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Randomized control trials

Energy-restricted, n-3 polyunsaturated fatty acids-rich diet improves the clinical response to immuno-modulating drugs in obese patients with plaque-type psoriasis: a randomized control clinical trial

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SUMMARY

Background & aims: Low-grade systemic inflammation associated with obesity may worsen the clinical course of psoriasis. This study aimed to assess the effectiveness of an energy-restricted diet, enriched in n-3 polyunsaturated fatty acids (PUFAs) and poor in n-6 PUFAs, on metabolic markers and clinical outcome of obese patients with psoriasis.

Methods: Forty-four obese patients with mild-to-severe plaque-type psoriasis treated with immuno-suppressive drugs were randomized to assume for six months either their usual diet or an energy-restricted diet (20 kcal/kg/ideal body weight/day) enriched of n-3 PUFAs (average 2.6 g/d). All patients continued their immuno-modulating therapy throughout the study.

Results: At 3 and 6 months, a significant clinical improvement was observed in patients assuming the low-calorie high n-3 PUFAs diet respect to controls. Specifically Psoriasis Area Score Index (7.7 ± 3.7, 5.3 ± 4.3 and 2.6 ± 3.0, respectively; $p < 0.05$), itch scores (15.4 ± 13.5, 12.3 ± 12.1 and 1.8 ± 5.9, respectively; $p < 0.05$) and Dermatological Life Quality Index (19.5 ± 1.9, 11.4 ± 3.5 and 5.1 ± 1.6; respectively, $p < 0.05$) all decreased respect to baseline. In these subjects but not in controls, a significant decrease in body weight (93.8 ± 10.1, 85.8 ± 11.4 and 83.1 ± 12.1 kg, respectively; $p < 0.05$), waist circumference (112.7 ± 7.2, 106.1 ± 10.3 and 101.9 ± 10.4 cm; $p < 0.05$), serum triglycerides (141.8 ± 51.1, 100.5 ± 26.6 and 90.2 ± 34.5 mg/dL; respectively, $p < 0.05$), serum total cholesterol (198.3 ± 31.7, 171.4 ± 29.0 and 176.5 ± 20.5 mg/dL; respectively, $p < 0.05$) and n-6/n-3 ratio intake also occurred (5.1 ± 0.9, 2.0 ± 0.9 and 2.3 ± 1.1; respectively, $p < 0.05$).

Conclusions: In obese psoriatic patients, an energy-restricted diet designed to increase n-3 and reduce n-6 PUFAs, ameliorated the metabolic profile and, by increasing the response to immuno-modulating therapy, improved the clinical outcomes of the disease (ClinicalTrials.gov identifier: NCT01876875).

1. Introduction

Psoriasis is one of the most common chronic inflammatory skin disorders, affecting about 2% of the general population. It is considered to be a T-cell-mediated inflammatory skin disease which is characterized by hyper-proliferation and poor differentiation of epidermal keratinocytes. Even if the susceptibility to psoriasis is inherited, the inflammatory reaction is modulated by diet, lifestyle and environmental factors such as infections and stress. Polyunsaturated fatty acids (PUFAs) are showing promise as safe adjunctive treatments for many skin disorders, including psoriasis.[1] There are two main families of PUFAs: n-3 and n-6 PUFAs. Alpha-

Non-standard abbreviations: AA, arachidonic acid; AHA, American Heart Association; ALA, alpha-linolenic acid; DGLA, dihomo-gamma-linolenic acid; DHA, docosahexaenoic acid; DLQI, Dermatology Life Quality Index; PUFAs, polyunsaturated fatty acids; EPA, eicosapentaenoic acid; GLA, gamma-linolenic acid; HRQL, health-related quality of life; PASI, Psoriasis Area and Severity Index; TNF, tumor necrosis factor; VAS, visual analog scale.

