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INTERMITTENT FASTING AS ADJUVANT TO
TOPICAL THERAPY IN THE MANAGEMENT OF MILD TO MODERATE
PSORIASIS

A Thesis Presented to
The Faculty of the School of Medicine
Yale University

In Candidacy for the Degree of
Master of Medical Science

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ABSTRACT

Psoriasis is a common chronic inflammatory skin condition with no known cure. Intermittent fasting involves limiting caloric intake to designated time periods and decreases markers of systemic inflammation, but the clinical efficacy of intermittent fasting for patients with psoriasis remains unclear. We propose a randomized controlled clinical trial to investigate the clinical impact of adjunctive intermittent fasting on plaque psoriasis. Patients with mild to moderate plaque psoriasis will be managed with topical calcipotriene/betamethasone dipropionate cream and randomized to either practice daily intermittent fasting with an 8-hour eating window or practice a diet without time restriction. We hypothesize that patients engaging in intermittent fasting as an adjunct to calcipotriene/betamethasone dipropionate will exhibit a significant reduction in psoriasis severity compared to those managed with calcipotriene/betamethasone dipropionate alone. This study aims to address the need for evidence-based recommendations for patients considering intermittent fasting in the management of their mild to moderate psoriasis.

CHAPTER 1: INTRODUCTION

1.1 Background

Psoriasis is a chronic inflammatory skin condition that is impacted by various factors, including diet. While psoriasis patients commonly make dietary modifications in an attempt to alleviate their symptoms, there is a lack of evidence-based dietary recommendations for managing psoriasis. Intermittent fasting is known to exert metabolic effects and mediate markers of systemic inflammation. However, the ability of intermittent fasting to significantly impact psoriasis has yet to be investigated in clinical trials, highlighting the need and novelty of research regarding the relationship between intermittent fasting and psoriasis.

1.1.1 Overview of Plaque Psoriasis

Psoriasis is a chronic autoinflammatory condition affecting approximately 2-3% of the global population and is characterized by raised, erythematous plaques with overlying scale.¹⁻³ Histologically, psoriasis manifests as hyperproliferation and aberrant differentiation of keratinocytes, hyperplastic blood vessels, and inflammatory cell infiltrates in the dermis and epidermis.^{2,3} However, psoriasis is largely a clinical diagnosis and rarely requires a skin biopsy.^{2,4} The condition can develop at any age, with two primary peaks in incidence at 20-30 years and 50-60 years of age.⁵ The most common form is plaque psoriasis, which occurs in over 80% of patients and manifests as well-demarcated erythematous scaled plaques, sometimes covering large portions of the patient's body.^{6,7} These plaques are often itchy or painful, and may develop in previously unaffected skin at the site of trauma or injury in a process known as the Koebner phenomenon.⁴

Most individual cases of psoriasis do not have a clear inciting cause, as the pathogenesis arises out of a complex interplay of factors including underlying genetic susceptibility, environmental triggers, and immunity.^{1,2,8} Genetic factors contributing to the development for psoriasis include HLA class I and class II genes as well as genes related to interleukin-17 (IL-17), IL-23, and nuclear factor- κ B signaling.¹ Males and females appear to be equally at risk.⁵ In susceptible individuals, the onset of psoriasis may be triggered by a variety of environmental factors including physical trauma, chemical irritants, microbial infections, or medications.^{2,9} Obesity, smoking, alcohol use, and air pollutants have been identified as additional risk factors for developing psoriasis.⁷ Diet has a role in both exacerbating and mediating psoriatic lesions, although the association between nutrition and psoriasis is not yet fully understood and remains the topic of ongoing research.¹⁰⁻¹²

A large body of research describes the role of immunomodulators in the pathogenesis and continued pathology of psoriasis, particularly cytokines such as interferon- γ (IFN- γ), tumor necrosis factor- α (TNF- α), IL-9, IL-12, IL-17, IL-22, and IL-23.^{1,2,5} While the underlying mechanisms are not fully understood, a IL-23/T helper 17 (Th17) cell axis is thought to play a crucial role in the formation and perpetuation of inflammatory skin lesions.¹ This inflammatory pathway may be initiated by a trigger such as physical trauma, causing autoantigens from keratinocytes to conjugate with other molecules and ultimately resulting in the activation of dermal dendritic cells.^{1,2,5-7} Activated dendritic cells produce several cytokines including IL-23, which skews the development of naïve T cells into Th17 cells.^{1,2,6,7} Th17 cells proliferate and migrate to the epidermis, where they respond to autoantigens and/or foreign antigens and produce

the cytokines TNF- α , IL-17, and IL-22.^{1,2,5-7} These cytokines further stimulate keratinocytes to produce autoantigens and proinflammatory mediators, manifesting clinically as chronic inflammation and epithelial hyperproliferation.^{1,2,5-7}

Studies evaluating the correlation between elevated serum cytokines and the severity of psoriasis offer mixed results.¹³⁻¹⁵ Clinically, the severity of psoriasis can be determined by the proportion of body surface area (BSA) involved or by using the Psoriasis Area and Severity Index (PASI). The PASI is used by clinicians to evaluate both the extent and severity of psoriatic lesions and results in a numeric score ranging from 0 to 72.¹⁶ Psoriasis is considered mild when it involves <3% of the individual's BSA or a PASI score below 5, moderate at 3-10% BSA involvement or a PASI score between 5 and 10, and severe at >10% BSA involvement or a PASI score above 10.⁴ Approximately two-thirds of patients with psoriasis have mild to moderate disease.⁴

Psoriasis carries significant physical and psychosocial consequences for patients.² Both mild and severe cases of psoriasis are associated with comorbidities including psoriatic arthritis, uveitis, increased risk of cardiovascular disease and major adverse cardiac events (MACE), metabolic syndrome, non-alcoholic fatty liver disease, and Crohn's disease.^{1,6,7,17} The mechanisms underlying these comorbidities include inflammation of non-skin tissue, systemic diffusion of inflammatory mediators from the skin, and diseases sharing susceptibility genes with psoriasis, such as in Crohn's disease.⁷ Several of these risks are attenuated with improved symptom control, as demonstrated by the correlation between an individual's body surface area affected by psoriasis and their risk of cardiovascular disease.⁷ Psychosocial consequences of psoriasis include an increased risk of experiencing depression, anxiety, stigma, and suicidal ideations

compared to the general population.^{4,5} Patients across multiple countries report that psoriasis negatively impacts their quality of life.^{1,5}

There is no known cure for psoriasis, but a variety of treatment modalities are available to manage the symptoms of the disease. Patients with mild to moderate psoriasis are commonly prescribed topical therapies such as corticosteroids, retinoids, vitamin D analogues, calcineurin inhibitors, keratolytic agents, and/or tar-containing products.^{4,6} Calcipotriene/betamethasone dipropionate (Cal/BD) is a commonly used combination product consisting of a vitamin D analogue and corticosteroid, and is more effective at managing psoriasis than either medication used alone.¹⁸ Clinically, Cal/BD reduces the erythema, edema, and scale of psoriasis. Adverse drug reactions are typically mild and may include skin atrophy, hypopigmentation, pruritis, skin irritation, burning, erythema, or rarely a paradoxical exacerbation of psoriasis.^{18,19} Treatment modalities for unresponsive or more severe psoriasis include systemic therapy, phototherapy, and molecularly targeted therapy.^{4,6}

Unfortunately, the literature suggests that psoriasis patients are generally dissatisfied by treatment results, with a recent systemic review encompassing 26 studies and 17,472 psoriasis patients finding that in most cases less than half of patients were satisfied with their treatment regimen and/or response to treatment.²⁰ Common reasons for dissatisfaction included treatment efficacy, adverse side effects, cost, and inconvenience. Patients managed with topical medications were more likely to be dissatisfied than those on regimens designed to manage more severe psoriasis, such as molecularly targeted therapy.²⁰ This lack of treatment satisfaction may explain the significant portion of patients with psoriasis who attempt alternative treatment modalities

such as diet modification to better manage their symptoms. One U.S. national survey of 1,206 psoriasis patients found that 86% of those surveyed had at some point attempted a dietary modification to control their symptoms.²¹ In stark contrast, evidence-based dietary recommendations for patients with psoriasis are very limited, with strong evidence supporting a hypocaloric diet in obese patients and strict avoidance of gluten in patients with confirmed Celiac disease, and moderate evidence for selenium and omega-3 fatty acid supplementation.^{11,12,22,23}

1.1.2 Intermittent Fasting

One diet with several promising clinical applications is intermittent fasting, although its impact on dermatoses is not yet well understood. Intermittent fasting (IF) is an eating pattern in which an individual consumes few or no calories for a specific period of time ranging from hours to days, in order to regularly induce a fasting metabolic state.²⁴ Intermittent fasting is distinct from calorie restriction in that there is no overt effort to induce a calorie deficit.²⁴ There are several common variations of intermittent fasting regimens. Time-restricted eating (TRE) involves restricting caloric intake to specific time periods of the day, typically between 6-12 hours each day. Alternate-day fasting (ADF) involves consuming no calories on fasting days, and alternating between one fasting day and one day of unrestricted caloric intake. Alternate-day modified fasting (ADMF) involves consuming less than 25% of baseline calorie needs on fasting days, alternated with a day of unrestricted food intake. Finally, there is periodic fasting (PF), in which individuals consume no more than 500 calories during 1 or 2 non-consecutive days per week, and consume food ad libitum the remaining days.^{24,25}

