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Research Article

Can ENZOTEIN (Proteolytic Enzyme Fortified Protein Supplement) be an Effective Alternative as Low Dose Protein Supplement in Malnourished Low Income End Stage Renal Disease Patients?

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ABSTRACT

Introduction: Nutritional derangements are commonly encountered in End Stage Renal Disease (ESRD) patients on hemodialysis. Severe protein energy wasting are observed in 6-8 percent of these patients. Hemodialysis leads to negative protein balance and aggravates renal failure related sarcopenia and cachexia. Often the commercially available nutritional supplements pose a therapeutic challenge in management of protein energy malnutrition (PEM) owing to its high cost and poor adherence. The present study was undertaken in the malnourished low-income group ESRD patients to find the effectiveness of exogenous proteolytic enzyme fortification of low dose protein supplement as an alternative strategy to high dose protein in managing malnutrition in low middle-income country patients undergoing hemodialysis.

Methodology: We conducted a single center prospective randomized controlled trial where 60 ESRD low-income patients on maintenance hemodialysis were included in the study. The candidates were categorised into three groups of 20 each. Baseline demographic, clinical and data for laboratory assessment of nutritional parameters were collected and repeated at the end of study (6 weeks). Apart from the standard care, Group 1 received Enzotein- Whey protein 15 grams plus Proteolytic enzyme with 70000 HUT (Haemoglobin unit tyrosine); Group 2 - 30 gms plain whey protein without proteolytic enzyme and Group 3 control group with no supplements.

Results: The intervention Groups 1 and 2 showed improvement in their dry weight by 1.6 kgs and1.4 kgs respectively. The post dialysis recovery time and serum C Reactive Protein (CRP) levels in groups 1 and 2 had declined, which was significant in group 1 compared to Gp 3 ($p < 0.05$). Clinical improvement in the mid arm circumference, Triceps fold thickness, hand grip strength and Malnutrition Inflammatory Score (MIS) were observed in group 1 and Group 2 but were not statistically significant.

Conclusion: Inadequate dietary protein ingestion and or its assimilation is the major cause of PEM in low socio-economic ESRD population. Proteolytic enzyme added low dose protein supplement improved nutritional and inflammatory status similar to that of high dose protein intake. Thus in a resource poor countries, proteolytic enzyme based nutritional supplement can be suggested as alternative strategy to combat PEM in ESRD patients undergoing hemodialysis.

Keywords: Protein energy malnutrition; End stage renal disease; Haemodialysis; Proteinase and protein supplement

INTRODUCTION

Nutritional supplement is a recommended therapeutic strategy to the challenging public health issue of Protein Energy Malnutrition (PEM) in End Stage Kidney Disease (ESRD) patients. Severe protein energy wasting are often observed in 6-8 percent ESRD and is more prevalent in lower socio-economic class. The etiology of PEM is multifactorial and is commonly observed in those undergoing Hemodialysis (HD) or Continuous Ambulatory Peritoneal Dialysis (CAPD) [1-3]. Nutritional derangements due to poor appetite, reduced protein intake, dietary restrictions, socio-economic factors, metabolic acidosis, enhanced protein degradation, coupled with hemodialysis associated loss of amino acids lead to negative protein balance and chronic inflammatory state perpetuating Protein Energy Wasting (PEW) and a syndrome collectively described as Malnutrition Inflammatory Cachexia Syndrome (MICS) [1,2,4]. The other clinical consequences of PEM includes an increase in frequency of infections, immune dysfunction, hormonal resistance, sarcopenia, cachexia, impaired quality of life, cardiovascular complications and a decrease in the overall state of well-being resulting to fourfold increased risk in mortality [5,6].

Pancreatic inflammation and malabsorption are often associated with impaired protein digestion in ESRD population [7,8] maldigested peptides upon degradation in the gut generate uremic toxins like p-cresyl sulfate, indoxyl sulfate and thiols. These toxins get absorbed into systemic circulation which create a uremic milieu. In addition to this altered microbial flora and gut dysbiosis also contribute to systemic inflammation in ESRD [9]. Efficient therapies or guidelines to correct this complex disorder have been a constant challenge [10].

It is a well-known fact that regular intake of protein rich meals during HD sessions helps to offset the muscle losses, HD induced catabolism and builds up the anabolic potential [11-13], similar observations have not been extensively studied in Low Middle Income Category (LMIC) patients.

