Weight Loss is Associated With Sustained Improvement of Disease Activity and Cardiovascular Risk Factors in Patients With Psoriatic Arthritis and Obesity: a Prospective Intervention Study With Two Years of Follow-up

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Research article

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Abstract

**Background** Obesity is overrepresented in patients with psoriatic arthritis (PsA) and associated with increased disease activity. We have previously shown in 41 patients with PsA (Caspar criteria) and obesity (body mass index; BMI $\geq 33$ kg/m$^2$) that weight loss treatment with Very Low Energy Liquid Diet (VLED), 640 kcal/day during 12-16 weeks, followed by a structured reintroduction of an energy restricted diet resulted in a median weight loss of 18.6% and concomitantly a significant improvement of the disease activity in joints, entheses and skin.

The objectives of this follow-up were to study the effects of the weight loss treatment on disease activity in longer term (12 and 24 months) and to study the effects on cardiovascular risk factors.

**Methods** The patients were assessed with 66/68 joints count, Leeds enthesitis index (LEI), body surface area, blood pressure, BMI, questionnaires and fasting blood samples at the 12- and 24-month visits.

**Results** In total, 39 and 35 PsA patients attended the 12- and the 24-month visits, respectively. Median weight loss since baseline was 16.0 % (IQR 10.5–22.4) and 7.4% (IQR 5.1–14.0) at the 12- and 24-months follow-up. The 66/68 swollen/tender joints score, LEI, CRP and HAQ score were still significantly reduced at the 12- and 24-month visits compared to baseline. The number of patients with Minimal Disease Activity increased from 28.2% (11/39) at baseline, to 38.5% (15/39; p=0.008) and 45.7 % (16/35; p=0.016) at the 12- and 24-month visits.

The weight loss was also associated with improved levels of serum lipids, glucose and urate and the antihypertensive treatment was reduced or stopped in five patients during the follow-up.

**Conclusions** Weight loss treatment with VLED included in the program was associated with long-term improvement of measures of disease activity, function and markers of the metabolic syndrome after 24-months follow-up.

**Trial registration**

ClinicalTrials.gov identifier: NCT02917434, Registered September 28, 2016- Retrospectively registered.

https://clinicaltrials.gov/ct2/show/NCT02917434

**Background**

Psoriatic arthritis (PsA) is an inflammatory disease characterized by psoriasis, arthritis, enthesitis and dactylitis.[1] Obesity, diabetes, hypertension, hyperlipidemia and the metabolic syndrome (MetS) are overrepresented in both psoriasis and PsA [2–4] and the patients are at increased risk of cardiovascular morbidity.[5–9] Studies indicate that obesity may play a pathophysiologic role in psoriasis and PsA, since obesity is associated with an increased risk of developing these conditions. [10–13] Obesity is also associated with increased disease activity [14, 15] and poorer effect of treatment [16–19]. Although
several studies have shown a relation between obesity and disease activity, there is a lack of studies investigating the effects of weight loss in PsA.

We have previously in an open interventional study shown that weight loss treatment with Very Low Energy Diet (VLED) in 41 patients with PsA and obesity resulted in a substantial weight loss of median 18.7 kg (interquartile range: IQR 14.6–26.5) after six months, which was associated with significant positive effects on the disease activity in joints, entheses and skin. [20] Significant improvements were noted regarding number of swollen and tender joints, enthesitis, extent of psoriasis, C-reactive protein (CRP), pain, fatigue and physical function at six months observation. The number of patients with Minimal Disease Activity (MDA) increased from 29–54% (p = 0.002).[20]

Short term weight loss can however easily be regained. Moreover, the anti-inflammatory effects seen in our previous study could have been caused by, both metabolic effects due to energy restriction during the initial phase of rapid weight loss, as well as loss of adipose tissue and lessened production of pro-inflammatory cytokines and adipokines therein.

The primary aim of this follow-up was to study the association between weight loss and disease activity in longer term; 12 and 24 months. A secondary aim was to study the effects of weight loss on aspects of the MetS.

**Methods**

**Patients**

The patients were recruited from the departments of Rheumatology at Sahlgrenska University Hospital and the hospitals of Borås and Alingsås. Inclusion criteria were having PsA fulfilling the Classification for Psoriatic Arthritis (CASPAR) criteria, a body mass index (BMI) of 33 kg/m$^2$ or more, and age 25–75 years. [21] If treated with conventional synthetic and/or biologic Disease-Modifying Anti-Rheumatic Drugs (cs and/or bDMARDs), the treatment doses had to be stable and unchanged from three months prior to baseline until six months after baseline. After six months the patients were allowed to change immunomodulating therapy. Exclusion criteria were pregnancy, porphyria, epilepsy, type 1 diabetes, severe heart, kidney or catabolic disease, binge eating disorder, treatment with warfarin, lithionin or phenantoin, mental imbalance affecting participation, a history of a myocardial infarction, stroke, major surgery or trauma during the last three months, or being treated for cancer during the last five years. The patients’ treatments for hypertension, diabetes and hyperlipidemi were monitored and could be changed throughout the duration of the study.

