

Article

Low-Phosphate Meals Accompanied by a Minimum Dose of CaCO_3 Downregulates Pro-inflammation by Reducing CKD-MBD Indicators and Triggers by Decreasing Dietary Phosphate Intake

Barbara Ying-Jung Chen¹, Mei-Yi Wu², Mei-Yun Chin³, Mai-Szu Wu² #, Jiun-Rong Chen^{1*}

¹ School of Nutrition and Health Science, Taipei Medical University, Taipei City, 110301, Taiwan; ef.bara@gmail.com (B. Y.-J. C.); syunei@tmu.edu.tw (J.-R. C.)

² Department of Nephrology, Taipei Medical University-Shuang Ho Hospital, Ministry of Health and Welfare, New Taipei City, 235041, Taiwan; e220121@gmail.com (M.-Y. W.); maiszuwu@gmail.com (M.-S. W.)

³ Department of Diet and Nutrition, Taipei Medical University-Shuang Ho Hospital, Ministry of Health and Welfare, New Taipei City, 235041, Taiwan; meiyunchin48@gmail.com (M.-Y. C.)

Co-Corresponding author; maiszuwu@gmail.com

* Corresponding author; syunei@tmu.edu.tw

Abstract: High dietary phosphate intake and poor adherence to phosphate-binding-therapy elevate the risk of hyperphosphatemia in maintenance hemodialysis (HD; MHD) patients. Therefore, chronic kidney disease-related mineral and bone disorder (CKD-MBD) indicators increase; consequently, risks of CKD-MBDs and inflammation are elevated. This double-blind, randomized control trial intervention study was designed to investigate the possibility of reducing blood CKD-MBD indicators and modulating inflammatory indicators by consuming low-phosphate (LP) meals accompanied by a minimum dose of a calcium-based phosphate binder (CaCO_3). MHD patients were recruited and randomly assigned to an LP meal group (LP group) or a control group. After initial data collection, blood collection, and dietary counseling, subjects were asked to consume a washout diet for 1 week. During the washout diet period, subjects consumed their usual diet but took 1 tablet of calcium carbonate (CaCO_3) as a phosphate binder with each meal. After the washout diet period, subjects in the LP group and control group respectively consumed LP meals and regular meals twice a day for 1 week. Meat in the LP meals was boiled before the regular cooking process, but meat in control meals was not. All meals were supplied by a central kitchen so that the contents of phosphate and other nutrients could be identified. In total, 40 MHD patients completed the study program. After 1 week of the dietary intervention, the blood $\text{Ca} \times \text{P}$ product and dietary phosphate had significantly decreased in the LP group compared to the control group ($p < 0.05$). The LP group had significantly lower variations in dietary phosphate intake, blood calcium, $\text{Ca} \times \text{P}$ product, and tumor necrosis factor (TNF)- α than the control group by comparing differences between after the dietary intervention and the baseline (Δ after intervention - baseline, $p < 0.05$). The increase in dietary phosphate intake (Δ 3rd - 2nd dietary phosphate intake) augmented the increase in the TNF- α level by 6.24-fold (odds ratio [95% confidence interval]: 6.24 [1.12~34.92], $p < 0.05$). These results highlighted the conclusion that LP meals accompanied by a minimum dose of CaCO_3 downregulated pro-inflammation by reducing CKD-MBD indicators which was triggered by decreasing dietary phosphate intake.

Keywords: Maintenance hemodialysis (MHD) patient, Low-phosphate meal, CKD-MBD (chronic kidney disease-related mineral and bone disorder), Proinflammatory cytokine, TNF- α (tumor necrosis factor-alpha)

1. Introduction

According to the Annual Report on Renal Disease in Taiwan [1], the incidence of dialysis increased from 331 to 504 per million population during the period of 2000 to 2017. Full coverage for dialysis therapy provided by National Health Insurance (NHI), high care quality, and low mortality of dialysis patients are possible reasons for the high utilization of dialysis. There are a high incidence and prevalence of end-stage renal disease (ESRD) in Taiwan [2]. The expenditure on dialysis was 10.6%~11.0% of the Taiwanese national health insurance for total outpatients in 2017. This evidence reveals the great impact of renal dialysis therapy on medical care, health insurance, and finances in Taiwan. Thus, good medical renal care should improve the health status of dialysis patients and also reduce medical expenditures. Dietary therapy is the most beneficial and economical option for renal care. Dietary therapy can well control dietary phosphate intake and blood phosphate levels, which prevents the incidence of hyperphosphatemia in dialysis patients [3].

Hyperphosphatemia, which results from a reduction in phosphate clearance during renal failure, frequently occurs in maintenance hemodialysis (HD; MHD) patients, especially in MHD patients that consume high dietary phosphate and have poor compliance with prescribed phosphate-binding therapy. There were 27.2% of Taiwanese MHD patients with hyperphosphatemia, and less than half of MHD patients achieved the target of serum phosphate of the Kidney Disease Outcomes Quality Initiative (K/DOQI) in 2017 [1]. Poor control of hyperphosphatemia elevates serum parathyroid hormone (PTH), decreases serum vitamin D (1,25(OH)₂D, vit. D), and increases serum calcium and the Ca x P product, which can induce impairment of bone turnover and mineralization and inflammation and also cardiovascular calcification. Systemic disorders of mineral and bone metabolism are defined as chronic kidney disease-related mineral and bone disorders (CKD-MBDs) [4, 5], and hyperphosphatemia triggers CKD-MBDs and is considered a risk factor for mortality in MHD patients [6, 7].

Inflammation is induced by the increasing production of proinflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor (TNF)- α , and plays an important role in dialysis-related morbidity [8]. Inflammation, which elevates resting energy expenditure, oxidative stress, and endothelial dysfunction, is associated with increases in proinflammatory cytokines and causes malnutrition and cardiovascular disease (atherosclerosis) in CKD and MHD patients [9]. High blood levels of proinflammatory cytokines may induce muscle wasting by enhancing protein catabolism through the ubiquitin-proteasome pathway which reduces albumin synthesis and inhibits the appetite. Thus, increases in proinflammatory cytokines predict hypoalbuminemia and mortality in dialysis patients [9]. The increased release of proinflammatory cytokines may have a long-term deleterious effect on mortality of uremic patients by altering immune responses and increasing susceptibility to infections. IL-6 is produced by immunocompetent cells, including monocytes and macrophages, and is released at an early stage of inflammation. TNF- α is mainly produced by macrophages, and induces tumor cell apoptosis and modulates immune responses and inflammation. MHD patients have a high prevalence of inflammation, and almost 30%~50% of HD patients have increased levels of proinflammatory markers, including C-reactive protein (CRP) and IL-6 [10]. In addition to IL-6, HD patients have significantly higher TNF- α levels than healthy people [11, 12]. Beberashvili et al. pointed out the hazard ratio of death from all causes was 1.06 (95% confidence interval [CI]: 1.01~1.10) with an increase of 1 pg/ml of blood IL-6 levels after adjusting for demographic and clinical parameters. Beberashvili et al. (2011) concluded that elevated proinflammatory cytokines were related to adverse outcomes, including malnutrition and higher mortality in HD patients [13].

