Can regular oral supplementation of fish oils improve symptoms in psoriasis?

Louise Miller-Malm and Nicole Pitulia

Examination paper, 15 ECTS
Dietician study programme 180/240 ECTS
Supervisor: Lena Hulthén
Examiner: Anna Winkvist
2012-04-11

Sahlgrenska akademin

GÖTEBORGS UNIVERSITET

Sahlgrenska Academy
at University of Gothenburg
Department of internal medicine and clinical nutrition

Abstract

Title: Can regular oral supplementation of fish oils improve symptoms in psoriasis?

Authors: Louise Miller-Malm and Nicole Pitulia

Supervisor: Lena Hulthén
Examiner: Anna Winkvist
Programme: Dietician study programme, 180/240 ECTS
Type of paper: Examination paper, 15 ECTS
Date: April 11, 2012

Background: Psoriasis is a chronic hereditary inflammatory disease that can affect both the skin and joints, and affects 2-3 % of the world's population. It presents with red and inflamed thick skin that has flaky silver-white patches, and 60% of those who suffer from it report it to be a large problem in their everyday life. Fish oils contain the omega-3 fatty acids EPA and DHA, which are precursors to eicosanoids that have been seen to reduce inflammation. As psoriasis is an inflammatory disorder, the supplementation of fish oils is hypothesised to improve patients symptoms and therefore also their quality of life.

Objective: The aim of this paper is to review the literature and evaluate whether or not the oral supplementation of fish oils for symptom alleviation is recommended in psoriasis.

Search strategy: The literature search was conducted through the databases PubMed, Scopus and Cochrane. In Pubmed and Scopus, the keywords used were "psoriasis and fish oil", "psoriasis and omega 3", "psoriasis and EPA" and "psoriasis and DHA". In Cochrane, the words "Psoriasis and fish oil" were used.

Selection criteria: The criteria were that the studies were to be randomized controlled trials conducted on humans written in English. The supplementation of fish oils should be oral and the condition should be psoriasis. No time limits when the studies were made were included.

Data collection and analysis: Three RCTs were identified in the literature search. These studies were examined using the template "Review template for randomized controlled trials" (granskningsmall för randomiserad kontrollerad prövning) and the selected outcomes were analysed according to the GRADE-system using the template "conclusive evidence form" (Sammanfattande evidensformulär). The outcomes measured were inflammation in form of erythema and coverage in form of affected area.

Main results: The outcome measures in two of the studies shows no statistic significant improvement of symptoms after the oral supplementation of fish oils. One of the studies showed a small but significant improvement in inflammation and a trend towards an improvement in the surface area affected. Both the outcome for inflammation and coverage ended up having a limited (++) evidence grade.

Conclusions: The clinical value of fish oil supplementation remains uncertain. Fish oil supplementation may possibly exert some positive effects when used in addition to established psoriatic therapies, but at present its use as an exclusive treatment is not justifiable. Both higher doses of fish oils and longer periods should be examined in double blind studies in the future.

Sahlgrenska Akademien
vid Göteborgs universitet
Avdelningen för invärtesmedicin och klinisk näringslära

Sammanfattning

Titel:	Kan ett regelbundet oralt tillskott av fiskolja förbättra symptom i psoriasis?
Författare:	Louise Miller-Malm och Nicole Pitulia
Handledare:	Lena Hulthén
Examinator:	Anna Winkvist
Linje:	Dietistprogrammet, 180/240 hp
Typ av arbete:	Examensarbete, 15 hp
Datum:	2012-04-11

Bakgrund: Psoriasis är en kronisk ärftlig inflammatorisk sjukdom som kan drabba huden såväl som lederna. 2-3 % av jordens befolkning uppskattas vara drabbade. Sjukdomen uppvisar röd och förtjockad inflammerad hud med silvervita flagor. 60% av de drabbade upplever sjukdomen orsakar svårigheter i deras vardagliga liv. Fiskolja innehåller omega-3 fettsyrorna EPA och DHA, två förstadier till eikosanoider som har en påvisad anti-inflammatorisk effekt. Då psoriasis är en inflammatorisk sjukdom, skulle ett tillskott av fiskolja kunna förbättra symtombilden och därmed även patienternas livskvalitet.

Syfte: Syftet med denna översikt är att undersöka om ett oralt tillskott med fiskolja förbättrar symtombilden i psoriasis.

Sökväg: Vid litteratursökningen användes databaserna PubMed, Scopus och Cochrane. I PubMed och Scopus användes sökorden ”psoriasis and fish oil”, ”psoriasis and omega 3”, ”psoriasis and EPA” och ”psoriasis and DHA”. I Cochrane användes sökorden ”psoriasis and fish oil”.

Urvalskriterier: Urvalskriterierna var att studierna skulle vara Randomiserade kontrollerade prövningar utförda på människor. De skulle vara skrivna på engelska. Tillskottet av fiskoljan skulle vara oralt och diagnosen psoriasis. Ingen tidsbegränsning på när studierna var gjorda sattes.

