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Effects of α-linolenic acid-rich supplementation on leukotriene generation by leucocytes in patients with asthma associated with lipometabolism

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Abstract: Dietary sources of α-linolenic acid, such as perilla seed oil, may have the capacity to inhibit the generation of leukotrienes (LTs) by leucocytes in patients with asthma, as has been reported with the consumption of other long-chain n-3 fatty a-cids.

The factors affecting the suppression of leukotriene (LT) C4 generation by leucocytes were examined by comparing the clinical features of patients with asthma who had been given dietary perilla seed oil (n-3 fatty acids). Group A consisted of patients in whom the leucocyte generation of dietary perilla seed oil LTC4 was suppressed by this procedure. Group B consisted of those in whom LTC4 generation was not suppressed.

LTC4 generation by leucocytes significantly decreased in group A for two ($P<0.05$) and four weeks ($P<0.05$), conversely, significantly increased in group B for four weeks ($P<0.05$). The two study groups differed significantly in LTC4 generation by leucocytes after four weeks of dietary supplementation ($P<0.05$). Ventilatory parameters such as peak expiratory flow (PEF), forced vital capacity (FVC) and forced expiratory volume in one second ($FEV_{1.0}$) increased significantly after four weeks of dietary supplementation in group A ($P<0.05$). Values of PEF, FVC, $FEV_{1.0}$ and V_{25} between groups A and B significantly differed prior to dietary supplementation. Serum levels of total cholesterol, LDL-cholesterol and phospholipid were significantly decreased by dietary supplementation in group A after four weeks. Serum levels of total-choles terol, triglyceride, HDL-Cholesterol, LDL-Cholesterol and phospholipid values between the two study groups differed significantly prior to dietary supplementation. Serum levels of triglyceride and LDL-cholesterol differed significantly between the two

study groups after four weeks of dietary supplementation.

The effects of dietary supplementation with perilla seed oil to patients with asthma by suppressing the generation of LTC4 is associated with clinical features such as respiratory function and lipometabolism.

key word : α-linolenic acid, leukotrieneC4, bronchial asthma, lipometabolism

Introduction

Asthma is a chronic inflammatory disease of the airways, that is characterized by recurrent episodes of wheezing, breathlessness, chest tightness, cough variable airflow obstruction (often reversible either spontaneously or with treatment) and bronchial hyperresponsiveness[1]. The airways of patients with asthma have increased numbers of both inflammatory cells and their products compared with normal individuals[2]. Airflow obstruction associated with asthma consists of airway wall swelling, elevated luminal secretion, increased presence of inflammatory cells in the airway wall, and muscle contraction[3]. Numerous chemical mediators including leukotrienes (LTs) released in the airways can elicit an allergic reaction. Four series LTs (LTC4, LTD4 and LTE4) increase postcapillary permeability, and are potent stimulators of airway smooth muscle cells that mediate airway inflammation through their involvement in vasoconstriction and mucus secretion[4]. LTC4 and D4 can stimulate the contraction of smaller airways of pulmonary parenchymal tissue[5] and the smooth muscle of the lobar and segmental bronchi in vitro[4]. Leukotrienes are present in the blood, bronchial alveolar lavage fluid and urine of asthmatics and are produced by cells that mediate airway inflammation in asthma[6]. The principal 5-lipoxygenase product of human eosinophils[7] and mast cells[8] is LTC4.

Our previous studies demonstrated that histamines and LTC4 participate in the onset mechanism of atopic asthma, whereas only LTC4 participates in the onset of non-atopic asthma[9]. Leukotrienes are generated from arachidonic acid (AA), which is released from membrane phospholipids during cell activation through the 5-lipoxygenase pathway[10]. Leukotrienes B4 and C4 are generated from AA derived from linoleic acid (LA) (n-6 fatty acid), and LTB5 and LTC5 are generated from eicosapentaenoic acid (EPA) derived from α-linolenic acid (α-LNA) (n-3 fatty acid) through in the same 5-lipoxygenase pathway.