Strong evidence indicates that consuming a low-phosphate (LP) diet, modifying one's regular cooking methods, and using phosphate binders can adequately attenuate high levels of serum phosphate [3, 14, 15, 16, 17]. Lowering phosphates through the cooking process, in particular boiling meat before the regular cooking process, is suggested to decrease

dietary phosphate intake from the food category of proteins [18, 19, 20]. Taking phosphate binders correctly entails taking an appropriate dose and also taking them at the right time. Calcium-based phosphate binders, especially calcium carbonate (CaCO_3), are usually used as a first-line medication for MHD patients all over the world [21] and in Taiwan due to their cost-effective characteristics. The major side effects of calcium-based binders include hypercalcemia, vascular calcification, and CKD-MBDs [22]. When MHD patients consistently have hyperphosphatemia for a period, they will have high levels of $\text{Ca} \times \text{P}$ products, hypercalcemia, and hyperparathyroidism and will have to avoid calcium-based binders. To prevent the over-absorption of calcium and the incidence of hypercalcemia, taking calcium-based phosphate binders with meals and at an appropriate dose is suggested. Taking calcium-based phosphate binders in an appropriate manner can enhance the binding ability of calcium and phosphate, which also reduces the risk of CKD-MBDs.

No study has investigated the effects of a LP cooking method and taking a minimum dose of a calcium-based binder on blood CKD-MBD indicators and inflammatory indicators. Thus, we designed LP meals by boiling meat before cooking it to decrease dietary phosphate and including one tablet of calcium carbonate (CaCO_3) with meals for MHD patients. We also designed a study to investigate the hypothesis if LP meals with a minimum dose of calcium-based binder can decrease blood CKD-MBD indicators and inflammation.

2. Materials and Methods

Study Design and Subjects

This study was designed as a randomized, double-blind control trial. In total, 80 MHD patients were recruited from the HD center of Taipei Medical University-Shuang Ho Hospital (New Taipei City, Taiwan). All study participants had to fill out an Institutional Review Board (IRB) consent form, and IRB approval was certified by the Taipei Medical University (TMU)-Joint IRB (JIRB). Inclusion criteria included being ≥ 20 years of age and a non-vegetarian. Exclusion criteria included having liver dysfunction, cancer, or pregnancy, being > 80 years of age or vegetarian, needing to avoid calcium-based binders, and having an intact parathyroid hormone (iPTH) of > 700 pg/mL.

Dietary Intervention

All subjects from the MHD center in Shuang Ho Hospital were randomly assigned to an LP meal group (LP group) or a control group. Dietary intake information was collected during dietary counseling by registered dietitians. Accordingly, all subjects were administered a washout diet for 7 days. During 7 days of the washout diet, all subjects were allowed to consume their usual diets but took one tablet of calcium carbonate (CaCO_3) as a phosphate binder with each meal. After completing the washout diet, subjects entered a period of the dietary intervention for 1 week. Diets of the LP group had LP contents, but the dietary phosphate contents of the control group were not modified. During the dietary intervention period, all subjects in both the LP group and control group maintained their usual customary behavior of a regular breakfast and took one tablet of calcium carbonate (CaCO_3) as a phosphate binder with every breakfast meal. The LP group and control group respectively replaced their usual daily lunch and dinner with LP or standard control meals. Both groups of subjects were asked not to take any extra phosphate binder when eating the study meals during the week of the dietary intervention.

To easily control the amounts of proteins, phosphate, and calcium, the main courses of the LP meals and the control meals were produced in a central kitchen. All study meals contained three portions of protein (around 25 g) and 1 portion of vegetables. There were four main courses for both meals. The phosphate (P) and P/protein (Pro) ratio in the LP meals were reduced by averages of 23.9% through boiling the meat for 30 min before the normal cooking process. The boiling method also removed 20%~40% of the sodium,

magnesium, and potassium from the meat of the LP meals. The boiling method was not conducted for control meals. Every meal, including all LP and control meals, contained one tablet of CaCO_3 . Therefore, additional phosphate binders were not allowed when eating the study meals. Subjects had to prepare carbohydrates themselves, and they could choose any source of carbohydrates they preferred. The nutrition compositions of both study meals were measured and are shown in Table 1.

Data Collection

Personal characteristics (including anthropometric indicators, disease history, and drug administration) and dietary intake levels were collected by registered dietitians during dietary counseling. Because all items of the dietary intake of this study were included and collected in regular dietary counseling, data of dietary intake of this study were based on records from dietary counseling. Dietary intake levels of phosphate were subjectively categorized by dietitians into three levels of low, moderate, and high, after determining the contents of the dietary intake. Thus, we scored low intake as 1, moderate intake as 2, and high intake as 3 for the data analysis.

Blood Collection

Blood indicators included blood CKD-MBD indicators (phosphate, calcium, $\text{Ca} \times \text{P}$ product, fibroblast growth factor 23 (FGF23), iPTH, indicators of renal function, and dialysis adequacy (blood urea nitrogen (BUN), creatinine, estimated glomerular filtration rate (eGFR), net ultrafiltration, potassium, sodium, and magnesium), nutritional indicators (prealbumin), and inflammatory indicators (C-reactive protein (CRP), IL-6, and TNF- α). All data were collected at the baseline, at 1 week after the washout period, and at the end of the 7-day dietary intervention.

Statistical Analysis

Data are presented as mean \pm standard deviation (SD) and analyzed by SPSS program vers. 18 (Statistical Package for Social Sciences, SPSS, Chicago, IL, USA). Comparisons of variables and differences of variables during two time points between the two groups were conducted by Student's t-test. A binary logistic regression was used to predict the odds ratio (OR) of inflammation with variables. $p < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics

In total, 40 patients (LP group $n=20$; control group $n=20$) completed data collection, blood collection, and the dietary intervention. The flowchart of this study program is displayed in Figure 1. Baseline characteristics, and biochemical and inflammatory indicators are given in Table 2. There were no statistically significant differences in baseline characteristics or indicators between the two groups. TNF- α levels were slightly higher in the LP group than in the control group, but it did not reach statistical significance.

3.2. Blood indicators and dietary intake

There were no statistically significant differences between the two groups after 7 days of the washout diet. After the dietary intervention, the LP group had significantly lower levels of the blood $\text{Ca} \times \text{P}$ product and dietary phosphate intake than the control group (blood $\text{Ca} \times \text{P}$ product: LP group at $51.61 \pm 15.54 \text{ mg}^2/\text{dL}^2$ vs. the control group at $63.31 \pm 18.54 \text{ mg}^2/\text{dL}^2$, $p < 0.05$; and dietary phosphate intake (score): LP group at 1.48 ± 0.42 vs. the control group at 1.86 ± 0.42 , $p < 0.01$). The distribution of blood indicators and dietary intake levels between the two groups during the study period are presented in Table 3.

