

Efficacy of Omega-3 Fatty Acids in Children and Adults with IgA Nephropathy Is Dosage- and Size-Dependent

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Previous studies that have evaluated fish oil preparations in patients with IgA nephropathy (IgAN) have produced a wide range of conclusions. Proposed explanations for these discordant results have not provided a unifying hypothesis. Results from two clinical trials were analyzed to examine whether there is a dosage-dependent effect of Omacor, a purified preparation of omega-3 fatty acids, in patients with IgAN. Whether changes in the level of proteinuria and plasma phospholipid fatty acid profiles were dependent on the dose of Omacor factored by body size was determined. In a *post hoc* analysis of the first trial results, correlations were found between (1) phospholipid eicosapentaenoic acid (EPA)/arachidonic acid (AA) and docosahexaenoic acid (DHA)/AA ratios and the dosage of Omacor, expressed as milligrams per kilogram of body weight ($r = 0.78$, $P < 0.001$ for EPA/AA; $r = 0.86$, $P < 0.001$ for DHA/AA), (2) phospholipid EPA/AA and DHA/AA levels and percentage change in urine protein/creatinine ratio after 21 to 24 mo of therapy ($r = -0.50$, $P = 0.02$ for EPA/AA; $r = -0.52$, $P = 0.01$ for DHA/AA), and (3) dosage of Omacor per kilogram of body weight and change in proteinuria after 21 to 24 mo ($r = -0.50$, $P = 0.02$). A similar relationship was observed between urine protein/creatinine ratio and dosage of Omacor per kilogram of body weight in trial 2 ($r = -0.38$, $P < 0.001$). It is concluded from these data that the effect of Omacor on proteinuria in patients with IgAN is dosage dependent and is associated with a dosage-dependent effect of Omacor on plasma phospholipid EPA and DHA levels.

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In the past 20 yr, there has been a series of conflicting reports dealing with the benefit or lack of benefit when fish oil preparations, containing varying concentrations of omega 3 fatty acids (O-3FA), are given to patients with a variety of diseases. This is exemplified by the results that were obtained in studies that involved patients with IgA nephropathy (IgAN) (1–9), as summarized in a meta-analysis by Dillon (10). In this report, we advance and test a hypothesis to explain the previous discordant trial results. This evolved from a *post hoc* analysis of results from our prospective clinical trial of O-3FA in patients with IgAN, the primary analysis of which was published recently in this journal (11). We have confirmed our observations using data from the prerandomization phase of a subsequent trial that is ongoing.

Materials and Methods

Medications

Patients in both of the studies received Omacor, a purified preparation of O-3FA at a dosage of 4 g/d. The active ingredients in the Omacor capsules have been developed by Pronova Biocare (Lysaker, Norway). This preparation is a formulation that consists of 84% highly purified ethyl esters of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

The daily administration of 4 g of this product provides each patient with 1.88 g/d EPA and 1.48 g/d DHA. The study design in each trial incorporated a provision for patients who had a body surface area (BSA) of <0.875 m² to receive a lower dosage of Omacor. However, this dosage modification was not necessary, because all of the patients were ≥ 0.875 m².

Patients in the first trial were given enalapril (provided by Merck & Co., West Point, PA) if they were hypertensive at dosages that were individualized to normalize their BP readings (11). Hypertension was defined in both studies as either systolic BP >140 mmHg or diastolic >90 mmHg in adults, and >95 th percentile for age in children and adolescents. Most of the patients in trial 2 were given lisinopril (also provided by Merck). An initial dosage of 5 to 20 mg/d was doubled after 1 mo of therapy to 10 to 40 mg/d if no adverse events were encountered and subsequently increased in persistently hypertensive patients to a maximum of 20 to 80 mg/d (the actual dosage depending on body weight; details of dosing regimen available upon request). The remainder of the patients in the second trial were unable to tolerate lisinopril; these patients were converted to losartan at a dosage of 25 to 100 mg/d, as tolerated.

Eligibility Criteria

Both studies required (1) a renal biopsy that showed IgAN (this could be obtained at any time before study entry); (2) estimated GFR (eGFR) ≥ 50 ml/min per 1.73 m² using an age-appropriate formula (Schwartz equation [12,13] or Cockcroft-Gault equation [14]) or ≥ 40 ml/min per 1.73 m² if the patient was receiving an angiotensin-converting inhibitor; (3) moderate to severe proteinuria, which consisted of a urine protein/creatinine (UP/C) ratio >0.5 on a first morning urine specimen in trial 1 and UP/C >0.6 in male and >0.8 in female patients in a 24-h urine collection in trial 2; and (4) age 2 to 41 yr at entry in trial 1 and 7 to 70 yr in trial 2.

