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Oral Protein Supplementation in Maintenance Hemodialysis Patients: Comparative study of Improvement in Serum Albumin levels

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Abstract:

Background: Hemodialysis has been shown to increase protein catabolism and led to significant loss of proteins during hemodialysis. Hypoalbuminemia has been associated with adverse outcomes.

Objectives: Main aim of this study is to determine the effect of intradialytic protein supplementation on serum albumin in hemodialysis patients.

Methods: 116 patients with hypoalbuminemia undergoing twice per week hemodialysis, from 15 september 2015 to 15 March 2016, were enrolled after obtaining informed consent. A randomized control trial was conducted after dividing the study population into 2 groups; the study group which received 20g oral protein supplementation and the control group which have not received any supplementation. Outcome in terms of improvement in serum albumin was recorded.

Results: There were 49 male and 67 female patients. Mean age of total patients was 57.25 years. 94.1% of the patients showed improvement in serum albumin in the intervention group and 56.9% in the control group. Patients of both genders between 46 to 75years, and those dialyzed for a shorter duration showed significant improvement in serum albumin levels.

Conclusion: Intradialytic oral protein supplementation significantly improved serum albumin levels, specifically in elderly patients, it is therefore recommended to routinely administer nutritional supplements in hypoalbuminemic hemodialysis patients in order to reduce the overall mortality associated with hypoalbuminemia.

Key words: Albumin, hemodialysis, malnutrition, supplementation, mortality, intradialytic, marasmus, kawashiorkor.

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Introduction:

Protein energy wasting is highly prevalent(about 28-54%) in patients on maintenance hemodialysis. [1] Hemodialysis is a catabolic process and results in loss of amino acids and proteins. [2] In the 2012 SBN census, the incidence of hypoalbuminemia in maintenance hemodialysis patients (MHD) was 15.2%, considering a <3.5g/dl. [3] Currently, with the use of high flux hemodialysis, there is greater risk of hypoalbuminemia with greater middle molecule clearance. [4] MHD patients are more prone to develop hypoalbuminemia for a number of reasons, which include uremic toxins (that are appetite suppressants), depression, dietary restriction, metabolic acidosis, and co morbidities like diabetes, cardiovascular disease, secondary hyperparathyroidism, gastrointestinal disorders, and infectious diseases and intradialytic protein loses. Hemodialysis patients loose approximately 15 to 20 grams proteins per session of dialysis. These patients are also immunocompromised, more susceptible to infection, inflammation, anemia and other medical illnesses and need greater protein intake. Dialysate protein and amino acid losses constitute a small but significant

proportion of total nitrogen appearance and thus may contribute to the increased dietary protein requirements of MHD patients; therefore, intradialytic oral nutrition now is preferred.

Several studies have been published, which indicate several favorable outcomes associated with intradialytic protein supplementation. These include improvement in physical function, reduction of inflammation, survival, quality of life, muscle mass, and improvement in hospitalization-free time. [5,6] In addition to this, correction of hypoalbuminemia is also associated with enhanced adequacy of hemodialysis[7]. Experts from the International Society of Renal Nutrition and Metabolism (ISRNM) suggest that intradialytic nutritional supplementation could be one of the useful strategy for prevention and treatment of protein energy wasting.[8] However, few studies have reported the possibility of associated adverse events with supplementation. [9] These include an increased risk of hemodynamic instability, broncho-aspiration and infections.

The aim of our study is to compare the effect of intradialytic oral nutritional supplementation in MHD patient in terms of improvement in serum albumin levels. Although, serum albumin level is not the only tool of accessing protein-energy wasting, still it is the powerful marker to predict mortality in MHD patients. [10-12] Therefore, in this study our main aim was to replace ongoing protein loses during dialysis session in order to monitor improvement in serum albumin level. Most of the previous studies have demonstrated the role of nutritional supplementation in malnourished hemodialysis patients but not in well-nourished dialysis patients. Besides this, there is a lack of local Pakistani data to support the relationship between intradialytic oral nutritional supplementation and improvement in hypoalbuminemia in MHD patients.