Datainsamling och analys: Efter sökning i ovanstående sökmotorer med nämnda sökord identifierades tre stycken RCT. Studierna granskades enligt mallen ”Granskningsmall för randomiserad kontrollerad prövning” och de valda effektmåtten analyserades enligt GRADE-systemet med hjälp av ”sammanfattande evidensformulär”.

Resultat: De två effektmåtten visade i två av studierna ingen signifikant förbättring vid tillskott av fiskolja. I en av studierna visades en liten men statistiskt signifikant förbättring av erytem och en tendens till förbättring av täckt hudyta. De två effektmåtten för inflammation samt täckning fick evidensstyrkan begränsad (++).

Slutsats: Den kliniska betydelsen av fiskoljetillskott är osäker. Supplementering av fiskolja kan ha viss positiv effekt i kombination med övriga behandlingar för psoriasis, men för tillfället finns det inte tillräcklig evidens för att det ska rekommenderas som primär behandling av sjukdomen. Högre dosering av fiskolja och längre prövningstid bör undersökas i dubbelblinda studier i framtiden.

Abbreviations

DHA – Docosahexaenoic acid

EPA – Eicosapentaenoic acid

IU – International Unit

MUFA – Monounsaturated fatty acid

PASI – Psoriasis Area and Severity Index

PUFA – Polyunsaturated fatty acid

SBU - The Swedish Council on Health Technology Assessment

SFA – Saturated fatty acid

Table of contents

Appendices

Introduction

Psoriasis

Psoriasis is a chronic hereditary inflammatory disease that can affect both the skin and joints. It is one of the most common endemic diseases in Sweden. According to the Swedish Psoriasis association, 250 000-300 000 swedes, 2-3% of the population, suffer from a sort of psoriasis (1). Worldwide, this number is 125 million, similarly 2-3% (2). It is just as common in men as well as in women and it often appears between the ages of 15 and 25 (2). It is a reoccurring disease that is triggered by a range of factors; weather, smoking, alcohol and stress being the most common (5).

Psoriasis in the skin presents with red and inflamed thick skin that has flaky silver-white patches known as scales (3). The redness of the skin, known as erythema, is caused by inflammation that arises as a result of accumulation of immune cells and chemicals that these cells release (16). Plaque-type psoriasis, which is characterized by round erythematous raised plaques with silvery scale, is the most common form comprising 90% of all cases (4). Other types of psoriasis include guttate psoriasis, pustular psoriasis and inverse psoriasis (7).

Nearly 60 percent of people suffering of psoriasis reported their disease to be a large problem in their everyday life. Patients with moderate to severe psoriasis often experience a large negative impact on their quality of life. (2)

The severity of psoriasis is often measured using the standardized Psoriasis and Severity Index or PASI. This index quantifies sclerosis (hardening of a tissue or an increase of connective tissue (12)), erythema, scale and extent of body surface area involvement in four body regions – these being the head and neck, trunk, upper extremities and lower extremities. (4)

Primary treatment of psoriasis consists of topical ointments and moisturizing creams with or without steroids and vitamin D derivatives, ultraviolet light therapy or steroid infusions (6).

There have been many ‘natural remedies’ that lay claim to being able to help or treat psoriasis. Most have little to no scientific basis and are based on theory rather than clinical trials. Natural medical practitioners have advised some of the following treatments for these patients: Dead sea salt, specialised diets (for example a diet low in saturated fats as these have been seen to exude an inflammatory effect), homeopathy, herbs, lifestyle changes-including physical activity, meditation, weight loss, and a reduced stress lifestyle. (25)

The biochemical and physiological effect of fish oil

Fish oils are derived from the tissues of oily fish and contain the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). EPA and DHA are precursors of eicosanoids that have been seen to reduce inflammation. (11)

Omega 6 fatty acids are another branch of unsaturated fatty acids that, similarly to omega 3 fatty acids are essential to the human body. The main sources of omega-6 acids are corn-, sunflower- and rapeseed oil. (25)

Fish oils can be acquired through eating fish or taking supplements. A lot of the benefit seems to come from the omega-3 fatty acids they contain (10). Fish that are especially rich in these omega-3 fatty acids are mackerel, tuna and salmon (10). Supplements with fish oil

usually contain small amounts of vitamin E to prevent the oils from becoming rancid (10). Side effects seen from the supplementation of fish oils include belching, bad breath, heartburn, nausea, loose stools, rashes and nosebleeds, sometimes affecting the outcome of clinical trials evaluating the effect of these oils (8).

