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The effect of eicosapentaenoic acid on renal function and volume in patients with ADPKD

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Abstract

Background. Soy protein ameliorates rat polycystic kidney disease with concomitant renal enrichment of ω3-polyunsaturated fatty acids. A study was conducted to examine the effects of eicosapentaenoic acids (EPA) on renal volume and function in patients with autosomal dominant polycystic kidney disease (ADPKD).

Methods. Non-azotemic patients were randomized to either a control group ($n = 20$) or an EPA group ($n = 21$). EPA capsules (2.4 g/day) were administered in the EPA group for 2 years. Twenty-four hours of urine was collected for the creatinine clearance (Ccr) measurement every year. At baseline and 24 months, fatty acid compositions in erythrocytes were measured and computerized tomographies were obtained for calculation of renal volume by the modified ellipsoid and volumetric methods.

Results. In the EPA group, the EPA concentration (1.80 ± 0.99 versus 4.40 ± 1.79 area%, $P < 0.001$) and the ω3/ω6 ratio in the erythrocyte increased, but docosahexaenoic acid (DHA) (6.76 ± 1.19 versus 5.64 ± 1.45 area%, $P < 0.010$) concentration decreased. Ccr decreased by 8.5 ± 9.5 and 9.0 ± 13.0 ml/min/1.73 m^2/2 years in the control and EPA groups, respectively (NS). The increases in renal volume calculated by either method were not significantly different between the two groups.

Conclusions. A beneficial effect of EPA on renal function and kidney volume in ADPKD patients could not be confirmed in the present study. Administration of EPA with DHA supplementation and/or longer intervention might be necessary to demonstrate preventive effects of ω3-polyunsaturated fatty acids on progression of ADPKD.

Keywords: eicosapentaenoic acid; kidney function; kidney volume; ω3polyunsaturated fatty acids; polycystic kidney disease

Introduction

Soy protein slows progression of renal injury in Han:SPRD-cy rats, a model of polycystic kidney disease associated with higher renal and hepatic linoleic acid but lower arachidonic acid content [1,2]. A flaxseed-fed Han:SPRD-cy rat had lower serum creatinine, less cystic change, less renal fibrosis and less macrophage infiltration of the renal interstitium than control rat chow-fed animals. Lipid analysis revealed significant enrichment of renal 18 and 20 carbon ω3 polyunsaturated fatty acids (increased ω3/ω6 ratio) in flaxseed-fed animals [3]. Dietary fish (menhaden) oil as well as soybean oil containing high *n*-3 polyunsaturated fatty acid ameliorated some of the detrimental effects of a high fat diet in early renal injury in Han:SPRD-cy rats [4]. An *n*-3 polyunsaturated fatty acid-rich diet [enriched in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] reduced cystic volume in DBA/2FG-pcy mice compared with sunflower seed oil-fed animals [5]. These studies demonstrated that *n*-3 polyunsaturated fatty acid has a beneficial effect to slow renal cystic enlargement and functional deterioration in an animal model of polycystic kidney disease.

In healthy volunteers, the synthesis of interleukin-1 and tumour necrosis factor (TNF), both potent inflammatory factors, was suppressed by dietary supplementation with long-chain *n*-3 fatty acids [6]. EPA suppressed the expression of TNF-α, an activator of NF-κB, in human monocytes, and prevented NF-κB activation by preventing Iκ B-α phosphorylation [7]. This inhibitory effect of EPA on NF-κB activation is thought to be mediated by the peroxisome proliferator-activated receptors (PPARs)-dependent

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pathway [8]. In another study, *n*-3 polyunsaturated fatty acid was shown to have an anti-inflammatory effect via activation of PPARs in human renal tubular cells [9]. Pioglitazone, a stimulator of PPARs, improved the phenotype of homozygous mutant PKD1$^{-/-}$ rat embryos [10].

Animal and *in vitro* studies have suggested that the beneficial effects of EPA on renal prognosis in autosomal dominant polycystic kidney disease (ADPKD) was through an anti-inflammatory process. We therefore examined the effect of EPA on renal function and volume in patients with ADPKD in a prospective and randomized manner.

Subjects and methods

This multicentre, prospective and randomized study examined the efficacy of treatment for 2 years with EPA on kidney volume and renal function in adult patients with ADPKD. Patients were randomly assigned to the two groups using the dynamic balancing method to ensure equal distributions of subject gender, age, serum creatinine levels and blood pressure between the two groups.

