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Systemic vitamin D and fish oil in the management of psoriasis

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SYSTEMIC VITAMIN D AND FISH OIL IN
THE MANAGEMENT OF PSORIASIS

by

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SYSTEMIC VITAMIN D AND FISH OIL IN
THE MANAGEMENT OF PSORIASIS
KERRI LISKA
ABSTRACT

Data from studies looking at the use of systemic vitamin D and omega-3 fatty acids independently in the treatment of psoriasis has shown that both these supplements have at least a modest effect when taken in above average doses. Recent advances in the understanding of the pathophysiology of psoriasis as well as the immunomodulatory and anti-inflammatory properties of these supplements suggest that they could have an additive effect in treating this life-long disease. The proposed study is a randomized placebo-controlled trial that aims to explore this supposition by supplying demographically diverse subjects, who have varying levels of psoriasis severity, with 4g of Omacor® fish oil (1.8g EPA + 1.5g DHA) and 4000IU of vitamin D3 (cholecalciferol) or placebo pills on top of their existing treatment regimen. The subjects will have a baseline evaluation and the trial will run for 1 year with 12 week follow up intervals. Every 12 weeks the subjects will have a clinician calculate their current PASI score and have blood drawn to measure vitamin D levels. Investigators will analyze the overall percent reduction of an individual’s PASI score as well as the mean final PASI scores of the intervention and control groups. The data from this study will provide information that could add another safe, inexpensive, and effective treatment modality to the dermatologist’s arsenal.
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LIST OF ABBREVIATIONS

AA ........................................................................................................... Arachidonic Acid
ALA ........................................................................................................... α-Linolenic Acid
BSA .......................................................................................................... Body Surface Area
BU ........................................................................................................... Boston University
CI ........................................................................................................... Confidence Interval
CLA ........................................................................................................ Cutaneous Lymphocyte-Associated Antigen
CVD ........................................................................................................ Cardiovascular Disease
DHA ........................................................................................................ Docosahexaenoic Acid
DLQI ....................................................................................................... Dermatology Life Quality Index
DNA ........................................................................................................ Deoxyribonucleic Acid
EPA ........................................................................................................ Eicosapentaenoic Acid
HLA .......................................................................................................... Human Leukocyte Antigen
IFN ........................................................................................................... Interferon
IFN-γ ...................................................................................................... Interferon-gamma
IL ........................................................................................................... Interleukin
IRB .......................................................................................................... Institutional Review Board
MHC ........................................................................................................ Major Histocompatibility Complex
MI ........................................................................................................... Myocardial Infarction
mRNA .................................................................................................... Messenger Ribonucleic Acid
NPF ......................................................................................................... National Psoriasis Foundation
PASI ........................................................................................................ Psoriasis Area and Severity Index
PCB ............................................................. Polychlorinated biphenyls
PDE4 ........................................................... Phosphodiesterase 4
PUFA .......................................................... Polyunsaturated Fatty Acids
RXR ............................................................ Retinoid X Receptor
TNF ............................................................. Tumor Necrosis Factor
TNF-α ........................................................... Tumor Necrosis Factor-alpha
UVB .............................................................. Ultraviolet B
VDRE .......................................................... Vitamin D Response Element
INTRODUCTION

Background

Psoriasis is a chronic cutaneous T-cell mediated inflammatory disease that affects about up to 3% of the population in the countries of the Western world.\textsuperscript{1} Difference in prevalence and severity depends on a host of environmental and genetic factors. The majority of patients diagnosed with psoriasis have mild-moderate disease.\textsuperscript{2} The definition of mild, moderate, and severe disease is largely subjective based on clinician’s assessment and the patient’s perception of quality of life.

There are several presentations of psoriasis ranging from scattered papules that are a few millimeters to large plaques that encompass almost the entire body. Psoriatic plaques are a result of hyperproliferation and early maturation of keratinocytes\textsuperscript{3} as well as infiltration of inflammatory and immune cells. This thickened epidermis along with inflammatory cells creates the well-demarcated, raised, erythematous lesions with a silver-white scale seen in classic plaque psoriasis.

There is no cure for psoriasis therefore the treatments available are for symptom management and are chosen based on the severity of the disease, aiming to balance risk with benefit. Topical medications such as retinoids, vitamin D derivatives and corticosteroids are indicated as monotherapy for mild disease and as adjuvant therapy in moderate to severe cases. Phototherapy with narrow band ultraviolet B (UVB) is used as second line treatment for psoriasis not adequately controlled with topical medications. Systemic oral medications such as chemotherapeutics and phosphodiesterase 4 (PDE4) inhibitors as well as injectable biologic agents are reserved for moderate and severe
disease given a host of possible adverse events. Despite a great deal of efficacy with these medications, patients with psoriasis often have some level of recalcitrant disease that requires combination therapy.

**Statement of the Problem**

Adherence to treatment regimens utilizing the currently available medications is a significant problem in this life-long disease. Topical medications are often messy, time consuming and many find them ineffective. Systemic medications are easier to take, but have significant possible side effects or adverse events and are often prohibitively expensive. These are often not covered by insurance until patients have failed several other less expensive medications, which can lead to weeks to months of living with a psychosocially debilitating level of disease. These obstacles to treatment adherence beg the question: Is there an effective treatment for this disease that is easy to administer, cost effective, and has minimal possible side effects/adverse events?

**Hypothesis**

Combination treatment with cholecalciferol and omega-3 fish oil will significantly decrease the Psoriasis Area and Severity Index (PASI) score in patients with chronic plaque psoriasis

**Objectives and specific aims**

Psoriasis is an autoimmune disorder that involves dysregulated cell proliferation and turnover as well as inflammation. There is significant data on the use of each vitamin D and fish oil in the treatment of other hyperproliferative and inflammatory conditions. Several studies show the use of topical vitamin D, oral vitamin D and oral fish oil
supplementation can be efficacious in psoriasis. There is also data suggesting a cumulative or synergistic relationship between these two supplements in the treatment of other conditions. There is biological rationale that could explain the mechanism by which these supplements could affect the underlying pathogenesis of this disease. This study aims to explore whether the natural supplements of vitamin D and fish oil, in combination, can provide a safe, efficacious, simply administered, cost effective treatment for patients with psoriasis.

• To show a statistically significant decrease in percent PASI score reduction in patients treated with cholecalciferol and omega-3 fish oil in a clinical trial
• To determine the magnitude of effect of the proposed treatment
• To determine if severity of disease has an impact on magnitude of effect
REVIEW OF THE LITERATURE

Overview

Psoriasis is an autoimmune, T cell mediated disease of systemic inflammation with skin, nail, joint and soft tissue manifestations that affects up to 11% of the population depending on regional variations. Incidence of the disease is not well studied, but a review of 3 studies by Parisi et al estimated the incidence to range from 73-230/100,000 person years. There is a bimodal distribution of the age of onset, peaking from 30-39 and again between 50 and 70. It is a heterogenous disease with many different manifestations and varying degrees of severity. Chronic plaque psoriasis is well-demarcated erythematous, raised plaques with silver grey scale that can range from a few millimeters to entire scalps, limbs or trunks. Lesions may also present as small diffusely distributed papules (guttate psoriasis), pustules on the hands and feet (palmoplantar pustulosis), generalized erythema that is not in well defined plaques (erythrodermic psoriasis), plaques clustered in the folds of the skin, particularly inframmamary, perineal and axillary, without scale (inverse psoriasis), or rarely generalized inflamed skin studded with pustules (pustular psoriasis). These different forms of psoriasis may be symptomatic with a burning or itching sensation and may arise acutely or exist for years as chronic lesions. Environmental triggers can cause the acute lesions seen in guttate psoriasis, which is often precipitated by a streptococcal infection. Trauma to the skin of a psoriatic patient can also result in new lesions, a process known as Koebnerization. Many patients also experience seasonal variation in the severity of their disease, with more severe symptoms commonly occurring during cooler, less sunny months.
These above mentioned differences in incidence and prevalence are thought to be a combination of environmental as well as genetic factors. Several twin studies show significant concordance between siblings. The search for certain susceptibility genes is an ongoing process. Many different human leukocyte antigen (HLA) genes, segments of several “gene dense” chromosomes named PSORS1-PSORS13 and many other genes are implicated in the disease (see table 1). PSOR1, in particular the major histone complex I (MHC1) genes in this chromosome segment have the strongest association with psoriasis.

