The Effects of Oral fat Based High-Energy Supplements on Nutritional and Inflammatory Status in Maintenance Hemodialysis Patients

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Research

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Abstract

**Background:** Protein-energy wasting (PEW) and inflammation have been recognized as two major factors associated with the poor prognosis of patients with maintenance haemodialysis (MHD). The aim of this study was to evaluate the effects of oral fat based high-energy supplements (Fresubin) on malnutrition and inflammation in MHD patients.

**Method:** This study was open-label, prospective, nonrandomized and comparative. A total of 47 MHD patients with PEW were randomly assigned into 2 groups: a control group, and a Fresubin treatment group, in which patients received daily diet intake and Fresubin nutrient support 120 mL/d for 80 days. Laboratory data and anthropometric parameters were measured.

**Result:** The results showed that compared with baseline, the level of serum albumin at 80 d in the Fresubin treatment group was significantly increased (35.4 ± 3.7 vs 38.9 ± 2.9, \( p = 0.003 \)), while there was no significant difference in the control group. In addition, the magnitudes of changes in albumin (\( p = 0.009 \)), serum prealbumin (\( p = 0.017 \)), and abdominal circumference (\( p = 0.037 \)) in the Fresubin treatment group were markedly increased compared with those in the control group. There was a downward trend in the inflammatory marker hypersensitive C-reactive protein in the Fresubin group (\( p =0.056 \)), which decreased more dramatically than that in the control group (\( p = 0.026 \)).

**Conclusion:** Fresubin treatment is well tolerated, and improves malnutrition and inflammatory status in MHD patients with PEW.

1. Introduction

In patients with end-stage renal disease (ESRD), inadequate nutrient energy intake is often observed [1, 2]. The term “Protein-energy wasting” (PEW), characterized by declines in body protein mass and energy reserves, is common concept that reflects nutritional status in patients with ESRD [3]. Inadequate protein and energy intake were tightly linked to PEW in maintenance haemodialysis (MHD) patients [4, 5]. The HEMO study showed that low values of protein and energy intake were associated with indexes of comorbidity, especially in older patients [4]. Araujo et al demonstrated that energy intake was an independent predictor of 10-year mortality in MHD patients [5]. Growing evidence has indicated that PEW and inflammation contribute to quality of life and high mortality in MHD patients [3, 6, 7]. Therefore, the interventions to ameliorate nutritional status and inflammation are crucial.

Individualized nutritional support, an optimized dialysis regime and the management of comorbidities (e.g., infection, metabolic acidosis, heart failure, and depression) are the most essential methods for managing ESRD [8, 9]. The guidelines strongly recommended nutritional interventions in MHD patients [10]. However, evidence regarding the effects of oral nutritional supplements (ONS) on the nutritional status of MHD patients is insufficient and inconsistent [11-14]. Most of the ONS used in previous studies were amino acid or protein-based supplements. Although protein and amino acids supplementation may be effective in improving PEW in MHD patients, the risk for metabolic waste (hyperphosphatemia,
hyperureaemia) can be substantial and should be carefully monitored [15-17]. Previous prospective cohort studies have suggested that total fat and individual types of fat were related to lower total mortality [18]. However, the effects of oral fat based high-energy supplements on the nutritional status and inflammation of MHD patients was largely unknown. Fresubin is an oral high-energy nutrient solution with a fat content of 53.8 g/100 mL that is rich in polyunsaturated fatty acids (12.5 g/100 mL) and free of phosphorus, potassium and protein. In the present study, we evaluated the effects of Fresubin treatment on nutritional and inflammatory status in MHD patients.

2. Methods

2.1 Research participants

This study was open-label, prospective, nonrandomized and comparative. It was performed at an outpatient hemodialysis center in a teaching hospital. Approval from the ethics committees of Zhongda Hospital, Southeast University School of Medicine was obtained before subject recruitment (2019ZDSYLL146-P01).