However, the role of plant-based protein supplements is increasingly recommended [14] there is sparse literature to support its favorable effects in LMIC ESRD population. The present study was undertaken to see if proteolytic enzyme fortified protein supplement at half the dose of regular protein supplement can halt or reverse the malnutrition in LMIC patients undergoing hemodialysis.

MATERIALS AND METHODS

Study design

We conducted a single center prospective randomized controlled trial where 60 ESRD low-income patients on maintenance hemodialysis enrolled in government subsidized dialysis programme in our hospital were included in the study out of 200 patients screened. Study conducted between October 2019 till December 2019 (6 weeks). The candidates categorized into three groups of 20 each. Apart from the standard care, each group of patient were given divided to receive the following

- Group I received Enzotein 15 grams (Proteolytic enzyme with 70000 Haemoglobin unit tyrosine (HUT) fortified with 15 Grams Whey Protein)
- Group II received double dose of plain whey protein (30 grams) without proteolytic enzyme
- Group III control group received no supplement.

The proteolytic enzyme, whey protein were all purchased from hospital pharmacy marketed by licensed pharmaceutical company. As per the laboratory certification proteolytic enzyme had ability to breakdown proteins to amino acid and lower peptides within fifteen minutes of constitution of whey protein with plain water. Enzyme fortified 15 Gm whey protein supplement and 30Gms plain whey powder was reconstituted with 150ml water and orally administered to Gp1 and Gp2 respectively. Whereas in Group 1 it was given after 10 Min of reconstitution, it was administered orally immediately in Gp2. Both groups received supplement 30 minutes before

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Hemodialysis (HD) session. Baseline demographic, clinical and data for laboratory assessment of nutritional parameters were collected and repeated at the end of study (6 weeks). The study had approval from the institutional ethical committee. N 010/09/2019/IEC/SMCH

Patients who were included in the study were screened for eligibility as per inclusion criteria with informed written consent.

Inclusion criteria

- Low income Patients were recognized as per their financial status wherein those whose family income was less than 350USD per month were considered as LMIC and the same criteria which made them eligible for Government subsidized dialysis programme (low income group)
- Age of 18 years and above with a BMI< 22 kg/m2 as less than 18 yrs were not eligible for providing consent
- Patients on maintenance hemodialysis for > 6 months fulfilling criteria of malnutrition
- Initiated in hemodialysis at least two times a week

Exclusion criteria

- Patients with hemodynamic instability and unstable dry weight
- Patients requiring frequent admissions
- Patients with gastrointestinal disturbances or history of gastrointestinal surgery.
- Patients on immunosuppressant
- Patients having co morbid chronic illnesses like tuberculosis / malignancy
- Patients with cognitive impairment and mental illness. Patients below 18 who cannot give consent and those diagnosed with genetic kidney diseases.
- Patients already receiving nutritional supplements.
- Participants with an allergy to any ingredients in the nutritional supplements or family history of intolerance to any milk products

Participants were asked short oral questionnaire during each dialysis session regarding their general well being, palatability, intradialytic oral intake and for those in the intervention arm information about the amount of supplement taken any adverse reaction noted during dialysis Baseline demographic data as well as comorbidities, etiology of CKD, dialysis vintage and dry weight recorded. Dry weight was defined by a state of euvolemia in dialysis patients by the application of clinical criteria in absence of breathlessness, symptomatic dialysis associated hypotension or hypertension, pulmonary rales, pedal oedema and muscle cramps. Anthropometric measurements like Handgrip strength, Malnutrition Inflammatory Score (MIS), triceps fold thickness, mid-arm circumference, Weight in kg. Handgrip strength was measured by dynamometry. MIS was calculated by a Questionnaire. Mid-arm circumference was measured using a measuring tape placed at the mid-point between the tip of the shoulder and the tip of the elbow (tip of olecranon process and the tip of acromian process) and triceps fold thickness was measured using calipers placed midway between the acromian process of the scapula and the olecranon process of the ulna. Laboratory parameters data included serum albumin, CRP, serum creatinine, serum electrolytes, serum bicarbonate were recorded at baseline, and at the end of the intervention (6 weeks).

Outcomes

This study was designed to assess feasibility outcomes and determine whether low dose protein supplement with enzyme fortification (ENZOIETIN) or without it is non inferior and cost effective alternative to high dose protein supplement in combating PEM in low income ESRD patients.