The fact that in many patients there is a correlation between severity of disease and the season, with being more severe psoriasis occurring in the winter months when there is less sun is cool and dry, is good evidence that there is also an environmental factor at play. The Koebner phenomenon, in which trauma triggers an eruption of psoriasis, is another indicator that the physical environment plays a role. Guttate psoriasis, which can be usually correlated with a streptococcal infection, is yet another clue to the role of exogenous factors in the pathogenesis of this disease.

The difference in prevalence of psoriasis in sub-Saharan Africa represents another prime example. The tropical climate of Western Africa shows the lowest prevalence at 0.05-0.4% whereas the dry area of Eastern Africa has an almost 10x increase in prevalence (2.8-3.5%) and yet these populations do not appear to have a difference in the frequency of HLA-Cw6. The highest rates of psoriasis in the aforementioned review by Raychaudhuri et al. occurred in a population that resides in the Artic Circle.
### Table 1. List of Reported Genetic Associations

(adapted from table 1. in Genetic and epigenetic basis of psoriasis pathogenesis by Chandra et al[^7])

<table>
<thead>
<tr>
<th>Genetic locus identified</th>
<th>Predicted candidate Genes associated</th>
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<tr>
<td>6p21.33 (PSORS1)</td>
<td>HLA-Bw7, DR4, DR7, HLA-A1, HLA-B13, B17, B27, B39, B57, <strong>HLA-Cw6</strong>, Cw7, PSORS1C3, CCHCR1, CDSN, POU5F1, CDKAL1, IRF4</td>
</tr>
<tr>
<td>17q25.3 (PSORS2)</td>
<td>NAT9, SLC9A3R1, RAPTOR, CMRF35A1, CMRF35A2-6, CMRF35H, CARD14, STAT3</td>
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<td>4q (PSORS3)</td>
<td>IL2, IL21</td>
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<tr>
<td>1q21 (PSORS4)</td>
<td>LOR, S100A8, S100A9, PGLYRP3, PGLYRP4, LCE3A, LCE3B/3C deletion, LCE3D, LCE3E, IVL, FLG</td>
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<td>3q21 (PSORS5)</td>
<td>CSTA, SLC12A8</td>
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<td>19p13 (PSORS6)</td>
<td>Jun-B, ILF3, BSG</td>
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<td>1p (PSORS7)</td>
<td>EPS15, IL23R, PTPN22, RUNX3, TNFRSF9</td>
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<td>16q (PSORS8)</td>
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<tr>
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<td>IL1RN</td>
</tr>
<tr>
<td>18q21.2</td>
<td>MBD2</td>
</tr>
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[^7]: Chandra et al. Genetic and epigenetic basis of psoriasis pathogenesis.
Older epidemiologic studies show an absence of psoriasis in Aborigines, Andean Indians, Amerindians, and Native Americans and more recent genetic assessments have shown a lack of several of the HLA loci associated with psoriasis. These races live in a variety of environments that would contribute differently to the prevalence of disease, but consistently lack known susceptibility genes. Chandra et al. reviewed several family based studies and came to the conclusion that though there are many genes associated with psoriasis, it is a heterogenic disease. Clearly disease incidence and severity represent an interplay between genetics and environment.

A German study published in 1970 discovered the possible immunologic basis of psoriasis and, since that time, there have been several other studies substantiating that claim that dysregulation of the immune system could be to blame for the overactive turnover of keratinocytes found in psoriasis. An article in the New England Journal of Medicine by Nestle et al. summarized several studies which found increased numbers of dendritic cells, T cells and cytokines in psoriatic skin.

This review will explore both the innate and adaptive immune response and the cytokine mediators that play a key role in the proposed intervention. Keratinocytes play a large role in the activation of the innate immune system, sending out cytokines to attract T cells and dendritic cells to the areas of skin. Trauma or infection can also stimulate the activity of dendritic cells, which further activates T cells. The main pathway for immune activation in psoriasis is mediated by interleukin-23 (IL-23) release from activated dendritic cells as well as keratinocytes (see figure 1). IL-23 stimulates survival and proliferation of T helper 17(Th17) cells. Th17 cells (CD4+) releases IL-17 and IL-22.
Figure 1. “Immunogenic pathway model in psoriasis” (IL-23/T17 axis (red) is dominant pathway). Taken from “The Immunopathogenesis of Psoriasis” by Kim et al.⁹

which in turn act on keratinocytes.¹⁰,¹¹ There are several other types of T cells that can produce IL-17 (CD8⁺, αβ T cells, γδ T cells, innate lymphoid cells) and therefore most literature refers to them as T17 cells⁹ as will be done here for simplicity. Lynda Grine et al explained in a 2014 paper looking at the role of tumor necrosis factor (TNF), type I interferons (IFNs) and IL-17, that when compared with healthy controls, psoriasis patients have a higher level of intralesional and circulating IL-17 and that there is a correlation between level of IL-17 and disease severity.¹⁰ Psoriatic skin has a 30-fold increase in BDCA-1⁺ dendritic cells, which are the “inflammatory” dendritic cells, and these have been proposed as a driver of T17 cells.⁹ According to Yiu and Griffiths who
reviewed the effect of several IL-17 medications in psoriasis, “Psoriasis is considered a prototypical IL-17-mediated disease.”

Prior to the discovery of T17 cell involvement, release of interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) produced by many cell types, especially Th1 cells, were thought to be the most important mediators of pathogenesis. These cytokines certainly do play a role upstream in the activation and proliferation of immune cells and cytokine release. Kim et al. proposed that IL-17 can synergize with TNF-α to induce key genes involved in psoriasis. TNF-α, which is produced by keratinocytes, dendritic cells and T cells in response to a host of inciting factors, can induce the proliferation of dendritic cells, T cells and therefore the release of more TNF-α, IFN-γ, and IL-17. There are cytokines in psoriasis that come from every T cell line, but more recent experiments exploring the effects of T17 induction and inhibition in psoriatic lesions have shown this to be the major factor. Furthermore Kim et al. stated in their review that IL-17 induces several other interleukins, which might lead to keratinocyte proliferation, a hallmark of this disease.

Psoriasis is most often evaluated based on the clinical characteristics a provider sees in the office. There is a significant amount of morbidity associated with the disease including psychological effects, medication side effects, and other associated inflammatory diseases such as Crohn’s disease, type 2 diabetes, and cardiovascular disease (CVD). Several assessment scales exist to standardize the clinical evaluation of plaque psoriasis. There is a debate on the best method given the diverse presentation and amount of subjective data required.
Management of psoriasis is based on clinical assessment of severity and risk versus benefit of certain medications. Knowledge of immune system involvement in the pathogenesis of psoriasis has led to the use of immune targeted therapies such as methotrexate and cyclosporine as well as less targeted anti-inflammatories such as topical steroids and phototherapy. Mild psoriasis is treated with topical medications because these often have the lowest risk profile and are capable of controlling limited disease. Consensus guidelines published in JAMA in 2012 gloss over the treatment of mild disease and simply define it as that which can be treated solely by topical treatment.

