The Effects of Modified Intermittent Fasting in Psoriasis (MANGO): a two-arm pilot randomized controlled open cross-over study

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Submitted to: JMIR Research Protocols
on: December 10, 2020

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Abstract

Background: Psoriasis is a complex disease associated with multiple comorbidities, including metabolic syndrome and leaky gut syndrome. Dietary lifestyle interventions have been reported to affect the disease in terms of lesional severity. It remains unclear how diets affect these comorbidities and the general health in psoriasis patients. Modified Intermittent Fasting (MIF) on 2 non-consecutive days has shown beneficial effects on metabolic parameters. A significant advantage of MIF over the currently investigated dietary changes is its feasibility.

Objective: Here, we aim to study the effects of MIF on skin, gut and metabolic health in psoriasis patients.

Methods: A two-arm pilot prospective cross-over randomized control trial (RCT) will be performed in 20 patients with psoriasis as a pilot study. Patients will be randomized 1:1 to either start with MIF and subsequent regular diet for 12 weeks each or to start with regular diet and subsequent MIF for 12 weeks each. The following parameters will be assessed: demographics, disease phenotype, medical and familial history, psoriasis severity, dermatology-specific and general quality of life, nutritional and physical habits, mental and intestinal health, intestinal and cutaneous integrity, inflammatory and metabolic markers, and satisfaction.

Results: The aim is to uncover the effects of MIF on psoriasis severity and gut health integrity through clinical and molecular investigation. More precisely, we want to map the evolution of the different markers in response to MIF as compared to the regular diet, such as psoriasis severity, permeability and inflammation.

Conclusions: Understanding how dietary lifestyles can affect epithelial lineages such as the skin and gut, will greatly improve our understanding on the development of psoriasis and may pose a non-pharmacological venue for treatments. Clinical Trial: ClinicalTrials.gov, NCT04418791. Registered June 5 2020, https://clinicaltrials.gov/ct2/show/NCT04418791. Current protocol date/version: May 20 2020

(JMIR Preprints 10/12/2020:26405)
DOI: https://doi.org/10.2196/preprints.26405

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Title: The Effects of Modified Intermittent Fasting in Psoriasis (MANGO): a two-arm pilot randomized controlled open cross-over study

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Abstract:

BACKGROUND: Psoriasis is a complex disease associated with multiple comorbidities, including metabolic syndrome and leaky gut syndrome. Dietary lifestyle interventions have been reported to affect the disease in terms of lesional severity. It remains unclear how diets affect these comorbidities and the general health in psoriasis patients. Modified Intermittent Fasting (MIF) on 2 non-consecutive days has shown beneficial effects on metabolic parameters. A significant advantage of MIF over the currently investigated dietary changes is its feasibility.

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RESULTS: A total of 24 participants have been enrolled in the study. The final visit is foreseen for June 2021.

CONCLUSIONS: The aim is to uncover the effects of MIF on psoriasis severity and gut health integrity through clinical and molecular investigation. More precisely, we want to map the evolution of the different markers in response to MIF as compared to the regular diet, such as psoriasis severity, permeability and inflammation. Understanding how dietary lifestyles can affect epithelial lineages such as the skin and gut, will greatly improve our understanding on the development of psoriasis and may pose a non-pharmacological venue for treatments.

TRIAL REGISTRATION: ClinicalTrials.gov, NCT04418791. Registered June 5 2020, https://clinicaltrials.gov/ct2/show/NCT04418791. Current protocol date/version: May 20 2020

Keywords: Modified Intermittent Fasting, psoriasis, leaky gut, permeability, gut-

skin axis, dietary intervention, epithelial integrity, chronic skin disease, intermittent fasting

INTRODUCTION

Psoriasis is a prevalent and chronic skin disease characterized by red, scaly and thickened skin lesions. The extent of the lesions determines the severity of the disease, commonly defined by the Psoriasis Area and Severity Index (PASI). The disease has a significant impact on quality of life (QoL) [1]. Currently, no cure is available, and the disease is mainly treated symptomatically.

