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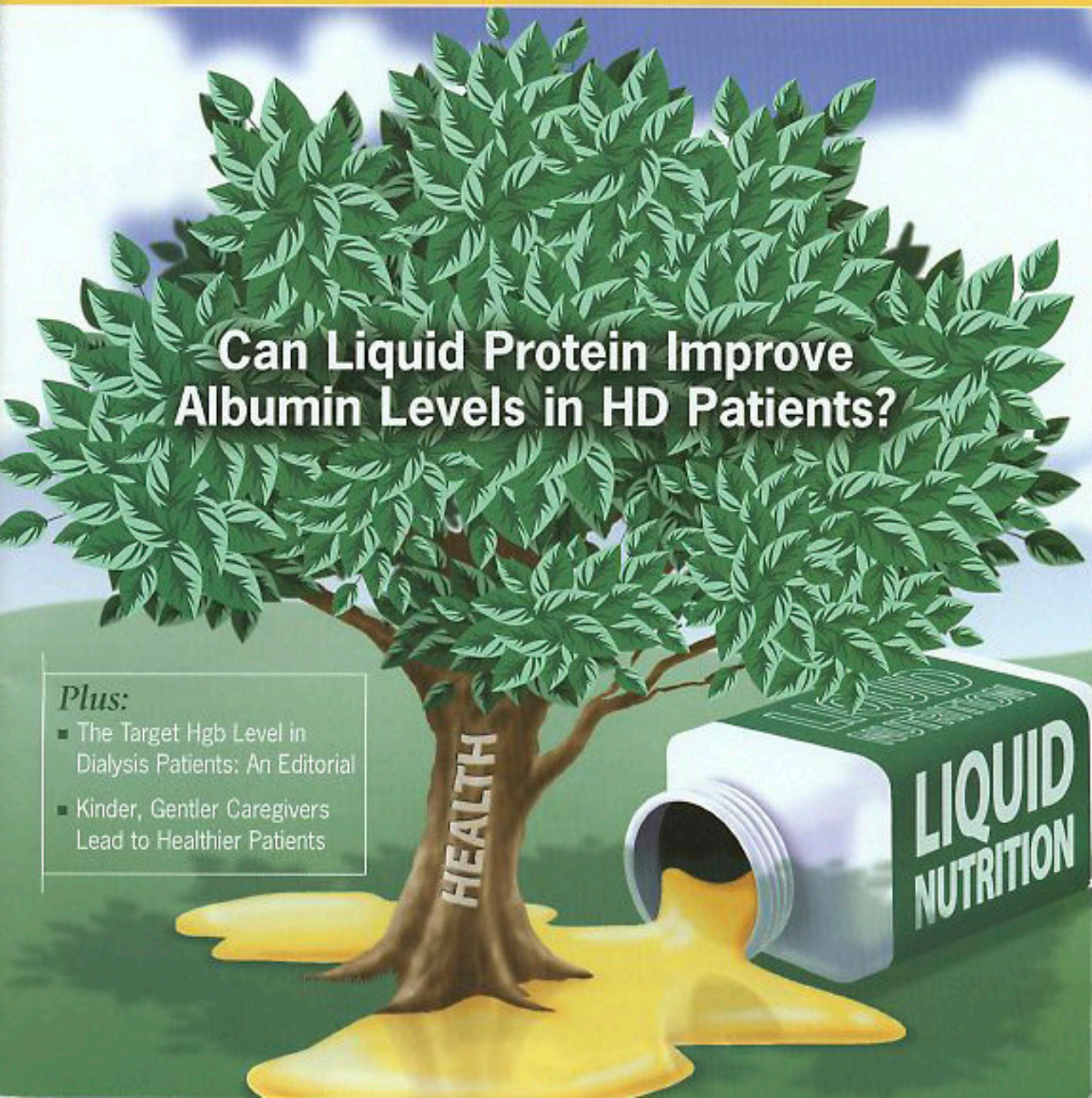

Plus:

- The Target Hgb Level in Dialysis Patients: An Editorial
- Kinder, Gentler Caregivers Lead to Healthier Patients

Can Oral Supplementation with a Collagen-Casein-Based Liquid Protein Improve Serum Albumin Levels in Hemodialysis Patients?