All patients (>18 y) were treated and received MHD for at least 3 months at our hospital. Patients were undergoing 4- to 4.5-h dialysis sessions 3 times per week. The blood flow rate ranged from 200 to 250 mL/min, and bicarbonate buffer was used. A 3-day diet record (one day of haemodialysis, 2 days of non-haemodialysis) was used to assess the participant's nutritional intake. According to the PEW diagnostic criteria recommended by the International Society of Renal Nutrition and Metabolism (ISRN) [19], the inclusion criteria for this study were as follows: 1) serum albumin (Alb) < 38 g/L or serum prealbumin (PA) < 0.3 g/L; 2) body mass index (BMI) < 23 kg/m²; and 3) dietary protein intake (DPI) < 0.8 g/kg/day. Patients had to meet any 2 of the above 3 conditions for inclusion in the study. Exclusion criteria: 1) gastrointestinal bleeding and an inability to eat; 2) serious infection and severe wasting diseases; 3) liver failure and cirrhosis; 4) cancer; 5) acute phase of disease; 6) not signed an informed consent; and 7) incomplete information. The flowchart was displayed in Figure 1.

A total of 47 patients were involved in this study from August to December, 2019. They were allocated to 2 groups based on subject preference: 1) control group, in which patients received daily diet intake only; and 2) Fresubin treatment group, in which patients received daily diet intake and Fresubin nutrition support 120 mL/d for 80 days. Fresubin (Fresenius Kabi Deutschland, Germany) was chosen because it was the formulary supplement prescribed to meet the nutritional needs (supplement 600 kcal energy) of patients receiving dialysis. The dosage is 120mL per day, divided into two to three times after meal.

2.2 Laboratory data

Blood samples were collected for at least 10-h fast and after an HD session respectively. Biochemical parameters, including haemoglobin (Hb), blood urea nitrogen (BUN), serum creatinine (Scr), Alb, PA, total cholesterol (CHO), triglyceride (TG), serum potassium (K), calcium (Ca), phosphate (P), glucose (Glu), serum ferritin (SF) and hypersensitive C-reactive protein (Hs-CRP), were obtained with routine laboratory
methods in clinical laboratory of Zhongda Hospital within 4 hours of blood collection. The adequacy of dialysis (Kt/V) was determined according to the Daugirdas method.

2.3 Anthropometric parameter assessment

Anthrometric measurements were obtained after haemodialysis (15 to 30 minutes). BMI was calculated using dry weight. Triceps-skinfold thickness (TSF) was measured using a conventional skinfold calliper with standard techniques, and the mid-arm circumference (MAC) and abdominal circumference (AC) were measured using plastic tape. Grip strength (GS) was measured using the same dynamometer with the hand on the non-fistula side. All the above parameters were tested 3 times, and the averages were taken.

2.4 Study outcomes

The primary clinical outcome of interest was change in nutritional status (Alb, PA, Hb) over the study period (80 days). The secondary clinical outcomes were inflammatory status, other laboratory markers and anthropometric parameters.

2.5 Statistical Analysis

Statistical analyses were performed using SPSS 20.0 software. The data are given as the mean ± SD for normally distributed variables and as the median and interquartile range for non-normally distributed variables. Univariate analyses were performed to compare the differences between two groups. All analyses were two-tailed, and a $P$ value < 0.05 was considered to be statistically significant.

3. Results

3.1 Baseline patient characteristics

Our study enrolled 47 participants: 22 in Fresubin treatment group and 25 in control group. Finally, 20 (91%) participants in Fresubin treatment group and 25 (100%) participants in the control group completed 80 days testing and were included in the complete case analyses. 2 participants from treatment group withdrew because they did not like the taste of Fresubin.

The baseline characteristics of the two groups were compared (Table 1). The mean ages were 58 ± 15 and 59 ± 16 years in the Fresubin treatment and control groups, respectively ($p = 0.825$). There were no significant differences in dry weight (60.3 ± 14.2 vs 63.2 ± 8.6, $p = 0.399$) or BMI (21.32 ± 3.83 vs 22.39 ± 2.46, $p = 0.264$) at the beginning of the study. The dietary energy intake (28.74 ± 2.83 vs 28.91 ± 3.58, $p = 0.868$) and dietary protein intake (0.84 (0.77, 0.96) vs 0.77 (0.73, 0.90), $p = 0.102$) between two groups had no significant differences. There were also no significant differences in any baseline clinical or nutritional parameters between the two groups (Table 1).
Table 1
Basic data of the patients between Fresubin and control groups

