Effect of Fish Oil on Oxidative Stress, Lipid Profile and Renal Function in IgA Nephropathy

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Abstract

The omega-3 polyunsaturated fatty acids in fish oil have been shown to produce beneficial effects, such as a reduction in blood pressure, proteinuria, lipid levels and inflammation. Aggregated immunoglobulin A obtained from IgA nephropathy patients induced greater oxygen free radicals in polymorphonuclear leukocytes than other glomerulopathy. All of which may affect the course of IgA nephropathy.

Twenty-three adult patients with biopsy proven IgA nephropathy, with proteinuria more than 1 g/day, serum creatinine less than 3 mg/dl and blood pressure control less than 130/80 mmHg were given omega-3 polyunsaturated fatty acids (PUFA) in the form of an Omacor® capsule 4 g/day equivalent to eicosapentaenoic acid (EPA) 1.88 g and docosahexaenoic acid (DHA) 1.48 g for 6 months. A 3 to 6 month follow-up was planned, with monthly evaluations of the patients.

By six months, the serum triglyceride was significantly reduced (143.45 ± 62.65 *vs* 91 ± 42.89 mg/dl, $p = 0.002$), serum cholesterol was also reduced but not statistically significant (234.16 ± 56.29 *vs* 219.76 ± 51.25 mg/dl, $p = 0.07$). There was a trend of increased serum high density lipoprotein (HDL)-cholesterol (39.26 ± 10.56 *vs* 42.72 ± 8.37 mg/dl, $p = 0.056$). Urine beta-2-microglobulin was elevated in IgA patients and decreased statistically significant after 3 months (453 ± 580 *vs* 308 ± 274 µg/24 h, $p < 0.001$) and 6 months of fish oil therapy (453 ± 580 *vs* 142 ± 182, $p < 0.03$) while urine N-acetyl-glucosaminidase (NAG) was of no significant difference both before and after fish oil administration (21 ± 10 *vs* 22 ± 10 and 21 ± 9 U/24 h, $p = 0.08$). Plasma malondialdehyde (MDA), the end product of oxidative stress was statistically, significantly decreased (1.09 ± 0.51 *vs* 0.89 ± 0.49 nmol/L, $p = 0.003$). The study did not show any change in blood pressure, proteinuria, or serum creatinine.

The authors conclude from the results of this study that patients with idiopathic IgA nephropathy with proteinuria and mildly reduced GFR did not benefit from short-term treatment with 4 g per

day of omega-3 PUFA regarding the total protein excretion and glomerular filtration rate (GFR), but the advantage was the improvement in tubular dysfunction, lipid profiles, and oxidative stress.

Key word : Fish Oil, Oxidative Stress, IgA Nephropathy

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IgA nephropathy, previously known as Berger's disease[1] thought to be a benign condition of macroscopic hematuria associated with upper respiratory infections, is now regarded as a major cause of end-stage renal disease. Longer observation showed that 15 per cent to 30 per cent of these patients progress to end stage renal failure after 20 years of clinical manifestations[2-4]. Several approaches to treatment have been promoted, including gluten-free diets, tonsillectomies, dipyridamole, phenytoin, steroids, cyclosporine, angiotensin-converting enzyme inhibitors and mycophenolate mofetil[4-6]. Because the pathogenesis remains enigmatic, therapy to ameliorate disease progression cannot be disease-specific. Drugs that slow disease progression are becoming available, including omega-3 (n-3) fatty acids.

In 1984, Hamazaki et al[7] reported that therapy with omega-3 fatty acids, in the form of fish oil, preserved renal function in individuals with IgA nephropathy. The active ingredient of fish oil was considered to be responsible for reducing circulating immune complexes and lowering triglycerides and platelet aggregation. Several studies have demonstrated the role of oxidant injury in IgA nephropathy [8-10] and fish oil has been found to reduce oxidative stress[11]. Therefore, the authors designed this study to investigate the effects of fish oil on renal functions, oxidative stress, and lipid profiles in patients with IgA nephropathy.

MATERIAL AND METHOD

Patients and study design

All 23 adult patients whose renal biopsy revealed IgA nephropathy with proteinuria more than 1 g/day and serum creatinine less than 3 mg/dl and blood pressure controlled 130/80 mmHg without angiotensin converting enzyme inhibitors (ACEI) were enrolled in this study. The exclusion criteria was renal allergy to marine products, low platelets and platelet dysfunction, concomitant antiplatelets or anticoagulant, chronic liver disease and chronic obstruction lung disease.

