
◎原 著

The clinical effects of dietary supplementation with n-3 fatty acids in bronchial asthma compared with n-6 fatty acids.

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Abstract: N-3 fatty acids, such as fish oil, have been reported to have some beneficial effects in patients with bronchial asthma by suppressing leukocyte function, followed by reduction of the need for pharmacologic agents. To examine the effects of dietary supplementation with perilla seed oil rich in α -linolenic acid (ALA), 23 patients with asthma took corn oil rich in linoleic acid (LA) for the former two weeks, perilla seed oil for the later two weeks. The asthmatic patients were classified into two groups by the changes of the generation of leukotrienes B₄ (LTB₄), C₄ (LTC₄), and B₅ (LTB₅) during the two courses of dietary modification: one was sensitive to dietary modification, and the other was insensitive to dietary supplementation. We compared the two groups in clinical characteristics. Significant differences were observed in peak flow (PEF), forced expiratory volume in one second (FEV_{1.0}), IgE, sex, obesity index (OI), concentration of serum total cholesterol, albumin, low density lipoprotein (LDL)-cholesterol, β -lipoprotein and phospholipids between two groups.

This study indicated that these factors influence the generation of LTB₄, C₄ and B₅ of asthmatic patients in dietary supplementation.

Key words: n-3 fatty acids, perilla seed oil, bronchial asthma, LTB₄, LTC₄.

Introduction

Bronchial asthma is characterized by airway inflammation, by bronchial hyperresponsiveness to non-specific stimuli, and episodic and reversible airflow

obstruction. Airway inflammation may be central to pathophysiology of bronchial asthma.

Leukotrienes (LTs) are one of the most important chemical mediators released from inflammatory cells, which are involved in the pathogenesis of bronchial

asthma. Peptide LTs (LTC₄, D₄ and E₄) have a bronchoconstrictor action and participate in the onset of asthma attacks¹⁾²⁾.

LTB₄ plays an important role in the process of asthmatic response by recruiting leukocytes 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 pathway³⁾.

LTB₄ and LTC₄ are generated from LA through AA and that LTB₅ from LA through eicosapentaenoic acid (EPA) in same 5-lipoxygenase pathway. Perilla seed oil-rich supplementation containing much ALA have been expected to suppress the LTs generation by leukocytes and increase the generation of LTB₅. As the same reason, corn oil-rich supplementation containing much LA are supposed to increase the generation of LTB₄ and LTC₄ and decrease the generation of LTB₅ by leukocytes.

Polyunsaturated fatty acids (PUFA) of the n-3 series -EPA and docosahexaenoic acid (DHA)-suppress the production of LTs by antagonistic metabolism, which is occurred at the level of LT hydrolase through the 5-lipoxygenase pathway and therefore they have a potential to alter LTs generation by leukocytes. These PUFAs have been reported to show an anti-inflammatory effects in patients with chronic inflammatory diseases such as rheumatoid arthritis, psoriasis, and chronic inflammatory bowel disease⁴⁾⁻¹⁰⁾. Several reports have focused the beneficial effects of EPA or fish oil on bronchial asthma¹¹⁾⁻¹⁴⁾. In contrast, other several reports have not demonstrated the beneficial effects of EPA in patients with bronchial asthma¹⁵⁾¹⁶⁾.

In previous study¹⁷⁾, we examined the effectiveness of a diet containing perilla seed oil, a vegetable oil rich in ALA for inhibition of LT generation. Perilla seed oil has a large amount of ALA compared with corn oil rich in LA.

In this study, we examined the effects of perilla seed oil supplementation in patients with asthma to show

the importance of the quality of the fatty acid that influences a ratio between n-6 and n-3 fatty acids (n-6:n-3) by affecting the LTs generation by leukocytes.

Subjects and Methods

Subjects

The subjects of this study were 23 patients (15 females and 8 males) with asthma. All patients were admitted to Misasa Branch Hospital for treatment of asthma. Their mean age was 57.4 years (ranged from 22 to 73 years) and the mean of serum IgE was 460.5IU/ml (ranged from 16.4 to 2811IU/ml).