3.3. Differences of blood indicators and dietary intake

Differences in blood indicators and dietary intake levels between the two groups during the study period are shown in Table 4. Variations in indicators after the washout diet and the baseline ($\Delta 2^{\text{nd}} - 1^{\text{st}}$) showed the effects of the usual diet accompanied by 1CaCO_3 , and differences in after the dietary intervention and after the washout diet ($\Delta 3^{\text{rd}} - 2^{\text{nd}}$) indicated effects of different kinds of study meals while controlling the same type and the same dose of the phosphate binder (1CaCO_3). Differences between after the dietary intervention and baseline ($\Delta 3^{\text{rd}} - 1^{\text{st}}$) revealed the effects of both kinds of study meals accompanied by 1CaCO_3 . There were no differences in the effects of the usual diet accompanied by 1CaCO_3 ($\Delta 2^{\text{nd}} - 1^{\text{st}}$) between the two groups. To compare differences between after the dietary intervention and after the washout diet ($\Delta 3^{\text{rd}} - 2^{\text{nd}}$), blood phosphate in the LP group significantly decreased compared to the control group ($\Delta 3^{\text{rd}} - 2^{\text{nd}}$ blood phosphate: LP group -0.04 ± 0.78 mg/dL, control group 0.65 ± 1.28 mg/dL) ($p < 0.05$). The LP group had a significantly greater decrease in $\Delta 3^{\text{rd}} - 2^{\text{nd}}$ Ca x P product than the control group (LP group at -0.08 ± 8.29 mg/dL vs. the control group at 7.06 ± 13.00 mg/dL) ($p < 0.05$). The difference in dietary phosphate intake scores between after the dietary intervention and after the washout diet ($\Delta 3^{\text{rd}} - 2^{\text{nd}}$) in the LP group was -0.42 ± 0.48 mg/dL, and the variation was significantly higher in the control group (0.01 ± 0.46) ($p < 0.01$). When comparing differences between after the dietary intervention and the baseline ($\Delta 3^{\text{rd}} - 1^{\text{st}}$), blood calcium, the Ca x P product, creatinine, TNF- α , and dietary phosphate intake significantly decreased in the LP group ($p < 0.05$) compared to the control group (calcium: LP group at -0.36 ± 0.57 mg/dL vs. the control group at 0.13 ± 0.61 mg/dL, $p < 0.05$; Ca x P product: LP group at 0.57 ± 10.19 mg²/dL² vs. the control group at 10.00 ± 14.81 mg²/dL², $p < 0.05$; creatinine: LP group at -0.17 ± 1.60 mg/dL vs. the control group at 0.87 ± 0.68 mg/dL, $p < 0.05$; TNF- α : LP group at -28.03 ± 31.28 pg/mL vs. the control group at -9.80 ± 22.96 pg/mL, $p < 0.05$; and dietary phosphate intake: LP group at -0.39 ± 0.48 vs. the control group at 0.03 ± 0.41 , $p < 0.01$).

3.4. The risk analysis of inflammation

ORs of high TNF- α (3rd) (TNF- α > 8.1 pg/dL) among the variations of blood indicators after the dietary intervention accompanied by CaCO_3 ($\Delta 3^{\text{rd}} - 1^{\text{st}}$) are presented in Table 5. The OR of $\Delta 3^{\text{rd}} - 1^{\text{st}}$ for IL-6 for predicting high TNF- α was 1.85 (95% CI: 1.01~3.40, $p < 0.05$). Blood prealbumin levels after the dietary intervention accompanied by 1CaCO_3 (3rd prealbumin) had a lower risk of high TNF- α (OR of 0.66, 95% CI: 0.47~0.94, $p < 0.05$). The increase in dietary protein intake after the dietary intervention and 1CaCO_3 ($\Delta 3^{\text{rd}} - 1^{\text{st}}$ dietary protein intake) decreased the high TNF- α level by 7% (OR of 0.93, 95% CI: 0.86~0.99, $p < 0.05$) (Table 6). The increase in the dietary phosphate intake ($\Delta 3^{\text{rd}} - 2^{\text{nd}}$ dietary phosphorous intake) augmented the increase of TNF- α level by 6.24-fold (OR of 6.24, 95% CI: 1.12~34.92, $p < 0.05$) (Table 7).

Table 1. The nutrition compositions of both study meals.

Nutrients	Total amount (per meal)		differences (per meal) LP (boiling process) vs Control (normal cooking process)	
	control-normal process	LP-boiling process	average	
	mean±SD	mean±SD	mean±SD	%
Calories (kcal)	341.2 ± 59.9	265.4 ± 45.9	-75.9 ± 60.9	-21.0%
Protein (g)	23.6 ± 1.1	23.5 ± 2.8	-0.1 ± 2.7	0.2%
Fat (g)	19.3 ± 5.7	12.3 ± 3.4	-6.9 ± 7.6	-28.3%
Saturated Fat (g)	5.8 ± 2.6	3.0 ± 1.1	-2.8 ± 3.3	-34.9%
Carbohydrate (g)	18.6 ± 4.4	15.1 ± 5.5	-3.5 ± 4.6	-18.3%
Total sugar (g)	7.5 ± 2.3	5.8 ± 2.4	-1.7 ± 0.8	-24.5%
Dietary fiber (g)	1.1 ± 0.1	0.8 ± 0.1	-0.3 ± 0.1	-27.5%
Calcium (mg)	265.6 ± 7.5	263.5 ± 25.3	-2.1 ± 15.7	-0.8%
Phosphate (mg)	214.8 ± 21.1	155.6 ± 20.3	-59.2 ± 37.0	-26.8%
Sodium (mg)	3.5 ± 0.4	4.2 ± 1.0	0.7 ± 0.4	19.4%
Potassium (mg)	577.6 ± 73.1	300.2 ± 77.8	-277.4 ± 112.0	-47.8%
Magnesium (mg)	42.5 ± 6.4	34.6 ± 4.6	-7.9 ± 7.1	-17.6%
P/Pro (Phosphate/Protein) ratio	9.2 ± 1.2	6.7 ± 1.2	-2.42 ± 1.94	-23.9%

The data of the nutrition compositions were the measured values.