Materials and Methods:

116 hypoalbuminemic patients undergoing twice per week MHD were included randomly after taking informed consent. The sampling technique was consecutive non probability sampling. They were divided into two groups; study and control group. A snack, rich in eggs, was prepared by FNSD (food and nutrition) department in collaboration and under supervision of expert nutritionist of the hospital. It was provided under direct supervision of the dialysis staff twice weekly to the study group. Patients and investigator were blinded for the accuracy of study. Patient with serum albumin level less than 3.5g/dL were taken as the study population, and the level above 3.5g/dL was considered as the desired outcome.

The sample size was calculated using the WHO sample size calculator. [13] The level of significance was kept 5%, power of the test was taken as 90, anticipated population proportion (P1) was 44% and the other anticipated population portion (P2) was 19%.The sample size of 58 in each group was calculated. All patients between 18-75 years of age and both genders on MHD were included. The patients were further divided in four groups; group 1 (18-30 years), group 2 (31-45 years), group 3 (46-60 years) and group 4 (61-75 years)

Patients with diseases leading to hypoalbuminemia like liver cirrhosis, hepatitis B and C, protein losing enteropathies, malignancy, terminal illnesses and sepsis were excluded from the study group. Besides this, all patients who have been hospitalized in the past three months were also excluded from the study population. All patients, who had received any nutritional supplements before the start of the study were also excluded.

After the completion of this trial, 6 months later, blood samples were sent for serum albumin levels, and the results were verified by the hospital pathologist.

Statitical Analysis: SPSS version 17 was used for the analysis of data. For the quantitative variables like age and albumin, mean ± standard deviation were calculated and for the qualitative variables like gender, improvement in albumin levels, frequency and percentages were calculated. Chi square test was used to compare improvement in serum albumin between group A or study group and group B or control group. p-value of <0.05 was considered significant.

Effect modifiers like age, gender and duration of hemodialysis were controlled by stratification, and post stratification Chi square test was applied. p-value of < 0.05 was considered significant.

Results:

Table 1 shows baseline characteristics of patients with and hypoalbuminemia. that there were total 49 male patients (42.2%) and 67 (57.8%) female patients enrolled in this study. In group A (received treatment), there were 25 (43.1 %) males and 33 (56.9%) female patients, while in group B (no treatment received), there were 24 males (41.4%) and 34 (58.6%) females.

Mean age (in years) of the total patients was 57.25 ±14.9SD.

Table 1: Baseline characteristics of 116 maintenance hemodialysis patients with hypoalbuminemia.

Group	A (Study Group)	B (Control Group)
Male	25(43.1%)	24(41.4%)
Female	33(56.9%)	34(58.6%)
Age years (Mean ±SD)	60±13.05	54.4±16.21
Age 18-30 Years n=10(8.6%)	3 (5.2%)	7 (12.1%)
Age 31-45 Years n=13(11.2%)	6 (10.3%)	7 (12.1%)
Age 46-60 Years n=34(29.3%)	15 (25.9%)	19(32.8%)
Age 61-75 Years n=59(50.8%)	34 (58.65%)	25 (43.1%)
Serum Albumin mg/dl (Mean±SD)	3.21±0.32	3.25±0.25

SD: standard deviation, n: number of patients

At the beginning of study, the mean albumin level of all patients was 3.23± 0.29 mg/dL. Upon completion of study, mean serum albumin was 3.44± 0.44 mg/dL. In Group A patients, the mean albumin level at initiation was 3.21± 0.32 mg/dL, and on completion of trial was 3.55± 0.43 mg/dL. In Group B patients, the mean albumin level at initiation was 3.25± 0.25 mg/dL, and on completion of study it was 3.34 ± 0.44 mg/dL, Table 2).

Table 2: Mean Serum Albumin values at initiation and completion of study among 116 maintenance hemodialysis patients.

