Dietary Omega-3 Fatty Acid, Ratio of Omega-6 to Omega-3 Intake, Inflammation, and Survival in Long-term Hemodialysis Patients

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Abstract

Background—Mortality among long-term hemodialysis patients is high, mostly attributed to cardiovascular events, and may be related to chronic inflammation. We hypothesized that the anti-inflammatory benefits of higher dietary omega-3, compared to omega-6, poly-unsaturated fatty acids may modulate the inflammatory processes and reduce death risk.

Study design—Prospective cohort study using linear and Cox proportional regressions.

Setting and Participants—145 hemodialysis patients from 8 DaVita dialysis clinics in Southern California during 2001-2007

Predictors—Intake of dietary omega-3 and ratio of omega-6 to omega-3 using 3-day food record supplemented by dietary interview.

Outcomes—One-year change in serum C-reactive protein (CRP) and 6-year survival.

Results—Patients were 53±14 years old (mean±SD) and included 43% women and 42% African-Americans. Median (25th-75 percentile) of dietary omega-3 intake, ratio of omega-6 to omega-3 intake, baseline serum CRP, and change in CRP over one year were 1.1(0.8-1.6) g/day, 9.3(7.6-11.3), 3.1(0.8-6.8) mg/L, and +0.2(−0.4 to +0.8) mg/L, respectively. In regression models adjusted for case-mix, dietary calorie and fat intake, body mass index and history of hypertension,

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each 1-unit higher ratio of omega-6 to omega-3 intake was associated with 0.55 mg/L increase in serum CRP (p=0.03). In fully adjusted model, the death hazard ratios (95% confidence interval) for the 1st(1.7-<7.6) 2nd(7.6-<9.3), 3rd(9.3-<11.3) and 4th(11.3-17.4) quartiles of dietary omega-6 to omega-3 ratio were 0.39(0.14-1.18), 0.30(0.09-0.99), 0.67(0.25-1.79) and 1.00(reference), respectively (p-for-trend=0.06).

Limitations—Three-day food record may underestimate actual dietary fat intake at individual level.

Conclusions—Higher dietary omega-6 to omega-3 ratio appears associated with both worsening inflammation over time and a trend towards higher death risk in hemodialysis patients. Additional studies including interventional trials are needed to examine the association of dietary fatty acids with clinical outcomes in these patients.

Keywords

Chronic kidney disease (CKD); hemodialysis; nutritional status; inflammation; mortality; dietary omega-3; omega-6 to omega-3 ratio; poly-unsaturated fatty acids

The mortality rate among individuals with chronic kidney disease (CKD) who receive maintenance hemodialysis (HD) remains high.(1) Cardiovascular disease, protein energy wasting (PEW), and inflammation are among the strongest predictors of mortality in these patients.(2) Maintenance HD patients with lower serum albumin levels have higher serum concentrations of C-reactive protein (CRP), suggesting the potential role of pro-inflammatory processes in the pathogenesis of PEW.(3) Although PEW is a multifactorial disorder, chronic inflammation seems to have an important role in its development.

Dietary omega-3 polyunsaturated fatty acids (PUFAs) have anti-inflammatory properties that can be protective against atherosclerosis and its consequences of myocardial infarction, sudden death, and stroke.(4) Additionally, omega-3 may have a broad range of beneficial effects on levels of triglycerides, high-density lipoprotein (HDL) cholesterol, and oxidative stress; blood pressure; cardiac excitability; and function of platelets, endothelium and vasculature, and the immune system.(4, 5) A study by Friedman *et al* showed that dietary fish consumption, a main source of omega-3, in maintenance HD patients was far below current American Heart Association (AHA) recommendations, leading to suboptimal omega-3 levels.(6) Given the evidence relating CKD to chronic inflammation(7, 8) and given that half of all CKD deaths are attributed to cardiovascular disease,(9) the anti-inflammatory and cardio-protective benefits of dietary omega-3 may play an important role in modifying the inflammatory processes and thus improving outcomes.

