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Association of Etretinate and Fish Oil in Psoriasis Therapy. Inhibition of Hypertriglyceridemia Resulting from Retinoid Therapy after Fish Oil Supplementation

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We studied the main papers concerning treatment with fish oil (EPA and DHA) of patients with psoriasis vulgaris, psoriatic arthritis and pustular psoriasis. In our investigation, 25 patients with psoriasis vulgaris evidenced a statistically significant increase in triglyceride serum levels, compared with controls. 10 of these patients underwent therapy with etretinate 0.75–1.0 mg/kg daily for 2 months followed by 2–3 months of etretinate 0.35–0.50 mg/kg daily associated with fish oil 1.5 g (EPA and DHA) daily. According with several authors, fish oil is able not only to produce good clinical results, but also to minimize the side effects of retinoid therapy, especially hypertriglyceridemia.

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INTRODUCTION

The essential fatty acids (EFA) are polyunsaturated acids with 18 or more carbon atoms and with the first double-link in position 3 or 6. The human organism cannot synthesize them, being unable to form double-links in position 3 or 6, which is why these substances must be introduced with the diet.

The omega-3 family is derived from the alfa-linolenic acid, after are synthesized eicosapenta-enoic acid (EPA) and docosohexa-enoic acid (DHA).

The omega-6 family derives from linoleic acid, after are synthesized gamma-linolenic acid (GLA), diomo-gamma-linolenic acid (DGLA) and arachidonic acid. The EPA therapeutic mechanism consists in promoting the formation of metabolites (monohydrossilic acids) with anti-inflammatory action which act as powerful inhibitors in vitro of LTB 4 which, on the contrary, produces a remarkable inflammatory effect (1).

Kragballe (2) found in psoriasic skin a mass of eicosanoids with an inflammatory action, particularly 12-idrossi-eicosatetraenoic acid (12-HETE) and LTB 4. By contrast, some EPA derivatives (PGE 3 and LTB 5) have an anti-inflammatory and competitive action towards the inflammatory eicosanoids (PGE 2 and LTB4).

These factors justify the therapeutic use of EPA in certain dermatologic diseases. This study deals with psoriasis, in particular, where the best results could be observed with EPA omega-3 series (fish oil). Interest in EPA developed after discovering that the eskimo population, whose diet is based mainly on fish and therefore rich in EPA omega-3 series, have an incidence of psoriasis equivalent to 1/20 in comparison with that found in the population of industrialized countries.

Since 1985, several authors have tested fish oil treatment on psoriatic patients, with doses varying between 1.8 and 9 g/daily for 2–3 months, obtaining encouraging clinical results (3–7).

Lassus treated 46 patients with psoriasis vulgaris and 34 patients with arthropathic psoriasis, using EPA and DHA, obtaining improvement of skin lesions and also reduction of articular pains (8).

Kettler (9) obtained positive clinical results in patients with psoriasis vulgaris as well as in a case of pustular psoriasis. By contrast, Bjorneboe (10) found no clinical improvement in 30 psoriatic patients treated with 1.8 g of EPA daily for 2 months.

Dewsbury (11) and Escobar (12) found clinical improvement in psoriatic patients treated topically with fish oil.

The association of EPA omega-3 series with omega-6 series also gave very good results: therapy with GLA and DGLA leads to the formation of PGE 1 as an anti-inflammatory compound (4).

Gupta (13) moreover obtained an appreciable improvement in clinical parameters in psoriatic patients, when combining EPA with UVB exposure.

However, the most interesting association for psoriasis treatment seems to be the one between fish oil (EPA and DHA) and etretinate. This association not only produces a twofold therapeutic effect, but it also reduces the hyperlipidemia due to etretinate, particularly hypertriglyceridemia (14, 15) and in a lower degree the total hypercholesterolemia (14).

The aim of this work was to verify these last reports and to study the possibility of reducing etretinate dosage if used in association with fish oil, in order to obtain good therapeutic results with the slightest side effects.

MATERIALS AND METHODS

We studied 25 psoriatic patients, 13 women and 12 men, 20 with psoriasis vulgaris, 2 with psoriatic arthritis, 2 with palmopustular psoriasis and 1 with pustular psoriasis; 5 of these patients were affected by diabetes and 4 were affected by thyroid diseases. 30 subjects were tested as controls. The range of age was 20–62 years. Blood samples were tested for: triglycerides (TG), total cholesterol (TC), HDL cholesterol and also total cholesterol/HDL cholesterol fraction.

In 10 out of 25 patients, 5 women and 5 men, exams were determined three times: before therapy, after therapy with retinoids and after therapy with retinoids associated with fish oil.

