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n-3 polyunsaturated fatty acids supplementation in psoriasis: a review

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Abstract

Psoriasis is an immune mediated chronic inflammatory disease of unknown etiology and characterized by epidermal hyperplasia and inappropriate immune activation, which affects the skin and joints as well.The immunopathogenesis of psoriasis involves changes in the innate and acquired (T lymphocytes) immune system. The cells of the innate immune system when activated produce growth factors, cytokines, and chemokines that act on cells of the acquired immune system and vice versa, being characterized as atype 1 immune response disease. Fish oil n-3 polyunsaturated fatty acids, mainly eicosapentaenoic (EPA), and docosahexaenoic acids (DHA), reduce symptoms in many inflammatory skin diseases. The mechanism of action of fish oil in the treatment of psoriasis is widely based on the alteration of epidermal and blood cell membrane lipid composition. In the present study, we performed a review of the several studies, which analyzed the action of n-3 polyunsaturated fatty acids in patients with psoriasis. Taken together, the majority of the studies showed that n-3 polyunsaturated fatty acids, mainly from marine origin, have beneficial effects and can be utilized as adjuvant therapy in psoriasis treatment. Both oral and intravenous administration of fish oil n-3 polyunsaturated fatty acids had positive effects. However, further studies are warranted to answer many intriguing questions, for instance, the ideal quantity of fish oil to be utilized, the effect on different forms and severity of psoriasis and last, but not least, the consequences of using fish oil n-3 polyunsaturated fatty acids on the cardiovascular features of patients with psoriasis.

Keywords: Fish oil, n-3 polyunsaturated fatty acids, Psoriasis, Immunopathogenesis

Background

Psoriasis is an immune-mediated chronic inflammatory disease of unknown etiology and characterized by epidermal hyperplasia and inappropriate immune activation, which affects the skin and joints as well. In the skin, it is characterized by multiple erythematous scaly lesions where well-defined plaques arise mainly in the elbows, knees, scalp, navel, and lower back, but it is possible that the disease spreads throughout the body in a systemic way as erythroderma: [1–3]. In the joints, it attacks the insertions of tendons by provoking pain and inflammation followed by a joint deformity, especially in small joints [2]. Psoriasis affects both sexes and people of all ages exhibiting peaks of incidence in adulthood (75% of the patients before 40 years of age) [3, 4]. It is a disease with bimodal prevalence peak, one being around 20 years old and another occurring later around 50 years old.

Clinical manifestations of psoriasis are different; they may vary from a limited disease to a very extensive skin lesion and is characterized by periods of remissions and exacerbations [5]. The clinical forms of psoriasis include vulgar or plaque, guttate, erythrodermic, and pustular. Psoriasis vulgaris affects approximately 85 to 90% of all patients with the disease; scaly, erythematous plaques develop in a fairly symmetrical distribution. Any part of the skin may be affected; the most common sites are the scalp, elbows, knees, shins, umbilicus, sacrum, and genitalia. Plaques may range in size from a few millimeters to a large part of the trunk or limb. Guttate psoriasis is characterized by small scaly erythematous papules and predominates in the members but not on palms and soles, usually occurring in adolescents or younger adults often after infectious conditions. Erythrodermic psoriasis affects more than 90% of body surface with scales and intense sub acute or chronic erythema and overall poor

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health. It may occur due to worsening of psoriasis plaques or generalized pustular form and possibly as an early manifestation of the disease. At last, the pustular psoriasis, this can have a local or generalized presentation. Whereas the local form is characterized by papules and/or erythematous plaques usually limited to the palms and/or plants (palmar-plantar pustular psoriasis) that occurs in adults, most commonly in females, the generalized pustular psoriasis is characterized by sterile pustules, with fever and overall poor health such as body pain and diarrhea. Mostly, it occurs in patients with psoriasis plaque, after exposure with aggravating factors, such as hypocalcemia, interruption of systemic corticosteroid therapy, infection, and untimely topical therapy [3, 4].

The relationship between psoriasis and other diseases has drawn increasing interest in recent years. Growing evidence suggests that cardiovascular disease, obesity, diabetes, hypertension, dyslipidemia, and metabolic syndrome are found at a higher prevalence in psoriasis patients when compared with the general population. These associations between psoriasis and these diseases may be due to the systemic inflammatory mediators, which are generated in all aforementioned conditions [6].

Immunopathogenesis of psoriasis

The immunopathogenesis of psoriasis involves changes in the innate and acquired (T lymphocytes) immune system. The cells of the innate immune system when activated produce growth factors, cytokines, and chemokines that act on cells of the acquired immune system and vice versa, being characterized as a type 1 immune response disease, such as diabetes mellitus and multiple sclerosis [7, 8].