Groups	Albumin at initiation of study		Albumin at completion of study	
	Mean mg/dL	SD±	Mean mg/dL	SD±
Group A (n:58)	3.21	0.32	3.5	0.43
Group B (n: 58)	3.25	0.25	3.3	0.44
Total (116)	3.23	0.29	3.44	0.44

SD: standard deviation, n: number of patients, ***Group A:*** *Protein Supplementation,* ***Group B:*** *control*

Overall 86/116 patients (74.1%) showed significant improvement in serum albumin. Chi-square analysis revealed, significant difference (p-value <0.001) of improvement of serum albumin in the Group A, Table 3.

Table 3: Improvement in Serum Albumin levels among maintenance hemodialysis patients supplemented with protein intake.

Groups	Patients with improvement. N(%)	Patients with No improvement. N(%)	p-value
Group A (n:58)	53 (91.4%)	5 (8.6%)	

Group B (n:58)	33 (56.9%)	25 (43.1%)	**<0.001**
Total	86 (74.1%)	30 (25.9%)	

Group A: *Protein Supplementation,* ***Group B:*** *control*

Controlling effects modifier:

The contributory role of three effect modifiers like age, gender and duration of hemodialysis was considered.

The duration of dialysis of the patients was studied as an effect modifier in both groups with reference to improvement in serum albumin. As shown in the table 4 below, patients were further divided into three groups. Majority of the patients were in the group 1 (recent on dialysis, 3 months -3 years) who showed significant improvement in serum albumin levels at the end of the study.

Table 4: Effect of duration of hemodialysis on serum albumin levels after protein supplementation.

Duration of hemodialysis	**Improvement in serum Albumin**		**p-value**
	Yes, n(%)	**No, n(%)**	
Group 1 (3months-3years)			**< 0.001**
Group A	33(94.2%)	2(5.7%)	
Group B	26(55.3%)	21(44.6%)	
Group 2 (3- 6 years)			0.18
Group A	11(84.6%)	2(15.3%)	
Group B	4(57.1%)	3(42.8%)	
Group 3 (6- 9 years)			0.47
Group A	9(90%)	1(10%)	
Group B	3(75%)	1(25%)	

Group A: *Protein Supplementation,* ***Group B:*** *control*

Effect of age on serum albumin:

Table 7 below describes about the effect of patients' age on serum albumin level. Majority of the patietns were in the age range >45 years and showed improvement in serum albumin with protein supplementation.

Table 5: Effect of protein supplementation in maintenance hemodialysis patients on serum albumin levels according to age.

Age groups	**Improvement in serum Albumin**		**p-value**
	Yes, n (%)	**No, n (%)**	
18-30years			
Group A	2(66%)	1(33.3%)	0.778
Group B	4(57.1%)	3(42.8%)	
30-45years			
Group A	5(83.3%)	1(16.6%)	0.612
Group B	5(71.4%)	2(28.5%)	
46-60years			
Group A	14(93.3%)	1(6.6%)	**0.01**
Group B	10(52.6%)	9(47.3%)	
61-75years			
Group A	32(94.1%)	2(5.8%)	**<0.001**
Group B	14(56%)	11(44%)	

Group A: *Protein Supplementation,* ***Group B:*** *control*

Effect of gender on serum albumin:

Gender was also studied as an effect modifier and in both males and females' protein supplementation improved the serum albumin levels.

Discussion:

The hypothesis before initiation of study was that intradialytic oral protein supplementation will result in improvement of albumin in hypoalbuminemic patients, which was found to be true in our current study. Although, there is a conflicting data regarding improvement in serum albumin with intradialytic nutritional supplementation, yet most studies showed improvement in serum albumin. [5,7] The findings of our study are consistent with the findings of most studies showing significant improvement with protein supplementation. [7]

Hypoalbuminemia is a strong determinant of nutritional status of MHD patients. The patients on MHD are more prone to malnourishment as compared to other population. Malnourishment and protein energy wasting are found to be strong predictors of morbidity and mortality worldwide. Recently, the possible mechanism of increased cardiovascular mortality in hypoalbuminemic hemodialysis patients was explained by Magzal et.al. study, which showed the role of in-vitro oxidized albumin, a pro-inflammatory marker associated with increased endothelial damage.[14]