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Trial 1

In the first IgAN trial, which was placebo controlled, the primary goal was to evaluate the efficacy of alternate-day prednisone and that of Omacor on preserving renal function, in 96 children and young adults with IgAN. Details of the study design and results of the primary analysis of the study results have been published previously in this journal (11). Each patient in the Omacor arm in this trial received 2 yr of treatment. UP/C data that were used in the analyses that are presented in this article were from first morning urine specimens that were obtained 18 and 24 mo after starting Omacor.

Trial 2

In trial 2, which is ongoing, all patients are given Omacor 4 g/d during a 3-mo lead-in period. This is designed to identify patients who have IgAN and have persistent proteinuria despite a 3-mo course of lisinopril and Omacor. Such patients subsequently are randomly assigned to receive mycophenolate mofetil or placebo. However, the results that are reported in this article are restricted to the prerandomization phase of the trial. UP/C ratios were obtained before and after 3 mo of therapy in 68 patients as of the time this report was prepared. These were obtained on overnight urine specimens in nine patients and 24-h specimens in 59 patients. This variability in specimen collection was the result of a change in study protocol early in the course of the trial. The findings in the 59 patients and 68 patients both are provided in the Results section. Two posttreatment specimens were obtained in each patient, usually on consecutive days, and the mean value used in the analysis.

Subanalysis of Patients Not Treated with O-3FA Supplements before Enrollment. Eighteen of the 68 patients had been treated with a fish oil supplement of varying strength for variable periods of time before their enrollment in the trial. These patients were set aside, and the analysis was repeated with the remaining 50 patients.

Controlling for Dose of Lisinopril. Finally, the analysis was conducted in 42 patients who received (and tolerated) lisinopril and who had received no fish oil before enrollment. In these patients, the analysis was adjusted for dosage of lisinopril (mg/kg) to control statistically for its potential effect on change in the UP/C ratio.

Laboratory Studies

Blood and urine specimens were sent to Laboratory Corporation of America (LabCorp) for routine studies and urinary protein concentration (using the Quantitest Total Protein Assay System, which has an intra-assay coefficient of variation <9.5% for urine; #40-02/87; Hawthorne, CA). In the first trial, urine and serum creatinine concentrations were determined using isocratic (succinic acid-mobile phase) ion-exchange HPLC with ultraviolet detection, as described previously (11). This method is sensitive, is free from drug interference and the effect of noncreatinine chromogens in serum, and provides results that range from 97 to 102% of those obtained using stable isotope mass spectrometry (15,16). In the second trial, the urine and serum studies also were done by LabCorp using standard techniques.

Measurement of Plasma Phospholipids. Twenty-three of the patients who received Omacor had plasma phospholipid fatty acid profiles measured in the laboratory of Bruce Holub, PhD, after 21 to 24 mo of therapy. The methods that were used have been described in detail previously (17,18).

Data Management

The two clinical trials that provide the data from which this report was generated have been conducted in 50 clinical centers in the United States and Canada (see the Appendix for list of centers and investiga-

tors), with overall coordination and data management being housed at the Administrative Coordinating Center (ACC) that was located at Medical City Hospital in Dallas, TX, from 1996 to 2004 and St. Joseph's Hospital and Medical Center in Phoenix, AZ, from 2005 to 2006.

Data were submitted to the ACC in two forms: Case report forms and LabCorp reports. LabCorp provides all laboratory data on standardized report forms. Trained ACC staff members reviewed the incoming forms for completeness and adherence to coding rules. The data manager and a clinical coordinator at the ACC completed double entry of the data into the database. Data from each patient were recorded with a unique contributing center code, study code, sequence number, and patient initials.

Statistical Analyses

Preliminarily, data were checked to ensure that normality assumptions were met. Pearson correlation was used to estimate the linear relationship between continuous variables. Multiple linear regression was used to estimate the relationship between dosage of Omacor and change in UP/C ratio over time and to control for the potentially confounding effects of lisinopril in trial 2. The criterion for statistical significance was set at $P = 0.05$, two tailed. Summary statistics for interval/ratio data are given as means \pm SD. Counts (percentages) are provided for nominal data. All analyses were performed using SPSS software (version 14; SPSS Inc., Chicago, IL).

