Effect of Weight Loss on the Cardiovascular Risk Profile of Obese Patients with Psoriasis

Psoriasis is associated with obesity and other cardiovascular risk factors including endothelial dysfunction. We aimed to investigate the effects of weight loss on the cardiovascular risk profile of obese patients with psoriasis. A randomised controlled study was conducted in which we measured the microvascular endothelial function with peripheral arterial tonometry, selected plasma markers of endothelial function, and traditional cardiovascular risk factors in 60 obese patients with psoriasis. The participants were randomised to either low-energy diet \( (n=30) \) providing 800–1,000 kcal/day for 8 weeks followed by 8 weeks of reduced food intake reaching 1,200 kcal/day or normal healthy foods \( (n=30) \) for 16 weeks. The intervention group lost significantly more weight than controls, which resulted in significant reductions of diastolic blood pressure, resting heart rate, total cholesterol, very low density lipoprotein cholesterol, triglyceride, plasma glucose, glycated haemoglobin, and tissue plasminogen activator inhibitor. Microvascular endothelial function assessed by peripheral arterial tonometry remained unchanged. We conclude that certain components of the cardiovascular risk profile of obese patients with psoriasis can be significantly improved by weight reduction. Key words: psoriasis, weight reduction, comorbidity, cardiovascular.

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Psoriasis is a chronic inflammatory skin disease affecting 2–3% of the population in Europe and North America (1). Psoriasis is characterised by a systemic immunological response, which is mainly elicited by activated T-helper (Th)1 and Th17 lymphocytes. These cells also play a key role in eliciting a systemic low-grade inflammatory state by interacting with other cellular and humoral mediators such as interleukins 2, 17, and 23, tumour necrosis factor-α, interferon-γ, macrophages, dendritic cells and keratinocytes (2, 3). Like psoriasis, atherosclerosis is characterised by Th1-driven inflammation both systemically and locally in arterial walls and atherosclerotic plaques (4). It therefore appears that the inflammatory mechanisms in psoriasis and atherosclerosis show considerable overlap. It is well established that psoriasis is associated with an increased prevalence of traditional cardiovascular risk factors, e.g. diabetes, hypertension, hyperlipidaemia, smoking, and obesity. Epidemiological studies have shown that psoriasis is associated with overweight, and that increased adiposity and weight gain are risk factors for incident psoriasis (5). Increasing evidence also suggests that psoriasis may confer independent risk of atherosclerotic cardiovascular disease such as myocardial infarction and cardiovascular mortality, especially in young adults with severe disease (6, 7). Case-control studies have added further evidence linking psoriasis to atherosclerosis and coronary artery disease by demonstrating an increased prevalence of surrogate markers for atherosclerotic disease such as endothelial dysfunction (8, 9). The endothelium plays a major role in the regulation of arterial tone and for maintenance of anti-thrombotic and anti-inflammatory conditions in the vascular wall. Obesity is associated with abnormal endothelial function owing to mechanisms elicited by the excess visceral fat mass including impaired glucose tolerance, systemic inflammation, insulin resistance, and metabolic dysregulation (10). Endothelial dysfunction is a predictor of future cardiovascular events and weight reduction has been shown to restore endothelial function (11, 12). Endothelial function is commonly measured by high-resolution ultrasound measurement of flow-mediated vasodilatation (FMD) in the brachial artery, which is operator-dependent and technically difficult (11). Digital peripheral arterial tonometry (PAT) enables non-specialists to measure microvascular endothelial function non-invasively and operator-independently (11). It has been shown that reduced microvascular endothelial function measured by PAT is correlated with presence of traditional cardiovascular risk factors and predicts future cardiovascular adverse events (13).
Also, measurements of certain soluble molecules such as intercellular adhesion molecule (ICAM)-1, vascular adhesion molecule (VCAM)-1, and tissue plasminogen activator inhibitor (tPAI)-1 have been used as markers of endothelial dysfunction (14, 15). Overweight patients with psoriasis are at increased cardiovascular risk imposed both by psoriasis and by excess body fat. Therefore, we examined the effect of weight reduction on traditional cardiovascular risk factors and on endothelial function assessed by PAT and selected plasma markers in these patients.

MATERIALS AND METHODS

Between June 2010 and June 2011 we conducted a prospective randomised trial at the Department of Dermato-Allergology, Copenhagen University Hospital Gentofte. The study aimed to investigate the effect of weight reduction on both the severity of psoriasis and on cardiovascular risk. The results on the effects of weight loss on the severity of psoriasis were recently reported (16). It was approved by the regional ethics committee (registration number H-2-2010-001) and was registered in www.clinicaltrials.gov (NCT01137188). Eligible for inclusion were patients with plaque psoriasis with a body mass index (BMI) > 27 kg/m². Briefly, we randomised 60 out of 69 eligible overweight patients with psoriasis to an intervention group receiving a low-energy diet (800–1,000 kcal/day, Cambridge Diet, the Cambridge Weight Plan®, UK) for 8 weeks followed by 8 weeks of reduced intake of normal food (1,200 kcal/day) or to a control group that received advice on ordinary healthy food. The mean weight patients with psoriasis to an intervention group receiving a low-energy diet (800–1,000 kcal/day, Cambridge Diet, the Cambridge Weight Plan®, UK) for 8 weeks followed by 8 weeks of reduced intake of normal food (1,200 kcal/day) or to a control group that received advice on ordinary healthy food according to the national guidelines. The primary investigator (PJ) assessed all participants at baseline and after 16 weeks. In addition, the patients met every 2 weeks for a total of 8 group sessions led by a study dietician.