Anthropological, epidemiological, and biochemical studies indicate that human beings evolved on a diet with an equal proportion of omega-6 to omega-3 PUFAs. Over the past 100 years, however, the ratio of omega-6 to omega-3 in Western diets has dramatically increased to ranges of 15/1 or even higher.(10-14) A high dietary omega-6 to omega-3 ratio may contribute to cardiovascular disease, cancer, osteoporosis, and autoimmune disorders. In contrast, higher omega-3 intake or lower omega-6 to omega-3 ratio in diet may exert suppressive effects on the same disease states.(13, 14) To the best of our knowledge, the amount of dietary omega-3 intake or the ratio of omega-6 to omega-3 and their associations with clinical outcomes including survival in CKD patients have not been evaluated. We hypothesized that the anti-inflammatory and cardio-protective benefits of dietary omega-3, compared to omega-6 PUFAs, may modulate the inflammatory processes and reduce death risk in maintenance HD patients. The present study was designed to determine the associations of dietary omega-3 and ratio of omega-6 to omega-3 and mortality in a cohort of maintenance HD patients.

Methods

Patient Population

We studied maintenance HD patients who participated in the NIH-funded NIED (Nutritional and Inflammatory Evaluation in Dialysis) Study.(15-22) The original patient cohort was derived from a pool of approximately 1,300 maintenance HD outpatients in eight DaVita dialysis clinics from the South Bay Los Angeles area. Inclusion criteria were outpatients who had been undergoing maintenance HD for at least 8 weeks, who were 18 years or older and who signed a local Institutional Review Board approved consent form. From October 1, 2001, through September 30, 2007, a total of 893 maintenance HD patients from the eight dialysis clinics gave written informed consent form and underwent the study. Dietary intakes of 145 randomly selected patients were assessed with a 3-day dietary record, accompanied by a diet interview, during the first 6 months of the study (see below). These 145 patients were followed for up to 72 months, i.e. until September 30, 2007. The medical chart of each maintenance HD patient was extensively reviewed by a collaborating physician, and data pertaining to underlying kidney disease and other comorbid conditions were extracted. A modified version of the Charlson comorbidity index was used to assess the severity of comorbidities.(23)

Anthropometric and Body Composition Measures

Anthropometric measurements were performed while patients were undergoing a maintenance HD treatment. Biceps and triceps skinfold thickness was measured with a conventional skinfold caliper using standard techniques as previously described.(20, 21) To estimate the percentage of body fat, portable near infrared (NIR) interactance was utilized at the same time as the anthropometric measurements.(20, 21, 24)

Laboratory Tests

Predialysis blood samples and postdialysis serum urea nitrogen were obtained on a mid-week day. The single-pool Kt/V was used to represent the weekly dialysis dose.(25) Except as indicated below, all laboratory measurements were performed by DaVita Laboratories (www.davita.com) using automated methods. In this study, 3-month averaged values were used, and all laboratory measurements used established assays with well-known coefficients of variation. Serum high sensitivity CRP was measured by a turbidimetric immunoassay (WPCI, Osaka, Japan; reference range: < 3.0 mg/l).(26, 27) Interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α) were measured with immunoassay kits (R&D Systems, www.rndsystems.com); reference ranges, < 9.9 pg/ml for IL-6 and < 4.7 pg/ml for TNF-α). (28, 29)

Three-Day Food Record with Diet Interview

A 3-day diet diary with diet interviews by a trained dietitian was used to assess usual dietary intake of the subjects participating in the NIED Sub-Study in GCRC. Dietary intake was recorded over the last hemodialysis treatment day of the week and the two adjacent non-dialysis days.(30, 31) All participants received standardized instructions on how to complete the 3 day diet record by trained dietitians. The reliability of the estimates of the dietary omega-3 intake derived from food records has been judged acceptable according to the *EURopean micronutrient RECommendations Aligned* (EURRECA) scoring system.(32) The instructions included the viewing of a 14 minute videotape, entitled on *the Record*.(33) The dietitians also reviewed additional instructional material with the participants to guide the details and types of information to be reported. The participants completed the 3 day food record and then returned to the study center for a supplementary dietary interview, in which the trained dietitian reviewed the records and obtained additional relevant information. The

American Dietetic Association (ADA) Portion Photos of Popular Foods book was used to assist the dietitian in the review of the food records for accuracy. The dietitian made edits, corrections, and additions on the food record and used the Minnesota Nutrient Data System software (version 2005 Nutrition Coordinating Center, Minneapolis, Min) to complete the nutrient analysis.