Statistical analysis

The IBM SPSS 19 software was calibrated which performed our statistical analysis and documentation was done using Microsoft Excel spreadsheet. The primary endpoint was the differences of laboratory and clinical outcome compared across all the groups at baseline and at the end of intervention at 6 weeks. The data is presented as mean+/-SD. The $p < 0.05$ was interpreted as statistically important as far as the significance of the tests were concerned.

RESULTS

Out of 200 screened candidates 60 patients were found eligible and met the criteria for the study. They were assigned into three groups of 20 each based on computer software for randomization. Comparison was made individually between Gp1 and Gp3 and Gp2 and Gp3 wherein Gp3 was control gp and Gp1 patients received half the dose of whey protein with proteolytic enzyme to that of gp2 which had only whey protein devoid of any enzymes. Their baseline demographic profile, co-morbidities and laboratory parameters and p value of significance are shown in tables 1 and 2.

Most of patients were male and the mean age of all the study groups was 52 years (+/-1.06), 76.66% patients were hypertensive while 38.33% had Type 2 Diabetes. During the study there was a mean of 10mmhg (+/-0.56mmhg) rise of intradialytic systolic blood pressure in 7 candidates of group 1 ,4 candidates of group 2 and 8 candidates of group 3 they were adequately controlled by readjusting their antihypertensives and dialysis prescription. Also we observed a rise in the blood sugar levels in groups 1 and 2 which were measured after each hemodialysis session, although it was not significant ($p > 0.05$). The interdialytic weight gain was 3-3.5kgs (+/-1.4kgs) seen in all the 3 groups. Three patients in Group 1 died during the study. Two patients at first week and one at third week of the study. The death occurred on non dialysis days at home of which two was due to sudden cardiac death and one intracranial hemorrhage due to sharp rise in blood pressure. One patient died each in Group 2 and Group 3 at home both related to cardiac failure and pulmonary edema. Dry weight increased in group 1and 2 by 1.6 kgs and1.4 kgs respectively at the end of 6 weeks as compared to baseline as shown in table 2 while a decline of 0.51 kgs was seen in the control group which has positive correlation with post dialysis recovery time in group 1 and group 2 compared to control. The absolute increase in dry weight was most in group 1. In between group comparison analysis in between group 1 and 2 showed that the improvement in dry weight was statistically significant in both gp 1($p < 0.05$) and 2 compared to gp 3 ($p < 0.05$).The post dialysis recovery time in group 1 and group 2 showed improvement with a mean difference of 2.5 hours in group 1 and 2 hours in group 2 respectively while in control no difference was observed though this was not statistically significant ($p > 0.05$). Serum CRP level in group 1 and group 2 was 18mg/l and 17mg/l at baseline while at the end of 6 weeks it was

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Table 1: Showing the results of the study.

		Group I	Group II	Group III	P value
Mean Age Yrs		52 +/- 1.06	51+/- 1.6	52 +/- 2.34	-
Male		12	15	13	-
Female		8	5	7	-
ESRD	duration	52 +/- 12	57 +/- 18	54 +/- 16	-
(months)					
Dialysis	vintage	25+/- 8	29+/-12	26 +/- 10	-
(months)					
Frequency of Dialysis		2/week	2/week	2/week	-
Residual Urine		<500ml/d	<500ml/d	<500ml/d	-

HBP	18/20		16/20		12/20	-	
DM	8/20		6/20		9/20	-	
						P Value Gp1 Vs Gp3	P Value Gp2 Vs Gp3
Parameters	Week0	Week6	Week 0	Week 6	Week 0	Week 6		
Mean Sys BP mmHg	140+/- 23	158+/- 22	146+/-10	158+/-8	150+/-16	150+- 18	NS	NS
Mean Dias BP	90 +/-12	92+/- 14	98+/-12	90+/-12	90 +/- 12	90+/- 8	NS	NS
Dry weight (kg)	49 +/- 1.3	50.3 +/-2.1	54+/- 0.9	55.4+/-2.1	51+/-1.7	50.49+/-1.2	P<0.05	P <0.05
No of death	0/20	3/20	0/20	1/20	0/20	1/20	-	-
Lab. Values								
s. cr. (mg/dl)	14.33+/2.2	12+/-3.4	14.25+/-1.5	13+/-2.3	14.2+/-3.2	13+/- 2.2	NS	NS
s. urea (mg/dl)	87.63	84	83.9	82	95.02	93	NS	NS
Hb (gm/dl)	8.63	8.7	8.86	8.9	8.74	8.6	NS	NS
C R P	18.89+/-2.3	15+/-2.2	18+/-3.23	16+/-2.29	17+/-2.5	18+/-5.4	P<0.05	NS
S. Albumin (mg/dl)	3.35+/-0.5	4+/-0.3	3.25+/-0.7	3.3+/-0.5	3.35+/-0.25	3.4+/-0.2	NS	NS
S. Potassium (meq/l)	5.28+/-0.8	4.8+/- 0.7	5.58+/-1.2	4.9+/-1.0	5.11+/-0.6	5.2+/-0.8	NS	NS
S.Po4	4.51+/-2.3	3.9+/-1.2	4.61+/-3.4	3.9+/-2.3	3.91+/-3.2	3.3+/-2.4	NS	NS
S. calcium(mg/dl)	8.66+/-0.9	9+/-0.5	8.71+/-0.4	8.9+/-1.0	8.67+/-0.8	8.8+/-1.2	NS	NS
S. Hco3	21.59+/-4	24/-1,5	20.7+/-2.0	23.5+/-1.8	21.57+/-1.9	22+/-3.4	NS	NS
S.Na(meq/l)	133.87+/-14.5	134+/-18	138.52+/- 12	136+/-10.9	132.8+/-12	136+/-8.9	NS	NS

