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MACROVASCULAR COMPLICATIONS IN DIABETES (VR ARODA AND A GETANEH, SECTION EDITORS)

New Areas of Interest: Is There a Role for Omega-3 Fatty Acid Supplementation in Patients With Diabetes and Cardiovascular Disease?

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Abstract

Purpose of Review Summarize studies on omega-3 fatty acids in prevention of albuminuria in subjects with diabetes.

Recent Findings Several small, short-term trials suggested benefit on albuminuria in subjects with diabetes; however, results were not definitive. Welty et al. showed that eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) for 1 year slowed progression of early-stage albuminuria in subjects with diabetes with clinical coronary artery disease on an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, the majority of whom had an albumin/creatinine ratio (ACR) < 30 μg/mg. Moreover, significantly more (3-fold) subjects on EPA and DHA had a decrease in ACR compared to control, and three on EPA and DHA had a change in category from > 30 μg/mg to < 30 μg/mg, whereas no controls did. Potential mechanisms for benefit are discussed.

Summary These results suggest that there is benefit and perhaps even reversal of albuminuria with EPA and DHA at an early stage of disease in those with ACR < 30 μg/mg and those with microalbuminuria (ACR > 30).

Keywords Omega-3 fatty acids · Diabetes · Albuminuria · Coronary artery disease · Eicosapentaenoic acid · Docosahexaenoic acid

Introduction

Diabetes mellitus (DM) is the leading cause of chronic kidney disease (CKD) worldwide. The prevalence of diabetic nephropathy, a type of CKD, has been increasing in patients with type 2 diabetes [1, 2]. Diabetic CKD is the leading cause of renal failure accounting for over 50% of cases of end-stage renal disease [1]. While albuminuria is common in patients with type 2 diabetes [3], it is also present in subjects with hypertension [4] and healthy subjects [5, 6]. Moreover, albuminuria independently predicts both all-cause and cardiac mortality in all these groups [7–19]. A recent striking finding was that at 11-year follow-up, subjects who were healthy and nondiabetic at baseline and had a urine albumin to creatinine ratio (ACR) between 7.5 and 30 μg/mg were at higher risk of new-onset hypertension and cardiovascular disease [20••] than those with an ACR < 7.5. This finding was surprising because an ACR < 30 μg/mg has been considered normal. The predictive ability for mortality after a myocardial infarction is actually better for albuminuria than C-reactive protein (CRP) (HR 1.8 [95% CI 1.1–3.1] for albuminuria vs 1.1 [95% CI 0.7–1.8] for CRP) [21]. It is unclear what the link is between albuminuria and cardiovascular diseases, but subclinical inflammation is a strong possibility based on the fact that the odds of albuminuria increased by 2% for every 1 mg/l increase in CRP [22, 23]. Another link is that albuminuria is a marker of endothelial dysfunction, which is seen in coronary artery disease (CAD) [24–26]. The Chronic Kidney Disease-Prognosis Consortium reported that an increase in urine albumin excretion as low as 10 μg/ml is associated with an increased risk of cardiovascular disease, end-stage renal disease and mortality in the general population and among those with kidney disease, a finding highlighting the need for studies targeting albuminuria as a risk factor [27, 28••]. An estimated 10% of the population worldwide is affected by CKD [29]. On the basis of this evidence, strategies to lower albuminuria are important not only to prevent CKD but also to prevent or delay atherosclerosis and cardiovascular disease [30].