Patient/Parent Informed Consent/Assent Procedures

Both of the trials have been conducted under an investigator-initiated Investigational New Drug (#48,977) in US centers and with the approval of Health Canada (control no. 076948) in Canadian sites. All participating sites obtained approval for their involvement in the studies from a local Institutional Review Board (IRB) or Central IRB (Western IRB). Written consent (or assent when applicable) was obtained from all participants in each of the studies.

Results

Trial 1

Twenty-three of the patients in the first trial who received a 24-mo course of 4 g/d Omacor were included in the analysis that follows. The mean dosage of Omacor in the 23 patients, when adjusted for body weight, was 59.5 ± 29.3 mg/kg per d (range 31.9 to 160). The patients ranged in age from 7.4 to 39.7 yr (mean 19.9 ± 9.9), and their average weight was 78.7 ± 27.9 kg (range 25.0 to 125.5 kg). These 23 patients and 13 patients who received placebo capsules had blood drawn for measurement of plasma phospholipid fatty acid profiles after 21 to 24 mo of therapy. The results of their phospholipid EPA/arachidonic acid (AA) and DHA/AA profiles are shown in Figure 1. Each of the patients is represented by a single point, and the data are grouped according to whether they received Omacor or placebo.

It is evident that the group of Omacor patients had substantially higher levels of both EPA/AA and DHA/AA than the placebo group, consistent with previous studies (6). However, there is a 15-fold range of variability among the levels in individuals who received Omacor, with the levels of EPA/AA ranging from 0.06 (comparable to placebo patients, who had levels from 0.03 to 0.06) to 0.92 (mean 0.42 ± 0.25), despite that all of the patients received the same dosage of Omacor (4 g/d). This range of values seemed to go beyond the scope of normal biologic variability and led to additional analysis. The first possibility that was tested was variability in the level of adher-

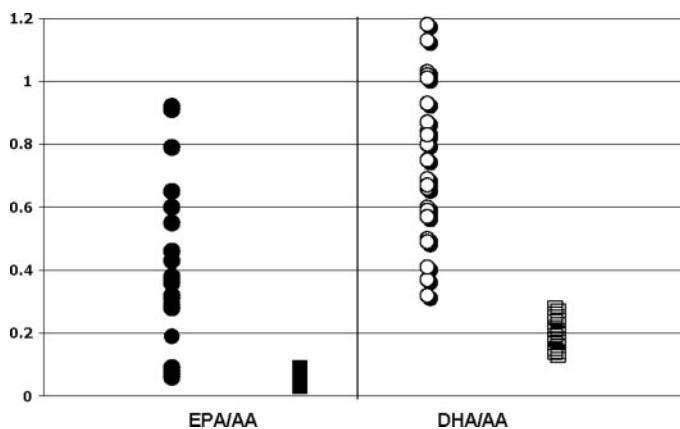


Figure 1. Plasma phospholipid eicosapentaenoic acid (EPA)/arachidonic acid (AA) and docosahexaenoic acid (DHA)/AA ratios in patients who received Omacor (circles) versus placebo (squares).

ence to the study protocol among the patients. However, pill counts that were conducted throughout the trial showed that overall adherence was 93.5% in the Omacor group and 96% in the placebo group ($P = 0.35$). There was no correlation between EPA/AA or DHA/AA ratios and the level of adherence in individual patients ($r = 0.20$). The second possibility, that the EPA/AA and DHA/AA profiles depended on the dosage of Omacor per unit of body size, showed a positive correlation. Individual patient results are depicted in Figure 2. It is apparent that the patients who were receiving a proportionately higher dosage of Omacor per kilogram of body weight (and hence EPA and DHA dosages per kilogram of body weight as shown in Figure 2) had higher phospholipid EPA/AA and DHA/AA ratios. Further analysis showed linear relationships between percentage change in UP/C ratio and both plasma phospholipid EPA/AA and DHA/AA ratios (Figure 3).

As shown in Figure 4, dosage of Omacor was correlated with percentage change in UP/C ratio ($r = -0.50$, $P = 0.02$). The phospholipid EPA/AA ratios also were correlated with body weight ($r = 0.80$, $P < 0.001$), BSA ($r = 0.75$, $P < 0.001$), and Omacor dosage expressed as mg/m^2 BSA ($r = 0.82$, $P = 0.0001$).

