
◎原 著

Effects of spa therapy combined with dietary supplementation with α -linolenic acids on bronchial asthma

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Abstract : N-3 fatty acids are reportedly effective for asthma. In addition, spa therapy has been reported to be effective for patients with asthma. In the present study, the effects of spa therapy combined with perilla seed oil-rich diet (rich in n-3 fatty acid)-were examined on asthma. A total of 14 asthmatic patients had a complex spa therapy and consumed a perilla seed oil-rich diet-rich in α -linolenic acid (α -LNA) for 8 weeks. Generation of Leukotriene (LT) C₄ by leucocytes, respiratory function were analyzed. The generation of LTC₄ by leucocytes decreased significantly for 2, 4 and 8 weeks ($P < 0.05$). Peak expiratory flow (PEF) values increased significantly for 2, 4, 6 and 8 weeks ($P < 0.05$). The values of ventilatory parameters [forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), forced expiratory flow after 25% of expired FVC (FEF_{25}), forced expiratory flow after 75% of expired FVC (FEF_{75}), mean expiratory flow during the middle half of the FVC (FEF_{25-75})] revealed a significant increase after 4 and 8 weeks of the modified diet ($P < 0.05$). The results suggest that spa therapy combined with a perilla seed oil-rich diet are effective in the treatment of asthma in terms of its ability to suppress LTC₄ generation by leucocytes, and in inducing an improvement of pulmonary function.

Key words : bronchial asthma, spa therapy, perilla seed oil, α -linolenic acid, Leukotriene C₄

Introduction

LTs are generated from arachidonic acid (AA) through the 5-lipoxygenase pathway, and AA is in turn released from membrane phospholipids during cell activation¹¹. LTB₄ and LTC₄ are generated from AA derived from linoleic acid (LA), while LTB₅ and LTC₅ are generated from eicosapentaenoic acid (EPA) derived from α -linolenic acid (α -LNA) via the same 5-lipoxygenase pathway. These two metabolic processes competitively antagonize each other. Whereas LTB₅ has a much weaker action than LTB₄, the action of LTC₅ is approximately equivalent to that of LTC₄. In addition, Cysteinyl LTs (LTC₄, LTD₄ and LTE₄) have been implicated in the pathogenesis of allergen-induced airway responses as potent contractile agonists for airway smooth muscles^{2,3}. Moreover, they mediate at a later stage of immediate airway obstruction, namely a fall in FEV₁ after allergen exposure^{4,5}.

Spa therapy has been reported to be effective for patients with asthma⁶⁻⁹, particularly for steroid-dependent asthma^{10,11}. Regarding action mechanisms of spa therapy for asthma, it has been demonstrated that clinical symptoms⁶⁻¹¹ and ventilatory function is improved by direct action of spa therapy¹²⁻¹⁴, and the effects on suppressed function of adrenal glands¹⁵, endocrine-automatic nerve system¹⁶, and psychological factors¹⁷ have been observed as indirect action of spa therapy.

We expected that spa therapy combined with dietary supplementation of perilla seed oil, which is rich in α -LNA, would suppress the generation of '4-series' leukotrienes (LTB₄ and LTC₄) by leucocytes. In the previous study¹⁸, we reported on the inhibitory effect on the generation of LTs by leucocytes by a diet containing perilla

seed oil, a vegetable oil rich in α -LNA. In addition, we previously reported that a spa efficacy for patients with asthma is related to a certain extent to the generation of LTC₄ by leucocytes¹⁹.

In the present study, the effects of spa therapy and perilla seed oil-rich supplementation were examined in patients with asthma.

Materials and Methods

Subjects were 14 patients with asthma (6 males and 8 females) admitted to our hospital to undergo pulmonary rehabilitation for the disease. The mean age of the patients was 63.8 years (range, 51 to 84 years) and the mean serum level of IgE was 548.9 IU/ml (range, 6 to 2562 IU/ml). Of the 14 patients, 6 were atopic while the remaining 8 were non-atopic. In this study, patients with positive IgE radioallergosorbent test (RAST) scores and/or IgE levels more than 250U/ml were assessed as atopic. All patients had moderate type asthma, in terms of severity. The mean duration of asthma was 11.8 years. All patients were treated with long-acting oral theophylline, inhaled β_2 adrenergic agonists and inhaled glucocorticosteroid (beclomethasone dipropionate : BDP). The mean dose of inhaled BDP was 371.4 μ g/day.

