EFFECT OF OMEGA-3 POLYUNSATURATED FATTY ACID SUPPLEMENTATION ON GLYCEMIC CONTROL AND RENAL FUNCTION IN TYPE 2 DIABETIC PATIENTS WITH CHRONIC KIDNEY DISEASE

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ABSTRACT

Introduction: *The aim of this study was to evaluate the short-term effects of omega-3 polyunsaturated fatty acids (n-3 PUFA) supplementation on glycemic control and renal function in type 2 diabetic patients with chronic kidney disease.*

Materials and methods*: Twenty-five diabetic patients received medication containing 2 g/day n-3 PUFA orally in addition to standard treatments. Their estimated glomerular filtration rates (eGFR) were <80 mL/min/1.73 m². Biochemical values were evaluated before and 3 months after treatment.*

Results*: After three months of supplementation, the changes in serum creatinine, uric acid, eGFR and urinary albumin excretion levels did not reach statistical significance. There was no difference between serum glucose, HbA1C and lipid profile values before and after the n-3 PUFA supplementation in patients. Only serum albumin significantly increased from 4.10±0.26 to 4.28±0.31 g/dL (p=0.016), and systolic blood pressure decreased from 121.4±14.5 to 116.6±14.9 mmHg (p=0.001).*

Conclusion*: Short-term n-3 PUFA supplementation did not affect renal function and glycemic control in patients with type 2 diabetes with chronic kidney disease.*

Keywords: *Type 2 diabetes mellitus, chronic kidney disease, cardiovascular disease, omega-3 polyunsaturated fatty acids, proteinuria, renal function.*

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Introduction

Cardiovascular events are the main cause of death in more than half of patients with chronic kidney disease (CKD). Endothelial dysfunction, dyslipidemia, oxidative stress and inflammation in these patients lead to cardiovascular events due to atherosclerosis[1-3]. Currently, type 2 diabetes mellitus (DM) is the most common cause of end-stage renal disease (ESRD) worldwide, and contributes to inflammation and atherosclerosis[4]. Various reports showed that dietary supplementation of omega-3 polyunsaturated fatty acids (n-3 PUFA) can reduce systemic inflammation by decreasing inflammatory markers, including tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), and interleukin 1β (IL-1β)[5-7]. n-3 PUFAs have been reported to play a beneficial role on chronic diseases such as type 2 DM, CKD, aging, gynecological cancer, cerebrovascular, inflammatory and autoimmune diseases[8-16], and are associated with lower cardiovascular risk in adults because they reduce the incidence of stroke, atherosclerosis and cardiovascular diseases[12].

Obesity, hypertriglyceridemia, insulin deficiency and impaired lipoprotein lipase activity were detected in diabetic patients. Dyslipidemia is common in diabetics and patients with all stages of CKD[17,18]. The American Diabetes Association (ADA) recommend lifestyle intervention (diet, weight loss, increased physical activity) to improve the lipid profile and reduce the risk of developing atherosclerotic cardiovascular disease in all patients with DM. The initiation of lipid-lowering therapy (statins, fibric acid derivatives or others) is based upon cardiovascular

risk[17]. Hypertriglyceridemia is the primary lipid abnormality among patients with CKD and ESRD, especially in those with insulin resistance and DM, and in those who are receiving peritoneal dialysis[18,19].

n-3 PUFAs with a daily dose of 2-4 g reduce triglyceride levels by up to 45%. It's effectiveness could not be shown on levels of low density lipoprotein (LDL) or high density lipoprotein (HDL) cholesterol in the general population or in patients with CKD or ESRD[19]. Generally, twice a week consumption of rich sources of n-3 PUFAs such as fatty fish (salmon) and plant sources (flaxseed and flaxseed oil, canola oil, soybean oil and nuts) is sufficient. In countries like Turkey where fatty fish are not regularly consumed, dietary supplementation is recommended to meet the body's daily need. Therefore, usage of dietary and supplements containing n-3 PUFA in diabetic patients, especially for the treatment of hyperlipidemia and prevention of cardiovascular diseases, may provide positive effects on atherosclerosis.