Statistical Methods

Changes in serum CRP over the first year and mortality over 6 years were the main outcome measures. We used linear regression analyses to examine the coefficient of change in CRP over time based on dietary omega-3 or the ratio of omega-6 to 3 intake. Cox-regression-based restricted cubic splines graph with two degrees of freedom were employed to illustrate systematic relations between dietary intakes and mortality. This method also served to examine the non-linear associations as continuous mortality predictors as an alternative to potential inappropriate assumptions concerning linearity.(34) Death hazard ratios were obtained using Cox proportional hazard models after controlling for covariates. We performed incremental levels of multivariate adjustment: (A) Case-mix variables included age, gender, race/ethnicity, diabetes mellitus, dialysis vintage, insurance (Medicare vs. others), marital status, modified Charlson comorbidity score and dialysis dose (single pool Kt/V). (B) Dietary intake variables included dietary intake of energy, saturated fat, trans fatty acids, cholesterol and fiber. (C) History of hypertension and body mass index (BMI). Descriptive and multivariate statistics were carried out with the statistical software Stata (version 10.0; Stata Corporation, www.stata.com).

Results

Baseline demographic, clinical, and laboratory values in the 145 maintenance HD patients are shown in Table 1. The patients' mean age (±SD) was 53±14 years; 43% of patients were women (n=62) and 42% (n=61) African-American. The mean dialysis vintage was 31±33 months (median, 19 months). Median of baseline serum CRP, was 3.1 (25th-75th percentile, 0.8-6.8) mg/L. After ranking subjects according to their dietary intakes, we categorized them into quartiles of dietary omega-3 and also quartiles of the ratio of omega-6 to omega-3. Table 1 shows relevant demographic, clinical and laboratory measures for the four quartiles. The proportions of women and African Americans were higher in the groups with lower and higher dietary omega-3 intake, respectively.

Table 2 shows the dietary intakes of 145 maintenance HD patients according to the quartiles of their dietary omega-3 intakes and ratio of omega-6 to omega-3. Median of dietary omega-3 intake and the ratio of omega-6 to omega-3 intake were 1.1 (25th-75th percentile, 0.8-1.6) g/day and 9.3 (25th-75th percentile, 7.6-11.3), respectively. Subjects with higher omega-3 intakes had higher intakes of energy, total fat, saturated fatty acids, monounsaturated fatty acids, PUFAs, omega-6 fatty acids, cholesterol and fiber, but lower omega-6 to omega-3 ratios. Subjects with higher ratio of omega-6 to omega-3 had higher intakes of monounsaturated fatty acids and omega-6 and lower intakes of omega-3.

In order to examine the association of omega-3 intake and the ratio of omega-6 to omega-3 with changes in inflammatory status over time, we studied changes in CRP levels over the first 12 months across quartiles of omega-3 and the ratio of omega-6 to omega-3 and examined the regression coefficients between these quartiles with changes in serum CRP. Median change in CRP over the first 12 months was +0.2 (25th-75th percentile, −0.4 to +0.8) mg/L. As shown in Table 3, in fully adjusted linear regression models each unit higher dietary omega-6 to omega-3 ratio was associated with 0.55 mg/L increase in serum CRP (p=0.03). Higher dietary omega-3 intake alone was associated with a non-significant trend towards a decrease in serum CRP.

Over the 6 years of the cohort follow up, 42 (29%) patients died. We examined death hazard ratios across the quartiles as shown in Table 4 and 5. Taking the highest quartile as the reference, the lower quartile of omega-6 to omega-3 ratio was associated with lower death risk (p for trend of 0.06 in fully adjusted models, Table 5). We also adjusted for the interaction between dialysis vintage and the ratio of omega-6 to omega-3, which showed similar associations (data not shown). Figure 1 shows the cubic splines graph illustrating the multivariate adjusted association between baseline the ratio of omega-6 to omega-3 intake ratio and mortality. A trend towards increased risk of death was observed in maintenance HD patients with higher omega-6 to omega-3 intake ratios.