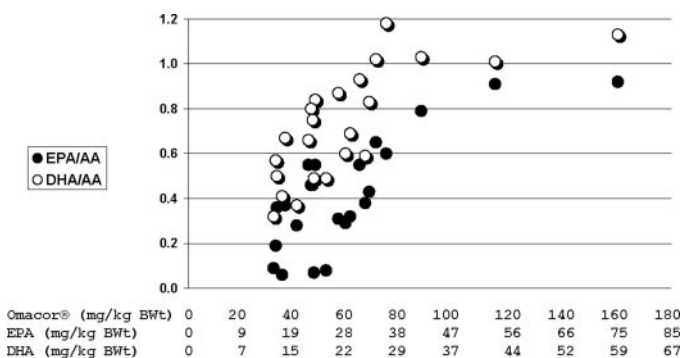


Figure 2. Relationship between plasma phospholipid EPA/AA and DHA/AA ratios and dosage of Omacor, EPA, and DHA (expressed as mg/kg body wt). For EPA/AA versus dosage, $r = 0.78$, $P < 0.001$; for DHA/AA versus dosage, $r = 0.86$, $P < 0.001$.

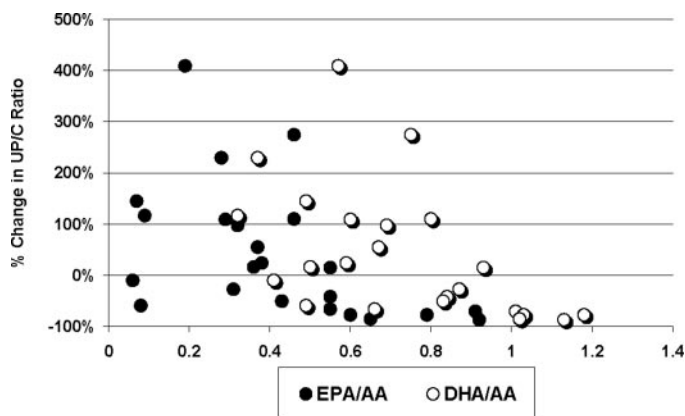


Figure 3. Relationship between percentage change in UP/C and plasma phospholipid EPA/AA and DHA/AA ratios. For change in urine protein/creatinine (UP/C) ratio versus EPA/AA, $r = -0.50$, $P = 0.02$; for change in UP/C ratio versus DHA/AA, $r = -0.52$, $P = 0.01$.

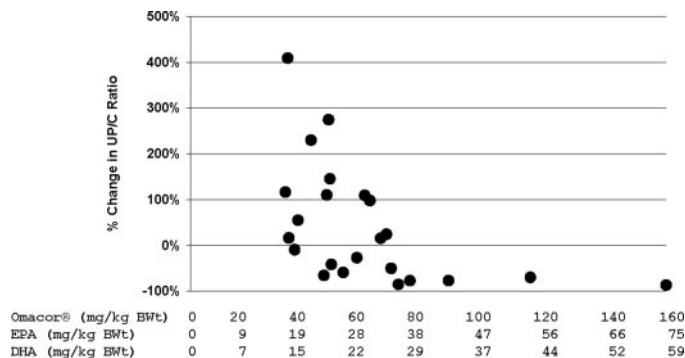


Figure 4. Relationship observed in trial 1 between percentage change in UP/C ratio and dosage of Omacor, EPA, and DHA (expressed as mg/kg body wt): $r = -0.50$, $P = 0.02$.

The phospholipid EPA/AA and DHA/AA ratios also were closely correlated with each other ($r = 0.85$, $P < 0.001$).

Trial 2

Sixty-eight patients were given a 3-mo course of 4 g/d Omacor (mean dosage adjusted for body weight 48 ± 14 mg/kg per d; range 25 to 95 mg/kg). The patients ranged in age from 12 to 61 yr (mean 29.9 ± 12.2) and weighed 42.2 to 158.3 kg (mean 88.9 ± 23.0). Sixty of these patients received lisinopril at a mean dosage of 0.36 ± 0.18 mg/kg per d (range 0.04 to 1.01), as tolerated. The other eight patients were intolerant to lisinopril and were prescribed losartan instead. Percentage fall in UP/C ratio after 3 mo of therapy in the entire group of patients was correlated with Omacor dosage (mg/kg ; $r = -0.38$, $P < 0.001$; Figure 5). This correlation also was significant when the analysis was restricted to patients in whom proteinuria was assessed on 24-h urine collections ($r = -0.30$, $P = 0.02$).

