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Factors influencing the effects of dietary supplementation with PUFAs on leukotriene generation by leucocytes in patients with asthma

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Abstract : Dietary supplementation with perilla seed oil, a vegetable oil rich in α-linolenic acid, inhibits the generation of leukotrienes(LTs) by leucocytes in patients with bronchial asthma. We examined the factors that affect the suppression of LT generation by leucocytes with perilla seed oil-rich supplementation in patients with asthma, by comparing the clinical features of patients with asthma, whose generation of leukotriene (LT) C4 was suppressed by dietary supplementation with perilla seed oil (n-3 fatty acids) (group A), with those of patients who showed no suppression of LTC4 generation (group B). Group A showed a significant increase in the generation of LTB4 and LTC4 by leucocytes after corn oil-rich supplementation (n-6 fatty acids), and a significant decrease in the generation of LTB4 and LTC4 after perilla seed oil-rich supplementation (n-3 fatty acid). However, this was not observed in group B. The level of serum IgE and peak expiratory flow (PEF) in group A were significantly higher than in group B. Furthermore, the serum levels of LDL-cholesterol, β-lipoprotein and phospholipid were significantly lower in group A than in group B. These results suggest that the clinical features differ between these two asthmatic populations with respect to suppression of LTB4 and LTC4 generation by n-3 fatty acids in perilla seed oil-rich supplementation.

Key words : perilla seed oil, bronchial asthma, leukotrienes, IgE, lipometabolism

Introduction

Bronchial asthma is characterized by airway inflammation followed by bronchial hyperresponsiveness to non-specific stimuli. Airway inflammation is a main feature in the pathophysiology of asthma, in which various cytokines are released from inflam-

matory cells. Leukotrienes (LTs) are one of the most important chemical mediators released from inflammatory cells. Peptide LTs (LTC4, D4 and E4) have a bronchoconstricting action and participate in the onset of asthma attacks[1, 2].

Our previous studies demonstrated that both histamines and LTC4 participate in the onset mechanism of atopic asthma, whereas only LTC4 participates in the onset of non-atopic asthma[3]. Furthermore, LTB4 plays an important role in the asthmatic response by recruiting leucocytes to allergic reaction sites in the airway. These LTs are generated from arachidonic acid (AA), which is released from membrane phospholipids during cell activation through the 5-lipoxygenase pathway[4]. LTB4 and LTC4 are generated from linoleic acid (LA) (n-6 fatty acid) through AA, and LTB5 and LTC5 are generated from α-linolenic acid (α-LNA) (n-3 fatty acid) through eicosapentaenoic acid (EPA) in the same 5-lipoxygenase pathway.

Polyunsaturated fatty acids (PUFAS) of the n-3 series—EPA and docosahexaenoic acid (DHA)—suppress the production of LTs by antagonistic metabolism, which occur at the level of LT hydrolase through the 5-lipoxygenase pathway. At this level, they may exert an effect by altering LT generation by leucocytes. PUFAs reportedly demonstrated anti-inflammatory effects in patients with chronic inflammatory diseases such as rheumatoid arthritis, psoriasis, and chronic inflammatory bowel disease[5-11].

Several studies have suggested the beneficial effects of EPA or fish oil on bronchial asthma[12-15], whereas others have demonstrated no such beneficial effects[16, 17].

Our previous studies showed that the dietary supplementation with perilla seed oil, a vegetable oil rich in α-LNA inhibits the generation of LTs by leucocytes[18]. In the present study, we examined the factors that affect the suppression of generation of LTs by leucocytes with perilla seed oil rich supplementation in patients with asthma.

Subjects and Methods

The subjects were 19 patients (12 females and 7 males) with asthma. All patients were admitted to our hospital for treatment of asthma. Their mean age was 58.9 years old (range 22 to 73 years). Their mean serum IgE at admission was 372.3 ± 513.8U/ml (range 16.4 to 1681U/ml).

