A Low-fat Diet Supplemented with Dietary Fish Oil (Max-EPA) Results in Improvement of Psoriasis and in Formation of Leukotriene B_5

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Several studies have indicated that certain lipoxygenation products of arachidonic acid, particularly leukotriene B_4 (LTB_4), may be involved in psoriatic pathophysiology. One way of inhibiting the formation of LTB_4 is to replace arachidonic acid in phospholipids with eicosapentaenoic acid. Eicosapentaenoic acid is converted into LTB_5, which has a lower biologic activity than LTB_4. In the present study psoriatic patients were put on a low-fat diet supplemented with dietary fish oil (Max-EPA 30 ml daily), a source of eicosapentaenoic acid, for 4 months. Twenty-six out of 30 patients with psoriasis vulgaris completed the study. Moderate or excellent improvement was observed in 58% of the patients, while mild improvement or no change was observed in 19% and 23%, respectively. The capacity of peripheral blood neutrophils to synthesize LTB_4 and LTB_5 in vitro was determined after stimulation with A23187. Before the study, negligible amounts of LTB_5 were formed. After 1 month the average of LTB_5/LTB_4 ratio was 0.42. No further increase of the LTB_5/LTB_4 ratio was found. There existed no relationship between the clinical response and the LTB_5/LTB_4 ratio. The results of the present study suggest that dietary fish oil supplementation may be used in the therapy in psoriasis. However, studies defining the dose and the quality of fish oils are imperative. (Accepted June 22, 1988.)

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Recent uncontrolled (1, 2) and controlled (3) studies have suggested that dietary supplementation with fish oil with or without a low-fat diet can improve psoriasis. The rationale to conduct such studies is based on observations concerning the biochemical constituents of normal and psoriatic skin. It has been shown that in lesional psoriatic tissue the cellular contents of free arachidonic acid (AA) (20:4,n6) and certain of its enzymatic derivatives are elevated (4, 5). There has been particular interest in the presence of leukotriene B_4 (LTB_4) (5, 6), because this 5-lipoxygenase product of AA is a potent mediator of skin inflammation (7) and a stimulator of epidermal proliferation (8, 9). However, the proval or disproval of the importance of LTB_4 in psoriatic pathophysiology still awaits the availability of specific and selective 5-lipoxygenase inhibitors.

Another way of inhibiting the formation of LTB_4, and possibly the effect of LTB_4 is to replace AA in phospholipids with other polyunsaturated fatty acids. Eicosapentaenoic acid (EPA) (20:5,n3), the pentaene analog of AA, is tranformed by the same enzymes as AA. Thus, 5-lipoxygenase activity results in the formation of LTB_5. LTB_5 expresses only 3–10% of the neutrophil chemotactic activity of LTB_4 (10) and furthermore inhibits LTB_4-induced neutrophil chemotaxis (11). The formation of LTB_5 at the expense of LTB_4 might, therefore, result in weaker inflammatory responses, because of competitive binding of the less potent LTB_5 to receptors for LTB_4 (10). EPA is the major polyunsaturated fatty acid of fish oil. In addition to EPA (18%), fish oil contains significant amounts of docosahexaenoic acid (DHA) (22:6, n3) (12%). Whether the presence of DHA is beneficial is not clear. DHA ap-

pears to exert a strong inhibitory effect on the prostaglandin synthetase pathway with negligible effect on the leukotriene pathway (12). Recently, DHA has been shown to be retro-converted to EPA in vivo (13). DHA may, therefore, serve as a precursor of EPA.

The main purpose of the present study was to determine the impact of dietary supplementation with fish oil on the production of LTB_4 and LTB_5 by neutrophils, and to determine whether there was any relation between the LTB_5/LTB_4 ratio and the clinical response to the dietary manipulation.