Patients who received no O-3FA before the trial ($n = 50$) had a similar response to the group overall; percentage fall in UP/C ratio was correlated with Omacor dosage (mg/kg ; $r = -0.45$, $P <$

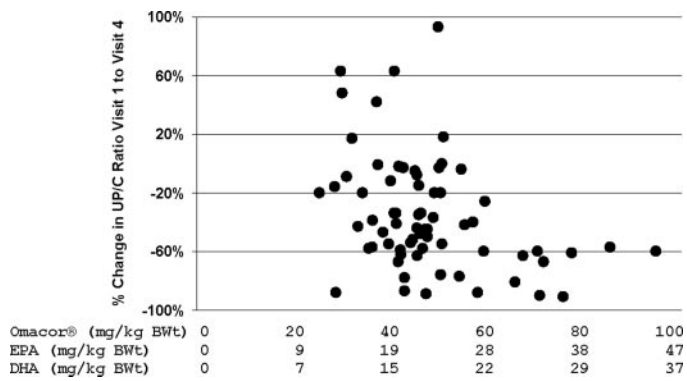


Figure 5. Relationship observed in trial 2 between percentage change in UP/C ratio and dosage of Omacor, EPA, and DHA (expressed as mg/kg body wt): $r = -0.38$, $P < 0.001$.

0.001). In contrast, there was no demonstrable correlation between percentage fall in UP/C ratio and Omacor dosage (mg/kg) in patients who had received fish oil supplements before the trial ($n = 18$; $r = -0.16$, $P = 0.54$). However, this latter result may have arisen from the fact that we had relatively few patients in this subgroup and most of them received Omacor dosages per body weight that were within a narrow range, thus restricting the potential for defining a dosage-dependent effect.

Among patients who tolerated lisinopril and had received no fish oil before enrollment ($n = 42$), when the relationship between dosage of Omacor and percentage change in UP/C ratio was adjusted for dosage of lisinopril (g/kg), the percentage fall in UP/C ratio still was significantly correlated with the dosage of Omacor (partial correlation = -0.38 , $P = -0.01$).

Discussion

Optimal therapy for patients with IgAN has been a subject of controversy for >30 yr. One of the more novel therapies, namely fish oil supplements that contain relatively high concentrations of O-3FA, first was described 20 yr ago (1). Subsequent studies have revealed conflicting results (2–9). Various hypotheses have been proposed to explain these discrepant findings, but they have not resolved the issue adequately. The dosage of O-3FA that has been used in the various studies has been variable, but the dosage that has been given to patients within an individual study has been fixed, regardless of the size of the patients being treated. The confusing situation with respect to the discrepant results in the literature was summarized recently by Dillon in a meta-analysis (10).

The rationale for using fish oil supplements in patients with IgAN is based on the premise that O-3FA may limit the production or action of cytokines and eicosanoids induced by the initial immunologic renal injury. The most favorable findings were reported by Donadio *et al.* (6), who showed that fish oil slowed the rate of renal deterioration in adults with IgAN, although there was no effect on proteinuria. During a 2-yr treatment period, only 6% of the fish oil group had an increase in serum creatinine concentration of 50% or more, compared with 33% in the placebo group. However, studies from Australia (2), China (3), and Sweden (5) reported no benefit from fish oil therapy in patients with IgAN.

Possible explanations for the conflicting findings include differences in the rate of progression of the disease in different patient populations, variations in the composition of the fish oil or placebo that was used, and/or the duration of treatment.

One of the goals of our first IgAN trial was to reevaluate the role of O-3FA for this condition in children and young adults up to 41 yr of age by monitoring changes in (1) the eGFR and (2) the level of proteinuria, because this now has been shown to be a good surrogate marker of progressive renal disease (19–21). However, in the primary analysis, we were unable to demonstrate any benefit on eGFR or proteinuria (11). In this report, we have demonstrated, in a *post hoc* analysis, significant correlations between the dosage of O-3FA, expressed as milligrams per kilogram of body weight, changes in the plasma phospholipid fatty acid profiles, and changes in the severity of proteinuria. We have confirmed the correlation between dosage per kilogram of body weight and UP/C ratio in a second trial after patients who were aged 7 to 70 yr received only 3 mo of Omacor (plus lisinopril). We believe that these observations may provide a unifying explanation for the discordant findings reported previously.

