbidities on nutritional status in continuous ambulatory peritoneal dialysis patients. *Blood Purif* 24: 517-523. [crossref]
6. Brunori G, Camerini C, Cancarini G, Manili L, Sandrini S, et al. (1992) Hospitalization: CAPD versus hemodialysis and transplant. *Adv Perit Dial* 8: 71-74. [crossref]
7. Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, et al. (2008) proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. *Kidney Int* 73: 391-398.
8. Lopes AA, Bragg-Gresham JL, Elder SJ, Ginsberg N, Goodkin DA, et al. (2010) Independent and joint associations of nutritional status indicators with mortality risk among chronic hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *J Ren Nutr* 20: 224-234. [crossref]
9. Clinical practice guidelines and NKF/K/DOQI 2000 guideline 15,16,17,19 check *Am J Kid Dis* 35 S2: 1-141.
10. Fouque D, Vennegoor M, ter Wee P, Wanner C, Basci A, et al. (2007) EBPG guideline on nutrition. *Nephrol Dial Transplant* 22: ii45-87. [crossref]
11. Jager KJ, Merkus MP, Huisman RM, Boeschoten EW, Dekker FW, et al. (2001) NECOSAD Study Group. Nutritional status over time in hemodialysis and peritoneal dialysis. *J Am Soc Nephrol* 12: 1272-1279.
12. Cancarini G, Costantino E, Brunori G, Manili L, Camerini C, et al. (1992) Nutritional status in long-term CAPD patients. *Adv Perit Dial* 8: 84-87.
13. Siren Sezer, Zeynep Bal, Emre Tutal, Mehtap Erkmen Uyar, Nurhan Ozdemir Acar, et al. (2014) Long-Term Oral Nutrition Supplementation Improves Outcomes in Malnourished Patients With Chronic Kidney Disease on Hemodialysis. *JPEN J Parenter Enteral Nutr* 38: 960-965.
14. D Rangarajan, S Ramakrishnan, KC Patro, G Vakrani, S Badrinath, et al. (2014) A study of impact of cost-effective nutritional supplement in patients on maintenance hemodialysis. *Indian J Nephrol* 24: 222-225.
15. RA Elias, A et al. (2008) R Poole Effectiveness of Protein S supplementation …*CAPD Adv Peritoneal Dial* 24.
16. Replacement of Renal Function by Dialysis edited by C. Jacobs, C. M. Kjellstrand, Karl-Martin Koch
17. Aguirre-Galindo BA, Prieto-Fierro JG, Cano P, Abularach L, Nieves-Renteria A, et al. (2003) Effect of polymerics diets in patients on continuous ambulatory peritoneal dialysis. *Perit Dial Int* 23: 434-439.
18. Boudville N, Rangan A, Moody H (2003) Oral nutritional supplementation increases caloric and protein intake in peritoneal dialysis patients. *Am J Kidney Dis* 41: 658-663.
19. SH Han, DH Han (2012) Nutrition in Patients on peritoneal dialysis Nature Reviews Nephrology 8, 163-175; Assessment Of Nutritional Status And Correlation Between Nutritional Status And Solute Clearance
20. Abdu A, Ladeira N, Naidoo S, Naicker S (2011) The nutritional status of continuous ambulatory peritoneal dialysis patients at a Johannesburg hospital. *Afr J Clin Nutr* 24: 150-153.
21. Ansen MM (2005) Predictors Of Survival In Anuric Peritoneal Dialysis Patients Kidney International 68: 1199-1205.
22. Kalantar-Zadeh K1, Streja E, Kovesdy CP, Oreopoulos A, Noori N, et al. (2010) The obesity paradox and mortality associated with surrogates of body size and muscle mass in patients receiving hemodialysis. *Mayo Clin Proc* 85: 991-1001. [crossref]
23. Pei-Yu Wu, Chien-Tien Su, Hui-Wen Chang, Alice Lan, Shwu-Huey Yang, et al. (2016) The Effect of a Nutritional Supplement on Chronic Kidney Disease Patients. *Journal of Food and Nutrition Research* 4: pp 115-120.
24. Gopalan C, Shashtri RBV, Balasubramaniam SC (2001) Nutritive Value of Indian Foods. National Institute of Nutrition, Indian Council of Medical Research, Hyderabad.