MATERIAL AND METHODS

Patients

Thirty patients with plaque psoriasis, stable in extent for at least 2 weeks were included in the trial. Patients had not received anti-psoriatic treatment topically for 2 weeks or systemically for 2 months. All patients were asked to apply an emollient once daily to the psoriatic lesions. No patient suffered from obesity, hyperlipidemia, diabetes mellitus or hypertension.

Clinical evaluations of the severity and the extent of psoriasis were made prior to the dietary intake and at monthly intervals. The severity of psoriasis was rated on 4-point scales (0 = absent, 1 = mild, 2 = moderate, and 3 = severe) for erythema, scaling and the thickness of the lesions. In addition, an overall assessment of the disease compared with baseline was made at each visit. The grading of the overall assessment was as follows: worse, no change, mild improvement, moderate improvement, and excellent improvement.

Diet

Each patient was instructed by a physician to follow a diet low in fat, particularly low in arachidonic acid and saturated fats for 4–6 months. The negative list of food induced fats and oils, red meats, whole-milk dairy products, baked goods, egg yolks, salad dressings and nuts. On the positive list of the administered diets were fish, poultry, fruits (except banana), vegetables (except avocado), grains, skim milk dairy products, carbonated beverages, coffee and tea. Adequate protein and carbohydrate intake were maintained. Total daily caloric intake was calculated for each patient to maintain prestudy body weight.

This diet was supplemented with 30 ml fish oil (MaxEPA) and 100 μg selenium daily. MaxEPA is an extract of fish oil triglycerides. The major fatty acids of MaxEPA are eicosapentaenoic acid (EPA) (18%) and docosahexaenoic acid (DHA) (12%). One milliliter MaxEPA contains 1 IU alpha-tocopherol as an anti-oxidant, 100 IU vitamin A and 10 IU vitamin D. Thus, the daily intake of EPA and DHA was 5.4 g and 4.8 g, respectively.

Laboratory analysis

Neutrophils were prepared from heparinized blood by use of the Hypaque-Ficoll technique as previously described (14). The cells were suspended at a concentration of 20×10^6/ml in Dulbecco's phosphate buffered saline (PBS), pH 7.0 (containing 0.87 mM $CaCl_2$), and incubated in duplicate for 5 min at 37°C with 5 μM A23187 (Calbiochem, La Jolla, CA, USA). The reactions were terminated by the addition of 2 ml ice-cold methanol. Lipids were extracted, and reversed-phase high performance liquid chromatography (RP-HPLC) was carried out as previously described (6). Briefly, lipids were extracted on ODS (octadecylsilyl) silica columns and subjected to RP-HPLC. RP-HPLC was carried out using a Hypersil C_{18} column (5 μm, 100×4.6 mm I.D.) eluted isocratically with methanol/water/acetic acid, 70 : 30 : 0.01 (V/V) at 0.7 ml/min UV-absorption was monitored at 270 nm. LTB_5 and LTB_4 were identified by coelution with authentic LTB_5 (a generous gift from Dr E. J. Goetzl, University of California Medical Center, San Francisco, CA, USA) and authentic LTB_4 (a generous gift from Dr J. Rokach, Merck-Frosst, Quebec, Canada). LTB_5 and LTB_4 were quantified by integrated optical density.

Table I. *Demographic data of psoriatic patients participating in the study*

Values are means and ranges

Age (years)	37 (12–69)
Sex (F/M)	20/6
Duration of psoriasis (years)	16 (1–35)
Extent of psoriasis (%)	12 (3–70)

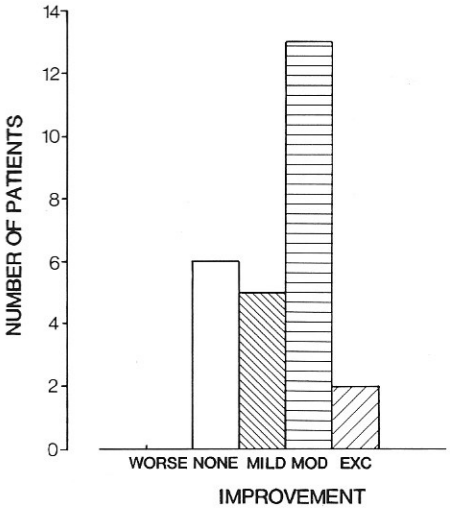

Fig. 1. Overall improvement of psoriasis after treatment for 4 months with dietary MaxEPA.

