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ORIGINAL ARTICLE

Anti-Inflammatory and Anti-Oxidative Nutrition in Hypoalbuminemic Dialysis Patients (AIONID) study: results of the pilot-feasibility, double-blind, randomized, placebo-controlled trial

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Abstract
Background Low serum albumin is common and associated with protein-energy wasting, inflammation, and poor outcomes in maintenance hemodialysis (MHD) patients. We hypothesized that in-center (in dialysis clinic) provision of high-protein oral nutrition supplements (ONS) tailored for MHD patients combined with anti-oxidants and anti-inflammatory ingredients with or without an anti-inflammatory appetite stimulator (pentoxifylline, PTX) is well tolerated and can improve serum albumin concentration.
Methods Between January 2008 and June 2010, 84 adult hypoalbuminemic (albumin <4.0 g/dL) MHD outpatients were double-blindly randomized to receive 16 weeks of interventions including ONS, PTX, ONS with PTX, or placebos.

Manoch Rattanasompattikul and Miklos Z. Molnar contributed equally to this study.

The study is registered at ClinicalTrials.gov under registration number NCT00561093.

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Nutritional and inflammatory markers were compared between the four groups.

Results Out of 84 subjects (mean ± SD; age, 59±12 years; vintage, 34±34 months), 32 % were Blacks, 54 % females, and 68 % diabetics. ONS, PTX, ONS plus PTX, and placebo were associated with an average change in serum albumin of +0.21 (P=0.004), +0.14 (P=0.008), +0.18 (P=0.001), and +0.03 g/dL (P=0.59), respectively. No related serious adverse events were observed. In a predetermined intention-to-treat regression analysis modeling post-trial serum albumin as a function of pre-trial albumin and the three different interventions (ref = placebo), only ONS without PTX was associated with a significant albumin rise (+0.17±0.07 g/dL, P=0.018).

Conclusions In this pilot-feasibility, 2×2 factorial, placebo-controlled trial, daily intake of a CKD-specific high-protein ONS with anti-inflammatory and anti-oxidative ingredients for up to 16 weeks was well tolerated and associated with slight but significant increase in serum albumin levels. Larger long-term controlled trials to examine hard outcomes are indicated.

Keywords Albumin · Hypoalbuminemia · Inflammation · Protein intake · Hemodialysis · Oral nutrition supplements · Anti-oxidant ingredients · Anti-inflammatory ingredients

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1 Introduction

Maintenance hemodialysis (MHD) patients do not only have a high prevalence of malnutrition, but also a higher occurrence of inflammation [1–5]. Some investigators suggest that anorexia and malnutrition are results of inflammation [4, 6–9]. However, inflammation may be secondary to malnutrition as shown in animal models [10]. Both malnutrition and inflammation are strongly associated with each other and can change many nutritional measures and outcomes in the same direction [11, 12]. Because the relative contributions of malnutrition and inflammation to each other, to wasting, and to atherosclerotic cardiovascular disease are not yet well defined, the terms "malnutrition–inflammation complex (or cachexia) syndrome" [13, 14], "malnutrition–inflammation–atherosclerosis," or kidney disease wasting [15] have been suggested [7, 16], and currently, "protein-energy wasting" (PEW) is the recommended terminology [17].

The PEW is a well-known predictor of mortality in MHD, chronic kidney disease (CKD), and transplant patients [18–21]. However, there is no effective and proven therapy to cure this syndrome. Indeed, there are no well-designed or large-scale randomized prospective studies in this field [12, 22]. There are sporadic non-randomized or non-controlled studies; for instance, in a non-controlled study, in-center (during hemodialysis) oral nutrition supplements (ONS) improved serum albumin in 85 MHD patients [23]. In another non-randomized but controlled study, in-center ONS increased serum albumin in 21 MHD patients with serum albumin <3.8 g/dL [24]. These studies, however, were not randomized, did not include anti-inflammatory interventions, and did not have a placebo control group. Virtually, all previous studies have methodological limitations, including small sample size, lack of randomization, failure to restrict the intervention to hypoalbuminemic patients, very short durations of intervention and follow-up periods, nonadherence to intent-to-treat, and failure to examine surrogates of inflammation and oxidative stress in subjects before and after the intervention [8, 25, 26]. However, based on previous studies [22], there are reasons to believe that oral nutritional therapies have the potential to improve nutritional status and outcomes in patients with PEW.