The cellular response precipitated by intermittent fasting results in an increase of antioxidant defenses, DNA repair, protein quality control, mitochondrial biogenesis and autophagy, and down-regulation of inflammation.²⁵ Murine studies have shown that periodic fasting promotes visceral fat loss even in the absence of an overall reduction in calorie intake.²⁶ Animal models have shown additional benefits of intermittent fasting in chronic conditions including obesity, diabetes, cardiovascular disease, cancers, irritable bowel disease, and neurodegenerative brain diseases.^{24,25,27-30} In humans, intermittent fasting improves cardiometabolic risk factors such as insulin resistance, dyslipidemia, and hypertension, decreases visceral fat mass, and reduces serum markers of inflammation and oxidative stress.^{24,25,27,28,31} Patients who fast have reduced symptoms of asthma, multiple sclerosis, and osteoarthritis.^{24,25,27,31,32} Long-term fasting from 1 to 3 weeks reduces pain and inflammation in patients with rheumatoid arthritis, although this inflammation generally returns with cessation of fasting.²⁷ Patients who regularly fast exhibit faster healing of thrombophlebitis and refractory cutaneous ulcers, and have a higher tolerance of elective surgery.²⁴ Fasting mice have demonstrated a reduction in inflammatory skin lesions, although human studies on intermittent fasting and dermatoses such as psoriasis are lacking.²⁶

The benefits of intermittent fasting are often attributed in part to the regular induction of a fasting metabolic state. There are two metabolic states in humans, commonly referred to as the “fed” and “fasting” states. During the fed state, glucose from meals is utilized as the main source of energy and lipids are stored in adipose tissues as triglycerides. When a human individual goes approximately 12 hours without consuming calories, their glycogen stores become depleted, and the body begins breaking down the

triglycerides stored in adipocytes to use as energy.^{24,25,27,33} This shift from glycogenolysis in the liver to lipolysis in adipose tissue represents the metabolic switch from the fed to the fasting state, and is ultimately evidenced by a rise in serum ketone levels.^{24,25}

A regular transition between the fed and fasting metabolic states has positive effects on both cellular processes and clinical manifestations of disease. While in a fed metabolic state, cells engage in processes related to growth and plasticity.²⁵ While in a fasting state, cellular processes remove and repair damaged molecules, enhancing an individual's defense against oxidative and metabolic stress.²⁵ The fasting state additionally serves to improve glucose regulation, increase stress resistance, and suppress inflammation.²⁵ As individuals with a typical Western diet eat three or more meals per day plus snacks, and overweight individuals require additional time to enter a fasting metabolic state due to insulin resistance, many individuals may rarely enter a metabolic fasting state.^{24,25} Ensuring a regular induction of a fasting metabolic state through intermittent fasting allows the body to carry out important cellular processes that help reduce systemic inflammation and perhaps modulate the severity of inflammatory conditions such as psoriasis. Past studies have shown promising results regarding the serologic and clinical impact of intermittent fasting in both animal models and human subjects, supporting the rationale for research into the impact of intermittent fasting and psoriasis.

1.2 Statement of the problem

Psoriasis is impacted by various genetic, epigenetic, and environmental factors, including diet. Patients with psoriasis commonly trial dietary modifications in addition to other treatment modalities in an effort to further manage their symptoms. However, evidence-based recommendations for patients with psoriasis are limited. Intermittent

fasting reduces marker of systemic inflammation and has exhibited benefits in animal models and human clinical trials regarding other disease processes, but studies regarding intermittent fasting and psoriasis are limited. The few available studies are observational and fall short of adequately characterizing the impact of intermittent fasting on psoriasis symptoms. Further research is needed to investigate the ability of intermittent fasting to attenuate symptoms of psoriasis.

1.3 Goals and Objectives

The proposed study will explore whether intermittent fasting is a viable adjunctive treatment for patients with mild to moderate psoriasis. The study population will consist of patients with mild to moderate plaque psoriasis managed only with topical medications. Study participants will be randomized to engage in a treatment regimen of once-daily application of calcipotriene/betamethasone dipropionate (Cal/BD) cream and adjunctive intermittent fasting versus treatment with Cal/BD alone. Evaluation of PASI scores and serum studies will be carried out at regular intervals and data will be collected over the course of 7 months. The two groups will be compared to evaluate whether those who practice intermittent fasting exhibit a significant improvement in PASI scores and biomarkers of inflammation compared to those without a time-restricted diet. The objective of this study is to determine whether intermittent fasting is associated with a significant reduction in symptoms of psoriasis. Results will further elucidate whether intermittent fasting is a viable adjunctive treatment for the management of mild to moderate psoriasis.

1.4 Definitions

Mild to moderate psoriasis: Mild psoriasis involves <3% of the individual's BSA or a PASI score below 5, and moderate psoriasis involves 3-10% BSA or a PASI score between 5 and 10.⁴

Psoriasis Area and Severity Index (PASI): A tool used by clinicians that accounts for the both the extent and severity of psoriatic lesions and produces a numeric score ranging from 0 to 72.¹⁶

Intermittent Fasting: An eating pattern in which an individual regularly consumes few or no calories for a specific period of time ranging from hours to days.²⁴

1.5 Hypothesis

In adults ages 18-70 with mild to moderate plaque psoriasis managed with once-daily calcipotriene/betamethasone dipropionate, those practicing intermittent fasting will exhibit a significant reduction in mean PASI score compared to those who are not practicing intermittent fasting.

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CHAPTER 2: REVIEW OF THE LITERATURE

2.1 Introduction

A systematic review of the literature was conducted using repeated searches of the Ovid, Cochrane, and Scopus databases between August 2021 and April 2022. The following search terms were utilized: Intermittent fasting, fasting, time-restricted eating, time-restricted feeding, psoriasis, psoriasis area and severity index, PASI, calcipotriene/betamethasone, topical therapy, corticosteroids, and vitamin D analogues. All articles written in the English language and published in 2007 or later were reviewed for relevance to the proposed study. Publications cited within these articles were additionally considered for inclusion. Studies involving continuous fasting regimens beyond 24 hours were excluded. Preference was given to randomized controlled trials (RCTs) and large-scale meta-analyses.

The current available evidence for intermittent fasting as adjuvant therapy in the management of mild to moderate psoriasis is summarized below. Intermittent fasting and its clinical applications is a relatively novel area of study, and accordingly the data on the association between intermittent fasting and psoriasis are limited. Therefore, this section also includes available evidence investigating the relationship between intermittent fasting and serum markers of inflammation, as well as the impact of intermittent fasting on related inflammatory conditions.

2.2 A Brief Discussion of Ramadan Fasting

Much of the available research on intermittent fasting centers around fasting during Ramadan, a 29- or 30-day period during which Muslims worldwide observe traditional fasting practices. While studies of Ramadan fasting generally benefit from

excellent adherence, it is important to note several confounding factors common to the observational Ramadan studies included throughout this literature review. Ramadan fasting occurs from sunrise to sunset, with the exact duration determined by the time of year and geographic location of participants. Generally, Ramadan involves between 12 and 17 hours of daily fasting. Participants are expected to abstain from eating, drinking, and smoking during the fasting period, but there is variation in whether participants consider oral and/or topical medications as breaking the fast.¹ Observers often engage in frequent washing rituals prior to prayer, which may affect pre-existing skin conditions. Ramadan fasting is also accompanied by changes in sleep patterns and dietary composition.² Participants typically consume a large meal after sunset and rise early for a lighter predawn meal, both of which may include dishes made only during Ramadan. Reported effects of Ramadan fasting on weight are mixed, with some studies reporting a decrease in BMI while others observing no effect or even an increase in BMI during the month of Ramadan.^{2,3} These lifestyle changes and variations in practice pose significant challenges to the validity of results obtained from observational studies examining the association between fasting and psoriasis during Ramadan. Controlled clinical trials designed to reduce the impact of confounding are needed in order to address this gap in the literature and more adequately characterize the relationship between intermittent fasting and psoriasis.

2.3 Evidence for the Relationship Between Intermittent Fasting and Serum Biomarkers of Inflammation

Many studies have investigated the impacts of intermittent fasting on serum markers of inflammation. Generally, these serum markers include white blood cell

(WBC) count, lymphocyte count, measurement of c-reactive protein (CRP), measurement of erythrocyte sedimentation rate (ESR), and levels of various pro-inflammatory cytokine. Inflammatory markers more strongly associated with psoriasis include IFN- γ , TNF- α , IL-9, IL-12, IL-17, IL-22, and IL-23.⁴

An observational study by Almeneesier et al examined the relationship between Ramadan diurnal intermittent fasting (DIF) and serum levels of the proinflammatory cytokines IL-1 β , IL-6 and IL-8. Serum samples were collected at three periods: after engaging in DIF for 1 week a month prior to the start of Ramadan, non-fasting samples 1 week prior to Ramadan, and after completing 2 weeks of Ramadan DIF. At each of the three study periods, participants reported to the study center and plasma levels were assessed at five different time points to account for variations due to circadian rhythm. Data analysis was performed using repeated measure analysis of variance (ANOVA) with statistical significance defined by a p-value < 0.05. Researchers observed a significant reduction in IL-1 β , IL-6 and IL-8 during both Ramadan fasting and fasting outside of Ramadan when compared to non-fasting (p < 0.05).⁵ These results suggest a significant association between intermittent fasting and a reduction in select inflammatory markers. A unique strength of this study that significantly increases the validity of the results is that the researchers controlled for sleep/wake pattern, meal composition, and the energy expenditure of participants throughout the study. The inclusion of a 1-week fasting period outside of Ramadan also strengthens the validity of the results. Some limitations of this study include a small sample size of 12 participants and a lack of generalizability as all participants were healthy non-smoking males ages 20-30 with BMI <30. These results

suggest that intermittent fasting can significantly attenuate the level of several pro-inflammatory cytokines, although the ones studied are not specific to psoriasis.