In 2013 Kidney Disease: Improving Global Outcomes (KDIGO) guideline provides pragmatic guidance for lipid-lowering treatment in CKD[20]. n-3 PUFAs reduce proteinuria with its reno-protective properties in patients with chronic glomerular disease[9-11]. Similarly, in patients with type 2 DM, n-3 PUFA supplementation may be considered as an additional treatment to renin angiotensin system blockers to reduce albuminuria. Therefore, administration of n-3 PUFA in order to control hyperlipidemia and prevent atherosclerosis in these patients may also provide additional benefits, such as reduction of proteinuria and prevention of progression of CKD. In the literature, there are limited studies about the efficacy of n-3 PUFA supplementation on renal disease progression in diabetic patients with CKD. Therefore, this retrospective study aimed to investigate the effect of short-term supplementation of n-3 PUFA on renal functions in type 2 diabetic patients with CKD.

Materials and methods

Twenty five stable adult type 2 diabetic patients (16 males and 9 females) included into this study. The estimated glomerular filtration rate (eGFR) values of the patients were below 90 mL/min/1.73 m^2. Patients with acute and chronic infection or inflammatory disease, uncontrolled hypertension and those receiving anticoagulant therapy excluded from the study. Informed consent was obtained from all participants, and the study was performed in accordance with the Declaration of Helsinki.

All patients were receiving insulin therapy, and the duration of known diabetes ranged from 8 to 20 years (median 12). When the atherogenic lipid profile (triglyceride levels ≥150 mg/dL and/or low HDL cholesterol: <40 mg/dL for men and <50 mg/dL for women) was considered before N-3 PUFA support, 18 of 21 patients had hypertriglyceridemia and 12 had low HDL cholesterol levels. Prior to the initiation of the support, 1 of 25 patients received fenofibrate, 3 received atorvastatin and 2 received rosuvastatin. Two gram daily oral salmon fish-oil concentrate n-3 PUFA [Salmon fish-oil, eicosapentaenoic acid (EPA) = 18%, docosahexaenoic acid (DHA) = 12%, total omega-3 fatty acid = 35%] was given to patients in addition to their standard treatments. Demographic data and laboratory results including urinary albumin excretion (UAE), renal functions, glucose, hemoglobin A1c (HbA1c) and lipid profile values at baseline and 3rd month of the supportive treatment were obtained from medical records. The UAE was analyzed using the Tina-quant Albumin Gen.2 kit by immunoturbidimetric method in Cobas Integra 400 system (1-14 mg/dL). The estimated glomerular filtration rate (eGFR) was calculated by CKD epidemiology collaboration (CKD-EPI) formula[21].

Statistical methods

All statistical analyses were performed using the IBM SPSS Software package of version 23.0 (IBM Corp, Armonk, NY, USA) licensed to Uludag University. The data was given as mean ± standard deviation (SD). The numerical variables at baseline and after n-3 PUFA supplementation were compared with Wilcoxon signed-rank test within groups. Kruskal-Wallis test and Mann-Whitney U test were used for comparison of means according to eGFR stages. The percentage of change of the numerical variables was calculated. The relation between the percentage of change of all parameters after 3 months within group was estimated with Pearson correlation test. Statistical significance was defined by $p < 0.05$.

Results

The median age and body mass index of the patients were 65 (53-82) years and 28.0 (23.8-33.2) kg/m^2, respectively. Before n-3 PUFA supplement, 6 of the patients were stage 4 CKD (19-29 mL/min/1.73 m2), 12 were stage 3 CKD (30-59 mL/min/1.73 m^2)

and 7 were stage 2 CKD (60-85 mL/min/1.73 m^2) CKD. The decrease in systolic blood pressure after the support was significant (from 121.4±14.5 to 116.6±14.9 mmHg, p=0.001), whereas the decrease in diastolic blood pressure was not significant (from 70.7±8.3 to 69.1±8.0 mmHg, p=0.059). After three months of supportive therapy, the changes in serum urea, creatinine, uric acid, UAE and eGFR levels were insignificant (Table 1).