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BACKGROUND: Decreased synthesis of albumin (Alb) results in hypoalbuminemia and occurs because of the interrelationship of inflammation and malnutrition (uremic malnutrition) observed in chronic hemodialysis (CHD) patients. Improving the nutrition status of CHD patients is necessary to prevent and treat uremic malnutrition. The issue remains of how to achieve this goal in CHD patients given the barriers to adequate and appropriate intake such as anorexia, impaired nutrient absorption, and necessary diet modifications.

OBJECTIVE: To determine if oral supplementation with a collagen-casein-based hydrolyzed liquid protein can improve Alb levels in hypoalbuminemic CHD patients.

PATIENTS AND METHODS: The study patients were adult outpatients on hemodialysis for at least 1 year whose serum Alb was between 2.8 and 3.7 g/dL and who had given written consent. Patients (age = 31–90 years) were divided into 2 groups according to days they had dialysis. Controls (n = 21; dialysis days Tuesday, Thursday, Saturday) received standard nutritional counseling. The study group (n = 29; dialysis days Monday, Wednesday, Friday) received 30 mL of liquid protein at the beginning and end of treatment. The main outcome measures were baseline and monthly Alb for 3 months and a subjective assessment of tolerance.

RESULTS: Five subjects in the control group (final n = 16 [49%]) and 12 subjects in the study group (final n = 17 [51%]) did not complete the study. There was not a statistically significant correlation between baseline Alb and baseline CRP, $r = -0.30$ ($p = 0.093$), or between baseline Alb and baseline URR, $r = 0.27$ ($p = 0.14$). Average Alb of the control group did not differ between the baseline (3.43 g/dL) and final (3.44 g/dL) measurements, $t = -0.54$; $df = 15$; $p = 0.60$. In the study group, however, the final average Alb (SD) of 3.73 (0.28) was statistically significantly greater than the baseline average of 3.49 (0.20), $t = -4.19$; $df = 16$; $p = 0.001$.

CONCLUSION: These statistically significant results indicate that oral supplementation with a collagen-casein-based hydrolyzed liquid protein can improve serum albumin levels of hypoalbuminemic CHD patients.

Patients with chronic kidney disease (CKD) undergoing maintenance hemodialysis (HD) have greater morbidity and mortality than individuals with similar demographics in the general population. Risk factors for early death of patients with CKD include advanced age, diabetes, hypertension, and malnutrition.[1]

Improving nutrition status is one of the primary goals of therapy in any metabolically stressed patient population. However, achieving this goal in patients undergoing chronic hemodialysis (CHD) is complicated by the sequelae of end-stage renal disease (CKD stage 5), which include chronic inflammation that results in anorexia and altered taste acuity.[2,3] Depending on the individual, dietary prescriptions can include multiple dietary modifications, such as alterations in the intake of fluid, potassium, sodium, phosphorous, cholesterol, and saturated fat, as well as of carbohydrates if the patient is diabetic. CHD patients are followed closely by renal dietitians, who counsel patients on dietary goals to maintain or improve nutritional status. However, 10%–30% of CHD patients have poor appetite. Malnutrition is evident in about 40% of patients,[4] with its prevalence varying between 23% and 73%.[5,6]

Uremic malnutrition, also referred to as malnutrition-inflammation complex syndrome, describes the interrelationship of malnutrition and inflammation that can occur in CHD patients who have CKD stage 5. In a study of 331 CHD outpatients, Kalantar-Zadeh et al. showed that "anorexia is associated with higher concentrations of proinflammatory cytokines (c-reactive protein and tumor necrosis factor) and higher levels of erythropoietin hyporesponsiveness and poor clinical outcomes, including a four-fold increase in mortality, greater hospitalization rates and poor Quality of Life scores."[2]

FINANCIAL DISCLOSURE: Evelyn Phillips is a consulting dietitian for National Nutrition, Inc., which manufactures Liquid ProSource. She is also a member of the Nestle Nutrition and Ross Nutrition speaker bureaus.