Well-designed, randomized, placebo-controlled clinical trials are needed to verify the safety and efficacy of nutritional intervention and its impact on clinical outcomes in hypoalbuminemic MHD patients [24]. We therefore tested the hypothesis that in hypoalbuminemic MHD outpatients, simple in-center oral nutritional and orexigenic (appetite stimulating) interventions with anti-

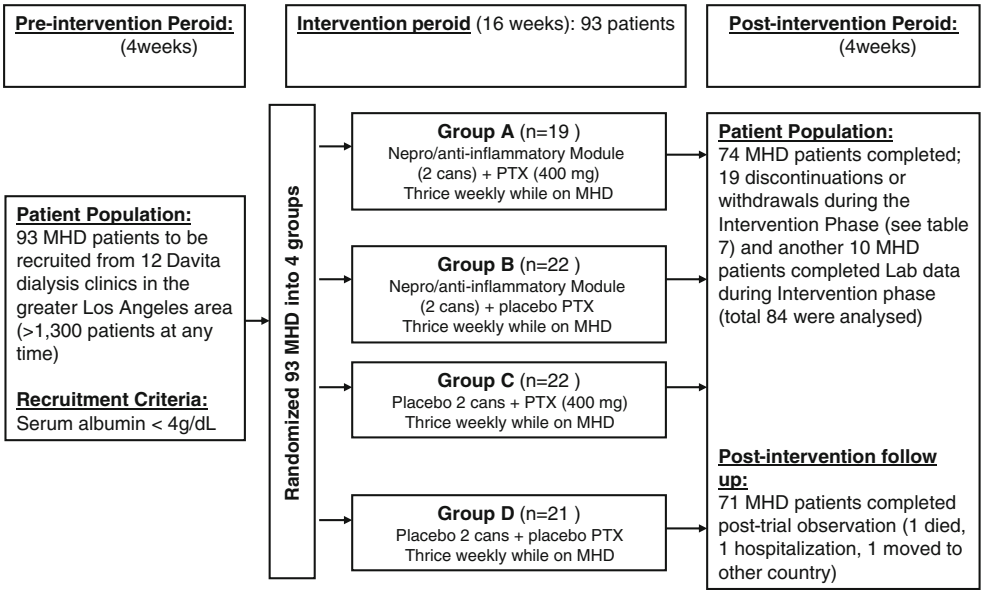

Fig. 1 Study protocol. Note that during each hemodialysis session, additional nutrition supplements and pill were given to the participating patient for home intake during the following day. *ONS* oral nutrition supplements, consisting of a high (19 g) protein supplement (Nepro®, 8 oz/day) combined with a concentrated anti-inflammatory and anti-oxidant module (fish oil, borage oil, beta-carotene, vitamins C and E, zinc, and selenium, 2 oz/day); *PTX* pentoxifylline (400 mg/day). The supplements and pills for the same day and the following day (6 days/week) were provided to the patients during each thrice-weekly hemodialysis treatment

inflammatory and anti-oxidant properties will (1) be feasible and safe and (2) have beneficial effects on nutrition, inflammatory, and oxidative stress as evidenced by clinical and laboratory measures.

2 Subjects and methods

2.1 Study description

Figure 1 shows the study protocol, which has been described at ClinicalTrials.gov website under protocol # NCT00561093 [27]. In short, during the pre-trial observation period, 80 MHD patients with a serum albumin <4.0 g/dL that persisted for at least 3 months were recruited from the patient pool of the "South Bay Dialysis Cohort" (consisting of several DaVita dialysis clinics in Los Angeles South Bay area) [28] and were each observed for 3 months. If serum albumin remained <4.0 g/dL by the end of the 3-month observation period, the recruited subjects were randomized into four equal groups according to a 2×2 factorial design, stratified according to presence or absence of diabetes mellitus.

The subjects were randomly assigned to receive, in a blinded protocol, (a) nutritional support consisting of one can of (8 oz) Nepro® and one module (2 oz) of an anti-inflammatory anti-oxidant (AIAO) nutrition based on the active components of a can of Oxepa® (see Table S1) or placebo can and placebo module resembling these two nutrition supplements with somewhat similar flavor and (b) pentoxifylline 400 mg/day or placebo ingested during each MHD session in the dialysis facility, thrice weekly for 16 weeks. An additional (duplicate) of the same package of combined nutrition supplements and pill was provided to take home for the following (non-dialysis) day. The intervention lasted for up to 16 weeks. Periodic dietary assessments and laboratory measurements were performed before, during, and after a 16-week interventional period.

2.2 Study population and recruitment criteria

A total of 93 MHD patients from the participated DaVita dialysis clinics in Los Angeles County, CA, agreed to attend the study consistent with prior power calculation indicating 22 to 25 qualified subjects in each of the four groups. The inclusion and exclusion criteria were described elsewhere [27], but in summary, these were adult hemodialysis patients who had been undergoing MHD for at least 4 weeks, who did not have terminal disease, and whose serum albumin remained below 4.0 g/dL for three consecutive months.

2.3 Interventions

2.3.1 Oral nutrition supplements

The intervention consisted of high-protein ONS tailored for chronic dialysis patients combined with anti-oxidants and anti-inflammatory ingredients with or without an anti-inflammatory appetite stimulator pentoxifylline (PTX). In the ONS treatment arms, the patients received Nepro® and AIAO module during hemodialysis sessions, thrice weekly for 16 weeks. The nutrient compositions of Nepro® and AIAO module are shown in Table S1 [23, 24, 29–35]. AIAO module contained constituents which are reported to have anti-inflammatory and anti-oxidant properties [30] and can be used for both non-CKD patients [31–34] and MHD patients [24]. All participants agreed to take one 8-oz can of Nepro® and one 2-oz module of AIAO in their entirety three time per week during the hemodialysis treatment

and also during the subsequent non-dialysis days, hence 6 days a week.