Omega-3 fatty acids, particularly EPA, have a similar chemical structure to aracadonic acid (AA) and partially replace this acid in epidermal and blood cell membrane lipid composition. AA is found in high levels the skin lesions seen in psoriasis and leukotriene B4, one if its metabolites, is thought to act as a mediator of inflammation in this disease. When EPA is metabolized in place of AA in the cell membranes, this has been seen to help mitigate inflammation, as the metabolites of EPA are less potent inflammatory mediators than those of AA. (17)

Further, they modulate enzymatic activity and membrane receptors as well as have antithrombotic and immuno-modulating properties that have been seen to improve inflammatory conditions (17). They have also been seen to supress the production of pro-inflammatory cytokines that are usually raised in patients with inflammatory disorders. (3, 19, 20)

The level of anti-inflammatory activity may vary among different fish oil supplements depending on the concentration of EPA, as this fatty acid is involved in the anti-inflammatory pathway of fish oils in cells (17). Further, essential fatty acids are involved in our skins protective moisture lipid barrier and as this protective barrier is frequently disrupted by inflammation, fish oils help restore the cell wall integrity (3). DHA similarly exhibits an anti-inflammatory effect, however it is not specific to the mechanism of inflammation seen in psoriasis (30). Not only does it decreases the risk of thrombosis in the blood, but has been seen to be beneficial in depression, cardiovascular disease and visual acuity (30).

There is strong evidence that the supplementation of fish oils can reduce high blood pressure, hypertriglyceridemia and reduce the risk of cardiovascular disease (9). There have been a number of low quality trials conducted on the effect of fish oils in psoriasis that show a positive outcome; however, they have not provided enough evidence to conclude whether or not they are recommended in this group of patients (17).

Problem

Psoriasis causes much discomfort, embarrassment and angst for people who suffer of this disease (2). It becomes increasingly important to find methods to help alleviate the symptoms and help with the improvement of the overall condition. In addition to prescriptive drug use, lifestyle and diet changes, it is important to investigate whether a nutritional supplement can have a positive effect on the overall disease state and quality of life for the patients.

Objective

The aim of this paper is to review the literature and evaluate whether or not the oral supplementation of fish oils for symptom improvement is recommended in psoriasis.

Issue

Can the regular oral supplementation of fish oil improve symptoms, in form of inflammation and coverage, in psoriasis?

Methodology

Inclusion and exclusion criteria

This thesis is based on a literature search. As there is a lot of research on the effect of fish oils and omega-3 fatty acids on psoriasis, inclusion and exclusion criteria were set to make the search more specific (17). It was decided that the studies were to be randomized controlled trials (RCT) conducted on humans, the supplementation of fish oils was to be oral and the articles were to be written in English. Further, the parameters that were looked at for subjects included in the studies were age, sex, type and stage of psoriasis, treatment history as well as the incidence of other medical conditions. As psoriasis is a disease that affects people of all ages and men and woman to the same extent, no age limit or sex specificity was set (12). Studies on all types of psoriasis were accepted but those involving patients with similar dermatological conditions were excluded. No time limit for when the studies were conducted or their duration was set.

Collection of Data

The literature search can be followed in table 1.

Table 1. Data collection. Where and how the literature search was conducted.

Database	Date	Search words, free search	Limitations	Hits	Chosen articles (duplicates)
Pubmed	21st February	Psoriasis AND Fish oil	Humans, RCT	18	3
Pubmed	21st February	Psoriasis AND omega 3	Humans, RCT	13	(3)
Pubmed	21st February	Psoriasis AND DHA	Humans, RCT	4	0
Pubmed	21st February	Psoriasis AND EPA	Humans, RCT	7	0
Scopus	21st February	Psoriasis AND Fish oil AND randomized controlled trial		11	(2)
Scopus	21st February	Psoriasis AND omega 3 AND randomized controlled trial		8	0
Scopus	21st February	Psoriasis AND DHA AND randomized controlled trial		2	0
Scopus	21st February	Psoriasis AND EPA AND randomized controlled trial		2	0
Cochrane Library	23rd February	Psoriasis AND fish oil	Trials	28	(3)

DHA: docosahexaenoic acid, EPA: eicosapentaenoic acid, RCT: Randomized controlled trial

The search for articles was conducted in PubMed, Scopus and in the Cochrane Library via the Gothenburg University library. The search in PubMed was limited to humane studies and Randomized controlled trials. The search words that were used were "psoriasis and fish oil", "psoriasis and omega 3", "psoriasis and DHA" as well as "psoriasis and EPA". Titles and abstracts for all hits were read and those articles that matched our demands for inclusion – three of them - were chosen. Those studies excluded after reading the titles and abstracts were not relevant to our subject as they looked at infusions of fish oils, topical treatment with fish oils and combination therapies. Three RCT's conducted on humans, that prior to the in-depth assessment were thought to be of high quality, were chosen. The authors to these three trials were Bittiner *et al* (13), Søyland *et al* (14) and Bjørneboe *et al* (15).

Processing of data

To begin with, the studies were assessed through the reading of their titles abstracts and it was decided whether or not they were relevant for this review. A template from The Swedish Council on Health Technology Assessment (SBU) was used (see Appendix 1). The criteria that had to be fulfilled were adequacy and relevance of the population, inclusion and exclusion criteria, a relevant intervention and control group as well as an adequate duration of the study. Further, the outcomes measured had to be of clinical relevance. The three studies (13-15) that met the inclusion criteria were classed as relevant.