Because of the chronic nature of uremic malnutrition, there is insidious loss of both somatic and visceral protein stores. As such, patients present with loss of lean body mass and low serum albumin (hypoalbuminemia). With loss of appetite, blood urea nitrogen (BUN) levels can also decrease. In CHD, an early clue to poor protein intake can be decreasing BUN. (If there is significant weight loss and muscle wasting, the BUN may actually stay the same or increase initially.)

In turn, low BUN level has been shown to be an indicator of poor prognosis in CHD. Pupim et al. suggest that some researchers view nutrition intervention as ineffective in CKD stage 5 because of inflammation. However, Pupim's group concluded that "the nutrition status of CHD patients predicts mortality independent of concomitant presence or absence of inflammatory response."[7] Dwyer et al. found that increases in albumin at any level were associated with reduced short-term relative risk of mortality in CHD patients, even after adjusting for case mix, treatment assignments, protein catabolic rate, total cholesterol, and serum creatinine.[8]

The combination of inflammation and protein malnutrition leads to decreased physical function, nutrient malabsorption, anorexia, weight loss, and impaired immune function.[9] If this scenario is allowed to continue, the risks for pressure ulcers, diarrhea, thrombosis, and infection increase. It is not surprising that in this population uremic malnutrition is strongly associated with an increased risk of hospitalization as well as death.[10]

A review of the current literature suggests that the loss of body protein is caused by a combination of decreased protein synthesis and increased proteolysis.[11] Animal studies suggest that decreased protein synthesis is likely triggered by the significant decrease in plasma amino acid concentrations which occurs during dialysis treatment. Consequently, protein needs are higher in CHD than in healthy adults, but nutrient intake is frequently much lower. In CHD, the amino acid pool is often already low which further compromises protein synthesis. According to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) nutrition guidelines for adults on hemodialysis, serum albumin levels are to be measured monthly in CHD patients with the target serum albumin level set at ≥4.0 g/dL.[12]

Unfortunately, the need to limit sodium intake can make food choices unpalatable. Additionally, some protein rich foods which are high in phosphorous may be limited. With frequent anorexia, taste changes, and specific nutrient goals, it seems prudent to consider nutrition supplementation during dialysis treatment to replace protein losses and potentially stimulate protein synthesis. Supplements should be protein rich to augment the amino acid pool. Ikizler et al. showed that "provision of nutrients, either in the form of intradialytic parenteral nutrition or oral feeding during hemodialysis, *can* adequately compensate for the catabolic effects of the hemodialysis procedure."[12]

Oral nutritional supplementation is more feasible and less costly than intradialytic parenteral nutrition. However, the issue remains as to how to provide additional dietary protein in CHD that:

- provides a significant amount of protein in a low volume;
- is palatable and well tolerated;
- can be easily dispensed and consumed at the dialysis unit; and
- complies with the recommended dietary goals for CHD.

As illustrated in *Table I*, standard oral supplements are high in sugar and electrolytes and may not comply with recommended CHD dietary goals. Each serving is 240 mL, which can represent 25% of the daily fluid allowance for CHD. Disease-specific renal supplements are available. These products are lower in electrolytes and more calorically dense, but the serving size, 240 mL, is still an issue for many patients. The caloric density can also increase the risk of decreased appetite and diarrhea. Protein powders can help to increase the protein content of foods and beverages already being consumed. However, these products require mixing which limits their use during dialysis. Liquid, collagen-casein based protein supplements are low volume and ready to serve which makes them well suited for CHD.

Collagen

Collagen is considered an incomplete protein because it lacks tryptophan, one of nine essential or indispensable amino acids (IAA). Collagen does contain the remaining 8 IAA and all 11 non-essential or dispensable amino acids (DAA). Additionally, hydrolyzed collagen is stable as a thin liquid at room temperature, making it versatile and easy to administer. Casein is a complete protein containing all 9 IAA, but is difficult to manufacture as a liquid. By augmenting collagen with casein and hydrolyzing the two proteins together, the end result is a concentrated liquid protein that contains all 9 IAA and 11 DAA. Thus concerns about the composition of collagen protein are addressed by the combination of collagen and casein.