Psoriasis is a complex and multifactorial disease that remains to be understood more thoroughly. Though genetic factors such as polymorphisms in *PSORS1-9, IL12B, IL23R and IL28RA* play a role [2], disease development and severity is also heavily affected by factors such as obesity, stress and smoking [3]–[11]. Our recent understanding of its pathophysiology has led to the development of drugs targeting disease-mediating cytokines such as Tumour Necrosis Factor alpha (TNF-α), Interleukin (IL)-17, and the subunits of IL-23 p40 and p19. Interestingly, the same cytokines also play important roles in comorbidities associated with psoriasis [12], [13]. Indeed, the disease complexity is evident from the associated physical and mental comorbidities, including cardiovascular diseases, metabolic syndrome, depression and leaky gut syndrome [14], [15], [24], [25], [16]–[23]. The latter is especially interesting, since it is characterized by an impaired intestinal barrier, and hence shows parallels with psoriatic skin which is also characterized by an impaired cutaneous barrier. The link between the gut and skin has been postulated several times and has been termed gut-skin axis [26], [27]. In the psoriasiform ‘imiquimod’ murine model, we have shown that gut-mediated inflammation drove the extent of the cutaneous lesions, mediated by the production of type I interferon beta (IFN-β) [28],

underscoring that gut health can affect skin health. In humans, intestinal permeability in psoriasis has been reported previously [24], [29], [30], underscoring the existence of an aberrant gut-skin axis in the disease as well.

The effect of dietary interventions has not been investigated in psoriasis related to this gut-skin axis, as the focus has mainly been on the skin only. Indeed, different studies have been conducted to investigate the effects of diets in psoriasis. For instance, a gluten-free diet was associated with a positive effect on psoriasis severity in patients who tested positive for gluten sensitivity [31], [32]. Another study investigating a diet aimed at weight loss showed a favorable outcome on psoriasis and the QoL, especially in patients with obesity [33]. This confirmed the findings of an earlier study that combined diet with physical exercise for weight loss [34]. Interestingly, treatment response can be improved by a very low-calorie ketogenic diet [35]. We also reported that treatment response to secukinumab, an IL-17 blocker for psoriasis treatment, may be negatively impacted by weight [36]. Recently, long-term weight loss was found favorable for psoriasis [37]. In 2019, a fasting diet related to Ramadan was conducted where participants had their meals and drinks, including water, only during evening hours [38]. This diet was found to be favorable for psoriasis, especially in patients treated with apremilast or mTOR inhibitors. More recently, an aggressive ketogenic weight-loss program led to a significant reduction in disease severity in drug-naive psoriasis patients who were overweight or obese [39]. Despite the positive effects of dietary changes on psoriasis outcomes, feasibility for daily implementation and effectiveness heavily depend on adherence. Gibson and Sainsbury propose strategies to increase adherence,

including avoiding overcompensation of caloric restrictions and tailoring to the individual's needs [40]. Here, we aim to investigate the effects of modified intermittent fasting (MIF), more specifically the 5:2 diet. In this diet, participants restrict their caloric uptake to 500 kilocalories (kcal) on 2 non-consecutive days per week. MIF has been associated with positive outcomes on plasma insulin levels, fat-to-lean ratio and other cardiovascular disease risk factors [41]–[44], yet its effects on psoriasis and gut health remains to be investigated. It has a successful adherence rate as it reduces the drive to overcompensate the calorie-restriction and allows the individual to incorporate the calorie-restricting days to their own scheme (tailored), reflecting the conditions postulated by Gibson and Sainsbury for optimal adherence [40].

Here, we present the study protocol of the study entitled "Modified Intermittent Fasting in Psoriasis (MANGO)": a randomized controlled open cross-over clinical trial to investigate the effects of a dietary intervention on the gut-skin axis in patients with psoriasis. The MANGO study will provide mechanistic evidence to inform whether there is a link between gut health and psoriatic lesions and give us insight in the benefit of MIF in psoriasis management and a consequent landmark shift in the holistic view of a chronic skin disease.

METHODS

We aim to investigate the impact of a MIF diet in patients affected by mild psoriasis on skin and gut health based on various markers. The main hypothesis is that a 5:2 diet over the course of 12 weeks will improve skin lesions and gut health biomarkers, in comparison to a standard diet. This study has been

registered on clinicaltrials.gov (NCT04418791) and has been approved by the ethics committee of the Ghent University Hospital (B6702020000141). The trial will be conducted according to the Declaration of Helsinki.

Primary objective

Comparison of MIF with a standard diet in terms of the proportion of patients obtaining an improvement in absolute PASI score from baseline, during or at the end of the 12 weeks post-intervention to prove superiority of MIF.