Polyunsaturated fatty acids (PUFA) 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. At this level, PUFA may exert an effect by altering LT generation by leucocytes. Anti-inflammatory effects of PUFA have been demonstrated in patients with chronic inflammatory diseases such as rheumatoid arthritis, psoriasis and chronic inflammatory bowel disease[11-16]. Several studies have suggested beneficial effects of EPA or fish oil on asthma[18-22], whereas others have demonstrated no such effects[23,24].

Our previous studies showed that dietary supplementation with perilla seed oil, a vegetable oil rich in α-LNA, inhibits the generation of LTs by leucocytes[25]. In the present study, we examined the factors that affect the suppressive effects of perilla seed oil supplementation on the generation of LTC4 by leucocytes in patients

with asthma.

Subjects and Methods

Twenty six patients (16 females and 10 males) with mild asthma were admitted to our hospital for treatment (mean age, 61.0 year ; range 30 -84 year). Their mean serum IgE level at admission was 771.6U/ml (range 21.1 to 9780U/ml). Thirteen patients were atopic and thirteen patients were non-atopic, and the mean duration of asthma for both groups was 8.7 years.

Asthma was evaluated according to the criteria of the International Consensus of Diagnosis and Management of Asthma[26]. All patients demonstrated a reversible airway response, as indicated by a 15% or greater increase in forced expiratory volume in one second ($FEV_{1.0}$) after inhaled bronchodilator use. The study was approved by the Institutional Human Investigation Committee at our hospital. Informed consent to participate in the study was obtained from all p atients. At the time of the study, all patients were undergoing regular treatment with long-acting oral theophylline, inhaled β_2 adrenergic agonists and glucocorticosteroid (beclomethasone dipropionate : BDP). The mean dose of inhaled BDP was 305.8 μ /day.

The patients consumed 10-20g of perilla seed oil (rich in α-LNA) per day as salad dressing and/or mayonnaise instead of other oils for 4 weeks. The mean dose of consumed perilla seed oil was 14.65±1.41g/day. Other dietary components were not changed, and the amount of oil used in the diet and supplemented diet was recorded throughout the study period.

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

The patients were classified according to the degree of suppression of generation of LTC4 by leucocytes after four weeks of dietary supplementation with perilla seed oil. Patients in whom LTC4 generation was suppressed by supplementation were classified as "Diet Inhibition" (group A), and those in whom no suppression was evident, were classified as "No Inhibition" (group B).

Group A included 11 females and 4 males with a mean age of 64.3 years (range 44 to 84 years). Group B included 5 females and 6 males with a mean age of 56.5 years (range 30 to 73 years).

The concentrations of serum total cholesterol, triglyceride, high density lipoprotein (HDL)-cholesterol and phospholipid were assayed using an enzymatic method[27-30]. Low density lipoprotein (LDL)-cholesterol concentration was calculated from the following formula : [(serum total chol esterol) − (HDL-cholesterol) − 0.2× (triglyceride)] (Friedwald's convert)[31], and β-lipoprotein was assayed by turbidimetry. Serum IgE levels were estimated by the radioimmunosorbent test (RIST).

Pulmonary function tests, forced vital capacity (FVC), forced expiratory volume in one second ($FEV_{1.0}$) and V_{25} were performed using a Chestac 33 (Chest Co. Tokyo, Japan) linked to a computer while the patients were at an attack-free state.

The generation of LTC4 by peripheral leucocytes was assessed as described[9,32]. Cells were separated by counterflow centrifugation elutriation using a JE 6B rotor (Beckman Co., Geneva, Switzerland) [33], as described[32,34]. The number of cells was then adjusted to 5×10^6/ml in Tris ACM (composition : 1ml of 0.1mol/l Ca^{2+}, 0.5 ml of 0.1mol/l Mg^{2+} and 98.5ml 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 and incubated for 15 min at 37℃. Leukotriene

C4 was quantified by HPLC as described by Lam et al[35]. Leukotrienes were extracted using a C18 Seppak (Waters Associates, Milford, MA) and the LTC4 concentrations were determined by HPLC, Model 510 (Waters Associates, Milford, MA), equipped with an ultraviolet detector. The column was a 5㎜×10㎝ Radial-Pax cartridge (Shimazu Co., Kyoto, Japan). The results are expressed as ng/5×10⁶cells.