TABLE I: Comparison of oral nutritional supplements.

Supplement Type	Collagen-Based Liquid Protein	Standard Liquid	Renal-Specific Liquid	Powdered Protein
Serving size	30–45 mL	240 mL	240 mL	7 g
Kilocalories	60–150	240	500	30
Protein (g)	10–15	9–13	9–17	6
CHO (g)	0–23	35–40	50–75	0
Fat (g)	0	4	20–25	< 1
Phosphorous (mg)	0–6	300–500	0–190	15–23
Potassium (mg)	4–20	375–400	0–300	19–35
Sodium (mg)	20–39	150–200	0–200	10-30

Protein Supplementation and Serum Albumin in HD Patients

Dietary intake of IAA is required because these amino acids cannot be synthesized in humans. Conversely, humans can synthesize DAA by converting other amino acids or by using the nitrogen from other amino acids; these precursor amino acids and nitrogen donor amino acids include both IAA and DAA. Each amino acid, IAA and DAA, participates in specific pathways and all 20 amino acids are necessary for human health. While DAA can be synthesized in healthy adults, this process requires adequate caloric intake as well as adequate precursor or nitrogen donor amino acids. However, adequate calories and precursor or nitrogen donor amino acids may not be available when protein supplementation is needed. Under certain disease states such as metabolic stress, several of the DAA are classified as "conditionally essential" because the rate of synthesis cannot keep up with the demand. In this situation dietary intake is required.

A potential benefit of collagen is that it provides high levels of the DAA, including the conditionally essential amino acids arginine, glycine, and proline. In uremic malnutrition, collagen supplementation, with its high levels of glycine, may help to modulate inflammation. Annuk et al. showed that patients with CKD KDOQI stage 3-5 have low levels of glutathione with corresponding endothelial dysfunction.[13] Glycine, glutamine, and cystine—3 DAAs—join to form glutathione, an antioxidant which acts to reduce oxidative stress.

Additionally, under normal conditions, intact or whole dietary proteins (long chains of amino acids known as polypeptides) are hydrolyzed by digestive enzymes. Enzymatic hydrolysis "digests" or breaks down whole proteins into smaller components of amino acids and peptides to facilitate absorption. Enzyme availability and activity are both suppressed by the inflammatory process and nutrient absorption is impaired. Digestibility studies on hydrolyzed collagen-casein protein are not available. However, a hydrolyzed protein supplement may help to ease the burden of digestion during stress.

Study Description

We conducted a pilot study of adult hemodialysis outpatients with hypoalbuminemia who had been undergoing HD for ≥1 year. The purpose of the study was to determine if a 30 mL serving of a collagen-casein based hydrolyzed liquid protein supplement (Liquid ProSource, National Nutrition/Medtrition, Lancaster, Pa.) at the beginning and end of each dialysis session would be well tolerated and improve serum albumin levels.

Methods

Patients were selected from two affiliated outpatient dialysis units located in a large metropolitan area. Of the 79 adult patients screened, 50 patients had Alb levels between 2.8 and 3.7 g/dL and consented to participate in the study. Subjects were divided into 2 groups based on their days of dialysis. The control group (n = 21) received dialysis on Tuesday, Thursday, and Saturday; the study group (n = 29) on Monday, Wednesday, and Friday.

Within the first month, 17 subjects withdrew for a variety of reasons, including transplantation, death, and intolerance to the supplement. A total of 33 subjects completed the study. The average age was 68.7 (± 12.3) with a range of 31 to 90. The final size of the control group was 16 participants (7 female, 9 male; 12 white, 3 African American, 1 Indian) and the study group included 17 participants (8 female, 9 male; 6 white, 11 African American). There was not a statistically significant difference in the number of patients with diabetes mellitus between the control and the study groups (5 [31%] versus 7 [41%] respectively, chi-square = 0.35; df = 1; p = 0.55). (*Table II*).