Once the studies were classed as relevant and fit the selection criteria, the quality of them was evaluated. This was done with the help of another template from SBU. This template (see Appendix 2) allowed us to assess the quality of the separate studies by assessing the level of accuracy and information given regarding selection bias, performance bias, detection bias, attrition, reporting bias, other considerations such as conflicts of interest and indirectness of evidence. After evaluating the studies on each of these points, a judicial and comprehensive decision was made regarding their quality; high, average or low.

Analysis of the outcomes

Once the relevant studies were chosen, appropriate outcomes were identified. The two outcomes that were chosen were erythema for inflammation and surface area for coverage. The reasons behind theses choices include the facts that inflammation is an indicator of the severity of the disease, and coverage is a symptom that patients perceive as very embarrassing and difficult to live with (2).

The two outcomes were analyzed and evidence graded according to the GRADE-system, using the template " conclusive evidence-form" from the University of Gothenburg (appendix 3). The strength of evidence for the outcomes inflammation, in form of erythema, and coverage, in form of affected area, were assessed using this template.

Results

A double blind randomized placebo-controlled trial of fish oils in psoriasis,* Bittiner *et al* *(13).

Tables 3, 4 and 5 present the results of the different trials. The trial conducted by Bittiner *et al* (13) was a double blind placebo controlled RCT. 32 patients with chronic stable plaque psoriasis were entered into this trial that aimed to investigate what effect the consumption of ten 1g capsules of fish oil MaxEpa®, consuming 1.8g of EPA daily, would have on itching, erythema, scaling and area. MaxEpa® capsules are composed of ethyl esters of omega-3. The effect was compared to that in a control group that received ten 1g capsules of olive oil/day.

All patients were instructed to continue with their usual topical treatment. If there had recently been any alterations in this treatment the patients were excluded from the trial.

The subjects were randomly allocated to receive either the fish oil or the olive oil. The capsules were indistinguishable and both contained peppermint oil to disguise the taste. The trial lasted for twelve weeks with assessments by the same observer at baseline, four, eight and twelve weeks. Erythema and scaling was assessed by a clinician on a 0-5 point grading system. The surface area was measured in a percentage of total body surface area and the itching on a subjective scale of 0-5 by the patient. The assessments took place in in a room with no outside windows to standardize the conditions. Compliance was measured by capsule counting and by assay of erythrocyte membrane lipids with liquid chromatography. Four patients were lost to follow up at eight weeks and another four at twelve weeks. One patient dropped out of the placebo group at week four as a treatment failure. 28 (88%) and 24 (75%) of the subjects completed eight and twelve weeks respectively. The patients that completed the trial were well matched for age, sex, disease duration and type of topical treatment.

At eight and twelve weeks, there was a significant improvement as regards to erythema in the intervention group ($p<0.05$). There was no change in the placebo group. The percentage surface area affected showed a trend towards improvement in the MaxEpa® group at twelve weeks. However, this trend did not attain statistical significance.

Quality assessment

The double-blind randomized placebo-controlled trial by Bittiner et al (13) was assessed to be of average quality. Reasons behind this decision were that 25% of the subjects did not fulfill the trial and that the reasons behind this were not stated. Further, the subjects continued with their usual topical treatments and these varied between the intervention group and the control group, possibly affecting the results. The population size and duration were not very large, decreasing this trials statistical power. However, all participants and clinicians were blinded, compliance was high and all of the relevant outcomes were measured, still giving this trial an average quality.

Table 2. Result of trial conducted by Bittiner *et al* (13).

Author/s	Study design	Population	Intervention	Coverage	Inflammation	Other	Quality
Bittiner *et al*, 1988, England	Double-blind placebo controlled RCT	32 patients with stable chronic psoriasis 16 female 12 male Mean age 35.6yrs	**I:** 10 capsules MaxEpa® 1.8g EPA/day **C:** 10 capsules of olive oil **I & C:** Capsules contain peppermint oil **Duration**: 12 weeks with assessments at 0, 4, 8 & 12 weeks	**I:** Percentage surface area affected showed a trend towards improvement. No significant change **C:** No change in placebo group.	**I:** Significant improvement seen at weeks 8 and 12. $p < 0.05$ **C:** No change in the placebo group.	Non-response: 28 (88%) and 24 (75%) completed the 8 and 12 weeks respectively. Compliance was satisfactory	Average

C: Control; I: Intervention; RCT: Randomised controlled trial

Effect of dietary supplementation with very-long-chain n-3 fatty acids in patients with psoriasis*, Søyland *et al (14).

The trial conducted by Søyland *et al* (14) was a four-month double blind multi-center trial aiming at investigating the effect of dietary supplementation with very-long-chain omega-3 fatty acids in patients with psoriasis. 145 patients with moderate to severe psoriasis were assigned to receive either six 1g capsules of fish oils or six capsules of corn oil, mainly composing of omega-6 acids. The fish oil capsules altogether contained 3g of EPA. Further, both the fish oil capsules and the corn oil capsules contained 3.6 IU of vitamin E. The results of this study are summarized in table 4 below.