2.3.2 The placebos

We used 8-oz cans and 2-oz modules of placebos with similar taste and volume as Nepro® and AIAO, respectively, but with substantially lower amounts of energy (<100 kcal/day or <50 kcal/can and 240 kcal/day or 120 kcal/module) and protein (<10 g/day) and no anti-inflammatory or anti-oxidant compounds. Both placebo products, Nepro and AIAO module were developed by Abbott Nutrition (the manufacturer of Nepro® and Oxepa®) [35].

2.3.3 The appetite stimulant

During each hemodialysis session, thrice-weekly pentoxifylline (Trental™, Sanofi-Aventis, USA) (400 mg) or its placebo was given to each participating subject. The daily dose of pentoxifylline (or its corresponding placebo) was prescribed on the same days that supplements were given to patients on both dialysis days and their subsequent non-dialysis days, 6 days out of 7 weekdays. No Investigational New Drug numbers are needed to be obtained from the FDA for pentoxifylline [24].

2.4 Randomization

Both the containers of the AIAO module and placebo and the cans containing the actual nutrition supplements were packaged in unidentifiable identical formats with unique ID numbers that were assigned blindly using a permuted block approach [36] to randomly selected, unidentifiable ID numbers of the patients. Pentoxifylline and placebo were randomized similarly.

2.5 Clinical and demographic measures

The following laboratory and demographic measures were recorded: post-dialysis (dry) weight and body mass index (BMI=weight (kg)/height^2 (m^2)), in-center and home medications, dialysis access events, routine blood laboratory values as well as serum high-sensitivity CRP measured by a turbidimetric immunoassay [37, 38], high-sensitivity IL-6, TNF-α, and IL-1β [39–41], prealbumin (transthyretin), leptin, and lipid panel (total cholesterol, triglycerides, LDL, and HDL).

2.6 Statistical analyses

Data were summarized using proportions, means (±standard deviation), or medians (interquartile range) as appropriate. Categorical variables were compared using chi-square tests, and continuous variables were compared using *t* tests or Mann–Whitney *U* tests, Kruskal–Wallis *H* tests, or analyses of variance, as appropriate. We used regression models to predict post-trial albumin by each interventional group. One-way ANOVA was used to analyze the difference among all four intervention groups. The regression equation that was applied to predict the post-trial serum albumin concentration was developed by the trial statistician (ML) prior to unblinding accounting for interaction between the two different arms of the study:

$$Post-trial\ albumin = pre-trial\ albumin + supplement + pill + both.$$

Data analysis was performed using Stata version 11.1 (Stata Corporation, College Station, TX).

3 Results

Table 1 shows the descriptive analysis of all 84 MHD patients overall and by intervention groups. Mean age was 59±12 years. The proportion of females was 54 %, and 68 % of patients had diabetes mellitus. Typical of Southern California dialysis facilities, this study population also had a high Hispanic contribution of 56 %, and 32 % of patients were Black. There were no statistically significant differences in race, language, type of insurance, or dialysis access. The most common cause of renal failure was diabetes mellitus (60 %).

Table 2 shows the comorbidities of the 84 study participants. There were no significant differences between the treatment groups. Most importantly, chronic liver disease (moderate to severe liver disease), which could affect nutritional markers such as albumin and prealbumin, was only present in two patients.

Table 3 shows the changes in serum albumin in the four intervention groups. Significant increments were found in serum albumin after all three interventions, but not in the placebo group. Figure 2 shows the serum albumin levels before and after the intervention in all four groups. In these analyses, ONS, PTX, both ONS and PTX, and all placebo were associated with average changes in serum albumin of +0.21 g/dL (P=0.004), +0.14 g/dL (P=0.008), +0.18 g/dL (P=0.001) and, +0.03 g/dL (P=0.587), respectively. In a logistic regression model predicting post-trial serum albumin from pre-trial serum albumin and the assigned treatments, determined by trial statistician as the main intent-to-treat analysis, only ONS was a significant predictor of post-trial albumin (+0.17±0.07, P=0.018).

Table 4 shows pre- and post-intervention biochemistries in the four intervention groups. Table 5 shows pre- and post-intervention values of various biochemistry markers comparing ONS intervention vs. no ONS intervention and PTX intervention vs. no PTX intervention. Serum albumin significantly increased in the ONS intervention group (with or without PTX) (3.51 to 3.71 g/dL; P<0.001) and also increased