Normally, the skin renewal occurs around 28 to 30 days with the formation of new cells on its lower layer and with the ripening, migrates to the top layer of skin dropping in an unnoticed way. In psoriasis, the cell cycle changes fast and can be reduced to 4 days. These altered cells accumulate composing whitish plates with erythroderma originating typical lesions of the disease [9].

There is activation of the innate immune system cells (dendritic cells and keratinocytes). Several environmental factors such as mechanical trauma, infections, drugs, emotional stress, or even change of the own skin in the constitution of keratinocytes are considered triggers of the disease [1]. The mechanical trauma, for example, can activate keratinocytes in the same way that the binding of antigens of infectious agents to toll-like receptors in dendritic cells and keratinocytes can lead to their activation, producing several chemokines, cytokines, interleukin 1 (IL-1), TNF-α, growth factors, and heat shock proteins [8].

In addition, in the dermis, T cells interact with macrophages and dendritic cells, forming new "immunological synapse". This interaction leads to the production of many cytokines, which maintain and amplify the inflammatory process [7].

The dendritic cells and the activated macrophages produce IL-12 and IL-23. IL-12 promotes the proliferation of Th1 and Th17 the enhancement of IL-23. The proliferation of Th1 and Th17 in psoriasis is also attributed to the decrease in regulatory T cells [10].The dermal dendritic cells also work functioning as APC to T cells and inflammatory cells, producing IL-20, IL-23, and TNF-α. The IL-20 stimulates the proliferation of keratinocytes, IL-23 promotes the proliferation of Th17 and IL-22, IL-17, TNF-α and IL-6. Keratinocytes also work functioning as pro-inflammatory cells and produce cytokines, such as TNF-α, IL-1, IL-6, and IL-8 [10, 11].

Fish oil and psoriasis

Humans, with the exception of long chain fatty acids omega-3 (n-3) and omega-6 (n-6), which are called essential, can synthesize many of the fatty acids. Omega-6 fatty acids as arachidonic acid (AA) can be synthesized by humans from linoleic acid (C18:2n−6, LA), where as omega-3 fatty acids represented by eicosapentaenoic (EPA), docosapentaenoic (DPA), and docosahexaenoic acids (DHA) are synthesized from α-linolenic acid (C18:3n−3, ALA) [12, 13]. LA is found in the oils of safflower, grape seed, poppy seed, sunflower, hemp, corn, wheat germ, cottonseed, and soybean [13], whereas ALA is found mainly in oils of canola, linseed and soy. However, the most important natural sources of omega-3 are marine organisms (fish, seafood, algae) that are fed directly or indirectly from marine phytoplankton, the primary producer of omega-3 [12].

Omega-3 fatty acids, EPA and DHA, reduce symptoms in many inflammatory skin diseases [14]. The mechanism of action of fish oil in the treatment of psoriasis is widely based on the alteration of epidermal and blood cell membrane lipid composition. The arachidonic acid (AA) is found in high levels in psoriatic skin lesions, and its metabolite, leukotriene B4, is considered the principal mediator of inflammation in psoriasis [15]. When cyclooxygenase or lipoxygenase, or both, in the place of AA in cell membranes metabolize EPA, it may help to attenuate inflammation. The metabolites of EPA, including leukotriene B5, are far less potent inflammatory mediators than the degradation products of AA [16]. The addition of fish oil to the diet of psoriasis patients leads to an increasing of the plasma and platelet EPA-to-AA ratios and to a significant in vitro decrease in leukotriene B4 synthesis by neutrophils [15].

Furthermore, fish oil has not just anti-inflammatory effects on cell membrane and eicosanoid synthesis, but it has also regulatory effect on the epigenetics. There are

emerging findings that support the suggestion that fatty acids, in particular n-3 polyunsaturated fatty acids, can modify the epigenome. However, there is a need for rigorous investigations to assess directly the effect of epigenetic modifications induced by fatty acids on gene function and metabolism and its relation with inflammatory conditions, such as psoriasis [17, 18].

Soyland et al. [19] conducted a 4-month, double-blind, randomized, placebo-controlled, multicenter trial among 145 patients with moderate-to-severe plaque psoriasis. The patients were randomly assigned to either the fish-oil group, in which each patient received six capsules daily (each capsule had 1 g of omega-3 fatty acids(51% EPA, 32% DHA) or to the control group in which each patient received six capsules of corn oil daily (each capsule containing 1 g of omega-6 fatty acids (26% oleic acid, 56% linoleic acid); the score of the Psoriasis Area and Severity Index (PASI) levels did not change significantly in either group at the end of the trial. No clinically important difference was found between groups when subparts of the PASI score were analyzed. However, fish oil group had a significant increasing in the ratio of EPA to AA in serum phospholipids and an increase in the ratio of polyunsaturated to saturated fatty acids (Table 1).