Liquid ProSource, a collagen-casein based liquid protein was used in the study. ProSource protein modulars are manufactured by National Nutrition/Medtrition, Lancaster, Pa. The liquid is available in 32-oz. bottles and individual 30 mL packs. We used the individual packets to insure accuracy and consistency in dosing.

The dialysis dietitian in-serviced the nursing staff who work the Monday-Wednesday-Friday shift at both units. In addition to nutrition counseling, study group participants were provided 30 mL of the liquid protein at the start of and 15 minutes prior to the end of their dialysis treatment. The dialysis dietitian was notified by the nurse of any patient complaints associated with the supplement. The control group participants received standard nutrition care provided by the dialysis dietitian, which included dietary counseling with recommendations for standard or renal specific supplements as appropriate. The supplements were provided by the facility for the patients to take at home.

Statistical Methods

All analyses were performed using SPSS for Windows (SPSS 14.0, SPSS, Chicago, Ill.). Both descriptive and inferential statistical methods were employed. All testing was based on determining statistical significance at a 2-sided alpha level of 0.05. Repeated measures analysis of ➲

TABLE II: Descriptive analysis of the study patients (n = 33).

	Sex		Race			Unit		DM	
	Female	Male	Black	White	Other	1	2	Yes	No
All patients	15 (45.5%)	18 (54.4%)	14 (42.4%)	18 (54.4%)	1 (3.0%)	23	10	12	21
Control group (n = 16)	7 (43.8%)	9 (56.2%)	3 (18.8%)	12 (75.0%)	1 (6.3%)	9	7	5	11
Study group (n = 17)	8 (47.0%)	9 (52.9%)	11 (64.7%)	6 (35.2%)	0	14	3	7	10

Protein Supplementation and Serum Albumin in HD Patients

covariance was used to test for a difference in the pattern of variation in the average Alb level ≥ 4 time points between the control and study group, after statistically removing the effects of C-reactive protein (CRP) and urea reduction ratio (URR).

The Greenhouse-Geisser method was used to adjust the degrees of freedom in case the sphericity assumption was violated. Error bar charts and paired *t*-tests were used to compare the average albumin level between baseline and last follow-up, separately for the control and study groups. Pearson's correlation coefficient was used to measure the correlation between baseline albumin and baseline CRP and baseline albumin and baseline URR levels.

Standard protocols for dialysis units include monthly blood tests for serum Alb and CRP, and calculation of URR. The dialysis dietitian recorded these values at the start of the study for baseline measures. Alb levels were recorded monthly for the following 3 months. The dialysis dietitian monitored study group subjects for complaints of nausea, diarrhea, or dislike for the intervention supplement.

Results

Five patients in the control group were not available for the duration of the study. Of these patients, one was transplanted and 4 died. In the study group, 12 patients did not complete the study. The reasons and timeline for withdrawal can be found in *Table III*. No other complaints were recorded.

There was no correlation between baseline Alb level and baseline CRP level, $r = -0.30$ ($p = .093$) and between baseline albumin level and baseline URR level, $r = 0.27$ ($p = .14$).

Even after statistically removing the effects of CRP and URR, the interaction effect between treatment group and time was statistically significant ($F = 3.63$; $df = 2.93, 81.9$; $p = 0.017$). The effect size of the interaction was 0.12, which means the interaction effect between treatment group and time explains 12% of the total variance in albumin levels.

Table IV and *Figure 1* show how the pattern of variation in the average albumin levels over time differed between the treatment groups. The pattern of variation over the first 3 time points was almost the same