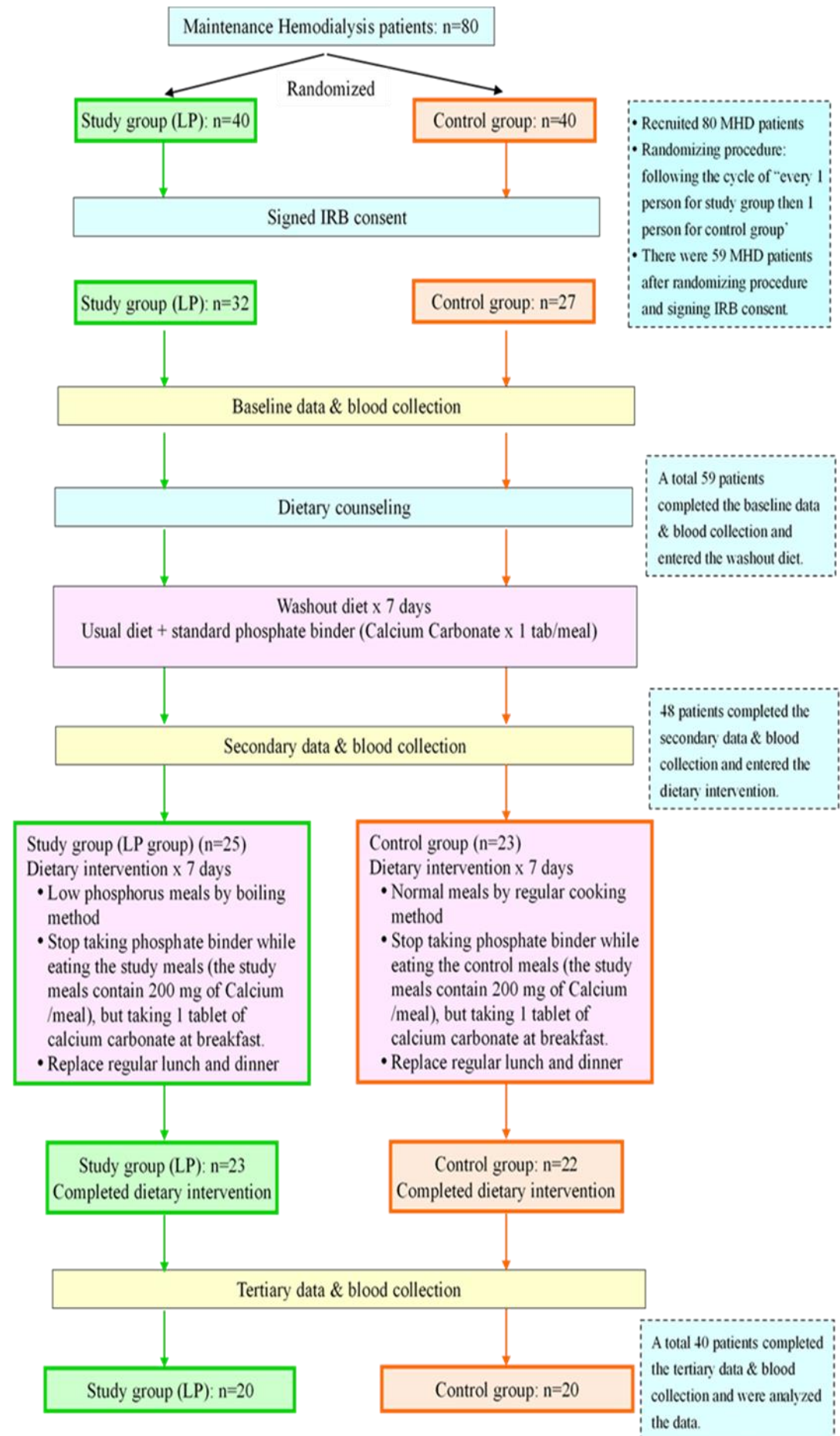


Figure 1. The flowchart and timeline of this study program**Table 2.** Baseline characteristics and biochemical indicators in the maintenance hemodialysis patients.

	All (n=40)		Control group (n=20)		LP group (n=20)		p value
	Mean	SD	Mean	SD	Mean	SD	
Gender							
Male	22 (55.0%)		10 (50.0%)		12 (60.0%)		0.5372
Female	18 (45.0%)		10 (50.0%)		8 (40.0%)		
Age(y/o)	60.50 ± 10.28		62.95 ± 6.41		58.05 ± 12.78		0.1335
BMI	25.21 ± 6.33		25.39 ± 4.48		25.03 ± 7.88		0.8588
Body weight after HD (Kg)	65.43 ± 13.40		64.81 ± 9.90		66.06 ± 16.42		0.7722
HD duration (yearrs)	5.88 ± 4.40		5.33 ± 2.87		6.43 ± 5.56		0.4367
HD duration (hrs)	4.0 ± 0.1		3.9 ± 0.2		4.0 ± 0.1		0.2773
Blood pressure							
Systolic blood pressure (mmHg)	147.1 ± 23.6		143.8 ± 17.1		150.5 ± 28.7		0.3790
Diastolic blood pressure (mmHg)	67.8 ± 14.6		63.9 ± 9.0		71.8 ± 18.0		0.0889
CKD-MBD indicators							
P (mg/dL)	5.50 ± 1.07		5.61 ± 1.14		5.38 ± 1.01		0.5054
Ca (mg/dL)	9.48 ± 0.82		9.51 ± 0.91		9.45 ± 0.75		0.8204
Ca x P product (mg ² /dL ²)	52.17 ± 11.36		53.31 ± 11.55		51.04 ± 11.35		0.5329
FGF23 (pg/mL)	277.8 ± 188.4		232.8 ± 125.1		322.8 ± 230.2		0.1326
iPTH (pg/mL)	316.1 ± 229.9		271.6 ± 188.2		360.6 ± 262.4		0.2249
Renal function and dialysis adequacy indicators							
BUN (before Dialysis) (mg/dL)	65.8 ± 15.9		65.1 ± 18.5		66.5 ± 13.3		0.7923
Creatinine (mg/dL)	10.62 ± 2.59		10.65 ± 2.71		10.60 ± 2.53		0.9528
eGFR (ml/min/1.73m2)	4.89 ± 1.43		4.81 ± 1.17		4.98 ± 1.67		0.7198
Kt/V	1.64 ± 0.22		1.66 ± 0.21		1.63 ± 0.24		0.7395
Net ultrafiltration (L)	1.86 ± 0.94		2.03 ± 0.77		1.70 ± 1.08		0.2806
Potassium (mEq/L)	4.53 ± 0.66		4.58 ± 0.59		4.49 ± 0.73		0.6709
Sodium (mEq/L)	137.8 ± 2.7		137.9 ± 2.5		137.7 ± 2.9		0.8186
Magnesium (mg/dL)	2.40 ± 0.23		2.40 ± 0.24		2.41 ± 0.22		0.8905
Nutritional indicator							
pre-Albumin (mg/dL)	32.84 ± 8.79		31.84 ± 8.48		33.83 ± 9.19		0.4811
Inflammatory indicators							
CRP (mg/dL)	0.89 ± 1.07		0.94 ± 1.26		0.83 ± 0.87		0.7483
IL-6 (pg/mL)	1.73 ± 2.67		1.77 ± 3.15		1.70 ± 2.17		0.9308
TNF-α(pg/mL)	20.98 ± 28.78		12.14 ± 22.35		29.81 ± 32.20		0.0509

The differences between two groups were tested by student's t test. *P* value < 0.05 indicated the statistically significant difference.