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Inflammation and Chronic Kidney Disease

Diabetic CKD may be related to chronic inflammation which leads to fibrosis and albuminuria. Severe acute or chronic renal inflammation is a characteristic of CKD. Chronic inflammation leads to glomerulosclerosis, tubular atrophy, and interstitial fibrosis, which in turn results in end-stage renal disease and dialysis or transplantation [31]. Inflammation and monocyte infiltration lead to renal fibrosis which is the final pathological manifestation of CKD [32]. In response to tubular or glomerular injury (hyperglycemia, hypoperfusion, hyperlipidemia), macrophage chemo-attractants stimulate renal macrophage infiltration, leading to the production of vasoactive eicosanoids, reactive oxygen species, pro-inflammatory cytokines, and pro-fibrotic growth factors [33]. Altogether, they lead to vascular inflammation, podocyte and tubular cell apoptosis, proteinuria (albuminuria), mesangial proliferation, fibrosis, and loss of renal function [33, 34]. Damage to the glomerulus can cause cytokine release which induces a pro-inflammatory tubular cell response and disruption of the tubular basement membrane. Forming an integral component of the glomerular filtration barrier, podocytes can detach in response to sustained injury, a process leading to albuminuria. Chronic inflammation in diabetic CKD causes significant organ injury. Hypertension and diabetes increase intraglomerular pressure, which leads to podocyte and tubular injury resulting in albuminuria. If not treated, persistent inflammation, mesangial cell activation, and glomerulosclerosis occur which leads to a decline in glomerular filtration rate (GFR) and CKD.

Current Therapy to Prevent Progression of Albuminuria

Activation of the renin–angiotensin aldosterone system (RAAS) is associated with albuminuria [22]. Use of an angiotensin-converting enzyme inhibitor (ACE-I) or an angiotensin-receptor blocker (ARB) to inhibit the RAAS in diabetic subjects reduced albuminuria and associated cardiovascular morbidity and mortality [35–37]. Therefore, ACE-I or ARB therapy is now considered standard of care for diabetic patients to reduce albuminuria and associated cardiovascular morbidity and mortality [38]. Current therapies for CKD rely on blockade of the RAAS [39]. Although RAAS inhibition slows the progression of CKD, it cannot reverse fibrosis; thus, safe and effective therapeutics to prevent CKD need to be developed [40]. Although management of hyperlipidemia and hyperglycemia have resulted in a decreased incidence of stroke, myocardial infarction and amputation in subjects with diabetes, optimal management of these risk factors has not slowed renal complications, reflecting inadequate therapeutic options [41]. Therefore, CKD and associated renal fibrosis present a major health care burden.

Effect of Omega-3 Fatty Acids on Albuminuria

The long-chain, omega-3 polyunsaturated fatty acids (FAs), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are a dietary component which can be obtained in fatty fish or as supplements. In a prospective study of 444 subjects, those with a low EPA/arachidonic acid (AA) ratio had a 3.45-fold higher odds ratio of microalbuminuria (ACR ≥ 30 mg/g Cr) after adjustment for confounding factors [42••]. In a retrospective study of subjects with type 2 DM who received omega-3 FAs to manage hypertriglyceridemia, those receiving 4 g/day of omega-3 FAs had a reduction in albuminuria after adjustment for multiple variables ($p < 0.001$) [43•]. In a cohort analysis of the Diabetes Control and Complications Trial, a higher dietary intake of EPA and DHA was associated with a lower risk of albuminuria in subjects with type 1 diabetes [44]. Urinary spot albumin decreased from 65 mg/g at baseline to 36 mg/g creatinine at 6 months ($p < 0.001$) with 1.8 g/day of EPA in 16 diabetic patients [45]. Omega-3 FAs of various doses significantly reduced urinary protein excretion 19% (95% confidence interval: −34 to −4, $p = 0.01$) in a meta-analysis of 17 clinical trials in patients with albuminuria due to either diabetes, IgA nephropathy, or mixed causes of renal disease [46, 47]. In seven trials of both patients with type 1 and type 2 diabetes, a nonsignificant 21% reduction was noted possibly due to a small sample size (−46 to 4, $p = 0.10$) [47]. Pure EPA significantly reduced albuminuria over a 12-month period in two clinical trials limited to subjects with type 2 diabetes but without CAD (Table 1) [48, 52]; however, only one trial was randomized and a small number of patients were involved, ranging from 21 to 45 [52]. In a crossover design of 6 months' duration of 3.6 g/day of EPA and DHA, a nonsignificant 20% reduction was observed, possibly due to only 24 subjects (Table 1) [49]. Omega-3 FAs had no benefit on albuminuria in a 6-week trial in type 2 diabetes for the total group, but subgroup analysis showed a significant reduction with the addition of omega-3 FAs to an ACEI or ARB (Table 1) [50].