Blood and urine collection were performed before starting the treatment and at the end of 3 and 6 months. They included 24 hour urine protein, urine beta-2-microglobulin[12] and N-acetyl-glucosaminidase (NAG)[13], serum urea nitrogen, creatinine, cholesterol, triglycerides, HDL-cholesterol, and end product of lipid peroxidation: malondialdehyde (MDA)[14].

Omacor® was obtained from the ASTRA ZENECA pharmacy, each capsule contained eicosapentaenoic acid (EPA) 0.468 g and docosahexaenoic acid (DHA) 0.34 g and 2 capsules twice daily for 6 months were administered to each patient.

Statistical analysis

All case record files were evaluated and analyzed using the SPSS program for window packages. The data is presented as mean ± SD or per cent. Student's *t*-test or ANOVA was used for analysis of continuous variables. The p-value of less than 0.05 was considered significant.

RESULTS

Baseline characteristics of the IgA patients are shown in Table 1. Most of them were female with hypertension of 43 per cent, the mean proteinuria was 2.67 ± 1.62 g per day and serum creatinine was 1.32 ± 0.7 mg/dl.

Proteinuria, urinary enzymes and creatinine clearance

Of the 23 patients who received fish oil therapy for 6 months, the blood pressure was reduced compared with the control period but there was no statistical significance. The patients tolerated the fish oil without any side effects. The level of proteinuria, plasma creatinine, and creatinine clearance was not statistically significantly different compared to the run-in period as shown in Table 2.

Urinary enzymes, beta-2-microglobulin and NAG were measured in IgA patients during fish oil therapy which revealed a difference in beta-2-microglobulin excretion before and after 3, 6 months treatment (453.4 ± 580 *vs* 308 ± 274 and 142 ± 182, p = 0.36, p = 0.03, respectively) as shown in Fig. 1 and Table 2. There was no statistically significant difference in urine NAG.

Table 1. Baseline characteristics of the IgA patients.

Age (yr)	33.39 ± 8.8
Male sex (%)	26
Hypertension (%)	43
Blood pressure	
Systolic (mmHg)	123 ± 11
Diastolic (mmHg)	78 ± 12
24 h urine protein (g/day)	2.67 ± 1.62
Creatinine clearance (ml/min)	77.45 ± 31.4
Plasma creatinine (mg/dl)	1.32 ± 0.70
Plasma total cholesterol (mg/dl)	227.6 ± 59
Plasma triglycerides (mg/dl)	161 ± 55
Plasma HDL-cholesterol (mg/dl)	39.2 ± 10.6

Effect of fish oil and oxidative stress

In the present study the authors measured malondialdehyde (MDA) the end product of oxidative stress, as in the plasma of IgA patients which showed decreased level of MDA which was statistically significant. The low value was already observed after 2 weeks of fish oil treatment and continued to 6 months (1.22 ± 0.57 *vs* 0.88 ± 0.49 mmol/L, $p < 0.003$) as shown in Table 2.

Effect of fish oil on lipid profiles

The cholesterol levels in IgA patients were not high but the triglycerides were increased from the beginning of the study. However, after 6 months of fish oil treatment, both the cholesterol and triglycerides were decreased and HDL-cholesterol was also increased. But only the triglycerides were statistically significantly decreased compared to the control period (143.45 ± 62.65 *vs* 91 ± 42, $p < 0.002$) as shown in Table 3.

Table 2. Change in blood pressure, serum creatinine, creatinine clearance, plasma MDA, proteinuria, urine β_2m and NAG after 3 and 6 months of fish oil administration (n = 23).

	Month 0	Month 3	Month 6
BP			
Systolic (mmHg)	123 ± 11	121 ± 11	118 ± 9
Diastolic (mmHg)	78 ± 12	76 ± 8	75 ± 9
Proteinuria (g/day)	2.67 ± 1.63	2.28 ± 2.3	2.29 ± 2.5
Plasma creatinine (mg/dl)	1.32 ± 0.7	1.37 ± 0.78	1.14 ± 0.75
Ccr (ml/min)	77.44 ± 31.42	74.62 ± 30.73	73.56 ± 29.32
Plasma MDA (mmol/L)	1.22 ± 0.57	1.13 ± 0.7	0.88 ± 0.49*
Urine β_2m (ug/24 h)	453.4 ± 580	308 ± 207	142 ± 182*
Urine NAG (U/24 h)	21.9 ± 10.4	22.3 ± 10.2	21.5 ± 9.7

*$p < 0.05$ compared to month 0

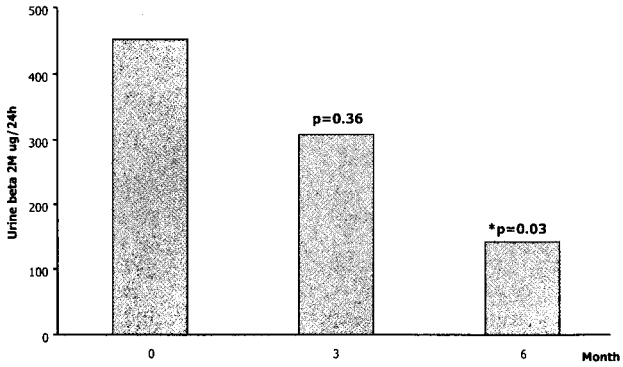

Fig. 1. Urine beta-2-microglobulin after fish oil therapy in IgA patients.

