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【 ORIGINAL ARTICLE 】

The Renoprotective Effects of Docosahexaenoic Acid as an Add-on Therapy in Patients Receiving Eicosapentaenoic Acid as Treatment for IgA Nephropathy: A Pilot Uncontrolled Trial

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Abstract:

Objective Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) have been reported to have beneficial effects in patients with IgA nephropathy (IgAN). Although DHA and EPA have different mechanisms of action, no study to date has assessed their individual actions in patients with IgAN. This study therefore analyzed the effects administering DHA in addition to EPA for the treatment of IgAN.

Methods Twenty-one IgAN patients who were being treated with EPA (1,800 mg/day) were switched to EPA (1,860 mg/day) and DHA (1,500 mg/day). The changes in their clinical parameters from 6 months before to 6 months after switching treatment were analyzed.

Results The triglyceride levels did not change during treatment with EPA alone, but tended to decrease-although not to a statistically significant extent-after the switch. The patients' low-density-lipoprotein cholesterol, blood pressure, proteinuria, and hematuria levels were similar before and after switching. The estimated glomerular filtration rate (eGFR) tended to decrease during EPA therapy, but became stable after switching and the median %⊿eGFR changed from -7.354% during EPA therapy to +1.26% during the 6 months after switching to EPA and DHA therapy (p=0.00132), and renal the function remained stable for another 6 months. Moreover, the median %⊿eGFR during the 6 months after switching was significantly higher in comparison to IgAN patients who were treated with EPA alone as a control (-3.26%, p=0.0361). No clinical parameters were independently associated with a stable renal function without switching to DHA/EPA.

Conclusion The addition of DHA to EPA stabilized the renal function of IgAN patients, and it seemed that there were pleiotropic effects beyond the improvement of the clinical parameters.

Key words: IgA nephropathy, fish oil, omega-3 polyunsaturated acid, eicosapentaenoic acid, docosahexaenoic acid

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Introduction

Almost 50 years has passed since IgA nephropathy (IgAN) was first reported in 1968 (1). A long-term analysis over a 30-year period indicated that approximately 50% of IgAN patients progressed to end stage renal disease during their follow-up period (2, 3). The prognosis has been improved by various therapies, including tonsillectomy, steroids, immunosuppressive agents, renin angiotensin system inhibitors, anti-platelet agents, and omega-3 polyunsaturated fatty acids (O3PUFAs) (2, 4). O3PUFAs include eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and alpha linolenic acid. Alpha linolenic acid is constructed from 18 carbon chains with 3 double bonds, EPA is converted from alpha linolenic acid to add 2 further carbon chains and 2 further double bonds (EPA; 20:5ω-3), DHA is converted from EPA to add 2 further carbon chains and 1 further dou-

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ble bond (DHA; 22: 6ω-3); these conversions affect the physiological actions of each of the O3PUFAs (5). Among these three fatty acids, EPA and DHA have been reported to have beneficial effects on IgA nephropathy (6-10). The beneficial effects of combination therapy with DHA with EPA were shown in almost all of these reports; however, no reports have analyzed the differences in the effects of DHA and EPA. Thus, the present study analyzed the effects of the additional administration of DHA to IgAN patients treated with EPA.

Materials and Methods

Patients

This retrospective cohort analysis enrolled patients with IgAN who were switched from treatment with EPA alone (1,800 mg/day) to treatment with EPA (1,860 mg/day) and DHA (1,500 mg/day) due to uncontrolled dyslipidemia or at the patient's request between May and August 2014. IgAN patients who were treated with EPA alone (1,800 mg/day) were enrolled as a control group, and the percent change in their estimated glomerular filtration rate (%⊿eGFR) was analyzed in the latter half of 2014. Patients with systemic diseases, such as collagen disease, diabetes mellitus, chronic liver disease, malignancy, and abnormal hypergammaglobulinemia, were excluded from this study. The patients who had previously been treated with steroids or immunosuppressive agents were included; however, patients who were treated with steroids or immunosuppressive agents during the observation period were excluded. Patients receiving other conservative treatments, including antihypertensive agents, anti-platelet agents, and statins, were included at the discretion of each physician. The data collected at the time of switching from EPA to EPA and DHA (baseline) included: sex, age, systolic blood pressure (S-BP), diastolic blood pressure (D-BP), time after renal biopsy, eGFR, urinary protein excretion (U-Prot), and urinary red blood cell (U-RBC) count; the levels of total protein (TP), blood urea nitrogen (BUN), serum creatinine (Cre), serum uric acid (UA), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), and triglycerides (TG); and the clinical grade according to the *Clinical Guidelines for IgA Nephropathy in Japan* (third version) (11). The S-BP, D-BP, LDL-C, and TG levels, eGFR, U-Prot concentration, and U-RBC count were also measured at 6 months and 3 months before, and 3 months and 6 months after switching from EPA to EPA and DHA. The eGFR was measured at 9 and 12 months after switching. The eGFR was calculated using the isotope dilution mass spectrometry modification of diet in renal disease equation for Japanese individuals [$eGFR=194\times S\text{-}Cre^{-1.094}\times age^{-0.287}\times 0.739$ (if female)] (12).