ESRD: End Stage Kidney Disease; HBP: High Blood Pressure; DM: Diabetes Mellitus; Sys: Systolic; Dias: Diastolic; S: Serum; Cr: Creatinine; Hb: Hemoglobin; CRP: C Reactive Protein; po4: phosphorus; Hco3: Bicarbonate; Na: Sodium; MIS: Malnutrition Inflammatory Score.

Table 2: Showing Athropometric results and Changes in dry weight and Post dialysis recovery time at the end of 6 weeks.

	Gp 1	Gp2	Gp3	P Value
Mean Dry Weight day 0	49 +/- 1.3	54+/- 0.9	51+/-1.7	-
Mean Dry weight 6Wk	50.3 +/-2.1	55.4+/-2.1	50.49+/-1.2	-
Mean Wt Gain end of study	1.6+/-0.8	1.4+/-0.5	-.0.51+/-0.23	<0.05
PDRT In hrs Day0	10.5+/-3.2	11.0 +/- 3.0	10.5+/- 3.4	--
PDRT day 6 WK	8.0+/- 1.2	9+/-1.2	10.5+/- 4.2	-
Mean Change in PDRT end of study	-2.5+/-0.76	-2.0+/- 0.5	0	<0.05
Midarm Circumference d 0	20.8+/-2.4	21.6+/-2.2	19.05+/-3.4	-NS
Midarm Circumference 6 Wks	20.9+/-2,8	21.8+/-3.0	19.05+/-2.3	NS
TFT day 0	15.68+/-3.5	16.75+/-2.3	14.85+/- 2.2	NS
TFT day 6 wks	15.8+/-1.2	16.9 +/-2.3	14.83+/-1.9	NS
Hand Grip D Day o	18/20	13/20	16/20	NS
Hand Grip C Day Wk	8/17	8/19	1/19	NS
MIS Day 0	10	11	10	NS
MIS wk	8	9	10	NS

PDR: Post Dialysis Recovery time; TFT: Tricuspid Fold Thickness; Wk week.

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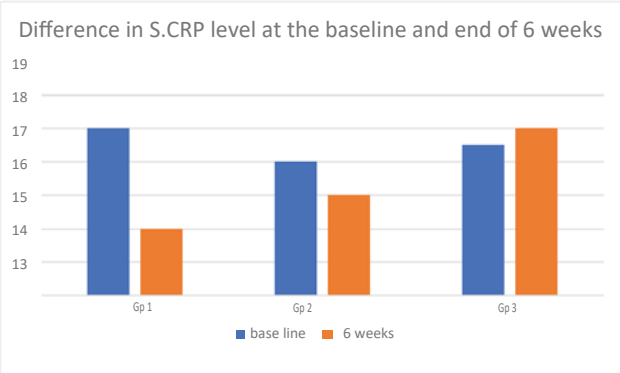

Figure 1: Mean difference in serum CRP at baseline and at the end of 6 weeks.