Table 2. Baseline characteristics and biochemical indicators in the maintenance hemodialysis patients (continued).

	All (n=40)		Control group (n=20)		LP group (n=20)		p value
	Mean	SD	Mean	SD	Mean	SD	
Disease history							
Hypertension	30		14		16		0.4780
Cardiovascular disease	15		7		8		0.7517
Cerebrovascular disease	0		0		0		0.1193
Diabetes	21		13		8		0.1544
GI disease	2		0		2		0.3236
Thyroid disease	0		0		0		0.1544
Parathyroid disease	0		0		0		0.3236
Osteoporosis	0		0		0		0.3888
Immunol dysfunction	0		0		0		0.3236
Anemia	1		1		0		0.3888
Constipation	6		2		4		0.3500
Drug administration							
EPO	39 (97.5%)		19 (95.0%)		20 (100%)		0.5000
Oral Fe	0 (0.0%)		0 (0.0%)		0 (0.0%)		1.0000
IV Fe	15 (37.5%)		4 (20.0%)		11 (55.0%)		0.0480
Oral Vitamin D3	6 (15.0%)		4 (20.0%)		2 (10.0%)		0.6610
IV Vitamin D3	17 (42.5%)		7 (35.0%)		10 (50.0%)		0.2060
Fecal softener	23 (57.5%)		14 (70.0%)		9 (45.0%)		0.4870
Insulin	2 (5.0%)		2 (10.0%)		0 (0.0%)		0.5000
Parathyroidectomy	1 (2.5%)		0 (0.0%)		1 (5.0%)		0.3888
Calcium concentration of Dialysate							0.2590
Low Calcium (2.5)	21 (52.5%)		8 (40.0%)		13 (65.0%)		
Medium Calcium (3.0)	18 (45.0%)		12 (60.0%)		6 (30.0%)		
High Calcium (3.5)	1 (2.5%)		0 (0.0%)		1 (5.0%)		
Phosphate binders							
Amount							
One kind of phosphate binders	36 (90.0%)		18 (90.0%)		18 (90.0%)		
Two kinds of phosphate binders	4 (10.0%)		2 (10.0%)		2 (10.0%)		
Type							
Calcium Carbonate	32 (80.0%)		18 (90.0%)		14 (70.0%)		
Aluminum-base	10 (25.0%)		3 (15.0%)		7 (35.0%)		
Phosphate binders scores	9.3 ± 7.7		7.6 ± 5.2		11.0 ± 9.3		0.1604
3 (TID, ter in die, Calcium Carbonate)	14 (35.0%)		8 (40.0%)		6 (30.0%)		
4-6 (Less than 6 tablets of Calcium Carbonate/day)	10 (25.0%)		6 (30.0%)		4 (20.0%)		
7-14	6 (15.0%)		3 (15.0%)		3 (15.0%)		
More than 15	10 (25.0%)		3 (15.0%)		7 (35.0%)		
Dietary intakes							
Calories intakes							
Calories (Kcal)	1478.1 ± 385.3		1434.5 ± 364.3		1521.8 ± 409.9		0.4811
Calories (Kcal/Kg BW)	23.42 ± 7.26		22.85 ± 7.34		23.98 ± 7.33		0.6265
Protein intakes							
Protein ammounts (g)	61.61 ± 17.34		59.83 ± 16.48		63.40 ± 18.42		0.5217
Protein ammounts (g/kg BW)	0.98 ± 0.32		0.95 ± 0.31		1.00 ± 0.33		0.6142
CHO intakes: portions (exchanges)	9.10 ± 2.84		9.05 ± 2.64		9.15 ± 3.10		0.9153
Vegetable intakes: portions (exchanges)	1.89 ± 1.47		1.75 ± 1.04		2.03 ± 1.82		0.5566
Fruit intakes: portions (exchanges)	0.60 ± 0.79		0.59 ± 0.66		0.61 ± 0.93		0.9454
Dietary phosphate intakes (quality, score)	1.85 ± 0.36		1.83 ± 0.42		1.87 ± 0.31		0.7166

The differences between two groups were tested by student's t test. *P* value < 0.05 indicated the statistically significant difference.

Table 3. The distribution of blood CKD-MBD indicators, inflammatory indicators and dietary intakes between two groups during the study period.