Bronchial asthma was evaluated according to the criteria of the International Consensus of Diagnosis and Management of Asthma¹⁸⁾. All patients revealed reversible airway response with a difference between prebronchodilator and postbronchodilator values of FEV_{1.0} exceeding 15%. An informed consent for study protocol was obtained from all patients. All patients had been taking long-acting oral theophylline, inhaled β_2 adrenergic agonists and inhaled glucocorticosteroid (beclomethasone) regularly.

Clinical symptoms, such as cough, wheeze, daytime activity, volume of sputum and dyspnea were observed daily and assessed by a score according to the evaluation system developed by the Committee of the Japanese Society of Allergology. Peak flow in the early morning and evening was recorded in all subjects using peak-flow meter (Assess: Health Scan Products Inc., Cedar Grove, NJ, USA).

The following parameters were evaluated by a formula described below.

Standard body weight(kg) = {body height (cm) -110} x 0.9

OI(%)=(body weight) (kg) / (standard body weight) (kg) x 100

Body mass index(BMI)=[{body weight(kg)} / {body height(m)}²] \times 100

The concentration of the serum total cholesterol, triglyceride, high density lipoprotein (HDL)-cholesterol, free fatty acid and phospholipid were assayed by

a enzyme (cholesterol oxydase) method. The concentration of the serum total protein was assayed by Biuret method and the concentrations of the serum albumin and albumin/globulin ratio (A/G ratio) were assayed by BCG method + Biuret method. LDL-cholesterol was calculated from the formula [(serum total cholesterol) - (HDL - cholesterol) - 0.2 x (triglyceride)] (Friedwald's convert)¹⁹⁾

Serum IgE level was examined by radioimmunosorbent test (RIST).

Pulmonary function tests, %forced vital capacity (%VC), FEV1.0, V25, residual volume (RV) and %diffusing capacity of lung (%DLco) were performed by CHESTAC33 (Chest Co. Tokyo, Japan) linked to a computer, when they were attack free.

The generation of LTB₄, LTC₄ and LTB₅ by perioheral leukocytes was assessed by a method previously described²⁰⁾²¹⁾. Cells were separated by counterflow centrifugation elutriation with a JE6B rotor (Beckman Co. Geneva, Switzerland)²²⁾, as described previously²³⁾. After the number of the cells was adjusted to 5x10⁶/ml in Tris ACM (composition: 1ml of 0.1 mol/l Ca²⁺, 0.5ml of 0.1 mol/l Mg²⁺ and 98.5ml Tris A buffer; Trizma preset crystal, pH7.7; Sigma Chemical Co., St. Louis, Mo, USA). Ca ionophore A23187 (1 μg) was added to the cell suspension. The mixed solution was incubated for 15 min at 4 °C. The HPLC analysis for extraction and quantification of LTB₄, LTC₄ and LTB₅ was performed by a method described by Lam et al.²⁴⁾. The extraction of LTs was performed using a C18 Seppak (Waters Associates). The concentrations of LTB₄, LTC₄ and LTB₅ were analysed by HPLC system, Model 510 (Waters Associates), equipped with an ultraviolet detector. The column used was a 5mm x 10cm Radial-Pax cartridge (Shimadzu Co. Kyoto, Japan). The results were expressed as ng/5x10⁶cells.

The subjects took 10-20 gram of corn oil per day as salad dressing and/or mayonnaise instead of other oils for the former 2 weeks and the same dosage of perilla seed oil per day for the later 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.

We classified the subjects into 2 groups by the generation of LTB₄, C₄ and B₅. After administration of corn oil for 2 weeks, an increase of generation of LTB₄ or LTC₄ or decrease of the generation of LTB₅ was counted as score 1. After supplementation perilla seed oil for 2 weeks, the decrease of the generation of LTB₄ or LTC₄ or the increase of the generation of LTB₅ was counted as score 1. The group of the total score more than 3 was evaluated as "sensitive to diet", and the group of the total score less than 3 was evaluated "insensitive to diet".