In another study, 32 patients with chronic stable plaque psoriasis were instructed to continue with their

Table 1 Fish oil in the treatment of psoriasis

Study	Type of study	No. of patients	Type of psoriasis	Therapy	Duration	Results	Ref.
Oral fish oil alone	Prospective, randomized, double-blind, placebo-controlled	175	Moderate-to-severe plaque psoriasis	Oral fish oil (5 g EPA + DHA) vs control corn oil	4 months	No significant change in PASI, increasing in the ratio of EPA to AA in serum phospholipids	[19]
Oral fish oil alone	Double-blind, randomized, placebo-controlled	32	Chronic stable plaque psoriasis	Oral fish oil (1.8 g EPA) vs control olive oil	12 weeks	Significantly better improvement in itching, erythema, scaling in the group fish oil, no significant change in the group olive oil	[20]
Oral fish oil alone	Double-blind, randomized, placebo-controlled	26	24 plaque psoriasis, 1 generalizedpustular, 1 palmoplantar	3.2 g EPA and 2.2 g DHA per day	8 weeks	Significant improvement only in the 1 patient with pustular psoriasis	[21]
Oral fish oil + UVB	Double-blind, randomized, placebo-controlled	20	Mild to moderate psoriasis vulgaris	UVB + oral fish oil (3.6 g of EPA and 2.4 g of DHA) vs olive oil	Fish oil 15 weeks; UVB from week 3 to 11	Significantly greater total decrease in total TBSA and greater clinical improvement vs olive oil group	[22]
Oral fish oil + tacalcitol	Prospective, open, controlled,	30	Mild to moderate plaque psoriasis	Oral fish oil(640 mg daily EPA/DHA) + tacalcitol vs control topical tacalcitol only	8 weeks	Omega-3 group significantly reduces PASI, injury scalp, itching, erythema, scaling and infiltration.	[14]
Oral fish oil + topical corticosteroid	Double-blind, randomized, placebo-controlled	25	Stable, plaque psoriasis	Fish oil (5.4 g EPA + 3.6 g DHA) vs olive oil + topical betamethasone dipropionate	9 weeks	No significance difference between fish oil and placebo	[23]
Intravenous fish oil	Randomized, double-blind, parallel-group, multicenter	83	Chronic, plaque psoriasis	Lipid emulsion 200 ml/day (4.2 g of both EPA and DHA) or omega-6 fatty acids emulsion (EPA + DHA < 0.1 g/100 ml).	14 days	PASI scores decreased by 11.2 ± 9.8 in the omega-3 group	[16]
Intravenous fish oil	Double-blind, randomized, placebo-controlled	20	Acute psoriasis guttate	Lipid emulsion 100 ml/day with (2.1 g EPA and 21 g DHA) or a omega-6 lipid emulsion (EPA + DHA < 0.1 g/100 ml)	10 days	Greater improvement in erythema, infiltration, desquamation in omega-3 group compared with omega-6 group	[24]
Topical fish oil	Randomized, placebo-controlled, single-blind	25	Plaque psoriasis	Topical fish oil (15.8% EPA + 10.1% DHA) vs liquid paraffin	4 weeks	Significantly improvement in scale score and thickness fish oil treated group	[25]
Topical fish oil	Multicenter, double-blind, placebo-controlled	52	Moderate, plaque psoriasis	Topical omega-3 (1 or 10%) vs placebo	8 weeks	No statistically significant difference between omega-3 and placebo group	[26]

AA, arachidonic acid; *DHA*, docosahexaenoic acid; *EPA*, eicosapentaenoic acid;*PASI*, Psoriasis Area and Severity Index; *TBSA*, total body surface area; *UVB*, ultraviolet B

usual topical treatments. They were randomly allocated to receive either 10 capsules fish oil daily containing 1.8 g EPA, or 10 capsules of olive oil. The treatment lasted for 12 weeks with assessments at 0, 4, 8, and 12 weeks. After 8 weeks treatment, there was a significant lessening of itching, erythema, scaling in the group treated with fish oil. No change occurred in the olive oil group [20]. In a third open study that included twenty-six patients with psoriasis, twenty-four had plaque-type psoriasis vulgaris, one had generalized pustular psoriasis, and one had palmo plantar pustulosis. The patients were instructed to take 18 capsules of EPA daily (3.2 g of EPA and 2.2 g of DHA per day), in addition to their regular daily diet for 8 weeks. No clinically significant improvement after fish oil supplementation in 8 weeks was found, although a single patient with pustular psoriasis showed significant improvement [21].