Discussion

Examining the association of daily intake of dietary omega-3 and the ratio of omega-6 to omega-3 PUFAs with changes in CRP over one year and survival over 6 years in 145 maintenance HD patients, we found that higher omega-6 to omega-3 ratio correlated with increased serum CRP and increased mortality. If our findings can be verified in additional studies, interventional trials are warranted to examine the effect of dietary PUFA in modulating inflammation and improving clinical outcomes of maintenance HD patients. The association of dietary omega-6 and omega-ratio and the risk of cardiovascular disease and mortality has been studied in the general population without apparent CKD.(35-39) Our study is one of the first ones to evaluate this association in advanced CKD patients who undergo maintenance HD. Although we did not directly measure markers of dietary fatty acid in plasma such as circulating omega-3 or omega-6 levels, a study by Svensson *et al* (40) showed a clinically meaningful correlation between dietary intake and plasma levels of omega-3 in maintenance HD patients.

In an observational study by Kutner *et al* higher dietary fish consumption, a rich source of omega-3 fatty acids, independently predicted patient survival in 3000 maintenance HD patients.(41) The focus of our current study, on the other hand, was the type and ratios of fatty acids rather than the kind of the ingested food such as fish. We did not find any significant association between dietary omega-3 intake per se and inflammation or mortality. There could be several reasons for our negative findings in this regard. First, there was low statistical power to find meaningful assocaitions because of the small population size and number of deaths overall. Second, the range of omega-3 levels in the dietary patterns of our study population may have been too narrow. This is due to the fact that intake was based on natural foods and not supplements. Third, our study was based on a single self-report of usual intake, a limitation that is common to most studies similar to ours. Mistakes in the record of food intake or changes in diet over time may have made it difficult to find any association between omega-3 PUFA intake and mortality. Fourth, subjects with higher omega-3 intake also consumed higher amounts of omega-6, thereby mitigating the benefit of increased omega-3 intake per se. This underscores the importance of examining the relative consumption of omega-3 vs. omega-6 PUFAs in determining the potential benefits of omega-3 intake.

There are a number of studies of the association of omega-3 and omega-6 PUFAs with inflammation. Ferruci *et al*.(42) suggested that a higher omega-6 to omega-3 ratio was associated with higher serum interleukin-10 concentrations and concluded that omega-3 is protective against diseases characterized by active inflammation. In observational studies of the secondary prevention of cardiovascular disease, a low omega-6 to omega-3 ratio of 2:1 to 3:1 was associated with less severe inflammation in patients with rheumatoid arthritis, and a ratio of 5:1 was associated with better outcomes in patients with asthma, whereas a ratio of 10:1 or higher was associated with adverse consequences.(12) These studies suggest

that the optimal dietary ratio of omega-6 to omega-3 may vary with the disease under consideration.(43)

The effect of dietary omega-3 intake on inflammatory response has been examined in only a few studies in maintenance HD patients, and all of them have focused on omega-3 administered as a dietary supplement rather than in the natural food. Saifullah *et al.*(44) studied maintenance HD patients who received 1.3 g of oral eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) daily for three months. Only a modest reduction in serum CRP levels was evident in the PUFA-treated group (p=0.03).(44) Perunicic-Pekovic *et al.* (45) reported omega-3 PUFA depletion in the membrane phospholipid composition of maintenance HD patients. Treatment with 2.4 g of omega-3 PUFAs daily for 2 months resulted in a significant increase in erythrocyte phospholipid fatty-acid composition, a decrease in serum TNFα and IL-6, and an increase in serum albumin and hemoglobin levels (p<0.001). Kalantar-Zadeh *et al.*(46) demonstrated that 4-weeks of supplementation with omega-3 that contained 1.08 g EPA per day was associated with an increase in patients' serum albumin, an important marker of nutritional or inflammatory status. In our study, an omega-6 to omega-3 PUFA ratio around 6 was associated with reduced inflammation and all-cause mortality in maintenance HD patients, providing evidence for a beneficial effect of a lower omega-6 to omega-3 PUFA ratio.

The biological mechanisms that may explain this finding are still incompletely understood. Mammalian cells cannot convert omega-6 into omega-3 PUFAs, because they lack the converting enzyme, omega-3 desaturase.(12) Vegetable oils rich in omega-6 have displaced other fats in the US diet because of the evidence of their hypocholesterolemic properties. Based on estimates derived from studies of Paleolithic nutrition and modern-day hunter-gatherers, humans evolved on a diet with substantially lower omega-6 to omega-3 PUFA ratios, indeed roughly equal amounts of omega-6 and 3.(47-49) When humans ingest omega-3, it replaces such omega-6 PUFAs as arachidonic acid in the membranes of a variety of cells, including platelets, erythrocytes, neutrophils, monocytes, and liver cells.(10)