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

Results

The group of the "sensitive to diet" included 5 females and 8 males. The mean age of the group was 54.5 years (ranged from 22 to 72 years). Ten subjects of the "insensitive to diet" were all females. The mean age of the group was 61.2 years (ranged from 55 to 73 years).

As the clinical backgrounds of the two groups given in Table 1 shows that the number of the male, height and serum IgE levels were significantly higher, and obesity index was significantly lower in the "sensitive to diet" group compared with those in the "insensitive to diet" group. However, there were not significantly, differences in age at onset and BMI between the two groups. The difference of the height might depend on the different number of male between the two groups.

The generation of LTB₄, C₄ and B₅ by leukocytes were shown in Fig. 1, 2, and 3. LTs generation before the beginning of this study was higher in the "sensitive to diet" group than that in the "insensitive to diet" group. In the "sensitive to diet" group, the generation of LTC₄ after corn oil-rich supplementation (Fig.2) and the generation of LTB₅ after the two

Table 1 The clinical differences in sex, onset age, age, weight, IgE, height, BMI and OI between the 2 groups.

	"sensitive to diet"	"insensitive to diet"
sex(female/male)**	13(5/8)	10(10/0)
onset age(year)	36.3±19.8	47.1±15.1
age(year)	54.5±17.0	61.2±5.8
weight(kg)	58.7±10.8	60.8±16.4
IgE(IU/ml)*	696.0±858.3	154.5±125.9
height(cm)**	159±8.9	151.3±4.7
BMI(%)	23.2±3.9	26.5±6.5
OI(%)*	111.6±20.3	131.7±31.2

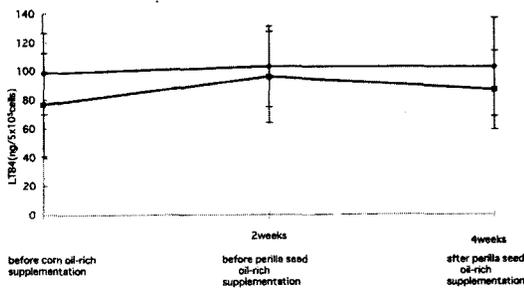


Fig 1. The changes of LTB4 in the 2 groups during 2 different courses of dietary supplementation. LTB4 generation in the "sensitive to diet" group (●) was higher than that in the "insensitive to diet" group (■).

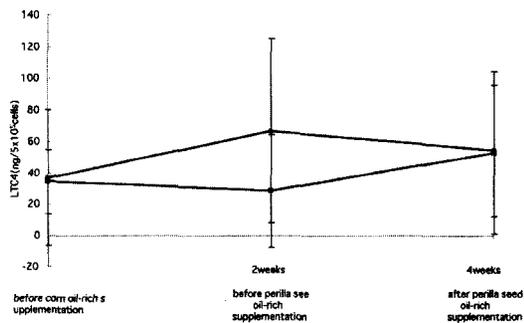


Fig 2. The changes of LTC4 in the 2 groups during 2 different courses of dietary supplementation. LTC4 generation in the "sensitive to diet" group (●) was higher than that in the "insensitive to diet" group (■).

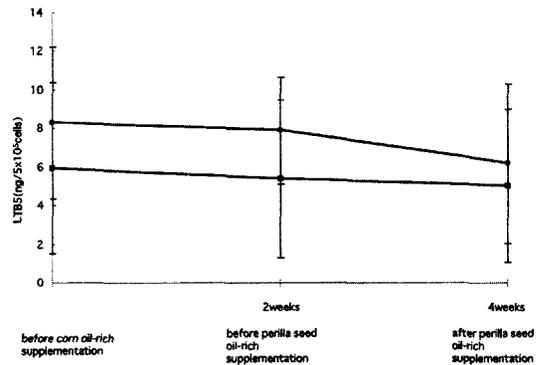


Fig 3. The changes of LTB5 in the 2 groups during 2 different courses of dietary supplementation. LTB5 generation in the "sensitive to diet" group (●) was higher than that in the "insensitive to diet" group (■).

kinds of supplementation (Fig.3) were larger compared with the generation in the "insensitive to diet" group.