In 2012 Faris et al performed a similar cross-sectional study that compared the serum levels of proinflammatory cytokines and immune cells of 50 observers of Ramadan fasting at three different time points- 1 week prior to Ramadan, 3 weeks into Ramadan, and 1 month after the end of Ramadan. The participants exhibited a significant decrease in all measured biomarkers during Ramadan when compared to baseline, including IL-6 (155.85 ± 121.18 pg/mL vs 67.42 ± 51.25 pg/mL; $p < 0.001$), IL-1 β (17.84 ± 17.92 pg/mL vs 3.89 ± 4.84 pg/mL; $p < 0.001$), TNF- α (179.62 ± 129.56 pg/mL vs 52.22 ± 57.25 pg/mL; $p < 0.001$), and total leukocyte count (2.32 ± 0.71 10^9 /L vs 2.06 ± 0.52 10^9 /L; $p < 0.001$). Most returned to baseline one month after Ramadan, with the exception of IL-6 which remained lower than baseline levels ($p < 0.05$). Because Islamic rules do not permit fasting during the menstrual period, the 29 female subjects experienced interruptions in fasting ranging from 3 to 7 days. There was not a significant difference in data derived from the female subjects compared to the male subjects.⁶ While this study was strengthened by an increased sample size, the participants of the study were all healthy subjects who did not take any chronic medications, making it challenging to generalize the results to patients with a chronic inflammatory condition such as psoriasis.

Faris et al. performed a meta-analysis in 2018 assessing the effect of diurnal intermittent fasting during Ramadan on inflammatory markers in healthy individuals. They included 12 studies conducted in 8 different countries involving a total 311 participants. The studied inflammatory markers were IL-1, IL-6 TNF- α , and CRP or

high-sensitivity CRP (hs-CRP). The results of the meta-analysis were suggestive of an inverse relationship between intermittent fasting and inflammatory markers, with an small effect size observed for IL-1 (Hedges' $g = 0.016$, $I^2 = 0.0\%$) and CRP/hs-CRP ($g = 0.119$, $I^2 = 26.9\%$) and a medium effect size for IL-6 ($g = 0.407$, $I^2 = 0.0\%$) and TNF- α ($g = 0.371$, $I^2 = 19.7\%$).⁷ This meta-analysis increased the total sample size and thereby the power of the studies in showing the effects of diurnal intermittent fasting during Ramadan. However, it does have its limitations. One limitation of this meta-analysis is that 86% of the included participants were male, which reduces the generalizability of the results. The inclusion of only healthy participants controlled for the effect of disease stage, comorbidities, and treatments on the outcomes of interest. However, this limits generalizability to patients considering intermittent fasting for its disease-modifying effects. While studies included both obese and non-obese participants, there was a significant reduction of total body and visceral fat reported at the end of the fasting period which may confound the absolute effect of intermittent fasting on the measured biomarkers. Additionally, the analysis of IL-1 only included two studies, which is the minimum number of studies that can be meta-analyzed.

In a randomized controlled trial to assess the effects of long term intermittent fasting (LIF) on biochemical and homeostasis parameters, 46 healthy participants were randomized to six months of no fasting or an intermittent fasting regimen consisting of fasting from food for two days a week. Biochemical and hemostasis parameters were assessed at baseline and six months later. Data was analyzed using paired t-test comparison between pre- and post- fasting values in both groups. The LIF group exhibited a significant decrease in mean blood glucose ($p < 0.01$) as well as levels of total

cholesterol, low-density lipoprotein (LDL), and CRP ($p < 0.05$) when compared to the non-fasting group.⁸ A strength of this study is the RCT design as well as the duration of the study, which was better able to demonstrate long-term effects on biomarkers. It is important to note that all participants were healthy and therefore results may be less generalizable to patients with chronic inflammatory conditions. Overall, the study findings indicate that long term intermittent fasting may be beneficial in reducing several markers of inflammation including CRP.

A randomized controlled trial evaluating the impact of long-term moderate calorie restriction (CR) on inflammation assigned healthy non-obese adults ages 20-50 years old to a 25% CR diet or an ad-libitum (AL) diet and collected data at baseline, 12, and 24 months. There were no significant biometric or demographic differences between the groups at baseline. Results were analyzed on an intention-to-treat basis with $n = 143$ in the CR group and $n = 75$ in the AL control. At 24 months the CR group exhibited a significantly reduced mean WBC ($p = 0.002$), with reductions of approximately 40% in CRP levels ($p = 0.001$), and 50% in TNF- α levels ($p = 0.025$) compared to the AL group. There were no significant changes in IL-6 or IL-8. Participants in the CR group exhibited a 9.1% ($p < 0.0001$) reduction in energy intake and 10.4% ($p < 0.001$) reduction in weight over the 2-year period that was significant compared to the AL group. The data analysis performed was notable in that the change in BMI correlated significantly with a decrease in TNF- α ($r = 0.15$, $p = 0.04$) and there was a borderline significant correlation between BMI and CRP ($r = 0.15$, $p = 0.05$).⁹ The results of this study suggest that long-term CR induces a significant and persistent inhibition of inflammation that is correlated to some extent with weight loss. Strengths of this study include the extended duration of

two years, as well as a larger population size compared to the majority of available intermittent fasting studies. As with previous studies, the subjects were healthy non-obese adults, reinforcing the need for trials involving participants with chronic inflammatory conditions.

In order to explore the effects of altered sleep and feeding patterns on various markers of health and inflammation, Alam et al conducted a longitudinal follow-up study of adult men who engage in recurrent circadian fasting (RCF) during the month of Ramadan. 78 adult healthy men fasted for 29 consecutive days from sunrise to sunset with an average fasting duration of 16 hours. Data was collected at baseline one week prior to fasting, during the fourth week of fasting, and one month after the fasting period. Multinomial and linear regression models from the study indicate that fasting promotes a reduction in the levels of TNF- α (coef. = -1.16; 95% CI [-1.91 to -0.42]), IL-9 (coef. = -0.56; 95% CI [-2.00 to 0.87]), IFN- γ (coef. = -0.74; 95% CI [-1.39 to -0.084]), and IL-17 (coef. = -1.26; 95% CI [-1.92 to -0.60]). In contrast, fasting was associated with an increase in IL-6 levels (coef. = +0.77; 95% CI [0.06 to 1.49]) that remained elevated into the post-fasting period ($p = 0.0056$). Fasting was also associated with a significant decrease in CRP levels (- 1.14 mg/L) across all participants. An important limitation to this study is that data from the female participants ($n=5$) were not included in analysis. Additionally, this study did not control for the sleep and diet changes that accompany Ramadan fasting.¹⁰

While the studies above suggest that intermittent fasting affects various inflammatory biomarkers, there is a lack of consensus on which biomarkers correlate clinically with psoriasis severity. A case-control study comparing the serum levels of

TNF- α , IL-12/23p40, and IL-17 in 32 plaque psoriasis patients with that of 32 healthy controls found that the mean serum levels of TNF- α were significantly elevated in psoriatic patients ($p=0.000$) while the mean serum levels of IL-12/23p40 and IL-17 were elevated but not statistically significant compared with the controls ($p = 0.968$ and $p = 0.311$, respectively). No significant correlations were found between PASI and any of the three cytokine serum levels (Spearman's rank test; $p > 0.05$).¹¹ In contrast, a more recent case-control study of 21 patients with plaque psoriasis and 20 controls observed a significant positive correlation between the IL-17 serum concentrations and PASI scores ($r = 0.61$; $p < 0.05$).¹² A cross-sectional study of 180 Thai psoriasis patients found that those with psoriasis exhibited significantly elevated serum levels of hs-CRP compared to a group of 30 controls ($p < 0.001$). This elevation in hs-CRP also corresponded significantly with patients' PASI scores upon multivariate analysis.¹³ A complete literature review of the correlation between serum biomarkers of inflammation and psoriasis severity is a topic for further research. The literature regarding intermittent fasting and serum biomarkers of inflammation suggests that intermittent fasting has the potential to significantly attenuate general inflammatory markers as well as several markers more closely associated with psoriasis, particularly IL-17, TNF- α , and CRP.

2.4 Impact of Intermittent Fasting on Inflammatory Disease

The 2020 observational study by Nessib et al recruited adults with rheumatoid arthritis (RA) or ankylosing spondylitis (SpA) to assess whether Ramadan intermittent fasting was associated with a reduction in rheumatic disease activity. Data on disease activity was collected from participants at 6 months prior to Ramadan and at one point a week or more into Ramadan fasting. There was a significant decrease in tender joint

counts (TJC) and swollen joint counts (SJC) in the RA group (TJC $p = 0.029$, SJC $p = 0.05$) but not in the SpA group (TJC $p = 0.356$, SJC $p = 1.000$). The RA group demonstrated a significant decrease in ESR measurements ($p < 0.001$) while decreases in average CRP for the RA group and decreases in ESR and CRP in the SpA group were not significant ($p = 0.06$, $p = 0.03$, and $p = 0.303$ respectively). The RA group demonstrated a statistically significant improvement in the 28-joint disease activity scores (DAS28) before and after fasting (DAS28 ESR $p < 0.001$, DAS28 CRP $p = 0.001$). The SpA group did not demonstrate significant changes in disease activity according to the Bath Ankylosing Spondylitis Disease Activity Index ($p = 0.944$) and Ankylosing Spondylitis Disease Activity Score CRP ($p = 0.338$). However, it was significantly lower according to the Ankylosing Spondylitis Disease Activity Score ESR ($p = 0.039$). Limitations of this study include the small sample size ($n = 36$ for patients with RA and $n = 20$ for patients with SpA), as well as the single instance of data collection before and during fasting. However, the validity of this study's results is strengthened by its evaluation of medication adherence during the period of fasting. Patients' compliance to methotrexate was impaired in 28.6% of patients, while those on biological agent reported complete compliance. This study attempted to reduce confounding by excluding data from participants who started, stopped, or changed dose of any disease-modifying medications during the study period. As with other Ramadan studies, the short duration of this study limits conclusions regarding the benefits of long-term intermittent fasting.