	Baseline (1st)						After washout diet (2nd)						After dietary intervention (3rd)					
	Control group			LP group			Control group			LP group			Control group			LP group		
	Mean	SD		Mean	SD	p value	Mean	SD		Mean	SD	p value	Mean	SD		Mean	SD	p value
Blood Phosphate (mg/dL)	5.61 ± 1.14			5.38 ± 1.01		0.5054	5.96 ± 1.64			5.68 ± 1.47		0.5667	6.61 ± 2.04			5.64 ± 1.46		0.0942
Blood Calcium (mg/dL)	9.51 ± 0.91			9.45 ± 0.75		0.8204	9.45 ± 0.99			9.17 ± 1.15		0.4227	9.64 ± 1.14			9.10 ± 0.89		0.1039
Blood Ca x P product (mg ² /dL ²)	53.31 ± 11.55			51.04 ± 11.35		0.5329	56.25 ± 16.00			51.69 ± 13.09		0.3298	63.31 ± 18.54			51.61 ± 15.54		0.0368
Blood FGF23 (pg/mL)	232.8 ± 125.1			322.8 ± 230.2		0.1350	270.3 ± 165.7			272.9 ± 212.0		0.9658	366.3 ± 131.3			406.0 ± 201.3		0.4650
Blood iPTH (pg/mL)	271.6 ± 188.2			360.6 ± 262.4		0.2249	240.9 ± 160.8			329.8 ± 289.9		0.2377	245.5 ± 183.7			295.3 ± 194.5		0.4098
Blood BUN(before dialysis) (mg/dL)	65.1 ± 18.5			66.5 ± 13.3		0.7923	70.0 ± 21.8			68.2 ± 18.3		0.7729	78.8 ± 21.3			72.5 ± 23.3		0.3771
Blood Creatinine (mg/dL)	10.65 ± 2.71			10.60 ± 2.53		0.9528	10.72 ± 2.96			10.60 ± 2.58		0.8925	11.51 ± 2.93			10.43 ± 2.42		0.2095
Blood Potassium (mEq/L)	4.58 ± 0.59			4.49 ± 0.73		0.6709	4.49 ± 0.60			4.41 ± 0.81		0.7243	4.77 ± 0.65			4.37 ± 0.73		0.0792
Blood Sodium (mEq/L)	137.9 ± 2.5			137.7 ± 2.9		0.8186	136.6 ± 3.4			136.3 ± 3.4		0.7807	139.6 ± 6.5			136.8 ± 4.4		0.1241
Blood Magnesium (mg/dL)	2.40 ± 0.24			2.41 ± 0.22		0.8905	2.40 ± 0.26			2.46 ± 0.25		0.4611	2.51 ± 0.31			2.45 ± 0.18		0.4167
Blood pre-Alb (mg/dL)	31.84 ± 8.48			33.83 ± 9.19		0.4811	31.02 ± 7.25			33.99 ± 8.62		0.4811	30.95 ± 7.20			32.55 ± 8.20		0.5159
Blood CRP (mg/dL)	0.94 ± 1.26			0.83 ± 0.87		0.7483	0.80 ± 1.03			0.56 ± 0.57		0.3686	0.70 ± 0.88			0.54 ± 0.53		0.4769
Blood IL-6 (pg/mL)	1.77 ± 3.15			1.70 ± 2.17		0.9308	1.30 ± 6.60			1.34 ± 6.37		0.9861	1.11 ± 2.26			1.25 ± 2.45		0.8496
Blood TNF-α(pg/mL)	12.14 ± 22.35			29.81 ± 32.20		0.0518	31.99 ± 46.19			30.96 ± 43.43		0.9426	2.34 ± 7.58			1.78 ± 8.70		0.8282
Dietary calories intakes (Kcal)	1434.5 ± 364.3			1521.8 ± 409.9		0.4811	1438.3 ± 363.2			1586.8 ± 413.4		0.2349	1530.9 ± 340.6			1577.5 ± 267.6		0.6334
Dietary calories intakes (Kcal/Kg BW)	22.85 ± 7.34			23.98 ± 7.33		0.6265	22.91 ± 7.31			25.28 ± 8.48		0.3502	24.45 ± 7.99			24.68 ± 5.69		0.9157
Dietary protein intakes (portions,	6.55 ± 2.21			7.05 ± 2.23		0.4844	6.60 ± 2.20			7.22 ± 2.14		0.3726	6.93 ± 1.77			7.39 ± 1.43		0.3723
Dietary protein intakes (g)	59.83 ± 16.48			63.40 ± 18.42		0.5217	60.18 ± 16.42			65.52 ± 18.16		0.3347	64.24 ± 14.73			67.02 ± 10.86		0.5022
Dietary protein intakes (g/kg BW)	0.95 ± 0.31			1.00 ± 0.33		0.6142	0.96 ± 0.31			1.04 ± 0.36		0.4070	0.78 ± 0.28			0.81 ± 0.22		0.6385
Dietary CHO intakes (exchange)	9.05 ± 2.64			9.15 ± 3.10		0.9150	9.05 ± 2.64			9.75 ± 3.08		0.4470	10.31 ± 2.28			10.07 ± 2.82		0.7690
Dietary vegetable intakes (exchange)	1.75 ± 1.04			2.03 ± 1.82		0.5570	1.70 ± 1.00			2.15 ± 1.78		0.3270	2.05 ± 0.76			2.29 ± 1.37		0.5020
Dietary fruit intakes (exchange)	0.59 ± 0.66			0.61 ± 0.93		0.9450	0.59 ± 0.66			0.65 ± 0.93		0.8220	0.25 ± 0.53			0.38 ± 0.54		0.4640
Dietary phosphate intakes (quality, scores)	1.83 ± 0.42			1.87 ± 0.31		0.7166	1.84 ± 0.43			1.90 ± 0.37		0.6689	1.86 ± 0.42			1.48 ± 0.42		0.0070
Phosphate binders	7.6 ± 5.2			11.0 ± 9.3		0.1604	3.0 ± 0.0			3.0 ± 0.0		0.9861	1.2 ± 0.4			1.1 ± 0.3		0.6429

The differences of various indicators between two groups were tested by student's t test. *P* value < 0.05 indicated the statistically significant difference.

Table 4. The differences of blood CKD-MBD indicators, inflammatory indicators and dietary intakes between two groups during the study period