The subjects were examined before the trial and once a month thereafter by the same clinician. Erythema, infiltration, desquamation and the area of skin involved were scored by this clinician and summed to produce a score on the Psoriasis Area and Severity Index (PASI).

124 (86%) patients, 62 in each group completed the trial. Out of the 124 subjects, 44 were women (35%) and 80 were men (65%), the mean age being 47 years. Ten patients in the fish oil group and eleven in the corn oil group withdrew due to demands placed on them, acute clinical exacerbations requiring treatment, a move to another area or the inability to swallow the capsules. Compliance was good, as evaluated through capsule count and the measuring of the fatty acid composition of serum phospholipids prior to and after the trial.

The patients were advised to decrease their intake of saturated fatty acids (SFA) by reducing their intake of full-fat milk products, hard margarine and meat. They received written and oral information on foods high in SFA. The dietary intake of SFA was assessed before and

after the trial in a subgroup of randomly selected patients by a nutritionist through a 48hr dietary recall. There was no significant difference in PASI score and clinical state between the groups at baseline and no significant change in score was seen in either group after one, two, three and four months.

Quality assessment

Søyland et al (14) conducted a four-month-double-blind multicenter trial that was assessed to be of high quality. The population size and duration were adequate and the blinding of the subjects and clinicians was sufficient. Even though the number of subjects that did not finish the trial was high (24%), reasons for this were well described and found acceptable. Compliance was high and the outcomes of interest were adequately reported.

Table 3. Result of trial conducted by Søyland *et al* (14).

Author/s	Study design	Population	Intervention	Coverage	Inflammation	Other	Quality
Søyland *et al*, 1993, Norway	Double-blind multicenter RCT	145 patients with stable plaque psoriasis 44 female 80 male completed the trial Mean age 47yrs	**I:** 6 capsules of fish oil 3g EPA/day **C:** 6 capsules of corn oil **I & C:** 21.6 IU of vitamin E/day **Duration**: 4 months with assessments every month	**I:** No significant change **C:** No significant change	**I:** Minimal change seen Before 3.8 ± 0.3 After 3.7 ± 0.3 No significant change **C:** Small change seen Before 4.0 ± 0.3 After 3.7 ± 0.3 No significant change	Non-response: 124 (86%) patients completed the trial Patients were advised to decrease intake of SFA during trial Compliance was satisfactory	High

C: Control; I: Intervention; PASI: Psoriasis Area and Severity index, RCT: Randomised controlled trial, SFA: Saturated fatty acids

***Effect of dietary supplementation with n-3 fatty acids on clinical manifestations of psoriasis*, Bjørneboe *et al* (15).**

The eight-week double-blind block randomized study conducted by Bjørneboe *et al* (15) investigated the effect of dietary supplementation with omega-3 fatty acids on clinical manifestations of psoriasis. 30 patients with stable psoriasis vulgaris were included in the trial. Patients who were on retinoid treatment, were taking warfarin or salicylic acid, had disease of the gastrointestinal tract or the liver were excluded. For two months prior to the trial all included subjects had stopped using topical treatments.

The included patients were randomly assigned to either the intervention or the placebo group. The subjects in the intervention group daily received ten 1g capsules of fish oil MaxEpa®

altogether containing 1.8g EPA whereas those in the placebo group received ten 1g capsules of olive oil/day. All capsules contained 1 IU of vitamin E, 100 IU of vitamin A and 10 IU of Vitamin D. Patients were instructed to keep their regular diet during the trial but were told not to consume cod liver oil. All patients were examined at baseline, after four and eight weeks by the same clinician. The outcome measures were erythema, infiltration, desquamation and area involved.

27 subjects (90%) completed the trial. The three patients that dropped out had difficulties swallowing the capsules. Compliance was measured by capsule count as well as by measuring the serum phospholipid fatty acid composition at baseline and after eight weeks.

No significant difference, with respect to clinical scores for psoriasis, was seen between the two groups at baseline or during the trial.

Quality assessment

The quality of the double-blind block randomized controlled study conducted by Bjørneboe et al (15) was, assessed according to GRADE, classed as average. The intervention group and the placebo group were compared and were similar at baseline. Subjects and clinicians were blinded and compliance was of a high level. A moderate amount of subjects (10%) did not finish the trial but acceptable reasons for this was stated. Furthermore, the outcomes of interest were satisfactorily reported. However, as there were only 30 subjects and these were block randomized the quality of the results will be lower (22). Also, a duration as short as eight weeks lowers the quality of the trial as results may not present in such a short period of time. This decreased the overall quality of this study.

Table 4. Result of trial conducted by Bjørneboe *et al* (15).