In an observational study investigating the effects of alternate day calorie restriction (ADCR) on asthma symptoms of overweight asthma patients, 10 participants with BMI > 30 underwent an 8-week dietary pattern in which they ate ad libitum every

other day and consumed less than 20% of their normal calorie intake on the remaining days. Intervention response was assessed with questionnaires, serum studies, daily peak expiratory flow (PEF) measurements, and pre- and post-bronchodilator spirometry. All three questionnaires utilized to assess for asthma control, symptoms, and quality of life exhibited significant improvement. Forced expiratory volume increased significantly during the first 3 weeks of the ADCR period and remained elevated throughout the 8-week study period ($p < 0.009$ at 8 weeks), and FEV1 after albuterol administration was significantly greater at 8 weeks compared to baseline, indicating improved bronchial responsiveness associated with the ADCR diet. Subjects lost an average of 8% (8.5 kg) of their body weight, accompanied by significant improvement in several cardiovascular markers but no significant effect on CRP. The researchers found a significant reduction in mediators of airway inflammation including TNF- α ($p < 0.01$), BDNF ($p < 0.001$), and ceramides ($p < 0.05$). By the end of the study period this significant reduction in inflammation was persistent on both calorie restricted and ad libitum days.¹⁴ Participants in this study exhibited a range of subjective and objective improvements in their symptom burden associated with intermittent fasting. As with many similar studies, it is challenging to determine whether the beneficial effect of intermittent fasting is due to mechanisms other than weight loss. While the researchers reference a larger observational study in which weight loss alone did not impact air way reactivity in obese patients with asthma, they did not conduct multivariate analysis to further characterize the correlation between weight loss and a decrease in airway reactivity in this study.

Approximately 10-30% of patients with psoriasis develop psoriatic arthritis, which can manifest as asymmetric inflammatory arthritis, enthesitis, and/or

sacroiliitis.^{15,16} The 2019 multicenter observational trial by Adawi et. al. assessed the association between Ramadan intermittent circadian fasting and the disease activity of psoriatic arthritis. 37 male and female adult participants with stable psoriatic arthritis fasted for 17 hours for the month of Ramadan, and baseline and interval psoriatic arthritis characteristics were collected. The study benefitted from a diverse sample population, with participants originating from 10 Middle Eastern countries, as well as a relatively balanced representation of males (n = 14) and females (n = 23). They found that a month of intermittent fasting was associated with a mean difference of -1.92 in CRP levels (95% CI -2.38 to -1.46; p < 0.0001), decreased Bath Ankylosing Spondylitis Disease Activity Index scores (p = 0.0078), and decreased Psoriasis Area Severity Index scores (p < 0.0001). Mean PASI decreased from 7.46 ± 2.43 to 5.86 ± 2.37 with a mean difference of -1.59 (95% CI -1.87 to -1.32; p < 0.0001). Enthesitis and dactylitis were also significantly decreased. Of note, the improvements in psoriatic arthritis disease activity were significant even when controlling for BMI and changes in weight.¹⁷ The researchers suggest that intermittent fasting may also provide benefits through mechanisms including a reduction in proinflammatory cytokines, increase in the function of T regulatory cells, and decrease in the activity of Th17 cells.

In 2021 Jiang et al conducted a literature review of dietary interventions and immune-mediated inflammatory diseases (IMIDs). Their review returned three studies involving fasting and three studies involving calorie restriction (CR). One observational study found that Ramadan fasting was associated with a significant decrease in Colitis Activity Index (p = 0.005) and a non-significant improvement in the Crohn's Disease Activity Index (p = 0.06).¹⁸ Two studies of patients with rheumatoid arthritis found

significant improvement in disease activity after 13 or 14 days of intermittent fasting compared to baseline.¹⁹ The three remaining studies found that calorie restriction may result in significant weight loss and improvement in clinical symptoms of patients with psoriasis and psoriatic arthritis.¹⁹

2.5 Animal models of intermittent fasting and psoriasis

This review of the literature returned a single animal model of intermittent fasting and skin inflammation. In 2015, Brandhorst et al conducted a trial studying the effects of prolonged fasting in 110 C57B1/6 strain middle-aged mice. 16-month-old mice were randomized to an ad lib diet or a fasting-mimicking diet (FMD). The FMD consisted of bimonthly 14-day cycles in which mice were fed at 50% of their normal daily intake on day 1, 10% of their normal daily intake on days 2-4, and 100% of their normal daily intake on days 5-14. C57BL/6 mice are prone to developing tumors and severe ulcerative dermatitis. On pathological analysis researchers reported that FMD mice exhibited a reduced number of tissues with inflammation compared to the control group. Additionally, approximately 10% of mice developed progressive ulcerative dermatitis requiring euthanizing compared to approximately 20% in the control group.²⁰ These observations suggest that FMD provides some protection against inflammation and inflammatory skin lesions in these mice, however these observations were not part of the primary outcomes of the study. They were not reported in a quantifiable manner nor evaluated for statistical significance, making it impossible to evaluate the validity or significance of these findings.

2.6 Clinical Trials of Intermittent fasting Involving Psoriasis and other Dermatoses

A multicenter prospective observational study published in 2021 enrolled 72 adult patients with stable dermatologic diseases to engage in one month of intermittent circadian fasting (ICF) from dawn to sunset. Disease severity was assessed by two dermatologists before and at the end of the fasting period, using the severity index appropriate for each condition. They found a significant decrease in early onset atopic dermatitis ($p < 0.0001$), lichen planus pilaris ($p = 0.0154$), acne vulgaris ($p = 0.0066$), seborrheic dermatitis ($p = 0.0016$), papulo-pustular rosacea ($p = 0.0004$), alopecia areata ($p = 0.0085$), prurigo nodularis ($p = 0.0514$), and urticaria pigmentosa ($p = 0.0111$). Decreases in chronic idiopathic urticaria ($p = 0.8291$) and erythematotelangiectatic rosacea ($p = 0.2254$) were not statistically significant. The study found no effect of age or gender. The median change in weight was 0 kg.²¹ The researchers propose that in the overall absence of weight loss, the observed benefits of ICF likely originate in the alteration of circadian rhythms. Strengths of this study include a measurement of effect in a wide variety of dermatologic conditions, although psoriasis is not included which weakens the implications of its results for the proposed study. Limitations include the lack of demographic data in order to determine generalizability as well as a small sample size with a range of $n = 3$ to $n = 14$ for each of the included conditions.

Damiani et al published a multicenter observational study on the impact of Ramadan fasting on PASI scores in patients with moderate to severe psoriasis. 108 adult patients with moderate to severe plaque psoriasis engaged in 17 hours of daily fasting for the month of Ramadan. Researchers observed a statistically significant difference in PASI before and after the fasting period of -0.9 ± 1.2 (95% CI -1.1 to -0.7, $p < 0.0001$). Univariate analysis revealed that only the type of drug significantly influenced the change

in PASI score before and after Ramadan fasting ($p < 0.0001$), with those on topical therapy exhibiting a mean decrease in PASI of 0.75 ± 1.12 . Age, gender, BMI, and disease duration did not have statistically significant impact on the change in PASI.²² One strength of this study is the strong representation of both males and females (62 males, 46 females) and a self-reported adherence rate of 97.3%. Participants were ethnically diverse and included a mix of normal weight and overweight or obese participants with an average BMI of $25.5 \pm 2.1 \text{ kg/m}^2$. This study was limited by a lack of information regarding dietary intake, and results may be confounded by the changes in sleep schedule that typically accompany the observance of Ramadan. Limitations notwithstanding, this study represents one of the only available trials directly exploring the association between intermittent fasting and psoriasis.

Another large prospective observational study of 121 Ramadan participants with chronic plaque psoriasis was conducted by Almutairi and Shaaban in 2021. Participants engaged in daily fasting for approximately 14 hours from sunrise to sunset. They continued topical or oral medication for psoriasis. All medications were in the maintenance phase and not the induction phase. PASI indexes and BSA were evaluated by the same dermatologist every week for the 5-week duration of the study. Serum studies were conducted 3 days prior and 3 days after the fasting period. Two-sided p -values of < 0.005 were considered to indicate statistical significance. PASI scores before fasting ranged from 1.82 to 10.73 with a mean of 4.26 ± 3.22 . The mean PASI was reduced to 3.51 ± 1.26 at the end of the study for a significant mean difference of 0.85 ± 1.32 ($p = 0.001$). It is important to note that there was no statistically significant change in the weight of 102 (84.30%) participants, whereas 14 (11.57%) gained 1 kg and 5

(4.13%) individuals gained 2 kg. No participants reported weight loss. A major strength in this study is the demonstration of a significant reduction in PASI in the absence of weight loss, which may indicate that the fasting process itself confers immunomodulatory effects that improve psoriasis disease activity. Additionally, all patients continued to take their prescribed oral and topical medications during the fasting period. As with all Ramadan studies, a change in diet and sleep patterns may pose significant confounding to the results of the study. Participants exhibited a range from mild to severe psoriasis and utilized different medication regimens. While univariate analysis indicated that the mean reduction in PASI scores was not significantly related to the type of treatment received by the patients, stratifying the results by initial PASI score and medication regimen would have provided additional clarity and context for interpreting the results and should be considered by future studies.³

2.7 Review of Relevant Methodology

2.7.1 Study Design

Currently, the only clinical trials investigating the effect of intermittent fasting on psoriasis are observational studies associated with Ramadan fasting. While these studies serve to highlight the potential applications of intermittent fasting, their design and methodology make it challenging to draw any definitive conclusions based on their results. Many of the studies cited above are impacted by selection bias and incomplete accounting of known confounding variables. Additionally, the fasting associated with Ramadan introduces situational variables that may impact results in ways that are challenging to quantify. The only experimental study on intermittent fasting and psoriasis yielded by the literature review is a crossover study examining the effects of modified

intermittent fasting on psoriasis that has not yet entered the recruiting phase.²³ This clearly demonstrates the need for a randomized controlled study investigating the relationship between intermittent fasting and psoriasis. The proposed study will be a multi-center parallel arm randomized controlled trial. This study design is the most robust method to determine if a significant cause-effect relationship exists between intermittent fasting and symptoms of psoriasis.