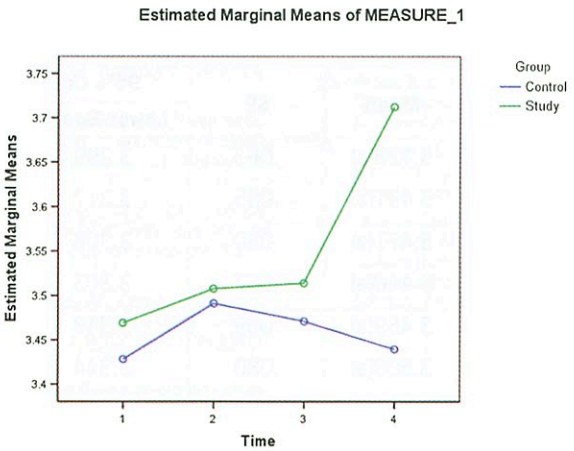

FIGURE 1. *Pattern of variation in the average albumin levels over time between the 2 treatment groups.*

for both groups, but the average Alb level at the fourth time point was larger in the study group when compared with the control group. The average Alb level at the fourth time point was 3.44 versus 3.71 for the control and study groups, respectively.

There was not a statistically significant difference in the average Alb level between baseline and last follow-up for the control group ($t = -0.54$; $df = 15$; $p = 0.60$). However, in the study group the last follow-up Alb level was statistically significantly greater than the baseline level. The average (SD) albumin level in the study group was 3.49 (± 0.20) versus 3.73 (± 0.28) at baseline and last follow-up, respectively ($t = -4.19$; $df = 16$; $p = 0.001$).

Discussion

The value of improving the nutritional status of CHD patients is well appreciated by the dialysis community. However, uremic malnutrition is associated with loss of appetite and nutrient malabsorption, limiting the potential benefits of nutrition supplementation. In our study, only one patient, who already had a history of poor tolerance to supplements, reported diarrhea after taking the initial dose of the liquid protein. In cases such as the 6 patients who disliked the taste of the product or complained of "stomach heaviness", the liquid protein could be mixed with 3–4 oz. of juice to adjust the flavor according to preference.

Of the 17 study group patients, fullness secondary to supplementation was not an issue. Often when patients take a nutrition supplement, they complain of being too full to eat their next meal. Study patients did not have to alter their post-treatment routines after beginning this liquid protein supplement. Patients who usually slept after dialysis continued to sleep after treatment, while others who usually ate a meal after

TABLE III: Reasons for withdrawal from the study.

Withdrawal Timeline	N	Reasons for Withdrawal				
		Intolerance (n = 7, 24%)			Death	Refused to Continue the Study
		Taste	Diarrhea	"Heaviness in the stomach"		
Within the first week	5	3	1	0	0	1
After 4 weeks	7	1	0	2	2	2

Patient had gastroparesis

Protein Supplementation and Serum Albumin in HD Patients

TABLE IV: Comparison of albumin level by group time.*

Group	Time	Mean	SE	95% Confidence Interval	
				Lower Bound	Upper Bound
Control	1	3.428(a)	.063	3.299	3.558
	2	3.491(a)	.085	3.317	3.666
	3	3.471(a)	.080	3.308	3.635
	4	3.440(a)	.067	3.303	3.576
Study	1	3.469(a)	.059	3.348	3.590
	2	3.508(a)	.080	3.344	3.671
	3	3.514(a)	.075	3.361	3.667
	4	3.712(a)	.063	3.584	3.840

*Covariates appearing in the model are evaluated at the following values: CRP = 1.8338 mg/dL, URR = 71.131%.

dialysis continued to do so. This suggests that the protein supplementation in this form did not affect appetite.

The analysis of Alb over time clearly indicated an increase in Alb levels after 3 months of intervention. This time period is consistent with the time needed to replenish Alb levels based on albumin's long half life of 12 to 21 days. Given the statistically significant increase in Alb levels in the study group, Alb levels would likely normalize with continued supplementation. Once the patient's serum Alb level reached 4.0 g/dL, the KDOQI target value, the supplement dose would be maintained or adjusted based on the individual patient response, i.e., monthly albumins.

Cost of Care

It is difficult to assess the impact of protein malnutrition on quality of life for individuals with CKD stage 5 and to determine a cost-benefit ratio. However, we know that protein malnutrition can impair immune response, decrease hemoglobin levels, cause anemia, and result in muscle wasting. These potential negative impacts of malnutrition are associated with an increased cost of care.