Omega-3 Fatty Acids Prevent Progression of Albuminuria in Subjects With Coronary Artery Disease

Welty et al. [51••] conducted the first clinical trial to examine the effect of 3.36 g EPA and DHA daily on albuminuria in patients with diabetes and coronary artery disease (CAD). The Slowing HEART diSease with lifestyle and omega-3 fatty acids trial was an open-label, single-

Table 1 Trials of EPA and DHA in subjects with diabetes

Trial	Design	No.	Mean ACR at baseline μg/mg	Omega-3 dose	Duration	% Decrease albuminuria	*P* value (95% CI)
Shimizu et al., [44]	Randomized	45	200 (control) 447 (EPA)	EPA 0.9 g/day	12 months	− 40.8%	< 0.01
Okuda et al., [48]	Single-arm trial	21	24.4	EPA 1.8 g/day	48 weeks	− 43.03%	< 0.05
Zeman et al., [49]	Crossover (sequential)	24	6.0 (placebo) 4.8 (omega-3) ACR < 300 μg/mg	EPA and DHA 3.6 g/day	6 months	− 20%	0.38
Miller et al., [50]	Crossover	60	161 mg/d [115–414]	EPA and DHA 4 g/day	6 weeks	− 7.2%	0.35 (− 20.6–8.5)
Miller et al., [50]	Subgroup type 2 DM on ACE-I or ARB	42	161 mg/day [115–414]	EPA and DHA 4 g/day	6 weeks	− 17%	0.04 (0.69–1.0)

(From Elajami et al. J Am Heart Assoc. 2017; 6:e004740, https://doi.org/10.1161/JAHA.116.004740) [51••].

center, randomized, controlled, parallel study of subjects with stable CAD recruited from the cardiovascular clinic at Beth Israel Deaconess Medical Center (BIDMC). Inclusion criteria included age 21 to 80 years with stable CAD and an estimated creatinine clearance as measured by the Cockcroft–Gault equation ≥ 60 ml/min/1.73 m^2. Two hundred and ninety-one subjects—239 men and 52 women—were randomly assigned to receive either open-label omega-3 ethyl esters (Lovaza) 4 capsules daily or no Lovaza (termed control). Subjects in the omega-3 ethyl-ester group received 3.36 g of Lovaza as four soft gels, each containing predominantly 465 mg EPA and 375 mg DHA for a total daily dose of 1.86 g EPA and 1.5 g DHA. The primary end point was change in progression of coronary artery plaque over a 30-month period and has been published [53•]. A prespecified secondary outcome was change in albuminuria over a 12-month period which has also been published and is summarized here [51••]. Two hundred and sixty-two subjects had measurements of ACR at randomization and at 1-year follow up. Women were 17.2% (45), and 30.2% had diabetes (74 with type 2 diabetes and 5, type 1). Eighty-five percent of the diabetic subjects were on an ACE-I or ARB. Glucose, hemoglobin A1c, ACR, BMI and waist circumference were all significantly higher in subjects with diabetes compared to subjects without diabetes at baseline; otherwise, there were no significant differences [51••]. Although subjects with diabetes receiving Lovaza had a significant within group reduction in triglyceride (TG) levels compared to control at 1-year, − 9.8% ($p = 0.006$) vs − 5.9% ($p = 0.246$), respectively, the between-group difference was not significant ($p = 0.587$). Otherwise, there were no significant differences at 1-year follow-up.