Variables	Baseline	Month 3	P value
Hemoglobin (g/dL)	12.7±1.40	12.7±1.65	0.312
Urea (mg/dL)	67.0±29.8	62.2±23.5	0.287
Creatinine (mg/dL)	1.71±0.63	1.73±0.64	0.931
Uric acid (mg/dL)	6.93±1.62	6.81±1.49	0.609
Serum albumin (g/dL)	4.05±0.31	4.23±0.35	0.016
eGFR (ml/min/1.73 m^2)	47.9±18.6	48.8±21.6	0.797
UAE (g/day)	4.45±6.33	3.04±3.10	0.313
Calcium (mg/dL)	9.54±0.52	9.52±0.43	0.903
Phosphorus (mg/dL)	3.65±0.53	3.56±0.54	0.547
CaxP	34.7±5.61	33.4±5.31	0.420
PTH (pg/mL)	146±92	152±97	0.382
Ferritin (ng/mL)	78.1±77.8	89.9±95.9	0.183
Glucose (mg/dL)	148.4±61.7	142.6±50.4	0.830
HbA1c (%)	6.96±1.27	6.95±1.13	0.954
Total cholesterol (mg/dL)	229.7±58.3	228.7±68.8	0.657
LDL cholesterol (mg/dL)	136.6±39.2	137.4±46.4	0.558
HDL cholesterol (mg/dL)	44.8±9.3	45.1±8.4	0.201
VLDL cholesterol (mg/dL)	46.8±32.7	45.6±41.7	0.617
Triglyceride (mg/dL)	234.1±163.6	228.3±208.5	0.617

Table 1: Changes in laboratory parameters of patients before and after n-3 PUFA supplement.
eGFR: estimated glomerular filtration rate, UAE: urinary albümin excretion, HbA1c: hemoglobin A1c, LDL: low density lipoprotein, HDL: high density lipoprotein, VLDL: very low density lipoprotein, CaxP: calcium-phosphorus product, PTH: parathyroid hormone.

Although eGFR increased and serum creatinine levels decreased in 12 patients, and UAE decreased in 13 patients, no significant difference was observed between the percentage changes in these parameters of stage 2, 3 and 4 groups according to CKD stages. When the patients were divided into nephrotic and nephritic proteinuria groups according to their degree of proteinuria, no significant change was found in the above parameters with n-3 PUFA support.

Serum glucose, HbA1c, triglyceride, total-, LDL-, HDL- and very low density lipoprotein (VLDL) cholesterol levels did not change significantly after treatment when compared to baseline values. Only serum albumin were significantly elevated from 4.10±0.26 to 4.28±0.31 g/dL (median 4.65%, p=0.016). Hemoglobin, calcium (Ca), phosphorus (P), CaxP product, parathyroid hormone (PTH) and ferritin also did not change after treatment (Table 1). Bivariate correlation analysis of percentage of change of variables at 3 months after the n-3 PUFA support was given in Table 2. Serious adverse events such as nausea, diarrhea and hemorrhage related to n-3 PUFA supplementation did not observe in our patients.

Variables	Correlated variable	r	P value
Diastolic BP	Uric acid	0.507	0.010
	Total cholesterol	0.456	0.022
	HDL cholesterol	0.508	0.010
eGFR	Creatinine	-0.960	<0.001
	Uric acid	-0.543	0.005
	Calcium	-0.611	0.001
	CaxP	-0.604	0.001
	HDL cholesterol	-0.470	0.018
	LDL cholesterol	-0.412	0.041
Creatinine	Uric acid	0.531	0.006
	Calcium	0.585	0.002
	Phosphorus	0.411	0.041
	CaxP	0.629	0.001
	Total cholesterol	0.438	0.029
	HDL cholesterol	0.456	0.022
	LDL cholesterol	0.532	0.006
UAE	Albumin	-0.579	0.002
	Calcium	-0.481	0.015
	CaxP	-0.420	0.036
Uric acid	Calcium	0.435	0.030
Albumin	Uric acid	0.401	0.047
	Body mass index	-0.412	0.041
	Calcium	0.475	0.016
	Phosphorus	0.450	0.024
	CaxP	0.570	0.003
Glucose	Body mass index	-0.510	0.009
	HbA1C	0.605	0.005
Triglyceride	VLDL cholesterol	1.000	<0.001
	Hemoglobin	0.423	0.035
	PTH	-0.486	0.014
Total cholesterol	Creatinine	0.438	0.029
	HDL cholesterol	0.521	0.008
	LDL cholesterol	0.862	<0.001
HDL cholesterol	LDL cholesterol	0.487	0.014
VLDL cholesterol	Hemoglobin	0.423	0.035
	PTH	-0.486	0.014

Table 2: Significant positive and negative correlations between percentage changes in variables after n-3PUFA supplement.
BP: blood pressure, eGFR: estimated glomerular filtration rate, UAE: urinary albümin excretion, LDL: low density lipoprotein, HbA1c: hemoglobin A1c, HDL: high density lipoprotein, VLDL: very low density lipoprotein, CaxP: calcium phosphorus product, PTH: parathyroid hormone.