Bronchial asthma was evaluated according to the criteria of the International Consensus of Diagnosis and Management of Asthma[19]. All patients demonstrated a reversible airway response, as indicated by a 15% or greater increase in their forced expiratory volume in one second ($FEV_{1.0}$) after inhaled bronchodilator use. Informed consent was obtained from all patients. At the time of the study, all patients were undergoing regular treatment with long-acting oral theophyline, β_2 adrenergic agonists inhalation and glucocorticosteroid (beclomethasone dipropionate : BDP) inhalation. The mean dose of inhaled BDP was $347.4 \pm 238.9 \mu$ g/day.

Peak expiratory flow (PEF) in the early morning and evening was recorded in all subjects using a peak-flow meter (Assess : Health Scan Products Inc., Cedar Grove, NJ, USA).

The subjects were classified into 2 groups according to the degree of suppression of generation of LTC4 by leucocytes after dietary supplementation with perilla seed oil. Patients who showed suppressed generation after two weeks of supplementation were classified as "Diet Inhibition Group" (group A),

and those who showed no suppression were classified as "No Inhibition Group" (group B).

Group A subjects included 2 females and 5 males with a mean age of 54.3 years (range 22 to 72 years). Group B subjects included 10 females and 2 males with a mean age of 61.6 years (range 55 to 73 years).

The concentration of the serum total cholesterol, triglyceride, high density lipoprotein (HDL)-cholesterol, and phospholipid were assayed using a previously reported enzymatic method[20-23]. Low density lipoprotein (LDL)-cholesterol concentration was calculated from the formula [(serum total cholesterol) − (HDL-cholesterol) − 0.2 × (triglyceride)] (Friedwald's convert)[24]. β-lipoprotein was assayed by turbidimetry. Serum IgE level was estimated by the radioimmunosorbent test (RIST).

Pulmonary function tests, forced vital capacity (FVC) and forced expiratory volume in one second ($FEV_{1.0}$) were performed by Chestac 33(Chest Co.Tokyo, Japan) linked to a computer while the subjects were in an attack-free state, and the percentage of predicted values were calculated.

The generation of LTB4 and LTC4 by peripheral leucocytes was assessed by a method previously described[1,3]. Cells were separated by counterflow centrifugation elutriation using a JE 6B rotor (Beckman Co., Geneva, Switzerland)[25], as described previously[1,26]. The number of cells was then adjusted to 5×10^6 /ml in Tris ACM (composition : 1 ml of 0.1 mol/lCa^{2+}, 0.5ml of 0.1mol/l Mg^{2+} and 98.5 ml Tris A buffer ; Trizma preset crystal, pH 7.7 ; Sigma Chemical Co., St. Louis, Mo, USA). The Ca ionophore A23187 (1 μg) was added to the cell suspension. The mixed solution was incubated for 15 min at 4℃. Quantification of LTB4 and LTC4 by HPLC analysis was performed by a method described by Lam et al[27]. The extraction of LTs was performed using a C18 Seppak (Waters Associates, Milford MA). The concentrations of LTB4 and LTC4 were analyzed by HPLC, 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 are expressed as ng/5×10^6 cells.

The subjects consumed 10−20 g of corn oil (rich in LA) per day as salad dressing and /or mayonnaise instead of other oils for the first 2 weeks and the same amount of perilla seed oil (rich in α-LNA) per day for the subsequent 2 weeks. Other dietary components were not changed, and the amount of oil used in the diet and supplemented diet was recorded throughout the study period.

Data are expressed as mean ± standard deviation (SD). Statistically significant differences between the means were estimated using the Student's t-test. A p value of $<$ 0.05 was regarded as significant.

Results

LTB4 generation by leucocytes was influenced by dietary supplementation with corn oil and perilla seed oil as evidenced by a significant increase following corn oil-rich supplementation for two weeks ($P<0.05$), and a significant decrease following perilla seed oil-rich supple-mentation for two weeks ($P<0.05$) in group A (Fig. 1). Similarly, LTC4 generation by leucocytes increased significantly following corn oil-rich supplementation in group A. However, LTC4 generation did not change following corn oil-rich supplementation in group B. A significant difference in LTC4 generation was observed between group A and group B after corn oil-

