A Pilot Study Exploring the Anti-Inflammatory Effects of Time-Restricted Eating in Control and Psoriasis Subjects

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Abstract

Background: Psoriasis is a chronic inflammatory disease associated with multiple comorbidities, including metabolic syndrome and cardiovascular disease. Although specific dietary interventions, such as intermittent fasting and caloric restriction, have been shown to ameliorate inflammation and promote weight loss, the effect of these interventions independent of weight loss remains unclear. Time-restricted eating (TRE), a type of intermittent fasting, limits the daily eating window to a fixed number of hours. Recent studies suggest TRE may improve immune function in individuals with metabolic syndrome and cardiovascular risk factors. A crucial advantage of TRE over other investigated dietary restriction strategies is its reported high adherence rate, making it a more feasible intervention for long-term use. Therefore, exploring the effects of TRE on metabolic and immunological parameters in psoriasis is warranted.

Objective: This study was designed to evaluate the effects of short-term, isocaloric TRE, independent of weight loss, on immune cell function and serum metabolite profiles of volunteers with mild-to-moderate psoriasis compared to healthy control subjects.

Methods: This pilot case-control prospective study was performed on 10 healthy male participants and 10 age-, BMI-, and sex-matched individuals with mild-to-moderate psoriasis. All psoriasis subjects had stable disease and were being treated with topical therapies without any exposure to immunomodulatory biologics. This study was conducted at the National Institutes of Health Clinical Center. Immune profiles and metabolic status of participants were assessed at baseline and after 3 days of TRE following a daily 6-hour eating window and 18-hour fast.

Results: A total of 20 participants enrolled in this study between June 2021 and February 2023. Datasets of gene expression, surface and intracellular proteins, and metabolites are being generated from peripheral blood mononuclear cells, CD4+-enriched T-cells, and serum samples. The integrated bioinformatics analyses will be reported once the data analysis is completed.

Conclusions: This clinical protocol was designed to characterize the effects of TRE on psoriasis, independent of weight loss, by comparing immune cell regulatory responses between control and psoriasis subjects. More specifically, we aim to map the molecular pathways activated by TRE and assess how they affect immune cell composition, activation, and metabolism. Additionally, components of the metabolic response to isocaloric TRE are being explored. Insights into how dietary interventions impact metabolism and the immune system will enhance our understanding of pathogenesis of psoriasis and may reveal new therapeutic avenues for managing this inflammatory condition. Clinical Trial: ClinicalTrials.gov NCT04728165; https://clinicaltrials.gov/study/NCT04728165

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Abstract

Background:
Psoriasis is a chronic inflammatory disease associated with multiple comorbidities, including metabolic syndrome and cardiovascular disease. Although specific dietary interventions, such as intermittent fasting and caloric restriction, have been shown to ameliorate inflammation and promote weight loss, the effect of these interventions independent of weight loss remains unclear. Time-restricted eating (TRE), a type of intermittent fasting, limits the daily eating window to a fixed number of hours. Recent studies suggest TRE may improve immune function in individuals with metabolic syndrome and cardiovascular risk factors. A crucial advantage of TRE over other investigated dietary restriction strategies is its reported high adherence rate, making it a more feasible intervention for long-term use. Therefore, exploring the effects of TRE on metabolic and immunological parameters in psoriasis is warranted.

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Trial Registration:
ClinicalTrials.gov NCT04728165

Keywords: psoriasis; calorie restriction; intermittent fasting; time-restricted eating; TRE; immunoregulation; immunometabolism

Introduction

Psoriasis is a chronic inflammatory skin disease that affects approximately 2–3% of the US population. Beyond its skin and joint manifestations, psoriasis predisposes individuals to premature cardiovascular comorbidities,

primarily due to immune activation and systemic inflammation-induced atherosclerosis.[1] Skin-initiated immune activation through non-professional immune cells, including keratinocytes and fibroblasts, initiates and amplifies both innate and adaptive immune responses. These responses include the activation of monocytes/macrophages, neutrophils and their subsets (including low-density granulocytes), as well as effector T- cells (predominantly T_H1 and T_H17 subsets). These immune cells exacerbate local disease and propagate systemic sterile inflammation. The centrality of immune activation in psoriasis is reinforced by the therapeutic efficacy of targeted therapies, such as anti-TNF and anti-IL-17 treatments, which aim to modulate these immune responses.[2, 3]

