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Effects of dietary supplementation with n-3 fatty acids  
on bronchial asthma associated with changes in lipids.  
— Comparison with n-6 fatty acids —

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**Abstract:** N-3 fatty acids have been reported to be effective for asthma. In the present study, the effects of perilla seed oil (n-3 fatty acids) on asthma were compared with the effects of corn oil (n-6 fatty acids) in terms of pulmonary function, lipometabolism and the generation of leukotriene C4 (LTC4) by leucocytes. A total of 28 asthmatic patients were randomly divided into two groups: Group A patients (15 subjects) consumed perilla seed oil-rich supplementation, while Group B patients (13 subjects) consumed corn oil-rich supplementation for 4 weeks. Generation of LTC4 by leucocytes, respiratory function and the serum levels of lipids were compared between the two groups. The generation of LTC4 by leucocytes decreased significantly in Group A subjects following perilla seed oil-rich supplementation for 2 ( $P<0.05$ ) and 4 weeks ( $P<0.01$ ). A significant difference in the generation of LTC4 was observed between the two groups after different dietary supplementations for 4 weeks ( $P<0.05$ ).

Significantly increased values for PEF ( $P<0.01$ ), FVC ( $P<0.05$ ) and FEV<sub>1.0</sub> ( $P<0.05$ ) were found in Group A subjects following perilla seed oil supplementation for 4 weeks, compared with the initial value prior to supplementation.

A significant decrease in the serum level of total cholesterol, LDL-cholesterol and phospholipid was detected in Group A subjects following perilla seed oil supplementation for 4 weeks. The present results suggest that perilla seed oil-rich supplementation is effective in the treatment of asthma in terms of its ability to suppress LTC4 generation by leucocytes, and in inducing an improvement in pulmonary function associated with changes in the serum level of lipids.

**Key words:** perilla seed oil,  $\alpha$ -linolenic acid, leukotriene C4, respiratory function, lipometabolism

## Introduction

Bronchial allergen challenge induces both an immediate asthmatic reaction (IAR) within 30 minutes and a late asthmatic reaction (LAR), which occurs 6-8 hours after the challenge. The LAR, in which inflammatory cells such as lymphocytes, neutrophils, eosinophils and basophils migrate into sites of allergic reaction in the airway<sup>1, 2)</sup>, is closely associated with bronchial hyperresponsiveness<sup>3, 4)</sup>. Leukotrienes (LTs), which are the major chemical mediators associated with asthma, and in particular LAR, are synthesized by inflammatory cells in large quantities during allergic reactions.

LTs are generated from arachidonic acid (AA) through the 5-lipoxygenase pathway, and AA is in turn released from membrane phospholipids during cell activation<sup>5)</sup>. LTB<sub>4</sub> and LTC<sub>4</sub> are generated from linoleic acid (LA) through AA, while LTB<sub>5</sub> and LTC<sub>5</sub> are generated from  $\alpha$ -linolenic acid ( $\alpha$ -LNA) through eicosapentaenoic acid (EPA) via the same 5-lipoxygenase pathway. Whereas LTB<sub>5</sub> has a much weaker action than LTB<sub>4</sub>, the action of LTC<sub>5</sub> is approximately equivalent to that of LTC<sub>4</sub>.

Dietary supplementation with perilla seed oil, which is rich in  $\alpha$ -LNA, is expected to suppress the generation of '4-series' leukotrienes (LTB<sub>4</sub> and LTC<sub>4</sub>) by leucocytes and to increase the generation of '5-series' leukotrienes (LTB<sub>5</sub> and LTC<sub>5</sub>). Conversely, supplementation with corn oil, which is rich in LA, is expected to increase the generation of '4-series' LTs, and to decrease the generation of '5-series LTs' by leucocytes. In a previous study<sup>6)</sup>, we reported on the inhibitory effects on the generation of LTs by leucocytes of a diet containing perilla seed oil, a vegetable

oil rich in  $\alpha$ -LNA.

The present study examined the effects of perilla seed oil-rich supplementation in contrast to the effects of corn oil-rich supplementation in patients with asthma.

## Materials and Methods

Subjects were 28 patients (8 men and 20 women) admitted to our hospital to undergo treatment for asthma. The mean age of the patients was 61.1 years (range, 12 to 84 years) and the mean serum level of IgE was 780.1IU/ml (range, 21.1 to 6300 IU/ml). Of the 28 patients, 13 were atopic while the remaining 15 were non-atopic. All subjects had moderate type asthma in severity. The mean duration of asthma was 13.6 years. All patients were treated with long-acting oral theophylline, inhaled  $\beta_2$  adrenergic agonists and inhaled glucocorticosteroid (beclomethasone dipropionate : BDP). The mean dose of inhaled BDP was 208.9  $\mu$ g/day.

