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Omega-3 Fatty Acids (Fish Oil) Supplementation and Albuminuria: Not a Slam Dunk

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Polyunsaturated fatty acids (PUFAs) include ω-3 PUFAs derived from plants or meat and ω-6 PUFAs derived from plants or marine life. Long-chain PUFAs include arachidonic acid (ω-6 PUFA) and docosahexaenoic acid, the latter 2 being ω-3 PUFAs. Long-chain ω-3 PUFAs have been the focus of experimental studies and clinical investigations in humans. ω-3 fatty acid supplementation has shown anti-inflammatory and antithrombotic properties along with an improvement in endothelial function.[1] Clinical trials have also studied the antihypertensive effects of ω-3 fatty acids.[2,3] Although it remains debatable, a recent scientific advisory from the American Heart Association concluded that the use of ω-3 fatty acids is reasonable only for secondary prevention of coronary heart disease and sudden cardiac death in patients with prevalent coronary heart disease (Class IIa recommendation, panel not reaching a consensus with some members preferring a Class IIb recommendation).[4]

Effects of ω-3 fatty acids on kidney function measures have been studied in various types of kidney diseases: IgA nephropathy, lupus nephritis, polycystic kidney disease, and other glomerulonephritis.[5-7] Secondary analysis of the Diabetes Control and Complications Trial and other observational data showed that higher dietary eicosapentaenoic acid and docosahexaenoic acid consumption was associated with lower risk of albuminuria among diabetics.[8] A meta-analysis examining the effects of ω-3 fatty acids supplementation suggested reduction in proteinuria among those with diabetes mellitus but argued for larger studies given the suboptimal quality of the studies included in the meta-analysis.[9] It is important to note that even a minimal increase in urinary albumin excretion is associated with an increased risk of kidney failure and cardiovascular disease both in the general population and among those with kidney disease, highlighting the need for studies targeting albuminuria as a risk factor.[10]

In a single-center study reported in this issue of *JAHA*, Elajami et al randomized 262 subjects with stable coronary artery disease to Lovaza® (a fish oil product that is a combination of 1.86 g of eicosapentaenoic acid and 1.5 g of docosahexaenoic acid) or no Lovaza (control).[11] The primary objective of this 12-month controlled clinical trial was to assess the effects of Lovaza on the progression of fibrous and calcified plaques in those with coronary artery disease. In a secondary analysis, which was described in this article, the investigators examined the effects of eicosapentaenoic acid and docosahexaenoic acid on urinary albumin excretion after 1 year of therapy with Lovaza. Urinary albumin-to-creatinine ratio (UACR) was measured in the morning spot urine sample using immunoturbidimetric and calorimetric assays for urine albumin and creatinine, respectively. Recruitment was restricted to only those with body mass index >27 or 25 to 26.5 kg/m^2 along with an increased waist circumference, as these subjects are likely to have a higher inflammatory burden. The investigators included only those patients with creatinine clearance >60 mL/min using the Cockcroft-Gault equation, and hence these study results are applicable to only those with preserved kidney function. All participants were taking aspirin and statin at the time of study entry. Mean age of the study population was 63.3 years, and >80% were men. Separate analyses were conducted among those with and those without diabetes mellitus and those who were on and not on angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

At 1-year follow-up, in the analyses restricted to diabetic subjects (n=79), those who were on Lovaza had no change in

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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J Am Heart Assoc. 2017;6:e006020. DOI: 10.1161/JAHA.117.006020.

UACR, whereas the control group had an increase in UACR (P=0.04). Among diabetics, change in UACR correlated with the change in systolic blood pressure (r=0.394, P=0.01). Similar results were noted when analyses were restricted to those with diabetes mellitus on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (n=67). Treatment with Lovaza improved serum triglyceride levels, but no significant changes in HDL cholesterol were noted among diabetics. Authors also stratified diabetic subjects based on baseline UACR (<30, 30 to 300, and >300 μg/mg). Among those with UACR <30 μg/mg, those receiving Lovaza had no significant change in UACR, although the control group had an increase in UACR. In the nondiabetic subjects UACR did not change significantly in both groups, and no statistically significant difference was noted between the study groups (P=0.56). Treatment with Lovaza improved both serum triglyceride levels and HDL cholesterol in those without diabetes mellitus.