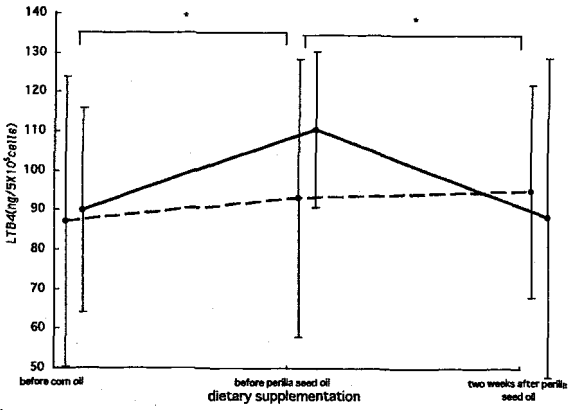

Fig. 1. Changes in LTB4 generation in the two study groups. LTB4 generation increased significantly following corn oil rich supplementation ($P<0.05$) and decreased significantly following perilla seed oil supplementation for two weeks in group A (Diet Inhibition Group) (●—●) ($P<0.05$). In contrast, LTB4 generation did not change significantly following either corn oil or perilla seed oil rich supplementation for two weeks in group B (No Inhibition Group) (● ··· ●). *:$P<0.05$

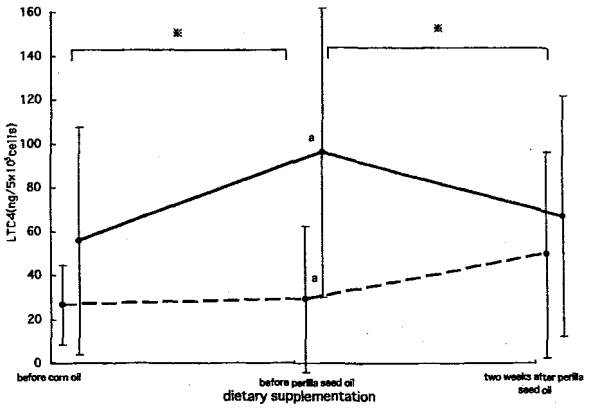

Fig. 2. Changes in LTC4 generation in the two study groups. LTC4 generation increased significantly following corn oil rich supplementation for two weeks in group A (●—●). In contrast, LTC4 generation did not change significantly following corn oil rich supplementation in group B (●···●). LTC4 generation differed significantly between the groups following corn oil rich supplementation for two weeks. ※$P<0.01$ a ; $P<0.05$.

rich supplementation for 2 weeks($P<0.05$) (Fig. 2).

Morning and evening PEF values prior to inhalation of the $\beta 2$ agonist were significantly higher in Group A than in group B during the study period (Table 1). The PEF value tended to increase in both group A and group B following dietary supplementation, although these increases were not significant.

The % FVC value did not differ between the two study groups before dietary supplementation. However, this value tended to increase in both groups following dietary supplementation. In group A, %FVC showed a significant increase following perilla seed oil rich supplementation for 2 weeks (Table 2). $FEV_{1.0}$ showed no significant change during the study period, although the value tended to increase in group A.

Table. 1. Comparison of morning and evening PEF value between the two groups.

		PEF value (L/min)		
		Before corn oil	Before perilla seed oil	After perilla seed oil
Group A	Morning	315.5±121.7[a]	357.1±138.3[c]	351.4±131.1[e]
	Evening	357.1±125.7[b]	377.1±125.1[d]	394.3±120.5[f]
Group B	Morning	173.3±121.7[a]	200.8±60.5[c]	222.1±50.9[e]
	Evening	204.2±59.5[b]	231.7±47.6[d]	232.5±50.5[f]

Group A: Suppression of LTC4 generation by dietary supplementation with perilla seed oil. Group B : no suppression of LTC4 generation observed PEF was significantly higher in group A than group B during the study period. *a,b,c,d,e and f:P<0.05*

The mean level of serum IgE was 794U/ml (range from 117U/ml to 1681U/ml) in

Table. 2. Comparison of %FVC value between the two study groups.