Table 2 shows the change in ACR stratified by diabetes status. Subjects without diabetes had no change in ACR in those on Lovaza compared to control (− 5.85% vs 4.29%, respectively, $P = 0.56$). In contrast, subjects with diabetes not on Lovaza had a significant 72.3% increase in ACR ($P < 0.001$) compared to no change in subjects with diabetes on Lovaza (4.63%) ($P = 0.04$ for Lovaza vs control). At 1-year follow-up in subjects with diabetes on an ACE-I or ARB, subjects with diabetes receiving Lovaza had no change in ACR compared to a 64.2% increase in ACR in controls ($P = 0.02$ for Lovaza vs control). Therefore, Lovaza attenuated the increase in ACR in those on an ACE-I or ARB. Of note, no significant differences in CrCl were noted at baseline compared to 1 year within the Lovaza group (109.7 ± 38.7 ml/min vs 109.3 ± 33.7 ml/min, respectively, $P = 0.67$) or control group (95.2 ± 22.1 ml/min vs 95.3 ± 26.3 ml/min, respectively, $P = 0.66$). Moreover, there were no significant differences in eGFR within the control group (75.7 ± 15.5 ml/min/1.73 m^2 vs 72.9 ± 17.0 ml/

Table 2 Median change in ACR at 1-year follow-up compared to baseline according to diabetic status and ACE-I or ARB status

	Albumin to creatinine ratio (ACR) in μg/mg creatinine			
	Baseline median [IQR]	1-Year median [IQR]	Median of % change	*P** value
Nondiabetic subjects				
Control ($n = 88$)	3.480 [2.46, 6.51]	3.643 [2.34, 8.68]	4.29%	0.558
Lovaza ($n = 95$)	4.237 [2.56, 9.13]	3.883 [2.27, 9.92]	− 5.85%	
Diabetic subjects				
Control ($n = 40$)	7.823 [4.07, 24.26]	14.571 [5.90, 32.88]	72.31%	0.043
Lovaza ($n = 39$)	5.670 [3.54, 32.79]	8.791 [3.08, 66.67]	4.63%	
Diabetic subjects on ACE-I or ARB				
Control ($n = 34$)	8.25 [4.08,28.21]	18.53 [6.56,32.89]	64.18%	0.022
Lovaza ($n = 33$)	6.38 [3.54,37.78]	10 [3.13,38.27]	2.74%	

Data presented as median [IQR]. (From Elajami et al. J Am Heart Assoc. 2017; 6:e004740, https://doi.org/10.1161/JAHA.116.004740) [51••]

**P* values–Wilcoxon–Mann–Whitney for Control vs Lovaza

min/1.73 m^2, respectively, $P = 0.94$) or within the Lovaza group (82.0 ± 17.4 ml/min/1.73 m^2 vs 81.3 ± 14.4 ml/min/1.73 m^2, respectively, $P = 0.81$).

Benefit of Omega-3 Fatty Acids in Subgroups of Albumin/Creatinine Ratio

Table 3 stratifies diabetic subjects by ACR < 30 μg/mg, 30–300 μg/mg, and > 300 μg/mg and shows the change in each group. Of note, 61 of the 79 diabetic subjects had ACR < 30 μg/mg, 15 had ACR of 30–300 μg/mg, and 3 had ACR > 300 μg/mg. In those with ACR < 30 μg/mg, the controls had a significant increase in ACR ($P < 0.001$), whereas those on Lovaza had no change; the between-group change approached significance ($P = 0.10$). In those with ACR 30–300 μg/mg, the increase in ACR in controls approached significance ($P = 0.063$), whereas those on Lovaza had no change. Although the number of subjects was small, those on Lovaza with ACR > 300 μg/mg had a decrease in ACR. Thus, these results suggest that in those with ACR < 30 μg/mg, Lovaza prevents progression of albuminuria at an early stage of disease. None of the seven control subjects with diabetes with baseline ACR 30–300 μg/mg had reduction in ACR to < 30 μg/mg at 1-year follow up. In contrast, three of the eight subjects on Lovaza had reversal of ACR from 30–300 μg/mg to ACR < 30 μg/mg (between group $P = 0.20$). Examining those who had any decrease in ACR, we found that five in control (12.5%) and 17 in Lovaza (43%) had a decrease in ACR (between group $P = 0.002$). This is a very significant 3-fold difference, which demonstrates an important change in an early phase of albuminuria.