Secondary objectives

Comparison of MIF with a standard diet, during or at the end of the 12 weeks post-intervention in the following aspects:

- Differences in total body fat, weight, BMI, and/or waist circumference during and after intervention to baseline
- Differences in inflammation markers in serum and/or skin during and after intervention to baseline
- Differences in metabolic markers in serum and/or skin during and after intervention to baseline
- Differences in permeability markers in serum, skin, gut and/or feces during and after intervention to baseline
- Correlation to dietary intake and/or disease severity
- Score of subject’s rating of satisfaction on intervention

Finally, the number of subjects who completed the study or single intervention window successfully will also be assessed to give us insights about the feasibility of the diet.

Study design

Open randomized controlled cross-over clinical trial to test the effects of MIF on the gut-skin axis in 20 adults with psoriasis. The total study duration is 34 weeks: 2 moments are included as baseline prior to randomization (week 0 and 2). Randomization is performed the Research Electronic Data Capture (REDCap) software's randomization module upon inclusion. Post-randomization, patients are assigned to either the intervention or control arm. This study is a cross-over design, and patients will switch arms at week 14 (Figure 1). Evaluations include clinical, biochemical and patient reported outcomes. Intermediate time points are included at weeks 8 and 20. Each subject will be in the study for a total of 26 weeks, with a single follow-up at week 34 after completing the second arm. The entire trial will run for 12 months, with a recruitment period of 3 months.

Recruitment, eligibility and randomization

Subjects are patients who attend the PsoPlus clinic at the Department of Dermatology at the Ghent University Hospital or who are willing to attend the PsoPlus clinic for the study visits. An additional call will be launched through the Flemish Psoriasis League for people with psoriasis to be screened and enrolled. A recruitment target of maximal 30 adult subjects will be recruited through consecutive sampling. Subjects should have a clinical diagnosis of mild psoriasis vulgaris. Mild psoriasis is defined as a score of 10 or less based on PASI. Eligibility criteria are listed further in Table 1. Subjects who meet any of the exclusion criteria at the time of enrollment or during the study period, will be excluded from study participation. Subjects will be allocated in a 1:1 manner to the control or intervention arm, using stratified randomization with variable permuted blocks with concealment of allocation based on age, gender and BMI, with a maximum of 15 subjects per arm.

Study interventions

Upon inclusion, subjects are expected to record their dietary and exercise habits for 2 full weeks using the MyFitnessPal app. Baseline measurements consists of two different time points: inclusion (week 0) and randomization (week 2), which will be averaged for analysis. Upon randomization, subjects are assigned to either the control or intervention arm in a 1:1 ratio. The intervention consists of a dietary intervention based on the 5:2 fasting diet. Subjects will perform MIF, where they will be asked to consume a total of 500 kcal in a window of 6 hours or less from 8:00 am till 2:00 pm, twice per week on 2 non-consecutive days. Subjects will receive a leaflet with examples of what 500 kcal constitutes. This intervention will last for 12 weeks, from randomization. The control arm resembles the baseline period where subjects can eat without restriction, for 12 weeks. A digital food diary will be completed using the MyFitnessPal app and subjects are asked to use the TARGID tag [45] present in the app's database. Subjects are expected to record their dietary and exercise habits twice a week through the MyFitnessPal app (on the fasting days in the intervention arm). The Food Frequency Questionnaire (FFQ) will be recorded during all visits to assess for any dietary changes. Clinical evaluation will be performed during PsoPlus consultations held at the Department of Dermatology at the Ghent University Hospital by the treating dermatologist and specialized nurse. Questionnaires regarding quality of life are completed in the waiting room prior to the consultation; questionnaires regarding dietary and exercise habits are completed at home by the patient. Demographic and clinical data will be collected, in addition to serum, skin (via tape stripping), feces, and data through the app MyFitnessPal, and questionnaires for patient-reported outcomes (Table 2).