We postulate that the relationship among (1) O-3FA dosing factored by body size, (2) widely varying plasma phospholipid O3/06 levels, and (3) dosage-dependent outcome effects also may apply to other conditions. A number of previous trials have drawn attention to two of these three factors in a wide array of diseases. For example, in 1990, Bonna *et al.* (22) showed that decreases in BP in patients who had mild essential hypertension and received an O-3FA preparation were more evident in the patients who developed higher levels of plasma phospholipid O-3FA. The 156 adult patients in this study all received 6 g/d of an 85% O-3FA preparation for 5 to 10 wk. The mean ratio of EPA/AA increased from 0.42 to 1.22 ($P < 0.0001$), and there was a significant inverse relationship between fall in systolic BP and rise in plasma phospholipid EPA concentration ($r = 0.27$, $P = 0.0007$) and DHA concentration ($r = 0.20$, $P = 0.014$). The fall in mean BP was significantly related to the change in O-3FA levels ($P = 0.027$). However, the authors did not report any relationship between these two sets of observations and the dosage of O-3FA factored by body size.

In a more recent report, Albert *et al.* (23) showed that data that were derived from the Physicians' Health Study revealed a significantly lower relative risk for sudden death among men who had higher O-3FA blood levels. However, the authors also noted that previous studies of the same cohort found no association between plasma levels of O-3FA and the risk for myocardial infarction (24). This issue was evaluated recently in an extensive systematic review of the potential benefit of O-3FA in improving cardiovascular disease outcomes by Wang *et al.* (25). They concluded that O-3FA consumption reduces all-cause mortality, cardiac death, and sudden death but noted that the results were inconsistent among studies. In another recent review, by Arterburn *et al.* (26), that involved a large number of studies involving heterogeneous patient populations, it was concluded that blood and tissue O-3FA levels (and potential health benefits) are modified in a dosage-dependent manner by EPA and DHA supplements. However, these conclusions were based only on interstudy comparisons of O-3FA dosages.

Another factor to be considered in the interpretation of our

findings is the potential role of obesity in maintaining higher levels of proteinuria among patients with greater body weights. A number of recent publications have implicated obesity as a causative factor in the induction of proteinuria (27–29). This possibility cannot be discounted with certainty in our study. Furthermore, angiotensin-converting enzyme inhibitors, which also were given to patients in our study, may have played some role in the varying reductions in levels of proteinuria. However, the relationship between

proteinuria and Omacor dosage factored by the body weight persisted when the lisinopril effect was partialled. Hence, we interpret our observations to be consistent with the hypothesis that Omacor causes dosage-dependent changes in phospholipid EPA/AA and DHA/AA ratios, which are, in turn, associated with similar dosage-related alterations in the level of proteinuria. Whether this will translate into dosage adjustments in the future treatment of patients with IgAN has yet to be determined.