25. Lady Irwin College (1995) Basic food Preparation. A Complete Manual. Orient Longman, New Delhi. Pp357.
26. Pasricha S, Rebello LM (1998) Some Common Indian Recipes and their Nutritive Values. National Institute of Nutrition, Indian Council of Medical Research, Hyderabad
27. Ketel IJG, Volman MNM, Seidell JC, Stehouwer CDA, Twisk JW, et al. (2007) Superiority of skinfold measurements and waist over waist-to- hip ratio for determination of body fat distribution in a population-based cohort of Caucasian Dutch adults. *Eur J Endocrinol* 156: 655-661.
28. Menke A, Muntner P, Wildman RP, Reynolds K, He J (2007) Measures of adiposity and cardiovascular disease risk factors. *Obesity (Silver Spring)* 15: 785-795. [crossref]
29. Ryan MC, Farin HMF, Abbasi F, Reaven GM (2008) Comparison of Waist Circumference Versus Body Mass Index in Diagnosing Metabolic Syndrome and Identifying Apparently Healthy Subjects at Increased Risk of Cardiovascular Disease. *Am J Cardiol* 102: 40-46.
30. HALT PKD, Quality of Life Questionnaire (SF-36v2 TM Health Survey), Form 38 Version 1, 05/06/2009
31. Early Intervention Improves Mortality and Hospitalization Rates in Incident Hemodialysis Patients: RightStart Program Clinical Journal of the American Society of Nephrology 2(6):1170-5 · December 2007
32. Moretti HD, Johnson AM, Keeling-Hathaway TJ (2009) Effects of protein supplementation in chronic hemodialysis and peritoneal dialysis patients. *J Ren Nutr* 19: 298-303.
33. Sohrabi Z, Eftekhari MH, Eskandari MH, Rezaianzadeh A, Sagheb MM (2016) Intradialytic Oral Protein Supplementation and Nutritional and Inflammation Outcomes in Hemodialysis: A Randomized Controlled Trial. *Am J Kidney Dis* 68: 122-130. [crossref]
34. Rangarajan, S Ramakrishnan, KC Patro, G Vakrani, S Badrinath (2014) A study of impact of cost-effective nutritional supplement in patients on maintenance hemodialysis. *Indian J Nephrol* 24: 222–225.
35. Tapiawala S, Vora H, Patel Z, Badve S, Shah B (2006) Subjective global assessment of nutritional status of patients with chronic renal insufficiency and end stage renal disease on dialysis. *J Assoc Physicians India* 54: 923-926. [crossref]
36. Pratim Sengupta, Sumanta Biswas, Tapas Roy, Dr.Sheuli Chowdhury, Jaita Singha Roy, et al. (2016) Therapeutic Effect of Intradialytic Renal Specific Oral Nutritional Supplementation in patients undergoing maintenance haemodialysis. *Journal of Renal Nutrition and Metabolism* 2: 35-42.
37. Early Intervention Improves Mortality and Hospitalization Rates in Incident Hemodialysis Patients: RightStart Program Clinical Journal of the American Society of Nephrology 2(6):1170-5 · December 2007
38. Lara B Pupim, Paul J Flakoll, John R Brouillette, Deanna K Levenhagen, Raymond M Hakim, et al. (2002) Intradialytic parenteral nutrition improves protein and energy homeostasis in chronic hemodialysis patients. *J Clin Invest* 110: 483-492.
39. Srinivasan Beddhu, Rebecca Filipowicz, Xiaorui Chen, Jill L Neilson, Guo Wei, et al. (2015) Supervised oral protein supplementation during dialysis in patients with elevated C-reactive protein levels: a two phase, longitudinal, single center, open labeled study BMC Nephrology 1-8.
40. Leavey SF, Strawderman RL, Jones CA, Port FK, Held PJ, et al. (1998) Simple nutritional indicators as independent predictor of mortality in hemodialysis patients. *Am J Kidney Dis* 31: 997-1006.
41. Kopple JD, Zhu X, Lew NL, Lowrie EG (1999) Body weight-for-height relationships predict mortality in maintenance hemodialysis patients. *Kidney Int* 56: 1136-1148.