The contribution of excess calorie consumption to the pathogenesis of psoriasis has been long debated. However, epidemiological and meta-analytic data support the notion that the incidence of obesity is higher in individuals with psoriasis and that the severity of psoriasis is positively correlated with an increased incidence of obesity.[4] The role of calorie excess in the pathophysiology of psoriasis is further strengthened by studies demonstrating the beneficial effects of calorie restriction on disease activity.[5, 6] Taken together, these data suggest that calorie intake may play a significant role in the pathophysiology of psoriasis and that dietary restriction interventions may contribute to disease amelioration by modulating inflammatory pathways.

Various dietary interventions, including prolonged fasting,[7, 8] intermittent fasting, fasting mimetic dietary supplementation, and calorie restriction per se, have all been shown to confer anti-inflammatory effects through mechanisms that are not yet fully understood.[9] The underlying biological mechanisms are complex, as the duration of fasting may act as an independent mediator, distinct from the effects of calorie restriction on inflammation. Moreover, distinguishing cell-mediated anti-inflammatory effects from other aspects of dietary interventions, such as changes in glucose sensitivity or weight loss, remains challenging. To explore these mechanisms, we designed a pilot study to examine the immune and metabolic responses in both control and psoriasis subjects to an isocaloric, short-term (3-day) time-restricted eating (TRE) regimen consisting of a 6-hour eating window and an 18-hour fasting period. The primary outcome of this study was to phenotype circulating immune cells in both cohorts before and after TRE, focusing on the composition and activation status of peripheral blood mononuclear cells (PBMCs), T-cell subsets (specifically T_H1 and T_H17), and other immune mediators implicated in psoriasis pathogenesis. In parallel, the interplay of metabolic changes is being assessed by quantifying glucose control and energy expenditure.

This study aims to provide mechanistic evidence of how TRE ameliorates inflammation, offering insight into its benefits for psoriasis management and whether its effects are independent of weight loss. Furthermore, this pilot study may serve as a proof-of-principle for future longitudinal investigations into the role of TRE in psoriasis symptomology and other inflammatory conditions.

Methods

Research Hypothesis

We aimed to investigate the impact of TRE in individuals with mild-to-moderate psoriasis compared with healthy controls. We hypothesized that a 6-hour eating window, followed by an 18-hour fast for 3 days, would lead to changes in sera metabolites and immune cell composition, activation status,

and cellular metabolism.

Primary Objective

The primary objective of this study was to evaluate the response to TRE in individuals with psoriasis compared to age-, sex-, and BMI-matched healthy controls. The primary outcome was to quantify the change in IL-17 secretion from activated $CD4^+$ T cells at baseline and the end of the study within both groups.

Secondary Objectives

The secondary objectives of this study were to compare the broader impact of TRE on immune cell regulatory pathways and immunometabolism. Additionally, we aimed to evaluate whether TRE modifies 24-hour glucose flux and glycemic excursions during meal tests. Energy expenditure was also compared at baseline and following three days of TRE. These measurements were taken over a 23-hour period in a metabolic chamber.