This retrospective cohort study was conducted in accordance with the Declaration of Helsinki, and was approved by the Medical Ethics Committee and Institutional Review Board of Tokyo Women's Medical University (#3912).

Statistical analysis

Normally distributed data were expressed as the mean ± standard deviation (SD) and were compared by an analysis of variance (ANOVA); skewed data were expressed as the median and interquartile range (IQR) and were compared using the Wilcoxon signed rank test or Mann-Whitney *U*-test. A univariate logistic analysis was performed to evaluate the factors associated with a stabilized renal function. All of the statistical analyses were performed using the JMP 11.0.0 software program (SAS Institute, Cary, USA). p values of < 0.05 were considered to indicate statistical significance.

Results

Baseline data

Twenty-one patients (male, n=13; female, n=8; mean ± SD age, 45.2 ± 11.4 years) were enrolled in the present study; their clinical and laboratory findings at the time of switching from EPA monotherapy to the combination of EPA and DHA are shown in Table 1. Hypertension was well controlled, with a mean ± SD S-BP and D-BP of 120.3 ± 9.25 mmHg and 70.6 ± 7.47 mmHg, respectively. The median duration after renal biopsy was 13.5 years. The renal function was slightly decreased, as the mean ± SD eGFR was 48.3 ± 25.7 mL/min/1.73 m^2, and 15 patients (68.2%) had chronic kidney disease grade 3. The patients' LDL-C levels were well controlled, but their TG levels were not, with a median level of 188.5 mg/dL. The median U-Prot concentration was 0.22 g/g Cre, and the median U-RBC count was 1.0 cell/HPF. The clinical grades, according to the Japanese clinical guidelines for IGAN (11), were as follows: clinical grade I, n=5; grade II, n=1; and grade III, n=15. Table 1 shows the treatments that were administered during the follow-up period. No patients were treated with corticosteroids or immunosuppressive agents, whereas 19 (90.5%) were treated with renin angiotensin system inhibitors, nine (42.9%) were treated with calcium channel blockers, 15 (71.4%) were treated with statins, and 14 (66.7%) were treated with anti-hyperuricemic agents.

Alterations in the patient's lipid levels

Figure 1 shows TG and LDL-C levels every 3 months, starting 6 months before and ending 6 months after switching therapy; each point represents the average of 3 months of consecutive data for each patient. During treatment with EPA alone, the TG levels remained high, at approximately 170-180 mg/dL; however, after switching to EPA and DHA, the TG levels decreased to approximately 140 mg/dL; however, this difference was not statistically significant (p= 0.6545) (Fig. 1a). The LDL-C level remained low, at approximately 90-100 mg/dL, both before and after switching treatment (Fig. 1b).

Table 1. Clinical and Laboratory Findings and Treatment at Baseline.