Asthma was evaluated according to the criteria of the International Consensus of Diagnosis and Management of Asthma<sup>7)</sup>. All patients showed reversible airway response, as indicated by a 15% or greater increase in their forced expiratory volume in one second (FEV<sub>1.0</sub>) after inhaled bronchodilator use. The study was approved by the Institutional Human Investigation Committee of our hospital. Informed consent for the study protocol was obtained from all patients.

Subjects were randomly divided into two groups : patients in Group A (15 subjects) consumed 10-20 grams of perilla seed oil per day as salad dressing and/or mayonnaise instead of other oils for 4 weeks, while patients in Group B (13 subjects) consumed an equivalent amount of corn oil per day for 4 weeks. All other dietary components were

left unchanged, and the amount of oil used in the diet and supplemented diet were recorded throughout the study period.

The concentration of serum total cholesterol, triglyceride, high density lipoprotein (HDL)-cholesterol, and phospholipid were assayed using a previously reported enzymatic method<sup>8-11</sup>. Low density lipoprotein (LDL)-cholesterol concentration was calculated using the following formula: [(serum total cholesterol) - (HDL-cholesterol) - 0.2 × (triglyceride)] (Friedwald's convert)<sup>12</sup>.  $\beta$ -lipoprotein was assayed by turbidimetry. Serum IgE levels were estimated using the radioimmunosorbent test (RIST).

Peak expiratory flow (PEF) in the early morning was recorded for all subjects using a peak flow meter (Assess: Health Scan Products Inc., Cedar Grove, NJ, USA). Pulmonary function tests, forced vital capacity (FVC) and forced expiratory volume in one second (FEV<sub>1.0</sub>) were performed using a Chestac 33 (Chest Co., Tokyo, Japan) linked to a computer at a point when patients were attack free.

The generation of LTC<sub>4</sub> by peripheral leucocytes was assessed using a previously described method<sup>13,14</sup>. Cells were separated by counterflow centrifugation elutriation using a JE 6B rotor (Beckman Co., Geneva, Switzerland)<sup>15</sup>, as described previously<sup>16</sup>. The number of cells was then adjusted to  $5 \times 10^6$ /ml in Tris ACM (composition: 1ml of 0.1mol/l Ca<sup>2+</sup>, 0.5ml of 0.1mol/l Mg<sup>2+</sup> and 98.5ml Tris A buffer; Trizma preset crystal, pH 7.7; Sigma Chemical Co., St. Louis, Mo, USA). The Ca ionophore, A23187 (1  $\mu$ g) was added to the cell suspension. The mixed solution was incubated for 15 min at 37°C. Quantitation of LTC<sub>4</sub> by HPLC analysis was performed using the method of Lam et al.<sup>17</sup>.

Extraction of LTs was performed using C18 Seppak (Waters Associates, Milford MA). Concentrations of LTC<sub>4</sub> were analyzed by the HPLC system Model 510 (Waters Associates, Milford, MA), equipped with an ultraviolet detector. The column used was a 5mm × 10cm Radial-Pax cartridge (Shimazu Co., Kyoto, Japan). The results were expressed as ng/5 × 10<sup>6</sup> cells.

Data were expressed as mean ± SEM. Student's t-test was used for paired analysis. For group comparisons, we used one-way analysis of variance (ANOVA). P < 0.05 was considered significant. Analyses were performed using StatView 5.0 (Abacus Concepts, Inc., Berkeley, CA).

## Results

The generation of LTC<sub>4</sub> by leucocytes in Group A patients following perilla seed oil-rich supplementation showed a significant decrease for 2 (P < 0.05) and 4 weeks (P < 0.01). In contrast, LTC<sub>4</sub> generation showed a tendency to increase in patients with corn oil-rich supplementation. Significantly increased LTC<sub>4</sub> generation was found after 4-week corn oil supplementation. Furthermore, a significant difference in LTC<sub>4</sub> generation was observed between the two groups at 4 weeks (P < 0.05) (Fig. 1).

PEF values in the morning increased in both two groups at 4 weeks after dietary supplementation. A significant increase in PEF was observed at 2 (P < 0.05) and 4 weeks (P < 0.01) after perilla seed oil-rich supplementation. A significant increase was also found in patients with corn oil after the 4-week supplementation (P < 0.05) (Table 1).