We commend the authors for the careful conduct of this clinical trial in which they enrolled a high-risk population with elevated inflammatory marker burden and focused on a key surrogate end point of kidney disease progression, UACR. Although it is encouraging to see the results of this clinical trial for those who are at high risk of kidney disease progression, some important limitations are worth discussing so that the results can be interpreted appropriately. First, this was an open-label trial with no placebo. Second, authors conducted multiple comparisons, some of which were prespecified, and did find a statistically significant difference between those who were on Lovaza than those who were not (P=0.04, among those with type 2 diabetes mellitus). However, no correction was performed for multiple testing using either Bonferroni adjustment or other methods.[12] Hence, a false-positive study result cannot be totally excluded, and at best, these results should be considered hypothesis generating, arguing for larger, long-term studies. Finally, the study enrolled predominantly men. In addition, those with preexisting kidney disease were excluded, thereby limiting its generalizability.

How do we explain the findings of this study? Diabetes mellitus and hypertension raise intraglomerular pressure, which leads to podocyte and tubular injury resulting in albuminuria. If left unabated, this leads to persistent inflammation, mesangial cell activation, and glomerulosclerosis, which results in a decline in glomerular filtration rate (GFR). Animal models suggest that the ω-3 fatty acid supplementation prevents the development of diabetic kidney disease.[13] In experimental models, fish oil supplementation also lowers inflammation and vascular stiffness with an improvement in blood pressure. In the study by Elajami et al a correlation between change in UACR and change in systolic blood pressure was also noted. Given the small sample size, further analyses were not conducted. It is worth noting that no change in blood pressure was noted with Lovaza use. However, based on the findings from previous trials on this topic, apart from other factors, improvement in blood pressure with ω-3 fatty acid supplementation could have contributed to the improvement in UACR.[14]

It is well known that albuminuria is a relevant and modifiable cardiovascular risk factor. Recent work from the Chronic Kidney Disease-Prognosis Consortium suggests that even a minimal increase in urine albumin excretion (as low as 10 μg/mg) is associated with an increased risk of cardiovascular disease, end-stage renal disease, and mortality.[15] This led to the reclassification of kidney disease by the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline based on the estimated GFR (eGFR) and UACR rather than by eGFR alone. In this trial the authors note that ω-3 fatty acid supplementation improved UACR.[11] Could this improvement in UACR potentially lower cardiovascular event incidence in this high-risk population? We can only speculate that it could, but additional trials are warranted to examine this.

For practitioners treating diabetic patients, apart from cardiovascular disease, decline in GFR and end-stage renal disease are important outcomes. Hence, it would be interesting to see if the effects on UACR noted in this study would translate to improvement in kidney function, ie, change in GFR. Unfortunately, change in eGFR was not different between the study groups. We believe that a 1-year follow-up is not sufficient to study change in GFR. The Alpha Omega trial (n=4837) examined the cardiovascular benefits of ω-3 fatty acids in those with cardiovascular disease and did not show any significant differences in cardiovascular outcomes between those receiving ω-3 fatty acids and those getting placebo.[16] In a secondary analysis of this trial, Hoogeveen et al studied the effects of ω-3 fatty acids on serum creatinine-cystatin–based eGFR.[17] After 40 months of follow-up, decline in creatinine-cystatin C–based GFR was 2.1 mL/min per 1.73 m^2 less among those receiving ω-3 fatty acids compared with those receiving placebo. However, other secondary end points such as incident chronic kidney disease (eGFR <60 mL/min per 1.73 m^2) or rapid decline in kidney function (>3 mL/min per 1.73 m^2) were not significantly different between the study groups. UACR data were not available for this study cohort. Considering the results of the studies by Hooegeveen et al and Elajami and colleagues,[11] we have some evidence suggesting that ω-3 fatty acids might impact both UACR and eGFR in those with preserved kidney function. However, it is worth noting that none of these trials was adequately powered to study these clinically important metrics.

Among those with type 2 diabetes mellitus and albuminuria, angiotensin-converting enzyme inhibitors/angiotensin

receptor blockers remain the standard of care. Recent studies suggest potential benefits of other agents such as sodium-glucose cotransporter 2 inhibitors and other agents in this population.[18,19] How does ω-3 fish oil supplementation fit into the treatment algorithm? Based on the data from previous studies and in this trial, ω-3 fatty acid supplementation seems to offer some incremental renal benefits for high-risk type 2 diabetic patients who are on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. However, further studies are needed to confirm the impact of ω-3 fatty acid supplementation on albuminuria and to study whether ω-3 fatty acid supplementation also slows down the progression of kidney disease and delays the development of end-stage renal disease. Because several studies have examined the use of ω-3 fatty acids in the general population, if relevant data are available, investigative teams of these studies could also examine the effects of ω-3 fatty acids on decline in kidney function. Until additional data become available, current evidence does not justify the routine use of ω-3 fatty acids in clinical practice to preserve kidney function.

Disclosures

None.

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Key Words: Editorials • clinical trial • fish oil • glomerular filtration rate • kidney (diabetes) • microalbumin