Table 1 Baseline characteristics of 84 patients in AIONID study

	All (*N*=84)	Group A (*N*=19) ONS + PTX	Group B (*N*=22) ONS	Group C (*N*=22) PTX	Group D (*N*=21) placebo	*P* value
Age	59±12	59±14	55±10	58±14	64±9	0.09
Gender (female, %)	45 (54)	10 (53)	10 (45)	12 (55)	13 (62)	0.76
Dialysis vintage (months)	34±34	23±23	36±34	29±30	48±43	0.11
Marital status (Divorced/married/single %)	7/33/34 (8/39/40)	2/6/8 (11/32/42)	4/9/9 (18/41/41)	1/9/8 (5/41/36)	0/9/9 (0/43/43)	0.08
Hispanic (%)	47 (56)	12 (63)	14 (64)	10 (45)	11 (52)	0.57
Black (%)	27 (32)	3 (16)	6 (27)	8 (36)	10 (48)	0.17
Language (%) (English/Spanish)	57/27 (68/32)	11/8 (58/42)	13/9 (59/41)	16/6 (73/27)	17/4 (81/19)	0.32
Diabetes (%)	56 (68)	13 (68)	14 (64)	16 (73)	13 (62)	0.90
Medical insurance (%) (Medicare-Medicaid/Regular Medicaid/Emergency Medicaid)	58/12/1 (70/14/1)	13/3/0 (69/16/0)	17/1/1 (77/5/5)	13/6/0 (59/27/0)	15/2/0 (75/10/0)	0.71
Dialysis access (AVF/AVG/tunnel catheter)	41/25/18 (49/30/21)	10/5/4 (53/26/21)	8/6/8 (36/28/36)	12/9/1 (54/41/5)	11/5/5 (52/24/24)	0.28
Cause of underlying renal disease (%)						
Diabetes mellitus	50 (60)	11 (58)	15 (68)	13 (59)	11 (52)	0.77
Hypertension	16 (19)	3 (16)	3 (14)	55 (23)	5 (24)	0.80
Glomerular disease	3 (4)	1 (5)	0 (0)	1 (5)	1 (5)	0.77
SLE	2 (2)	0 (0)	1 (3)	1(5)	0 (0)	0.60
Interstitial disease	1 (1)	0 (0)	1 (5)	0 (0)	0 (0)	0.42
Polycystic kidney disease	1 (1)	0 (0)	0 (0)	1 (4.55)	0 (0)	0.42

See Fig. 1 for description of groups A through D

ONS oral nutrition supplements, consisting of a high (19 g) protein supplement (Nepro®, 8 oz/day) combined with a concentrated anti-inflammatory and anti-oxidant module (fish oil, borage oil, beta-carotene, vitamins C and E, zinc, and selenium, 2 oz/day); *PTX* pentoxifylline (400 mg/day). The supplements and pills for the same day and the following day (6 days/week) were provided to the patients during each thrice-weekly hemodialysis treatment

Table 2 Comorbidities of 84 MHD patients in AIONID study

	All (*N*=84) (%)	Group A (*N*=19) ONS + PTX	Group B (*N*=22) ONS	Group C (*N*=22) PTX	Group D (*N*=21) placebo	*P* value
Hypertension	16 (19)	3 (16)	3 (14)	5 (23)	5 (24)	0.79
Coronary artery disease	10 (11)	3 (16)	4 (18)	1 (5)	2 (10)	0.50
Coronary artery disease (post-CABG)	3 (4)	0 (0)	1 (5)	0 (0)	2 (10)	0.29
Congestive heart failure	19 (23)	3 (16)	5 (23)	6 (27)	5 (24)	0.85
Cerebrovascular disease	7 (8)	0 (0)	3 (14)	3 (14)	1 (5)	0.30
Peripheral vascular disease	12 (14)	4 (21)	4 (18)	2 (9)	2 (10)	0.60
COPD	11 (13)	3 (16)	5 (23)	2 (9)	1 (5)	0.32
Peptic ulcer	6 (7)	2 (11)	1 (5)	2 (9)	1 (5)	0.84
Moderate to severe liver disease	2 (2)	1 (5)	0 (0)	0 (0)	1 (5)	0.52
Depression	9 (11)	1 (5)	3 (14)	2 (9)	3 (14)	0.77
Cancer	1 (1)	0 (0)	(0)	0 (0)	1 (5)	0.39
Hepatitis C	7 (8)	2 (11)	0 (0)	2 (9)	3 (14)	0.38
Hepatitis B carrier	1 (1)	0 (0)	0 (0)	1 (5)	0 (0)	0.41

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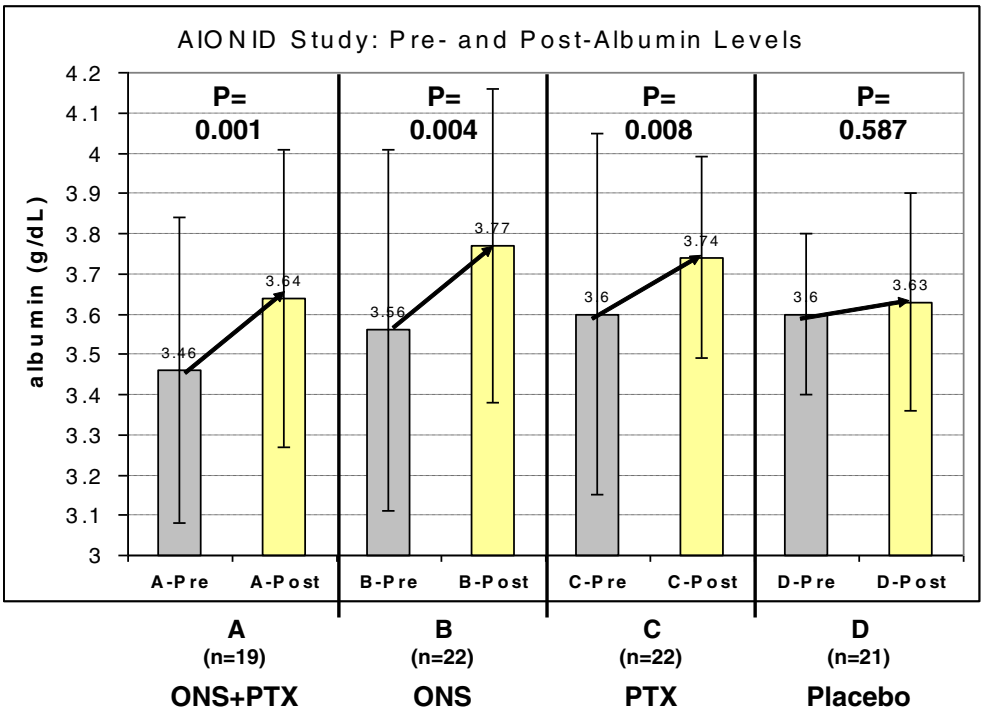