2.7.2 Study Population and selection criteria

Inclusion criteria for the study population will be adults ages 18 to 70^{17,22} with mild to moderate plaque psoriasis managed with only topical medications. Participants will be recruited on a rolling basis and undergo simple allocation to the intervention or control group using software-guided randomization. Mild to moderate psoriasis will be defined as a Psoriasis Area and Severity Index (PASI) score <10 and body surface area (BSA) involvement $\leq 10\%$.²⁴ Upon enrollment, participants must be willing to cease use of all topicals used for psoriasis for a 4-week treatment washout period prior to initiation of the study intervention.²⁵

Exclusion criteria will include patients who are pregnant or nursing as well as those with diabetes, CHF, cardiac arrhythmias, CKD, cirrhosis, terminal illness, BMI < 18.5, history of eating disorders, history of malignancy, history of tuberculosis, history of hepatitis infection, history of HIV, and age over 70.^{17,20,22,26} Those who will also be excluded are patients with current or prior severe psoriasis, those on systemic or oral medications for psoriasis, those who currently adhere to an intermittent fasting diet, those who smoke, and night-shift workers.² Patients with skin disorders other than chronic

plaque psoriasis or who have undergone phototherapy in the last three months will be excluded.²⁶⁻²⁸

2.7.3 Selection of intervention and control

The proposed study will employ an intermittent fasting regimen with a consistent daily 8-hour eating window. Prior studies involving time restricted feeding models in rodents have used 8- to 12- hour eating windows, with the greatest cardiometabolic benefits observed with windows less than 12 hours.²⁹ In humans, eating windows of 6 hours or less have been associated with an increase in mild adverse side effects such as headaches, while an eating window of 8 to 10 hours has shown promising metabolic benefits as well as increased adherence.²⁹ The length of the study intervention will be six months, and the total duration of involvement for each participant will be eight months.

Calcipotriene 0.005% and betamethasone dipropionate 0.064% (Cal/BD) is a first-line two-compound topical agent for patients with mild to moderate plaque psoriasis²⁴ and will be the only topical used throughout the proposed study period. A large Cochrane review comparing the efficacy of topical treatments to placebo for chronic plaque psoriasis found a significant mean difference in PASI with the use of vitamin D analogues (SMD -0.58; 95% CI -0.71, -0.45), betamethasone dipropionate (SMD -0.97; 95% CI -1.31, -0.62), and combination Cal/BD (SMD -1.24; 95% CI -1.53, -0.95).²⁸ Similar results are reported by a systematic review of topicals used for psoriasis that found that once-daily application of a combination product containing a potent corticosteroid and vitamin D analogue was the most effective at achieving clear/nearly clear status (OR 22.62, 95% CI 9.679, 59.38).³⁰ While these reviews included data from

over 200 RCTs with a heterogeneity of designs and study populations, the results support the use of Cal/BD as a safe and effective option for control of psoriasis symptoms.

2.7.4 Patient Safety

The intermittent fasting regimen in the proposed study not involve overt calorie restriction or an alteration in diet composition, and is not expected to have any serious adverse effects on the subjects of the study. Clinical trials support the safety and tolerability of short-term intermittent fasting, including in middle aged and older adults.^{31,32} The adverse effects reported by an observational study of 121 participants in Ramadan consisted of feelings of hunger, fatigue, and constipation, without any reports of serious adverse effects throughout 5 weeks of intermittent fasting.³ Additionally, a RCT published in 2021 demonstrated that twelve months of intermittent fasting with an 8-hour eating window was feasible and safe in 20 healthy adult males.³³ The use of once-daily Cal/BD has been validated in multiple clinical trials to be safe and tolerable for up to 52 weeks of daily use.³⁴ Any participant that who fails to meet the inclusion criteria or develops any of the exclusion criteria, including the progression to severe psoriasis, will be removed from the study for their safety.

2.7.5 Primary and Secondary Outcome measures

The Psoriasis Area and Severity Index is a validated clinician-scored tool that is widely used in psoriasis clinical trials to assess response to treatment.^{35,36} The primary outcome in the proposed study will be the mean difference in PASI scores before and after the study period, as operationalized by previous observational studies.^{17,22} PASI scores will be determined by taking the average of three blinded clinician assessors in order to minimize the risk of detection bias. Secondary outcomes include the mean score

difference in the Dermatology Life Quality Index (DLQI), which is validated in patients with psoriasis as a patient-reported quality of life measure.³⁷⁻³⁹ A systematic review found a high level of correlation ($r^2 = 0.898$, $p < 0.01$) between PASI and DLQI scores in patients with severe psoriasis.⁴⁰ A minimal clinically important difference (MCID) for the DLQI of 3.3 will be used in the proposed study.^{40,41} It is important to note that further studies may be required to validate this benchmark in patients with mild to moderate psoriasis.

Despite the mixed results regarding their clinical correlation, changes in the serum levels of WBC, CRP, TNF- α , IL-23, IL-17, and IL-12 are often used as proxy for measuring the response of psoriasis to interventions, and these serum markers will therefore be measured as secondary outcomes.^{6-10,14,42} Inclusion of these parameters in the proposed study will serve to further elucidate the subclinical response of psoriasis to intermittent fasting. A change in Disease Activity Index for Psoriatic Arthritis (DAPSA) has been described in response to intermittent fasting in an observational study and will be collected as an exploratory outcome.¹⁷

2.7.6 Sample Size

While PASI scores are frequently utilized as a primary outcome measure in psoriasis trials, there is no defined minimal clinically important difference (MCID) for patients with psoriasis. Using the correlation of DLQI with PASI scores, most clinical trials use a 75% reduction in PASI score as the current benchmark for determining adequate efficacy of treatment.³⁶ However, the proposed study is investigating intermittent fasting as an adjuvant therapy in the setting of mild to moderate psoriasis managed with topicals. As such, a statistically significant difference between the intervention and control groups

will be considered a successful trial. The review of the literature did not yield any randomized controlled trials exploring the effect of intermittent fasting on plaque psoriasis. Therefore, the sample size of the proposed study was calculated using a 2019 observational study examining the impact of Ramadan fasting on PASI scores of patients with moderate to severe psoriasis.²² After 4 weeks of fasting for 17 hours each day, the subset of participants with psoriasis managed only with topical therapy exhibited a statistically significant decrease in PASI of 0.75 ± 1.12 ($p < 0.0001$). Unfortunately, this study did not specify which topical therapies the participants were using, nor the absolute value of the mean PASI scores in order to provide more context for this difference. This writer reached out to the designated corresponding author of the study but was unable to receive clarification. Again, due to the limited available research on intermittent fasting and psoriasis, it was necessary to use data involving participants with moderate to severe psoriasis rather than the target study population of patients with mild to moderate psoriasis. In line with previous clinical trials involving 1-2 years of intermittent fasting or calorie restriction, the final sample size for the proposed study will account for an attrition rate of 25% in each study arm.^{9,33} Ramadan studies were intentionally not considered in the estimation of attrition rates for the proposed study as they would likely result in an underestimation of dropout rates in the general population due to the religious component of Ramadan.

2.7.7 Measurement of adherence

Clinical trials involving intermittent fasting commonly assess adherence via daily meal logs or a written record of the first and last calorie ingestion, with reported adherence rates of 80% and above.²⁹ An RCT cross-over trial of adults aged 55 to 79

found that 84% exhibited complete adherence to a 6-week period of intermittent fasting with an 8 hour eating window.³¹ The proposed study will utilize Way to Health, a web-based platform designed by the UPenn Center for Health Incentives and Behavioral Economics to test behavioral interventions in clinical trials.⁴³ The Way to Health platform will send text message reminders to participants and allow them to directly report their first and last calorie intake of the day via text message. It is expected that this method will match or surpass reported rates of adherence via written records.

2.8 Review of Possible Confounding Variables

There are many factors that can impact participants' PASI scores and markers of inflammation that may serve as confounders in the proposed study. Possible confounders will be addressed through the matching of the study groups, exclusion criteria, and study design.

It is unclear whether participants' sex will be a confounding factor. In the US psoriasis is equally prevalent in males and females, with some variation in other countries that report a slight male or female predominance.⁴⁴ While a recent Swiss cross-sectional study of psoriasis patients receiving systemic therapy found that men had statistically significantly higher median PASI scores than women across all ages (7.7 and 5.4, respectively; $p < 0.001$), these results cannot be generalized to the study population in the proposed study.⁴⁵ In order to approximate the population of psoriasis patients in the US, a 1:1 male to female ratio will be sought in both arms of the study.

A significant potential confounder in this study is obesity. It is well established that obesity is a predisposing factor for developing psoriasis.^{46,47} A systemic review on the association between psoriasis and obesity analyzed 16 observational studies spanning

201,831 participants, and found that psoriatic patients exhibited significantly higher odds of obesity compared to individuals from the general population (OR 1.66; 95% CI 1.17-1.82), with a hazard ratio of 1.18 (95% CI 1.14-1.23) for developing new-onset obesity.⁴⁸ Patients with severe psoriasis had an even stronger likelihood of being obese (OR 2.23, 95% CI 1.63-3.05).⁴⁸ These results are suggestive of a bidirectional association between obesity and psoriasis severity. Previous trials of intermittent fasting report the proportion of participants who are normal weight, overweight, or obese but fail to provide results that are stratified by these categories. The proposed study will seek to address this shortcoming by analyzing the effect of intermittent fasting on PASI stratified by BMI.

Clinical trials have further demonstrated that weight loss is significantly associated with an improvement in psoriasis symptoms.^{47,49-51} However, these trials were conducted in overweight and obese individuals and it remains unclear whether weight loss can similarly impact psoriasis in individuals who are not overweight or obese. Of note, intermittent fasting has been observed to significantly improve psoriasis symptoms independent of weight loss. An observational study of 121 participants found that Ramadan fasting resulted in a mean reduction in PASI of 0.85 ± 1.32 ($p = 0.001$). There was no statistically significant difference in the weight of 102 (84.30%) participants, while 14 (11.57%) subjects gained 1 kg and 5 (4.13%) gained 2 kg.³ The proposed study will collect data regarding participants' weight and perform statistical analysis to evaluate whether weight loss, operationalized as a decrease in BMI, is significantly associated with participants' change in PASI in response to intermittent fasting.