DISCUSSION

Recently, Donadio et al[15] reported in a double-blinded study, in a large consortium of IgA patients associated with proteinuria of more than 1 g/d, that 2-year fish oil supplementation reduced the proteinuria and retarded renal progression. However, several other studies showed lack of such a renoprotective effect of fish oil[16-18]. In the present study, the authors could not demonstrate a decrease in proteinuria or improvement in creatinine clearance after 6 months of fish oil therapy. It could be that the time was too short to see the benefit of fish oil. The active element in fish oil is omega-3 polyunsaturated fatty acid[2,15]. It could be reasoned that an increase in the renal content of eicosapentaenoic acid reduced arachidonic acid availability for thomboxane production and promoted series 5 leukotrienes and series 3 prostaglandins with subsequent suppression of glomerular inflammatory reaction and scarring. In the present study the authors observed that there was a trend of reduction in proteinuria but of no statistical significance. As well as the level of blood pressure which seemed to decrease but was of no statistical significance. The triglycerides level was markedly reduced after fish oil which could be seen after only 2 weeks fish oil supplementation. The average reduction was 40 per cent which corresponded with other previous reports[19-21]. The effect of fish oil on triglyceride reduction involved an increase in lipolysis, beta-oxidation, a decrease in synthesis of triglycerides, VLDL, and small dense low density lipoprotein (LDL)[19-21]. The study of Syrjänen et al[22] showed that hypertriglyceridemia at the time of diagnosis of IgA nephropathy was important and sometimes an underestimated predictor of poor outcome in IgA nephropathy. The observation of an association between hypertriglyceridemia and progression of IgA nephropathy is in agreement with the findings of Samuelsson et al[23,24]. The authors could not demonstrate a change in cholesterol and HDL-cholesterol in the present study. In the present study, the authors also found elevated urine beta-2-microglobulin, which was the marker for tubular dysfunction from the beginning of the study and it was reduced after 3 and 6 months of fish oil treatment. The pathogenesis of IgA nephropathy might involve tubular cells and cause tubular damage, reversed by omega-3 PUFA shown in the present study. Urine NAG was rather less specific than beta-2-microglobulin and did not show any statistically significant difference.

Oxidative stress has been found in leukocytes[25], mesangial cells[26] in human IgA nephropathy and in rat macrophages[27] in experimental IgA nephropathy. The severity of proteinuria in patients with IgA nephropathy has been correlated to increased superoxide production[28]. Recently, several evidences supported the concept that the pathogenesis of IgA nephropathy is related to free radical injury[25,28]. Therefore, fish oil supplementation in the present study showed reduction of malondialdehyde, which may account for part or of the beneficial effects. The present study was the first study to demonstrate that fish oil could reduce the MDA level. The rational for using fish oil in IgA nephropathy is based on experi-

Table 3. Effect of fish oil on lipid profiles.

Lipid profiles (mg/dl)	Month 0	Month 3	Month 6
Total cholesterol	227 ± 59	218 ± 43	221 ± 46
Triglycerides	160 ± 55	93 ± 46*	94 ± 43*
HDL-cholesterol	39 ± 10	39 ± 9	41 ± 8

* $p < 0.002$

mental studies *in vitro* and *vito* that omega-3 PUFA incorporated in cell membrane phospholipids to produce favorable eicosanoid product when lipid peroxidation occurs in the glomerular basement membranes: thomboxane A_3 and leukotrienes B_5. Both had less chemo tactic factors for leukocytes, less vasoconstriction and mesangial cell contraction[29,30]. The omega-3 PUFA also inhibits production of the pro-inflammatory cytokines interleukin-1 and tumor necrosis factor by mononuclear cells. Therefore, free radicals from leukocytes and macrophages were inhibited which led to less oxidant injury shown in this study. The present findings support the importance of fish oil in the reduction of tubular dysfunction, oxidative stress and hypertriglyceridemia. Prolonged treatment should be explored for more beneficial effects in IgA nephropathy.