Fig. 2 Changes in serum albumin concentration from baseline to end-of-intervention in the four study groups. Note that for patients who withdrew prior to 16 weeks of intervention, the last monthly serum albumin during the intervention was used according to intention-to-treat principle. See Fig. 1 for description of groups A through D. *ONS* oral nutrition supplements, consisting of a high (19 g) protein supplement (Nepro®, 8 oz/day) combined with a concentrated anti-inflammatory and anti-oxidant module (fish oil, borage oil, beta-carotene, vitamins C and E, zinc, and selenium, 2 oz/day); *PTX* pentoxifylline (400 mg/day). The supplements and pills for the same day and the following day (6 days/week) were provided to the patients during each thrice-weekly hemodialysis treatment

in patients who received PTX with or without ONS (3.51 to 3.69 g/dL; $P<0.001$). There was a trend of an increment in serum prealbumin in the ONS intervention group (22.7±1.3 to 24.6±1.4; $P=0.05$). Inflammatory markers showed no significant decline. The MHD patients who took daily doses of the anti-inflammatory and appetite stimulating agent (PTX) displayed no significant decline in serum CRP, IL-1b, or IL-6. There was no significant decline in serum leptin with PTX treatment. We compared different laboratory values in each intervention group vs. the placebo group. The detailed information about the reasons for discontinuations and withdrawals during the intervention phase in 19 patients are listed in Table S2 and Table S3, respectively. Four patients from 93 randomized patients (4 %) discontinued from this study due to gastrointestinal side effect.

4 Discussion

In this double-blind, randomized, placebo-controlled, 2×2 factorial trial, the daily intake for up to 16 weeks of a CKD-specific high-protein ONS combined with anti-inflammatory and anti-oxidative ingredients was well tolerated and associated with slight improvement in serum albumin level of hypoalbuminemic MHD patients. This improvement is similar to the 0.2-g/dL change associated with improved survival, so while it may be a slight improvement, it is clinically relevant. PTX with or without the ONS combination also showed a trend towards improving serum albumin, but this trend was not deemed statistically significant using the predetermined intent-to-treat equation that accounted for interaction. These results can serve as proof of concept for the use of ONS with anti-inflammatory and anti-oxidative ingredients in hypoalbuminemic dialysis patients, in whom mortality risk is usually quite high.

Hypoalbuminemia is a strong predictor of both cardiovascular [42] and all-cause mortality [20] in CKD patients including end-stage renal disease patients undergoing dialysis treatment [8, 43] and kidney transplant recipients [44]. The debate continues as to whether low serum levels of albumin in patients with CKD are a surrogate of inadequate protein intake or other conditions related to PEW, such as inflammation or comorbidities [12]. A low serum albumin concentration could be related to acute or chronic comorbidities, such as infections, or to proteinuria, especially if residual renal function with marked proteinuria persists [12, 45]. Kaysen et al. showed that the serum albumin concentration in MHD patients changes with inflammation and nutritional status through their effects on albumin catabolism and synthesis, respectively. They showed that nutritional variables primarily affected albumin synthesis, whereas inflammation caused hypoalbuminemia by increasing the albumin fractional catabolic rate [46]. De Mutsert et al. [47] reported that the increased mortality risk that is associated with low serum albumin levels could partially be explained by an increase in the levels of C-reactive protein. Anorectic but otherwise healthy people who display no inflammation or cachexia may still show small drops in serum albumin level [48]. Many inflammatory molecules appear to cause reduced food intake in animal models acutely, leading to malnutrition and hyapoalbuminemia [49].