Moderate to severe disease requires treatment with systemic (oral and/or phototherapy) and biologic medications. These both have system wide effects, side effects, and require more monitoring than topical therapies. The adverse reactions possible with these medications make the risk/benefit acceptable for only those with moderate-severe and severe disease. Oral systemic medications include methotrexate (folate biosynthesis inhibitor) and cyclosporine (calcineurin inhibitor), which inhibit cell turnover and cell synthesis, acitretin (an oral retinoid), which regulates gene transcription for “nuclear differentiation, antiproliferation, anti-inflammation, antikeratinization and inhibition of neutrophil chemotaxis”, and the newly approved Apremilast (PDE4 inhibitor) which downregulates the inflammatory response mediated by Th1, Th17 and type 1 IFN pathways. These mediations may also require lifestyle changes such as avoiding alcohol, pregnancy, and excessive sunlight. Several biologic medications exist, some of which inhibit cytokines known to be involved in the pathogenesis of psoriasis such as TNF (etanercept, infliximab, adalimumab), IL-12/23 (ustekinumab), and
IL-17 (secukinumab, ixekizumab, brodalumab).\textsuperscript{12,14} The most recent of these biologic medications are those targeting IL-17 and only one (secukinumab) is currently on the market.\textsuperscript{12} A review of data from several phase II and III trials of IL-17 inhibitors by Yiu et al. showed significant superiority over older treatments and even raised the standard of care for those with severe psoriasis showing a consistent, high percentage of patients reaching a 90% decrease in PASI score.\textsuperscript{12}

Treatment adherence with medications is a significant issue. There have been several studies looking at patient adherence, which are nicely summarized in literature reviews performed by Thorneloe et al. and Saeki et al. Both reviews showed that topical medication adherence is worse than systemic treatment modalities.\textsuperscript{2,19} In a review done by Deveaux et al. topical medication non-compliance was largely due to four major complaints: time needed to apply treatment, poor efficacy, fear of side effects and cosmetic effects. Time commitment was the largest contributor.\textsuperscript{20}

The review by Saeki et al. also found a significant percentage of what they defined as medium and low treatment adherence (32.5% and 55.4% respectively) in the oral treatment group, but noted that these percentages decreased with higher annual income, a correlation that was not seen in the topical medication group.\textsuperscript{19} Phototherapy, oral, and biologic medications are much more expensive than topical treatment. An estimation of monthly costs done by D'Souza and Payette showed prices ranging from around $800/month for methotrexate to around $15,200 for infliximab.\textsuperscript{21}
Table 2 shows several adverse events that are possible with these systemic treatments. Armstrong et al. reviewed findings from National Psoriasis Foundation (NPF) surveys of treatment type for mild, moderate, and severe disease done from 2003-2011.

**Table 2. Possible Safety Concerns of Systemic Psoriasis Treatments**

<table>
<thead>
<tr>
<th>Phototherapy</th>
<th>Oral</th>
<th>Biologic</th>
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<tbody>
<tr>
<td>Skin Cancer</td>
<td>Liver toxicity</td>
<td>Serious Infection</td>
</tr>
<tr>
<td>Nausea (with psoralen)</td>
<td>Renal toxicity</td>
<td>Autoimmune conditions</td>
</tr>
<tr>
<td>Skin aging/freckling</td>
<td>Hypertriglyceridemia</td>
<td>Lymphoma</td>
</tr>
<tr>
<td></td>
<td>Teratogenicity</td>
<td></td>
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<tr>
<td></td>
<td>Abortifacient</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drug interactions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Skin cancer</td>
<td></td>
</tr>
</tbody>
</table>

and found the most common reason for the use of only topical medication was fewer adverse effects. It also showed that as of 2008 the main reason (28%) for discontinuing biologic treatment was adverse side effects. They also found that patient satisfaction with any form of psoriasis treatment was low at only 47.7% as of 2011. For reasons not explained in the review up to 49.2% of those with mild, up to 35.5% of those with moderate, and up to 29.7% of those with severe disease over the time period studied were not receiving treatment at all. This could be rationalized by any of the aforementioned
reasons for discontinuation or non-adherence: time consumption, expense, and/or adverse events.

**Existing research**

*Fish Oil*

N-3 fatty acids found in fish oil have been explored as an adjunctive treatment in several other inflammatory conditions such as Crohn’s disease, rheumatoid arthritis, and CVD. Like these other diseases, psoriasis is a disease of systemic inflammation. It is proposed here that since this supplement has proven efficacious in reducing inflammation in CVD, it may have a similar effect in psoriasis.

The association with CVD is well studied for over 35 years beginning with investigations into lipid metabolism and ischemic heart disease in Greenland Eskimos by Bang and Dyerberg. Hundreds of studies have explored the relationship between N-3 fatty acids and CVD aiming to find biological pathways to explain the observed benefits. Though many studies explored the effects of these polyunsaturated fatty acids (PUFAs) on the levels of the lipids involved in CVD they also looked at the connection between PUFAs and inflammation. Inflammation is known to play a large role in atherosclerosis. A review by Fleming et al. exploring α-linolenic acid (ALA) as compared with docosahexaenoic acid (DHA) + eicosapentaenoic acid (EPA) in CVD reduction cited several studies which showed that the two components of omega-3 supplementation (DHA and EPA) had an inverse relationship with several markers of inflammation. Increased incorporation of n-3 fatty acids into cell membranes provides less substrate for inflammatory eicosanoids (metabolites of PUFA, arachidonic acid
(AA), EPA, and dihomogamma linolenic acid oxidation). Two separate reviews of the literature looking at fish oil and CVD both showed that there was conflicting evidence on the efficacy of fish oil and various mortality and cardiovascular endpoints. In both reviews they stated this could be due to a lack of control of fish consumption in the control study as well as an estimated omega-3 consumption rather than blood monitoring. They came to the conclusion that despite conflicting data there was significant data showing a benefit. Therefore there is a place for fish oil supplementation in CVD that is due not only to beneficial changes in lipid profiles but also because of anti-inflammatory properties.

For decades an association between psoriasis and CVD has been seen in the hospital setting and been studied by many researchers. Charles McDonald MD and Paul Calabresi MD noted almost twice the amount of vaso-occlusive events in psoriatic patients at Roger Williams Hospital from 1968-1972. They performed a study that was published in 1978 examining the records of 323 psoriatic and 325 non-psoriatic patients who were admitted to the dermatology service at Roger Williams Medical Center. In this larger, more organized study they still found a significant increase in the amount of occlusive vascular events in those with psoriasis.

Gelfand et al. found that many studies showing a correlation of psoriasis with CVD were done on hospitalized patients. Therefore they did a population based prospective study looking at the incidence of myocardial infarction in patients with mild or severe psoriasis when compared to demographic and risk factor-matched controls. In this study they found that both mild and moderate psoriasis conferred a higher relative
risk for younger individuals. Their data showed a relative risk of “1.29 (95% CI, 1.14-1.46) and 3.10 (95% CI, 1.98-4.86)” for mild and severe psoriasis respectively for a 30 year-old patient with relative risk dropping to “1.08 (95% CI, 1.03-1.13) and 1.36 (95% CI, 1.13-1.64), respectively” for a 60 year-old patient. When they controlled for major cardiovascular risk factors they found the attributable and excessive risk of myocardial infarction (MI) due to psoriasis increased with both mild and moderate degrees of severity.

A study done by Neimann et al. sought to answer the question of whether psoriasis could in fact be associated with CVD risk factors. Their literature review showed a selection bias of patients with significant additional co-morbidities due to the fact that most studies were done on hospitalized patients. Neimann et al. carried out a population-based study and control matched each case with 5 non-psoriatic patients with similar demographics. Their data suggested that psoriasis is, in fact, associated with metabolic syndrome (hypertension, dyslipidemia, obesity, and impaired glucose tolerance) and the association increases with increasing severity of psoriasis. Furthermore they explained from review of the literature on metabolic syndrome, that like psoriasis, metabolic syndrome is a disease of inflammation involving increased T cell and cytokine activity. Both have a Th1 inflammatory profile and psoriasis is sometimes “included in the chronic inflammatory spectrum of the metabolic syndrome.” This association with metabolic syndrome is fast gaining support and being recognized as a key intervention target for psoriasis patients with lifestyle and diet changes.
Cutaneous inflammation is mediated through eicosanoids produced by skin cells in response to injury that aids in repair of the skin. Eicosanoids are therefore a central part of many dermatoses such as psoriasis. Essential fatty acids provided by the diet, omega-6 (AA) and omega-3 (DHA + EPA), are converted into eicosanoids, which have both pro-inflammatory and anti-inflammatory properties. Psoriatic skin is found to have higher levels of AA which in turn leads to pro-inflammatory cytokines and the attraction of immune cells. As mentioned above EPA can compete with AA when levels are high enough and in turn lead to anti-inflammatory cytokines. According to McCusker et al. in a paper on the healing fats of the skin, EPA and DHA are often not abundant in the epidermis because of a lack of consumption or increased usage. Diets supplemented with fish oil have an alteration in this profile. Kendall et al. also examined the distribution of bioactive lipids in the skin and they showed that the lipid profile in the dermis and epidermis changed with the addition of omega-3 PUFAs to include more of the “less inflammatory” eicosanoids, endocannabinoids, and anti-inflammatory lipid resolvins and maresins.