Asthma was evaluated according to the criteria of the International Consensus of Diagnosis and Management of Asthma 20). All patients showed reversible airway response, as indicated by a 15% or greater increase in their forced expiratory volume in one second (FEV₁) 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.

All patients had a complex spa therapy comprised of swimming training in a hot spring pool,

fango therapy and inhalation with iodine salt solution²¹) and consumed 10-20 grams of perilla seed oil (oleic acid 20.9%, linoleic acid 13.2%, α -linolenic acid 57.0%) per day (The mean dose of consumption was 14.55 ± 1.55 g/day) as salad dressing and/or mayonnaise instead of other oils for 4 weeks, while 11 patients in Group B consumed an equivalent amount of corn oil (oleic acid 34.7%, linoleic acid 50.5%, α -linolenic acid 1.5%) per day (The mean dose of consumption was 14.65 ± 1.41 g/day) for 8 weeks (Analysis of the composition of fatty acids in these diets was performed by gaschromatography). These diets were provided for the patients. Subjects and laboratory staff were blinded to the study groups. The characteristics of the subjects in this study are shown in Table 1.

Table 1. Backgrounds of patients

Patients (Male/Female)	14(6/8)
age(years)	$63.8 \pm 9.3(51-84)$
Onset(years)	$52.0 \pm 12.8(25-78)$
atopy/non-atopy	6/8
IgE(U/ml)	$548.9 \pm 821.8(6-2562)$

There were no significant differences between the groups prior to dietary supplementation. 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. Other than supplementation with perilla seed oil or corn oil, all the subjects received the same meals. And food wastage measured and taken into consideration. The contents of the two courses of dietary supplementation are shown in Table 2.

Serum IgE levels were estimated using the radioimmunosorbent test (RIST).

Peak expiratory flow (PEF) in the early morning was recorded daily for all subjects using a

peak flow meter (Assess : Health Scan Products Inc., Cedar Grove, NJ, USA). PEF values were estimated at prior to, 2, 4, 6 and 8 weeks after dietary supplementation corresponding with the measurement of LTC₄ generation by leucocytes. Ventilatory function tests, forced vital capacity (FVC), forced expiratory volume in one second (FEV₁), forced expiratory flow after 25% of expired FVC (FEF₂₅), forced expiratory flow after 50% of expired FVC (FEF₅₀), forced expiratory flow after 25% of expired FVC (FEF₇₅) and mean expiratory flow during the middle half of the FVC (FEF₂₅₋₇₅) were performed using a Chestac 33 (Chest Co., Tokyo, Japan) linked to a computer at a point when patients were attack free. Bronchodilators were withheld prior to measurements of lung function for more than 12hours. All patients were clinically stabilized during all study periods. There were no significant differences in ventilatory parameters between the groups prior to dietary supplementation. During this study medicine requirements (involving bronchodilator use) and symptom scores were recorded daily.

The generation of LTC₄ by peripheral leucocytes was assessed using a previously described method^{3,22}.

Data were expressed as mean \pm SEM. Student's t-test was used for unpaired analysis. For group comparisons, we used one-way analysis of variance (ANOVA). A $p < 0.05$ was considered significant. Analyses were performed using Stat-View 5.0 (Abacus Concepts, Inc., Berkeley, CA).

Results

The generation of LTC₄ by leucocytes following perilla seed oil-rich supplementation showed a significant decrease for 2 (85.01 ± 55.03 to 77.67 ± 65.37 ng/ 5×10^6 cells) ($P = 0.016$), 4 (85.01 ± 55.03 to 75.41 ± 46.33 ng/ 5×10^6 cells)

($P=0.038$) and 8 weeks (85.01 ± 55.03 to $66.41 \pm 37.26 \text{ ng}/5 \times 10^6 \text{ cells}$ ($P=0.030$) (Fig 1.).

