Systemic treatment and narrowband ultraviolet B differentially affect cardiovascular risk markers in psoriasis

Gunnthorunn Sigurdardottir, MD,[a] Anna-Karin Ekman, PhD,[a] Mona Ståhle, MD, PhD,[b] Cecilia Bivik, PhD,[a] and Charlotta Enerbäck, MD, PhD[a]
Linköping and Stockholm, Sweden

Background: Psoriasis is associated with a systemic inflammation and an increased frequency of the metabolic syndrome, both of which are believed to link psoriasis to an increased risk of cardiovascular disease.

Objective: The study aimed to investigate the systemic expression of markers of cardiovascular risk and determine their response to ultraviolet B therapy and treatment with the tumor necrosis factor-alfa inhibitor, etanercept.

Methods: Six markers of cardiovascular risk were measured in 28 patients with psoriasis and 28 control subjects.

Results: Five of the 6 investigated markers were elevated in patients with psoriasis. Four of these correlated to the body mass index and waist-hip ratio, suggesting a link to the metabolic syndrome. Total plasminogen activator inhibitor-1 remained elevated independently of these factors. The levels of the investigated risk markers decreased considerably after tumor necrosis factor-alfa inhibitor treatment but remained unaffected by ultraviolet therapy.

Limitations: A relatively limited study population and nonrandomization are limitations.

Conclusion: These findings suggest that the choice of treatment in psoriasis may influence the cardiovascular risk in patients with psoriasis and the metabolic syndrome. (J Am Acad Dermatol 2014;70:1067-75.)

Key words: cardiovascular risk; matrix metalloproteinase-9; myeloperoxidase; psoriasis; soluble E-selectin; soluble intercellular adhesion molecule-1; soluble vascular cell adhesion molecule-1; total plasminogen activator inhibitor-1; tumor necrosis factor-alfa inhibitor; ultraviolet B.

Psoriasis is a chronic, immune-mediated inflammatory skin disease that affects 2% to 3% of the population worldwide. In addition to running an increased risk of psoriatic arthritis, patients with psoriasis run a higher risk of developing obesity, dyslipidemia, hypertension, and diabetes, all components of the metabolic syndrome.[1,2] Psoriasis may also confer an elevated risk of

From the Ingrid Asp Psoriasis Research Center, Department of Clinical and Experimental Medicine, Faculty of Health Sciences, Linköping University,[a] and Unit of Dermatology and Venereology, Department of Medicine, Karolinska Institutet, Stockholm.[b]

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Drs Sigurdardottir and Ekman contributed equally to this work.

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Reprint requests: Charlotta Enerbäck, MD, PhD, Ingrid Asp Psoriasis Research Center, Department of Clinical and Experimental Medicine, Linköping University, SE-581 85 Linköping, Sweden. E-mail: charlotta.enerback@liu.se.

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cardiovascular disease, such as myocardial infarction and stroke, independently of major risk factors for these diseases. An increase in mortality is observed in patients with severe disease and is most pronounced in young patients.[3-8]

Specific biomarkers aid in detecting disease, determining the activity and the severity and evaluating the response to therapy and monitoring disease progression. Cardiovascular biomarkers, many of which are also mediators of inflammation, have previously been studied in patients with psoriasis. These studies have mainly focused on cardiovascular markers related to the obesity-associated systemic inflammation. The expression of the adipokine leptin and the soluble leptin receptor is higher in the serum of patients with psoriasis[9] and is most pronounced in severely affected individuals. Systemic psoriasis treatment decreases the levels of the adipokine resistin and increases the levels of the anti-inflammatory cardioprotective adipokine adiponectin.[10]

CAPSULE SUMMARY

- Patients with psoriasis have an increased risk of cardiovascular disease.
- Markers of cardiovascular risk that are increased in patients with psoriasis are reduced by tumor necrosis factor-alfa inhibitor treatment but not by ultraviolet B therapy.

In a former study, we investigated circulating chemokines in psoriasis as a sign of an ongoing systemic inflammation. Five chemokines of a T helper (Th)1-, Th2-, or Th17-associated phenotype were elevated in psoriasis plasma but not in healthy control subjects.