15mg/l and 16mg/l in the intervention groups. The decline in the level of serum CRP from baseline was higher in group 1 which was statistically significant ($p < 0.05$) while in group 2 and group 3, it was statistically insignificant. There was an increase in serum albumin levels in all the 3 groups with a p value of 0.07 making it statistically insignificant. Similarly, the changes in serum electrolytes, serum bicarbonate, serum calcium, serum phosphate, serum urea, serum creatinine were also not significant. There was an improvement in the mid arm circumference observed in intervention groups as compared to baseline yet no statistically significant change could be observed. Improvement were also observed in Triceps fold thickness and hand grip strength in Group 1 and Group 2 compared to Group 3, however changes were minimal and not statistically significant. Malnutrition Inflammatory Score (MIS) in group 1,2 and 3 at baseline was 10,11,10 respectively while at 6 weeks it was 8,9,10. Although it had improved in intervention groups, it was not significant statistically.

DISCUSSION

Important factors for Protein Energy Malnutrition in dialysis patients are the poor nutritional status of the patient before and after commencing dialysis therapy due to poor intake and associated acute and chronic illnesses. Improving the nutrient intake of maintenance dialysis patients is a challenging task because most chronic renal failure patients with malnutrition are anorexic, and dietary counseling has had limited success at increasing their nutrient intake [1]

Proteases are protein splitting degradative enzymes and show specificity and selectivity in protein modification. Although its use in medical therapeutics is increasingly recognized for its ability to digest whey protein and improved absorption of amino acids no proven data exists for its use in ESRD patients who have impaired ability in protein digestion. *Julius Oben* [15] et al in their study has demonstrated digestive proteases increased the absorption rate of processed whey protein concentrate over controls, with significant increases in Area Under Curve, total serum amino acid levels and nitrogen balance. Along with significant decreases in CRP levels and fluxes in amino acid levels. In the present study oral nutritional supplement ONS given just before HD sessions over a period of 6 weeks significantly improved nutritional parameters in both high protein Group 2 and proteinase fortified lower dose protein Group-1 when individually compared with Group 3 in whom no supplement was given.

Amino acids as supplements are effective in combating dialysis induced amino acid losses. This sudden loss of amino acid from the serum in the first hour of dialysis through dialysate which in turn triggers release of muscle degrading factors resulting in muscle wasting and delays post dialysis recovery time. Limitations in use of amino acid supplement include its cost and administration though intravenous route which makes it a limitation in regular use [15].

CKD-related sarcopenia develops rapidly as a result of the negative energy-protein balance owing to nutritional derangements coupled with increased protein catabolism, reduced regenerative potential, enhanced resistance to anabolic hormones in HD patients. Sarcopenia reflects not just the loss of muscle mass and reduced muscle strength but also a decline in the physical function due to chronic inflammatory state causing significant weight loss and cachexia [16]. The loss of muscle mass, especially of skeletal muscle mass, is directly associated with diminished strength and indirectly associated with worse Quality of Life (QoL), increased vulnerability to undesirable long-term fatal outcomes such as falls, loss of independency and, ultimately, higher hospitalization rates and mortality [17].

Sezer et al [18] had observed that of 62 malnourished patients with CKD on HD receiving long-term ONS there was significant improvement in serum albumin and dry weight compared to control group apart from reduction in need for erythropoietin dose there was also reduction in malnutrition inflammatory score MIS. In our study although we observed significant improvement in dry weight yet the short duration of study was inadequate to look into long term improvement in other parameters.

Post Dialysis recovery time in the present study showed a significant reduction in both gp1 and gp 2 when compared each with Gp3. In many studies that describes non invasive evaluation of muscle mass by ultrasonography or improved outcomes after oral nutritional supplement study on post dialysis recovery time being subjective has not been taken into consideration in most of the study [19,20] . Initial amino acid loss during dialysis from the serum is a major trigger for muscle wasting and delay in recovery post dialysis, supplement given prior to dialysis was important factor that reduced the post dialysis recovery time. Further long term multicenter trial is needed to find if such enzyme fortified protein supplement pre-dialysis can reduce the dose of protein supplement commonly used. *Wang et al,* [20] studied association of MIS with anthropometry and concluded that MIS is strongly linked with indicators of nutrition and is simple and practical tool for assessing nutritional status in patients with CKD. In our study we have observed the improvement in the MIS score at the end of six weeks which indicates a positive sign for patients with malnutrition and CKD in modifying the risk factors. *Rambod et al,* [21] studied association of MIS with quality of life and mortality in patients on HD wherein it was concluded that in patients undergoing HD, MIS is associated with inflammation, poor nutritional status, reduced quality of life, and higher 5-year prospective mortality. The mortality predictability of the MIS appears equal to serum interleukin 6 and somewhat greater than C-reactive protein levels. Considering the other anthropometric parameters which are the true predictors of malnutrition and can be repeated to assess the response to the treatment. Although the nutritional supplement was given only during dialysis days, the improvement in the anthropometric parameters suggest that this could be due to improved nutrition, increased appetite and their wellbeing on the non-dialysis days that allowed protein assimilation. Six weeks were short period to make any conclusion on significance in the present study.