Appendix: Participating centers/investigators in IgAN Trial 1 and/or 2

Center	Investigator(s)
University of Alabama	Bruce Julian, MD; Bryson Waldo, MD
Texas Children's Hospital, Houston	Eileen Brewer, MD
Stanford University Medical Center	Steve Alexander, MD
Cook Children's Hospital	Watson Arnold, MD
Arkansas Children's Hospital	Eileen Ellis, MD
University of Colorado HSC	Isaac Teitelbaum, MD
University of Tennessee	Robert Wyatt, MD
UTHSC at San Antonio	Ihsan Elshihabi, MD
UT Medical Branch, Galveston	Steven Diven, MD
UTHSC at Houston	Ronald Portman, MD
University of Chicago	John Dillon, MD
Johns Hopkins University	Barbara Fivush, MD
Schneider Children's Hospital, New Hyde, NY	Howard Trachtman, MD
University of Kentucky Medical Center	Beth Jackson, MD; Peter Sawaya, MD
Kapi'olani Medical Center—University of Hawaii	James Musgrave, MD
Loma Linda University Medical Center	Shoba Sahney-Long, MD
Children's Mercy Hospital, Kansas City, MO	Uri Alon, MD
University of Cincinnati	John Galla, MD
Cardinal Glennon Memorial Hospital	Ellen Wood, MD
Children's Hospital and Medical Center, Seattle, WA	Ruth McDonald, MD
University Medical School, Durham, NC	Delbert Wigfall, MD
UCLA Medical Center	Ora Yadin, MD
Children's National Medical Center, Washington, DC	Kanwal Kher, MD; Asha Moudgil, MD
SUNY at Buffalo, NY	Rocco Venuto, MD
Mayo Clinic, Rochester, MN	James V. Donadio, Jr., MD; Dawn Milliner, MD; Fernando Fervenza, MD
University of North Carolina, Chapel Hill	Ron Falk, MD; Debbie Gipson, MD
University of Iowa College of Medicine	Craig Porter, MD; John Bertolatus, MD
Dallas Nephrology Associates	Sumit Kumar, MD
Rhode Island Hospital	Lance Dworkin, MD
University of Florida	Robert Fennell, MD; Richard Neiberger, MD
Toronto Hospital, Toronto, Ontario, Canada	Daniel Cattran, MD
LSU Medical Center, New Orleans, LA	Matti Vehaskari, MD
The Nemours Children's Clinic, Orlando, FL	Jorge Ramirez, MD
University of Rochester	Melissa Gregory, MD
University of Michigan	Joseph Flynn, MD; Sean Leavey, MD
Carolina's Medical Center, Charlotte	Susan Massengill, MD
Gunderson Lutheran/LaCrosse	Philip Dahlberg, MD
Cincinnati Children's Hospital	Fred Strife, MD
Kidney & Hypertension Center, Cincinnati, OH	Danny Fischer, MD
Kidney Specialist of Oklahoma	Brad Carter, MD
Medical College of Wisconsin	Cynthia Pan, MD
British Columbia Children's Hospital	Morrison Hurley, MD
Dialysis Associates, Saginaw, MI	Mohammed Bashir, MD
Ohio State University	Dan Spetie, MD
St. Justine Hospital, Montreal, Canada	Aicha Merouani, MD
St. Joseph's Hospital and Medical Center, Phoenix	Ronald Hogg, MD
Providence Health Care—St. Paul's Hospital, Vancouver, BC, Canada	Beverly Jung, MD
Vancouver General Hospital, Vancouver BC, Canada	Choi Kit Yeung, MD
Columbia Nephrology Associates, Columbia, SC	Koshy Abraham, MD
Columbia University College of Physicians, New York, NY	Gerald Appel, MD
Piedmont Nephrology, Hickory, NC	Richard Paul, MD
Capital District Renal Physicians, Albany, NY	Jorge Cerda, MD