PUFAs also have an immunologic effect. Murine studies done by Allen et al. and Monk et al. showed omega-3 influence on Th1, Th2 and Th17 activation and signal transduction. These studies cited information regarding fish oil suppression of CD4⁺ transformation to Th1 inflammatory subset and sought to explore the effects on Th17 transformation. Allen et al. showed that fish oil incorporation into T cell membranes interrupted the signal axis involved in Th17 differentiation. As mentioned above, the
pathogenesis of psoriasis is greatly driven by Th17 cells and therefore fish oil could play a role in suppressing this process.

Several older studies done in the 1980’s and early 1990’s have looked at topical, oral, and IV supplementation with fish oil with little or even no success. Grimminger and Mayser reviewed several of the past attempts to test oral supplementation with free fatty acids. Many of the studies they reviewed showed modest change in the characteristics of psoriatic plaques.\textsuperscript{39,41} According to Grimminger and Mayser the controlled studies seem to show more of a benefit than randomized controlled trials.\textsuperscript{39} A more recent review by Millsop et al in 2014 showed more promising outcomes with 12 of 15 studies showing significant improvement with an even split of controlled and uncontrolled studies showing significant improvement. They found in their review of several nutritional supplements that the data for fish oil, as monotherapy or in combination with topicals, phototherapy or retinoids, was the most encouraging. Their findings are summarized in appendix A.\textsuperscript{45}

Not only is CVD a common comorbidity with psoriasis, but both are also diseases of systemic inflammation. Therefore it is proposed that a medication that works by decreasing the amount of systemic inflammation in CVD may have a similar effect in psoriasis. The epidemiologic reviews cited above noted a significant decrease in coronary artery disease, diabetes and psoriasis in the people who live in the arctic circle. They believe this is possibly due to a diet rich in polyunsaturated fats and both suggest that fish oil may be an appropriate supplemental therapy for psoriasis.\textsuperscript{4,6} The anti-inflammatory effects of DHA and EPA in the skin and immunomodulation of fish oil further supports
the idea that it could be beneficial in psoriasis. The studies reviewed above also show that there is in fact a moderate improvement in the disease. The added benefit in aspects of metabolic syndrome and CVD makes fish oil a promising supplement in psoriasis.

There are many OTC fish oil supplements on the market. The VITAL trial currently occurring in affiliation with Brigham and Women’s Hospital in Boston is exploring a combination of vitamin D and fish oil supplementation in CVD and cancer prevention. In this trial they chose Omacor® fish oil as it “has undergone an extensive purification process and is free of environmental toxins (e.g., methylmercury, polychlorinated biphenyls [PCBs], and dioxins) found in some fish. It has also undergone extensive quality control testing for stability of nutrient content and other parameters at a range of temperatures and humidity levels.” The ratio of EPA to DHA is 1.3:1 in Omacor® fish oil with 465mg EPA and 375mg of DHA per 1gm capsule. Through the intense purification process these capsules have a very minimal “fishy” smell and taste. The VITAL trial suggested that 1gm of fish oil, or 1 Omacor® capsule would provide 5-10 times the daily amount of omega-3 fatty acids consumed by the average person. The aforementioned studies exploring fish oil in treating psoriasis showed that a significantly higher amount was needed to have an effect in this disease. In a review of complementary and alternative methods for treating psoriasis Talbott and Duffy looked at other reviews focusing on fish oil supplementation in psoriasis and found that in the trials which showed a positive effect of fish oil had an average daily dose of 4g of EPA and 2.6g of DHA. They also found that the average PASI score reduction ranged from 40-75% in
these trials and that fish oil as a monotherapy took anywhere from 6 weeks to 6 months to show these effects.\textsuperscript{29}

With such high doses used in these prior trials, subjects would need to consume 8 Omacor\textsuperscript{®} capsules. Millsop et al.’s review showed several positive trials that used lower amounts of EPA and DHA. Two prospective, double-blind placebo controlled trials done in England and Germany showed significant improvement with around 2g of EPA and as low as 1.2g of DHA.\textsuperscript{45}

The VITAL trial also explored the safety profile of fish oil supplementation, as it has known inhibitory effects on platelet function. They found in their research that the FDA stated 3g of fish oil per day was “generally recognized as safe” and other studies showed that up to 4g per day did not cause any excess bleeding risk.\textsuperscript{46,48} Omacor\textsuperscript{®} is given at 4g per day doses to treat hypertriglyceridemia with no reports of “hyperglycemia, abnormal bleeding, elevations in muscle or liver enzymes, and/or abnormalities in kidney or nerve function”.\textsuperscript{47}

\textit{Vitamin D}

Vitamin D can manipulate the immune system in several ways including its ability to regulate T cell tracking and differentiation as well as keratinocyte proliferation, the two major components in the pathogenesis of psoriasis. Vitamin D and its analogues as potential psoriasis treatments were discovered 30 years ago in Japan when a patient suffering from both osteoporosis and psoriasis was “cured” of his psoriasis during treatment for osteoporosis, which prompted research into the use of vitamin D either orally or topically in psoriasis.\textsuperscript{49} Providers have also treated psoriasis patients with
phototherapy for years. UVB converts 7-dehydrocholesterol in keratinocytes to cholecalciferol (D₃), some of which is hydroxylated in the skin to calcitriol (1,25 (OH)₂D₃), the active form of vitamin D.¹¹,⁵⁰ Keratinocytes and T cells both have vitamin D receptors (VDRs), which heterodimerize with the retinoid X receptor (RXR). This complex binds to specific DNA sequences called vitamin D response elements (VDREs) and effects the expression of genes.¹¹

Prior to the discovery of Th17 and subsequently IL-17 and IL-22 involvement in the pathogenesis of this disease it was believed that vitamin D simply interfered with proliferation and enhanced differentiation of keratinocytes and had some lymphocyte activation regulation.⁴⁹ The expansion of the understanding of the immunologic basis of this disease has lead to further research regarding the mechanism of action of vitamin D in psoriatic lesions. Yamanaka et al. showed that active vitamin D interferes with T cell tracking to the skin via alteration of the expression of cutaneous lymphocyte-associated antigen (CLA) on T cells, dampening the inflammatory response.⁵¹ In a subsequent study done by Yamanaka et al. on the vitamin D analog tacalcitrol (1,24 (OH)₂D₃) they found similar results with less expression of CLA. They also showed that this effect of decreased CD⁴⁺ skin infiltration occurs not only in a petri dish but also in vivo in mice.⁵²

Dyring-Anderson et al. studied the expression of CD⁸⁺ and CD⁴⁺ cells, especially those producing IL-17, in psoriatic lesions treated with topical calcipotriol, a vitamin D analog. They noted that in 1-3 weeks there was a significant thinning of the psoriatic lesions due to decreased keratinocyte proliferation, but the change in T cell profile occurred after 4 weeks of treatment. They found after 4 weeks there was an overall
decrease in IL-17^+ cells, to a point at which CD4^+IL-17^+ and CD8^+IL-17^+ were undetectable in lesions treated with calcipotriol.\textsuperscript{11}

A review by van Etten et al. explored vitamin D interaction with the immune system and showed many avenues of immuoregulation. They found that vitamin D targets cytokine transcription of several Th1 cell cytokines and indirectly changes the T cell profile to favor a Th2 differentiation and therefore attenuates autoimmunity. Although it interacts with T cells, vitamin D’s primary target is the antigen presenting cell. Monocytes express much less MHC II when exposed to vitamin D and therefore have a reduced ability to stimulate T cells. Vitamin D also inhibits maturation of dendritic cells, which are the key initiator of the T cell response. TNF-\(\alpha\) expression from mature monocytes/macrophages is also downregulated. Unlike many of the products available to treat immune system diseases, vitamin D is less immunosuppressive and exerts its effect by shifting immune activity and inducing regulatory cells.\textsuperscript{53} As of 2008, Mora et al. concluded in a review of vitamin A and D immunoregulation that “the net result of 1,25(OH)2VD3 action on T cells is to block the induction of T-helper-1 (TH1)-cell cytokines, particularly IFN\(\gamma\), while promoting TH2-cell responses”.\textsuperscript{50} They noted that vitamin D also inhibits Th17 via inhibition of other cytokines including IL-23. They came to this conclusion based on work done by Daniel et al. that showed a change from a Th1/Th17 to Th2 and regulatory T cell profile in mice with colitis who were treated with vitamin D.\textsuperscript{54}