|                      | Fresubin treatment group (n = 20) | Control group (n = 25) | P      |
|----------------------|-----------------------------------|------------------------|--------|
| Age (y)              | 58±15                             | 59±16                  | 0.825  |
| sex (male)           | 14 (63.6%)                        | 13 (52.0%)             | 0.380  |
| Dry weight (kg)      | 60.3 ± 14.2                       | 63.2 ± 8.6             | 0.399  |
| BMI (kg/m\(^2\))     | 21.32 ± 3.83                      | 22.39 ± 2.46           | 0.264  |
| Dialysis time (month)| 66.5 (38, 89)                     | 64 (53, 98)            | 0.495  |
| Etiology of ESRD     |                                   |                        | 0.455  |
| Diabetes             | 6 (27.3%)                         | 7 (28.0%)              |        |
| Hypertension         | 7 (31.8%)                         | 7 (28.0%)              |        |
| Glomerulonephritis   | 6 (27.3%)                         | 7 (28.0%)              |        |
| Polycystic kidney    | 2 (9.0%)                          | 3 (12.0%)              |        |
| Other                | 1 (4.5%)                          | 1 (4.0%)               |        |
| Hb (g/L)             | 112 ± 17                          | 106 ± 21               | 0.332  |
| Alb (g/L)            | 35.4 ± 3.7                        | 37.0 ± 2.3             | 0.108  |
| PA (g/L)             | 0.29 ± 0.08                       | 0.28 ± 0.07            | 0.839  |
| K (mmol/L)           | 4.62 ± 0.68                       | 4.46 ± 0.69            | 0.443  |
| Ca (mmol/L)          | 2.29 ± 0.18                       | 2.22 ± 0.19            | 0.215  |
| P (mmol/L)           | 1.87 ± 0.48                       | 1.71 ± 0.48            | 0.262  |
| BUN (mmol/L)         | 26.50 (21.23, 28.78)              | 22.70 (18.90, 27.65)   | 0.184  |
| SCr (µmol/L)         | 790.0 (736.3, 1124.5)             | 899.0 (604.0, 1010.0)  | 0.506  |
| TG (mmol/L)          | 1.80 ± 0.86                       | 1.97 ± 1.55            | 0.661  |
| Glu (mmol/L)         | 7.59 ± 4.25                       | 8.17 ± 4.68            | 0.670  |
| CHO (mmol/L)         | 3.84 ± 1.30                       | 4.16 ± 0.81            | 0.304  |
| SF (µg/L)            | 209.4 ± 311.8                     | 221.4 ± 224.7          | 0.883  |

BMI, body mass index; Hb, haemoglobin; Alb, albumin; PA, prealbumin; K, potassium; Ca, calcium; P, phosphate; BUN, blood urea nitrogen; SCR, serum creatinine; UF, ultra filtration; TG, triglyceride; Glu, serum glucose; CHO, total cholesterol; SF, serum ferritin; Hs-CRP, hypersensitive C-reactive protein; Kt/V, adequacy of dialysis; GS, grip strength; MAC, mid arm circumference; AC, abdominal circumference; TSF, triceps-skinfold thickness.
| 0d | Fresubin treatment group (n = 20) | Control group (n = 25) | P |
|----|-------------------------------|-----------------------|---|
| Hs-CRP (mg/L) | 3.66 (0.82, 9.87) | 3.60 (0.82, 6.31) | 0.399 |
| UF (L) | 2.0 (1.8, 2.5) | 2.5 (1.6, 3.0) | 0.293 |
| Dietary energy intake, kcal/IBW/d | 28.74 ± 2.83 | 28.91 ± 3.58 | 0.868 |
| Dietary protein intake, g/IBW/d | 0.84 (0.77, 0.96) | 0.77 (0.73, 0.90) | 0.102 |
| Kt/V | 1.21 ± 0.26 | 1.17 ± 0.23 | 0.599 |
| GS (N/m) | 24.45 ± 11.49 | 20.80 ± 7.20 | 0.226 |
| MAC (cm) | 26.62 ± 3.58 | 26.56 ± 4.09 | 0.960 |
| AC (cm) | 85.18 ± 16.59 | 90.82 ± 9.70 | 0.161 |
| TSF (mm) | 20.40 ± 6.17 | 18.60 ± 8.18 | 0.420 |

BMI, body mass index; Hb, haemoglobin; Alb, albumin; PA, prealbumin; K, potassium; Ca, calcium; P, phosphate; BUN, blood urea nitrogen; Scr, serum creatinine; UF, ultra filtration; TG, triglyceride; Glu, serum glucose; CHO, total cholesterol; SF, serum ferritin; Hs-CRP, hypersensitive C-reactive protein; Kt/V, adequacy of dialysis; GS, grip strength; MAC, mid arm circumference; AC, abdominal circumference; TSF, triceps-skinfold thickness.