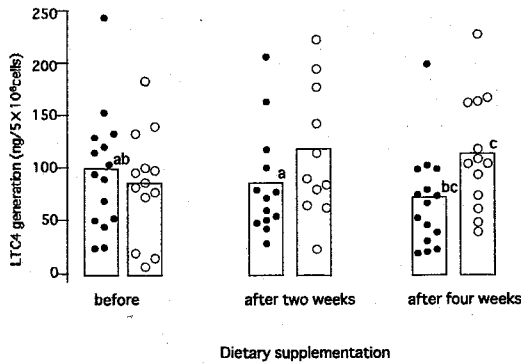


Fig. 1. Changes in LTC<sub>4</sub> generation in the two study groups. LTC<sub>4</sub> generation decreased significantly after perilla seed oil-rich supplementation for two and four weeks (●). In contrast, LTC<sub>4</sub> generation increased after corn oil-rich supplementation (○). A significant difference in LTC<sub>4</sub> generation was observed between the two study groups after different dietary supplementations for 4 weeks. a and c: P<0.02 b: P<0.01. LTC<sub>4</sub>: leukotriene C<sub>4</sub>

Table.1. Comparison of morning PEF values between groups

	PEF value (L/min)		
	before	after two weeks	after four weeks
Group A	241.3±134.9 <sup>ab</sup>	259.3±113.9 <sup>a</sup>	271.3±105.1 <sup>b</sup>
Group B	280.0±102.4 <sup>c</sup>	309.1±113.7	318.2±106.7 <sup>c</sup>

a and c:P<0.05. b:P<0.01

A significant increase in the value of FVC was observed at 4 weeks after perilla seed oil-rich supplementation (P<0.05). The FEV<sub>1.0</sub> value also significantly increased at 4 weeks after dietary supplementation with perilla seed oil (P<0.05). In contrast, no significant increase was observed in either FVC or

FEV<sub>1.0</sub> after the 4-week corn oil-rich supplementation (Table 2).

Table.2. Comparison of FVC and FEV<sub>1.0</sub> values between groups

		Dietary supplementation	
		before	after four weeks
FVC(L)	Group A	2.31±0.50 <sup>a</sup>	2.43±0.40 <sup>a</sup>
	Group B	2.60±1.10	2.66±1.10
FEV <sub>1.0</sub> (L)	Group A	1.45±0.48 <sup>b</sup>	1.68±0.51 <sup>b</sup>
	Group B	1.90±0.91	1.87±0.98

a, b:P<0.05

In terms of lipid metabolism, the serum levels of total cholesterol, LDL-cholesterol and phospholipid decreased significantly in patients with perilla seed oil after the 4-week supplementation, but not in patients with corn oil-rich supplementation. The serum levels of triglyceride, HDL-Cholesterol, and β-lipoprotein did not differ significantly between groups after the dietary supplementation (Table 3).

Table.3. Comparison of the serum lipid level of between groups

		Dietary supplementation	
		before	after four weeks
Total Cholesterol(mg/dl)	Group A	216.5±39.5 <sup>a</sup>	198.0±45.9 <sup>a</sup>
	Group B	202.4±38.5	189.3±39.9
Triglyceride(mg/dl)	Group A	65.2±25.8	62.4±13.1
	Group B	75.4±17.0	73.4±28.5
HDL-Cholesterol(mg/dl)	Group A	70.1±22.5	65.6±22.1
	Group B	67.3±25.2	53.0±13.9
LDL-Cholesterol(mg/dl)	Group A	152.0±20.1 <sup>b</sup>	137.8±24.3 <sup>b</sup>
	Group B	139.1±25.4	125.7±33.6
β-Lipoprotein(mg/dl)	Group A	428.6±71.2	419.7±76.8
	Group B	464.0±55.2	462.7±108.6
Phospholipid(mg/dl)	Group A	250.8±19.2 <sup>c</sup>	216.4±35.0 <sup>c</sup>
	Group B	223.7±21.4	233.2±42.9

b and c:P<0.05. a:P<0.01

Eosinophil counts in the two groups did not change significantly during the study period.

### Discussion

Asthma is characterized by airway inflammation, bronchial hyper-responsiveness to non-specific stimuli, and episodic and reversible airflow obstruction. Airway inflammation is the main pathophysiological manifestation of asthma. Leukotrienes (LTs) are among the most important chemical mediators released from inflammatory cells, which are in turn involved in the pathogenesis of asthma.

Generation of LTB<sub>4</sub> is reportedly reduced by n-3 fatty acids<sup>18, 19</sup>. In addition, LTB<sub>4</sub> generated from LA and LTB<sub>5</sub> from  $\alpha$ -LNA have similar biological activities. However, LTB<sub>5</sub> has a much weaker action than LTB<sub>4</sub>. Cysteinyl LTs (LTC<sub>4</sub>, LTD<sub>4</sub> and LTE<sub>4</sub>) are implicated in the pathogenesis of allergen-induced airway responses as potent contractile agonists for airway smooth muscle<sup>1, 10</sup>. Moreover, they mediate at a latter stage of immediate airway obstruction, namely a fall in FEV<sub>1.0</sub> after allergen exposure<sup>20, 21</sup>.