	Unit	Data
Sex	(Male/female)	13/8
Age	(Years)	45.2±11.4
S-BP	(mmHg)	120.3±9.25
D-BP	(mmHg)	70.6±7.47
Duration after renal biopsy	(Years)	13.5 (3.0–17.0)
TP	(g/dL)	6.77±0.30
BUN	(mg/dL)	18.3 (11.7–29.1)
Cre	(mg/dL)	1.49±0.69
eGFR	(mL/min/1.73 m^2)	48.3±25.7
UA	(mg/dL)	5.5±1.14
LDL-C	(mg/dL)	91.9±23.6
HDL-C	(mg/dL)	53.1±17.8
TG	(mg/dL)	188.5 (115.5–228.8)
U-Prot	(g/g·Cre)	0.22 (0.12–0.71)
U-RBC	(counts/HPF)	1.0 (0.1–10)
Clinical grade	(I/II/III)	(5/1/15)
Steroids	Number (%)	0 (0%)
Immunosuppressive agents	Number (%)	0 (0%)
RAS-I	Number (%)	19 (90.5%)
Calcium channel blockers	Number (%)	9 (42.9%)
Other anti-hypertensive agents	Number (%)	4 (19.1%)
Statins	Number (%)	15 (71.4%)
Anti-hyperuricemic agents	Number (%)	14 (66.7%)
Anti-platelet agents	Number (%)	3 (14.3%)

S-BP: systolic blood pressure, D-BP: diastolic blood pressure, TP: total protein, BUN: blood urea nitrogen, Cre: serum creatinine, eGFR estimated glomerular filtration ratio, UA: serum uric acid, LDL-C: low-density lipoprotein-cholesterol, HDL-C: high-density lipoprotein-cholesterol, TG: triglycerides, U-Prot: urinary protein excretion, U-RBC: urinary red blood cell, RAS-I: inhibitors of renin-angiotensin system

Alterations in blood pressure and urinary abnormalities

The patients' S-BP and D-BP were well controlled during the follow-up period, with a mean S-BP of <120 mmHg and a mean D-BP of <75 mmHg (Fig. 1c). The U-Prot concentration and U-RBC count remained low both before and after switching treatment, with a median U-Prot concentration of <0.5 g/g Cre and a median U-RBC count of 1.0 cell/HPF, with no significant differences (Fig. 1d and e).

Alterations in the mean eGFR, and each patient's eGFR and ⊿eGFR values

Figure 2a shows the mean eGFR over time, and Fig. 2b shows each patient's eGFR, starting at 6 months before to 12 months after switching treatment. The mean eGFR decreased during EPA treatment, becoming stable after switching to EPA and DHA; however the difference was not statistically significant (p=0.9996). The assessment of individual patients showed that-in many patients-the eGFR decreased from 6 months before the switch in treatment to baseline, becoming stable, or increasing over the 12 months after the switch. The median of the slope of the ⊿eGFR from 6 months before switching treatment to baseline was -7.35%, whereas the slope from baseline to 6 months after switching treatment was 1.26%; this change was statistically significant (p=0.0132) Fig. 2c. The slope from 6 to 12 months after switching treatment was 0.37%; the change from baseline to 6 months after switching treatment was not significantly different (p=0.6163). Moreover, the slope from baseline to 6 months after treatment in IgAN patients treated with EPA and DHA was significantly higher than the slope for the same duration in IgAN patients treated with EPA alone (control group; n=33) [1.26 (4.1 and 6.77)% vs. -3.26 (-8.63 and 1.52)%, p=0.0361].

Factors associated with the stabilization of the renal function

A univariate regression analysis was performed to assess the factors independently associated with the stabilization of the renal function (Table 2). The factors that were analyzed included sex, age, mean arterial pressure (MAP), eGFR, LDL-C, TG, U-Prot, U-RBC, ⊿MAP, ⊿eGFR, ⊿LDL-C, ⊿TG, ⊿U-Prot, and the additional administration of DHA