### 3.2 Fresubin improves serum Alb levels in MHD patients

After 80 days intervention, the level of Alb was significantly increased compared with baseline in the Fresubin treatment group (35.4 ± 3.7 vs 38.9 ± 2.9, p = 0.003), while there was no significant difference in the control group (37.0 ± 2.3 vs 37.3 ± 2.6, p = 0.656). The serum PA concentration was much higher after intervention in Fresubin treatment group (0.29 ± 0.08 vs 0.33 ± 0.07, p = 0.095), but the difference was not statistically significant. Other biochemical indexes (such as K, Ca, P, CHO and TG) and anthropometric parameters were almost the same compared with baseline in both groups (Table 2). Additionally, as shown in Figure 2, the level of Alb increased significantly at 30 days compared with baseline (p = 0.003), and the increase continued until the end of the study (p = 0.003).
Table 2
The data of patients on Fresubin and control groups from 0 and 80day

|                          | Fresubin group (n = 20) | Control group (n = 25) |
|--------------------------|-------------------------|------------------------|
|                          | 0d          | 80d        | P            | 0d          | 80d        | P            |
| Dry weight (kg)          | 60.3 ± 14.2 | 61.4 ± 14.3 | 0.818        | 63.2 ± 8.6  | 61.2 ± 11.4 | 0.474        |
| BMI (kg/m²)              | 21.32 ± 3.83 | 21.72 ± 3.84 | 0.743        | 22.39 ± 2.46 | 22.55 ± 2.46 | 0.498        |
| Hb (g/L)                 | 112 ± 17    | 117 ± 13   | 0.297        | 106 ± 21    | 111 ± 18   | 0.448        |
| Alb (g/L)                | 35.4 ± 3.7  | 38.9 ± 2.9 | **0.003**    | 37.0 ± 2.3  | 37.3 ± 2.6 | 0.656        |
| PA (g/L)                 | 0.29 ± 0.08 | 0.33 ± 0.07 | 0.095        | 0.28 ± 0.07 | 0.29 ± 0.06 | 0.816        |
| K (mmol/L)               | 4.62 ± 0.68 | 4.72 ± 0.63 | 0.660        | 4.46 ± 0.69 | 4.54 ± 0.52 | 0.669        |
| Ca (mmol/L)              | 2.29 ± 0.18 | 2.85 ± 2.27 | 0.284        | 2.22 ± 0.19 | 2.26 ± 0.20 | 0.439        |
| P (mmol/L)               | 1.87 ± 0.48 | 1.87 ± 0.56 | 0.985        | 1.71 ± 0.48 | 1.74 ± 0.46 | 0.792        |
| BUN (mmol/L)             | 26.75 (22.33, 28.93) | 25.19 (23.68, 26.80) | 0.351        | 22.70 (18.90, 27.65) | 24.00 (21.20, 28.90) | 0.756        |
| SCr (µmol/L)             | 790.0 (736.3, 1124.5) | 775.6 (772.0, 796.0) | 0.602        | 899.0 (604.0, 1010.0) | 877.3 (681.5, 1004.3) | 0.726        |
| TG (mmol/L)              | 1.80 ± 0.86 | 1.85 ± 0.85 | 0.854        | 1.97 ± 1.55 | 2.06 ± 1.37 | 0.838        |
| Glu (mmol/L)             | 7.59 ± 4.25 | 8.01 ± 4.11 | 0.757        | 8.17 ± 4.68 | 7.57 ± 3.15 | 0.600        |
| CHO (mmol/L)             | 3.84 ± 1.30 | 4.11 ± 1.06 | 0.476        | 4.16 ± 0.81 | 4.10 ± 0.83 | 0.769        |
| SF (µg/L)                | 209.4 ± 311.8 | 243.2 ± 293.0 | 0.733        | 221.43 ± 224.7 | 236.8 ± 191.7 | 0.796        |
| Hs-CRP (mg/L)            | 3.66 (0.82, 9.87) | 0.82 (0.82, 1.90) | 0.056        | 3.60 (0.82, 6.31) | 3.40 (0.82, 6.64) | 0.876        |
| GS (N/m)                 | 24.45 ± 11.49 | 25.17 ± 10.10 | 0.836        | 20.80 ± 7.20 | 20.82 ± 6.80 | 0.994        |