	%FVC (%)		
	Before corn oil	Before perilla seed oil	After perilla seed oil
Group A	93.8±28.9*	104±27.9	104.3±32.2*
Group B	93.8±15.8	96.3±16.3	96.8±8.6

Group A: Suppression of LTC4 generation by dietary supplementation with perilla seed oil. Group B : no suppression of LTC4 generation observed A significant increase after two weeks of perilla seed oil supplementation in group A was seen. *:P<0.05

group A, and 126U/ml (range from 16.4IU /ml to 353U/ml) in group B. The mean level was significantly higher in group A than in group B (P<0.02) (Fig.3). As a marker of serum lipometabolism, the levels of LDL-cholesterol, β-lipoprotein and phosphlipid were all significantly lower in group A than in group B prior to dietary supplementation (Table 3).

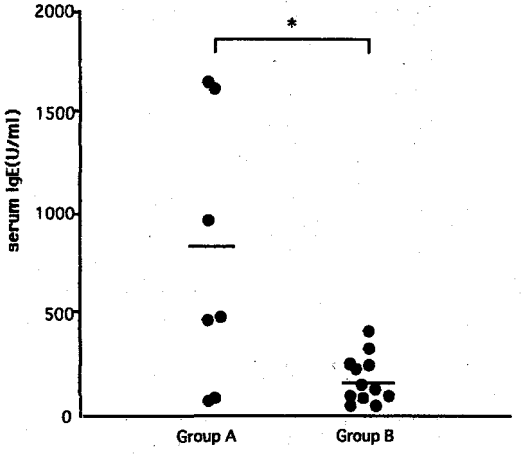

Fig. 3. Serum IgE levels in the two study groups. Mean IgE level was significantly higher in group A than group B. *: P<0.02

Discussion

LTs represent a major chemical mediator in asthma and play an important role in late asthmatic reaction (LAR). Large quantities

Table. 3. Serum lipometabolism in the two study groups

	Group A	Group B	P value
Total cholesterol(mg/dl)	187.9±34.9	208.4±23.5	NS
Triglyceride(mg/dl)	65.1±30.7	79.9±35.3	NS
HDL-Cholesterol(mg/dl)	63.6±17.3	72.1±26.5	NS
LDL-Cholesterol(mg/dl)	95.7±31.0	136.4±43.1	P<0.05
β-Lipoprotein(mg/dl)	307±58.2	434±24.0	P<0.05
Phosphlipid(mg/dl)	189.1±22.7	224.6±30.3	P<0.05

Group A: Suppression of LTC4 generation by dietary supplementation with perilla seed oil.
Group B : no suppression of LTC4 generation observed
NS: not significant

of these mediators are synthesized and/or released by inflammatory cells during an allergic reaction. The generation of LTB4 is reduced by n-3 fatty acids[28, 29]. LTB4 generation from LA and LTB5 from α-LNA have similar biological activities. However, the action of LTB5 is much weaker than that of LTB4. Cysteinyl LTs (LTC4, LTD4 and LTE4) have been implicated in the pathogenesis of allergen-induced airway responsiveness as potent contractile agonists for airway smooth muscle by mediating a later part of immediate airway obstruction −fall in $FEV_{1.0}$ − after allergen exposure[30, 31].

Dietary supplementation with perilla seed oil, which is rich in α-LNA has been proposed as a means to suppress the LT4 series generation by leucocytes and increase the generation of LT5 series through the 5-lipoxygenase pathway. Our previous study supported this hypothesis by demonstrating a significant suppression of LTB4 and LTC4 generation by leucocytes following perilla seed oil-rich supplementation[18].

Conversely, supplementation with corn oil, which is rich in LA, has been proposed to increase the generation of LTB4 and LTC4 from AA through the 5-lipoxygenase pathway.