Author/s	Study design	Population	Intervention	Coverage	Inflammation	Other	Quality
Bjørneboe *et al*, 1987, Norway	Double-blind block RCT	30 patients with stable psoriasis vulgaris Mean age 39.5yrs Range 17—72yrs	**I:** 10 capsules Of MaxEpa®, 1.8g EPA/day **C:** 10 capsules of olive oil **I & C:** 10 IUs vitamin E, 1000 IU vitamin A, 100 IU vitamin D/day **Duration**: 8 weeks with assessments after 4 and 8 weeks	Clinical scores **I:** Before Mean: 32 Range 8-80 After Mean: 33 Range 8-80 No significant change **C:** Before Mean: 36 range: 10-80 After Mean: 33 range: 10-80 No significant change	Clinical scores **I:** Before Mean: 6.7 Range 4-11 After Mean: 6.6 Range 4-12 No significant change **C:** Before Mean: 6.2 Range 2-11 After Mean: 6.1 Range 2-11 No significant change	Non-response: 27 (90%) patients completed the trial Compliance was satisfactory	Average

C: Control; I: Intervention; IU: International Unit; RCT: Randomised controlled trial

Analysis of the outcomes

The analysis of the outcomes is presented below in table 2. The inflammation was assessed to have a limited strength of evidence (++). The population size in two of the studies (13,15) was relatively small and the trials lasted for short durations, hence reducing their statistical power. Regarding the sympathy between the results, there were also some limitations. Two out of the three studies (14, 15) reach similar results seeing no significant change in inflammation between the intervention and placebo group. However, Bittiner *et al* (13) did see a significant improvement in inflammation. There were some limitations regarding publication bias as two of the trials were sponsored by 7 seas pharmaceuticals®. However, these limitations were not believed to degrade the strength of evidence further.

Coverage was assessed as limited strength of evidence (++). The strength of evidence was weakened by the fact that coverage was not directly measured and only presented as a PASI-score in one of the trials, this decreasing the strength of evidence. Further, the short durations, small population sizes and risk of publication bias were relevant for this outcome as well.

Table 5. Analysis of the outcomes.

Outcome	No° of studies	Internal validity	Sympathy	External validity	Unsure foundation	Strength of evidence
Inflammation (erythema)	3 RCT	Certain limitations[2]	Certain limitations[3]	No limitations	Certain limitations[4]	Limited (++)
Coverage (area)	3 RCT	Certain limitations[1,2]	No limitations	No limitations	Certain limitations[4]	Limited (++)

[1] Outcome of interest not directly measured, [2] Small study populations and short durations, [3] Results vary between the studies. [4] Risk of publication bias.

Discussion

Upon reviewing the three studies, only one produced a positive outcome regarding inflammation (13), whereas the other two did not show any significant change on either outcome in either group (14, 15). These results will be related to the fact that the studies vary in strength and composition of supplement, duration and group sizes.

The subjects entered into the Bittiner *et al* (13) double-blind trial consumed either ten 1g capsules of fish oils containing 1.8g of EPA or 10g of olive oil. The finding that there was an improvement with fish oils regarding inflammation when compared to the placebo suggests that fish oils do have an anti-inflammatory effect in psoriasis. However, as this trial ultimately only looked at 24 patients for twelve weeks this trial is not believed to have statistical power. This is one of the reasons that this trial was assessed to be of average quality. A further weakness of this trial is the fact that the patients were assessed for erythema using a 0-5 grading scale. This is not further explained or specified and therefore we cannot directly draw comparisons between these results and those in the other trials (14, 15) where the PASI is used. There are no significant clinical differences that would determine the outcome of this trial as no other high standard trials have shown similar results, and conclusions cannot be drawn from one single trial.

The supplementation in Soyland *et al* (14) consisted of either six 1g capsules of ethyl esters of very-long-chain omega-3 fatty acids or the same amount of corn oil. The MaxEpa® capsules used in the other trials (13, 15) are also composed of ethyl esters of omega 3. The 6g of fish oils per day consumed by the intervention group contained 3g of EPA, almost twice as much as consumed in the other trials (13, 15). As this trial is the largest and longest lasting one, and as no significant improvement was seen in either outcome, this suggests that EPA does not have a significant effect in symptom improvement in psoriasis.

All capsules contained 3.6 IU of vitamin E as an antioxidant to prevent the oils from becoming rancid, this adding up to 36 IU per day. As vitamin E has antioxidant properties that contribute to cell membrane stability, the possibility that this has affected the outcome of the intervention cannot be excluded (12).

The patients in this trial were advised to limit their intake of saturated fat. This may have played a role in the outcome, as a diet high in saturated fats is associated with an increase in inflammation (24). This may possibly have worsened the symptoms.

Further, the patients in the Soyland *et al* trial (14) were allowed to continue on using their current topical treatments. Patients in this group had previously been treating their psoriasis with various topical ointments for a long duration of time. However, no significant outcome had yet been demonstrated prior to the trial. Therefore, the addition of fish oil may possibly have demonstrated a positive outcome.