Other notable factors that may impact psoriasis severity are comorbid inflammatory conditions,^{52,53} exposure to tobacco and alcohol,^{53,54} and shifts in sleep-

wake cycles.^{53,55} Chronicity of topical use and of eating may also be confounding factors. While studies regarding chronotherapy are few and the impact of circadian rhythms on skin is not fully understood, recent research has identified dozens of genes in skin whose expression is associated to time of day.⁵⁶ As such, participants in the intervention group will follow a consistent 8-hour eating window from 9 am to 5 pm. Once-daily application of Cal/BD must occur in the morning prior to noon. Efforts will be taken to identify and minimize changes in diet composition, which is a significant potential confounder affecting studies of Ramadan fasting.

2.9 Conclusion

This review of the literature demonstrates that intermittent fasting is consistently associated with a decrease in various biomarkers of inflammation, most notably CRP and TNF- α . There is some evidence to suggest that fasting significantly lowers IL-6 and IL-17, which are key cytokines in the pathophysiology of psoriasis. However, results are mixed and there is a need for further research to determine the clinical correlation of these serum inflammatory markers in patients with psoriasis. The review of the literature yielded only two observational studies of intermittent fasting with psoriasis as a primary outcome and did not yield any randomized controlled trials on intermittent fasting and psoriasis. Studies of intermittent fasting in any clinical context tend to be centered around Ramadan fasting, with limited sample sizes and study duration. Additionally, Ramadan studies are subject to confounding as a result of the changes in sleep, diet, and medication compliance that accompany this form of fasting. This review of the literature highlights the novelty of the proposed study as well as the need to further characterize the relationship between intermittent fasting and psoriasis. The data for intermittent fasting is

strongest for obese individuals with psoriasis due to the association of intermittent fasting and weight loss, coupled with the association of weight loss with improvement in psoriasis. Results from prior observational studies suggest a modest reduction in PASI scores conveyed by intermittent fasting which supports the decision to study intermittent fasting as an adjuvant therapy in patients with mild to moderate psoriasis. The study will have an intervention period of six months and control for known confounders in order to better examine the effect of intermittent fasting on symptoms of psoriasis.

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CHAPTER 3: STUDY METHODS

3.1 Study design

This study is a multi-center parallel arm randomized control trial to evaluate the efficacy of intermittent fasting as adjuvant therapy to calcipotriene-betamethasone dipropionate (Cal/BD) cream for patients with mild to moderate psoriasis.

3.2 Study population and sampling

The study population will be sampled from the 27 outpatient primary care offices associated with the Yale New Haven Health System within 15 miles of New Haven. Eligible participants will undergo randomization to intermittent fasting and Cal/BD versus Cal/BD therapy alone.

3.2.1 Inclusion Criteria

Adults ages 18-70 with mild to moderate plaque psoriasis currently managed with topical medications will be enrolled. All participants must be willing to cease use of all topicals for psoriasis for a 4-week treatment washout period after enrollment. Participants must be willing to adhere to an intermittent fasting diet for six months and be able to attend a total of 6 follow-up appointments throughout the study.

3.2.2 Exclusion Criteria

Patients who cannot safely fast for extended portions of the day will be excluded from the study and will include patients who are pregnant or nursing as well as those with diabetes, CHF, cardiac arrhythmias, CKD, cirrhosis, terminal illness, BMI < 18.5, history of eating disorders, , history of malignancy, history of tuberculosis, history of hepatitis infection, history of HIV, and age over 70.¹⁻⁴ Also excluded are patients with current or prior severe psoriasis, those on systemic or oral medications for psoriasis, those who

currently adhere to an intermittent fasting diet, those who smoke, and night-shift workers.⁵ Patients with skin disorders other than chronic plaque psoriasis or who have undergone phototherapy in the last three months will be excluded.^{3,6,7}

3.3 Recruitment

Participants will be recruited on a rolling basis from outpatient primary care offices associated with the Yale New Haven Health System. The offices involved will consist of the 27 primary care offices located within 15 miles of New Haven.

Participating offices will help identify and refer eligible patients. Patients who express interest in participating in the study will be contacted via phone call by a research coordinator, who will confirm eligibility based on the established inclusion and exclusion criteria. Eligible participants will be invited for in-person screening in New Haven. Those who meet the inclusion and exclusion criteria will return 4 weeks later for enrollment and to provide informed written consent (Appendix B).

3.4 Subject Protection and Confidentiality

The protocol for this study will be submitted to the Yale Human Research Protection Program for review by the Institutional Review Board (IRB) using the Yale University IRES IRB electronic submission system. The Principal Investigator and all persons who will be interacting with research participants, their data, or their biological samples will complete the human subject protection training. All patients will be consented in accordance with the institutional ethics guidelines and all patient information will be maintained strictly in accordance with the Health Insurance Portability and Accountability Act (HIPAA). All study personnel will complete HIPAA training. Written consent forms will be made available in multiple languages as needed.

In order to maintain subject confidentiality, each participant will be randomly assigned a unique numerical identifier upon enrollment. This identifier will be used to de-identify patient data and specimens for the duration of the study.

3.5 Assignment of Intervention and Blinding

Recruitment and enrollment will be made on a rolling basis. After provided informed written consent, participants will undergo software-guided 1:1 randomization to intermittent fasting and Cal/BD versus Cal/BD alone. As this study involves a diet intervention, participants will not be blinded to their group assignment. However, study personnel and clinician assessors will interact with patients using only their numerical identifier and will not be aware of participants' group allocation to reduce observational bias.

3.6 Study Variables and Measures

Study participants will be randomized into the intervention group, which will practice intermittent fasting in addition to once-daily application of Cal/BD, or the control group, who will utilize once-daily Cal/BD only for their psoriasis. The intermittent fasting regimen will consist of a daily 8-hour eating window from 9 am to 5 pm for all participants. Caloric intake and diet composition will not be restricted, and patients will be encouraged to maintain a diet similar in composition to their baseline. Participants in the control group will have no restrictions placed on their diet. All participants will manage their psoriasis with once-daily application of a two-compound topical agent consisting of calcipotriene 0.005% and betamethasone dipropionate 0.064% cream. This medication will be dispensed by the Principle Investigator at the study site. Patients will be instructed by the Principal Investigator in the correct application of the

calcipotriene-betamethasone using fingertip units (FTU) per body surface area to ensure uniform use of topicals across patients. The once-daily application of Cal/BD cream must take place prior to noon and will be the only disease-modifying medication for psoriasis that participants may use throughout the duration of the study. Other vehicle formulations of Cal/BD such as foam, ointment, or suspension will not be allowed. The primary outcome for the two groups will be the mean difference in PASI score before and after the six-month study intervention period. Secondary outcomes will include changes in BMI, WBC, CRP, TNF- α , IL-23, IL-17, and IL-12. The mean change in scores on the Dermatology Life Quality Index (DLQI) and Disease Activity Index for Psoriatic Arthritis (DAPSA) will also be included as secondary outcomes. Participant baseline characteristics of age, sex, race, ethnicity, and starting BMI will be used to assess the quality of randomization and identify sources of potential confounding.

3.7 Data Collection

Upon recruitment, patients will come to an in-person screening 4 weeks prior to the initiation of the study intervention. Those who are determined eligible and provide informed written consent (Appendix B) will be enrolled. They will fill out a demographic survey including age, sex, race, and ethnicity. At that time, clinician assessors will determine their baseline PASI score. For the duration of the study, PASI scores will be determined by taking the average of the scores of 3 blinded clinician assessors. The same 3 assessors will score all participants throughout the study. Participants will be instructed to cease all use of topical medications for psoriasis for a 4-week period prior to initiation of the study. They will return for follow-up in four weeks, where participants' PASI scores will again be determined. Study personnel will collect samples for serum studies

(WBC, CRP, TNF- α , IL-23, IL-17, and IL-12) and measure participants' height and weight. Height and weight values will be used to determine a baseline BMI for each participant. DLQI scores will be obtained through a self-administered form (Appendix C) and DAPSA scores will be obtained through evaluation by a blinded clinician assessor. Cal/BD cream will be dispensed by the study site and the weight of each tube of medication will be recorded. Participants will be instructed to only use the medication from the tube provided to them and to bring it to each follow-up appointment to be weighed. This will allow for the determination of topical use as a function of BSA. At the end of week 1 and week 4 of the study, all participants will receive a phone call by study personnel in order to conduct a survey of adherence and possible adverse events (Appendix D). Participants will be encouraged to continue eating foods that are typical for them and not make any major changes in the types of foods they eat in order to reduce the confounding effects of alterations in diet composition. Data will be collected at subsequent in-person follow-up appointments as outlined below. Serum studies will always consist of the above-mentioned biomarkers. Both participants' height and weight will be measured at the specified follow-up appointments to ensure accurate calculation of BMI, particularly in younger participants. Of note, follow-up appointments will take place on the last day of the corresponding week of the subjects' participation, and always between the hours of 3 pm – 7 pm in order to minimize the effects of circadian variation on serum studies across participants. Data regarding adherence will be operationalized as average eating window duration.

Table 1: Study Protocol Timeline

Type	Study Timing	Data Collected
Phone screening	-	Inclusion/Exclusion Criteria Screening

In-person screening and enrollment	4 weeks prior to initiation	Written informed consent, demographic survey, PASI score
In-person follow-up and intervention initiation	Day 0	PASI score, serum studies, height, weight, DLQI, DAPSA, initial medication weight
Phone follow-up	Week 1	Adherence survey, adverse event screening
Phone follow-up	Week 4	Adherence survey, adverse event screening
In-person follow-up	Week 8	PASI score, serum studies, DLQI, DAPSA, remaining medication weight
In-person follow-up	Week 16	PASI score, serum studies, DLQI, DAPSA, remaining medication weight
In-person follow-up	Week 24	Adherence survey, adverse event screening, PASI score, serum studies, height, weight, DLQI, DAPSA, remaining medication weight
In-person follow-up	4 weeks post-intervention	Adherence survey, adverse event screening, PASI score, serum studies, height, weight, DLQI, DAPSA

3.8 Adherence

Diet adherence will be monitored via Way to Health, a web-based platform designed for use in clinical trials. In order to minimize confounding, subjects in both groups will interact with this platform. Members of both groups will be encouraged to send a photo of their first and last calorie of the day, in order to determine the average duration of each participant's eating window over the course of the study. Participants in the intervention group will be sent daily text message reminders notifying them of the start and end of the daily 9 am – 5 pm eating window as well as reminding them to photograph their first and last calorie of the day. Members of the control group will also

get text messages at 9 am and 5 pm reminding them to photograph their first and last calorie of the day. Additionally, all participants will bring in their tubes of Cal/BD cream. These will be weighed to determine the grams of medication used in the interim period, which will be extrapolated to determine their average weekly usage in grams as a function of BSA.