The effects of n-3 fatty acids such as EPA and fish oil on asthma are controversial. Some investigators have suggested beneficial effects of n-3 fatty acids on asthma[12-15], whereas others have reported little effect[16, 17]. In the present study, the clinical features of patients whose generation of LTC4 by leucocytes was suppressed by perilla seed oil-rich supplementation (group A) were examined in comparison with those of patients who demonstrated no suppression (group B). LTB4 and LTC4 generation by leucocytes in group A significantly increased following corn oil-rich supplementation, whereas a significant decrease was observed following perilla seed oil-rich supplementation. In contrast, LTB4 and LTC4 generation in group B did not change following supplementation with either dietary substance. These results indicate that two asthmatic populations exist with respect to suppression of LTB4 and LTC4 generation by n-3 fatty acids in perilla seed oil, such that patients who demonstrate suppression of LT generation by leucocytes are sensitive to PUFAs in their diet. The results also suggest that n-3 fatty acid administration are effective in these patients.

The subjects in group A showed significantly higher PEF compared to group B, suggesting that group A subjects had a clinically better state of asthma than group B. The significant improvement of %FVC in group A following perilla seed oil-rich supplementation indicates that cysteinyl LTs could affect respiratory function.

LTs, which are IgE-dependent chemotactic factors, mediate IgE-dependent constriction of human bronchi[32-36]. A significant influence of dietary PUFA on the concentration of plasma IgE has been demonstrated by several researchers[37, 38]. Gosset P et al. demonstrated that IgE-dependent stimulation of alveolar macrophages (AMs) produces a neutrophil and eosinophil chemotactic activity that can be observed in a low molecular weight fraction, possibly related to LTs. Furthermore, they emphasized the role of AMs in inflammatory lung processes during allergic asthma[39]. Watanabe S et al. reported a significantly lower IgE antibody response against egg albumin in mice on a high α-LNA diet compared to those on a high LA diet, and emphasized the suppressive effects of a high α-LNA diet on the severity of immediate-type allergic hypersensitivity, together with the suppressive effects on the formation of lipid-derived allergic mediators, including LTs[38]. In the present study, group A subjects had higher IgE levels than group B subjects, indicating that IgE-dependent allergic reaction is influenced by LTB4, LTC4, and α-LNA diets through LT generation by leucocytes.

Previous reports have suggested that PUFA —particularly α-LNA— diets decrease serum cholesterol, LDL-cholesterol[39-43]. Recent dietary trends have included high consumption of saturated fatty acids and n-6 PUFAs and low n-3 PUFAs in our country[44]. The present results showed significantly lower levels of serum LDL-cholesterol, β-lipoprotein and phos-pholipid in group A compared to group B prior to the dietary supplementation, suggesting that group A subjects consumed n-3 fatty acids rich diets prior to the beginning of this study. The present results indicate that dietary supplementation with α-LNA affects LT generation by leucocytes through various factors such as IgE and lipometabolism. In particular, perilla seed oil supplementation rich in α-LNA may be effective in the treatment of asthma in select subjects.

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気管支喘息患者における白血球ロイコトリエン産生能に対する不飽和脂肪酸食の効果に影響する因子

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α－リノレン酸の豊富なエゴマ油の食事は気管支喘息患者の白血球ロイコトリエン（ＬＴ）産生能を抑制する。気管支喘息患者の内，エゴマ油食によりＬＴＣ４の産生が抑制された群（Ａ群）と抑制されない群（Ｂ群）の臨床データを比較することにより，気管支喘息患者の白血球ロイコトリエン産生能に影響する因子を検討した。Ａ群はコーン油（n-6系脂肪酸）の豊富な食事後，白血球ＬＴＢ４，ＬＴＣ４の産生能が増加し，エゴマ油（n-3系脂肪酸）の豊富な食事後ＬＴＢ４，ＬＴＣ４の産生能が減少した。これらの変化はＢ群では認められなかった。Ａ群のＩｇＥ値，ピークフロー（ＰＥＦ）値はＢ群に比し，有意に高値であった。またＬＤＬ－コレステロール，β－リポ蛋白，リン脂質はＡ群ではＢ群に比し，有意に低値であった。これらの結果はエゴマ油の豊富な食事のn-3系脂肪酸によるＬＴＢ４，ＬＴＣ４の産生能の抑制に関して２群の気管支喘息患者群間に臨床データの相違があることを示唆している。

索引用語：エゴマ油，気管支喘息，ロイコトリエン，ＩｇＥ，脂質代謝