Table 3 Benefit of omega-3 fatty acids by subgroups of albumin/creatinine ratio

ACR category	Albumin to creatinine ratio (ACR)				
	Baseline* median [IQR]	1-Year* median [IQR]	Median of % change [IQR]	*P* value	*P* value
ACR < 30 μg/mg					
Control ($n = 32$), μg/mg	6.7 [3.8, 10.6]	9.5 [5.2, 28.3]	86.9 [21.7, 192.3]	< 0.001	0.10
Lovaza ($n = 29$), μg/mg	4.9 [3.0, 7.4]	4.7 [2.2, 12.6]	21.9 [− 21.0, 146.2]	0.096	
ACR 30–300 μg/mg					
Control ($n = 7$), μg/mg	47.4 [36.0, 112.7]	79.5 [41.1, 284.5]	26.3 [−.1, 105.8]	0.063	0.20
Lovaza ($n = 8$), μg/mg	62.3 [38.2, 75.5]	83.9 [24.5, 96.2]	− 19.4 [− 44.2, 109.2]	1.000	
ACR > 300 μg/mg					
Control ($n = 1$), μg/mg	449.0 [449.0, 449.0]	552.4 [552.4, 552.4]	23.0 [23.0, 23.0]	NA	0.70
Lovaza ($n = 2$), μg/mg	762.8 [436.0, 1089.6]	567.4 [494.6, 640.2]	− 13.9 [− 41.2, 13.4]	0.66	

(From Elajami et al. J Am Heart Assoc. 2017; 6:e004740, https://doi.org/10.1161/JAHA.116.004740) [51••]

NA not available

* Data presented as median [interquartile range] in ug/mg.

Potential Mechanisms for Beneficial Effects of Omega-3 Fatty Acids

Systolic Blood Pressure and Albuminuria

Animal models suggest that EPA and DHA supplementation prevent the development of diabetic kidney disease by lowering inflammation and vascular stiffness with an improvement in blood pressure [54]. In the subjects with diabetes receiving Lovaza in the Welty trial [51••], the change in ACR was significantly directly correlated with change in SBP ($r = 0.394$, $P = 0.01$); however, Lovaza itself was not associated with a reduction in SBP. Rather, in those with a reduction in blood pressure, those on Lovaza had a significant median 19% reduction in ACR compared to controls who had a median 84.3% increase ($P = 0.002$), a finding suggesting that beneficial hemodynamic effects may be contributing to the attenuation of worsening of ACR in those receiving Lovaza. This finding underscores the importance of minimizing change in SBP in future clinical trials of omega-3 fatty acids and albuminuria in order to see the effect of omega-3 fatty acids independent of BP change. The correlation between change in ACR and change in diastolic blood pressure was not significant ($r = 0.166$, $P = 0.31$) [51••].

Dyslipidemia and Albuminuria

A postulated beneficial effect of omega-3 fatty acids on albuminuria may be through improvement of dyslipidemia. Elevated levels of serum triglyceride [55], which lead to tissue accumulation of lipids in the kidney, are associated with albuminuria and may underlie the development of diabetic nephropathy [56, 57]. Although subjects with diabetes receiving Lovaza in our trial had a significant reduction in triglyceride level, no correlation existed between attenuation of worsening of albuminuria and reduction in plasma triglyceride ($r = 0.059$, $P = 0.72$). Although this finding suggests that attenuation of worsening of albuminuria is not due to plasma triglyceride reduction, we cannot exclude changes in tissue accumulation of triglyceride [51••].