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References

- Hamazaki T, Tatenos S, Shishido H: Eicosapentaenoic acid and IgA nephropathy. *Lancet* 1: 1017–1018, 1984
- Bennett WM, Walker RB, Kincaid-Smith P: Treatment of IgA nephropathy with eicosapentaenoic acid (EPA): A two-year prospective trial. *Clin Nephrol* 31: 128–131, 1989
- Cheng IKP, Chan PCK, Chan MK: The effect of fish-oil dietary supplement on the progression of mesangial IgA glomerulonephritis. *Nephrol Dial Transplant* 5: 241–246, 1990
- Donadio JV Jr: Omega-3 polyunsaturated fatty acids: A potential new treatment of immune renal disease. *Mayo Clin Proc* 66: 1018–1028, 1991
- Pettersson EE, Rekola S, Berglund L, Sundqvist KG, Angelin B, Diczfalusy U, Bjorkhem I, Bergstrom J: Treatment of IgA nephropathy with omega-3-polyunsaturated fatty acids: A prospective, double-blind, randomized study. *Clin Nephrol* 41: 183–190, 1994
- Donadio JV Jr, Bergstralh EJ, Offord DP, Spencer DC, Holley KE: A controlled trial of fish oil in IgA nephropathy. *N Engl J Med* 331: 1194–1198, 1994
- Donadio JV, Holub BJ, Bergstralh EJ: *Effects of n-3 Fatty Acids: Prevention and Treatment in Vascular Disease*, Bi & Gi Publishers, Verona, Springer Verlag, 1995, pp 173–180
- Donadio JV, Grande JP, Bergstralh EJ, Dart RA, Larson TS, Spencer DC: The long-term outcome of patients with IgA nephropathy treated with fish oil in a controlled trial. *J Am Soc Nephrol* 10: 1772–1777, 1999
- Donadio JV, Larson TS, Bergstralh EJ, Grande JP: A randomized trial of high-dose compared with low-dose omega-3 fatty acids in severe IgA nephropathy. *J Am Soc Nephrol* 12: 791–799, 2001
- Dillon JJ: Fish oil therapy for IgA nephropathy: Efficacy and interstudy variability. *J Am Soc Nephrol* 8: 1739–1744, 1997
- Hogg RJ, Lee J, Nardelli N, Julian BA, Cattran D, Waldo B, Wyatt R, Jennette JC, Sibley R, Hyland K, Fitzgibbons L, Hirschman G, Donadio JV Jr, Holub BJ: Clinical trial to evaluate omega-3 fatty acids and alternate day prednisone in patients with IgA nephropathy: Report from the Southwest Pediatric Nephrology Study Group. *Clin J Am Soc Nephrol* 1: 467–474, 2006
- Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A: A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. *Pediatrics* 58: 259–263, 1976
- Schwartz GJ, Gauthier B: A simple estimate of glomerular filtration rate in adolescent boys. *J Pediatr* 106: 522–526, 1985
- Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 16: 31–41, 1976
- Rosano TG, Ambrose RT, Wu AHB, Swift TA, Yadegari P: Candidate reference method for determining creatinine in serum: Method development and interlaboratory validation. *Clin Chem* 36: 1951–1955, 1990
- Welch MJ, Cohen A, Hertz HS, Ng KJ, Schaffer R, Van der Lijn P, White E 5th: Determination of serum creatinine by isotope dilution mass spectrometry as a candidate definitive method. *Anal Chem* 58: 1681–1685, 1986
- Holub BJ, Skeaff CM: Nutritional regulation of cellular phosphatidylinositol. *Methods Enzymol* 141: 234–245, 1987
- Holman RT, Johnson SB, Bibus D, Spencer D, Donadio JV Jr: Essential fatty acid deficiency profiles in idiopathic immunoglobulin A nephropathy. *Am J Kidney Dis* 23: 648–654, 1994
- Ruggenenti P, Perna A, Mosconi L, Mosconi L, Pisoni R, Remuzzi G; on behalf of “The Gruppo Italiano Di Studi Epidemiologici in Nefrologia” (GISEN): Urinary protein excretion rate is the best independent predictor of ESRF in non-diabetic proteinuric chronic nephropathies. *Kidney Int* 53: 1209–1216, 1998
- Ruggenenti P, Gaspari F, Perna A, Remuzzi G: Cross sectional longitudinal study of spot morning urine protein:creatinine ratio, 24 hour urine protein excretion rate, glomerular filtration rate, and end stage renal failure in chronic renal disease in patients without diabetes. *BMJ* 316: 504–509, 1998
- Donadio JV, Bergstralh EJ, Grande JP, Rademacher DM: Proteinuria patterns and their association with subsequent end-stage renal disease in IgA nephropathy. *Nephrol Dial Transplant* 17: 1197–2003, 2002
- Bonna KH, Bjerve KS, Straume B, Gram IT, Thelle D: Effect of eicosapentaenoic and docosahexaenoic acids on blood pressure in hypertension. *N Engl J Med* 322: 795–801, 1990
- Albert CM, Campos H, Stampfer MJ, Ridker PM, Manson JE, Willett WC, Ma J: Blood levels of long-chain n-3 fatty acids and the risk of sudden death. *N Engl J Med* 346: 1113–1118, 2002
- Guallar E, Hennekens CH, Sacks FM, Willett WC, Stampfer MJ: A prospective study of plasma fish oil levels and incidence of myocardial infarction in US male physicians. *J Am Coll Cardiol* 25: 387–394, 1995
- Wang C, Harris WS, Chung M, Lichtenstein AH, Balk EM, Kupelnick B, Jordan HS, Lau J: n-3 Fatty acids from fish or fish oil supplements, but not a-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: A systematic review. *Am J Clin Nutr* 84: 5–17, 2006
- Arteburn LM, Hall EB, Owen H: Distribution, interconversion, and dose response of n-3 fatty acids in humans. *Am J Clin Nutr* 83[Suppl]: 1467S–1476S, 2006
- Tozawa M, Iseki K, Iseki C, Oshiro S, Ikemiya Y, Takishita S: Influence of smoking and obesity on the development of proteinuria. *Kidney Int* 62: 956–962, 2002
- Ramirez SP, McClellan W, Port FK, Hsu SIH: Risk factors for proteinuria in a large, multiracial, southeast Asian population. *J Am Soc Nephrol* 13: 1907–1917, 2002
- Iseki K, Ikemiya Y, Kinjo K, Inoue T, Iseki C, Takishita S: Body mass index and the risk of development of end-stage renal disease in a screened cohort. *Kidney Int* 65: 1870–1876, 2004