Table 3 Changes in serum albumin in the four intervention groups and regression of prediction of post-trial serum albumin: Post–trial albumin=pre−trial albumin+supplement+pill+both

	Group A (n=19)		Group B (n=22)		Group C (n=22)		Group D (n=21)	
	ONS + PTX		ONS		PTX		Placebo	
	Pre-trial	Post-trial	Pre-trial	Post-trial	Pre-trial	Post-trial	Pre-trial	Post-trial
Albumin (g/dL)	3.46±0.38	3.64±0.37	3.56±0.45	3.77±0.39	3.60±0.45	3.74±0.25	3.60±0.20	3.63±0.27
Post-trial−pre-trial (g/dL)		+0.18±0.23		+0.21±0.30		+0.14±0.26		+0.03±0.24
P value (paired t test)		**0.001**		**0.004**		**0.008**		0.587
Post−trial albumin=pre−trial albumin+supplement+pill+both		−0.16±0.10		+0.17±0.07		+0.11±0.07		(Reference group)
P value (regression)		0.104		**0.018**		0.125		

For patients who withdrew prior to 16 weeks of intervention, the last monthly serum albumin during the intervention was used according to intention-to-treat principle

ONS oral nutrition supplements, consisting of a high (19 g) protein supplement (Nepro®, 8 oz/day) combined with a concentrated anti-inflammatory and anti-oxidant module (fish oil, borage oil, beta-carotene, vitamins C and E, zinc, and selenium, 2 oz/day); *PTX* pentoxifylline (400 mg/day). The supplements and pills for the same day and the following day (6 days/week) were provided to the patients during each thrice-weekly hemodialysis treatment

Bold means the difference was significant, significant P value.

This pilot/feasibility study is the first randomized controlled trial that assesses the effect of combined oral nutrition supplement with anti-inflammatory and anti-oxidative properties in MHD during the hemodialysis treatment session. This clinical trial serves as the proof of concept that high-protein ONS with anti-inflammatory and anti-oxidative ingredients can result in improved serum albumin levels. Evidence indicates that patients undergoing chronic dialysis are subject to multiple metabolic and nutritional derangements that lead to a chronic and persistent negative nutrient balance [50]. The catabolic consequences of dialysis therapy can be mitigated or even converted to an anabolic state by provision of intra-dialytic (during the hemodialysis treatment) nutrition supplementation, especially in the form of meals or oral nutrition supplements. Studies have been carried out that assess the acute physiological response to dialysis and administration of intra-dialytic oral nutrition supplementation, including stable isotope kinetic studies and those measuring readily available nutritional markers such as serum levels of albumin and prealbumin [12]. Pupim et al. [51] showed that in eight malnourished MHD patients who received either intra-dialytic parenteral nutrition or an oral nutrition supplement during a hemodialysis session, as compared to no nutritional intervention, highly positive whole-body net protein balance occurred, and there was improvement in skeletal muscle protein anabolism [51]. Oral therapy during hemodialysis resulted in anabolic benefits for muscle protein metabolism that persisted for several hours into the post-hemodialysis phase, whereas the anabolic benefits of intra-dialytic parenteral nutrition dissipated as soon as the infusion ended [12].

In this study, serum levels of prealbumin showed a nonsignificant improvement trend, whereas inflammatory markers such as CRP and IL-6 did not change during the study. These observations may be related to the small sample size or the short period intervention. There were no serious adverse events related to the treatment in our study. Some nephrologists and dialysis care providers are concerned that patients who receive ONS or ingest meals during dialysis treatment are at increased risk for hypotension, emesis with the risk of aspiration, hygiene control challenge, increased staff burden and distraction, and problems with diabetes mellitus and phosphorus control. Nonetheless, over the past few years, a number of dialysis clinics have provided and even encouraged the provision of meals or oral nutrition supplements to MHD patients during the hemodialysis procedure [12]. This change in practice has coincided with the emergence of several studies indicating that provision of oral nutrition supplements with high protein content during hemodialysis is associated with an increase in serum albumin levels and other favorable outcomes [12, 51–53]. In our study, diarrhea was reported by some patients, which may be due to the fiber content or high osmolality of the oral nutrition supplements. Other potential limitations include higher proportion of Hispanic population

Table 4 Change in pre- and post-intervention serum or blood chemistries overall and by intervention arms