All data are expressed as means ±SEM. Student's t-test was used for paired analysis. Groups were compared by the one-way analysis of variance (ANOVA) and $p<0.05$ was considered significant. Analyses were performed using StatView 5.0 (Abacus Concepts, Inc., Berkeley, CA).

Results

Group A leucocytes generated significantly less LTC4 after two and four weeks of supplementation with perilla seed oil ($P<0.05$). However, LTC4 generation increased significantly after four weeks of dietary supplementation in group B ($P<0.05$). Leukotriene C4 levels significantly differed between the two study groups after four weeks of dietary supplementation ($P<0.05$) (Fig. 1).

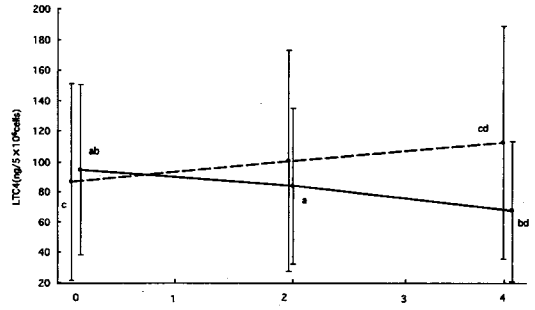

Fig 1.

Figure 1. Changes in LTC4 generation in two study groups. LTC4 generation decreased significantly after two and four weeks of perilla seed oil supplementation in group A (●—●). In contrast, LTC4 generation increased significantly after four weeks of supplementation in group B (●···●). Levels of LTC4 significantly differed between groups A and B after four weeks of dietary supplementation. Each points represents the mean±SEM for 15 subjects (group A) and 11 subjects (group B).

a, b, c and d, $P<0.05$. LTC4 : leukotriene C4.

Morning PEF values were significantly lower in group A than in group B during the study period ($P<0.05$). These values increased significantly in both groups after two ($P<0.05$) and four weeks ($P<0.05$) of dietary supplementation (Table1).

Table1. Comparison of morning PEF values between groups A and B.

	PEF value(L/min)		
	before	after two weeks	after four weeks
Group A	241.3±134.9^{a,b,f}	259.3±113.9^{a,c,g}	271.3±105.1^{b,c,h}
Group B	366.7±163.0^{d,e,f}	386.7±148.6^{d,g}	388.9±138.6^{e,h}

Group A : LTC4 generation suppressed by diet ary supplementation wit h perilla seed oil.
Group B: no suppression of LTC4 b y supplementation.
Each value represents t he mean±SEM for 15 subjects(group A) and 11 subjects(group B)
a,b,c,d,e,f,g and h ,$P<0.05$.

The FVC, $FEV_{1.0}$ and V_{25} values were significantly lower in group A than in group B prior to dietary supplementation. The FVC and FE $V_{1.0}$ values increased significantly in group A following dietary supplementation ($P<0.05$). However, supplementation did not significantly increase these ventilatory parameters in group B. In contrast, FVC and $FEV_{1.0}$ values between the two study groups differed significantly after four weeks of dietary supplementation (Table2).

Table 2. Comparison of ventilatory parameters between groups A and B.