Outcome measures

Table 2 lists the parameters per study visit. During the study, data on demographics will be collected including age, gender, and medical and familial

history. Furthermore, the disease phenotype will be assessed and psoriasis severity will be evaluated by an independent assessor. In addition to psoriasis-related parameters, the clinical assessment will include metabolic parameters such as weight, waist circumference, BMI, and total body fat. Lifestyle habits will be registered: patients will keep a diary twice a week their diet in the online app MyFitnessPal (MFP); in the intervention arm this will be done on the fasting days. General diet and physical exercise habits will be recorded via the Food Frequency Questionnaire (FFQ) and the International Physical Activity Questionnaire (IPAQ), respectively. Questionnaires will also be used to evaluate quality of life and mental health, including Dermatology Life Quality Index (DLQI), EuroQol-5 Dimension-5 Level (EQ-5D-5L), Hospital Anxiety and Depression Scale (HADS), Beck's Depression Index (BDI), Perceived Stress Scale (PSS), and a Visual Analogue Scale (VAS) for satisfaction.

Cutaneous barrier integrity will be checked through the measurement of transepidermal water loss (TEWL) at 2 different body sites: one perilesional and one non-lesional site. These will be documented to ensure measurement at the same body sites throughout the study.

Intestinal barrier integrity will be assessed in 2 serological and fecal samples. Permeability markers zonulin, claudin-3, Ileal Fatty Acid Binding Protein (I-FABP) will be quantified in serum, and calprotectin (S100A8/S100A9) will be measured in both serum and stool samples. Participants will also be asked to report on intestinal symptoms based on the Dutch questionnaire for Irritable Bowel Syndrome (Prikkelbaar Darm Syndroom Questionnaire; PDSQ).

Serological levels of inflammatory and metabolic messengers such as IL-6, TNF-

alpha, leptin and adiponectin will be measured in serum and skin. The latter will be collected through skin tape stripping at the same body sites where TEWL measurement is performed.

Finally, microbiome sampling will be performed through cutaneous and fecal samples for future follow-up projects.

Study visits will be planned on the fasting days and participants will be scheduled as such to account for circadian rhythm and reduce intra-individual variability.

Sample size calculations

The sample size was determined by power analyses and available study budget. Sample size was calculated with the power calculator of masc.org.au, applying a two-tailed t test with alpha at 0.05 and power at 0.80. The predicted effect size was estimated based on a prior study of intermittent fasting [38]. We estimated that at a two-sided p-value of 0.05 and with 80% power, we would need 16 participants to complete the study to detect a within-individual effect size of 0.75 standard deviations. We estimated a dropout rate of 20%, leading to a sample size of 20 subjects. To minimise drop-outs, recruiting personnel will emphasize on considering the requirements of the study before enrolling. In cases of dropouts, extra subjects will be recruited to maintain statistical power.

Statistical analysis

The primary aim is to explore the effect of MIF on mild psoriasis. Secondary outcomes include changes from baseline to selected time-points during and post-intervention in QoL, body weight, BMI, total body fat, inflammation and metabolic markers in serum

and skin, and permeability markers in serum and feces. Furthermore, differences in dietary and physical exercise habits will be investigated. Comparisons will be made within a single arm (paired) and between both arms (unpaired). Chi-squared test and Mann-Whitney U-test will be used to compare groups and regression-binary logistics will be performed with identified independent variables to determine their influence on the outcome. Demographics will be analyzed as confounding variables. Cytokine data that are not normally distributed, and differences in cytokine levels between groups will be analyzed using the non- parametric Mann-Whitney U test. Correlations will be assessed using Spearman's rho. For each group, we will use multivariate logistic regression modeling to detect associations between cytokine levels and the primary endpoint, and to adjust for confounding effects of age, sex, and the intervention. Cytokine data will be log transformed prior to use in multivariate models. Pre-existing differences between groups at baseline will be examined using a one-way analysis of variance featuring a factor for diet allocation. Significant differences emerging from these tests will be explored using appropriate post-hoc tests to adjust for multiple comparisons and isolate the source(s) of variance. In addition to these analyses at the group level, individual responses will also be closely examined for outliers that may affect interpretation. Further analysis, such as sub-group analysis, may also be conducted in light of patterns emerging in the final dataset. Baseline characteristics of participants who withdraw during the fasting intervention will also be compared against the final population using t-tests to assess tolerability. P-values will be reported to four decimal places with p-values less than 0.0001 reported as $p < 0.0001$. A p value < 0.05 will be considered statistically significant. Data analysis will be executed with SPSS 23.0 (SPSS Inc., Chicago, USA) and Graphpad Prism (San Francisco, USA).