All the patients of the study gave their written informed consent. The study was approved by the Regional Ethics Committee in Gothenburg and carried out in accordance with the Helsinki declaration.

**The intervention: weight loss treatment with Very Low Energy Diet (VLED)**
Weight loss treatment with VLED was provided at the Regional Obesity Centre of the Region Western Sweden at Sahlgrenska University Hospital, within a framework of medical follow-up, dietary advice and support during 12 months. The VLED treatment consisted of four doses of VLED per day, dissolved in cold or hot water and consumed as shakes or soups, providing a daily intake of 640 kcal, including recommended doses of vitamins, minerals and other essential nutrients (Cambridge Weight Plan Limited, Corby, UK). Depending on baseline BMI, < 40 or \( \geq 40 \) kg/m\(^2\), the strict VLED treatment was maintained during 12 or 16 weeks. After the strict VLED period, food was gradually reintroduced during a period of 12 weeks and each participant was given a personal dietary advise based on individual energy requirements for weight stability with a reduction of 30% to achieve further weight loss. After 12 months the patients were no longer followed at the Regional Obesity Centre, but at the departments of Rheumatology. In addition, all patients were seen by a physiotherapist at baseline and after six, 12 and 24 months and were instructed to engage in health-enhancing physical activity at least 150 minutes per week.

**Measures of assessment**

The patients were assessed at baseline and after three, six, 12 and 24 months. Body height was measured at baseline, and weight was measured at baseline and at every follow-up and BMI was calculated. Waist circumference was measured in standing position with a tape measure midway between the lower rib and iliac crest. Joints were examined with 66/68 swollen/tender joints count and entheses with Leeds enthesis index.[22] The extent of psoriasis was evaluated with Body Surface Area (BSA).[23] Quality of life related to psoriasis was assessed with the Dermatology Life Quality Index (DLQI). [24] The patients’ experience of global disease activity, pain and fatigue and the physician's evaluation of the patients’ global disease activity was assessed with Visual Analogue Scales (VAS). Activity limitations and function were assessed using the Health Assessment Questionnaire (HAQ) and Bath Ankylosing Spondylitis Functional Index (BASFI).[25, 26] Both the Disease Activity Score using 28 joint counts based on CRP (DAS28CRP) and the Disease Activity in PSoriatic Arthritis (DAPSA) score were calculated.[27, 28] Minimal disease activity (MDA) was defined as meeting five of the seven following criteria: tender joint count \( \leq 1 \), swollen joint count \( \leq 1 \), psoriasis BSA \( \leq 3\% \), patient pain VAS \( \leq 15 \) mm, patient global disease activity VAS \( \leq 20 \) mm, HAQ \( \leq 0.5 \) and tender entheseal points \( \leq 1 \).[29]

At the 24 month visit the questionnaire Patient Global Impression of Change (PGIC) was used, where patients are asked to rate their overall status from the start of the study using the following scale: (1) very much improved, (2) much improved (3) minimally improved, (4) no change, (5) minimally worse, (6) much worse, (7) very much worse.[30]

Blood samples were drawn from the patients in the morning after \( \geq 8 \) hours of fasting and analysed for haemoglobin (Hb), white blood cell count (WBC), platelet count (PLT), C-reactive protein (CRP), alanine transaminase (ALT), creatinine, urate, glucose, glycosylated hemoglobin (HbA1c), total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides (TG) using standard laboratory techniques at Sahlgrenska University Hospital.
Occurrence of MetS was defined as exhibiting three or more of the following five criteria [31]: 1 elevated waist circumference (≥ 80 cm for women and ≥ 94 cm for men), 2 elevated TG (TG ≥ 1.7 mmol/L or drug treatment for elevated TG), 3 reduced HDL (HDL < 1.3 mmol/L for women and < 1.0 mmol/L for men or drug treatment for reduced HDL), 4 elevated blood pressure (BP) (systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg or antihypertensive drug treatment), 5 elevated fasting glucose (plasma glucose ≥ 5,6 mmol/L or previously diagnosed type 2 diabetes).

**Statistical analyses**

Statistical analyses were made using SPSS Statistics version 25 (IBM, Chicago, USA). Descriptive statistics are presented as median and IQR. Wilcoxon Signed Rank Test was used to compare continuous related samples and McNemar’s test to compare categorical related samples. Correlations were calculated using Spearman’s correlation ($r_S$). All tests were two-tailed and $p \leq 0.05$ was considered statistically significant. Only the 39 and 35 patients who attended the 12- and 24-month visits respectively, were included in the statistical analyses.