The intervention group in the Bjorneboe *et al* (15) trial received ten 1g capsules of MaxEPA®, altogether consuming 18g of EPA/day. The control group consumed ten 1g capsules of olive oil/day. Each capsule contained 1 IU of vitamin E as an antioxidant, 100 IU vitamin A and 10 IU of Vitamin D. In total the subjects would have consumed 10 IU vitamin E, 1000 IU vitamin A and 100 IU vitamin D per day. The vitamin A translates to 300mcg/day, when the daily recommendation in Sweden is 700-900mcg/day (28). As previously discussed, the antioxidant effect of vitamin E may have played a role in the outcome of this trial as well (12). In a review written by Rickets *et al* (17) looking at nutrition in psoriasis, the oral supplementation of Vitamin D was shown to have a positive effect in some patients with psoriasis, primarily those with vitamin D deficiency. In a 1-year cross-sectional study conducted on 145 patients with chronic plaque psoriasis, 57.8% of these subjects were seen to be vitamin D deficient (21). As the three trials that were analyzed were conducted in countries with limited sunlight and the vitamin D status of the subjects was not reported or discussed in either trial, we cannot exclude the possibility that this has affected the results.

The same review discusses that vitamin A derivatives applied topically, orally or intravenously may also potentially confer benefits in patients with psoriasis. This is important to keep in mind when interpreting the results seen in Bjorneboe *et al*s trial (17).

Two of the studies were conducted in Norway (14,15) and one in England (13). As the subjects most likely would have been locals, their lifestyles and eating habits most certainly may vary from each other. It is important to keep this in mind when interpreting the results, as it is likely that the subjects' previous diet may have affected the outcome of the trials. Overall, Scandinavian diets are higher in fish oils than those in the more southern parts of Europe, including the UK (14).

The Placebo in the three trials was either corn oil or olive oil. These differ in the sense that corn oil is high in polyunsaturated fats (PUFA) whereas olive oil mainly consists of monounsaturated fats (MUFA) (18). 1g of olive oil contains 0.73g of MUFA whereas 1g of corn oil consists of 0.59g of PUFA (26). Further, corn oil has an omega-3 to omega-6 ratio of 1:49 compared to the same ratio in olive oil, which is 13:3 (25). A high omega-3 to omega-6 PUFA ratio is associated with anti-inflammatory effects (27). Omega-6 acids have been seen to produce pro-inflammatory metabolic responses, possibly resulting in a larger difference in the outcomes between the corn oil placebo group and the fish oil intervention group in (26).

The patients were advised to limit their intake of saturated fat, which may have played a role in the outcome. A diet high in saturated fats is associated with an increase in inflammation, possibly worsening the symptoms of psoriasis (24).

The durations of the trials also vary in length from eight weeks to four months. A short duration is likely to result in a poorer clinical outcome (17, 22). The trial lasting for four months (14) has greater statistical power than the other two (13, 15), as there was more time

for the subjects to present with any clinical improvement. As no significant improvement was seen in this trial (14), it suggests that fish oil does not improve symptoms in psoriasis.

An important point to discuss is the fact that two of the studies (14, 15) are sponsored by 7 seas pharmaceuticals®. When clinical trials are sponsored it is important to keep in mind that there is a risk of publication bias (22). 7 seas pharmaceuticals® may have influenced what was published and swayed the results for personal gain. There are moral concerns raised by sponsored research as the companies typically focus on generating profits, and sometimes their priority focus is not on the health of the patients but on making a profit (23).

As the three trials have not demonstrated significant outcomes inflammation and coverage, trials with longer durations, higher doses and larger populations would ultimately provide more solid evidence for whether or not a supplementation of fish oils is recommended in psoriasis. Based on the trials that have been reviewed, as both positive and negative outcomes have been perceived, further research is required to solidify the effect of fish oil supplementation in psoriasis.

Conclusion

In conclusion, this review shows that there is limited (++) evidence for that a daily oral supplementation of fish oils improves either inflammation or coverage in psoriasis. As only one randomized controlled trial demonstrated an improvement of the disease state, and as this one only looked at a small population for a short period of time, there is not enough evidence to support oral supplementation of fish oils as a primary treatment of psoriasis.

Based on current research, the clinical value of fish oil supplementation remains uncertain regarding psoriasis. Fish oil supplementation may possibly exert some positive effects when used in addition to established psoriatic therapies, but at present its use as an exclusive treatment is not justifiable. To see whether a supplementation of fish oils produces a clinical response, trials for longer periods of time and higher doses of fish oils are in demand. Further research in this area is needed.

References

1. Psoriasis förbundet. 2012; Available from: http://www.psoriasisforbundet.se/psoriasis/
2. National psoriasis foundation. about psoriasis, statistics. Portland 2012 [cited 20/03/12]; Available from: www.psoriasis.org/learn_statistics.
3. Chilton FH, Rudel LL, Parks JS, Arm JP, Seeds MC. Mechanisms by which botanical lipids affect inflammatory disorders. The American Journal Of Clinical Nutrition. 2008;87(2):498S-503S.
4. Stoff AMB. Psoriasis: Mason Punlishing LTD; 2010.
5. AB Abbot Scandinavia. Psoriasis. Stockholm: Abbott Nutrition; 2008 [updated 02/04/2008; cited 2012 20/03/12]; Psoriasis]. Available from: www.abbott.se/?id_site=1&id_item=488.
6. Vårdguiden. Psoriasis. Stockholm: Jessika Bjurel; 2011 [cited 2012 20/003/12]; Available from: www.vardguiden.se/Sjukdomar-och-rad/Omraden/Sjukdomar-och-besvar/Psoriasis/.
7. eMedicineHealth. Types of Psoriasis. New York 2012 [cited 2012 20/03/12]; Types of Psoriasis]. Available from: www.emedicinehelath.com/types_of_psoriasis/articles_em.htm.
8. Health NNIo. Fish oil. Bethesta: US National Library of Medicine; 2012 [updated 14/03/12; cited 2012 20/03/12]; Available from: www.nlm.nih.gov/medlineplus/druginfo/natural/993.html.