Many of the aforementioned immunoregulatory properties of vitamin D correlate with the immunopathogenic derangements in psoriasis. Multiple studies have shown that
psoriatic patients are often vitamin D deficient\textsuperscript{55-57} and one even showed an inverse relationship between vitamin D levels and severity of psoriasis.\textsuperscript{55} Ricceri et al. performed a case-control study exploring vitamin D serum concentrations in patients with psoriasis and found that 97\% of the cases were at least vitamin D insufficient (<30ng/mL) and 68\% were deficient (<20ng/mL) whereas just over 50\% of the controls were insufficient and only about 9\% were deficient. Furthermore the correlation between serum concentration and severity of psoriasis showed a relatively linear, inverse relationship with a correlation coefficient of -0.88 (see Figure 2).\textsuperscript{55}

![Figure 2](image_url)

\textbf{Figure 2.} Inverse relationship of serum vitamin D concentration and the severity of psoriasis (from \textit{Deficiency of serum concentration of 25-hydroxyvitamin D correlates with severity of disease in chronic plaque psoriasis} by Ricceri et al.)\textsuperscript{55}
Aloia et al. performed a study to examine what level of vitamin D3 (cholecalciferol) intake was necessary to raise serum levels of 25-hydroxyvitamin D to a sufficient level. They found that an average of 3300 IU/day of vitamin D3 was needed to reach this goal, but the range was anywhere from 800-6800 given several confounding factors (age, sex, gender, weight, ethnicity) and the level of vitamin D deficiency of the subject prior to the study.58

A study by Orgaz-Molina et al. also showed an association of vitamin D deficiency with psoriasis as well as an association between markers of metabolic syndrome in psoriasis patients and an even lower level of vitamin D. From this they hypothesized that vitamin D may be of most benefit in these people who suffer from both vitamin D deficiency and metabolic syndrome.59 Prior to that study, Orgaz-Molina et al. completed a case-control study, which showed an association of low serum vitamin D (25.6% of cases versus 9.3% of controls were deficient) and psoriasis as is commonly found in other inflammatory and autoimmune diseases. They reviewed several studies in which oral vitamin D supplementation in patients with psoriasis had shown clinical improvement and therefore concluded that further studies exploring supplementation were warranted.57

Millsop et al. reviewed multiple vitamin D supplementation studies when exploring the effect of diet in psoriasis. In this review they found only one controlled study done in 1990, which showed only mild improvement in those supplemented with vitamin D and no statistical significance when compared to the control group. However, four other uncontrolled studies reviewed by Millsop et al. as well as case study published
in 2011 by Werner de Castro et al. showed a range from mild to complete improvement
in psoriasis with administration of oral vitamin D. \textsuperscript{45,60} The case study by Werner de
Castro et al. showed resolution of medication-induced psoriasiform lesions with high
dose vitamin D administration.\textsuperscript{60} Millsop et al.’s review involved the use of several
different forms of vitamin D (1,25 Dihydroxyvitamin D, 1-Hydroxyvitmain D,
Cholecalciferol), all of which led to clinical improvement (see appendix B).\textsuperscript{45} Overall
these studies showed a moderate improvement in PASI scores with systemic vitamin D,
but given that these studies are all uncontrolled, further study is warranted.

The potential for toxicity is a major hindrance to the use of vitamin D
systemically in many autoimmune diseases. According to van Etten et al., “high
supraphysiological doses of 1,25(OH)2D3 have to be given systemically leading to
detrimental side effects such as hypercalcemia and increased bone resorption” to reach
immunomodulating levels of vitamin D (10\textsuperscript{-10} M or higher).\textsuperscript{53} They state this as the basis
behind the production of analogs, but they also suggest that this can often be avoided
with the use of vitamin D in combination therapy rather than as monotherapy. They state
that vitamin D and its analogs have synergistic effects with other immunomodulators in
several animal models of autoimmune diseases and post-transplantation.\textsuperscript{53}

The use of vitamin D and fish oil in combination is documented in two studies on
cancer cells. One study done by Chiang et al. explored combination treatment of human
hepatoblastoma cells. This study also expressed concern about the potential for vitamin D
toxicity. They explored each treatment individually and in combination. Both treatments
were found to be effective in a dose dependent manner. They were able to show that by
using combination therapy, lower levels of vitamin D could be used with similar anti-proliferative effects.\textsuperscript{61} Chatterjee et al. showed a similar effect of combination therapy with vitamin D and fish oil in their study on rat mammary carcinogenesis. Administration of vitamin D and fish oil in combination had greater suppression of DNA and mRNA mutations and retardation of proliferation than either treatment alone.\textsuperscript{62} Therefore it is conceivable that this enhanced anti-proliferative effect could be beneficial in psoriasis as well given that keratinocyte proliferation is a major component of this disease.

Danno and Sugi showed an increased effect of a vitamin A analog and fish oil in the treatment of psoriasis in their study of low doses of etretinate in combination with EPA. They had faster and greater improvement in chronic plaque psoriasis with combination treatment. The efficacy of this low dose etretinate plus EPA treatment was equivalent to that of higher dose monotherapy with etretinate. They were unable to comment on whether this was an additive or synergistic relationship.\textsuperscript{63} Regardless of the type of relationship, this study showed a lower level of the potentially toxic etretinate can be efficacious as higher dose therapy when used in combination with EPA.

A study by Marquez- Balbas et al. explored the combination of topical tacalcitol, a vitamin D derivative, and oral fish oil in psoriasis and showed enhanced efficacy. The reduction in PASI score was almost twice as large in the combination group with a 6.8 point reduction versus only a 3.5 point reduction in the tacalcitol only control group.\textsuperscript{35} The almost 2-fold reduction in PASI scored seen with the combined topical vitamin D and oral fish oil therapy demonstrates an additive effect.
There is quite a bit of scientific evidence that both fish oil and vitamin D should be successful in the treatment of psoriasis. Both of these treatments modulate the immune system and have effects on many of the cytokines that are implicated in the pathogenesis of this disease. The aforementioned combination studies show that these medications can have at least an additive if not a synergistic effect in disorders of excessive proliferation.

Psoriasis Assessment

Psoriasis severity is usually classified as mild, mild-moderate, moderate, moderate-severe, and severe based on different scales such as the PASI score, body surface area (BSA), and/or the Dermatological Life Quality Index (DLQI). Furthermore, the Consensus Guidelines for the Management of Plaque Psoriasis by Hsu et al. considers the ability to manage the disease by topicals alone to be the difference between mild or moderate versus severe psoriasis. In the clinical setting, aspects of these scales are often combined to account broadly for a provider’s global assessment of disease activity and the affect the disease has on the patient’s quality of life.

In addition to formally assessed qualities, patients with psoriasis can also present with pruritus, pitting of the nails, onycholysis, pustules, geographic tongue, and arthritis. Therefore in clinical practice these formal assessment scales do not provide adequate understanding of the burden of the disease. A position paper written by several past and present members of the Medical Advisory Board of the NPF and the Board of the NPF states that dermatologists “have learned how to assess the severity of disease; this assessment includes the needs of the patient, the time needed for treatment, the cost of treatment, the benefit of the treatment and the willingness of the patient to accept
potential life-altering side effects to achieve a better QOL” and use that to define the severity of a patient’s disease.  

There are three basic attributes of psoriatic lesions that providers assess: redness, thickness, and degree of scale. As mentioned above these can be relatively subjective characteristics. In a review of assessment methods by Langley and Ellis they stated “PASI was developed in 1978 by Fredricksson and Pettersson for use in a single clinical trial. Subsequently, the PASI became popular as a research tool but is not used in clinical practice.” The PASI has been considered the gold standard for clinical trials as it addresses the aforementioned attributes, but it has been shown to be less sensitive to changes in smaller lesions. Many also feel that the PASI assessment is time consuming, difficult to interpret, and can be insensitive to those with mild to moderate disease.