Lalramenga et al, [22] studied CRP significance in CKD patients

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and concluded that high rate of inflammation is seen in them which along with low eGFR and low albumin levels contributes to malnutrition. Markers of inflammations like CRP have also been linked to higher mortality in patients with CKD. In our study a statistically significant difference in CRP levels were observed which showed a decline in significant number of patients receiving Enzotein post intervention which correlates with reduced inflammation. Whereas though the patients in gp2 also showed reduction in CRP levels compared to Gp 3 it was not significant as seen in table 1. However, rest of the laboratory parameters like phosphorus etc did not show any significant difference in their levels in three gps.

Vishal singh [23] in his study done on Chronic ambulatory peritoneal dialysis CAPD patients using bacterial derived protein enzyme along with egg protein had shown improvement in albumin levels in the patients over six months period. The present study was to allow ENZOTEIN after mixing with water to breakdown whey protein to smaller peptides just before ingestion. Based on the in vitro study done by the manufacturer where in at fifteen minutes protein were digested into peptides and amino acids, a reason we were able to meet results with half the regular dose of protein supplement in Group 1 where it showed similar results to that of Group 2 who received 30 grams plain whey protein without enzyme supplement. Hypoalbuminemia is most likely the strongest predictor of the mortality among MHD patients. Although our study showed improvement in serum albumin levels in group 1 and 2, it was statistically insignificant owing to the short-term follow-up. However, long-term studies are warranted to assess the improvement in serum albumin levels.

In our study two patients developed vomiting following intake of Enzotein during first 2 sessions this due to change in the regular taste of whey protein after constitution with water. However, they continued the study and no further similar episodes occurred. The breakdown of protein leads to mild bitter taste due to formation of amino acids and peptides which can be masked using flavors and taste enhancers in future studies.

Three patients in group 1 and one patient in group 2 and group 3 died during the study period. One developed hypertensive complications in the form of intracranial hemorrhage and sudden cardiac death in two patients. Death occurred at home in all three patients in gp 1. In Group 2 and 3 one patient each died of cardiac failure and pulmonary edema. There is an association between blood pressure and serum albumin levels in studied by *Kamal Hassan et al,* [24,25] in the peritoneal dialysis patients who showed that low albumin levels are associated with more extracellular volume overload, decreased ultrafiltration rates, higher MAP and hypertension. In ESRD who are dependent on hemodialysis fluid shift that happens with rise in oncotic pressure is not associated with increased urine output which results in rise of blood pressure. Though this was observed in group 1 and group 2 patients was immediately corrected with escalation of their antihypertensive drugs. Whether sharp rise in BP can happen with nutritional supplement as a result of refilling of vessels subsequent to improvement in oncotic pressure needs close evaluation in future study. This observation is significant in ESRD patients with no residual urine. In normal functioning kidney the filling of vessels is compensated by improved urine output and reduction in blood pressure. This phenomenon is not observed in ESRD patients who develop raise in BP even when hemoglobin level improves. This can be life threatening sometime.

While importance of ONS in patients of PEM in ESRD is well established, literature on the effectiveness of these therapies is limited. In the present study exposure of whey protein with proteolytic enzyme allowed use of lower dose protein thereby reducing not only the cost of supplement but also the side effect of undigested protein that can itself be a cause of inflammation when protein is metabolized in large intestine.

Though this is a single centered study with a small sample size and short duration follow up yet we were able to establish safety of use of proteolytic enzyme based low dose protein supplement to dialysis patients. We also observed that lower dose protein improved inflammatory markers like CRP better that higher dose non enzyme supplemented whey protein gp2 patients. However further multicentre trial is needed to evaluate its long term utility as regular use supplement.

CONCLUSION

Inadequate dietary protein ingestion and or its assimilation is the major cause of PEM in low socio-economic ESRD population. Proteolytic enzyme added low dose protein supplement improved nutritional and inflammatory status similar to that of high dose protein intake. Thus in a resource poor countries, this kind of nutritional supplement is additional choice and alternative strategy to combat PEM in ESRD patients undergoing HD.

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