RESULTS

Twenty-six of the 30 psoriatic patients completed the study (4 months). The demographic data of these 26 patients are shown in Table I. Two patients were lost for follow-up, and 2 withdrew because of difficulties complying with the study diet.

Fig. 1 depicts the overall assessment of psoriasis after treatment for 4 months compared with baseline. Moderate or excellent improvement was observed in 58% of the patients, while the rest had no change (23%) or mild improvement (19%) of their disease. In most patients experiencing a satisfactory response (moderate or excellent improvement) some improvement was already present after 1 month, but maximal improvement was obtained after 4 months. In patients that stayed on the diet and MaxEPA beyond 4 months the improvement was maintained (data not shown). In parallel with the overall improvement, there was a decrease of erythema, thickness and scaling (data not shown).

A comparison between the clinical response and the extent of the disease showed that a greater fraction of patients with less than 10% involvement had a satisfactory clinical response than patients with more extensive disease (Table II). However, these differences did not reach statistical significance. The severity (erythema, scaling, thickness) of the psoriatic lesions did not differ between patients with a satisfactory clinical response and those with an unsatisfactory clinical response (data not shown).

The effect of the low-fat diet and the dietary supplementation with MaxEPA on the formation of leukotrienes B_4 and B_5 by neutrophils in vitro were analyzed in 19 of the 26 patients.

Table II. *Relation between the extent of psoriasis and the clinical response to dietary supplementation with fish oil*

Extent (% of body surface)	Improvement			
	None	Mild	Moderate	Excellent
<10	0	2	5	1
10–50	2	2	4	1
>51	2	1	0	0

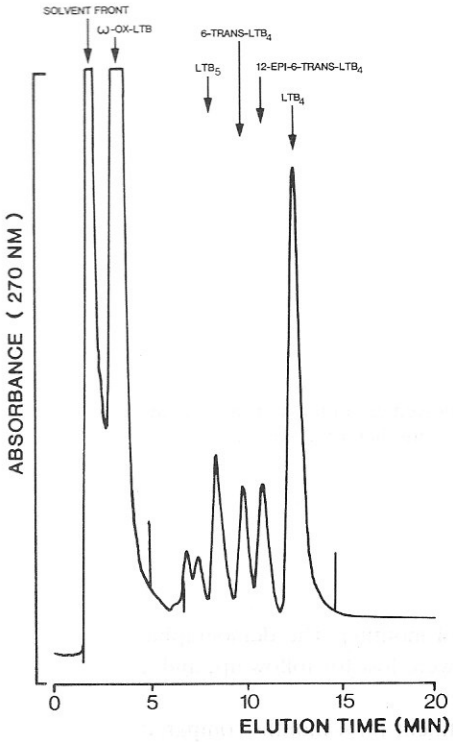

Fig. 2. Reversed-phase high pressure liquid chromatogram of lipids extracted from neutrophils stimulated with A23187. Neutrophils were isolated from a patient after one month on the fish oil diet.

At baseline negligible amounts of LTB_5 were formed. After 1 month, LTB_5 could be detected (Fig. 2). Beyond that time no further increases of LTB_5 formation was observed. No significant decrease of LTB_4 formation was observed during the study. The ratio of LTB_5 to LTB_4 was chosen as an integrated expression of the effect of the dietary manipulation on the leukotriene formation (Table III). Patients with a satisfactory clinical response had, on average, a 34% greater LTB_5/LTB_4 ratio than non-responders. However, this difference was not statistically significant (Table III).