Schmitt and Wozen make the argument that, despite its shortcomings, the PASI is still the best studied, most objective assessment method for psoriasis. In clinical trials, evidence based medicine, and approval by the FDA, a method of formal, objective assessment is needed. Walsh et al. explain that the PASI is “widely considered the gold standard measure of disease severity and is frequently used as a primary efficacy end point in clinical trials of moderate to severe psoriasis” but it does have shortcomings in mild disease and is cumbersome to use. They also explained that in recent years the FDA has also required the use of the static Physician Global Assessment for most of the last phase III clinical trials. This method however does not take into account the BSA, which is a major component of the disease. Exploration of new and improved systems of
psoriasis evaluation is ongoing. New methods are being tested against known standard scales, but none are commonly used at this time.

**PASI**

The PASI score assessment scale is still the most widely used method for clinical trials. It splits the body up into head, arms, trunk and legs and requires the clinician to provide a percentage surface area of each section. The degree of erythema, scale and thickness of each of these sections is also given a score from 0-4 (see appendix C). The percent surface area and these scores are computed into a final PASI score ranging from 0-72. There are several calculators available which will compute the PASI score given these data points.
METHODS

Study design
This study will be a randomized, placebo-controlled clinical trial examining the use of vitamin D and fish oil in combination to treat psoriasis.

Study population and sampling
The study population will be selected from several clinics in or around the city of Boston who meet the inclusion and exclusion criteria. Given that there is an interest in the effect of the proposed intervention on patients with varying degrees of severity, patients will not be excluded if they are currently taking medication as this would most likely result in few patients with severe or even moderate disease. Inclusion and exclusion criteria are in table 3.

Table 3. Inclusion and Exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
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<tbody>
<tr>
<td>18 years or older</td>
<td>Recently started, new psoriasis medication (oral/topical within 3 months)</td>
</tr>
<tr>
<td>Diagnosed with chronic plaque psoriasis</td>
<td>Only arthritic or pustular presentation</td>
</tr>
<tr>
<td>Stable disease after being on current regimen for at least 3 months</td>
<td>Taking vitamin D or fish oil supplementation prior to study</td>
</tr>
<tr>
<td>Any level PASI or body surface area</td>
<td>Expecting prolonged periods of sun exposure during study (&gt;10 days of &gt;3hrs/day)</td>
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</table>
A sample size of 63 participants in each group for a total of 126 total will yield 80% power to detect a 50% reduction in PASI score with an alpha of 0.05. The study will have two arms, one that receives vitamin D and fish oil supplementation and one that receives placebo pills. The study population will be randomized into these two groups. It will be double-blinded and the study coordinator will do the randomization prior to the initial evaluation by the study clinician.

The proposed treatment will be four Omacor® fish oil capsules and two 2000 IU vitamin D3 (cholecalciferol) tablets per day. This will provide 1.8g EPA, 1.5g DHA, and 4000IU of cholecalciferol. These pills will be given to the patient in 12 week supplies and the patient will be asked to bring the bottles to their 12 week appointments as a simple way to monitor compliance.

**Study variables and measures**

The method of assessment used in this trial will be the PASI score as determined by the study clinician. The data will be put into the PASI calculator on pasitraining.com. This site also provides training on how best to estimate the percentage of each body section via eyeball or palmar method and how to score the degree of each of the three characteristics judged by this scale.

**Institutional Review Board**

A proposal will be submitted for full IRB approval. This study would fall into the full review category, as it is a randomized, double-blinded clinical trial using a placebo.
Recruitment

Patients will be obtained via provider referral from several clinics around Boston. The need for patients for this study will be expressed in a letter given to local clinics and it will ask for providers to seek out patients who meet the aforementioned inclusion and exclusion criteria and are interested in participating in a study. These may be patients that wish to find alternative ways to treat their psoriasis as an alternative to traditional methods or it may be those who wish to supplement their current regimen.

Data collection

All subjects will have an initial visit with a study-associated clinician at which time, following appropriate consent procedures, a baseline PASI score and photographs will be taken. The same clinician will perform all the subsequent exams in an effort to minimize the subjective nature of the PASI scoring system. The baseline vitamin D level will also be measured at this visit. This initial visit will be performed in a rolling fashion so as to provide ample time for a single evaluator to see all enrolled subjects. At 12 week intervals the subjects will return for evaluation and photographs by the same clinician. Vitamin D levels will be drawn at each visit. The study will continue for 1 year.

Data analysis

The PASI scores will be measured by their change from the baseline score. This will show the absolute benefit to each individual subject. It will also provide a more standardized measure of the effect of the treatment as subjects may have a wide variety of baseline PASI scores. A reduction in absolute score may be vastly different between
mild, moderate and severe disease, which would make statistical analysis between the two treatment arms difficult.

Mean, median, range and standard deviation will be calculated based on PASI scores. Pre-and-post intervention PASI scores will be compared via Paired t-Test and the intervention and control group means compared with a two-sided Student’s t-Test. Correlation between vitamin D levels and percent PASI reduction will be analyzed using Pearson’s correlation coefficient. Subgroup analysis will be done on patients classified as mild, moderate, and severe to see if there is a statistically significant difference in effect depending on the baseline severity of disease. The analysis will be done using an intention-to-treat regardless of patient adherence.

**Timeline and resources**

**Personnel**

- Study coordinator
- Clinician for PASI assessment, photographs
- Technician for blood draw
- Primary Investigator
- Statistician

**Special Resources**

- Laboratory Assay
- Camera
- Fish oil and vitamin D capsules, similar-appearing placebo pills
Table 4. Timeline

<table>
<thead>
<tr>
<th>Period</th>
<th>Events</th>
</tr>
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<tbody>
<tr>
<td>April-August 2016</td>
<td>• IRB proposal submitted/approved</td>
</tr>
<tr>
<td>September 2016 – April 2017</td>
<td>• Letter sent to providers in Boston</td>
</tr>
<tr>
<td></td>
<td>• Identification of subjects</td>
</tr>
<tr>
<td>September 2016-April 2018</td>
<td>• Initial assessment by study appointed clinician</td>
</tr>
<tr>
<td></td>
<td>• Initial blood draw</td>
</tr>
<tr>
<td></td>
<td>• Administration of intervention with four 12 week follow up assessments/ blood draws</td>
</tr>
<tr>
<td>Fall 2017-Spring 2018</td>
<td>• Final visit at the end of year of treatment</td>
</tr>
<tr>
<td>Spring 2018</td>
<td>• Data analysis</td>
</tr>
<tr>
<td></td>
<td>• Preparation and submission of manuscript</td>
</tr>
</tbody>
</table>
CONCLUSION

Discussion

To date this investigator was unable to find studies exploring a combination of systemic vitamin D and fish oil. Both of these supplements have known anti-proliferative and anti-inflammatory effects. Fish oil modulates the cytokines produced by skin cells as well as the immune profile by regulating the differentiation of CD4$^+$ T cells. Vitamin D also influences this systemic T cell profile, mainly acting on the antigen presenting cells. By acting on two different levels of T cell differentiation, both of these supplements promote a less inflammatory, Th2, immune profile. This study will look at the possible additive effects of these supplements in this highly inflammatory disease.

The proposed study is limited in regards to its ability to accurately assess the effect of the proposed intervention without confounding variables. The exclusion criteria are aimed at limiting these so that the observed effects are most likely due to the intervention. The subjects will have different pre-study treatment regimens. This study will require these be unchanged over the 3 months prior to participation and that they be held constant for the duration. It is unethical to stop a patient’s treatment regimen if the regimen has a positive effect and the efficacy of the proposed intervention is controversial. Psoriasis is a disease with a natural ebb and flow in disease severity, at times correlated with weather. This could also skew the study findings. A rolling admission to the study over a 6 month timeframe aims to partially minimize the effects of this potential confounder. Another limitation would be that all subjects in this study will be living in Massachusetts and therefore might have a different baseline vitamin D level.
than patients in other parts of the country. Our results may not be generalizable to other locations. A final potential limitation of this study could be that the PASI scoring system is less sensitive to change in mild disease, often defined as less than 10% body surface involvement.

This study will provide information about the effects of the proposed treatment on varying degrees of psoriasis severity. The generalizability of the findings of this study will be based on the ability to attract a diverse group of subjects, which is likely in the Boston area.

The greatest strength of this study is the fact that it proposes a novel intervention in the management of psoriasis. Investigators have researched each of these supplements alone for psoriasis or in combination for other diseases, but never in combination for the treatment of psoriasis. Another advantage is that it will be a placebo-controlled trial, whereas many of the studies on fish oil or vitamin D alone were not.