Forty-one patients aged between 18 and 60 years with clinical and image diagnoses of ADPKD were selected for study participation. Patients with end-stage renal disease, haemorrhagic lesions such as gastric ulcer, intracranial aneurysm and past history of central nervous vascular disease and any condition that could prevent completion of the planned follow-up were not considered eligible for the study participation. Pregnant or lactating women or fertile women without effective contraception were also excluded from the study.

The enrolled patients were randomly assigned to the two groups. Patients in the EPA group ($n = 21$) took 2.4 g/day of EPA ethyl ester (Epadel-S, purity >98%, Mochida Pharmaceutical Co. Ltd, Tokyo) for 2 years. The untreated control group had 20 patients. All subjects were asked not to take any EPA-rich supplement in the trial period.

At 0 (baseline), 6 and 24 months (the end) of the trial, the fatty acid composition of the total phospholipid fraction of erythrocytes [11], plasma cholesterol and triglyceride were measured. Using 24-h urine samples, creatinine clearance (Ccr) and urinary albumin excretion were measured every year. Abdominal computerized tomographies (CT) were obtained at baseline and at the completion of the 2-year study.

Patients with hypertension were treated to reduce their blood pressure to <130/85 mmHg measured at out clinic in the sitting position. Angiotensin II receptor blocker (ARB) was selected as the first choice drug. If targeted blood pressure was not achieved by ARB alone, calcium-channel blocker (CCB), angiotensin converting enzyme inhibitor (ACEI) and/or alpha- or beta-adrenergic blockers were added appropriately [12].

The total kidney volume was determined by CT scan using a standard formula for a modified ellipsoid [13] and volumetric measurement of cross-sectional imaging [14,15]. CT films were sent to one institute and the volume measurement was performed by a single analyst (KN). In the modified ellipsoid method, renal volume was calculated by measuring the anteroposterior diameter, width and length of the kidney [13]. In volumetric measurement, the area of the kidney in each image was calculated from the collection of selected points that overlaid the kidney regions and converting the point count to a pixel count to obtain area measurements. The total kidney volume was calculated from the set of contiguous images by summing the products of the area measurements and the slice thickness [15]. Cyst volumes were not calculated because of unclear identification of cyst margin on non-enhanced CT images. The kidney volumes calculated by the modified ellipsoid and volumetric methods were compared with each other and also with Ccr.

The study was approved by the ethics committee of each participating hospital, and written informed consent was obtained from each patient before entering the trial.

Results are expressed as means ± SD. StatView (version 5.0) was used for the statistical analysis. The kidney volume, the fatty acid composition of erythrocytes and other clinical data were analysed parametrically (paired *t*-test for comparison between the control and EPA groups and ordinary ANOVA for multiple group comparison). $P < 0.05$ was considered to be significant.

Table 1. Basic characteristics of the patients

	Control group ($n = 20$)	EPA group ($n = 21$)	*P*-value*
Age (year)	47.5 ± 12.5	46.8 ± 11.4	0.865
Male/female	M 14/f 6	M 15/F 6	ns
Creatinine (mg/dl)			
Male	1.77 ± 0.88	1.58 ± 0.64	0.520
Female	1.69 ± 0.62	1.41 ± 0.64	0.459
Blood pressure (mmHg)			
Systolic	126 ± 17	132 ± 12	0.186
Diastolic	81 ± 13	83 ± 8	0.612
Antihypertensive treatment			
Treated patients number	17	16	ns

Data are shown as mean ± SD.
*P-value for the comparison of the EPA group versus the control group by the unpaired t-test.

Results

Characteristics of the patients

Of the 41 patients assigned to the study, no patient dropped out from the trial. Basic characteristics of the patients are shown in Table 1, and there was no significant difference in pertinent parameters between the control and EPA groups. Seventeen patients received antihypertensive treatment in the control group; 16 in the EPA group. Antihypertensive treatments included ARB alone for 14 patients (6 in the control and 8 in the EPA group), ARB plus other drugs (CCB, alpha-adrenergic blocker, beta-adrenergic blocker and/or ACEI) in 11 (6 in control and 5 in EPA), CCB alone in 6 (3 each) and CCB plus another drugs in 2 (2 in control and 0 in EPA).