Dissemination of project findings

The findings of this study will be disseminated by various means, determined by

the target audience. To reach the academic dermatology community, we will publish the results in a scientific international peer-reviewed dermatology journal and present our findings at (inter)national congresses with a focus on dermatology and psoriasis. The psoriasis patient community will receive info on the results through the National Psoriasis Foundation and the Flemish Psoriasis League, including a laymen summary of the findings. Lastly, we will reach the general public by communicating the main results through the research team's social media channels.

RESULTS

The study initiation was delayed due to the COVID-19 pandemic. Active recruitment of patients began in July 2020, and the first patient was included in October 2020. As of December 2020, we enrolled a total of 24 patients. The last patient last visit is foreseen in June 2021 and results are expected to be published December 2021.

DISCUSSION

Recently, psoriasis has been accepted to be a multi-morbid disease with a large impact from lifestyle factors. Obesity has been found to be an independent predictor for the development of psoriasis, and to be associated with disease severity [46]. A growing body of evidence suggests the existence of a gut-skin axis, which may be of importance in psoriasis as well, urging the need to address the question of how diet may affect the disease. To our knowledge, the MANGO study is the first comprehensive trial to investigate the effects of MIF on cutaneous, intestinal and mental health in a chronic skin disease.

We expect that the MIF intervention will have beneficial effects on the psoriatic

lesions and be associated with favorable changes in metabolic parameters. We anticipate to detect shifts in intestinal parameters that may be associated with skin improvement. In addition, the data generated from this trial will inform the design for future large scale trials to evaluate the presence and role of the gut-skin axis in psoriasis. The study additionally includes collection of cutaneous and fecal samples for future microbiome analysis, if the intervention proves beneficial.

To overcome the difficulty of diet-based interventions in terms of confounding factors and the small sample size, we have chosen the design of a prospective cross-over randomized trial. As such, each patient will be monitored over more than 6 months and serve as his/her own control. Another strength of this study is the combination of clinical, biochemical and patient reported outcomes for cutaneous, intestinal and mental parameters. Moreover, since some parameters can vary, the study includes two baseline points in order to assess normal variation. We opted to perform the pilot trial in a cohort of mild psoriasis who are not on systemic agents, to reduce any confounding effects of immunomodulators that may directly impact the outcomes. Lastly, since we introduced a restrictive time window to consume the 500 kcal on fasting days, we will be able to reduce confounding effects of the circadian rhythm [47]. A potential limitation includes health bias amongst subjects.

Results from this study may have multidimensional consequences and assets. On the one hand, beneficial effects of fasting may be potentially viewed as a non-pharmacological add-on treatment for psoriasis. A subset of psoriasis patients dislikes pharmacological treatments, and therefore opt to gain

additional control over their disease through a diet. On the other hand, evidence that a free intervention may have health benefits in patients requiring costly drugs such as biologics, may give rise to a moral dilemma: how do we define health responsibility in terms of lifestyle with the rising healthcare costs? This debate, applicable to many other (chronic) illnesses, is highly relevant and should not be postponed. It should take place in the near future, with a multidisciplinary panel in a transparent manner in order to cope with results from comparable trials.

To conclude, if patients with psoriasis tolerate MIF well and experience improvement, there is potential for the diet to be widely adopted by psoriasis sufferers in a sustainable manner. In addition, it provides a positive impact on their general health as this diet has already proven to be effective in obesity and seems to be effective in diabetes as well [48], two common comorbidities associated with psoriasis. As such, we may discern the importance of the gut-skin axis and use it to our advantage in the disease management of psoriasis.

List of abbreviations:

BDI: Beck Depression Index

BMI: Body Mass Index

BSA: Body Surface Area

DLQI: Dermatology Life Quality Index

DSM-5: Diagnostic and Statistical Manual of Mental Disorders Fifth edition

EQ-5D-5L: EuroQol 5 Dimensions 5 Level

FFQ: Food Frequency Questionnaire

HADS: Hospital Anxiety and Depression Scale

IL: Interleukin

IPAQ: International Physical Activity Questionnaire

MANGO: Modified intermittent fAstiNG in PsOriasis

MFP: MyFitnessPal app

MIF: Modified Intermittent Fasting

MUST: Malnutrition Universal Screening Tool

PASI: Psoriasis Area Severity Index

PDSQ: Prikkelbaar Darm Syndroom Quesionnaire (Irritable Bowel Syndrome Questionnaire)

PSS: Perceived Stress Scale

QoL: Quality of Life

TEWL: Trans Epidermal Water Loss

TNF: Tumour Necrosis Factor

VAS: Visual Analogue Scale

DECLARATIONS

Ethics approval and consent to participate

This study has been registered on clinicaltrials.gov (NCT04418791) and has been approved by the ethics committee of the Ghent University Hospital

(B6702020000141). The trial will be conducted according to the Declaration of Helsinki. Informed consent will be obtained verbally as well as in writing.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable. The results of the trial, however, will be published at the end of the trial in a journal.