Fish oil has also been studied in combination with other therapies. Gupta et al. [22] conducted a double blind, randomized, placebo-controlled study in 20 patients with mild to moderate psoriasis vulgaris. One group received10 fish oil capsules twice daily (for a daily total of 3.6 g of EPA and 2.4 g of DHA), whereas controls received 10 capsules of olive oil. Patients were given fish oil (or placebo) for the first 3 weeks of the study (weeks 0–3). At this point, concomitant twice-weekly therapy with suberythemal doses of UVB phototherapy for the next 8 weeks was initiated (weeks 3–11). For the last 4 weeks of the study (weeks 11–15), only fish or olive oil was given.The total body surface area (TBSA) was significantly lower at week 15 in the fish oil treated group compared with the olive oil group (22 vs 45%) and greater clinical improvement (scale, erythema, thickness) was also observed in the fish oil group. Therefore, fish oil showed great benefit as an adjuvant therapy with suberythemal doses of ultraviolet UVB. In an open study of 30 patients with mild to moderate plaque psoriasis, 15 patients were given topical tacalcitol, a synthetic vitamin D3 analogue, and 2 daily capsules of Oravex® (280 mg of EPA and 40 mg of DHA per capsule), whereas the remaining 15 patients received topical treatment with tacalcitol for 8 weeks. Supplementary treatment with omega-3 fatty acids complemented topical treatment and contributed significantly to reduction of PASI and in reducing injury to the scalp itching, erythema, desquamation, and infiltration of the treated areas [14]. In another study, 25 patients with stable plaque psoriasis were randomly assigned to the fish or placebo oil groups. The daily intake of 10 fish oil capsules included 5.4 g of EPA and 3.6 g of DHA or 10 olive oil capsules, 3 times daily for 9 weeks. For the first 3 weeks both groups applied betamethasone dipropionate cream (moderate potency corticosteroid) (45 g/week) to the plaques of psoriasis twice daily. No clinically significant improvement occurred after fish oil supplementation [23].

Intravenous omega-3 fatty acid lipid infusions produced a significant improvement over the shortest time as compared to oral administration. Mayser et al. [16] and Grimminger et al. [24] each conducted double blind, randomized, controlled studies comparing the effect of intravenous omega-3 fatty acids to omega-6 fatty acids for the treatment of psoriasis. In the Mayser et al. [16] study, eighty-three patients hospitalized for chronic plaque-type psoriasis, participated in a 14-day trial. They were randomly allocated to receive daily infusions with either an omega-3 fatty acid-based lipid emulsion (Omegavenous; 200 ml/day with 4.2 g of both EPA and DHA) or a conventional omega-6 fatty acids emulsion (Lipovenous; EPA + DHA < 0.1 g/100 ml). The PASI scores decreased 11.2 ± 9.8 in the omega-3 group versus 7.5 ± 8.8 in the omega-6 group ($p = 0.048$), with significantly better improvement in the omega-3 group in erythema, scale, and induration. In Grimminger et al. study [24], twenty patients hospitalized for acute guttate psoriasis with a minimum 10% of body surface area involvement (range 10–90%) received daily infusions with either an omega-3 fatty acid-based lipid emulsion (100 ml/day with 2.1 g of EPA and 21 g of DHA) or a conventional omega-6 lipid emulsion (EPA + DHA < 0.1 g/100 ml) for 10 days. The omega-3 group demonstrated greater improvement across all clinical scores for erythema, infiltration, desquamation, compared with the omega-6 group.

Escobar et al. [25] treated 25 patients with plaque psoriasis, applying topical fish oil (containing 15.8% EPA and 10.1% DHA) or liquid paraffin under an occlusive dressing daily for 4 weeks. Significant decreases in scale score and thickness were found in the fish oil treated group compared with control. No significant change in erythema was found. On the other hand, Henneicke-von Zepelin et al. [26] studied 52 patients with moderate plaque psoriasis given topical omega-3 polyunsaturated fatty acid (1 or 10%) therapy or placebo and have not found any statistically significant difference between the treatment and placebo groups for local PASI, TBSA involvement, erythema, desquamation, induration, or pruritus after 8 weeks.