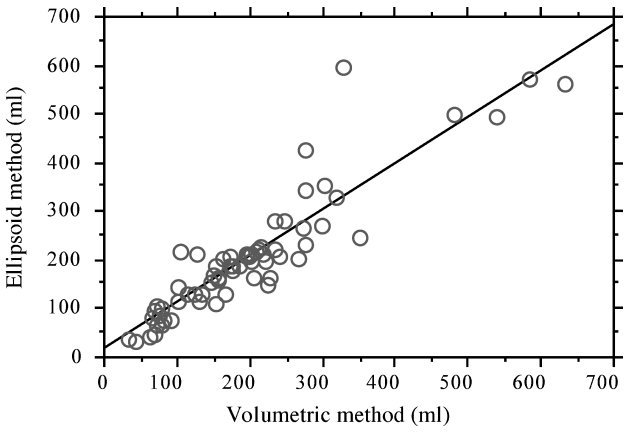

Fig. 1. Relationship between renal volume measured by the volumetric (X) and ellipsoid (Y) methods. $Y = 0.95X+186.15$, $R^2 = 0.832$, $P < 0.0001$.

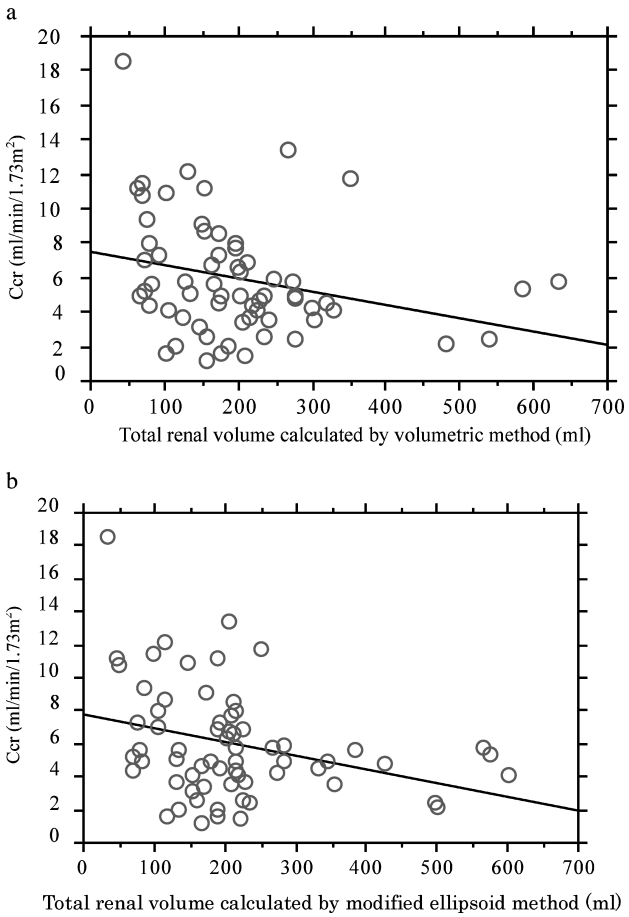

Fig. 2. Relationship between Ccr (Y) and total renal volume (X) calculated by the volumetric (**A**) and ellipsoid methods (**B**). In the volumetric method (A), $Y = -0.008X+75.595$, $R^2 = 0.078$ and $P = 0.025$. In the ellipsoid method (B), $Y = -0.008X+77.899$, $R^2 = 0.102$ and $P = 0.0089$.

Comparison of the volumetric and modified ellipsoid methods

The relationship between renal volume calculated by the volumetric and modified ellipsoid methods is illustrated in Figure 1. The regression coefficient is 0.832 and renal volumes calculated by the two methods are highly correlated ($P < 0.001$). Total renal volumes calculated by the two methods are plotted against Ccr in Figure 2A and B. The regression analysis indicates that the correlation between Ccr and renal volume calculated by either method was significant. These data confirmed the inverse relationship between kidney volumes and renal function (Ccr) which was reported previously [13,15]. We found that kidney volume calculated by the modified ellipsoid method gave larger values than those calculated by the volumetric method. The difference may be derived from the measurement of the outermost kidney configuration by the ellipsoid method. This method ignores the cystic irregular configuration and gives a larger estimate of kidney volume.

EPA effects on renal function and renal volume

The changes in renal function and volume are shown in Table 2. Ccr, urinary albumin excretion and plasma creatinine were not significantly different between the two groups through the study period. During 2 years, Ccr decreased by 8.48 ± 9.55 and 9.02 ± 13.04 ml/min/1.73 m^2 in the control and EPA groups, respectively ($P = 0.925$). The percent changes in Ccr for 2 years were −15.8 ± 12.4 and −17.6 ± 24.7% in the control and EPA groups, respectively ($P = 0.778$).

The total renal volume calculated by the volumetric method increased by 110 ± 260 ml and 144 ± 452 ml in the control and the EPA groups, respectively ($P = 0.811$). The percent volume increases per 2 years were 7.4 ± 15.1 and 8.2 ± 25.7, respectively ($P = 0.925$). The renal volume data calculated by the modified ellipsoid method were qualitatively similar to those calculated by the volumetric method.