**Results**

**Characteristics of the study population**

The number of patients and drop-outs at the study visits are given in Fig. 1.

In total, 46 patients with PsA were included and started VLED treatment, whereof 41, 39 and 35 patients attended the six, 12- and 24-month visits respectively. The 11 patients (8 women and 3 men) lost to follow-up during the whole study were significantly younger than the patients who continued in the study ($p = 0.005$). The demographics and the medication of the completers are shown in Table 1. Treatment with cs/bDMARDs was unchanged compared to baseline in 89% (31/35) at the 12-month visit and in 74% (26/35) at the 24-month visit.
Table 1
Age, sex and medication of the patients with psoriatic arthritis at baseline (BL) and the 12- months (M12) and 24-months (M24) visits.

|                | BL  (N = 39) | M12 (N = 39) | M24 (N = 35) |
|----------------|-------------|--------------|--------------|
| **Women, n(%)**|             | 25 (64.1)    | 21 (60.0)    |
| **Men, n(%)**  |             | 14 (35.9)    | 14 (40.0)    |
| **Age, years (IQR)** |   | 56 (49–63)  | 59 (51–56)  |
| **NSAIDs, n (%)** | 27 (69.2) | 25 (64.1)  | 21 (60.0) |
| **TNFi all, n (%)** | 15 (38.5) | 16 (41.0)  | 14 (40.0) |
| **TNFi in monotherapy** | 4 (10.3)   | 4 (10.3)   | 3 (8.6)   |
| **TNFi + csDMARD** | 11 (28.2) | 12 (30.7)  | 11 (31.4) |
| **Ustekinumab monotherapy, n (%)** | 1 (2.6) | 0 | 0 |
| **Secukinumab monotherapy, n (%)** | 0 | 1 (2.6) | 2 (5.7) |
| **csDMARD without biologic, n (%)** | 17 (43.6) | 16 (41.0) | 14 (40.0) |
| **Methotrexate** | 11 (28.2) | 11 (28.3) | 10 (28.6) |
| **Sulfasalazine** | 2 (5.1) | 1 (2.6) | 1 (2.9) |
| **Apremilast** | 1 (2.6) | 1 (2.6) | 2 (5.7) |
| **Methotrexate + Sulfasalazine** | 3 (7.7) | 3 (7.7) | 1 (2.9) |
| **Prednisolone, n (%)** | 3 (7.7) | 2 (5.1) | 2 (5.7) |
| **Anti-hypertensives, n (%)** | 17 (43.6) | 14 (35.9) | 14 (40.0) |
| **Lipid lowering therapy, n (%)** | 6 (15.4) | 5 (12.8) | 5 (14.3) |
| **Oral anti-diabetics, n (%)** | 1 (2.6) | 2 (5.1) | 2 (5.7) |
| **Allopurinol, n (%)** | 2 (5.1) | 2 (5.1) | 2 (5.7) |

csDMARD = conventional synthetic Disease Modifying Anti-Rheumatic Drug, IQR = inter-quartile range, NSAID = non-steroidal anti-inflammatory drug, TNFi = tumour necrosis factor inhibitor

Body weight and disease activity after 12 months
Totally 39 patients with PsA attended the 12-month visit. At baseline their median weight was 106.0 (IQR 93.5–112.5) kg and at 12 months 87.5 (80.6–95.5) kg (p < 0.001). In median, the patients had lost 16.1 (10.5–22.8) % of their baseline weight. In total, 77% (N = 30/39) of the patients had a weight loss of 10% or more compared to baseline, and 17.9% (N = 7/39) a weight loss of 5–10%. The majority of patients (34/39) had however regained some weight between the six- and 12-month visits, in median 3.9 (IQR 1.5–6.6) kg.

A majority of the disease activity variables were still significantly improved at the 12-month follow-up compared to baseline, including swollen/66 and tender/68 joints count, Leeds enthesis index, BSA, CRP, VAS for global health and fatigue, HAQ, BASFI, DAS28-CRP and DAPSA. Criteria for MDA was met by 28.2% (11/39) at baseline and 38.5% (15/39) at the 12-months follow-up (p = 0.008). However, no significant difference was found in VAS pain and DLQI at 12 months follow-up, compared to baseline. (Table 2 and Fig. 2)
Table 2
Body weight, BMI and measures of disease activity and function before weight loss treatment at baseline (BL) and after 12-months (M12) and 24-months (M24) in patients with psoriatic arthritis. Values are median and inter-quartile range (IQR).