Competing interests

The authors declare that they have no competing interests.

Funding

This project is funded by the Nutrition Team of the Ghent University Hospital and has been awarded an Early Career Research Grant by the National Psoriasis Foundation. These funding sources had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Authors' contributions

LG drafted the manuscript and designed the figures. NH, NM, SH, SDH and JL contributed to the writing of the manuscript. LG designed the trial in collaboration with NH, NM, SH and JL. All authors revised the final version of the article before submitting it.

Acknowledgements

Not applicable.

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TABLES

Table 1: Eligibility criteria

INCLUSION CRITERIA	EXCLUSION CRITERIA
• Between 18-70 years old • Clinically diagnosed psoriasis by a dermatologist • Predominantly present with psoriasis vulgaris • Present with PASI ≤ 10 at time of enrollment	• Present with type 1/2 diabetes mellitus • Present with a history of cardiac condition(s) • Present with comorbidities that cannot be combined with the intervention (e.g. cancer)

• Reported stable weight (< 5% weight loss/gain) for last 3 months • Be treated exclusively with topical treatment for psoriasis at the time of enrollment and throughout study • Able to give informed consent • Willing and able to comply with study procedure • Willing and able to use MyFitnessPal app to record diet during intervention period • Willing and able to attend all scheduled visits through the study period • Willing and able to provide blood, cutaneous and fecal samples as stated in the procedure • Willing to apply measures to prevent pregnancy throughout study period	• History of, or current eating disorder (anorexia, bulimia, etc.)* • Malnourished patients** • Present with gout • Be pregnant, having pregnancy plans, or breastfeeding • Use diuretics at time of sampling • Use of anti-, pre-, and/or probiotics in the last 3 months prior to enrollment or during the study period
**Screening via the Diagnostic and Statistical Manual Method for Mental Disorders Fifth edition (DSM-5) if indicated* ***Screening via the Malnutrition Universal Screening Tool (MUST) if indicated*	

Table 2: Study visits and parameters

PARAMETER	STUDY VISIT	*Screening*	*Visit 1 (BA1)*	*Visit 2 (BA2)*	*Visit 3 (IA1)*	*Visit 4 (IA2)*	*Visit 5 (IA3)*	*Visit 6 (FA)*	*Visit 7 (FU)*

S	TIMING		Week 0	Week 2	Week 8	Week 14	Week 20	Week 26	Week 34
CLINICAL	**General**	Gender Age Medical history	Medical history Familial history						
	Psoriasis	PASI	PASI BSA Phenotype	PASI BSA	PASI BSA	PASI BSA Phenotype	PASI BSA	PASI BSA	PASI BSA
	Metabolism	BMI*	BMI* Waist circumference Total body fat	BMI* Waist circumference Total body fat		BMI* Waist circumference Total body fat		BMI* Waist circumference Total body fat	BMI* Waist circumference Total body fat
	Quality of life		DLQI HADS BDI PSS VAS satisfaction PDSQ EQ-5D-5L	DLQI HADS BDI PSS VAS satisfaction PDSQ EQ-5D-5L	DLQI HADS BDI PSS VAS satisfaction PDSQ EQ-5D-5L	DLQI HADS BDI PSS VAS satisfaction PDSQ EQ-5D-5L	DLQI HADS BDI PSS VAS satisfaction PDSQ EQ-5D-5L	DLQI HADS BDI PSS VAS satisfaction PDSQ EQ-5D-5L	DLQI HADS BDI PSS VAS satisfaction PDSQ EQ-5D-5L
LIFESTYLE	**Diet**	MUST** DSM-5**	MFP FFQ	MFP FFQ	MFP FFQ	MFP FFQ	MFP FFQ	MFP FFQ	
	Physical activity		IPAQ			IPAQ		IPAQ	
BIOCHEMICAL	**Blood (serum)**		Inflammation markers Metabolic markers Permeability markers	Inflammation markers Metabolic markers Permeability markers	Inflammation markers Metabolic markers Permeability markers	Inflammation markers Metabolic markers Permeability markers	Inflammation markers Metabolic markers Permeability markers	Inflammation markers Metabolic markers Permeability markers	
	Skin (tape)		Inflammation markers TEWL Microbiome***	Inflammation markers TEWL Microbiome***	Inflammation markers TEWL	Inflammation markers TEWL Microbiome***	Inflammation markers TEWL	Inflammation markers TEWL Microbiome***	TEWL
	Gut (fecal)		Permeability markers Microbiome***	Permeability markers Microbiome***	Permeability markers	Permeability markers Microbiome***	Permeability markers	Permeability markers Microbiome***	