In respiratory function, PEF in the morning and evening and FEV1.0 values before inhalation of β 2 agonist significantly more increased in the "sensitive to diet" group compared with the "insensitive to diet" group (Table 2). No significant differences in %VC, FEV1.0%, RV and DLco values were observed between the two groups.

Table 2 The differences in respiratory functions between the 2 groups.

	"sensitive to diet"	"insensitive to diet"
PEF(morning)(l /min)*	266.8±110.1	189.0±88.9
PEF(evening)(l /min)*	295.7±122.6	226.0±63.5
%VC(%)	93.43±21.40	93.99±16.99
FEV1.0(l)*	1.90±0.80	1.48±0.31
FEV1.0%(%)	76.55±25.42	79.74±13.39
V25(l)	0.60±0.57	0.48±0.27
%V25(%)	29.33±21.70	32.54±20.28
RV(l)	4.22±6.52	1.75±0.52
%DLCO(%)	89.38±22.93	94.03±19.60

Symptomatic score (SS), Therapeutic score (TS) and Asthmatic score (AA) were not significantly different between the 2 groups (Table 3). Regarding to lipometabolism, the "sensitive to diet" group showed

significantly lower levels of total cholesterol, LDL-cholesterol, β -lipoprotein and phospholipid, and significantly higher levels of serum albumin compared with the levels in the "insensitive to diet" group (Table 4). No significant differences were observed in serum total protein and A/G ratio between the two groups.

Table 3 The differences in asthmatic severity between the 2 groups.

	"sensitive to diet"	"insensitive to diet"
SS	1.7 \pm 2.6	1.9 \pm 2.1
TS	14.3 \pm 9.1	14.1 \pm 7.3
AS	16.0 \pm 9.5	16.0 \pm 6.6

Table 4 The lipometabolic differences between the 2 groups.

	"sensitive to diet"	"insensitive to diet"
total cholesterol(mg/dl)**	182.5 \pm 32.0	216.3 \pm 15.9
triglyceride(mg/dl)	81.6 \pm 35.1	31.6 \pm 0.2
HDL-cholesterol(mg/dl)	67.2 \pm 27.2	68.9 \pm 15.9
LDL-cholesterol(mg/dl)*	99.1 \pm 27.0	133.1 \pm 21.7
β -lipoprotein(mg/dl)*	367.1 \pm 90.2	430.5 \pm 62.3
free fatty acid(mEq/l)	0.46 \pm 0.16	0.46 \pm 0.25
phospholipid(mg/dl)**	187.9 \pm 22.8	232.3 \pm 16.6
total protein(g/dl)	7.09 \pm 0.80	7.04 \pm 0.43
albumin(g/dl)*	3.89 \pm 0.21	3.58 \pm 0.35
A/G ratio	1.28 \pm 0.30	1.15 \pm 0.31

Discussion

Bronchial allergen challenge induces an immediate asthmatic reaction (IAR) within 30 minutes and a late asthmatic reaction (LAR), in which occurs 6-8 hours after the challenge. The LAR, in which inflammatory cells such as lymphocytes, neutrophils, eosinophils and basophils migrate into allergic reaction sites in the airway²⁾²⁵⁾, is closely associated with bronchial hyperresponsiveness²⁶⁾²⁷⁾. LTs are one of the major chemical mediators in asthma and play important roles in the LAR.