|                      | BL     | M12    | M24    | BL vs M12 p-value | BL vs M24 p-value |
|----------------------|--------|--------|--------|-------------------|-------------------|
| **Weight**           |        |        |        |                   |                   |
| kg                   |        |        |        |                   |                   |
| N = 39               | 106.0  | 87.5   | 92.7   | < 0.001           | < 0.001           |
| (93.5–112.5)         | (80.6–95.5) | (85.7–100.7) |       |                   |                   |
| **BMI**              |        |        |        |                   |                   |
| kg/m²                |        |        |        |                   |                   |
| N = 39               | 35.2   | 30.5   | 32.3   | < 0.001           | < 0.001           |
| (33.9–37.9)          | (28.0–32.9) | (30.3–35.4) |       |                   |                   |
| **Tender joints 68** |        |        |        |                   |                   |
| count                | 4      | 3      | 2      | 0.001             | < 0.001           |
| (1–14)               | (0–6)  | (0–7)  |       |                   |                   |
| **Swollen joints 66**|        |        |        |                   |                   |
| count                | 0      | 0      | 0      | 0.015             | 0.003             |
| (0–1)                | (0–1)  | (0–0)  |       |                   |                   |
| **Leeds enthesitis index**, count | 1    | 0      | 1      | < 0.001           | 0.002             |
| (0–4)                | (0–2)  | (0–3)  |       |                   |                   |
| **BSA**              |        |        |        |                   |                   |
| %                    | 0.75   | 0.25   | 0.25   | 0.018             | 0.194             |
| (0–2)                | (0–1)  | (0–1.5)|       |                   |                   |
| **CRP**              |        |        |        |                   |                   |
| mg/L                 | 5      | 2      | 3      | 0.009             | 0.011             |
| (3–9)                | (1–5)  | (2–5)  |       |                   |                   |
| **Hb**               |        |        |        |                   |                   |
| g/L                  | 144    | 143    | 142    | 0.296             | 0.537             |
| (131–150)            | (131–150) | (135–149) |       |                   |                   |
| **WBC**              |        |        |        |                   |                   |
| 10⁹/L                | 6.1    | 5.7    | 5.9    | 0.133             | 0.346             |
| (5.3–7.7)            | (5.0–7.4) | (4.7–7.8) |       |                   |                   |

BASFI = Bath Ankylosing Spondylitis Functional Index, BMI = Body Mass Index, BSA = Body Surface Area, CRP = C-reactive protein, DAPSA = Disease Activity in Psoriatic Arthritis, DAS28CRP = Disease Activity Score using 28 joint counts based on CRP, DLQI = Dermatology Life Quality Index, ESR = erythrocyte sedimentation rate, HAQ = Health Assessment Questionnaire, Hb = haemoglobin, MDA = Minimal Disease Activity, PLT = platelet count, VAS = Visual Analogue Scale, WBC = White Blood Cell count
|                           | BL N = 39 | M12 N = 39 | M24 N = 35 | BL vs M12 p-value N = 39 | BL vs M24 p-value N = 35 |
|---------------------------|-----------|------------|------------|--------------------------|--------------------------|
| PLT 10^9/L                | 270 (202–299) | 262 (203–308) | 273 (220–332) | 0.368 | 0.334 |
| VAS Pain mm               | 35 (15–60) | 30 (14–46) | 35 (15–55) | 0.073 | 0.799 |
| VAS Global health, mm     | 40 (20–70) | 30 (17–52) | 40 (20–60) | **0.023** | 0.282 |
| VAS Fatigue mm            | 50 (30–70) | 30 (20–60) | 60 (30–80) | **0.021** | 0.064 |
| HAQ score                 | 0.63 (0.13–1.00) | 0.25 (0–0.63) | 0.25 (0.13–0.88) | **0.002** | **0.033** |
| BASFI score               | 2.6 (1.4–5.2) | 1.6 (0.57–3.6) | 2.1 (0.9–4.2) | **< 0.001** | 0.131 |
| DLQI score                | 1 (0–4) | 1 (0–4) | 1 (0–4) | 0.380 | 0.982 |
| DAS-28CRP score           | 3.1 (2.1–3.7) | 2.4 (1.8–3.3) | 2.4 (1.7–2.9) | **< 0.001** | **< 0.001** |
| DAPSA score               | 16.1 (6.2–23.3) | 9.5 (4.8–18.1) | 9.7 (5.3–19.0) | **< 0.001** | **< 0.001** |
| MDA n (%)                 | 11 (28.2) | 15 (38.5) | 16 (45.7) | **0.008** | **0.016** |

**BASFI** = Bath Ankylosing Spondylitis Functional Index, **BMI** = Body Mass Index, **BSA** = Body Surface Area, **CRP** = C-reactive protein, **DAPSA** = Disease Activity in Psoriatic Arthritis, **DAS28CRP** = Disease Activity Score using 28 joint counts based on CRP, **DLQI** = Dermatology Life Quality Index, **ESR** = erythrocyte sedimentation rate, **HAQ** = Health Assessment Questionnaire, **Hb** = haemoglobin, **MDA** = Minimal Disease Activity, **PLT** = platelet count, **VAS** = Visual Analogue Scale, **WBC** = White Blood Cell count.