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REFERENCES

1. Berger J, Hinglais N. Les depots intracapillaires d'IgA-IgG. J Urol Nephrol 1968; 74: 694-5.
2. Donadio JV Jr, Grande JP. Immunoglobulin A nephropathy: A clinical perspective. J Am Soc Nephrol 1997; 8: 1324-32.
3. Galla JH. Perspectives in clinical nephrology. IgA nephropathy. Kidney Int 1995; 47: 377-87.
4. Julian BA, Waldo FB, Rifai A, Mestecky J. IgA nephropathy, the most common glomerulonephritis worldwide. A neglected disease in the United States? Am J Med 1988; 84: 129-32.
5. Cattran DC, Greenwood C, Ritchie S. Long-term benefits of angiotensin-converting enzyme inhibitor therapy in patients with severe immunoglobulin A nephropathy: A comparison to patients receiving treatment with other antihypertensive agents and to patients receiving no therapy. Am J Kidney Dis 1994; 23: 247-54.
6. Scheinman JI, Trachtman H, Lin CY, Langman CB, Chan JC. IgA nephropathy: to treat or not to treat? Nephron 1997; 75: 251-8.
7. Hamazaki T, Tateno S, Shishido H. Eicosapentaenoic acid and IgA nephropathy. Lancet 1984; 1: 1017-8.
8. Kashem A, Endoh M, Yamauchi F, et al. Superoxide dismutase activity in human glomerulonephritis. Am J Kidney Dis 1996; 28: 14-22.
9. Futenma A, Yamada H, Kato K, Taki K. Distribution of glutathione peroxidase in the glomeruli of IgA nephropathy. Rinsho Byori 1994; 42: 1171-81.
10. Arao F, Yamada H, Katsumi K. Cu, Zn-superoxidase dismutase, glutathione peroxidase location in kidney of IgA nephropathy. Nippon Jinzo Gakkai Shi 1992; 34: 1047-53.
11. Singh RB, Niaz MA, Sharma JP, Kumar R, Rastogi V, Moshiri M. Randomized, double-blind, placebo-controlled trial of fish oil and mustard oil in patients with suspected acute myocardial infarction: The Indian experiment of infarct survival-4. Cardiovasc Drugs Ther 1997; 11: 485-91.
12. Hemmingsen I, Skaarup P. β_2-Microglobulin in urine and serum determined by ELISA technique. Scand J Clin Invest 1985; 45: 367-71.
13. Moor JC, Moris JE. A simple automated colorimetric method for determination of N-acetyl-β-D-glucosamonidase. Ann Clin Biochem 1982; 19: 157-9.
14. Knight JA, Smith SE, Kinder VE, Pier RK. Urinary lipoperoxides quantified by liquid chromatography and determination of reference values for adults. Clin Chem 1988; 34: 1107-10.
15. Donadio JV Jr, Bergstralh EJ, Offord KP, Spencer DC, Holley KE. A controlled trial of fish oil in IgA nephropathy. Mayo Nephrology Collaborative Group. N Engl J Med 1994; 331: 1194-9.
16. Bennett WM, Walker RG, Kincaid-Smith P. Treatment of IgA nephropathy with eicosapentanoic acid (EPA): A two-year prospective trial. Clin Nephrol 1989; 31: 128-31.
17. Cheng IK, Chan PC, Chan MK. The effect of fish-oil dietary supplement on the progression of mesangial IgA glomerulonephritis. Nephrol Dial Transplant 1990; 5: 241-6.
18. Pettersson EE, Rekola S, Berglund L, et al. Treatment of IgA nephropathy with w-3-polyunsaturated fatty acids: A prospective, double-blind, randomized study. Clin Nephrol 1994; 41: 183-90.
19. Harris WS. Fish oils and plasma lipid and lipoprotein metabolism in humans: A critical review. J Lipid Res 1989; 30: 785-807.