We measured microvascular endothelial function by PAT using the Endo-PAT2000® device (Itamar Medical Ltd, Caesarea, Israel). This method uses plethysmographs attached to both index fingers and measures pulsatile arterial volume changes before and during reactive hyperaemia achieved by inflating a pressure cuff placed on the upper arm for 5 min followed by cuff deflation. The contralateral arm serves as control and is used to correct for changes in arterial tone. Software is then used to calculate the reactive hyperaemia index (RHI) (11). In addition, we measured the plasma concentrations of 3 soluble biomarkers associated with endothelial dysfunction, i.e. PAI-1, VCAM-1, and ICAM-1. PAI-1, VCAM-1, and ICAM-1 concentrations in EDTA plasma were determined in duplicates using a commercial enzyme-linked immunosorbent assay (Quantikine®, R&D Systems, Minneapolis, MN, USA). Also, we measured body weight, height, BMI, blood pressures, resting heart rate, blood lipids, blood glucose, glycated haemoglobin (HbA1c), and high-sensitivity C-reactive protein (hs-CRP). Relevant also in the present context is changes in plasma insulin levels, which were reported in the main study (16). Leisure-time and sport physical activity indices were calculated using the Baeecke formula (17). The severity of psoriasis was measured using the psoriasis area and severity index (PASI). All values were obtained at baseline and after week 16. Blood was drawn in the fasted state and analyses were performed at the Department of Clinical Biochemistry, Copenhagen University Hospital Gentofte, Hellerup, Denmark.

We used software by IBM SPSS (Version 19.0, Chicago, IL, USA) and GraphPad Prism (Version 5.00, GraphPad Software, San Diego, CA, USA) for statistical analysis. Results are shown as the difference between the group means and 95% confidence intervals (CIs) with associated p-values based on the independent samples t-test. We logarithmically transformed skewed variables for statistical purposes and then back-transformed them to their natural units. The Mann-Whitney U-test was used in case normality did not improve with logarithmic transformation, and skewed variables are presented as median (interquartile range). p < 0.05 was considered statistically significant.

RESULTS

Table I shows the baseline demographic and clinical data. The patients were moderately obese (class I obesity) with a mean BMI of 34.2 kg/m². Levels of hs-CRP were increased (median 3.15 mg/l, interquartile range 1.53 to 5.10 mg/l) consistent with a state of systemic low-grade inflammation. The patients had mild to moderate psoriasis with a median PASI of 5.4.

Table II shows the changes in outcomes from baseline after 16 weeks. As expected, the intervention group had a significantly greater mean weight loss of –15.8 kg compared to –0.4 kg in the control group resulting in a mean difference of 15.4 kg (95% CI 12.3–18.5 kg, p < 0.001).

The weight loss led to significant reductions of several obesity- and cardiovascular risk-associated endpoints.
in the intervention group compared to controls, i.e. BMI, diastolic blood pressure, resting heart rate, total cholesterol, very low density lipoprotein cholesterol, triglycerides, glucose, and HbA1c (Table II). One plasma marker related to endothelial function, tPAI-1, was significantly reduced in the intervention group (mean difference 3.48 ng/ml, 95% CI 1.50–5.46 ng/ml, \( p = 0.001 \)). RHI assessed by PAT remained unchanged and there were no significant differences between the 2 groups after 16 weeks with regard to changes in VCAM-1, ICAM-1, HDL cholesterol, hs-CRP levels, levels of physical activity. PASI appeared to improve more in the LED group compared to controls although this did not reach statistical significance, \( p = 0.06 \).

**DISCUSSION**

After 16 weeks, obese patients with psoriasis randomised to low-energy diet lost significantly more weight compared to controls encouraged to eat normal healthy foods. This resulted in significant reductions of several endpoints associated with increased cardiovascular risk including circulating levels of tPAI, a marker of endothelial function. It is worth noting that in the patients randomised to low-energy diet, the weight loss improved HbA1c levels by 0.7%, equivalent to reductions achieved by treatment with an anti-diabetic drug. However, these changes were not associated with improvement of microvascular endothelial function assessed by PAT. Macrovascular endothelial function assessed by FMD of the brachial artery has been shown to improve in obese individuals after weight loss (12). However, as opposed to measurement of FMD (conduit artery endothelial function), PAT measures microvascular endothelial function. Recently, data have suggested that FMD and PAT are only weakly correlated and that they may be differently affected by various cardiovascular risk factors (11, 18–20). Patients with psoriasis are at increased risk of macrovascular cardiovascular events, i.e. myocardial infarction and stroke, and it is possible that FMD captures alterations of endothelial function in these patients more accurately than PAT. To the best of our knowledge, effects of weight reduction on endothelial function in patients with psoriasis have not been reported previously and the small non-randomised series by Farias et al. (21) is the only study reporting on effects of weight reduction on hypertension and metabolic comorbidities in obese patients with psoriasis. In that study, 10 obese patients with psoriasis underwent weight reduction surgery, which resulted in resolution rates of 75% for diabetes, 100% for insulin resistance, and 57% for hypertension. Our study was limited by a relatively short follow-up period, but our results are in line with previously published non-randomised data (21) showing that certain components of the cardiovascular risk profile of obese patients with psoriasis can be effectively reduced by weight reduction. Future randomised studies with longer follow-up periods are needed to confirm these findings.

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