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linolenic acid (ALA) is the only essential n-3 PUFA, while linoleic acid is the only essential n-6 PUFA. Through consecutive desaturation and elongation reactions n-6 PUFAs are sequentially converted to γ-linolenic acid (GLA), dihomo-γ-linolenic acid (DGLA) and, finally, to arachidonic acid (AA). The latter is the precursor of series 2 prostaglandins (PGs) and series 4 leukotrienes, whereas DGLA is transformed in series 1 PGs and series 3 leukotrienes. On the n-3 side, a small amount of ALA converts to eicosapentaenoic acid (EPA), and then to docosahexaenoic acid (DHA). EPA serves primarily as a precursor to series 3 PGs and inhibits both the production of AA from DGLA and the production of PGE2 or thromboxane from AA. PUFAs modulate inflammatory responses by multiple mechanisms.[2] Specifically, they cause changes in intracellular Ca^{2+} concentration acting both on intracellular Ca^{2+} stores and on plasmamembrane ion channels such as TRPC6.[2] In addition, PUFA affect the activity of intracellular signaling cascades including the PKC and MAPK pathways.[2] Recent evidence also show that these polyunsaturated lipids modify lipid raft composition thus affecting the intracellular distribution of key signaling proteins such as PKC-hand PLCγ-1.[2] Finally, it has been demonstrated that n-3 PUFAs may alter the transcriptional activity of several transcription factors including SBRP, PPARs and NFkB.[3] Acting through these multiple mechanisms n3-PUFAs may significally impair T-cell differentiation and activity.[2] In addition, PUFAs may indirectly interfere with the immune response through compounds generated by their metabolism. Specifically, PGE2 exerts proinflammatory effects whereas series 1 and series 3 PGs are antinflammatory. New PUFA-derived lipid mediators that contribute to resolve the inflammatory response were recently discovered through lipidomic studies. Some of them known as resolvins and maresins are products of DHA and EPA metabolism while others, the lipoxins, derive from AA. Intriguingly, the biosynthetic pathways of these resolving lipid mediators involve reactions catalyzed by lipoxygenases, a class of enzymes that was classically proposed to have a role in psoriasis.[4] GLA and DGLA exert antinflammatory effects either directly by interacting with plasmamembrane GPR120 receptors or indirectly after transformation in anti-inflammatory series 1 PGs. All these mechanisms may be relevant in psoriasis. Skin cells produce, indeed, eicosanoids in response to various stimuli contributing to inflammatory conditions.[5] Moreover, these fatty acids have a role in maintaining epidermal barrier function.[5] Interestingly, different enzymes involved in PG biosynthesis like cyclooxygenase-2 (COX-2), cytochrome P450 4F8 (CYP4F8), and microsomal PGE synthase-1 (mPGES-1) have been shown to be upregulated in psoriatic lesions.[6] This suggests that eicosanoids could be involved in the genesis of psoriatic lesions and that dietary interventions aiming to modify the ratio between n-3 and n-6 derived lipid mediators could be helpful in this disease. Epidemiological observations of a lower incidence of autoimmune and inflammatory disorders, including psoriasis, in a population of Greenland Eskimos compared with gender- and age-matched groups living in Denmark[7] provided early suggestive evidence of the important role of n-3 PUFAs dietary intake on inflammation. An improvement in psoriasis has also been observed during daily dietary supplementation with fish oil containing n-3 PUFAs.[8] As mentioned, AA is a proinflammatory fatty acid. As a result, a low dietary intake of AA, typical of low-protein and vegetarian diets, may produce a less inflammatory effects. The Western diet is “deficient” in n-3 PUFAs, with an n-6/n-3 ratio of 15/1 to 16/1, as compared to the 1/1 ratio as found in wild animals and presumably human beings prior to the industrial revolution.[9] Although the ability of a low-protein diet to improve symptoms in psoriasis patients has not been consistently supported[10] a remarkable treatment efficacy was reported for a patient by Schamberg.[11] In a case-control study, Naldi et al. showed that an increased intake of fresh fruits and certain vegetables was linked to a decreased prevalence of psoriasis, although the mechanism was not clear.[12]

Calorie restriction and/or weight loss may also influence symptom severity in psoriasis.[13] In obese patients with moderate-to-severe plaque psoriasis, weight loss was shown to improve the therapeutic response to cyclosporine.[14] In mice, four weeks of calorie restriction (by 33% of energy intake) led to a decrease of 45% in the epidermal cell proliferation rate.[15] Likewise, symptoms of inflammatory diseases such as rheumatoid arthritis have been shown to be improved through fasting or low-energy diets.[16] Associations have also been recognized between psoriasis and an increased incidence of metabolic syndrome (visceral obesity, diabetes or insulin resistance, hypertension, and dyslipidemia).[17] Although the link between psoriasis and individual components of metabolic syndrome is not completely elucidated, visceral fat, which releases proinflammatory cytokines, appears to play a role in both metabolic syndrome and psoriasis.[18]

Although there is no generally recognized decisive cure for psoriasis, many treatments are commonly used to reduce the severity of symptoms and lessen their impact on the patient’s quality of life. For moderate-to-severe psoriasis, phototherapy and topical and/or systemic therapies are the standard medical therapies. Examples include corticosteroids, emollients, tar, methotrexate, and cyclosporine. However, many of these treatments are associated with significant adverse effects.[19] Some alternative systemic therapies include monoclonal antibodies against T-cell surface receptors like CD1 or CD11a, fumaric acid esters, vitamin D analogs, novel retinoids, macrolactams, and biologic immune modifiers such as anti-tumor necrosis factor (TNF) agents.[20]

The present study explores the effectiveness of an energy-restricted n-3 fatty acid-rich diet on the nutritional and clinical outcome of obese patients with mild-to-severe psoriasis.

2. Methods

2.1. Subjects

Forty-four patients affected by plaque-type psoriasis (32 males, 12 females, mean age: 52.18 ± 11.12 years) were referred to the Departments of Dermatology and Neuroscience, Physiology Nutrition Unit, of the University Federico II of Naples, and enrolled in the study between April 2007 and March 2008. Patients were matched for age, height, weight and body mass index (Table 1). All subjects gave their informed consent. The study was approved by the Ethical Committee of the Medical School of the University Federico II of Naples.

Table 1
Baseline characteristics of 44 obese subjects with mild-to-severe psoriasis in both intervention and control groups.

	Intervention	Control
Number of subjects (n)	22	22
Gender (M/F)	16/6	16/6
Mean Age (yr)	52 ± 12	52 ± 10
Body weight (kg; lb)	93.8 ± 10.1; 206 ± 22.3	89.7 ± 12.6; 197.4 ± 27.7
Height (cm)	167.6 ± 9.8	172.1 ± 8.7
Body mass index (kg/m^2)	33.4 ± 3.4	31 ± 2.6
Waist circumference (cm)	112.7 ± 7.2	111.3 ± 7.5
Daily medication (n; % of subjects)		
Etanercept	6; 28%	6; 28%
Adalimumab	4; 18%	4; 18%
Infliximab	4; 18%	4; 18%
Methotrexate	4; 18%	4; 18%
Cyclosporine	4; 18%	4; 18%