**Body weight and disease activity after 24 months**
In total, 35 patients were examined at the 24-month visit. The median weight was 92.7 (IQR 85.7–100.7) kg and the median weight loss 7.4 (IQR 5.1–14.0) % of the baseline weight. Forty percent (N = 14/35) of the patients still had a weight loss of 10% or more compared to baseline, and 37.1% (N = 13/35) had a weight loss of 5–10%. All patients had however regained some weight since the 12-month visit, in median 6.3 (IQR 3.4–9.3) kg.

At 24 months the swollen/66 and tender/68 joints count, Leeds enthesis index, CRP, HAQ, DAS28-CRP and DAPSA scores were still significantly lower compared to baseline. (Table 2 and Fig. 2) Criteria for MDA was met by 45.7% (16/35) at the 24-month visit (p = 0.016, compared to baseline). There were however no significant differences in BSA, DLQI, BASFI and VAS global health, pain and fatigue between baseline and 24 months.

Using PGIC to rate the patients’ overall impression of change in status since study start, 54% of the patients reported “very much or much improved”, 23% “minimally improved”, 17% “no change” and 6% “worse”. (Fig. 3)

**Change in disease activity and function in relation to weight loss**

At 12-months follow-up the change in BMI compared to baseline (ΔBMI) was significantly correlated with ΔDAS28-CRP (r_s=0.526, p = 0.001), ΔDAPSA (r_s=0.383, p = 0.017), ΔCRP (r_s=0.455, p = 0.004), ΔBASFI (r_s=0.455, p = 0.004) and ΔVAS for global health (r_s=0.483, p = 0.002) (Fig. 4a-d) At 24-months follow-up ΔBMI was correlated with ΔHAQ (r_s=0.466, p = 0.005) and ΔVAS for fatigue (r_s=0.455, p = 0.006). (Fig. 4e) PGIC was also significantly associated with ΔBMI (r_s= -0.412: p = 0.014) at 24 months.

**Change in variables associated with the metabolic syndrome**

Data is given in Table 3. At the six-month visit blood pressure, HbA1c and serum levels of TC, LDL, TG and glucose were significantly reduced, and HDL was significantly increased, compared to baseline. After 12-months there were still significant reductions in HbA1c, TG and glucose and an increase in HDL, and after 24-months a lowered TG and higher HDL remained. Criteria for MetS were met by 76.9% (30/39) at baseline, 35.9% (14/39) after six months, 38.5% (15/39) after 12-months, and by 60% (21/35) after 24-months.
Table 3
Parameters associated with the metabolic syndrome at baseline (BL) and after weight loss at 6 months (M6), 12 months (M12) and 24 months (M24) in patients with psoriatic arthritis and obesity. Values are median and inter-quartile range (IQR).

|               | BL       | M6       | M12      | M24      | BL-M6 p-value | BL-M12 p-value | BL-M24 p-value |
|---------------|----------|----------|----------|----------|---------------|----------------|----------------|
| **BMI kg/m²** | 35.2 (34.0-37.8) | 29.7 (26.2-31.4) | 30.5 (28.0-33.0) | 32.3 (30.2-35.4) | <0.001         | <0.001         | <0.001         |
| **Waistline cm** | 115 (112-122) | 95 (8-102) | 97.5 (90-105) | 107 (96-113) | <0.001 | <0.001 | <0.001 |
| **BP systolic mmHg** | 127.5 (115-136) | 120 (102.5-130) | 121 (113.5-140) | 124 (115-145) | <0.001 | 0.410 | 0.701 |
| **BP diastol mmHg** | 77.5 (70-82.5) | 70 (62.5-77.5) | 72.5 (65-82.5) | 75 (70-86) | <0.001 | 0.073 | 0.891 |
| **S-TC mmol/L** | 5.5 (4.6-6.2) | 4.9 (4.4-5.7) | 5.4 (4.7-5.9) | 5.6 (4.6-6.0) | 0.019 | 0.508 | 0.227 |
| **S-LDL mmol/L** | 3.6 (3.0-4.4) | 3.2 (2.6-3.9) | 3.4 (2.8-4.0) | 3.9 (2.8-4.5) | 0.003 | 0.468 | 0.596 |
| **S-HDL mmol/L** | 1.4 (1.1-1.6) | 1.4 (1.2-1.6) | 1.65 (1.4-2.0) | 1.6 (1.3-1.7) | 0.001 | <0.001 | 0.005 |
| **S-TG mmol/L** | 1.6 (1.2-2.4) | 1.1 (0.9-1.6) | 1.2 (1.0-1.7) | 1.4 (1.0-2.1) | <0.001 | <0.001 | 0.007 |
| **HbA1c mmol/mol** | 35.5 (32.0-37.2) | 32.5 (29.8-36.0) | 34 (31-36) | 35 (32-38) | <0.001 | 0.002 | 0.203 |