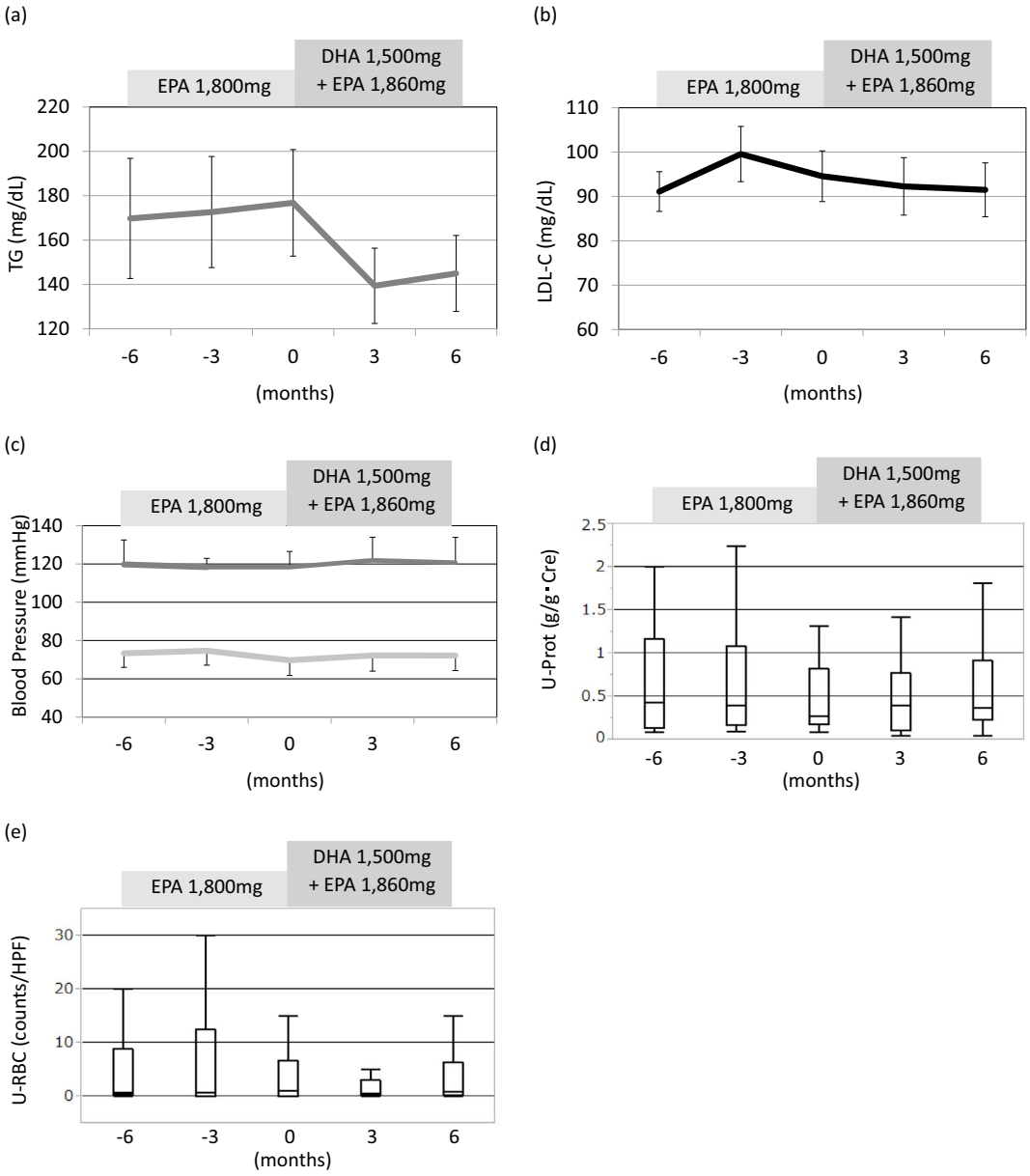

Figure 1. **The levels of (a) triglycerides (TG), (b) LDL cholesterol (LDL-C), (c) blood pressure and (d, e) the urinary findings starting 6 months before, and at 3-month intervals until 6 months after switching from EPA monotherapy to a combination of EPA and DHA. a: The patients' TG levels were unchanged from 6 months before switching treatment to baseline, but tended to decrease at 3 and 6 months after the switch (p=0.6545). The results are expressed as the mean ± SE, and were compared by an ANOVA. b: The patients' LDL-C levels remained unchanged from 6 months before to 6 months after switching treatment (p=0.8456). The results are expressed as the mean ± SE, and were compared by an ANOVA. c: The patients' S-BP (p=0.7805) and D-BP (p=0.3710) levels remained unchanged from 6 months before to 6 months after switching treatment. The results are expressed as the mean ± SD and were compared by an ANOVA. d: The patients' U-Prot concentrations remained unchanged from 6 months before to 6 months after switching treatment (p=0.7956). The results are expressed as the median (IQR) and were compared by a Wilcoxon signed-rank test. e: The patients' U-RBC concentrations remained unchanged from 6 months before to 6 months after switching treatment (p=0.8851). The results are expressed as the median (IQR), and were compared by a Wilcoxon signed-rank test.**

to patients receiving EPA treatment. With the exception of DHA and EPA treatment, none of these factors was independently associated with the stabilization of the renal function. The renal function of the patients who received DHA and EPA was significantly improved in comparison to those who received EPA alone (odds ratio, 3.20; 95% confidence index (CI), 1.05-10.3; p=0.0415).