Although the inventory of cellular proteins is determined at the gene level, the contributions of various PUFAs to cell membranes is largely dependent on dietary intake. The metabolites of PUFAs, arachidonic acid and EPA, are parent compounds for the production of mediators of immunity and inflammation, known as eicosanoids.(10) On account of the Western diet's higher levels of omega-6 PUFAs, eicosanoid metabolic products from arachidonic acid (eg, prostaglandins, thromboxanes, leukotrienes, hydroxy fatty acids and lipoxins) are produced in greater amounts than in diets that include more omega-3 PUFAs, specifically EPA.(10) The eicosanoids from arachidonic acid have biological activity even in minute amounts, and if they occur in greater quantities they can help lead to thrombi and atheromata, the development of allergic and inflammatory disorders, and to the proliferation of cells. These changes can result in vasospasm, vasoconstriction, increased blood viscosity, and decreased bleeding time. In the study of Cleland *et al.*(50), 30 healthy male subjects consumed omega-3 derivatives. After 4 weeks, the incorporation of omega-3 derivatives in phospholipids of the cell membranes neutrophils was greatest in the group which consumed the lowest levels of omega-6 derivatives, suggesting that consuming omega-6 PUFAs is important in setting EPA incorporation into neutrophil membranes.

Some limitations should be considered in interpreting our findings. First, although our major interest was all-cause mortality, our ability to determine the specific causes of death associated with increased mortality were greatly diminished by the relatively small sample size and low numbers of deaths in this study. The present study lacked statistical power to conduct meaningful analyses of omega-6 to omega-3 intake and the specific cause of mortality for each. Second is our limited statistical power which may have resulted in large

confidence intervals. Third is potential selection bias during enrollment, in that patients with PEW were less likely to enroll. However, selection bias in this direction would lead to bias toward the null; therefore, without this bias our results may have been even stronger. Fourth is the lack of information regarding dialysis access, dialysis membranes used, and several other known confounders, such as healthy life-styles or socioeconomic status, as well as unknown confounders. Fifth, we did not assess the food pattern of these patients, whose lower omega-6 to omega-3 ratio may have been associated with a healthier dietary pattern which could confound our results. There are several strengths to this study including the relatively long follow-up period (72 months), the comprehensive laboratory evaluations and the detailed evaluation of the clinical and comorbid states. Our cohort has been extensively characterized for markers of inflammation and nutritional status, energy intake, types of fat intakes and direct total body fat measurements. Finally, participants were selected randomly without the investigators or the patients having prior knowledge of their inflammatory status.

In conclusion our study suggests that a lower dietary omega-6 to omega-3 ratio in the ingested food may be associated with both decreased inflammation and lower mortality risk in maintenance HD patients even after adjusting for intakes of energy, saturated fatty acid, trans-fats, cholesterol and fiber. These findings, if verified in additional studies, and particularly in randomized prospective clinical trials, may imply that the lower ratios of omega-6 to omega-3 PUFA intakes should be recommended to maintenance HD patients. Future studies should also examine the association of different kinds of omega-3 PUFAs; i.e., EPA and DHA, with inflammatory status and mortality in maintenance HD patients.

Acknowledgments

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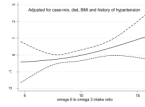
Figure 1.
Cubic spline models of the Cox proportional regression analyses reflecting adjusted mortality-predictability (with 95% CI) according to omega 6 to omega 3 intake ratio in the entire cohort of 145 maintenance hemodialysis patients followed for over 6 years (from Oct. 2001 to Sep. 2007). Spline models are with 2 degrees of freedom. Case-mix variables include age, gender, race/ethnicity, diabetes mellitus, dialysis vintage, insurance, marital status, modified Charlson comorbidity score, dialysis dose (Kt/V). Diet includes intakes of saturated fat, trans-fat, cholesterol and fiber.