**Summary**

Many genes on several genetic loci are common to psoriasis patients, but environmental factors also play a large role in regulating disease severity and prevalence. Psoriasis is a disease of T-cell mediated inflammation regulated by pro-inflammatory cytokines produced by immune cells as well as the keratinocytes themselves. These cytokines in turn create a pro-inflammatory Th1 and Th17 immune profile, which is the target of many of the medications used to treat this disease.

The available treatments for psoriasis have many undesirable potential side effects, are often cumbersome to use and can be prohibitively expensive. This experiment
aims to eliminate all three of these pitfalls by exploring natural supplements that are taken orally only once per day and can be purchased over the counter at a drug store or grocery store.

Both omega-3 fish oil and vitamin D have been tested in the past as possible treatments for psoriasis. The literature shows that higher than average doses of both of these supplements can result in a significant reduction in psoriasis severity. Further studies that explored combining these supplements to prevent and to treat cancer have also shown promising results. Combining fish oil with retinoids used to treat psoriasis was shown to reduce the amount of the potentially toxic retinoid needed to provide significant results. These findings suggest that combining fish oil and vitamin D, treatments that have been shown to work on their own, could have an additive or even synergistic effect when treating psoriasis.

This study will provide data supporting or refuting the efficacy of this inexpensive, simply administered, and safe alternative to the psoriasis medications that are on the market today. It could also provide information about using this treatment strategy to complement existing regimens rather than stepping up to a stronger immunomodulating agent with more potential adverse events.

**Clinical and/or public health significance**

As mentioned above, if the data from this project show significant improvement in psoriasis with these natural supplements, it could add a complementary treatment option to a provider’s arsenal. Many patients shy away from medications with a long list of potential side effects or those that make them change their lifestyle. This proposed
treatment could eliminate many of those tribulations. This would benefit patients, but also providers who often struggle with patient compliance, particularly in those with mild disease. Furthermore, the ever-expanding literature connecting psoriasis with metabolic disorder and cardiovascular disease makes this proposed treatment, which includes a supplement known to have benefit in CVD, even more enticing.
APPENDIX A

“Studies examining the efficacy of fish oil supplementation in psoriasis” Adapted from Table 1 in *Diet and Psoriasis, Part III: Role of Nutritional Supplements*45

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>EPA dose g/d</th>
<th>DHA dose g/d</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayser et al, 1998 (controlled)</td>
<td>75</td>
<td>4.2</td>
<td>4.2</td>
<td>PASI score decreased by 11.2 ± 9.8 in the omega-3 group and by 7.5 ± 8.8 in the omega-6 group (P = .048)</td>
</tr>
<tr>
<td>Bittiner et al, 1988 (controlled)</td>
<td>28 at 8 wk; 24 at 12 wk</td>
<td>1.8</td>
<td>1.2</td>
<td>Improvement in: erythema P &lt; .05 at 8 and 12 wk; itching at 8 wk P &lt; .05 in treatment group vs control</td>
</tr>
<tr>
<td>Grimminger et al, 1993 (controlled)</td>
<td>20</td>
<td>2.1</td>
<td>2.1</td>
<td>Greater improvement in erythema, infiltration, desquamation in omega-3 group compared with omega-6 group (P &lt; .05 for all categories)</td>
</tr>
<tr>
<td>Lassus et al, 1990 (uncontrolled)</td>
<td>76</td>
<td>1.1</td>
<td>0.8</td>
<td>Decrease in mean PASI score after 4 and 8 wks (P &lt; .001); 7 patients with complete response; 13 with &gt;75% improvement; 14 with poor response</td>
</tr>
<tr>
<td>Kragballe and Fogh, 1989 (uncontrolled)</td>
<td>26</td>
<td>5.4</td>
<td>3.6</td>
<td>Moderate-excellent improvement in 15/26 (58%) patients; mild improvement in 5/26 (19%); no change in 6/26 (23%)</td>
</tr>
<tr>
<td>Kragballe, 1989 (uncontrolled)</td>
<td>17</td>
<td>0.54</td>
<td>0.36</td>
<td>Moderate-excellent improvement in 10 patients; mild improvement in 4; no change in 3</td>
</tr>
<tr>
<td>Ziboh et al, 1986 (uncontrolled)</td>
<td>13</td>
<td>10.8-13.5</td>
<td>7.2-9.0</td>
<td>Improvement in: scaling (P &lt; .001); erythema (P &lt; .02); thickness (P &lt; .004); 8/13 (62%) subjects demonstrated &quot;clinically significant&quot; improvement</td>
</tr>
<tr>
<td>Maurice et al, 1987 (uncontrolled)</td>
<td>10</td>
<td>12</td>
<td>8</td>
<td>8/10 (80%) Showed modest improvement in erythema in scale</td>
</tr>
<tr>
<td>Kojima et al, 1989</td>
<td>9</td>
<td>3.6</td>
<td>-</td>
<td>At 6 mo, 2/7 (29%) showed marked improvement, 4/7 (57%)</td>
</tr>
<tr>
<td>Study</td>
<td>Patients</td>
<td>Effect Size</td>
<td>Significance</td>
<td></td>
</tr>
<tr>
<td>------------------------------</td>
<td>----------</td>
<td>-------------</td>
<td>--------------</td>
<td></td>
</tr>
<tr>
<td>Danno and Sugie, 1998</td>
<td>40</td>
<td>1.8</td>
<td>Moderate improvement, and 1/7 (14%) no improvement</td>
<td></td>
</tr>
<tr>
<td>Balbas et al, 2011</td>
<td>30</td>
<td>5.6</td>
<td>Improvement statistically greater in treatment group compared with control for PASI score (P &lt; .0001), DLQI (P = .0056), pruritus (P &lt; .0001)</td>
<td></td>
</tr>
<tr>
<td>Gupta et al, 1989</td>
<td>18</td>
<td>3.6</td>
<td>Fish oil group improved more than olive oil group in erythema (P = .02), thickness (P = .006), scale (P = .008), and total body surface area (P = .0001)</td>
<td></td>
</tr>
<tr>
<td>Soyland et al, 1993</td>
<td>145</td>
<td>3.1</td>
<td>No significant difference in change in PASI score, scaling, erythema, infiltration of selected area between treatment vs control group</td>
<td></td>
</tr>
<tr>
<td>Bjorneboe et al, 1988</td>
<td>27</td>
<td>1.8</td>
<td>No significant change in clinical scores of erythema, infiltration, desquamation, and surface area in either group</td>
<td></td>
</tr>
<tr>
<td>Kettler et al, 1988</td>
<td>23</td>
<td>3.2</td>
<td>Significant improvement only in the 1 patient with pustular psoriasis; minimal improvement in 8 patients; no change in 10; mild worsening in 5</td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX B

“Studies examining vitamin D supplementation in psoriasis” adapted from Table II in *Diet and Psoriasis, part III: Role of Nutritional Supplements* by Millsop et al.45

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Vitamin D3 form dose, µg/d</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perez et al., 1996 (uncontrolled)</td>
<td>85</td>
<td>1,25-Dihydroxy started at 0.5 and increased by 0.5 every 2 wk as long as 24-h urinary calcium concentrations remained normal</td>
<td>26.5% Had complete improvement; 36.2% had moderate improvement; 25.3% had slight improvement; mean PASI score 18.4 ± 1.0 at baseline, 9.7 ± 0.8 at 6 mo, 7.8 ± 1.3 at 24 mo</td>
</tr>
<tr>
<td>Siddiqui et al., 1990 (controlled)</td>
<td>41</td>
<td>1-Hydroxy 1.0</td>
<td>9/20 (45%) on Vitamin D showed slight improvement vs 8/21 (38%) on placebo showed slight improvement, no statistically significant difference</td>
</tr>
<tr>
<td>Morimoto et al., 1986 (uncontrolled)</td>
<td>17</td>
<td>1-Hydroxy 1.0</td>
<td>76% of Patients displayed moderate or greater improvement after 2.7 ± 0.6 mo</td>
</tr>
<tr>
<td>Smith et al., 1988 (uncontrolled)</td>
<td>14</td>
<td>1,25-Dihydroxy 0.5-2.0</td>
<td>7/14 (50%) Improved &gt;75%; 3/14 (21%) improved 25%-50%; 4/14 (29%) improved 0%-25%</td>
</tr>
<tr>
<td>Finamor et al., 2013 (uncontrolled)</td>
<td>9</td>
<td>Cholecalciferol 875.0</td>
<td>There was a statistically significant improvement in PASI scores from baseline to 6 mo (P &lt; .01); PASI scores inversely correlated with serum 25-hydroxyvitamin D3 levels (P &lt; .001)</td>
</tr>
<tr>
<td>el-Azhary et al., 1993 (uncontrolled)</td>
<td>8</td>
<td>1,25-Dihydroxy 0.5-2.0</td>
<td>1/8 (12.5%) Improved markedly; 1/8 (12.5%) improved moderately; 6/8 (75%) with no or mild improvement</td>
</tr>
<tr>
<td>Takamoto et al., 1986 (uncontrolled)</td>
<td>7</td>
<td>1-Hydroxy 1.0</td>
<td>2/7 (29%) Showed complete remission; 2/7 (29%) showed marked improvement; 3/7 (43%) showed no improvement</td>
</tr>
</tbody>
</table>
APPENDIX C