According to recent studies, the mean cost of infections in dialysis patients (including re-admissions and outpatient costs) is approximately $24,000 per patient per episode. Infections represent the most significant component of the healthcare costs and are the second leading cause of mortality in CKD stage 5 patients.[14]

In addition to enhanced immunity with potentially fewer infections, the cost benefits of adequate protein intake for CHD patients can be illustrated in the fees associated with anemia management in ESRD. There are several contributing factors to the etiology of anemia in CKD stage 5 such as insufficient iron stores and iron utilization, recurrent infections, and malnutrition. Epogen, a replacement drug for the hormone erythropoietin used to treat anemia in CHD patients, is the single most expensive item in CKD stage 5 care.[15,16] Medicare costs for Epogen are more $1 billion a year.

Production of erythropoietin and hemoglobin are both dependent on adequate protein intake. Adequate iron stores and iron utilization, both of which are influenced by body proteins, are also required for the efficacy of Epogen therapy. As noted by Kalantar-Zadeh et al, malnutrition-inflammation complex syndrome increases resistance to Epogen.[17] Therefore, in the presence of malnutrition, higher doses of Epogen can be required. The average cost of a 4,000 unit/mL vial of Epogen is $45–$50. Typically, more than 1 vial of Epogen is used per dose per patient. Thus, measures to reduce Epogen usage are clearly worth the effort. The cost of providing an effective protein supplement to dialysis patients may be small when compared with the cost of treating malnutrition-associated complications.

Limitations and Confounding Factors

The primary limitation of this study was sample size. Only 33 (66%) of the initial 50 patients eligible to participate completed the study. Additionally, since dietary intake was not monitored, there could have been improvements in appetite and/or intake of conventional foods that explain some of the improvement in Alb levels.

Since Alb levels are dependent on many factors, we did not include patients who had become hospitalized or had developed infections. Some logistics of the study were difficult. Because the supplements had to be given during dialysis, there were time limitations. We had to rely on the patient's inclination to take the supplement.

Occasionally, patients requested a small amount of liquid to follow the supplement and eventually we offered a small graham cracker with each 30 mL supplement. There were incidences where the patient refused the second dose at the end of treatment.

In addition, we had to rely upon the nurses to administer the supplement since the dietitians were not always available throughout the treatment days and times. They were responsible for additional documentation and interaction with the patient. Certainly consideration for their workload and education to help them understand the potential benefit to the patient was provided. Subsequently, the nurses were able to answer questions related to the supplement and were instrumental in achieving compliance with the study protocol.

Conclusion

Oral supplementation at the beginning and end of hemodialysis treatment 3 days per week for 3 months with 30 mL of a collagen-casein based hydrolyzed liquid protein significantly increased serum albumin levels in hypoalbuminemic CHD patients. Further studies are needed to validate these results and to determine length of time required to normalize Alb levels and maintenance supplement requirements. The potential health benefits

of oral supplementation with a collagen-casein based hydrolyzed liquid protein and the associated cost savings justifies the consideration of this intervention in the Standards of Care for CHD patients. D&T

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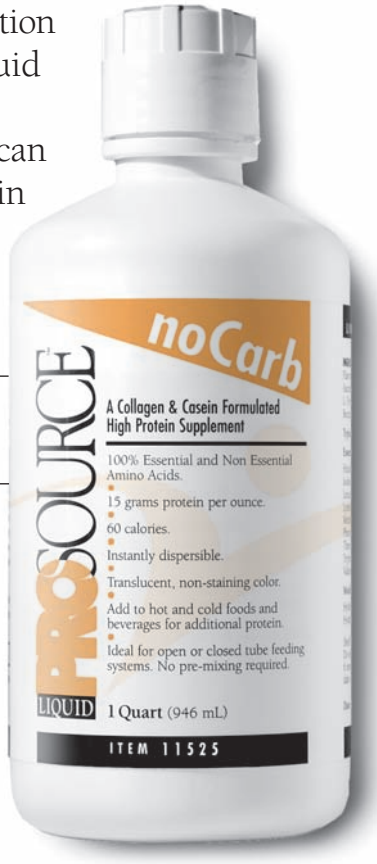

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