These data suggest that EPA administration for 2 years had no significant effect on renal volume enlargement or the deterioration of renal function.

Changes in polyunsaturated fatty acid levels in erythrocyte

EPA and docosapentaenoic acid (n-3) concentrations in the total phospholipid fraction of erythrocytes significantly increased in the EPA group during the trial, with no significant changes in the control group. The ω3/ω6 ratio increased in the EPA group but did not increase in the control group. In contrast, arachidonic acid and DHA concentration decreased significantly in the EPA group, without any significant changes in the control group (Table 3). Food analyses showed no significant difference in the average intakes of macronutrients and n-3- and n-6 fatty acids between groups (data not shown).

Discussion

Increasing evidence from animal and *in vitro* studies indicates that n-3 fatty acids present in fatty fish and fish oils, especially long-chain polyunsaturated fatty acids EPA

Table 2. Changes in renal function and total renal volume

	Control group	EPA group	*P*-value*
Renal function			
Creatinine clearance (ml/min/1.73 m^2)			
Baseline	56.9 ± 25.5	63.7 ± 32.8	0.483
12 months	48.6 ± 17.1	54.9 ± 29.4	0.475
24 months	48.6 ± 22.8	54.7 ± 32.9	0.502
Δ/24 mo.[a]	−8.48 ± 9.55	−9.02 ± 13.0	0.925
Urinary albumin excretion (mg/day)			
Baseline	83.1 ± 184.0	135.9 ± 205.0	0.435
12 months	95.2 ± 149.7	185.6 ± 218.2	0.318
24 months	193.5 ± 332.0	275.9 ± 459.4	0.538
Plasma creatinine (mg/dl)			
Baseline	1.75 ± 0.80	1.56 ± 0.63	0.432
12 months	1.85 ± 0.83	1.89 ± 1.02	0.882
24 months	2.11 ± 1.06	2.27 ± 2.27	0.700
Total renal volume (ml)			
Modified ellipsoid method			
Baseline	1901 ± 980	1559 ± 592	0.230
24 months	2348 ± 1475	1811 ± 710	0.185
Δ/24 mo.[a]	447 ± 663	252 ± 347	0.292
% change[b]	18.6 ± 30.5	17.4 ± 22.3	0.897
Volumetric method			
Baseline	1806 ± 796	1563 ± 653	0.359
24 months	1917 ± 831	1708 ± 868	0.507
Δ/24 mo.[a]	110 ± 260	144 ± 452	0.811
% change[b]	7.4 ± 15.1	8.2 ± 25.7	0.925

Data are shown as mean ± SD.
*P-value for the comparison of the EPA group versus the control group by the unpaired t-test.
[a]Δ/24 mo.: total renal volume (24-month baseline).
[b]% change: Δ/24 mo./baseline renal volume × 100.

Table 3. Changes in some polyunsaturated fatty acid levels (area%) and their ratios in the total phospholipid fraction in erythrocytes

	Control group	EPA group	*P*-value*
Arachidonic acid (AA)			
baseline	10.36 ± 1.22	10.19 ± 1.52	0.689
6 month	11.13 ± 1.29	9.13 ± 1.38	<0.001
24 month	9.92 ± 1.43	7.97 ± 1.86	<0.001
Eicosapentaenoic acid (EPA)			
baseline	1.87 ± 0.81	1.85 ± 0.92	0.934
6 month	1.87 ± 0.87	5.50 ± 1.67	<0.001
24 month	1.80 ± 0.99	4.40 ± 1.79	<0.001
Docosapentaenoic acid			
baseline	1.88 ± 0.31	1.91 ± 0.29	0.758
6 month	2.01 ± 0.29	4.30 ± 0.89	<0.001
24 month	1.93 ± 0.39	3.72 ± 1.00	<0.001
Docosahexaenoic acid (DHA)			
baseline	7.20 ± 1.17	6.86 ± 1.20	0.370
6 month	7.61 ± 1.35	6.28 ± 1.40	0.004
24 month	6.76 ± 1.19	5.64 ± 1.45	0.010
ω3/ω6 ratio			
baseline	0.48 ± 0.13	0.45 ± 0.14	0.640
6 month	0.49 ± 0.15	0.84 ± 0.18	<0.001
24 month	0.48 ± 0.15	0.74 ± 0.21	<0.001
EPA/AA ratio			
baseline	0.19 ± 0.10	0.19 ± 0.11	0.921
6 month	0.18 ± 0.10	0.63 ± 0.24	<0.001
24 month	0.19 ± 0.13	0.62 ± 0.32	<0.001