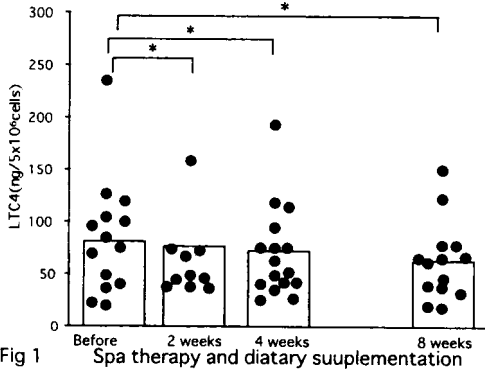


Fig 1 Changes in LTC4 generation by leucocytes. LTC4 generation decreased significantly after spa therapy and perilla seed oil-rich supplementation for 2, 4 and 8 weeks
*: $P < 0.05$. LTC4 : leukotriene C4

PEF values in the morning increased at 2 (232.14 ± 129.45 to $257.86 \pm 112.40 \text{ L}/\text{min}$: $P=0.004$), 4 (232.14 ± 129.45 to $272.86 \pm 107.59 \text{ L}/\text{min}$: $P=0.001$), 6 (232.14 ± 129.45 to $287.14 \pm 101.41 \text{ L}/\text{min}$: $P=0.003$) and 8 weeks (232.14 ± 129.45 to $308.57 \pm 100.22 \text{ L}/\text{min}$: $P=0.001$) after spa therapy and dietary supplementation (Fig 2.).

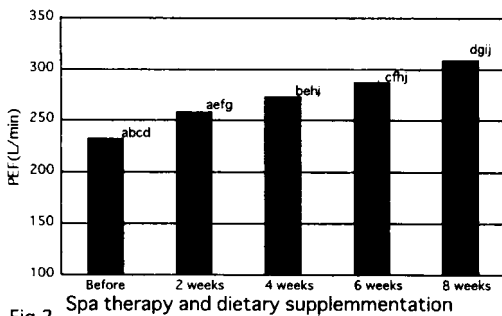


Figure 2. Changes in PEF values.
PEF values increased significantly after spa therapy and perilla seed oil-rich supplementation for 2, 4, 6 and 8 weeks.
a, b, c, d, e, f, g, h, i and j : $P < 0.05$ PEF : peak expiratory flow

A significant increase in the values of FVC, FEV₁, FEF₂₅, and FEF₂₅₋₇₅ was also observed at

4 and 8 weeks after spa therapy and dietary supplementation with perilla seed oil ($P < 0.05$) (Table 2.).

Table 2. Changes of ventilatory parameters by spa therapy and dietary supplementation

	spa therapy and dietary supplementation		
	Before	4 weeks	8 weeks
VC(L)	2.61 ± 0.85^a	2.73 ± 0.70	2.87 ± 0.62^a
FEV ₁ (L)	1.54 ± 0.61^{bc}	1.72 ± 0.46^{bd}	1.86 ± 0.42^{fd}
FEF ₇₅ (L/sec)	0.35 ± 0.21	0.37 ± 0.16^e	0.43 ± 0.14^e
FEF ₅₀ (L/sec)	1.16 ± 0.61	1.31 ± 0.57	1.44 ± 0.63
FEF ₂₅ (L/sec)	2.65 ± 1.37^f	2.82 ± 1.11^g	3.10 ± 1.19^{fg}
FEF ₂₅₋₇₅ (L/sec)	1.24 ± 0.62^h	1.35 ± 0.50^i	1.52 ± 0.64^{hi}

a,d,e,f,g,h and i: $P < 0.05$; b and c: $P < 0.01$

Discussion

Polyunsaturated fatty acids (PUFAs) of the n-3 fatty acids [EPA and docosahexaenoic acid (DHA)] suppress the production of '4-series' LTs by competitive antagonistic metabolism, which occurs at the level of LT hydrolase through the 5-lipoxygenase pathway. Therefore, PUFAs may potentially alter LT generation by leucocytes²³⁾. The above PUFAs have been reported to show antiinflammatory effects in patients with chronic inflammatory diseases, such as rheumatoid arthritis, psoriasis, and chronic inflammatory bowel disease²⁴⁾.