Study Design

This pilot study explored the immunometabolic features of a calorie restriction intervention by comparing the effect of TRE (6-hour eating/18-hour fast) to a more conventional dietary regimen (12-hour eating/12-hour fast). The 12/12 hour eating/fasting regimen was defined as the baseline for this study. Data was collected from subjects with mild-to-moderate psoriasis, and age (± 10 years) and BMI (± 5 kg/m^2)-matched healthy controls. As this is a small pilot study, only male participants were enrolled to eliminate the confounding variable of menstrual cycle phases on low-grade inflammation and insulin sensitivity.[10]

Participants were screened with a medical history and medicine review, a physical exam, blood tests, skin examination, nutritional evaluation, and resting energy expenditure measurements. Study participants were admitted as inpatients to the Metabolic Clinical Research Unit at the National Institutes of Health (NIH) Clinical Center, where they stayed in individual rooms for 5 days. The first and final 23 hours were spent in metabolic chambers to measure baseline and TRE effects on energy expenditure. The clinical protocol is schematized in **Figure 1**.

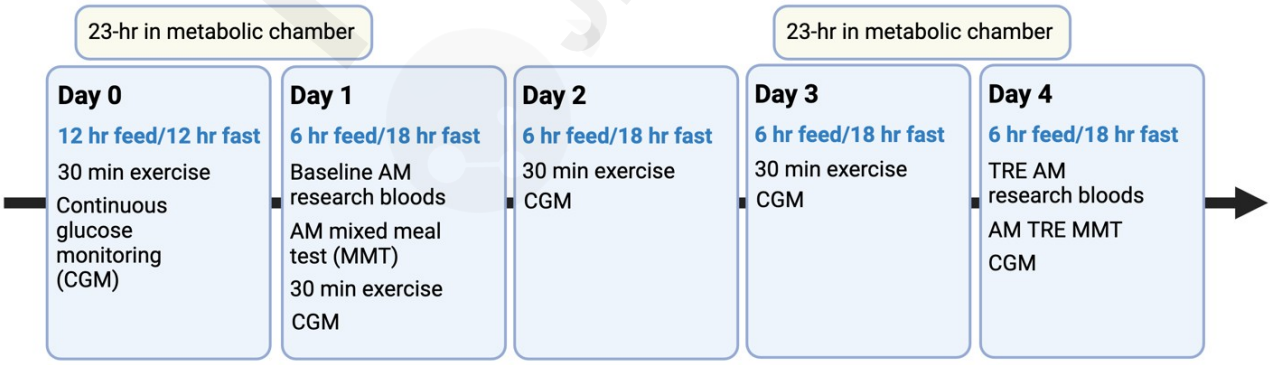

Figure 1: Schematic of clinical study (ClinicalTrials No. NCT04728165).

Study Intervention

The study was designed to explore the effects of TRE, using a 6-hour eating window and an 18-hour fasting window. Participants followed a weight-maintaining metabolic diet to meet 100% of their daily caloric needs throughout the inpatient visit. All foods and beverages were consumed in their rooms during designated hours of the day. On Day 0, participants ate during a typical 12-hour window from 08:00 to 20:00 and then fasted from 20:00 to 08:00 the following day. From Days 1-4, participants consumed all calories within a 6-hour eating window (08:00 - 14:00), followed by an 18-hour fast. Meals were provided at 08:00, 10:30, and 13:30, with participants given 30 minutes to consume each meal. Throughout the study, participants consumed a eucaloric diet consisting of 50% carbohydrate, 35% fat, and 15% protein. Each meal provided 33% of the participant's estimated daily energy requirements. Energy needs for the metabolic diet were calculated based on the resting energy expenditure measured at the screening visit and an activity factor of 60%. Participants had access to water throughout the study intervention.

Blood samples for immune and metabolic measurements were taken via intravenous catheter on Day 1 and Day 4. Participants wore a continuous glucose monitor throughout the 5-day inpatient stay. Liquid mixed meal tests (MMT) were conducted on day 1 (baseline) and day 4 (after 3 days of TRE). On MMT days, participants consumed a liquid meal for breakfast.

This study has been registered on clinicaltrials.gov (NCT04728165). This study was approved by the National Heart, Lung, and Blood Institute (NHLBI) Institutional Review Board (IRB), and participants signed informed consent prior to participation.