20. Illingworth DR, Connor WE, Hatcher LF, Harris WS. Hypolipidaemic effects of omega-3 fatty acids in primary hyperlipoproteinaemia. J Intern Med Suppl 1989; 225: 91-7.
21. Phillipson BE, Rothrock DW, Connor WE, Harris WS, Illingworth DR. Reduction of plasma lipids, lipoproteins, and apoproteins by dietary fish oils in patients with hypertriglyceridemia. N Engl J Med 1985; 312: 1210-6.
22. Syrjänen J, Mustonen J, Pasternack A. Hypertriglyceridaemia and hyperuricaemia are risk factors for progression of IgA nephropathy. Nephrol Dial Transplant 2000; 15: 34-42.
23. Samuelsson O, Mulec H, Knight-Gibson C, et al. Lipoprotein abnormalities are associated with increased rate of progression of human chronic renal insufficiency. Nephrol Dial Transplant 1997; 12: 1908-15.
24. Samuelsson O, Aurell M, Knight-Gibson C, Alaupovic P, Attman PO. Apolipoprotein-B-containing lipoproteins and the progression of renal insufficiency. Nephron 1993; 63: 279-85.
25. Chen A, Chen WP, Sheu LF, Lin CY. Pathogenesis of IgA nephropathy: *In vitro* activation of human mesangial cells by IgA immune complex leads to cytokine secretion. J Pathol 1994; 173: 119-26.
26. Pei Y, Scholey J, Thai K, Suzuki M, Cattran D. Association of angiotensinogen gene T235 variant with progression of immunoglobulin A nephropathy in Caucasian patients. J Clin Invest 1997; 100: 814-20.
27. Yi ZW, Rodriguez GE, Krieg RJ Jr, Tokieda K, Chan JC. Rat macrophages in experimental IgA nephropathy. Biochem Mol Med 1996; 57: 152-5.
28. Kashem A, Endoh M, Nomoto Y, Sakai H, Nakazawa H. $Fc_{\alpha}R$ expression on polymorphonuclear leukocyte and superoxide generation in IgA nephropathy. Kidney Int 1994; 45: 868-75.
29. Grande JP, Donadio JV Jr. Dietary fish oil supplementation in IgA nephropathy: A therapy in search of a mechanism. [Editorial] Nutrition 1998: 2: 240-2.
30. Schmitz PG, Zhang K, Dalal R. Eicosapentaenoic acid suppresses PDGF-induced DNA synthesis in rat mesangial cells: Involvement of thromboxane A2. Kidney Int 2000; 57: 1041-51.

ผลของน้ำมันปลาต่อหน้าที่ไต ระดับไขมันในเลือดและออกซิเดทิฟ สเตรส ในผู้ป่วยที่เป็นโรคไตชนิด ไอจีเอ

อุไรวรรณ ปริญญาศิริ, พบ, ลีนา องอาจยุทธ, พบ*, ไพศาล ปาริชาติกานนท์, พบ**, สมพงษ์ องอาจยุทธ, วทม***, สมพงษ์ เหลี่ยมมงคลกุล, วทม***, สุรินทร์ ขันหยก, วทม****

มีผู้รายงานกรดไขมันประเภท โอเมก้าสาม ที่มีอยู่ในน้ำมันปลาว่า สามารถลดความดันโลหิต, โปรตีนในปัสสาวะ, ระดับไขมันในเลือด, และการอักเสบได้ การศึกษานี้ผู้ป่วยเป็นโรคไตอักเสบชนิด IgA จำนวน 23 ราย ที่มีโปรตีนในปัสสาวะมากกว่า 1 กรัมต่อวัน มีระดับคริอะตินินในเลือดน้อยกว่า 3 มก/ดล ควบคุมความดันโลหิตน้อยกว่า 130/80 มม.ปรอท โดยผู้ป่วยได้ omacor จำนวน 4 กรัมต่อวัน ซึ่งเทียบเท่า EPA 1.88 กรัม และ DHA 1.48 กรัมต่อวัน ระยะเวลานาน 6 เดือน เปรียบเทียบหน้าที่ไต ระดับไขมันในเลือดและโปรตีนในปัสสาวะ ก่อนให้ยา หลังให้ยา นาน 3 เดือนและ 6 เดือน ตามลำดับ ผลการศึกษาพบว่า ระดับไตรกลีเซอไรด์ในเลือดลดลงอย่างมีนัยสำคัญทางสถิติหลัง 6 เดือนของการรักษา ระดับโคเลสเตอรอลมีแนวโน้มลดลง แต่ไม่พบมีนัยสำคัญทางสถิติ ส่วน เอช-ดี-แอล โคเลสเตอรอล สูงขึ้น แต่ไม่พบมีนัยสำคัญทางสถิติ ระดับเบต้า ทู ไมโครโกลบูลิน ในปัสสาวะลดลงหลังได้น้ำมันปลา ระดับพลาสมา MDA ซึ่งเป็นผลลัพธ์ของ oxidative stress ลดลงอย่างมีนัยสำคัญทางสถิติหลังได้น้ำมันปลา การศึกษานี้ไม่พบมีการเปลี่ยนแปลงของระดับความดันโลหิต โปรตีนในปัสสาวะหรือระดับคริอะตินินในเลือด

คำสำคัญ : น้ำมันปลา, ออกซิเดทิฟ สเตรส, ผู้ป่วยโรคไตชนิด ไอจีเอ

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