ALT = alanine transaminase, BMI = Body Mass Index, BP = blood pressure, HbA1c = glycosylated hemoglobin, HDL = high-density lipoprotein cholesterol, LDL = low-density lipoprotein cholesterol, S= serum, TC = total cholesterol, TG = triglycerides, Mets = metabolic syndrome
No significant differences were found for systolic and diastolic blood pressures at the 12- and 24-month visits compared to baseline, although three patients were able to stop treatment for hypertension during the study, and two patients could halve the dose of antihypertensives. Two patients stopped lipid-lowering therapy, while two other patients started lipid-lowering therapy during the follow-up. In addition, one patient started treatment with glucose-lowering medication during the study.

Serum urate was also significantly reduced at the six, 12- and 24-month visit compared to baseline (Table 4). Baseline serum urate was significantly higher in the men compared with the women (p = 0.002) and the men also had the greatest reduction in serum urate. The decrease in serum urate (D-urate) was however only significantly correlated with D-BMI at the 24-month visit in the women (r = 0.493; p = 0.032) and not in the men at any time-point.
Table 4

Serum urate in median and inter-quartile range (IQR) at baseline (BL) and after weight loss at 6 months (M6), 12 months (M12) and 24 months (M24) in women and men with psoriatic arthritis and obesity.

|       | S-urate µmol/L | BL (IQR) | M6 (IQR) | M12 (IQR) | M24 (IQR) | BL-M6 p-value | BL-M12 p-value | BL-M24 p-value |
|-------|----------------|----------|----------|-----------|-----------|---------------|---------------|---------------|
| All   |                |          |          |           |           |               |               |               |
| patients |                | 330 (280–400) | 301 (244–356) | 306 (250–348) | 324 (264–351) | 0.001          | 0.001          | 0.005          |
|        |                | N = 39   | N = 39   | N = 39    | N = 35    |               |               |               |
| Women  |                | 309 (269–361) | 259 (232–350) | 286 (242–348) | 294 (234–338) | 0.023          | 0.053          | 0.033          |
|        |                | N = 25   | N = 25   | N = 25    | N = 21    |               |               |               |
| Men    |                | 394 (324–416) | 324 (304–367) | 319 (294–357) | 334 (306–368) | 0.017          | 0.003          | 0.064          |
|        |                | N = 14   | N = 14   | N = 14    | N = 14    |               |               |               |

Discussion

In this prospective, open intervention study, we analysed the long-term effects of weight loss on disease activity, self-reported physical function and variables associated with the MetS in patients with PsA and obesity. After 12 months of structured weight loss treatment, a median weight reduction of 16% was associated with improvement of a majority of disease activity measures compared to baseline, including swollen/tender joints count, enthesitis, extent of psoriasis, CRP, HAQ, BASFI and VAS global health and fatigue. After 24 months, all patients had regained some weight, but a significant improvement could still be shown in swollen/tender joints count, enthesitis, CRP and HAQ, compared to baseline. Additionally, several variables of the MetS, such as waist circumference, HDL, TG, were significantly improved after 12 and 24 months, and some patients were able to stop anti-hypertensive treatment. The results of the study support the hypothesis of obesity as a promotor of disease activity in PsA, showing what could be attained by adding a weight loss program to routine medical care in patients with PsA and obesity.

In the present study the weight loss treatment with VLED was judged as easy to implement by most patients, but the transition from VLED to normal food was perceived as harder. A substantial weight reduction was noted during the VLED treatment, but as expected the patients started to gain weight already at six months. The patients were given an energy-reduced dietary advice and were instructed to engage in health-enhancing physical activity at least 150 minutes per week, but no follow up was made between 12- and 24-month visits. At the 24-month visit 40% still had a weight reduction of 10% or more
compared to baseline in the present study. Several studies in both specialist and primary care have included VLED as part of a structured weight loss program for subjects with severe obesity and have shown clinically meaningful weight loss, and the results of the present study are comparable with those. [32–36] Given the difficulties to treat obesity in a longer perspective once it is established, more attention should be given to prevent weight gain and the development of obesity in patients with psoriasis and PsA. We propose that the patients should be informed about the unfavourable effects of obesity on disease course and cardiovascular risk during patient educational programs and that body weight should be routinely measured and discussed during medical follow-ups. We also argue that patients with overweight should aim for weight maintenance and patients with obesity should be offered a weight loss program and be encouraged to participate in health-enhancing physical activity throughout the disease course.