Recruitment, Eligibility, and Randomization

A total of 10 male participants, aged 18 to 80, with mild-to-moderate active psoriasis (measured by PASI score), enrolled in the study. Ten healthy subjects within the same age range (± 10 years) and BMI (± 5 kg/m^2) were also enrolled in the control group. The inclusion and exclusion criteria are outlined in **Textbox 1**.

Textbox 1. Inclusion and exclusion eligibility criteria for study participation.

Inclusion criteria:

- Males between the ages of 18 and 80 with mild-to-moderate active psoriasis, as determined by PASI score.
- Age- (± 10 years) and BMI- (± 5 kg/m^2) matched male subjects for inclusion in the control group.
- Ability to provide informed consent.
- Willingness and ability to participate in study procedures.

Exclusion criteria:

- A Psoriasis Area and Severity Index (PASI) score above 12.
- Treatment with systemic biologic immune modifying agents within the last two months.
- Currently receiving treatment for allergies or other inflammatory diseases.
- Has taken Vitamin B or tryptophan supplementation within two weeks of participation.
- Unwillingness/inability to provide informed consent.
- Individuals with a known history of type 1 and 2 diabetes mellitus or other metabolic conditions that would interfere with study parameters, including chronic kidney disease, chronic liver disease, or history of hypoglycemia.
- Use medications that would interfere with study parameters, including anti-hyperglycemic medications, systemic steroids, adrenergic-stimulating agents, and/or other medications known to affect sleep, circadian rhythms, or metabolism.
- Caffeine consumption in excess of three 8 oz cups per day.
- Factors affecting circadian rhythm, such as overnight shift work, irregular sleep and/or eating schedules, or regularly fasting for more than 15 hours/day.
- Regular use of tobacco product(s) within the last 3 months.
- Consuming more than three servings of alcohol per day.
- Engagement in competitive sports training.
- Moderate to severe claustrophobia.
- Unstable weight, with more than 5% change in body weight in last 3 months.
- Food allergies or intolerances or dietary patterns that would prohibit consumption of the metabolic diet or mixed meal test.

Study Interventions

The participants were required to fast for 12 hours prior to the screening visit, during which fasting energy expenditure was measured using the ventilated hood technique. This assessment was used to calculate isocaloric diets for each individual, which they followed during the 12/12 and 6/18 hour eating/fasting cycles.

On admission to the metabolic unit on Day 0, a continuous glucose monitor was placed following an initial breakfast meal. Total energy expenditure was determined by indirect calorimetry during a 23-hour stay in the respiratory chamber. Participants entered the respiratory chamber after breakfast on Day 0 and Day 4. At 08:00 on Day 1, blood samples were drawn for immune parameter studies. Following this, participants underwent a mixed meal test at breakfast after completing the 12/12 feeding-fasting period (Day 1) to measure metabolic hormones and sera metabolites.

Participants then initiated the isocaloric 6/18 hour eating-fasting cycle for 3 days. On Day 4, after

breakfast, they entered the respiratory chamber again for a 23-hour analysis to assess the potential metabolic effects of the TRE protocol. On the following morning (Day 5), blood samples were drawn at 08:00 for immune parameter studies after completing the 3rd 18-hour fast. While still in the respiratory chamber, participants underwent a final mixed meal test to assess the metabolic features of TRE. The study was completed once participants exited the chamber.

Summary of Tests and Calculations:

Anthropometrics: Participant weight and height were measured on Day 0. Daily weight measurements were subsequently obtained from Day 1 to Day 4.