BMI based on weight measured with empty bladder To be used in screening procedure if indicated ***Stored until use in a follow-up project*

Abbreviations: BA: Baseline analysis; BDI: Beck Depression Index; BMI: Body Mass Index; BSA: Body Surface Area; DLQI: Dermatology Life Quality Index; DSM-5: Diagnostic and Statistical Manual of Mental Disorders Fifth edition; FA: Final analysis; FFQ: Food Frequency Questionnaire; FU: Follow-up; HADS: Hospital Anxiety and Depression

Scale; IA: Intermediate analysis; IPAQ: International Physical Activity Questionnaire; MFP: MyFitnessPal app; MUST: Malnutrition Universal Screening Tool; PASI: Psoriasis Area Severity Index; PDSQ: Prikkelbaar Darm Syndroom Questionnaire (Irritable Bowel Syndrome Questionnaire); PSS: Perceived Stress Scale; TEWL: Trans Epidermal Water Loss; VAS: Visual Analogue Scale

FIGURES

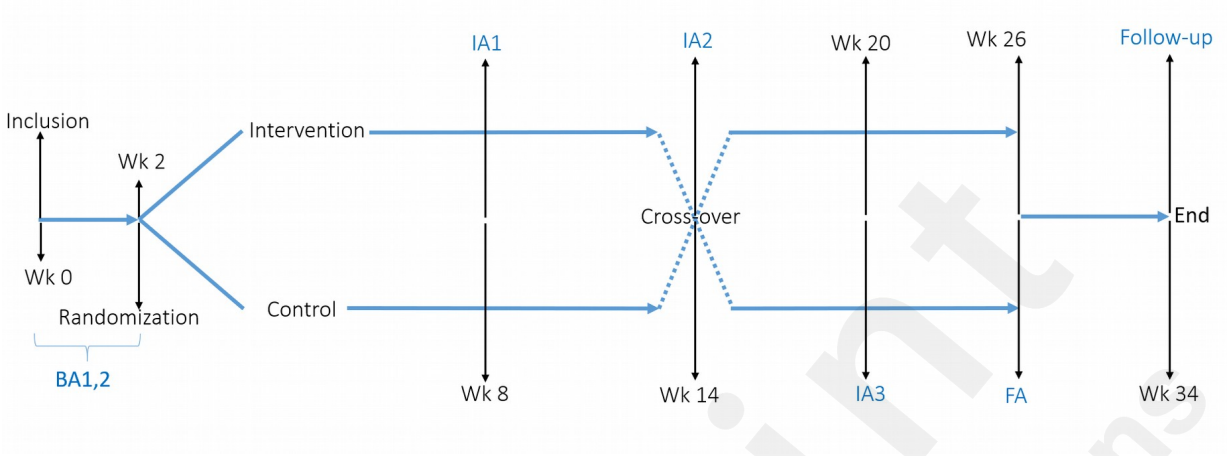


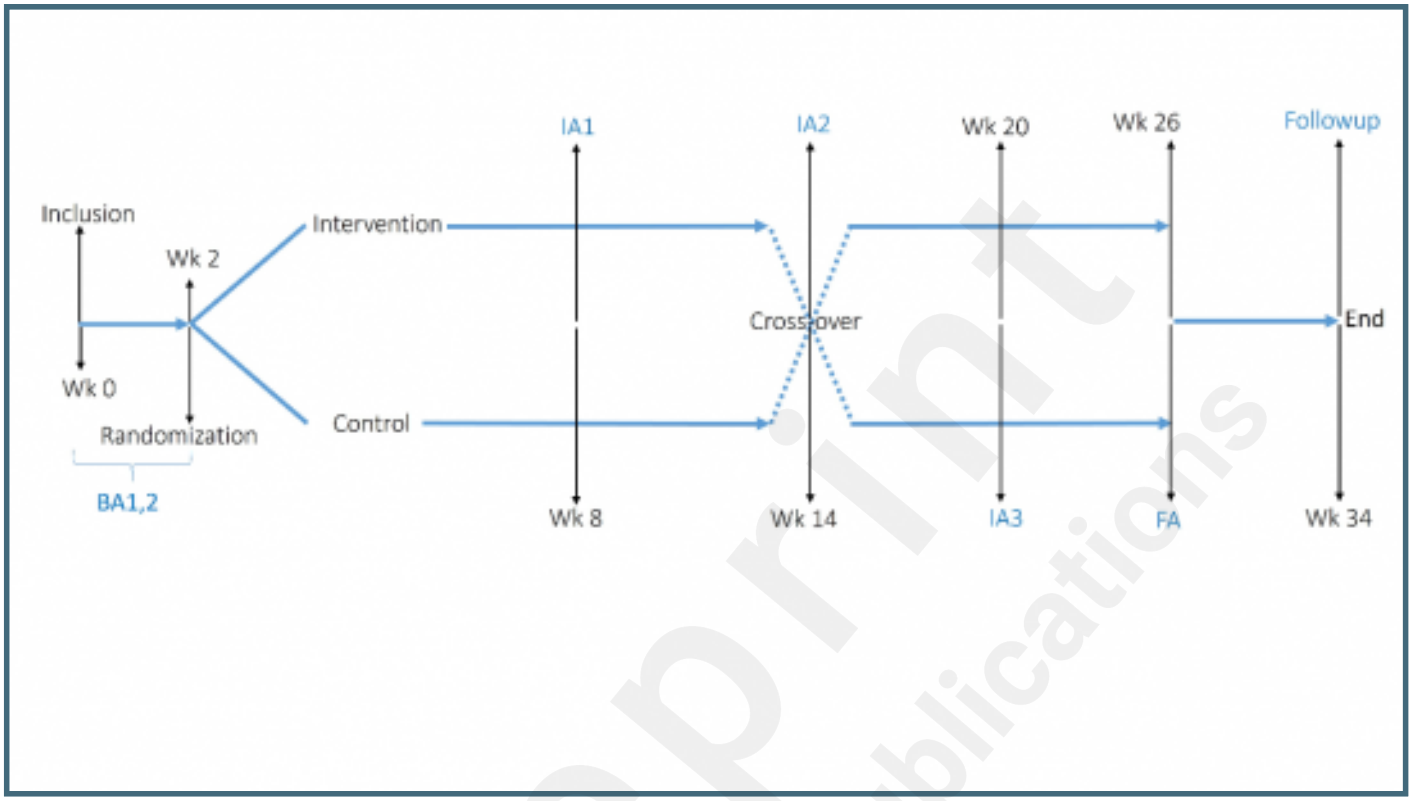