Inflammation and Albuminuria

EPA and DHA have shown anti-inflammatory and antithrombotic benefit and improvement in endothelial function [58]. Omega-3 supplementation has been shown to attenuate inflammation, glomerulosclerosis, and tubulointerstitial fibrosis in the remnant kidney of the 5/6 nephrectomy model of renal disease [59]. Inflammation is divided into two general stages: initiation and resolution [reviewed in 60]. In the initiation phase, arachidonic acid is converted via cyclooxygenases (COX) to pro-inflammatory, pro-thrombotic, and vasoactive eicosanoids that include prostaglandin (PG) E_2, $PGF_{2\alpha}$ and thromboxane (Tx) A_2 and via 5-lipoxygenase (LOX) to the pro-inflammatory leukotriene (LT) B_4, a potent chemoattractant that recruits leukocytes into tissues [reviewed in 61, 62]. As the inflammatory response proceeds, lipid mediator class switching occurs in which PGE_2 activates biosynthesis of specialized pro-resolving lipid mediators (SPMs)—lipoxins (LX), resolvins (Rv), protectins (PD), and maresins (MaR) [63, 64]. Low-dose aspirin acetylates COX-2 promoting the biosynthesis of epimeric (also called aspirin-triggered [AT]) forms of SPMs such as 15(R)-lipoxins, 17(R)-resolvins, and 17(R)-protectins [64]. Statins also promote 15(R)-epimers of LXA_4 via S-nitrosylation of COX-2 [64]. These SPMs are involved in pro-resolution pathways which can actively terminate acute inflammation by stopping further neutrophil recruitment to inflamed tissues and stimulating nonphlogistic infiltration of monocytes which differentiate into reparative macrophages (termed M2) [64]. These resolution macrophages then phagocytize and clear apoptotic neutrophils and debris, key steps to resolution and prevention of chronic inflammation [64, 65]. The overwhelming experimental evidence that SPMs promote the resolution of inflammation is supportive of a role in preempting fibrotic responses.

Omega-3 FAs are the precursors of SPMs. The E-series resolvins (RvE) are derived from EPA, and the D-series resolvins (RvD), maresins (MaR1), and protectins (PD-1) are derived from DHA [64]. The known bioactions of SPMs include pro-resolving and anti-inflammatory properties without causing immunosuppression [reviewed in 36]. Studies in animal models have shown a benefit of SPMs in decreasing inflammation in renal injury. In a kidney ischemia/reperfusion (I/R) mouse model, the D-series resolvins and PD1 reduced neutrophil and monocyte influx [66]. In another study using the I/R mouse model, systemic delivery of PD1 and AT-LXA_4 also reduced neutrophil recruitment [67]. Kieran et al. [68] have shown that administration of the AT-LXA_4 analogue inhibits the expression of many pro-inflammatory cytokines, growth factors, adhesion molecules, and proteases in the I/R mouse model. Moreover, LXA_4 has been shown to inhibit connective tissue growth factor-induced NF-κB activity in mesangial cells in rats [69]. LXA_4 inhibits mesangial proliferation and fibrosis by cross-talk between its receptor and growth factor receptors [70]. The unilateral ureteric obstruction (UUO) rat model has been used as a model of progressive tubulointerstitial fibrosis and inflammation relevant to CKD. Using this model, Börgeson et al. [71] showed that LXA_4 and its synthetic analogue, benzo-LXA_4, reduced collagen deposition and renal apoptosis ($P < 0.05$) and shifted the inflammatory microenvironment toward the resolution phase by inhibiting TNF-α and IFN-γ expression, increasing the production of pro-resolving IL-10 and switching the macrophage phenotype to anti-inflammatory/pro-resolving M2 macrophages. LXA_4 also inhibited the UUO-induced pro-inflammatory mitogen-activated protein kinases, Akt and SMADs