Totally six patients were lost to follow-up between the six- and 24-month visits. It is possible that the patients who did not come to follow-up had a poorer weight maintenance than the patients who continued in the study.

Studies on the effects of weight loss on disease activity in PsA are scarce, but there are a few studies on psoriasis. Effect on disease severity in psoriasis has been shown after weight loss by bariatric surgery [37, 38] and dietary interventions [39–42]. Improved response to cyclosporine [43] and TNFi [44] has also been shown in psoriasis after weight loss. Additionally, bariatric surgery in obesity has been associated with a lower future risk of developing psoriasis in one study [45], and psoriasis and PsA in another study. [46] One prior randomized controlled study on dietary interventions in patients with PsA and overweight or obesity starting treatment with TNFi demonstrated that a weight loss of $\geq 5\%$ increased the chance of reaching MDA at six months follow-up. [47] The odds ratio (OR) for achieving MDA at a weight loss 5–10\% and >10\% was 3.75 (95% CI 1.36–10.36) and 6.67 (95% CI 2.41–18.41) respectively.

Obesity is a pro-inflammatory state, where the adipose tissue is invaded by activated M1-type macrophages and B- and T-lymphocytes, with an over-production of cytokines, such as tumour necrosis factor-a (TNFa) and interleukin (IL)1, IL6, IL17 and IL23, which are all involved in the pathogenesis of psoriasis and PsA. [48, 49] Moreover, pro-inflammatory adipokines (resistin, fetuin-A, chemerin, leptin) are over-expressed in the adipocytes in obesity and adipokines with mainly anti-inflammatory effects (adiponectin, omentin) are suppressed. [50] In the present study we show sustained lowered disease activity at the 12- and 24-month visits, when the patients were unlikely to be affected by the severe initial energy restriction from VLED, although the majority of participants had kept, to a different degree, an energy reduced diet. The anti-inflammatory effect of the weight loss may rather be explained by decreased production of pro-inflammatory cytokines and adipokines by the adipose tissue. Lowered mechanical loading by weight loss and less risk of microdamage, enthesitis and arthritis could also be explanatory factors.

In the present study, weight loss was associated with a reduction of other cardiovascular risk factors such as hypertension and dyslipidemia, and additionally lowered levels of blood glucose and HbA1c.
MetS is defined as a set of cardiovascular risk factors that cluster together; enlarged waist circumference, high blood glucose levels, elevated blood pressure and TG, and reduced HDL.[31] Insulin resistance, central obesity and overabundance of circulating fatty acid are suggested mechanisms underlying the MetS.[51] The MetS is associated with increased mortality and poorer health outcomes in several aspects, such as a doubled risk of cardiovascular disease [52] and increased risk of various types of cancer [53]. In psoriasis and PsA there is a clear overrepresentation of cardiovascular risk factors and of MetS [4, 14, 54, 55] and the patients are at higher risk of developing cardiovascular events.[5, 9] The present study shows that treatment of obesity entails both reduction in disease activity, possibly through reduction in pro-inflammatory state, as well as cardiovascular risk factor.

Patients with psoriasis and PsA are at increased risk of developing gout.[56] In the present study weight loss was associated with a significant decrease in serum urate especially in the male patients. We could however not demonstrate any systematic correlation between the reduction in serum urate and the magnitude of weight loss, perhaps due to a small sample size and large interindividual weight change. Changes in dietary habits, including consumption of alcohol and sugar-sweetened soft drinks, may also have played a role in the reduction of serum urate.

**Strengths and limitations**

Strengths of the study are the prospective design with a long follow-up and the powerful intervention which resulted in a considerable weight loss.

There are also limitations of the present study to be acknowledged. Firstly, this is not a randomized controlled study and the absence of a control group is a major short-coming. Secondly, treatment with cs/bDMARDs was held constant from three month prior to baseline until the six-month visit, but change in cs/bDMARD treatment was allowed after the six-month visit, due to ethical reasons. We cannot exclude that change in treatment may have affected the results regarding disease activity at the 12- and 24-month visits. In the vast majority of patients, the medication with cs/bDMARDs was however held unchanged during the whole study period. Thirdly, pharmacological treatment against hypertension, hyperlipidemia and diabetes could not be held constant throughout the study, which may have affected levels of blood pressure, blood lipids and glucose metabolism during the follow-up. During the initial period with intense weight loss, some patients experienced hypotension and antihypertensive treatment had to be tapered.