BMI, body mass index; Hb, haemoglobin; Alb, albumin; PA, prealbumin; K, potassium; Ca, calcium; P, phosphate; BUN, blood urea nitrogen; Scr, serum creatinine; TG, triglyceride; Glu, serum glucose; CHO, total cholesterol; SF, serum ferritin; Hs-CRP, hypersensitive C-reactive protein; GS, grip strength; MAC, mid arm circumference; AC, abdominal circumference; TSF, triceps-skinfold thickness.
|                  | Fresubin group (n = 20) | Control group (n = 25) | P-value | P-value |
|------------------|-------------------------|------------------------|---------|---------|
| MAC (cm)         | 26.62 ± 3.58            | 27.47 ± 3.61           | 0.460   | 0.790   |
| AC (cm)          | 85.18 ± 16.59           | 86.90 ± 15.91          | 0.743   | 0.859   |
| TSF (mm)         | 20.40 ± 6.17            | 21.55 ± 5.37           | 0.538   | 0.782   |

BMI, body mass index; Hb, haemoglobin; Alb, albumin; PA, prealbumin; K, potassium; Ca, calcium; P, phosphate; BUN, blood urea nitrogen; Scr, serum creatinine; TG, triglyceride; Glu, serum glucose; CHO, total cholesterol; SF, serum ferritin; Hs-CRP, hypersensitive C-reactive protein; GS, grip strength; MAC, mid arm circumference; AC, abdominal circumference; TSF, triceps-skinfold thickness.

### 3.3 Fresubin improves nutritional and inflammatory status in MHD patients

We also compared the change values between the two groups from 0 to 80 days and found that the changes in the biochemical indexes Alb and PA in the Fresubin treatment group were markedly increased compared with those in the control group, and the differences were statistically significant ($p = 0.009$ for Alb, $p = 0.017$ for PA). We also found a significant decrease in the inflammatory marker Hs-CRP in the Fresubin treatment group compared with the change in the control group ($p = 0.026$). With the improvement of patients’ nutritional status, the change in abdominal circumference was also increased in the Fresubin group compared with the control group ($p = 0.037$) (Table 3).
Table 3
The change values data of patients on Fresubin and control groups from 0 to 80days

|                                      | Fresubin treatment group (n = 20) | Control group (n = 25) | P    |
|--------------------------------------|-----------------------------------|------------------------|------|
| Dry weight (kg)                      | 0.5 (0.0, 0.8)                    | 0.0 (0.0, 0.4)         | 0.077|
| BMI (kg/m^2)                         | 0.16 (0.02, 0.25)                 | 0.03 (-0.01, 0.10)     | 0.077|
| Hb (g/L)                             | 3 (-6, 13)                        | 1 (-5, 10)             | 0.927|
| Alb (g/L)                            | 3.1 (0.0, 5.3)                    | 0.3 (-1.2, 1.2)        | 0.009|
| PA (g/L)                             | 0.04 ± 0.05                       | 0.00 ± 0.05            | 0.017|
| K (mmol/L)                           | 0.08 ± 0.77                       | 0.07 ± 0.69            | 0.976|
| Ca (mmol/L)                          | 0.03 (-0.09, 0.11)                | 0.03 (-0.01, 0.14)     | 0.265|
| P (mmol/L)                           | -0.01 ± 0.48                      | 0.04 ± 0.33            | 0.734|
| TG (mmol/L)                          | 0.01 ± 0.93                       | 0.09 ± 1.29            | 0.829|
| Glu (mmol/L)                         | 0.61 (-0.70, 1.89)                | -0.32 (-1.20, 1.50)    | 0.094|
| CHO (mmol/L)                         | 0.27 ± 0.82                       | -0.07 ± 0.71           | 0.155|
| SF (µg/L)                            | 37.0 (8.2, 120.8)                 | 0.0 (-11.2, 53.1)      | 0.540|
| BUN (mmol/L)                         | -0.05 (-4.02, 0.61)               | 1.50 (-1.80, 2.20)     | 0.185|
| Scr (µmol/L)                         | 8.9 (-173.6, 53.6)                | -3.8 (-77.8, 124.0)    | 0.362|
| Hs-CRP (mg/L)                        | -0.90 (-6.40, 0.00)               | -0.75 (0.00, 0.17)     | 0.026|
| GS (N/m)                             | 2.00 (-2.50, 5.40)                | 0.30 (-1.00, 1.45)     | 0.471|
| MAC (cm)                             | 1.00 (0.00, 4.00)                 | 0.00 (-0.85, 0.10)     | 0.142|
| AC (cm)                              | 1.50 (-0.50, 4.00)                | 0.00 (-0.75, 0.00)     | 0.037|
| TSF (mm)                             | 0.00 (-1.00, 4.00)                | 0.00 (-0.50, 1.00)     | 0.992|