It has been suggested that by administrating intradialytic protein supplementation not only improves serum albumin but also benefits other markers of nutritional status like subjective global assessment and malnutrition inflammation score.[15] In addition to this, several studies have reported significant benefits of intradialytic protein supplementation. These include reduced hospitalization, improved quality of life, increased muscle mass, increased hemodialysis adequacy and reduced inflammation. [10,16]

There are several factors which correlate with the serum albumin level. [17] These include advanced age, female gender, diabetes, serum ferritin and longer hemodialysis vintage. In our study, there was significant positive correlation of advanced age with hypoalbuminemia in our patients, for patients above 46 years of age. The possible reason behind hypoalbuminemia in elderly can be due to anorexia and reduced oral intake. With regards to gender predisposition, majority of our female patients were hypoalbuminemic, and responded significantly.

In our patients, there is also a positive significant correlation between shorter vintage of hemodialysis and greater improvement in serum albumin. The reason for significant improvement in these patients is possibly due to less associated debilitating conditions and complications of dialysis in this group. These complications include recurrent infections and gradual loss of residual renal function with prolonged duration of dialysis, thus predisposing them to low serum albumin levels. It has also been shown that longer duration of hemodialysis is associated with greater mortality, possibly because of coexistent hypoalbuminemia.

In a review, it has been debated whether hypoalbuminemia is in fact a marker of illness or malnutrition and supplementation improves the level of albumin or not.[18] It was also suggested that in case of improvement in serum albumin post supplementation; these MHD patients might be suffering from malnutrition and their protein intake might be even less than 0.5g/kg/day. Majority of our patients have shown significant improvement in serum albumin after supplementation with 20g of protein and that only twice per week; therefore, it can be suggested that majority of our patients had significantly reduced protein intake.

Protein intake above 1.1g/kg/day is recommended in patients on MHD; however, in our experience this is not possible due to the finanacial constraints in majority of our patients. We did not make a food diary and that would have been beneficial in terms of documenting actual intake of protein during the week. In addition, majority of our patients suffer from multiple co-morbidities out of which diabetes is the most common as a cause of lack of proper dietary intake as mentioned in the review. [18] we have shown in the current study that even with twice wee weekly supplementation of 20 grams of protein may be beneficial especial in the patients initiating MHD recently and in >45 years of age.

Nutritional counselling is essential for MHD patients, if there is no improvement in nutritional parameters, then energy intake of 10Kcal/kg and protein supplementation of 0.3-0.4g/kg is recommended. [19] For this, intradialytic oral nutritional supplementation is an effective way of providing nutrition that alleviate the hyper catabolic effects of hemodialysis since intradialytic parenteral nutrition is not possible in majority of patients due to cost issues.

However, several disadvantages of protein supplementation in previous studies have been reported. These include increase in the risk of hyperkalemia, hyperphosphatemia, intradialytic hypotension, gastrointestinal symptoms, risk of aspiration, risk of contamination, increased staff burden and dialysis inadequacy[20]. None of these potential disadvantages can counteract the importance of improvement in serum albumin, the most important surrogate marker of protein energy wasting and a major predictor of mortality. In one recently published study, however, no correlation was found between intradialytic supplementation and hypotensive episodes [21].

Although the study has provided our local data, still it has some limitations. We are unaware of the routine diet taken by these patients at home and their psychological status. Besides this, the residual renal function have not been studied in this study. Further studies are needed with larger sample sizes with considerations to the limitations of our study to determine factors which can aid in the improvement of hypoalbuminemia in MHD.

Conclusion:

We have shown that intradialytic oral protein supplementation leads to significant improvement in the level of serum albumin in MHD patients >45 years of age, both genders and shorter vintage of dialysis. Further studies are required to observe more detailed nutritional markers after oral supplementation during the dialysis sessions.

Conflict of interest: None

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