Low-grade systemic inflammation associated with obesity may worsen the clinical course of psoriasis. Guida et al. [27] conducted a randomized control clinical trial study with 44 obese patients (body mass index-BMI > 30 kg/m^2) with mild-to-severe plaque-type psoriasis treated with immunosuppressive drugs. The patients consumed for 6 months either their usual diet or an energy restricted diet (20 kcal/kg/ideal body weight/day) enriched with n-3 polyunsaturated fatty acids (PUFAs) (average 2.6 g/d). All patients continued their immunomodulation therapy throughout the study. More specifically, subjects were instructed to minimize their intake of n-6 PUFAs by eating less meat, eggs, whole grains, and cereals. At the same

time, they were instructed to eat a generous amount of foods naturally rich in n-3 PUFAs such as seafood (salmon, sardines, herring, and bluefish) and an n-3 rich margarine. In the intervention group, BMI and waist circumference decreased ($p < 0.05$) and these changes were associated with significant reductions in serum triglycerides and serum total- and LDL cholesterol levels ($p < 0.05$) and a greater than 50% reduction of PASI was reached at 6 months.

The role of nutrition in the treatment of psoriasis has been studied for many years. Recent evidence has confirmed that adherence to a healthy diet over time reduces the risk of long-term inflammation [28]. The antioxidants present in the diet, such as omega-3 from fish oil, some vitamins (A, E, and C), and oligoelements (iron, copper, manganese, zinc, and selenium), which decrease oxidative stress and the production of reactive oxygen species, might be of particular relevance mainly in a chronic systemic inflammatory diseases, like psoriasis [29]. The Mediterranean diet is a healthy diet it is characterized by a high intake of fruit and vegetables, legumes, grains and cereals, fish and seafood, and nuts; a low intake of dairy products, meat and meat products; and a moderate ethanol intake mainly in the form of wine and during meals. Extra virgin olive oil (EVOO) is the main added lipid and its increased consumption is reflected in the high monounsaturated to saturated fatty acid intake [28, 29]. However, there are few studies that relate to the Mediterranean diet with psoriasis.

The feed can influence psoriasis in two ways—as a cause of metabolic disorders and in disease treatment and prevention [30].Thus, the nutritional care of patients with psoriasis, along with control of biochemical and anthropometric variables, ensures greater clinical stability to these individuals, preventing chronic non-communicable diseases (NCD), commonly associated with the disease and providing greater longevity with quality. However, despite the fact that nutrition might be considered an aadjunctive tool for the treatment of psoriasis, and fish oil may influence both aforementioned conditions, there are no national or international guidelines that recommend an adequate diet or supplementation for such patients.

In sum, the majority of the studies analysed were double-blind, randomized, and placebo-controlled, varying from 4 weeks to 4 months and with doses between 640 mg and 5.4 g of the active substances (EPA and DHA). Some studies used fish oil supplementation with other therapies, in the topic form or as short-term intravenous infusion.

Conclusions

Taken together, the majority of the studies showed that n-3 polyunsaturated fatty acids, mainly from marine origin, have beneficial effects and can be utilized as adjuvant therapy in psoriasis treatment. Both oral and intravenous administration of fish oil n-3 polyunsaturated fatty acids had positive effects. However, further studies are warranted to answer many intriguing questions, for instance, the ideal quantity of fish oil to be utilized, the effect on different forms and severity of psoriasis and last, but not least, the consequences of using fish oil n-3 polyunsaturated fatty acids on the cardiovascular features of patients with psoriasis.

Abbreviations

AA: Arachidonic acid; ALA: α-linolenic acid; APC: Antigen presenting cell; BMI: Body mass index; DHA: Docosahexaenoic acid; DPA: Docosapentaenoic acid; EPA: Eicosapentaenoic acid; EVOO: Extra virgin olive oil; IL: Interleukin; INF-γ: Interferon-γ; IP-10: Interferon gamma-induced protein 10; LA: Linoleic acid; MHC: Major histocompatibility complex molecule; NCD: Chronic non-communicable diseases; PASI: Psoriasis area and severity index; PUFA: Polyunsaturated fatty acids; STAT: Signal transducer and activator of transcription; TBSA: Total body surface area; Th: T helper cells; TNF-α: Tumornecrosis factor-α; UVB: Ultraviolet B

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Authors' contributions

Author's contributions were as follows: NML wrote the present review. ANCS had the idea of the review and helped to write the item entitled. Immunopathogenesis of psoriasis. ID had the idea of the review and helped to write the item entitled ¨Fish oil in Psoriasis. All authors read and approved the final manuscript.

Competing interests

There are no competing interests of any participant of the study.

Consent for publication

Not applicable.

Ethics approval and consent to participate

We performed a review of the literature on action of n-3 polyunsaturated fatty acids in psoriasis. Therefore, this item is not applicable to the present study.

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