Several studies have focused on the beneficial effects of EPA or fish oil on bronchial asthma²⁵⁻²⁹⁾. However, other reports have failed to show any beneficial effect of EPA in patients with bronchial asthma^{30,31)}. This study was designed to certify the effect on asthma of spa therapy

combined with an α -LNA rich (perilla seed oil) diet to examine the role of polyunsaturated fatty acids (PUFAs) in the pathogenesis of asthma. The results revealed that subjects who received spa therapy and perilla seed oil (n-3 PUFA)-rich supplementation showed significantly suppressed generation of LTC₄ and larger increases in ventilatory parameters (PEF, FVC, FEV₁, FEF₂₅ and FEF₂₅₋₇₅) levels after the 8-week dietary supplementation. These results suggested that spa therapy combined with perilla seed oil-rich supplementation is beneficial for bronchial asthma by suppressing LTC₄ generation by leucocytes.

In the present study, the beneficial effects on asthma were observed after 8 weeks of supplementation, which was relatively short compared with those in previous studies using EPA^{25,26}. Shoda et al. examined the effects of perilla seed oil on experimental Crohn's disease and suggested that the therapeutic efficacy of α -LNA in controlling inflammation may be superior to that of EPA or DHA³², because α -LNA competitively inhibits not only the 5-lipoxygenase pathway but also the elongation and desaturation process in which LA is converted to AA. It is also known that Δ -6-desaturase is the rate-limiting enzyme in the elongation and desaturation of PUFAs³³. This may explain why they have weaker antiinflammatory effects than α -LNA. In addition, the magnitude of the benefit with perilla seed oil in this study is greater than the improvement with leukotriene antagonists (5% improvement in FEV₁ with leukotriene antagonists in patients already on treatment with inhaled steroids⁵). The action of perilla seed oil might include the effects of perilla seed oil itself in addition to the inhibition of the generation of leukotrienes.

The effects of spa therapy are affected by various factors such as disease severity, degree

of release of chemical mediators. Our previous studies have shown that spa therapy is effective for patients with asthma⁶⁻¹¹ and pulmonary emphysema^{40,43}. The direct actions of spa therapy improve clinical symptoms⁶⁻¹¹ and ventilatory function¹²⁻¹⁴, and suppress bronchial hyperresponsiveness in patients with asthma^{38,39}. The indirect function of spa therapy improve the function of the adrenocortical glands^{40,41}.

Bronchial asthma is characterized by transient bronchoconstriction, accompanied with hypersecretion and edema of mucous membrane. Chemical mediators such as histamine, LTC₄ and LTB₄, which are released from tissue mast cells during the time of immediate asthmatic reaction (IAR)^{42,43}, and from inflammatory cells during late asthmatic reaction (LAR), play an important role in the onset mechanisms of asthma attacks^{44,45}.

Effects of spa therapy on asthma are often affected by disease severity, degrees of bronchial hyperresponsiveness, and release of chemical mediators such as histamine and LTB₄ and LTC₄, and airway inflammation⁴⁶.

In the present study, 8 weeks spa therapy and dietary supplementation with perilla seed oil-rich in α -LNA, were significantly beneficial for bronchial asthma by suppressive effects of LTC₄ generation by leucocytes.

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気管支喘息に対する温泉療法と α -リノレン酸強化食の効果

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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。また喘息に対する温泉療法の有効性も報告されている。今回我々は温泉療法とn-3系脂肪酸を多く含むエゴマ油食の喘息に対する効果を

検討した。14名の喘息患者に温泉療法及び α -リノレン酸 (n-3系) を多く含むエゴマ油食の摂取を8週間行い, その間の白血球ロイコトリエンC4 (LTC4) の産生能と呼吸機能の変化を検討した。その結果白血球LTC4の産生能は治療開始2週後より4, 8週後と抑制された ($P < 0.05$)。ピークフロー値 (PEF) は治療2, 4, 6, 8週後に有意な増加がみられた ($P < 0.05$)。また呼吸機能 [努力肺活量 (FVC), 1秒量 (FEV_1), FEF_{25} , FEF_{75} , FEF_{25-75}] は治療開始4週, 8週後に有意に改善した ($P < 0.05$)。これらの結果より温泉療法とエゴマ油食は白血球LTC4の産生能を抑制することにより, 呼吸機能を改善させ, 気管支喘息の治療に有効であることが示唆された。