	ΔAfter washout diet-Baseline (Δ2nd-1st)						ΔAfter dietary intervention-After washout diet (Δ3rd-2nd)						ΔAfter dietary intervention-Baseline (Δ3rd-1st)					
	Control group			LP group			Control group			LP group			Control group			LP group		
	Mean	SD		Mean	SD	<i>p</i> value	Mean	SD		Mean	SD	<i>p</i> value	Mean	SD		Mean	SD	<i>p</i> value
Blood Phosphate (mg/dL)	0.35 ± 0.94			0.30 ± 1.26		0.8766	0.65 ± 1.28			-0.04 ± 0.78		0.0491	1.00 ± 1.56			0.26 ± 1.16		0.0993
Blood Calcium (mg/dL)	-0.07 ± 0.45			-0.28 ± 0.76		0.2825	0.19 ± 0.53			-0.08 ± 0.68		0.1757	0.13 ± 0.61			-0.36 ± 0.57		0.0139
Blood Ca x P product (mg ² /dL ²)	2.94 ± 9.81			0.65 ± 7.59		0.4153	7.06 ± 13.00			-0.08 ± 8.29		0.0450	10.00 ± 14.81			0.57 ± 10.19		0.0243
Blood FGF23 (pg/mL)	37.6 ± 131.1			-49.9 ± 182.6		0.0900	96.0 ± 120.9			133.1 ± 189.7		0.4658	133.6 ± 62.8			83.2 ± 107.8		0.0809
Blood iPTH (pg/mL)	-30.6 ± 136.3			-30.8 ± 93.4		0.9971	4.6 ± 97.8			-34.5 ± 201.8		0.4405	-26.1 ± 123.4			-65.3 ± 191.4		0.4458
Blood BUN (before dialysis) (mg/dL)	4.9 ± 13.1			1.7 ± 13.9		0.4583	8.8 ± 13.6			4.4 ± 18.2		0.3872	13.7 ± 11.2			6.1 ± 14.9		0.0749
Blood Creatinine (mg/dL)	0.07 ± 0.86			0.00 ± 1.59		0.8634	0.79 ± 0.96			-0.17 ± 1.24		0.0089	0.87 ± 0.68			-0.17 ± 1.60		0.0113
Blood Potassium (mEq/L)	-0.09 ± 0.44			-0.08 ± 0.57		0.9507	0.28 ± 0.55			-0.04 ± 0.48		0.0615	0.19 ± 0.49			-0.12 ± 0.68		0.1124
Blood Sodium (mEq/L)	-1.3 ± 3.0			-1.4 ± 1.7		0.8987	3.0 ± 6.8			0.5 ± 4.3		0.1806	1.7 ± 5.9			-0.9 ± 4.0		0.1156
Blood Magnesium (mg/dL)	0.00 ± 0.24			0.06 ± 0.18		0.4566	0.11 ± 0.17			-0.02 ± 0.17		0.0284	0.12 ± 0.27			0.04 ± 0.18		0.2997
Blood pre-Alb (mg/dL)	-0.83 ± 4.76			0.16 ± 4.82		0.5218	-0.07 ± 3.59			-1.44 ± 5.20		0.3386	-0.89 ± 4.78			-1.28 ± 5.75		0.8168
Blood CRP (mg/dL)	-0.14 ± 1.25			-0.27 ± 0.79		0.6968	-0.10 ± 0.54			-0.02 ± 0.19		0.5624	-0.24 ± 1.01			-0.29 ± 0.81		0.8520
Blood IL-6 (pg/mL)	-0.47 ± 7.57			-0.36 ± 5.36		0.9577	-0.19 ± 7.54			-0.09 ± 6.96		0.9633	-0.66 ± 3.13			-0.44 ± 2.73		0.8164
Blood TNF-α(pg/mL)	19.85 ± 53.02			1.15 ± 61.14		0.3080	-29.65 ± 50.86			-29.18 ± 46.59		0.9761	-9.80 ± 22.96			-28.03 ± 31.28		0.0423
Dietary calories intakes (Kcal)	3.8 ± 16.8			65.0 ± 186.8		0.1600	92.7 ± 329.4			-9.3 ± 347.5		0.3470	96.4 ± 322.3			55.8 ± 297.6		0.6807
Dietary calories intakes (Kcal/Kg Body	0.07 ± 0.29			1.30 ± 3.74		0.1592	1.54 ± 5.42			-0.60 ± 5.22		0.2126	1.60 ± 5.31			0.70 ± 3.92		0.5438
Dietary protein intakes (portions, exchanges)	0.05 ± 0.22			0.18 ± 0.67		0.4362	0.33 ± 2.01			0.17 ± 2.15		0.8093	0.38 ± 1.94			0.34 ± 2.16		0.9573
Dietary protein intakes (g)	0.35 ± 1.57			2.13 ± 6.80		0.2625	4.07 ± 15.40			1.49 ± 16.72		0.6152	4.42 ± 14.80			3.62 ± 16.38		0.8719
Dietary protein intakes (g/kg BW)	0.01 ± 0.03			0.04 ± 0.13		0.2363	-0.18 ± 0.24			-0.23 ± 0.26		0.5157	-0.17 ± 0.23			-0.19 ± 0.25		0.8566
Dietary CHO intakes (exchange)	0.00 ± 0.00			0.60 ± 1.96		0.1864	1.26 ± 2.50			0.33 ± 2.42		0.2357	1.26 ± 2.50			0.93 ± 1.59		0.6142
Dietary vegetable intakes (exchange)	-0.05 ± 0.22			0.13 ± 0.46		0.1342	0.35 ± 0.81			0.14 ± 1.10		0.4854	0.30 ± 0.92			0.26 ± 1.12		0.9023
Dietary fruit intakes (exchange)	0.00 ± 0.00			0.04 ± 0.23		0.4469	-0.34 ± 0.47			-0.27 ± 0.98		0.7831	-0.34 ± 0.47			-0.23 ± 1.07		0.6827
Dietary phosphate intakes (quantity, scores)	0.02 ± 0.07			0.03 ± 0.27		0.8440	0.01 ± 0.46			-0.42 ± 0.48		0.0055	0.03 ± 0.41			-0.39 ± 0.48		0.0049
Phosphate binders	-4.6 ± 5.2			-8.0 ± 9.3		0.1604	-1.9 ± 0.4			-1.9 ± 0.3		0.6429	-6.5 ± 5.3			-9.9 ± 9.3		0.1556

The differences of various indicators during any two time points were shown by Δ, and the average differences between two groups were tested by student's t test. Δ after washout diet-baseline meant the effects of usual diet accompanying with one tablet of calcium carbonate, Δ after dietary intervention-after washout diet meant the effects of both kinds of study meals, and Δ after dietary intervention-baseline meant the effects of both kinds of study meals accompanying with one tablet of calcium carbonate. *P* value < 0.05 indicated the statistically significant difference.

Table 5. The odds ratio of high TNF-α (3rd) among the variations of blood indicators after dietary intervention accompanying with one tablet of calcium carbonate.

	significance (p value)	odds ratio	95% CI (Confidence Interval))	
			Lower limit	Upper limit
Δ3rd-1st Blood Phosphate	0.133	31640000.00	0.01	19630000000000000.00
Δ3rd-1st Blood Calcium	0.294	288.64	0.01	11300000.00
Δ3rd-1st Blood CaxP product	0.154	0.20	0.02	1.82
Δ3rd-1st Blood BUN	0.098	0.88	0.76	1.02
Δ3rd-1st Blood Creatinine	0.441	0.58	0.14	2.33
Δ3rd-1st Blood IL-6	0.047	1.85	1.01	3.40
Δ3rd-1st Blood FGF23	0.478	0.99	0.98	1.01
Δ3rd-1st Blood iPTH	0.336	0.99	0.98	1.01
3rd preAlbumin	0.021	0.66	0.47	0.94

Binary logistic regression was analyzed to predict the odds ratios of high TNF-α (TNF-α>8.1 pg/dL) by the variations of variables. *P* < 0.05 was considered statistically significant.

Table 6. The odds ratio of high TNF-α among the variations of dietary intakes after dietary intervention accompanying with one tablet of calcium carbonate.

	significance (p value)	odds ratio	95% CI (Confidence Interval)	
			Lower limit	Upper limit
Δ3rd-1st Dietary protein intakes (g)	0.032	0.93	0.86	0.99
Δ3rd-1st Dietary phosphate intakes	0.972	0.97	0.17	5.39
Δ3rd-1st Phosphate binder	0.122	1.14	0.97	1.35

Binary logistic regression was analyzed to predict the odds ratios of high TNF-α (TNF-α>8.1 pg/dL) by the variations of variables (Δ3rd-1st). *P* < 0.05 was considered statistically significant.

Table 7. The odds ratio of the increase of TNF-α among the variation of dietary intakes between after dietary intervention and after washout diet.

	significance (p value)	odds ratio	95% CI (Confidence Interval)	
			Lower limit	Upper limit
Δ3rd-2nd Dietary calories intakes	0.997	1.00	1.00	1.01
Δ3rd-2nd Dietary protein intakes (g)	0.770	0.98	0.88	1.10
Δ3rd-2nd Dietary phosphate intakes	0.037	6.24	1.12	34.92

Binary logistic regression was analyzed to predict the odds ratios of the increase of TNF-α after dietary intervention (Δ3rd-2nd) by variables. *P* < 0.05 was considered statistically significant.

4. Discussion

Prealbumin is the precursor of albumin and is also produced by the liver. Because the half-life of prealbumin is around 2~4 days, prealbumin more immediately reflects the nutritional status than albumin (with its half-life of around 21 days). In addition to albumin, prealbumin is also the gold standard of the nutritional status and is a good predictor of mortality of HD patients [9, 14, 23, 24, 25, 26]. Due to the short duration of this study period, we used prealbumin as the main nutritional indicator instead of albumin.