DISCUSSION

The present study shows that long-term treatment of psoriasis vulgaris with a low-fat diet supplemented with dietary fish oil (MaxEPA) results in a satisfactory improvement in almost

Table III. *LTB_5/LTB_4 ratios in psoriatic patients with a satisfactory and an unsatisfactory response to dietary supplementation with fish oil*

Results are means ± SD

Response	*n*	LTB_5/LTB_4
Satisfactory (moderate/excellent)	10	0.47±0.06
Unsatisfactory (none/mild)	9	0.35±0.05

$p>0.10$.

60% of the patients. In our patients it was impossible to predict from the extent of their disease or the severity of their lesions whether they would respond to dietary treatment or not. Although this was an open, uncontrolled study, it is our impression that the response rate is much higher than with placebo. In support of this idea are the results of a double-blind placebo (olive oil) controlled study (3). The reason for not using a double-blind design was that the smell and taste of fish oil might spoil an attempt to use a blind design. In the beginning all patients were given MaxEPA as a fluid. However, some patients had to change to encapsulated MaxEPA because of the taste of the fluid. Therefore, we intend to use encapsulated fish oil in future studies. The fact that our patients had no difficulties complying with the low-fat diet may reflect their high degree of motivation. It appears from our study that it is necessary to be on the low-fat diet supplemented with MaxEPA for 4 months before it can be decided whether a given patient will respond clinically or not. This fact may explain why no improvement was observed in an 8-week clinical trial (15). An additional explanation for the lack of effect in the latter study may be that the patients were kept on a regular diet.

To assess the biochemical changes resulting from the dietary manipulation, the formation of leukotrienes B_4 and B_5 was determined in neutrophils isolated from the peripheral blood. Except in one patient, the formation of LTB_4 was higher than the formation of LTB_5. Maximum levels of LTB_5/LTB_4 ratios were obtained already after 1 month of therapy. One reason why no further increases of the LTB_5/LTB_4 ratios occurred, may be that no significant decrease of LTB_4 formation took place during the study. This finding is in contrast to that of Maurice et al. (2). In their patients, a substantial reduction of the LTB_4 formation was observed. An explanation of the unchanged LTB_4 levels in our patients may be that the levels of arachidonic acid, the parent compound, was not reduced in cell membrane phospholipids. Our earlier finding of unchanged skin levels of arachidonic acid in psoriatic patients treated with a fish oil-supplemented, low-fat diet (1) supports this possibility.

The inability of the low-fat diet to reduce the tissue levels of arachidonic acid gives rise to several questions. The recommended diet may not have the optimal composition or it may be adhered to for too short a time. Because it appears to be difficult to obtain a reduction of arachidonic acid levels and of LTB_4 formation by dietary means, it becomes more important to give an adequate supply of fish oil to obtain a high ratio of eicosapentaenoic acid to arachidonic acid.

In our patients, maximum LTB_5/LTB_4 ratios preceded the maximum clinical improvement. Furthermore, greater LTB_5/LTB_4 ratios were found in responders than in non-responders, although this difference was not statistically significant. Taken together, these data are compatible with the idea that manipulation of leukotriene formation may have an anti-psoriatic effect.

Although the present results suggest that dietary fish oil supplementation may be used as adjunctive therapy in psoriasis, there are still many unsolved questions that need to be answered. First, a proper dose-finding study need to be conducted. Secondly, the commercial fish oil products have to be standardized. Recently, we have found that fish oils from different manufacturers are of highly variable quality (unpublished data). Furthermore, different batches from the same manufacturer may have different EPA contents. This apparent lack of quality control has several implications. First of all, it becomes impossible to compare results obtained with different fish oil products. Of equal importance is the high content of potentially harmful lipid oxidation products in certain fish oils on the market (unpublished data). The products of lipid oxidation may act as initiators or promotors of carcinogenesis (16) and should therefore be kept on the lowest possible level. This is partially accomplished by having alpha-tocopherol in the fish oil. However, it can only be assured by taking additional anti-oxidants such as selenium orally.

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