Table 1

Baseline demographic, clinical, and laboratory values in study participants

Dietary Omega-3 Intake		Quartile of Omega-3 intake				
	All Patients	1 (0.1-<0.8 mg/d)	2 (0.8-<1.1 mg/d)	3 (1.1-<1.6 mg/d)	4 (1.6-3.5 mg/d)	P for trend
No.	145	37	36	37	35	
Age, years	53±14	52±15	52±15	54±14	53±12	0.8
Women	43	51	42	40	37	0.2
African-American	42	32	45	38	54	0.1
History of hypertension	16	16	18	11	17	0.8
Diabetes mellitus	55	51	55	57	57	0.5
Charlson comorbidity score	1.9±1.7	1.6±1.5	2.0±1.6	2.2±2.0	1.9±1.5	0.8
Body mass index, kg/m2	26.1±5.9	24.5±4.4	27.5±7.4	26.9±5.9	25.6±5.0	0.4
Percentage body fat*	25.5±10.2	24.5±10.0	27.2±11.2	26.2±10.0	24.0±9.6	0.6
Dialysis vintage, months	31±33	29±27	36±36	31±34	29±35	0.7
Dialysis dose, spKt/Vurea	1.67±0.30	1.68±0.33	1.71±0.28	1.63±0.25	1.64±0.35	0.2
Serum albumin, g/dl	3.97±0.31	3.91±0.32	4.02±0.21	4.02±0.22	4.04±0.31	0.07
Serum creatinine, mg/dl	10.7±3.2	10.6±2.7	10.7±3.1	10.6±3.5	11.0±3.5	0.4
Serum total homocysteine, µmol/l	25.6±8.7	25.3±10.2	25.4±8.1	24.0±8.7	27.6±7.6	0.3
Serum CRP, mg/l	5.4±7.3	5.1±5.1	7.0±11.6	5.1±5.3	4.4±4.4	0.6
Serum IL-6, pg/ml	18.4±60.9	11.7±16.6	30.0±27.0	12.7±31.0	18.8±37.3	0.6
Serum TNF-α, pg/ml	7.4±7.7	7.0±6.8	7.5±6.5	9.0±11.2	5.8±4.7	0.4

Dietary Omega-6 to Omega-3 Ratio	Quartile of Omega-6 to Omega-3 Ratio				
	1 (1.7-<7.6)	2 (7.6-<9.3)	3 (9.3-<11.3)	4 (11.3-17.4)	P for trend
No.	37	36	36	36	
Age, years	55±12	53±15	53±13	50±14	0.1
Women	43	47	42	39	0.6

Dietary Omega-6 to Omega-3 Ratio					
	Quartile of Omega-6 to Omega-3 Ratio				P for trend
	1 (1.7–<7.6)	2 (7.6–<9.3)	3 (9.3–<11.3)	4 (11.3–17.4)	
African-American	32	47	53	39	0.5
History of hypertension	11	19	11	19	0.5
Diabetes mellitus	62	56	53	50	0.3
Charlson comorbidity score	1.8±1.4	2.1±1.8	1.7±1.8	1.8±1.6	0.6
Body mass index, kg/m2	25.6±5.2	26.5±6.4	27.2±6.0	25.2±6.2	0.6
Percentage body fat[*]	26.1±10.1	26.6±10.4	25.8±10.5	23.9±9.9	0.3
Dialysis vintage, months	19.6±15.5	27.5±42.4	33.1±40.6	34.5±25.5	0.01
Dialysis dose, spKt/Vurea	1.7±0.3	1.7±0.3	1.6±0.2	1.6±0.3	0.3
Serum albumin, g/dl	3.96±0.32	3.96±0.32	3.98±0.22	3.98±0.25	0.7
Serum creatinine, mg/dl	10.5±3.8	11.0±3.3	10.7±3.2	11.0±2.5	0.6
Serum total homocysteine, μmol/l	26.8±7.9	25.4±7.8	25.1±9.1	24.6±9.1	0.1
Serum CRP, mg/l	3.8±3.3	4.2±3.7	8.2±12.2	5.1±6.0	0.4
Serum IL-6, pg/ml	25.5±10.7	25.1±25.3	13.9±23.7	8.2±8.6	0.4
Serum TNF-α, pg/ml	6.3±3.9	9.3±12.9	6.3±4.0	7.8±6.7	0.5

Note: values shown are percentage or mean +/− SD.

[*] measured by NIR interactance

Abbreviations: IL-6: interleukin-6, TNF: tumor necrosis factor; CRP, C-reactive protein.

Conversion factors for units: albumin in g/dL to g/L, ×10; creatinine in mg/dL to umol/L, ×88.4; total homocysteine in umol/L to mg/dL, ×0.14.