BMI: body mass index; Hb: hemoglobin; Alb: albumin; PA: prealbumin; K: potassium; Ca: calcium; P: phosphate; TG: triglyceride; Glu: serum glucose; CHO: total cholesterol; SF: serum ferritin; BUN: blood urea nitrogen; Scr: serum creatinine; Hs-CRP: hypersensitive C-reactive protein; GS: grip strength; MAC: mid arm circumference; AC: abdominal circumference; TSF: triceps-skinfold thickness.

4. Discussion

Among the many risk factors that affect the outcomes of ESRD patients, especially MHD patients, nutritional deficiency plays a major role. The prevalence of malnutrition among MHD patients varies from 30–75% [20, 21]. In this study, we evaluated the effects of oral fat based high-energy supplements (Fresubin) on nutritional and inflammatory status in MHD patients. These findings suggested that
Fresubin nutritional support could continuously and effectively improve the nutritional status and inflammation in MHD patients after 80 days intervention.

Inadequate dietary protein and energy intake levels are important causes of PEW in ESRD patients and may be caused by anorexia. Furthermore, there is additional nutritional loss during dialysis, such as amino acids, albumin and some trace elements, in the dialysate and inflammatory stimuli associated with the dialysis procedure [3]. The recommended daily protein and energy requirements for haemodialysis patients are 1.2 g/kg of ideal body weight per day and 30-35 kcal/kg of ideal body weight per day [22]. In fact, in many dialysis patients, the levels of protein and energy intake do not reach the recommended proper goals. The protein and energy intake of these research participants are both insufficient.

The ISRNM proposed 4 main categories to diagnose PEW: biochemical criteria, low body mass, decreased muscle mass and low protein intake [19]. Among biochemical indicators, serum albumin is a consistent indicator for PEW, and low serum albumin is one of the strongest predictors of mortality in MHD patients [9, 23]. More importantly, a change in the serum level of Alb over time is associated with alterations in the risk of mortality, in that only a small increase or decrease in serum Alb concentration over a period of time is associated with increased or decreased survival, respectively [24, 25]. In this study, we treated patients who had poor nutrition status with an oral high-energy nutrient solution, Fresubin 120 mL/day, for 80 days and found that the level of Alb increased quickly and that the increase continued until the end of the study. Another nutritional marker, PA, also increased in the treatment group, and the difference in the change in PA between the two groups was significantly different.

There is an important consideration when we ask patients to improve their dietary intake or provide nutrition support. The potential increase in the intake of several harmful elements, especially phosphorus, is a troublesome clinical problem. Hyperphosphatemia is an independent risk factor for cardiovascular disease and death in patients with CKD [26, 27]. Interestingly, the amount of dietary protein is usually correlated with phosphorus content and serum phosphorus concentration in ESRD patients. In adenine-induced CKD rats, a high-phosphorus diet was found to induce systemic inflammation and oxidative stress, resulting in the development of PEW, weight loss and hypoalbuminemia [28]. We need to find a method of compromise that does not increase phosphorus intake but improves the nutritional status of patients. Some foods with a low P/protein ratio should be suggested. In our test, we used the ONS Fresubin to improve the nutritional status of patients while improving the serum Alb without a significant effect on phosphorus. Fresubin treatment also had no effect on other biochemical indexes that we should closely monitor, such as blood lipids, Glu, K and Ca.