**Conclusions**

Weight loss treatment with VLED in patients with PsA and obesity was associated with sustained lowered disease activity after 12 months and 24 months of follow-up, with concurrent improvements in cardiovascular risk factors and lowered serum urate. The results of the study provide support to the hypothesis of obesity as promotor of disease activity in PsA and shows what can be achieved by 5–15% weight loss in patients with PsA and obesity.
Abbreviations

ACR
American College of Rheumatology

ALT
alanine transaminase

BASFI
Bath Ankylosing Spondylitis Functional Index

BMI
Body Mass Index

BSA
Body Surface Area

CRP
C-reactive protein

CASPAR
Classification for Psoriatic Arthritis

CV
cardiovascular

DAPSA
Disease Activity in Psoriatic Arthritis

DAS28CRP
Disease Activity Score using 28 joint counts based on CRP

DLQI
Dermatology Life Quality Index

cs/b DMARD
conventional synthetic / biologic Disease Modifying Anti-Rheumatic Drug

ESR
erythrocyte sedimentation rate

HAQ
Health Assessment Questionnaire

Hb
haemoglobin

HbA1c
glycosylated hemoglobin

HDL
high-density lipoprotein cholesterol

IL
interleukin

IQR
interquartile range
Declarations

Ethics approval and consent to participate

The study was approved by the Regional Ethics Committee in Gothenburg and carried out in accordance with the Helsinki declaration. All participants gave their written informed consent.

Consent for publication

Not applicable
Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no financial or nonfinancial competing interests. The patients were able to buy the VLED at a reduced price from Cambridge Weight Plan Limited, Solna, Sweden.

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Author's contributions

E.K. was responsible for study design, recruitment of patients, rheumatologic evaluations, data collection, statistical analyses and drafting of the article.

S.B. participated in recruitment and examination of patients, weight loss treatment and follow-up, collection and interpretation of data.

B.E. participated in study design, recruitment and examination of patients, collection and interpretation of data and was responsible for the weight-loss treatment and follow-up.

I.L. participated in study design, recruitment and examination of patients, collection and interpretation of data and was responsible for the weight-loss treatment and follow-up.

A.B. participated in study design, recruitment and examination of patients, collection, analysis and interpretation of data.

All authors have critically reviewed the manuscript, approved the final version to be published and agreed to be accountable for all aspects of the work.

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Figures
Figure 1: Participants lost to follow-up

PsA patients
Baseline: 46 patients included

3 months: N=44

Lost to follow-up
2 patients

6 months: N=41

3 patients

12 months: N=39

2 patients

24 months: N=35

4 patients

Figure 1
Flow chart for the study from baseline to 24 months showing participation and participants lost to follow-up.
Figure 2: BMI and DAPSA scores during the follow-up

Boxplots showing the distribution of body mass index (BMI) and Disease Activity in PSoriatic Arthritis (DAPSA) scores at baseline and the visits at three, six, 12 and 24 months.
Figure 3: Patient Global Impression of Change (PGIC)

“Since the start of the study, my overall status is...”

N=8
N=11
N=8
N=6
N=1
N=1
N=0

1. Very Much Improved  
2. Much Improved  
3. Minimally Improved  
4. No change  
5. Minimally Worse  
6. Much Worse  
7. Very Much Worse

Figure 3

The Patient Global Impression of Change (PGIC) since the start of the study.
Figure 4a The correlation between ΔBMI and ΔDAPSA score at the 12-month visit

\[ r_s = 0.383; \ p = 0.017 \]

Figure 4
change in body mass index (ΔBMI) and change in Disease Activity in PSoriatic Arthritis score (ΔDAPSA) at the 12-month visit
Figure 4b The correlation between $\Delta$BMI and $\Delta$CRP at the 12-month visit

$r_s = 0.455; p = 0.004$

Figure 5

$\Delta$BMI and change in C-reactive protein ($\Delta$CRP) at the 12-month visit
Figure 4c: The correlation between ΔBMI and ΔBASFI score at the 12-month visit.

\[ r_s = 0.455; \ p = 0.004 \]

Figure 6

ΔBMI and change in Bath Ankylosing Spondylitis Functional Index (ΔBASFI) at the 12-month visit.
Figure 4d The correlation between ΔBMI and ΔGlobal VAS score at the 12-month visit

$r_5=0.483; p=0.002$

Figure 7

BMI and change in Global Visual Analogue Scale (Global VAS) at the 12-month visit
Figure 4e The correlation between ΔBMI and ΔHAQ score at the 24-month visit

$r_c=0.466; p=0.005$

Figure 8

ΔBMI and change in Health Assessment Questionnaire score (ΔHAQ) at the 24-month visit