		Dietary supplementation	
		before	after four weeks
FVC(L)	group A	2.31±0.50^{a,b}	2.43±0.40^{a,c}
	group B	3.39±1.16^{b}	3.43±1.30^{c}
$FEV_{1.0}$(L)	group A	1.45±0.48^{d,e}	1.68±0.51^{df}
	group B	2.68±0.98^{e}	2.62±1.07^{f}
V_{25}(L/sec)	group A	0.43±0.34^{g}	0.51±0.47
	group B	0.97±0.62^{g}	0.86±0.61

Group A : LTC4 generation suppressed by diet ary supplementation wit h perilla seed oil.
Group B: no suppression of LTC4 b y supplementation.
Each value represents t he mean±SEM for 15 subjects(group A) and 11 subjects(groupB).
a, b, c,d, e, f, and g,$P<0.05$.

Serum levels of total-cholesterol, HDL-Chol-

esterol, LDL-Cholesterol and phosphlipid were significantly higher in group A than in group B prior to dietary supplementation ($P<0.05$). The serum level of triglyceride was significantly lower in group A than in group B ($P<0.05$). Serum levels of total cholesterol, LDL-Cholesterol and phospholipid decreased significantly after four weeks of dietary supplementation in group A ($P<0.05$). The serum level of LDL-cholesterol in both groups decreased significantly after four weeks of dietary supplementation ($P<0.05$). Sereum levels of triglyceride and LDL-cholesterol differed significantly between the two groups after four weeks of dietary supplementation ($P<0.05$) (Table 3).

Table 3. Comparison of lipometabolism between group s A and B.

		dietary su pplementation	
		before	after four weeks
Total cholesterol(mg/dl)	group A	216.5±39.5^{ab}	198.0±45.9^{a}
	group B	191.0±20.9^{b}	179.8±31.8
Triglyceride(mg/dl)	group A	65.2±25.8^{c}	62.4±13.1^{d}
	group B	90.9±41.3^{c}	80.6±20.1^{d}
HDL-Cholesterol(mg/dl)	group A	70.1±22.5^{e}	65.6±22.1
	group B	54.7±16.8^{e}	51.6±26.0
LDL-Cholesterol(mg/dl)	group A	145.8±36.7^{fg}	135.9±22.2^{fh}
	group B	121.3±15.1^{gi}	108.2±20.0^{hj}
β-Lipoprotein(m g/dl)	group A	428.6±71.2	419.7±76.8
	group B	410.1±48.1	386.0±63.0
Phospholipid(mg/dl)	group A	250.8±19.2^{jk}	216.4±35.0^{i}
	group B	199.5±23.8^{k}	194.0±28.9

Group A : LTC4 generation was suppressed by dietary su pplementation.
Group B: no suppression of LTC4 generation by perilla seed oil.
Each value represents the mean ±SEM for 15 subjects(group A) and 11 s ubjects(group B).
a, b,c, d, e, f, g, h, i, j and k,P<0.05.

Discussion

Leukotrienes constitute a group of major chemical mediators in asthma that play an important role in the late asthmatic reaction (LA R). Large quantities of these mediators are synthesized and/or released by inflammatory cells during an allergic reaction. Leukotrienes C4, D4 and E4 are implicated in the pathogenesis of allergen-induced airway responsiveness as potent contractile agonists of airway smooth muscle that act by mediating the late stage of immediate airway obstruction (fall in $FEV_{1.0}$) after exposure to an allergen[36,37].

Dietary supplementation with perilla seed oil, which is rich in α-LNA, has been proposed as a means of suppressing LT4 series generation by leucocytes and of increasing the generation of the LT5 series through the 5-lipoxygenase pathway. Our previous study supported this notion by demonstrating a significant suppression of LTB4 and LTC4 generation by leucocytes following perilla seed oil supplementation[25].

The effects of n-3 fatty acids such as EPA and fish oil on asthma are controversial. Some investigators have suggested beneficial effects[17-22], whereas others have reported little effect[23, 24]. Our preliminary examinations suggested two asthmatic populations with respect to suppression of LTC4 generation by the n-3 fatty acids in perilla seed oil. We therefore compared the clinical features of patients in whom LTC4 generation by leucocytes was suppressed (group A) or not (group B) by perilla seed oil supplemetation. Dietary supplementation with perilla seed oil for two and four weeks significantly suppressed LTC4 generation by leucocytes in group A. In contrast, LTC4 generation in group B increased significantly after four weeks of supplementation. These results show that patients in whom LT generation by leucocytes is suppressed, are sensitive to dietary PUFAs. The results also suggest that n-3 fatty acids were effective in these patients.