Data are shown as mean ± SD.
*P-value for the comparison of EPA group versus controls by unpaired t-test.

and DHA, inhibit carcinogenesis and inflammatory diseases [16,17]. The association between high fish consumption and a low incidence of prostate cancer was reported by a population-based prospective epidemiological study [18]. The prostate cancer incidence in Japanese men who moved to the United States increased to a number that was intermediate between the low-risk group in Japan and the high-risk group in the United States [19]. In patients with IgA nephropathy and chronic glomerular disease, treatment with *n*-3 fatty acids either retarded the rate at which renal function was lost or reduced proteinuria [20,21].

Animal and *in vitro* studies have suggested a beneficial effect of EPA on renal prognosis in ADPKD via the anti-inflammatory effects of EPA. However, there are almost no epidemiological or clinical studies examining the relationship between EPA intake and renal prognosis in ADPKD patients.

In the present study, the preventive effects of EPA on the decline in renal function and on the increase in renal volume could not be demonstrated in ADPKD patients. The reasons are not clear; however, there are several possible explanations.

First, the beneficial effects of soy protein or flaxseed on kidney volume and renal function were demonstrated in Han:SPRD-cy rat when a dietary modification was started from weaning [1–3]. In contrast, when dietary treatment started at the late stage (2-month-old rat), renal cystic growth and serum creatinine levels were not altered [22]. The present study included patients with apparent disease progression showing deteriorated renal function and large renal volume. In addition, patients in high-risk subpopulation with deteriorated renal function or enlarged kidney generally have worse renal prognosis and it is difficult to slow the progression by therapeutic intervention at the advanced stage [13,23,24]. Second, unlike human ADPKD, Han:SPRD-cy rat is characterized by an accelerated course in male animals and a good response to therapeutic intervention. Furthermore, the responsible gene in the Han:SPRD-cy rat does not correspond to the human *ADPKD* gene [1,2]. Third, the DHA concentration in erythrocytes was decreased in the EPA-treated group (Table 3). Similar findings were reported previously [25,26]. The ω3 index (a percentage of EPA + DHA) in erythrocytes was shown to correlate with this index in the human myocardium and buccal mucosa [27]. Taking into consideration that DHA accounts for >80% of the ω3 index [27], the DHA concentrations in kidney tissue might have been low in the EPA group during the 2 years of intervention. During the conversion of EPA to DHA, Δ6-desaturase is necessary. EPA competitively inhibits this enzyme [25,26] leading to DHA incorporation into the position *sn*-2 of phospholipids that may compete with EPA, which is also incorporated into the position *sn*-2. If DHA, irrespective of EPA, is important to prevent renal deterioration, intervention with fish oils containing DHA and EPA might have given different results. The level of α-linolenic acid, which might be one of the risk factors for inflammation, did not change significantly in any group during the present study (data not shown). In this regard, it is interesting to note that the treatment with EPA alone did not alter the course of established IgA nephropathy [28]; this is in contrast to a beneficial effect of dietary supplementation with EPA plus DHA in reducing end-stage renal failure and proteinuria in patients with IgA nephropathy [20] and chronic glomerular disease [21]. Although there are many potential explanations, the reasons for the lack of an effect of EPA treatment on renal volume and function await further studies.

In conclusion, ω3-polyunsaturated fatty acids might have beneficial effects on ADPKD patients as many laboratory data suggest. However, the present study showed that administration of EPA decreases the DHA concentration in erythrocytes, while fish and soybean intake increased DHA as well as EPA. The integrated roles of EPA and DHA are not clear and the combination of EPA and DHA might give different results. The administration of EPA with DHA supplementation, intervention from early disease stage and/or longer treatment period might be necessary to demonstrate the significant favourable effects of ω3-polyunsaturated fatty acids on the prognosis of ADPKD.

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Conflict of interest statement. EPA ethyl ester capsules (Epadel-S®) and research funds were provided by Mochida Pharmaceutical Co. Ltd (Tokyo, Japan) to each participating institute. All authors are currently conducting research entitled 'Comparison between ARB and ARB plus CCB on Incidence of Renal and Cardiovascular Events in Hypertensive ADPKD patients (Comparison between Candesartan and Candesartan plus Cilnidipine on Incidence of Renal and Cardiovascular Events in Hypertensive ADPKD patients)' (ClinicalTrials.gov Identifier:NCT00541853), which is partly sponsored by Mochida Pharmaceutical Co. Ltd.

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