Inflammation is a major driving force for many uremic complications, including PEW. Persistent, low-grade inflammation has been recognized as a component of CKD [28]. Animal studies have shown that infusions of TNF, IL-1, and IL-6 cause increased muscle protein breakdown, resulting in muscle atrophy [29]. Clinical studies have shown that malnutrition, inflammation and atherosclerosis are closely related in patients with ESRD [30]. Our study found that the level of the inflammatory biomarker Hs-CRP tended
to decrease after nutritional intervention, and the difference in the change value between the two groups was statistically significant. This phenomenon has also been observed in other nutritional interventions [31-33].

Anthropometric and body composition parameters are also independent predictors of mortality in haemodialysis patients [34]. Contrary to the general population, many studies in ESRD patients have reported a “reverse epidemiology”, where higher BMI is paradoxically associated with better survival, especially among those with a higher muscle mass[35, 36]. In our study, only the change value of AC was different between the two groups, with no significant differences in other parameters, which may be related to the short intervention time.

Throughout the study period, most patients in the treatment group were able to adhere to daily oral nutrient solution support, 2 patients developed nausea after taking Fresubin and withdrew, and 3 patients developed mild abdominal distension, but it resolved on its own. Fresubin therapy was well tolerated, and no other significant adverse reactions were observed.

This study has several limitations. First, the sample size was small. Second, the time interval between the two groups was short, and a longer follow-up period would yield more information.

5. Conclusion

The oral fat based high-energy supplements (Fresubin) were well tolerated and could effectively improve the nutritional and inflammation status in MHD patients with PEW.

Abbreviations

AC, abdominal circumference; Alb, albumin; BMI, body mass index; BUN, blood urea nitrogen; Ca, calcium; CHO, total cholesterol; DPI, dietary protein intake; ESRD, end-stage renal disease; Glu, glucose; GS, grip strength; Hb, haemoglobin; Hs-CRP, hypersensitive C-reactive protein; ISRNM, International Society of Renal Nutrition and Metabolism; K, potassium; Kt/V, adequacy of dialysis; MAC, mid arm circumference; MHD, maintenance hemodialysis; ONS, oral nutritional

Declarations

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Author contributions

Bin Wang, Jing-yuan Cao: conceptualization, funding acquisition, project administration; Ming-ming Pan, Min Gao: resources, formal analysis, writing- original draft preparation; Jing-yuan Cao, Jing Zheng: writing- reviewing and editing; Ji-rong Yu: data curation; Sheng-chun Xu, Mei-xia Xia, Wen-jie Liu, Liu-ping Zhang: visualization, investigation; Xiao-liang Zhang, Bi-Cheng Liu: supervision.

Author Declarations

The authors declare that they have no competing interests with regard to any organization or entity with a financial interest in competition with the subject matter or materials discussed in this publication.

Ethical Approval and Consent to participate

The design of the present study was approved by the ethics committees of Zhongda Hospital, Southeast University School of Medicine was obtained before subject recruitment (2019ZDSYLL146-P01).

Competing interests

The authors declare that they have no competing interests in this paper.

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Availability of data and materials

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable

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**Figures**
Flowchart of study participants for the study.

Adult MHD participants from our hemodialysis center
August 2019 to December, 2019
( n = 378)

Patients who were met any of the following conditions were exclude:
(1) Gastrointestinal bleeding and an inability to eat (n = 9)
(2) Serious infection and severe wasting diseases (n = 12)
(3) Liver failure and cirrhosis (n = 4)
(4) Cancer (n = 6)
(5) Acute phase of disease (n = 13)
(6) Not meeting inclusion criteria (n = 189)
(7) Not signed an informed consent (n = 43)
(8) Incomplete information (n = 55)

Participants included in this study
( n = 47)

Fresubin treatment group
( n = 22)

Control group
( n = 25)

20 (91%) participants in Fresubin treatment group and 25 (100%) participants in the control group completed 80 days testing.

Figure 2

The data of patients (Alb, PA, Hs-CRP) in Fresubin treatment group on 0, 30 and 80 days.
(A) Alb level during the study in Fresubin treatment group. (B) PA level during the study in Fresubin treatment group. (C) Hs-CRP level during the study in Fresubin treatment group.