Discussion

In this study, we evaluated the effect of n-3 PUFA supplementation on renal function, glycemic control and lipid profile in diabetic patients with CKD. The results of various large-scale clinical trials on the cardiovascular protective effect of n-3 PUFAs are not always consistent[22]. n-3 PUFAs have been shown to differ in their effects on individual lipid parameters.

A review of the effects of n-3 PUFAs from fish-oils (EPA and DHA) and plant oils (alpha-linolenic acid) on serum lipids and lipoproteins revealed that its practical doses had a clinically important effect on serum triacylglycerol concentrations, but not in total, LDL and HDL cholesterol[23]. Different n-3 PUFA formulations are effective treatment options for patients with severe hypertriglyceridemia. DHA-containing formulations may also increase LDL cholesterol[24]. The mechanisms of action of n-3 PUFAs are not clear. Reduced hepatic VLDL triglyceride synthesis and/or secretion, enhanced triglyceride clearance from circulating VLDL particles, decreased hepatic lipogenesis and increased plasma LPL activity are the possible mechanisms stated[19]. Many studies assessed impact of n-3 PUFAs on glycemic homeostasis and lipid profiles in patients with type 2 diabetes reported controversial results[25]. In type 2 diabetes, n-3 PUFAs had a favorable effect on triglyceride levels but no significant effect on glucose, HbA1c, total, HDL and LDL cholesterol. Additionally, n-3 PUFAs also did not affect plasma insulin or insulin resistance in type 2 diabetics or metabolic syndrome[26].

However, the ratio of EPA/DHA and early intervention with n-3 PUFAs may affect their effects on glucose control and lipid levels[25]. There are many risk factors related to cardiovascular diseases in patients with ESRD, including DM, hypertension, dyslipidemia, obesity and factors related to uremia (anemia, secondary hyperparathyroidism etc). In addition, new risk factors such as inflammation and oxidative stress have been described[3,4]. It is generally thought that n-3 PUFA supplementation may prevent cardiovascular events due to its anti-inflammatory and anti-atherosclerotic effects. In our study, glucose, HbA1C and lipid parameters did not significantly change in diabetic patients after n-3 PUFA support, although HDL cholesterol increased in 16 patients and triglyceride levels decreased in 12 patients. The percentage change of glucose was negatively correlated with body mass index and positively correlated with HbA1C. n-3 PUFA supplement (1 g capsules containing 180 mg EPA and 120 mg DHA, 3 times a day) in chronic hemodialysis patients increased serum Ca and HDL cholesterol levels without changes in serum LDL cholesterol and triglyceride levels, and lowered vascular cell adhesion molecule level[27].

Previous studies in dialysis patients revealed no significant change in serum albumin levels after n-3 PUFA supplementation[27,28]. In our study, serum albumin levels significantly increased after n-3 PUFA. The percentage change of albumin was negatively correlated with body mass index and positively correlated with uric acd, Ca, P and CaxP. However, inflammation and oxidative stress markers were not evaluated in our study. In a systematic review and meta-analysis including 371 patients on hemodialysis, n-3 PUFA supplementation significantly decreased serum levels of C-reactive protein (CRP) and high-sensitivity CRP but did not significantly improved albumin, TNF-α and IL-6[29].

n-3 PUFAs can potentially slow down the progression of CKD by preventing the development and progression of cardiovascular disease by reducing serum lipid levels, blood pressure, inflammation and vascular resistance and preventing thrombosis. There is limited information regarding the effects of n-3 PUFAs on kidney diseases. One year of dietary supplementation with fish-oil (15 g/day) in patients with stable lupus nephritis did not affect proteinuria, serum creatinine, GFR or disease activity, but did alter serum triglycerides and VLDL cholesterol levels[30]. Subsequently, the same group obtained similar results with 6 g/day or 18 g/day n-3 PUFA supplementations in 26 patients with lupus nephritis at 2 years follow-up[31]. EPA (10 g/day) treatment for 2 years did not alter the course of IgA nephropathy except two patients who had improvement in renal function[32]. In patients with IgA nephropathy, a higher daily dose of a fish-oil product (55% EPA and 30% DHA) for 6 months resulted in a slight significant reduction in GFR compared to initial isotope GFR[33]) n-3 PUFAs in fish-oil affecting eicosanoid and cytokine production have the potential to alter renal hemodynamics and inflammation. In 55 patients with IgA nephropathy, treatment with fish-oil (12 g/day) for 2 years slowed the rate of loss of kidney function, and cumulative percentage (10% vs 40%) of patients who died or had ESRD in the fish-oil group was lower than in the placebo group after 4 years[34]. Low-dose (EPA 1.88 g and DHA 1.47 g) and high-dose (EPA 3.76 g and DHA 2.94 g) n-3 PUFA supplementation for a minimum of 2 years were similar in slowing the rate of renal function loss in high-risk patients with IgA nephropathy[35]. The benefits of 1.8 g of EPA and 1.2 g of DHA per day on slowing the progression of kidney disease in high-risk patients continued after 6.4 years of follow-up[36].