	All (*N*=84)		Group A (*N*=19)		Group B (*N*=22)		Group C (*N*=22)		Group D (*N*=21)		*P* value*
			ONS + PTX		ONS		PTX		Placebo		
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
Albumin (g/L)	3.56±0.34	3.70±0.32	3.46±0.38	3.64±0.37	3.56±0.45	3.77±0.39	3.60±0.45	3.74±0.25	3.60±0.20	3.63±0.27	0.10
Prealbumin (mg/dL)	23.6±8.1	24.9±8.3	22.2±8.3	23.2±9.0	23.3 ±6.9	25.4±7.6	25.7±9.7	27.8±9.8	23.3±7.3	22.8±6.1	0.83
Hemoglobin (g/dL)	11.9 ±1.3	11.7±1.1	11.9±1.3	11.2±1.2	11.7±1.4	11.8±1.4	12.1±1.5	11.8±1.0	11.9±1.1	11.9±0.9	0.39
Ferritin (ng/mL)	545±291	624±331	584±299	604±272	481±263	437±199	464±301	789±396	673±304	640±357	0.96
TSAT (%)	29±15	34±18	28±13	32±13	31±17	35±23	26±12	32±9	32±16	35±22	0.99
LDH (U/L)	202±53	194±50	209±60	211±49	212±65	196±63	203±45	191±32	183±36	180±50	0.77
Cholesterol (mg/dL)	135±41	140±41	135±50	143±54	129±35	135±33	134±41	138±37	143±42	144±44	0.96
Triglyceride (mg/dL)	130±82	133±93	147±101	172±150	120±66	116±78	131±93	117±55	123±67	132±69	0.38
HDL (mg/dL)	40±15	40±17	41±15	37±14	38±15	37±16	40±18	41±19	41±12	44±18	0.61
LDL (mg/dL)	67±35	71±35	58±37	64±45	67±32	70±31	66±33	74±26	78±36	74±39	0.85
K (mmol/L)	5.0±0.8	4.9±0.6	4.8±1.0	4.8±0.8	5.2±0.8	5.0±0.5	5.1±0.6	4.9±0.8	4.9±0.5	4.8±0.7	0.48
Cl (mmol/L)	99±5	98±4	99±5	97±4	99±5	98±4	99±5	98±4	99±4	99±4	0.52
CO2 (mmol/L)	22.2±4.1	23.6±3.6	21.3±5.2	24.4±3.7	21.8±4.0	22.7±3.4	21.6±3.6	23.8±3.8	24.0±3.4	23.7±3.6	0.15
Globulin (g/L)	3.2±0.6	3.2±0.6	3.1±0.7	3.2±0.8	3.3±0.6	3.1±0.5	3.2±0.6	3.1±0.7	3.4±0.6	3.3±0.6	0.88
SGOT (mg/dL)	19±10	19±15	17±5	17±7	17±10	18±13	20±9	18±10	23±12	24±24	0.92
A/G ratio (g/L)	1.08±0.23	1.14±0.26	1.12±0.26	1.16±0.37	1.04±0.22	1.13±0.18	1.13±0.22	1.2±0.26	1.05±0.24	1.09±0.25	0.92
Correct Ca (mg/dL)	8.95±0.58	8.92±0.66	8.98±0.54	8.81±0.56	8.99±0.56	8.91±0.49	8.69±0.59	8.82±0.61	9.15±0.55	9.12±0.89	0.89
Phosphorus (mg/dL)	5.43±1.34	5.52±1.54	5.35±1.39	5.27±1.73	5.39±1.21	5.96±1.56	5.77±1.14	5.88±1.36	5.18±1.60	4.95±1.39	0.37
Alkaline Phosphatase (U/L)	126±73	118±79	134±64	140±106	124±66	100±54	117±101	98±44	131±53	135±96	0.34
CRP (mg/dL)	1.5±2.2	1.5±2.3	2.2±2.3	2.4±2.1	1.7±1.8	1.9±3.7	1.3±3.1	0.6±0.7	1.0±1.4	1.2±1.4	0.77
lnCRP (mg/dL)	−0.39±1.39	−0.30±1.29	−0.02±1.7	0.47±1.1	−0.05±1.22	−0.01±1.02	−0.08±1.41	1.12±1.34	−0.63±1.21	−0.4±1.20	0.78
IL6 (pg/mL)	15.6±30.5	20.9±55.6	10.1±5.8	14.0±12.1	14.2±17.3	10.1±0.4	12.8±23.8	20.2±27.1	24.7±52.7	38.2±104.5	0.62
lnIL6 (pg/mL)	2.08±1.06	2.22±1.16	2.14±0.65	2.3±0.88	2.10±1.07	1.89±0.93	1.80±1.12	2.31±1.31	2.29±1.28	2.39±1.40	0.45
Leptin (ng/mL)	81.4±114.3	71.6±110.1	60.4±85.9	63.9±90.7	88.1±145.6	78.1±118.3	90.9±111.6	75.0 ±96.1	83.8±107.9	68.3±135.2	0.96

Ca calcium; *A/G ratio* albumin/globulin ratio; *TSAT* transferrin saturation; *CRP* C-reactive protein; *IL-6* interleukin-6; *IL-1b* interleukin-1b; *ONS* oral nutrition supplements, consisting of a high (19 g) protein supplement (Nepro®, 8 oz/day) combined with a concentrated anti-inflammatory and anti-oxidant module (fish oil, borage oil, beta-carotene, vitamins C and E, zinc, and selenium, 2 oz/day); *PTX* pentoxifylline (400 mg/day). The supplements and pills for the same day and the following day (6 days/week) were provided to the patients during each thrice-weekly hemodialysis treatment

**P* value was analyzed from statistical difference between all the four intervention groups (group A to group D)

Table 5 Comparing pre-intervention and post-intervention biochemistry markers between the two arms of the 2×2 design, i.e., groups with or without oral nutrition supplement and with or without pentoxifylline administration