Table 2

Baseline dietary intakes of study participants

Dietary Omega-3 Intake	All Patients	Quartile of Omega-3 intake				P for trend
		1 (0.1<0.8 mg/d)	2 (0.8<1.1 mg/d)	3 (1.1<1.6 mg/d)	4 (1.6-3.5 mg/d)	
No.	145	37	36	37	35	
Energy intake(kilocalorie/day)	1657±639	1151±352	1558±502	1700±450	2254±687	0.002
Total fat intake (g/day)	64±29	39±15	58±21	66±20	92±30	0.003
Saturated fat intake (g/day)	20±11	12±5	19±9	21±9	27±13	0.003
PUFA intake (g/day)	13.2±6.7	7.3±2.6	10.8±0.1	13.5±3.7	21.5±6.7	0.006
Omega-3 intake (g/day)	1.3±0.7	0.6±0.2	1.0±0.1	1.4±0.2	2.3±0.5	0.001
Omega-6 intake (g/day)	11.9±6.0	6.7±2.4	10.2±2.7	12.1±3.7	19.1±6.5	0.009
Ratio of omega-6 to omega-3	9.7±3.1	11.7±3.6	10.3±2.7	8.7±2.6	8.3±2.3	0.009
MUFA intake(g/day)	24.3±11.2	15.4±6.4	22.5±9.2	25.1±7.5	34.6±12.0	0.002
Cholesterol intake(mg/day)	287±154	221±133	242±128	321±143	368±169	0.001
Fiber intake(g/day)	13.1±6.7	11.2±5.8	12.8±7.3	11.6±4.9	16.9±7.2	0.009

Dietary Omega-6 to Omega-3 Ratio	Quartile of Omega-6 to Omega-3 Ratio				P for trend
	1 (1.7-<7.6)	2 (7.6-<9.3)	3 (9.3-<11.3)	4 (11.3-17.4)	
No.	37	36	36	36	
Energy intake(kilocalorie/day)	1592±525	1652±715	1710±585	1716±714	0.5
Total fat intake (g/day)	58±26	65±33	67±23	68±32	0.09
Saturated fat intake (g/day)	18.0±9.0	20.0±12.0	20.4±7.9	21.9±12.8	0.08
PUFA intake (g/day)	12.0±5.5	13.5±7.2	14.1±5.4	13.8±8.2	0.1
Omega-3 intake (g/day)	2.0±1.6	1.4±0.8	1.3±0.5	1.0±0.6	0.001
Omega-6 intake (g/day)	10.3±4.8	12.0±6.4	12.7±4.9	13.2±7.4	0.03
Ratio of omega-6 to omega-3	6.0±1.6	8.5±0.4	10.1±0.5	13.6±1.7	<0.001
MUFA intake(g/day)	22.2±10.9	24.7±12.9	25.6±9.6	26.0±11.1	0.05

Dietary Omega-6 to Omega-3 Ratio

	Quartile of Omega-6 to Omega-3 Ratio				P for trend
	1 (1.7-<7.6)	2 (7.6-<9.3)	3 (9.3-<11.3)	4 (11.3-17.4)	
Cholesterol intake(mg/day)	327±112	266±161	280±159	289±179	0.1
Fiber intake(g/day)	12.4±6.7	13.2±6.0	11.8±5.8	14.9±7.9	0.3

Note: values shown are percentage or mean +/− SD.

PUFA, polyunsaturated fatty acid; MUFA, monounsaturated fatty acid

Table 3

association of omega 3 intake and the ratio of omega 6 to omega 3 with changes in inflammatory status

Association of Omega-3 with Inflammatory Status				
	Quartile of Omega-3 intake			
	1 (<0.8 mg/d)	2 (0.8-<1.1 mg/d)	3 (1.1-<1.6 mg/d)	4 (1.6-<3.5 mg/d)
No. of patients	37	36	37	35
CRP change [*] (mg/dl)	+1.0 (+0.2 to +1.8)	+0.6 (−0.6 to +1.8)	−0.7 (−1.7 to +0.3)	+0.9 (−0.4 to +1.9)

Association of Omega-6 to Omega-3 Ratio with Inflammatory Status				
	Quartile of Omega-6 to Omega-3 Ratio			
	1 (1.7<7.6)	2 (7.6-<9.3)	3 (9.3-<11.3)	4 (11.3-17.4)
No. of patients	37	36	36	36
CRP change [*] (mg/dl)	−0.4 (−1.0 to +0.2)	+0.4 (−0.4 to +1.2)	−0.2 (−1.4 to +1.0)	+1.5 (+0.3 to +2.7)