In 262 stable patients with coronary artery disease, there was no change in the urine albumin-creatinine ratio (ACR) of non-diabetic and diabetic subjects receiving 1.86 g EPA and 1.5 g DHA sup-

plementation per day for 1 year. On the other hand, ACR in diabetic subjects not receiving EPA plus DHA increased by 72.3%[37]. EPA and DHA supplementation can be considered as additional treatment to renin angiotensin system blockers in subjects with type 2 DM, hypertriglyceridemia and/or coronary artery disease. Because n-3 PUFAs can be useful in reducing albuminuria and protecting renal function. Contrary to our study findings, in a recent study evaluating the effect of n-3 PUFA supplementation for at least 3 months (mean 1.9 ± 1.6 years supplement duration with median 1.4 years) on urine ACR and GFR in 344 type 2 diabetic patients with nephropathy and hypertriglyceridemia, a significant decrease in serum total cholesterol, triglycerides and urine ACR was reported (38). In renal disease, n-3 PUFAs had varying effects on serum creatinine and creatinine clearance. Single studies demonstrated reduced progression to ESRD[26].

In our study, we could not find any relationship between the effect of n-3 PUFA supplementation on renal parameters and the degree of proteinuria of CKD stage. In 20 nephrotic patients with chronic glomerulonephritis, soy diet decreased both hyperlipidemia and proteinuria. The addition of 5 g/day fish-oil to soy diet for 2 months had no further beneficial effect on proteinuria[39]. In the study of Han et al.[38], 125 (36.3%) patients had a GFR with a positive slope while there was no loss of renal function in 172 (50%) patients. The positive effect of n-3 PUFA on preservation of GFR can be dose dependent, because patients treated with 4 g/day of n-3 PUFA had more maintenance function than those treated with a low dose (1 or 2 g/day) (38). In our study cohort, serum creatinine decreased in 12 patients, eGFR increased in 12 patients and UAE decreased in 13 patients at 3rd month of n-3 PUFA support, but the changes in these parameters were not significant.

Long chain n-3 PUFA such as EPA and DHA may regulate the mechanisms of development and progression of atherosclerosis through effects on triglyceride levels, blood pressure, platelet function, inflammation, cardiac excitability and stability of atheroma plaque[40]. n-3 PUFA can reduce blood pressure, platelet aggregation and influence fibrinolysis[5]. The effect of n-3 PUFA on blood pressure is controversial and some studies have reported no effect[41,42]. n-3 PUFA (4 g/day for 8 weeks) reduced blood pressure, heart rate and triglycerides in nondiabetic patients with moderate-to-severe CKD. There was no change in GFR, urinary protein excretion, total cholesterol, HDL cholesterol, LDL cholesterol, glucose, insulin or high-sensitivity CRP[43]. Although increase in systolic blood pressure (8±3 mmHg) and serum creatinine, and decrease in GFR in those received placebo, n-3 PUFA usage (3.4 g/day for 1 year) did not change serum creatinine, GFR, blood pressure or systemic vascular resistance in clinically stable hypertensive heart transplant recipients[44]. The antihypertensive effect of n-3 PUFA was associated with an increase in serum EPA and DHA.

In our study, daily 2 gr n-3 PUFA supplementation in diabetic patients with CKD significantly reduced systolic blood pressure, but did not affect diastolic blood pressure, UAE and renal function.