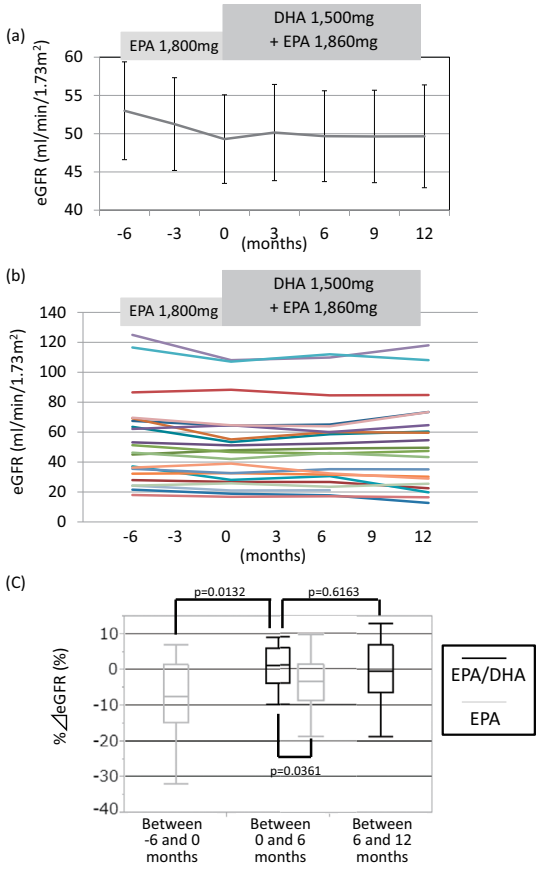

Figure 2. **(a) The mean eGFR, (b) individual eGFR's, and (c) median ΔeGFR, at 3-month intervals starting from 6 months before switching and continuing until 12 months after switching from EPA monotherapy to a combination of EPA and DHA. a: The mean eGFR tended to decrease from 6 months before switching treatment to baseline, but did not change after switching (p=0.9996). The results are expressed as the mean ± SE and were compared by an ANOVA. b: In almost all patients, the eGFR decreased before switching treatment, but increased or stabilized after switching. c: The median ΔeGFR decreased by 7.35 (14.89 and 1.56) % before switching treatment, but increased by 1.26 (4.13 and 6.77) % during the 6 months after switching-a difference that was statistically significant (p=0.0132) according to a Mann-Whitney *U*-test-and remained stable from 6 months to 12 months after switching [0.37 (6.24 and 6.91) %, p=0.6163]. The median ΔeGFR decreased in IgAN patients who were treated with EPA/DHA after switching and was significantly higher than that in patients who were treated with EPA alone (control) [1.26 (-4.1 and 6.77) % vs. -3.26 (-8.63 and 1.52) %, p=0.0361].**

Adverse events

None of these patients experienced any adverse events in the 12 months after switching therapy.

Discussion

DHA and/or EPA have been reported to have lipid-modulating effects; reduce plasma TG levels (13); have anti-hypertensive effects (14); have beneficial effects on non-alcoholic fatty liver disease (15, 16); improve vascular compliance and vasodilatation to make atherosclerotic plaques stable (17, 18); and prevent stroke (19) and cardiovascular events (20-22). Physiologically, O3PUFAs have been reported to have anti-inflammatory effects and to suppress pro-inflammatory cytokines, lymphocyte proliferation, cytotoxic T-cell activity, natural killer cell activity, macrophage-mediated cytotoxicity, neutrophil/monocyte chemotaxis, and the expression of major histocompatibility complex class II, and antigens (23). These anti-inflammatory effects seem to benefit the organs (5, 13-22).