Serum triglycerides (TG) and total cholesterol (TC) were measured by automated enzymatic methods. HDL cholesterol was measured with the above procedures after isolation by polyanion precipitation of other lipoprotein classes with heparin/magnesium/chloride.

In these patients we also considered certain clinical features, especially erythema and desquamation. We denoted no clinical change with 0 and progressive improvement with +, ++, +++, indicating with ++++ the complete remission of psoriatic lesions. Good results were considered ++ or more, corresponding to a reduction by at least 50% of psoriatic lesions. Our 10 patients were submitted to therapy with etret-

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Table I. *Mean values of TG, TC, HDL and TC/HDL in controls and psoriatic patients*

	TG	TC	HDL	TC/HDL
Controls (n=30)	131.5±71.4*	219.0±39.1	59.1±15.5	3.7
Psoriasic patients (n=25)	193.1±80.2**	230.0±40.2	52.2±16.1	4.3

*p <0,001 **v.s

Table II. *Mean values of TG, TC, HDL and TC/HDL in psoriatic patients before and after therapy*

Psoriatic patients (n=10)	TG	TC	HDL	TC/HDL
Before therapy	190.0±80.4^{+}	228.2±41.3	53.1±17.2	4.4
After retinoids	218.5±86.2^{++}	240.5±46.2	55.2±15.1	4.4
After retinoids + Fish Oil	169.0±75.1^{+++}	235.4±48.2	61.7±16.5	3.8

^{+}p <0.05 $^{++}$vs and + $^{+++}$vs.
^{++}p <0.001 $^{+++}$vs.

inate 0.75–1.0 mg/kg daily and fish oil 1.5 g daily (0.9 EPA and 0.6 DHA).

RESULTS

Clinical improvement with remarkable reduction of erythema and desquamation was observed in 5 patients after 2 months (retinoids) and in 3 patients after 4–5 months (retinoids associated with fish oil).

In the other 2 patients there were no clinical results. Alterations of triglycerides (TG), total cholesterol (TC), HDL cholesterol and total cholesterol/HDL cholesterol fraction are shown in Tables 1 and 2.

DISCUSSION

Dietary supplementation with fish oil rich in eicosapenta-enoic (EPA) and docosohexa-enoic (DHA) may alleviate psoriasis (3–7).

In involved plaques of psoriasis there is a marked increase in eicosanoids (leukotriene B4 and 12-HETE) related to the 5-lipoxygenase pathway: this increase is associated with inflammation and cell proliferation (1, 2). By contrast, some EPA and DHA derivatives (PGE3, LTB5, 15-HETE), have an anti-inflammatory action: this action is competitive toward the inflammatory eicosanoids (PGE2, LTB4, 12-HETE) (16).

Several authors drew attention to the importance of EFA omega-3 series in the treatment of psoriasis vulgaris, but there were good results also in arthropathic psoriasis (8) and in pustular psoriasis (9). Only Bjorneboe did not find clinical improvement of psoriatic patients treated with fish oil (10).

Other authors found improvement in psoriasis following topical treatment with fish oil (EPA) (11, 12) alone or associated with GLA (omega-6 series): this therapy leads to the synthesis of another anti-inflammatory compound as PGE 1 (4). In recent years there have been only two reports on the treatment of psoriasis with etretinate and fish oil combined (14, 15): the EFA supplementation results in decreased hypertriglyceridemia (14, 15) and hypercholesterolemia following etretinate therapy (14).

Psoriatic patients sometimes evidenced high levels of total cholesterol and triglycerides in serum, even before etretinate therapy: in our 25 psoriatic subjects, versus 30 healthy controls, we found a high level of TG. Our study showed a significant improvement in clinical features (remarkable reduction of erythema and desquamation of psoriasis in 8 of 10 patients) after treatment with retinoids and fish oil. There is a significant difference in TG serum levels between psoriatic patients before therapy (190.0±80.4 mg/dl) and after therapy with retinoids (218.5±86.2 mg/dl) compared with those treated with retinoids and fish oil together (169.0±75.1 mg/dl).

It is very important to consider that supplementation with EPA and DHA can reduce the dosage of etretinate (0.75–1.0 mg/kg daily for 2 months, followed for 2–3 months by etretinate 0.35–0.50 mg/kg daily) and minimize the side effects (hypertriglyceridemia) of retinoids (17). The treatment with fish oil (0.9 g of EPA, 0.6 g of DHA daily for 2–3 months) increases the clinical improvement in psoriasis vulgaris after etretinate therapy.

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