Fibroblast growth factor 23 (FGF23) is an independent risk factor for cardiovascular mortality in CKD. A recent data did not support n-3 PUFA supplementation to reduce FGF23 levels in post-myocardial infarction patients with CKD (45). We did not find a change in Ca, P, CaxP product and PTH levels in diabetic patients with CKD after n-3 PUFA supplement for 3 months. However, there were negative or positive significant correlations between Ca, P or CaxP with eGFR, creatinine, UAE, uric acid or albumin. A recent meta-analysis including 20 randomized controlled trials involving 1,461 patients with ESRD found that n-3 PUFA supplementation was associated with lower several serum lipids and vascular inflammation markers in patients with ESRD. n-3 PUFA reduced triglycerides by 0.61, LDL cholesterol by 0.35 and CRP by 0.56 without significant effect on blood pressure, total and HDL cholesterol, albumin, hemoglobin, homocysteine, glucose, lipoprotein (a) and ferritin[46].

Actually, there is little evidence to support the use of n-3 PUFAs to reduce cardiovascular events or mortality in different populations including patients with CKD or ESRD[19]. The Reduction of Cardiovascular Events with EPA-Intervention Trial (REDUCE-IT) trial involving patients with established cardiovascular disease or with diabetes and other risk factors, who had been receiving statin therapy and who had a fasting triglyceride level of 135 to 499 mg/dL and a LDL cholesterol level of 41 to 100 mg/dL demonstrated that usage of icosapent ethyl (a highly purified EPA preparation) at a total dose of 4 g/day resulted in an extraordinary outcome of 25% relative reduction in cardiovascular events[47].

However, this study excluded patients on dialysis and those with a creatinine clearance <30 mL/min[19]. An ongoing placebo-controlled Outcomes Study to Assess Statin Residual Risk Reduction with Epanova in High Cardiovascular Risk Patients with

Hypertriglyceridemia (STRENGTH) trial will determine whether high dose epanova (4 g/day, mix of n-3 PUFAs, 75% EPA and DHA) will reduce cardiovascular events in statin-treated high-risk patients with atherogenic dyslipidemia (triglyceride ≥180 mg/dL to <500 mg/dL and HDL cholesterol <42 mg/dL for men or <47 mg/dL for women) (48). STRENGTH includes patients with microalbuminuria (albumin:creatinine ratio >30 mg/g) and an eGFR of <45 mL/min/1.73 m^2 to be criteria for a high risk of future cardiovascular events[19]. Dietary and supplemental long chain n-3 PUFA may reduce cardiovascular mortality in patients on hemodialysis but it is uncertain whether supplementation prevents mortality or ESRD in patients with CKD[49].

The limitations of our study were the low number of patients and the absence of the control group. Furthermore, the duration of our study may be insufficient for the effect of n-3 PUFA on GFR. The daily 2 g dose of n-3 PUFA was lower than other studies. In several original studies and meta-analyzes, conflicting results regarding the effect of n-3 PUFA supplementation in patients with diabetes and cardiovascular disease may be partially explained as a result of variable dose and duration of supplementation. The possible beneficial cardiovascular effects of n-3 PUFA supplements can only be expected at daily doses above 2000 mg[50]. Therefore, there is also a need for higher doses of supplementation studies in this population with longer duration.

In conclusion, in our study, short-term n-3 PUFA support (2 g / day) decreased systolic blood pressure and increased serum albumin levels in type 2 diabetic patients with CKD. However, diastolic blood pressure, creatinine, eGFR, UAE, glycemic control and lipid profile did not significantly affect. Therefore, the results of other studies on the use of n-3 PUFA in diabetic and non-diabetic kidney diseases may clarify this issue. More evidence is needed for its effects on kidney and cardiovascular prognosis, especially with appropriate dosing and duration of support.

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Abbrevations:
n-3 PUFA: omega-3 polyunsaturated fatty acids.
eGFR: Estimated glomerular filtration rates.
CKD: Chronic kidney disease
HbA1C: Hemoglobin A1C
DM: Diabetes mellitus
ESRD: End-stage renal disease
TNF-α: Tumor necrosis factor α
IL-1β: Interleukin 1β
ADA: American Diabetes Association
LDL: Low density lipoprotein
HDL: High density lipoprotein
KDIGO: Kidney Disease: Improving Global Outcomes
EPA: Eicosapentaenoic acid
DHA: Docosahexaenoic acid
UAE: Urinary albumin excretion
HbA1c: Hemoglobin A1c
CKD-EPI: CKD epidemiology collaboration
Ca: Calcium
P: Phosphorus
PTH: Parathyroid hormone
VLDL: Very low density lipoprotein
CRP: C-reactive protein
REDUCE-IT: Reduction of Cardiovascular Events with EPA-Intervention Trial
STRENGTH: Statin Residual Risk Reduction with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia

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