With regard to IgAN, several reports have shown that DHA and/or EPA can improve or stabilize the renal function (7), reduce proteinuria (6, 8-10), and reduce hematuria (8). However, the effects of the dose of EPA and DHA are unclear. One study reported that DHA and EPA had dose-dependent effects on the reduction of proteinuria (6), whereas other studies reported that the dosage of DHA and EPA was not associated with the reduction of proteinuria or the protection of the renal function (10, 24, 25). Moreover, no studies (to our knowledge) have compared the effects of EPA and DHA in patients with IgAN, despite EPA and DHA having some different effects. This retrospective study analyzed the add-on effects of DHA in IgAN patients who were being treated with EPA. We found that the addition of DHA stabilized the renal function, with the eGFR slope changing from -7.35% during 6 months before switching to +1.26% during the first 6 months after switching, and 0.37% during the following 6 months. However, there were no significant differences in blood pressure, U-Prot concentration, U-RBC count, or the TG and LDL-C levels. Moreover, a logistic regression analysis could not identify any factors that were independently associated with the stabilization of the renal function other than the addition of DHA to EPA treatment. These results indicated that the renoprotective effects of DHA and EPA depended on their physiological pleiotropic effects, but not on their anti-proteinuric, anti-hyperlipidemic, or anti-hypertensive effects.

These pleiotropic effects have been validated by several basic experiments. EPA and DHA have been shown to reduce the expression of several pro-inflammatory cytokines (26-30) and pro-fibrotic genes (31, 32) in mesangial cells and a mouse model of IgAN. Those effects led to a decrease in serum IgA, serum IgA immunocomplexes, the deposition of IgA in the mesangium (29, 30), the inhibition of the mesangial cell proliferation (33) and matrix (34), and a reduction of proteinuria (34). These reports indicate that some of the effects of EPA and DHA differ, supporting our hypothesis that the *in vivo* activities of DHA in patients with IgAN differ from those of EPA and that the two together have pleiotropic renoprotective effects beyond the anti-proteinuric and anti-hypertensive effects.

This study is associated with several limitations. It was a retrospective cohort analysis, with relatively small study population. To our knowledge, however, this is the first

Table 2. Univariate Logistic Analysis to Relate with Stabilizing Renal Function.

	Odds ratio	95%CI	p
Male (vs. female)	1.33	0.19–11.9	0.7750
Age (per 10-year decrease)	1.80	0.70–6.00	0.2300
MAP (per 10-mmHg decrease)	0.72	0.15–2.87	0.6455
eGFR (per 20 mL/min/1.73 m^2 increase)	1.29	0.58–3.01	0.5255
LDL-C (per 20 mg/dL decrease)	1.71	0.44–3.19	0.8538
TG (per 50 mg/dL decrease)	0.67	0.30–1.21	0.1975
U-Prot (per 0.2 g/g·Cre decrease)	1.94	0.90–6.62	0.0987
U-RBC (per 10/HPF decrease)	1.22	0.52–3.54	0.6582
⊿ MAP (decrease vs. increase or not)	1.33	0.14–10.9	0.7880
⊿ LDL-C (decrease vs. increase)	8.00	0.84–187.7	0.0724
⊿ TG (decrease vs. increase)	1.11	0.15–10.1	0.9183
⊿ U-Prot (decrease vs. increase)	3.00	0.28–33.0	0.3442
DHA and EPA (vs. EPA alone)	3.20	1.05–10.3	0.0415

MAP: mean arterial pressure, eGFR estimated glomerular filtration ratio, LDL-C: low-density lipoprotein-cholesterol, TG: triglycerides, U-Prot: urinary protein excretion, U-RBC: urinary red blood cell, DHA: docosahexaenoic acid, EPA: eicosapentaenoic acid

study to show the add-on effect of DHA, when it is administered IgAN patients receiving EPA. We consider this report to be a pilot study, and we believe that this is the first step connect to a randomized control trial.

In conclusion, the addition of DHA to EPA better protected the renal function of IgAN patients through pleiotropic effects beyond the anti-proteinuric, anti-hypertensive, and anti-dyslipidemic effects of these agents.

The authors state that they have no Conflict of Interest (COI).

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