Figure 1: Open randomized controlled cross-over clinical trial to test the effects of modified intermittent fasting on the gut-skin axis in adults with psoriasis. Cross-over includes 12 weeks intervention and 12 weeks control period. Evaluations include clinical and biochemical parameters. Intermediate time points are included.

Supplementary Files

Untitled.
URL: https://asset.jmir.pub/assets/c903d8562537ff00ee8f961dd807bfbd.pdf

Figures

Open randomized controlled cross-over clinical trial to test the effects of modified intermittent fasting on the gut-skin axis in adults with psoriasis. Cross-over includes 12 weeks intervention and 12 weeks control period. Evaluations include clinical and biochemical parameters. Intermediate time points are included.



Multimedia Appendixes

Review from funding agency.
URL: https://asset.jmir.pub/assets/695fbf0e03b5c5369153669087cc6d81.pdf

CONSORT (or other) checklists

SPIRIT Checklist.
URL: https://asset.jmir.pub/assets/e9b5c883e299b5b14ba5ce309cf5b802.pdf

Existing Peer-Review Reports from Funding Agencies (for protocols/proposals only)s

National Psoriasis Foundation 'Early Career Research Grant' review.
URL: https://asset.jmir.pub/assets/40c557f7056c3d903dc897b3e17ced5c.pdf