3.9 Safety and Monitoring of Adverse Events

All participants will be provided with the phone number of a clinician and encouraged to contact them if they experience any adverse events or symptoms. All subjects will receive a phone call from a registered nurse at the end of weeks 1 and 4 to screen for adverse events and study adherence. The content of these phone calls will be transcribed, de-identified, and added to participants' trial in order to evaluate for any possible confounding factors related to changes in dietary composition.

3.10 Sample Size Calculation

The literature review did not yield any randomized controlled trials involving intermittent fasting and psoriasis. An observational study examining the impact of Ramadan fasting on PASI scores of patients with moderate to severe psoriasis was used to calculate the sample size for this study.² ClinCalc.com was used to determine that a sample size of 70 participants would be required to detect a statistically significant difference in PASI of 0.75 ± 1.12 with 80% power using a two-tailed test and $\alpha = 0.05$ (Appendix A). This study will account for an attrition rate of 25% in each study arm, resulting in a total of 88 participants needed for enrollment. Participants will be randomized on a 1:1 basis with a target of $n = 44$ in each study arm. Each study arm will need to have at least 35 members in order to achieve the designated power.

3.11 Analysis

The baseline characteristics will be compared between the two groups to assess for significant differences as outlined below in Table 2. If a significant difference in demographic variables is found between the two study arms, that variable will be included in multivariate analysis of the primary outcome. Analysis of outcomes will be performed as below in Table 3. The primary outcome, mean difference in PASI score, will be analyzed on an intention-to-treat basis in order to more closely evaluate the real-world efficacy of intermittent fasting on psoriasis. Outcomes that are continuous and normally distributed will be analyzed using the student t-test. DLQI and DAPSA scores will be analyzed using the Wilcoxon rank-sum test. Simple linear regression will be used to carry out stratified analyses. The effect of intermittent fasting on the mean difference in PASI will be stratified by sex, baseline BMI, mean difference in BMI, weekly topical use/BSA, and average duration of eating window. The standard for statistical significance for all tests will be an alpha error of 5% ($P \leq 0.05$).

Table 2: Analysis of Participant Baseline Characteristics

Characteristic	Control	Intervention	P-value
Age	Mean \pm SD	Mean \pm SD	Student t-test
Sex	N (%)	N (%)	Chi-square test
Race	N (%)	N (%)	Chi-square test
Ethnicity	N (%)	N (%)	Chi-square test
BMI	Mean \pm SD	Mean \pm SD	Student t-test
Average weight (BMI 18.5-24.9)	N (%)	N (%)	Chi-square test

Overweight (BMI 25.0 – 29.9)	N (%)	N (%)	
Obese (BMI ≥ 30)	N (%)	N (%)	

Table 3: Analysis of Primary and Secondary Outcomes

Outcome	Variable Type	Control	Intervention	P-value
ΔPASI	Continuous	Mean ± SD	Mean ± SD	Student t-test
Δ WBC Δ CRP Δ TNF-α Δ IL-23 Δ IL-17 Δ IL-12	Continuous	Mean ± SD	Mean ± SD	Student t-test
ΔDLQI	Ordinal	Mean ± SD	Mean ± SD	Wilcoxon rank-sum test
ΔDAPSA	Ordinal	Mean ± SD	Mean ± SD	Wilcoxon rank-sum test

3.12 Timeline and Resources

Eligible study participants will be recruited from 27 primary care sites associated with the Yale New Haven Health System within 15 miles of New Haven. This health system has a high patient volume and it is expected that 9 months of rolling recruitment and enrollment will be sufficient to reach the targeted sample size of 88 participants. The duration of the study intervention will be 24 weeks with a 4-week treatment washout

period prior to the intervention and a 1-month post-intervention follow-up appointment outlined above in Table 1. The duration of involvement of each participant from recruitment to the final follow-up appointment is estimated to be 8 months. The entire study from the start of enrollment to the completion of follow-up and data collection will be 18 months.

The study center will be located in New Haven. Dr. William Damsky will be the Principle Investigator and Grace Queiroz PA-SII will be the co-Principle Investigator for this study. Additional required personnel will include 3 dermatologists to determine PASI scores and administer the DAPSA index. An RN will collect serum samples, measure values needed to calculate BMI, and call participants to administer the adherence survey and adverse event screenings. Subsequent diet surveys and adverse event screenings will be conducted at in-person follow-ups and will be self-administered. The RN will be available by phone throughout the study duration for participants to contact regarding potential adverse events. A research assistant will identify and confirm participants who meet the inclusion and exclusion criteria, obtain informed consent, and manage data collection. The research assistant will also track and arrange the follow-up appointments for participants.

Chapter 3 References

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CHAPTER 4: CONCLUSION

4.1 Study Advantages

The proposed study has several strengths. It will be the first RCT examining the efficacy of intermittent fasting as adjuvant therapy for psoriasis. Much of the current literature surrounding intermittent fasting and psoriasis consists of observational studies conducted in patients observing Ramadan. These studies are limited by a short time frame, small sample sizes, and lack of controlling for confounding factors such as weight loss, changes in diet, changes in sleep, or the use of different medications for psoriasis. This study will address several of these shortcomings by taking place over a period of six months. Participants will be surveyed regarding any changes in diet, and will not be allowed to take disease-modifying medications for psoriasis other than Cal/BD. Gathering data on starting on BMI and weight loss during the study period will add to the understanding of the relationships among obesity, weight loss, and psoriasis. Stratifying participant's mean difference in PASI scores based on initial BMI and weight loss will help determine whether fasting confers a significant benefit independent of weight loss.

The use of randomization and blinding of the clinician assessors will decrease selection bias that could influence the results. The sample size of 88 participants ensures that the study will be able to detect a significant difference in PASI score of 0.75 ± 1.12 between the two study groups, and allows for an attrition rate of 25% without loss of power. The 16:8 regimen of intermittent fasting that will be used in this study has been shown to be safe in a wide range of participants, with good adherence even in long-term studies exceeding the length of the proposed study.^{1,2} The use of multiple sites and

inclusion of patients who have medical conditions that do not preclude them from fasting will generate results that are generalizable to a wider group of patients than previous studies.

4.2 Study Disadvantages

One limitation of this study is the inability to control for all of the factors that may impact psoriasis, making it challenging to distinguish causation vs correlation of intermittent fasting and changes in PASI score. This study attempts to control for factors that may impact psoriasis such as changes in diet and disease-modifying medications, but it will not control for environmental triggers, changes in weather, or stress. Limitations notwithstanding, a significant correlation between intermittent fasting and PASI scores would be valuable information in furthering our understanding of the clinical applications of intermittent fasting. Another disadvantage is that intermittent fasting is a relatively new area of study, and the mechanisms by which intermittent fasting affects psoriasis will not be fully addressed by the results of this proposed study. However, the statistical analysis will address the level of association between weight loss and improvements in PASI, and explore whether participants practicing intermittent fasting exhibited improvements in PASI scores independent of weight loss. Finally, the pathogenesis of psoriasis is still an active area of research, and there are many biomarkers used as indicators for systemic inflammation and psoriasis severity. This study does not include all of the potential biomarkers that have been identified to date, but efforts have been made to include the most widely studied. The primary outcome is mean difference in PASI score, as the focus of this study is the clinical impact of intermittent fasting on patients with psoriasis. The inclusion of both clinical and serum biomarker outcomes may

provide a more comprehensive picture of participants' response to intermittent fasting, although the causes of observed disparities between clinical and serum biomarker response will not be addressed by this study. The limitation of the study population to patients with mild to moderate psoriasis managed with topical therapy means that results will not be generalizable to those with more severe psoriasis or those utilizing systemic medications for psoriasis.

4.3 Clinical Significance

Psoriasis is a common condition with no known cure, and has both physical and psychological impacts on those affected.³ Poor control of psoriasis has been linked to psychosocial effects as well as increase comorbidities including MACE, metabolic syndrome, and cardiovascular disease. It is known that many patients with psoriasis attempt to alleviate their symptoms with changes in diet, but there is a lack of evidence-based dietary guidelines for patients with psoriasis.⁴ If effective, intermittent fasting may be an additional modality of treatment that will give patients self-efficacy and improved control of their psoriasis. On a larger scale, the results of this study have the potential to inform the practice of physician assistants working in primary care or dermatology who are likely to develop treatment plans for patients with psoriasis, as well as PAs working in other specialties who are almost certain to encounter patients with psoriasis. Even a modest clinical benefit conveyed by intermittent fasting would give providers direction when faced with their patients with psoriasis who wish to add dietary changes into their therapeutic regimen in order to achieve better symptom control. Data from this study regarding adverse events will help clinicians and patients understand the likely risks

associated with intermittent fasting. Ultimately the results of this study will serve to direct future research regarding intermittent fasting and psoriasis.