Metabolic Cart – Resting Energy Expenditure (REE): REE was measured to assess basal energy requirements for designing the eucaloric diets for each study participant. Measurements were performed in the morning after a 12-hour fast using indirect calorimetry with the ventilated hood technique.[11]

Mixed Meal Test (MMT): After a 10-12 hour overnight fast, one intravenous catheter was placed in each arm for blood draws upon arrival in the morning. A liquid meal (Boost Plus) was provided to meet 33% of the estimated daily calorie requirements. Blood samples were obtained at 0, 10, 20, 30, 40, 50, 60, 90, and 120 minutes to measure plasma glucose, serum insulin and C-peptide, and triglyceride concentrations.[12]

Respiratory Chamber: Total body energy expenditure was assessed in an in-room metabolic respiratory chamber over 23 hours on Day 0-1 and Day 3-4.[13] In this isolation chamber, resting and sleeping energy expenditure, the thermic effect of food,[14] and the energy cost of physical activity can be assessed.[15] Blood samples were obtained through an isolette system, allowing direct nursing contact with the subject. Telemetry and a nurse call were available to ensure subject safety. A 24-hour urine specimen was collected while in the chamber to measure changes in urea and nitrogen levels; a random urine creatine sample was also collected.

Respiratory chamber measurement periods were approximately 23 hours, and data were extrapolated to represent 24-hour periods by assuming the mean of the measured periods accurately represented the full 24-hour period. The formula used to calculate energy expenditure was as follows:

$$\textbf{Energy expenditure (kcal)} = 3.88 \times VO_2\,(L) - 0.32\,(L/g) \times Kexcr\,(g) + 1.08 \times VCO_2\,(L) - 1.57 \times N\,(g)$$

VO_2 and VCO_2 are the volumes of oxygen consumed and carbon dioxide produced, respectively. N refers to the 24-hour urinary nitrogen excretion.

Sleeping energy expenditure was determined as the lowest energy expenditure over a continuous 180-minute period between 00:00 and 06:00.

Continuous Glucose Monitoring: Participants wore FDA-approved continuous glucose monitors (CGMs) during their inpatient admission. The devices recorded real-time serum glucose levels approximately every 5 minutes. The system consisted of a small sensor, transmitter, and handheld receiver (roughly the size of a pager). The sensor was inserted with a small introducer needle that was retracted after subcutaneously inserting the sensor. The transmitter, attached to the sensor, sent the measured glucose readings to the receiver. The data stored in the receiver was uploaded to a server for future analyses. To compare the change in 24-hr glycemic profiles, glucose data from Day

0 at 12:00 will be compared to data from Day 4. A CGM R package was used to calculate active wear time, wear days, percent wear days, and glycemic metrics, including average blood glucose, time in range, standard deviation, coefficient of variation, and mean amplitude glucose excursion. [16, 17]

Metabolic Analyses: Fasting concentrations of glucose, insulin, C-peptide, and triglycerides were measured in serum using the Roche Cobas 6000 analyzer (Roche Diagnostics, Indianapolis, IN). Hemoglobin A1c (HbA1c) was measured using the HPLC D10 instrument (Bio-Rad, USA).

Outcome Measures

The primary outcome was to quantify IL-17 secretion from T cell receptor-activated $CD4^+$ T cells isolated from samples collected on Day 1 and Day 4. The delta (change) in IL-17 secretion was compared using a two-tailed paired t-test. IL-17 secretion in response to TRE was compared between the two cohorts using a two-tailed, two-sample t-test in each study group. Transcriptomic and protein changes of PBMCs will be assessed using high-throughput multimodal platforms, including single-cell RNA sequencing (scRNA-seq), Cellular Indexing of Transcriptomes and Epitopes sequencing (CITE-seq), Cytometry by Time-Of-Flight (CyTOF), and flow cytometry. Analysis of glucose levels across the study and the metabolic rates were compared using paired two-tailed t-tests (within the groups) or unpaired two-tailed t-tests (between groups). A *P* value of <0.05 was considered statistically significant.