Systemic inflammation, induced by the overproduction of proinflammatory cytokines, in MHD patients results for several reasons, including patient-related factors, such as underlying diseases, comorbidities, oxidative stress, the Ca x P product, infections, and HD-related factors. Overproduction of proinflammatory cytokines causes complications in MHD patients, which include fever, hypotension, sleep disorders, dialysis-related amyloidosis, impaired immunity, bone diseases, malnutrition, and anemia [8, 27]. Systemic inflammation is related to malnutrition, protein-energy wasting (PEW), and muscle

protein wasting, and the malnutrition-inflammation-cachexia syndrome (MICS) denotes the association of systemic inflammation and malnutrition in CKD patients and MHD patients [28, 29, 30]. One possible mechanism is that proinflammatory cytokines promote protein catabolism and anorexia and reduce protein synthesis. This increases the need for proteins and energy (calories) and decreases both appetite and food intake. These facts reveal the importance of the nutritional status as it relates to inflammation in MHD patients. Beberashvili et al. (2011) pointed out decreases in the daily energy intake, biochemical markers (albumin, transferrin, cholesterol, and creatinine), and the body composition estimated higher levels of IL-6 ($p < 0.05$). After controlling for fixed factors, a 1-pg/ml increase in IL-6 over time was associated with a 0.06-g/L decrease in blood albumin ($p < 0.001$) [13]. Molfino et al. (2013) and Dalrymple et al. (2013) reported a significant negative correlation between prealbumin and the proinflammatory cytokine, IL-6 [25], [26]. Results of this study after the dietary intervention failed to show a negative correlation between prealbumin and IL-6, but results of the risk analysis in this study showed that the OR of blood prealbumin predicting high TNF- α was 0.66 (95% CI: 0.47~0.94, $p < 0.05$) after the dietary intervention accompanied by 1CaCO_3 . This result of the risk analysis provides evidence that a better nutritional status decreases the production of proinflammatory cytokines and inflammation.

Our results demonstrated the increase in the dietary protein intake after the dietary intervention and 1CaCO_3 ($\Delta 3^{\text{rd}}$ - 1st dietary protein intake) significantly decreased the high TNF- α level by 7%. After analyzing data of 8,805 HD patients in 12 countries from 248 facilities, Yamamoto et al. (2021) indicated that the medical practice of increased dietary protein intake in MHD patients with hyperphosphatemia was associated with potentially lower all-cause mortality [31]. That result emphasizes the important role of dietary protein intake in MHD patients. The results of our study also revealed the importance of sufficient protein intake in MHD patients.

A high blood phosphate concentration is associated with increasing levels of proinflammatory indicators (CRP and IL-6) in patients with CKD and MHD, and the evidence indicates that high blood phosphate is a risk factor for inflammation with renal disease [10, 32]. Poor medication adherence of phosphate binders is a common problem causing hyperphosphatemia in MHD patients. A systematic review study indicated that non-adherence to phosphate-binding medication appears to be prevalent in ESRD patients, and the reported rate of non-adherence was around 51% (22%~74% of patients were non-adherent) [33]. Taking phosphate binders, especially CaCO_3 , with meals is a useful way to increase the efficacy of preventing hyperphosphatemia and decrease the occurrence of hypercalcemia. To facilitate the correct administration of calcium-based binders (calcium carbonate) and decrease the pill burden of phosphate binders, mixing a calcium-based binder and meals is a useful method for MHD patients to achieve the goal (i.e., taking calcium-based phosphate binders with meals). Thus, we put 1CaCO_3 into both study meals, and subjects were asked not to take any additional phosphate binders. The process also ensured the dosage of the phosphate binder (CaCO_3) and enhanced compliance in this study. Strong evidence shows that reducing phosphate-rich food intake and boiling meats before the regular cooking process can decrease dietary phosphate, and the optimal dose of a phosphate binder can attenuate hyperphosphatemia [16, 17, 34]. That was the reason why the results of our study emphasized significant reductions in dietary phosphate intake, blood calcium, $\text{Ca} \times \text{P}$ product, and TNF- α in the LP group after consuming LP meals accompanied by 1CaCO_3 compared to relatively high phosphate diets (baseline). The obvious rise in TNF- α by 6.24-fold under the control of the minimum dose of a calcium-based phosphate binder (1CaCO_3) marked the downregulation of TNF- α by decreasing the dietary phosphate intake.

Tsai et al. (2019) compared differences in blood CKD-MBD indicators after consuming a very-LP diet (with a phosphate to protein ratio of 8 mg/g) and a LP diet (with a

phosphate to protein ratio of 10 mg/g) for 2 days. The very-LP diet significantly decreased blood phosphate levels (with a mean difference of 0.6 mg/dl; 95% CI: 0.2~1.0; $p=0.002$). The difference of FGF23 did not significantly decrease after consuming the very-LP diet for 2 days, and the authors mentioned that a possible reason was the short duration of the dietary intervention [35]. The duration of the dietary intervention in our study was 7 days, and the average of phosphate to protein ratio in the LP meals was 6.7 mg/g. Our results also showed a significant decrease in blood phosphate levels after consuming LP meals ($\Delta 3^{\text{rd}} - 2^{\text{nd}}$) for 7 days. Our study also did not show a difference in FGF23 levels after consuming LP meals. Future studies should prolong the study duration to evaluate the effects of LP meals on MHD patients.

The skills of lowering dietary phosphate from food and correct use of a phosphate binder are recognized as useful. Due to shortages of medical manpower, dietary and medication education is often incompletely implemented, and skills about lowering intake of dietary phosphate and lowering absorption of dietary phosphate are not intensively or extensively taught. So, adding a calcium-base phosphate binder, especially CaCO_3 , to meals for MHD patients is suggested.

5. Conclusions

The decreasing variations in the dietary phosphate intake, blood CKD-MBD indicators (blood calcium and $\text{Ca} \times \text{P}$ product), and $\text{TNF-}\alpha$ after consuming the study meals and 1CaCO_3 compared to the relatively high-phosphate diets (baseline) were more significant in the LP group than in the control group. The increased dietary phosphate intake augmented the increase in the $\text{TNF-}\alpha$ level by 6.24-fold. These results highlighted the conclusion that LP meals accompanied by a minimum dose of CaCO_3 downregulated pro-inflammation by decreasing CKD-MBD indicators and were triggered by a decreased dietary phosphate intake. LP meals, which lowered the phosphate amount of meat before the regular cooking process, with a minimum dose of CaCO_3 are suggested for MHD patients.

6. Patents

Eighty MHD patients were recruited from the HD center of Taipei Medical University-Shuang Ho Hospital (New Taipei City, Taiwan). Inclusion criteria included being ≥ 20 years of age and a non-vegetarian. Exclusion criteria included having liver dysfunction, cancer, or pregnancy, being >80 years of age or vegetarian, needing to avoid calcium-based binders, and having an intact parathyroid hormone (iPTH) of >700 pg/mL. In total, 40 patients (LP group $n=20$; control group $n=20$) completed data collection, blood collection, and the dietary intervention.

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Data Availability Statement: The data that support the findings are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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