9. Mayo foundation for medical education and research. Omega-3 fatty acids, fish oil, alpha-linolenic acid. 2011 [updated 01/10/2011; cited 2012 20/03/12]; Available from: www.mayoclinic.com/health/fish-oil/NS_patient-fishoil/DSECTION=evidence.
10. WebMD. Fish Oil: uses, side effects, interactions and warnings 2009 [cited 2012 20/03/12]; Available from: http://www.webmd.com/vitamins-supplements/ingredientmono-993-FISH%20OIL.aspx?activeIngredientId=993&activeIngredientName=FISH+OIL
11. Moghadasian MH. Advances in dietary enrichment with n-3 fatty acids. Critical Reviews In Food Science And Nutrition. 2008;48(5):402-10.
12. Clark Ka. Clinical Medicine Clark PKaM, editor: Saunders and Elsevier; 2009.
13. Bittiner SB, Tucker WF, Cartwright I, Bleehen SS. A double-blind, randomised, placebo-controlled trial of fish oil in psoriasis. Lancet. 1988;1(8582):378-80.
14. Søyland E, Funk J, Rajka G, Sandberg M, Thune P, Rustad L, et al. Effect of dietary supplementation with very-long-chain n-3 fatty acids in patients with psoriasis. The New England Journal Of Medicine. 1993;328(25):1812-6.
15. Bjørneboe A, Smith AK, Bjørneboe GE, Thune PO, Drevon CA. Effect of dietary supplementation with n-3 fatty acids on clinical manifestations of psoriasis. The British Journal Of Dermatology. 1988;118(1):77-83.
16. International atomic energy agency. Erythema. Vienna Austria2011 [cited 2012 21/03/12]; Available from: http://rpop.iaea.org/RPOP/RPoP/Content/InformationFor/HealthProfessionals/5_InterventionalCardiology/erythema.htm
17. Ricketts JR, Rothe MJ, Grant-Kels JM. Nutrition and psoriasis. Clinics In Dermatology. 2010;28(6):615-26.
18. Sirtori CR, Gatti E, Tremoli E, Galli C, Gianfranceschi G, Franceschini G, et al. Olive oil, corn oil, and n-3 fatty acids differently affect lipids, lipoproteins, platelets, and superoxide formation in type II hypercholesterolemia. The American Journal Of Clinical Nutrition. 1992;56(1):113-22.
19. Grimble RF TP. Modulation of pro-inflammatory cytokine biology by unsaturated fatty acids. Z Ernahrungswiss 1998;37(1):57-65.
20. Blok WL KM, van der Meer JW. Modulation of inflammation and cytokine production by dietary (n-3) fatty acids. Journal of Nutrition. 1996.
21. Gisondi P, Rossini M, Di Cesare A, Idolazzi L, Farina S, Beltrami G, et al. Vitamin D status in patients with chronic plaque psoriasis. The British Journal Of Dermatology. 2012;166(3):505-10.
22. Ejlertsson G. Statistik for Halsovetenskaperna. Stockholm: Studentlitteratur AB; 2003.
23. Wender D. The Ethics of Clinical Research Stanford 2009 [cited 2012 21/03/12]; Available from: http://plato.stanford.edu/cgi-bin/encyclopedia/archinfo.cgi?entry=clinical-research
24. Hechtman L. Clinical Naturopathic Medicine. Chatswood: Elsevier Australia; 2011.
25. Simopoulos AP. Omega-3 fatty acids in inflammation and autoimmune diseases. Journal Of The American College Of Nutrition. 2002;21(6):495-505.
26. Wardhana, Surachmanto ES, Datau EA. The role of omega-3 fatty acids contained in olive oil on chronic inflammation. Acta Medica Indonesiana. 2011;43(2):138-43.
27. Galland L. Diet and inflammation. Nutr Clin Pract. 2010;25(6):634-40.
28. National food Agency. Vitamin A, Fordjupning. Stockholm2012 [updated 2012-02-1524/03/12]; Available from: http://www.slv.se/sv/grupp1/Mat-och-naring/Vad-innehaller-maten/Vitaminer/Vitamin-A/Vitamin-A/
29. Steele T, Rogers CJ, Jacob SE. Herbal remedies for psoriasis: what are our patients taking? Dermatology Nursing / Dermatology Nurses' Association. 2007;19(5):448
30. Horrocks LA, Yeo YK. Health benefits of Docohexaenoic acid (DHA). Pharmacol Res, 1999 Sep;40(3):211:225.