Sample Size Calculations and Statistical Analyses

This is a pilot study as there are no published data on TRE in either healthy control or psoriasis subjects on which to base calculations for the number of subjects required to uncover distinct effects on IL-17 cytokine release. Hence, to justify sample size and facilitate power calculations for 10 subjects per group, we referred to data from a previous fasting study in which isolated $CD4^+$ T cells were analyzed in 13 healthy control subjects at the NIH Clinical Center (clinicaltrials.gov - NCT02719899). In that study, the mean and standard deviation for the paired refed-fasting differences in IL-17 release were 187.1 pg/ml and 398.79 pg/ml, respectively.[8]

For the first primary objective, our computations for change from baseline IL-17 secretion in psoriasis patients assumed the standard deviation from the aforementioned fasting study. Using a two-tailed paired t-test with $\alpha=0.05$ and $n=10$, we estimated 80% power to detect a clinically significant change of 396.36 pg/ml or greater. To compare the change in IL-17 secretion between control and psoriasis patients, we assumed a 187.1 pg/ml change from baseline in controls (the value observed in the fasting study). With a two-tailed paired t-test with $\alpha=0.05$ and $n=10$ for the 1:1 matched subjects, the study would have 85% power to detect a 209.26 (396.36 – 187.1) pg/ml or greater difference between the psoriasis and control groups in IL-17 secretion from baseline. For these computations, we assumed a standard deviation of 199.4 pg/ml for the paired differences in IL-17 secretion from baseline between matched psoriasis and control subjects (half the standard deviation for controls in the fasting study).

Therefore, we requested approval to enroll up to 15 healthy control subjects and 15 mild-to-moderate psoriasis subjects for this pilot study, with the goal of having at least 10 subjects complete the study in each group. The primary intention-to-treat (ITT) analysis will include data from non-completers with conservative imputation of missing values (assuming no change from baseline in IL-17

secretion).

Dissemination of Project Findings

The findings of this study will be disseminated through various channels to reach a diverse audience. To engage the dermatology clinical community, we aim to share our results at (inter)national congresses focusing on dermatology and psoriasis. Additionally, our findings will be disseminated to the scientific communities focused on immunology and metabolism by publishing our findings in peer-reviewed journals germane to those fields. We seek to engage the patient community through potential collaborations with the National Psoriasis Foundation and via laypeople summary of the findings. Finally, we want to reach the general public by communicating the key results through social media platforms.

Results

Patients enrolled in the study from June 2021 through February 2023. scRNA-seq, CITE-seq, and CyTOF were performed in 2024. Data analysis is currently being performed concurrently with sera metabolomics. We aim to publish and share our findings by 2026.

Discussion

In psoriasis, the major circulating immune cell lineages operational in the disease pathophysiology include neutrophils, low-density granulocytes, monocytes, and $CD4^+$ T cells.[18-20] This study was designed to explore the gene regulatory and metabolic pathways altered in most of these cells, except for neutrophils, which are excluded in the polymorphonuclear cell fraction isolation protocol. Including a control group will allow us to evaluate whether the immune effects of TRE are more pronounced in an inflammatory disease cohort compared to individuals without baseline inflammation.

The primary outcome of this study, aimed at determining T_H17 immune responsiveness through IL-17 secretion, was performed in negatively selected T cell receptor-activated $CD4^+$ T cells. As the samples were paired (baseline and post-TRE), these $CD4^+$ T cells were also analyzed for changes in intracellular and serum steady-state metabolite levels. This analysis will help characterize whether TRE evokes systemic metabolite changes that influence $CD4^+$ T cell signaling and provide insights into how TRE modulates intracellular metabolic pathways.

From an unbiased discovery perspective, high-throughput multimodal technologies, including scRNA-seq, CITE-seq, CyTOF, and flow cytometry, will be analyzed and integrated [21] to explore the effects of TRE in both healthy control and psoriasis subjects. These analyses will offer crucial insights into how TRE exerts anti-inflammatory effects across different immune cell populations in PBMCs.

Finally, this pilot study was designed to dissociate the effects of weight loss and/or glucose sensitivity from the direct immunomodulatory effects of TRE. The robustness of the eucaloric study design will be determined by changes in weight, continuous glucose monitoring, and energy expenditure as measured by indirect calorimetry.

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Conflicts of Interest

None declared.

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Supplementary Files

Figures

Untitled.