Chapter 4 References

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Appendices

APPENDIX A: Sample size calculation

RESULTS

Continuous Endpoint, Two Independent Sample Study

Sample Size	
Group 1	35
Group 2	35
Total	70

Study Parameters	
Mean, group 1	0.75
Mean, group 2	0
Alpha	0.05
Beta	0.2
Power	0.8

[View Power Calculations](#)

$$k = \frac{n_2}{n_1} = 1$$
$$n_1 = \frac{(\sigma_1^2 + \sigma_2^2/K)(z_{1-\alpha/2} + z_{1-\beta})^2}{\Delta^2}$$
$$n_1 = \frac{(1.12^2 + 1.12^2/1)(1.96 + 0.84)^2}{0.75^2}$$
$$n_1 = 35$$
$$n_2 = K * n_1 = 35$$

$\Delta = |\mu_2 - \mu_1|$ = absolute difference between two means
 σ_1, σ_2 = variance of mean #1 and #2
 n_1 = sample size for group #1
 n_2 = sample size for group #2
 α = probability of type I error (usually 0.05)
 β = probability of type II error (usually 0.2)
 z = critical Z value for a given α or β
 k = ratio of sample size for group #2 to group #1

APPENDIX B: Sample Informed Consent Form

CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT YALE UNIVERSITY SCHOOL OF MEDICINE PHYSICIAN ASSOCIATE PROGRAM

Study Title: INTERMITTENT FASTING AS ADJUVANT TO
TOPICAL THERAPY IN THE MANAGEMENT OF MILD TO MODERATE
PSORIASIS

Principle Investigator(s): Dr William Damsky and Grace Queiroz PA-SII

Introduction

You are being asked to join a research study. The following information will explain the purpose of the study, what you will be asked to do, and the potential risks and benefits. It is important that you understand why the research is being done and what it will involve before deciding to participate in the study. Please read the following information carefully. Please ask the researcher if there is anything that is not clear or if you need more information.

Purpose

The purpose of this study is to investigate the effectiveness of intermittent fasting in the management of psoriasis symptoms.

Study Procedures

This study involves 6 in-person visits during a 7-month time period. A researcher has already called you to make sure that you meet the requirements for this study. Today your skin was assessed by 3 dermatologists to determine your level of psoriasis symptoms and it was found that you are eligible to enroll in this study. Today we will collect some information about you including your age, sex, race, and ethnicity. A nurse will measure your height and weight and three dermatologists will examine your joints. You will be asked to fill out a form about how psoriasis affects your life. We will also collect a small sample of your blood today.

One of the reasons you were selected for this study is that you treat your psoriasis with medications that are applied to the skin. Today, you must stop using any medications that you use to treat your psoriasis. A nurse will go over these medications with you. You must not use any medication for psoriasis for the next four weeks. In four weeks, you will return to the study center and you will be provided with a medicine called Calcipotriene-Betamethasone Dipropionate. This is a cream that helps treat psoriasis. Throughout this study, you should apply this cream to all areas where you have psoriasis once in the morning prior to noon. We will instruct you on the proper way to apply this cream. You should not apply the cream more than once, and should not use any other medicines for psoriasis. Please bring the tube of this medication with you to every appointment, so we

can weigh it and estimate how much of the medication you are using. You should continue to use any medications that are prescribed to you that are not for psoriasis.

In four weeks, you will be randomly assigned to one of two groups. One group will start a diet called intermittent fasting, and the other group will not make any changes to their diet. If you are assigned to the intermittent fasting group, you can only consume calories between the hours of 9 am to 5 pm. If it is before 9 am or after 5 pm, you may only drink water. You do not have to count calories and should try not to change the types of foods that you normally eat. If you are assigned to the group that is not doing intermittent fasting, you should not make any changes to the foods or the times that you normally eat.

Everyone who participates in this study will be asked to make an online Way to Health account and send a text message photo of their first and last calorie intake of each day for the six months of the study. Way to Health will send you text message reminders in the morning and at night.

In 5 weeks and in 9 weeks a nurse will call you to ask questions about your diet and medications and to make sure you are not experiencing any new or uncomfortable symptoms. You can call the nurse at any time if you develop any new symptoms or have questions.

After your in-person appointment in 4 weeks, the next in-person appointments will be at the end of 2, 4, and 6 months. At the 2- and 4- month appointment, dermatologists will again assess your skin and joints. You will fill out a form about the way psoriasis affects your daily life, and we will collect a small sample of your blood. The 6-month appointment will also involve all of these tests, in addition to two surveys about your diet and any symptoms that you are experiencing. A nurse will measure your height and weight. The 6-month appointment marks the end of the study. You will not have to do intermittent fasting or submit photos of your first and last calorie of the day any more. There will be one more in-person follow-up appointment 4 weeks after you finish the study. We will collect all of the same information that we did at the 6-month appointment.

Potential Risks

There are some risks associated with participation in this study. These risks are related to intermittent fasting, phlebotomy, and your health information.

Intermittent fasting for short periods such as in this study is overall considered to be very safe. However, intermittent fasting may commonly cause minor effects such as hunger, fatigue, constipation. These side effects usually resolve after several weeks of intermittent fasting. Uncommon side effects include dizziness, dehydration, and fainting. Patients with serious medical conditions that make it unsafe for them to fast have been excluded from this study. Please reach out to the researcher if you feel that it may be unsafe for you to practice intermittent fasting.

Phlebotomy is the process of drawing a sample of a person's blood. Throughout this study you will be asked to provide a sample of blood a total of 5 times. Possible risks of drawing blood include discomfort, bruising, bleeding, dizziness, fainting or infection. Blood draws will only be carried out by a professional registered nurse in order to minimize these risks.

Finally, participating in this research study may put your health information at risk of compromise. There are several procedures in place to protect your information. Please see below for more details.

Potential Benefits

Intermittent fasting may help your psoriasis to improve and/or result in weight loss. Even if you do not get assigned to intermittent fasting, the results from this study may help further scientific knowledge about the potential effects of intermittent fasting on psoriasis.

Privacy/confidentiality

If you agree to participate in this study, you will be assigned a random 4-digit number. This number will be used on all paper and electronic forms instead of your name to protect your privacy. The records connecting your name and this number will be stored in an encrypted file. All forms, blood samples, and other records will use this unique 4-digit identifier. Additionally, the dermatologists who interact with you will not know what group you have been assigned to. All collection and storage of health information, both physical and electronic, will comply with the standards and regulations of the Health Insurance portability and Accountability Act (HIPAA). We will only collect information from you that is necessary for the purposes of this study.

Voluntary Participation

Participation in this study is completely voluntary. You can choose to enroll in this study today and you can choose not to enroll. If you enroll in this study you may change your mind at any time. Withdrawing from the study will cancel all of your future appointments. You do not give up any of your legal rights by participating in this study or by withdrawing from the study.

Study Contact Information

At any point during this study you may call the nurse at XXX XXX XXXX to discuss new symptoms or ask health-related questions. At any point during this study you may call the research assistant at XXX XXX XXXX with questions related to this study, questions related to upcoming appointments, or if you would like to withdraw from the study.

Questions

Please take your time to look over this entire consent form and ask any questions that you have. Please ask for clarification if you would like more information about anything mentioned in this form.

Consent

I have read and I understand the provided information and have had the opportunity to ask questions. I understand that my participation in this study is voluntary and that I am free to withdraw at any time. I understand the purpose, risks, benefits, and requirements of this study. I understand that I will be given a copy of this consent form. I voluntarily agree to take part in this study.

Participant's Printed Name Participant's Signature Date

Research Assistant's Printed Name Research Assistant's Signature ___ Date

APPENDIX C: DLQI self-assessment form

DERMATOLOGY LIFE QUALITY INDEX

Score:

4-Digit Identifier:

Date:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please check one box for each question.

1.	Over the last week, how itchy, sore, painful or stinging has your skin been?	Very much A lot A little Not at all	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
2.	Over the last week, how embarrassed or self conscious have you been because of your skin?	Very much A lot A little Not at all	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
3.	Over the last week, how much has your skin interfered with you going shopping or looking after your home or yard ?	Very much A lot A little Not at all	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Not relevant <input type="checkbox"/>
4.	Over the last week, how much has your skin influenced the clothes you wear?	Very much A lot A little Not at all	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Not relevant <input type="checkbox"/>
5.	Over the last week, how much has your skin affected any social or leisure activities?	Very much A lot A little Not at all	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Not relevant <input type="checkbox"/>
6.	Over the last week, how much has your skin made it difficult for you to do any sport ?	Very much A lot A little Not at all	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Not relevant <input type="checkbox"/>
7.	Over the last week, has your skin prevented you from working or studying ?	yes no	<input type="checkbox"/> <input type="checkbox"/>	Not relevant <input type="checkbox"/>

	If "No", over the last week how much has your skin been a problem at work or studying ?	A lot A little Not at all	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
8.	Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives ?	Very much A lot A little Not at all	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Not relevant <input type="checkbox"/>
9.	Over the last week, how much has your skin caused any sexual difficulties ?	Very much A lot A little Not at all	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Not relevant <input type="checkbox"/>
10	Over the last week, how much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Not relevant <input type="checkbox"/>

Please check you have answered EVERY question. Thank you.

Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19(3):210-216.

APPENDIX D: Adverse Events and Adherence Survey

4-Digit Identification Number:

Date:

- Screening administered by RN via phone call
- Screening is self-administered by participant via paper form

- Please list any new or worsening symptoms along with a brief description:

- Please review the list of common and uncommon symptoms and circle any that apply. A nurse will review this list to ask questions and discuss next steps with you:

Hunger	Fainting
Abdominal pain	Nausea
Fatigue	Vomiting
Weakness	Constipation
Mood changes	Diarrhea
Headache	Vision changes
Dizziness	

- Please describe the types of foods that you eat on a daily basis. Has this changed at all since starting our survey? If so, how?

- Please provide the following information on how you have been using Calcipotriene-Betamethasone Dipropionate cream.

- Days used in the last week:
- Applications per day:
- Time of application(s): morning afternoon evening before bed

- Please list all the medications and supplements that you have taken in the last week, and what days you have taken them:

- For those undergoing intermittent fasting:
 - Number of days in the last week that you consumed calories outside of the 9 am – 5pm window:
 - Number of days in the last week that you submitted a photo of your first and last calorie:

- To be filled out by RN only: Please provide details on discussion with the participant and list any next steps or recommendations provided:

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