Polyunsaturated fatty acids (PUFAs) of the n-3 series [EPA and docosahexaenoic acid (DHA)] suppress the production of LTs by antagonistic metabolism, which occurs at the level of LT hydrolase through the 5-lipoxygenase pathway. Therefore, PUFAs may potentially alter LT generation by leucocytes<sup>22</sup>. The above PUFAs have been reported to show anti-inflammatory effects in patients with chronic inflammatory diseases such as rheumatoid arthritis, psoriasis, and chronic inflammatory bowel disease<sup>23-28</sup>. Several studies have focused on the beneficial effects of EPA or fish oil on bronchial asthma<sup>29-33</sup>.

In the present study, the effects of  $\alpha$ -LNA

rich perilla seed oil on asthma were compared with the effects of LA-enriched corn oil. The results revealed that  $\alpha$ -LNA-rich perilla seed oil supplementation significantly suppressed the generation of LTC<sub>4</sub>. Furthermore, subjects given perilla seed oil-rich supplementation showed significantly higher increases in PEF, FVC, and FEV<sub>1.0</sub> levels after the 4-week dietary supplementation. However, both groups showed an increase in PEF values during the study period. This was concluded to be due to other therapies (drugs and respiratory rehabilitation) that accompanied the diet therapy.

Several reports have failed to detect any beneficial effect of EPA in patients with bronchial asthma<sup>34, 35</sup>. The present study demonstrated the efficacy of perilla seed oil in treating asthma. Perilla seed oil is metabolized to form EPA. Therefore, the action of perilla seed oil might include not only the effects of perilla seed oil itself but that of EPA as well. The present study did not examine changes in the serum IgE value, nor did it examine the n-3 fatty acids/n-6 fatty acids ratio. Some reports have documented a significant influence of dietary PUFA on the serum IgE and n-3 fatty acids/n-6 fatty acids ratio<sup>36, 37</sup>.

Previous reports have suggested that PUFA diets that include  $\alpha$ -LNA - decrease serum lipids<sup>37-46</sup>. In particular, some studies have reported that perilla seed oil-rich supplementation decreased serum lipids in rats<sup>45, 46</sup>. Recent dietary supplementation trends in Japan have included a high consumption of saturated fatty acids and n-6 PUFAs and low n-3 PUFAs<sup>47</sup>. The present study findings revealed that perilla seed oil-rich supplementation decreased serum levels of total cholesterol, LDL-cholesterol and phospholipid.

The present study findings suggested that dietary supplementation with perilla seed oil, rich in  $\alpha$ -LNA, was significantly more beneficial for asthma than that with corn oil, rich in LA, in terms of its suppressive effect on the generation of LTs by leucocytes associated with lipometabolism.

The present study may represent an important step in the development of a diet therapy for asthmatic patients. Future studies are needed to further develop a nutritionally balanced diet therapy for asthma.

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### 脂肪の変化と関連した気管支喘息に対するn-3系脂肪酸食の効果—n-6系脂肪酸との比較

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n-3系脂肪酸は喘息に有効であることが報告されている。今回、エゴマ油 (n-3系脂肪酸) の喘息に対する効果を呼吸機能、脂質代謝、白血球ロイコトリエンC4 (LTC4) 産生能の観点から、コーン油 (n-6系脂肪酸) のそれと比較した。28例の喘息患者を無作為に2群に分け、A群 (15例) はエゴマ油食を、B群 (13例) はコーン油食をそれぞれ4週間摂取した。白血球LTC4産生能、呼

吸機能、血清脂質を2群間で比較した。白血球LTC4産生能はエゴマ油食を摂取したA群で2週後 ( $P < 0.05$ )、4週後 ( $P < 0.01$ ) に有意に低下した。食事摂取4週後に2群間でLTC4産生能に有意差が認められた ( $P < 0.05$ )。エゴマ油食を4週摂取したA群ではピークフロー ( $P < 0.05$ )、肺活量 ( $P < 0.01$ )、1秒量 ( $P < 0.05$ ) が食事摂取前に比し、有意に増加した。またA群ではエゴマ油食摂取4週後に血清総コレステロール値、LDL-コレステロール値、リン脂質の有意な低下がみられた。これらの結果より、エゴマ油食は白血球LTC4産生能を抑制することにより、呼吸機能を改善し、血清脂質の変化と関連して、喘息の治療に有効であることが示唆された。

牽引用語：エゴマ油、 $\alpha$ -リノレン酸、ロイコトリエンC4, 呼吸機能、脂質代謝