Psoriasis Area and Severity Index

### Head

<table>
<thead>
<tr>
<th>Area</th>
<th>0%</th>
<th>&lt;10%</th>
<th>10-29%</th>
<th>30-49%</th>
<th>50-69%</th>
<th>70-89%</th>
<th>90-100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<tr>
<td>Induration</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desquamation</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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### Trunk

<table>
<thead>
<tr>
<th>Area</th>
<th>0%</th>
<th>&lt;10%</th>
<th>10-29%</th>
<th>30-49%</th>
<th>50-69%</th>
<th>70-89%</th>
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</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
</tr>
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<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desquamation</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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</table>

### Upper Extremities

<table>
<thead>
<tr>
<th>Area</th>
<th>0%</th>
<th>&lt;10%</th>
<th>10-29%</th>
<th>30-49%</th>
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<th>70-89%</th>
<th>90-100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induration</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desquamation</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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</table>

### Lower Extremities

<table>
<thead>
<tr>
<th>Area</th>
<th>0%</th>
<th>&lt;10%</th>
<th>10-29%</th>
<th>30-49%</th>
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<th>70-89%</th>
<th>90-100%</th>
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</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<td></td>
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<tr>
<td>Induration</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desquamation</td>
<td>0</td>
<td>1</td>
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<td>3</td>
<td>4</td>
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</tr>
</tbody>
</table>
LIST OF JOURNAL ABBREVIATIONS

Acta Derm Venereol  Acta Dermato Venereologica
Adv Nutr  Advances in Nutrition
Am J Cardiol  The American Journal of Cardiology
Am J Clin Dermatol  The American Journal of Clinical Dermatology
Am J Clin Nutr  The American Journal of Clinical Nutrition
Ann Rheum Dis  Annals of the Rheumatic Diseases
Anticancer Res  Anticancer Research
Arch Dermatol  Archives of Dermatology
Br J Dermatol  British Journal of Dermatology
Br J Nutr  British Journal of Nutrition
Chem Biol Interact  Chemico-Biological Interactions
Clin Cosmet Investig Dermatol  Clinical, Cosmetic and Investigative Dermatology
Clin Dermatol  Clinics in Dermatology
Contemp Clin Trials  Contemporary Clinical Trials
Cytokine Growth Factor Rev  Cytokine & Growth Factor Reviews
Dermatol Clin  Dermatologic Clinics
Dermatol Online J  Dermatology Online Journal
Expert Opin Drug Saf  Expert Opinion on Drug Safety
Expert Opin Investig Drugs  Expert Opinion on Investigational Drugs
Int Heart J  International Heart Journal
<table>
<thead>
<tr>
<th>Journal Abbreviation</th>
<th>Full Journal Title</th>
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</thead>
<tbody>
<tr>
<td>J Allergy Clin Immunol</td>
<td>Journal of Allergy and Clinical Immunology</td>
</tr>
<tr>
<td>JAMA Dermatol</td>
<td>The Journal of the American Medical Association Dermatology</td>
</tr>
<tr>
<td>J Autoimmun</td>
<td>Journal of Autoimmunity</td>
</tr>
<tr>
<td>J Bone Miner Res</td>
<td>Journal of Bone and Mineral Research</td>
</tr>
<tr>
<td>J Clin Endocrinol Metab</td>
<td>The Journal of Clinical Endocrinology &amp; Metabolism</td>
</tr>
<tr>
<td>J Dermatol</td>
<td>The Journal of Dermatology</td>
</tr>
<tr>
<td>J Eur Acad Dermatol Venereol</td>
<td>Journal of the European Academy of Dermatology and Venereology</td>
</tr>
<tr>
<td>J Invest Dermatol</td>
<td>Journal of Investigative Dermatology</td>
</tr>
<tr>
<td>J Nutr</td>
<td>The Journal of Nutrition</td>
</tr>
<tr>
<td>J Pharmacol Exp Ther</td>
<td>Journal of Pharmacology and Experimental Therapeutics</td>
</tr>
<tr>
<td>Mol Immunol</td>
<td>Molecular Immunology</td>
</tr>
<tr>
<td>Nat Rev Immunol</td>
<td>Nature Reviews Immunology</td>
</tr>
<tr>
<td>PLEFA</td>
<td>Prostaglandins, Leukotrienes and Essential Fatty Acids</td>
</tr>
<tr>
<td>Postgrad Med</td>
<td>Postgraduate Medicine</td>
</tr>
<tr>
<td>Psoriasis Targets Ther</td>
<td>Psoriasis Targets and Therapy</td>
</tr>
<tr>
<td>Rheumatol Int</td>
<td>Rheumatology International</td>
</tr>
<tr>
<td>Scand J Immunol</td>
<td>Scandinavian Journal of Immunology</td>
</tr>
</tbody>
</table>
REFERENCES


21. D’Souza LS, Payette MJ. Estimated cost efficacy of systemic treatments that are approved by the US Food and Drug Administration for the treatment of


CURRICULUM VITAE

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1989
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S. Boston, MA 02127
508.523.0079
kerri.liska@gmail.com,

EDUCATION

Boston University  
Physician Assistant Program Boston, MA  
Master of Science 2014-2016  
Degree conferred September 2016

Boston College Chestnut Hill, MA  
College of Arts and Sciences 2007- 2011  
Bachelor of Arts in Biology

EXPERIENCE

Dermatology of Cape Cod North Falmouth, MA  
Medical Assistant 2011-2013

• Roomed patients, recorded chief complaint, and updated personal/family medical history
• Consented, set up, and aided in dermatologic surgery
• Removed sutures and checked wounds for infection or excessive bleeding
• Administered Photodynamic Therapy treatment
• Cauterized and anesthetized under physician supervision

HONORS AND AWARDS

Golden Key National Honor Society 2008-2011
Dean’s List 2007-2011
Wellesley Book Award 2007

CERTIFICATION AND LICENSURE

Physician Assistant License, 2016- present
State of Massachusetts pending

Certification by the National Commission on Certification of Physician Assistants pending
ACLS certification 2015-present

RESEARCH

Systemic Vitamin D and Fish Oil in the Management of Psoriasis  
- Literature Review and Clinical Trial Design 2014-2016  
- Mentor: Allison Larson, MD

TEACHING AND TRAINING

Complications of Blood Product Transfusion  
- Shriner’s Hospital for Children: Boston 2016
  - 15 min presentation

Diagnosis and Surgical Management of Small Bowel Obstruction  
- Roger Williams Medical Center 2015
  - 20 min presentation

Benign or Malignant: SK, Atypical Nevus, Melanoma  
- Boston University PA Program 2015
  - 20 min presentation

Delusional Infestation  
- West Roxbury VA Medical Center 2015
  - 30 min presentation

COMMUNITY SERVICE

Life Guard Skin Cancer Screening  
- Dermatology of Cape Cod 2005-2013
  - Registering and rooming patients, taking histories

LEADERSHIP

Massachusetts Academy of Physician Assistants  
- PA Day on Beacon Hill 2015
  - Lobbied a bill to recognize Physician Assistants as healthcare providers under MassHealth insurance to Massachusetts State Legislators