	ONS intervention group		*P* value	No ONS group		*P* value	PTX intervention group		*P* value	No PTX group		*P* value
	Pre	Post		Pre	Post		Pre	Post		Pre	Post	
Albumin (g/dL)	3.51±0.06	3.71±0.06	<0.001	3.60±0.04	3.68±0.04	0.02	3.53±0.05	3.69±0.05	<0.001	3.58±0.05	3.70±0.05	0.008
Prealbumin (mg/dL)	22.7±1.3	24.6±1.4	0.05	24.0±1.3	24.7±1.4	0.47	23.7±1.6	25.0±1.7	0.30	23.0±1.1	24.4±1.1	0.10
Hemoglobin (g/dL)	11.9±0.2	11.8±0.2	0.54	12.1±0.2	11.7±0.2	0.06	11.8±0.2	11.7±0.2	0.60	12.2±0.2	11.7±0.2	0.048
BUN (mg/dL)	76±18	65±3	0.53	62±3	61±3	0.70	59±3	63±3	0.15	79±18	62±3	0.37
Creatinine (mg/dL)	7.7±0.4	8.0±0.4	0.24	8.7±0.5	8.7±0.5	0.98	8.2±0.5	8.5±0.5	0.08	8.2±0.4	8.2±0.3	0.97
TSAT (%)	30±2	30±2	0.95	32±3	35±3	0.36	32±3	33±2	0.86	30±2	32 ±3	0.42
Ca (mg/dL)	8.7±0.1	8.7±0.1	0.75	8.7±0.1	8.6 ±0.1	0.82	8.7±0.1	8.7±0.1	0.67	8.7±0.1	8.6±0.1	0.35
P (mg/dL)	5.4±0.2	5.8±0.2	0.24	5.5±0.2	5.5±0.2	0.90	5.4±0.2	5.7±0.3	0.15	5.6±0.2	5.6±0.2	0.84
CO2 (mg/dL)	22±0.5	22±0.6	0.88	23±0.5	23±0.5	0.60	23±0.5	22±0.6	0.26	22±0.6	22±0.5	0.76
Cholesterol (mg/dL)	133±7	139±7	0.37	137±6	138±6	0.80	134±8	137±7	0.52	136±6	139±6	0.52
Triglyceride (mg/dL)	131±14	144±19	0.35	126±13	124±10	0.89	136±16	139±18	0.82	121±10	130±12	0.45
HDL (mg/dL)	39±2	38±2	0.62	41±2	42±3	0.53	40±3	39±3	0.52	40±2	41±3	0.53
LDL (mg/dL)	65±5	66±6	0.95	69±5	71±5	0.75	62±6	67±6	0.38	72±5	70±5	0.63
CRP (ng/mL)	1.92±0.32	2.20±0.48	0.57	1.22±0.38	1.05±0.21	0.52	1.87±0.48	1.59±0.30	0.43	1.29±0.23	1.63±0.42	0.40
IL-1b (pg/mL)	2.53±0.64	2.39±0.91	0.88	2.73±0.76	5.40±3.97	0.52	2.09±0.72	5.62±4.42	0.44	3.10±0.68	2.49±0.83	0.52
IL-6 (pg/mL)	12.66±2.13	12.63±2.07	0.99	18.56 ±6.58	31.30±12.03	0.09	11.24±2.95	20.59±4.91	0.09	19.21±6.02	23.59±11.0	0.51
Leptin (ng/mL)	79.8±20.2	67.4±16.6	0.38	84.3±17.4	73.1±18.0	0.31	79.4±17.1	72.1±15.4	0.42	84.4±20.0	68.8±18.5	0.28

BUN blood urea nitrogen; *Ca* calcium; *P* phosphorus; *TSAT* transferrin saturation; *CRP* C-reactive protein; *IL-6* interleukin-6; *IL-1b* interleukin-1b; *ONS* oral nutritional supplements, consisting of a high (19 g) protein supplement (Nepro®, 8 oz/day) combined with a concentrated anti-inflammatory and anti-oxidant module (fish oil, borage oil, beta-carotene, vitamins C and E, zinc, and selenium, 2 oz/day); *PTX* pentoxifylline (400 mg/day). The supplements and pills for the same day and the following day (6 days/week) were provided to the patients during each thrice-weekly hemodialysis treatment

in Southern California and younger participants than the general MHD population in the USA [54]. Moreover, our pilot-feasibility study did not assess the exact amount of energy and protein intake at baseline. Supplement and pill intake was by self-report therefore true compliance to the supplements or pills on non-dialysis days was not examined. Finally, the main outcome measure was the change in serum albumin, while morbidity or mortality was not examined directly. Despite these potential limitations, this study is one of the few randomized placebo-controlled studies to date, which assesses the effect of oral nutrition supplementation on serum albumin in MHD patients.

5 Conclusion

Daily intake of a CKD-specific high-protein ONS with anti-inflammatory and anti-oxidative ingredients for up to 16 weeks was well tolerated and associated with slight improvement in serum albumin levels. Larger, long-term, multicenter controlled trials of ONS with similar contents are indicated to examine whether such supplements will improve clinically relevant outcomes.

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Conflict of interest Ms. Debbie Benner is an employee of DaVita. Dr. Voss is an employee of Abbott Nutrition. Dr. Kalantar-Zadeh has also received grants and/or honoraria from Abbott Nutrition, DaVita, and Fresenius Kabi. Other authors have not declared any conflict of interest.

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