LTs are synthesized by inflammatory cells in large amounts during allergic reactions. The generation of LTB₄ is reduced by n-3 fatty acids²⁸⁾²⁹⁾. LTB₄ generation from LA and LTB₅ from ALA have similar biological activities. However, the action of LTB₅ is much weaker than that of LTB₄. The cysteinyl LTs

(LTC₄, LTD₄ and LTE₄) are 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 exposure³⁰⁾³¹⁾. In this study, the "sensitive to diet" group showed significantly higher values of FEV_{1.0} and PEF compared with the values in the "insensitive to diet" group. The results show that the "sensitive to diet" group had clinically better states of bronchial asthma than the "insensitive to diet" group and that cysteinyl LTs might affect respiratory function as expiratory FEV_{1.0} and PEF in asthmatic patients.

LTs, as IgE-dependent chemotactic factor, mediate IgE-dependent constriction of human bronchi³²⁾³⁶⁾. Significant influence of dietary PUFA to the concentration of plasma IgE has been demonstrated in several reports³⁷⁾³⁸⁾. Gosset P et al. have demonstrated that IgE-dependent stimulation of alveolar macrophages (AMs) produces a neutrophil and eosinophil chemotactic activity, present in a low molecular weight fraction possibly related to LTs, and emphasized the role of AMs in inflammatory lung processes during allergic asthma³³⁾. Watanabe S et al. have reported that IgE antibody response against egg albumin was significantly lower in the high ALA diet group than in the high LA diet group in mice and emphasized suppressive effects of a high ALA diets on the severity of immediate-type allergic hypersensitivity, together with the suppressive effects on the formation of lipid-derived allergic mediators, including LTs³⁸⁾. Our study showed the "sensitive to diet" group had higher IgE levels than the "insensitive to diet" group. This indicates that ALA diet affect IgE-dependent allergic reaction through LTs generation by leukocyte.

Many reports have demonstrated that the PUFA-especially ALA- diets decreases serum cholesterol, LDL-cholesterol³⁹⁾⁴³⁾. And de Lorgeril M. et al. also reported ALA diets increased serum albumin⁴⁴⁾. Recent diets tends to contain high saturated fatty acids and n-6 PUFAs and low n-3 PUFAs. Our study

showed the "sensitive to diet" group has significant low serum cholesterol, LDL-cholesterol, phospholipid and free fatty acid and high serum albumin compared with the "insensitive to diet" group, suggesting that the "sensitive to diet" group were considered to have had n-3 rich diets before this study compared with the "insensitive to diet" group.

In the present study, effects of ALA enriched perilla seed oil on bronchial asthma were examined by comparing with LA enriched corn oil. The results have revealed that the effects of the dietary supplementation with ALA on the bronchial asthma through the LTs generation by leukocytes is affected by various factors including respiratory condition and lipometabolism.

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n-3系脂肪酸食の気管支喘息に対する臨床効果： n-6系脂肪酸との比較

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気道への炎症性白血球の集合が気管支喘息の病態に関わっている。魚油などのn-3系脂肪酸が白血球の機能を抑制することにより気管支喘息患者に良好な効果をもたらし、薬剤の必要性を減じたとの報告がなされている。 α -リレノン酸を豊富に含有するエゴマ油食の効果を調べるため、気管支喘息患者23名に2コースの食事-リノール酸の豊富なコーン油食を2週間摂取後、エゴマ油

食を2週間-を摂取してもらった。喘息患者は2コースの食事間のロイコトリエン B4(LTB4), CA(LTC4), B5(LTB5) の変化から2群-1群は食事に対し感受性のある群, もう1つは感受性の無い群-に分類した。我々はこの2群を臨床的に検討したところ, ピークフロー(PEF), 1秒量(FEV10), IgE, 性別, 肥満率(OI), 血清総コレステロール, アルブミン, 低比重リポ蛋白(LDL)-コレステロール, β -リポ蛋白, リン脂質において2群間に有意差が認められた。

今回の研究から, これらの因子が, 喘息患者において, LTB4, LTC4, LTB5の産生に対する食事療法の効果に影響を及ぼしていることが示唆された。

キーワード: n-3系脂肪酸, エゴマ油, 気管支喘息, LTB4, LTC4