ANCOVA and Correlation Coefficients		
	P for ANCOVA	Beta for regression (p-value)
Dietary Omega-3		
after adjustment for case-mix[**]	0.4	−0.58 (0.2)
after adjustment for case-mix and diet	0.7	−0.62 (0.3)
after adjustment for case-mix , diet, BMI, HTN, and baseline CRP	0.9	−0.58 (0.3)
Dietary Omega-6 to Omega-3 Ratio		
after adjustment for case-mix	0.2	+0.52 (0.09)
after adjustment for case-mix and diet	0.1	+0.50 (0.04)
after adjustment for case-mix , diet, BMI, HTN, and baseline CRP	0.5	+0.55 (0.03)

[*] CRP change= CRP after one year minus baseline CRP; values shown are mean (95% confidence interval).

[**] Case-mix = age, gender, race/ethnicity, diabetes, dialysis vintage, modified Charlson comorbidity score, dialysis dose (Kt/V); diet, intakes of energy, saturated fat, trans fat, cholesterol and fiber.

Abbreviations and definitions: HTN= history of hypertension; BMI, body mass index; HR, hazard ratio; CI, confidence interval; CRP, C-reactive protein; ANCOVA, analysis of covariance

Table 4

HR of 6-year mortality by quartile of dietary omega-3

	Quartile of omega-3 intake				Across quartiles	P for trend
	1 (n=37)	2 (n=36)	3 (n=36)	4 (n=36)		
Age and gender adjusted						
HR (95% CI)	1.00 (ref)	1.02(0.47-2.23)	0.39(0.15-0.98)	0.65(0.28-1.54)	0.78(0.59-1.04)	
P value		0.9	0.04	0.3		0.09
Case-mix + diet adjusted						
HR (95% CI)	1.00 (ref	1.39(0.60-3.23)	0.28(0.10-0.87)	0.65(0.21-1.97)	0.75(0.52-1.09)	
P value		0.4	0.02	0.2		0.1
Case-mix + BMI + HTN						
HR (95% CI)	1.00 (ref)	1.69(0.69-4.13)	0.30(0.10-0.93)	1.10(0.22-2.21)	0.76(0.52-1.11)	
P value		0.2	0.04	0.5		0.2

Note: for 145 maintenance hemodialysis patients in October 2011 to September 2007. Case-mix= age, gender, race/ethnicity, diabetes, dialysis vintage, modified Charlson comorbidity score, dialysis dose (Kt/V); diet, intakes of energy, saturated fat, trans fat, cholesterol, and fiber.

Abbreviations and defintions: HTN= history of hypertension; BMI, body mass index; HR, hazard ratio; CI, confidence interval

Table 5

HR of 6-year mortality by quartile of dietary omega-6 to omega-3 ratio

	Quartile of omega-6 to omega-3 ratio				Across quartiles	P for trend
	1 (n=37)	2 (n=36)	3 (n=36)	4 (n=36)		
Case-mix						
HR (95% CI)	0.54(0.21-1.38)]	0.58(0.22-1.49)	0.84(0.36-1.96)	1.00 (ref)	1.25(0.93-1.69)	
P value	0.2	0.3	0.7			0.1
Case-mix and diet adjusted						
HR (95% CI)	0.37(0.14-1.08)	0.29(0.09-0.93)	0.61(0.24-1.57)	1.00 (ref)	1.40(0.98-1.02)	
P value	0.08	0.04	0.3			0.04
Case-mix, diet, BMI, and HTN						
HR (95% CI)	0.39(0.14-1.18)	0.30(0.09-0.99)	0.67(0.25-1.79)	1.00 (ref)	1.38(0.96-1.99)	
P value	0.1	0.01	0.4			0.06

Note: for 145 maintenance hemodialysis patients in October 2011 to September 2007. Case-mix= age, gender, race/ethnicity, diabetes, dialysis vintage, modified Charlson comorbidity score, dialysis dose (Kt/V); diet, intakes of energy, saturated fat, trans fat, cholesterol, and fiber.

Abbreviations: HTN= history of hypertension; BMI, body mass index; HR, hazard ratio; CI, confidence interval