Group A had significantly lower ventilatory parameters-PEF, FVC, $FEV_{1.0}$ and V_{25}-compared with group B, suggesting that group A subjects had a clinically more severe state of asthma

than group B. The FVC and $FEV_{1.0}$ values were significantly improved only in group A after four weeks of perilla seed oil supplementation. This indicates that LTC4 affects respiratory function in group A. PEF values increased in both two groups during the study. This was thought tobe caused by the other therapy (drugs and respiratory rehabilitation) accompanied with diet therapy.

Recent dietary trends in Japan include increasing consumption of saturated fatty acids and n-6 PUFAs, whereas that of low n-3 PUFAs was decreased[38]. The present results showed significantly higher levels of serum total-cholesterol, HDL-Cholesterol, LDL-Cholesterol and phospholipid and a significantly lower level of serum triglyceride in group A than in group B prior to dietary supplementation, suggesting that group A patients consumed diets that were rich in n-6 fatty acids prior to the beginning of this study.

Other reports suggest that PUFA diets—including α-LNA—decrease serum lipids[39-48]. Some researchers have demonstrated that perilla oil supplementation decreases serum lipids in rats[47,48]. In the present study, the levels of serum total cholesterol, LDL-cholesterol and phospholipid decreased significantly in group A after four weeks of perilla seed oil supplementation and the serum levels of triglyceride and LDL-cholesterol differed significantly between the two groups after four weeks of dietary supplementation. These results indicate that dietary supplementation with α-LNA affects lipometabolism.

The results obtained in the present study suggest that perilla seed oil supplementation helps in treating selected patients with asthma by suppressing leukotriene generation by leucocytes. In addition, lipometabolism may be associated with this effect. The present study also indicates that dietary therapy may help attenuate asthmatic symptoms. Further studies are needed so that a nutritionally balanced therapeutic diet can be developed for patients with asthma.

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脂質代謝に関連した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α－リノレン酸食の効果

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エゴマ油のようなα－リノレン酸食が他のn-3系不飽和脂肪酸食において報告されてきた様に喘息患者の白血球ロイコトリエン（LTs）産生能を抑制すると考えられる。そこでエゴマ油（n-3系脂肪酸）を摂取した気管支喘息患者の臨床所見を比較することによって白血球ロイコトリエン（LT）C4の抑制に影響する因子を検討した。A群はエゴマ油摂取により白血球LTC4の産生能が抑制された群であり、B群は白血球LTC4の産生能が抑制されなかった群である。A群では食事摂取2週後（$P<0.05$），4週後（$P<0.05$）に白血球LTC4産生能が低下した。逆にB群では摂取4週後有意に増加した（$P<0.05$）。2群間で食事摂取4週後に白血球LTC4産生能に有意差がみられた（$P<0.05$）。ピークフロー値（PEF）、努力性肺活量（FVC）、1秒量（FEV_1）といった呼吸機能はA群において食事摂取4週後に有意に上昇した（$P<0.05$）。食事摂取前のPEF、FVC、FEV_1、V_{25}はA群，B群の2群間で有意差がみられた。A群において血清総コレステロール、低比重リポ蛋白（LDL）コレステロール、リン脂質は食事摂取4週後に有意に低下した。食事摂取前の血清総コレステロール、中性脂肪、高比重リポ蛋白コレステロール、LDLコレステロール、リン脂質において2群間に有意差がみられた。血清中性脂肪、LDLコレステロールは食事摂取4週後2群間に有意差がみられた。気管支喘息患者のある群へのエゴマ油食はLTC4産生能を抑制し、それには呼吸機能や脂質代謝といった臨床因子が関連していると考えられた。