($P < 0.05$). Qu et al. [72] demonstrated that RvE1 and D1 inhibited collagen deposition and the production of platelet derived growth factor and reduced myofibroblast proliferation, thus inhibiting interstitial fibrosis in the UUO mouse model and identifying RvE1 as a novel anti-fibrotic therapy. Taken together, these findings suggest that both lipoxins and resolvins may benefit CKD/renal injury or dysfunction by reducing monocyte/neutrophil recruitment, inhibiting cytokines, growth factors, and pro-inflammatory gene expression, stimulating the clearance of apoptotic cells and attenuating fibrosis. Thus, these animal studies suggest that SPMs may reduce pathogenic mechanisms that can contribute to CKD or dysfunction at specific points within pathogenesis; hence, specific SPMs may be beneficial in preventing CKD. Evidence supports that omega-3 fatty acids increase SPM levels in humans with CKD. In a double-blind, placebo-controlled intervention in 85 patients with CKD, supplementation of 4 g of omega-3 fatty acids for 8 weeks significantly increased plasma levels of 18-HEPE (RvE intermediate) and 17-HDHA (RvD intermediate) ($P < 0.0001$), and RvD1 ($P = 0.036$), whereas no change was seen in SPMs or intermediates with 200 mg of co-enzyme Q10 or 4 g of olive oil (control) [73••].

Conclusions

Several of the small, short-term trials in Table 1 suggested benefit on ACR in subjects with diabetes [47–50, 52]; however, results are not definitive possibly due to low-dose, short trial duration and differences in study subject characteristics. Our parent trial is the first to show that EPA and DHA for 1-year slow progression of early-stage albuminuria in diabetic subjects with clinical CAD on an ACE-I or ARB, the majority of whom had an ACR < 30 μg/mg [51••]. Moreover, significantly more (3-fold) subjects on Lovaza had a decrease in ACR compared to control and three on Lovaza had a change in category from > 30 to < 30 μg/mg, whereas no controls did. These results suggest that there is benefit and perhaps even reversal of ACR with EPA and DHA at an early stage of disease in those with ACR < 30 μg/mg and those with microalbuminuria (ACR > 30). A strength of our clinical trial is that it was large (262 subjects), included both diabetics and nondiabetics, used a uniform dose of omega-3 fatty acids (3.36 g EPA/DHA daily), was longer than the prior reported trials, and confirmed compliance with omega-3 fatty acids with plasma EPA and DHA levels [51••]. Nondiabetic, healthy subjects with a baseline ACR of 7.4 to 30 μg/mg, which has been considered in the normal range, were found to have an increased incidence of hypertension and cardiovascular mortality in 11-year follow-up compared to those with ACR < 7.4 μg/mg [20••]. Cardiovascular outcomes are predicted by changes in ACR < 30 μg/mg [20••], suggesting that an ACR < 30 μg/mg may be an early indicator of pathology. Since albuminuria will develop in the majority of subjects with diabetes, development of strategies to decrease albuminuria at an early stage to prevent or delay atherosclerosis and cardiovascular disease is important [74]. Our results suggest that if a preventive strategy is started early, slowing or prevention of significant disease may occur. If one waits until structural renal disease as fibrosis is present, reduction in albuminuria may be less likely to be achieved. Based on the totality of evidence presented, it is justified to study EPA and DHA further for prevention of progression of albuminuria in subjects with diabetes. Dietary modalities which can prevent albuminuria progression would be cost-effective on a population basis; their relative lack of side effects and easy availability make them attractive interventions. If EPA and DHA attenuate worsening of albuminuria in subjects with diabetes, high-dose EPA and DHA could be an inexpensive and safe nutritional treatment to prevent progression of albuminuria; provide additional benefit over the current standard of care, ACE-I or ARB; and thus decrease chronic kidney disease and related healthcare costs.

Compliance with Ethical Standards

Conflict of Interest The author declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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- • Of importance
- •• Of major importance

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