The expression of the chemokine (C-C motif) ligand (CCL) 20 correlated strongly with disease severity.[11] However, although these chemokines were highly expressed in patients with psoriasis, they were not affected by narrowband (NB) ultraviolet (UV)-B treatment, despite the relief of disease symptoms in the skin. In this study, selected risk-associated molecules implicated in the process of cardiovascular disease, soluble vascular cell adhesion molecule (sVCAM)-1, soluble intercellular adhesion molecule (sICAM)-1, soluble E (sE)-selectin, matrix metalloproteinase (MMP)-9, myeloperoxidase (MPO) and total plasminogen activator inhibitor (tPAI)-1, were analyzed. The aim of the study was 2-fold: firstly, to assess the plasma levels of the selected cardiovascular risk molecules in patients with psoriasis compared with age-, gender-, body mass index (BMI)-, and waist-hip ratio (WHR)-matched control subjects; and, secondly, to investigate the effects of local (NB-UVB therapy) and systemic (tumor necrosis factor [TNF]-alfa inhibitor) treatment.

METHODS

Study design

All patients and control subjects included in the study were examined and the diagnosis of psoriasis was verified by a dermatologist at the departments of dermatology at Linköping University Hospital, Sahlgrenska University Hospital in Gothenburg, or Karolinska University Hospital in Stockholm, Sweden. Disease severity was assessed with the Psoriasis Area and Severity Index (PASI). The study was approved by the local ethics committee and every participant gave his/her written informed consent.

Six cardiovascular risk markers were analyzed in plasma from 28 patients with psoriasis and 28 age- and gender-matched control subjects. This study group was complemented with additional patients and control subjects to enable the matching of 26 age-, gender-, and BMI-matched and 13 age-, gender-, and WHR-matched pairs. The patients had not received systemic TNF-alfa inhibitor treatment for at least 4 weeks before the study.

The BMI matching was performed within the range of ± 1.0 kg/m^2 and the WHR matching within the range of ± 0.05, where both individuals in a matched pair either had WHR values within the normal range or could be defined as having abdominal obesity.[12]

Finally, the systemic expression of selected risk markers was quantified in 21 patients with psoriasis before and after 12 weeks of treatment with NB-UVB and in 20 patients with psoriasis before and after treatment with the TNF-alfa inhibitor etanercept (Enbrel, Pfizer, Morris Plains, NJ). The patients had not received UV therapy or TNF-alfa inhibitor treatment for at least the previous 4 weeks. The study was nonrandomized and the evaluations of markers were performed unblinded.

Blood samples

Blood was collected in cell preparation tubes (CPT) (Becton Dickinson, Stockholm, Sweden) coated with sodium heparin anticoagulant, or in serum tubes with clot activator (Terumo Europe, Västra Frölunda, Sweden) for the isolation of plasma and serum, respectively. The CPT tubes were centrifuged at 1400 rcf for 25 minutes, separating the leukocytes from the plasma. The serum tubes were allowed to sit for 30 minutes before separating the

Abbreviations used:

Apo-B:	apolipoprotein B
BMI:	body mass index
CCL:	chemokine (C-C motif) ligand
hs-CRP:	high-sensitivity C-reactive protein
ICAM:	intercellular adhesion molecule
IL:	interleukin
MMP:	matrix metalloproteinase
MPO:	myeloperoxidase
NB:	narrowband
PAI:	plasminogen activator inhibitor
PASI:	Psoriasis Area and Severity Index
sE:	soluble E
sICAM:	soluble intercellular adhesion molecule
sVCAM:	soluble vascular cell adhesion molecule
Th:	T helper
TNF:	tumor necrosis factor
tPAI:	total plasminogen activator inhibitor
UV:	ultraviolet
VCAM:	vascular cell adhesion molecule
VEGF:	Vascular endothelial growth factor
WHR:	waist-hip ratio

serum from the clotted blood by centrifugation at 1900 rcf for 10 minutes. Plasma and serum were frozen immediately after isolation and stored at −80°C until analysis.

Measurements of the cardiovascular risk markers

The levels of the biomarkers, sVCAM-1, sICAM-1, sE-selectin, MMP-9, MPO, and tPAI-1 were measured in plasma or serum. The measurements were performed using the Milliplex Cardiovascular Disease Panel 1 Multiple Analytes Profiling (MAP) kit (Millipore Corp, Billerica, MA), according to the manufacturer's instructions. The samples were analyzed on a Luminex 200 instrument (Biosource, Nivelles, Belgium) and the data were analyzed using StarStation 3.0 software (Applied Cytometry, Sheffield, United Kingdom).

Statistical analysis

Data analysis was performed in GraphPad Prism 5.0 (GraphPad Software, San Diego, CA). Data were compared using the nonparametric Mann-Whitney U test or Wilcoxon matched-pair signed rank test. Correlations were determined by Spearman test. A P value of less than .05 was considered significant.

RESULTS

Elevated cardiovascular markers in patients with psoriasis

Measurements of the 6 selected cardiovascular risk markers in plasma from 28 patients with psoriasis and 28 age- and gender-matched control subjects revealed increased levels of sICAM-1 (P = .0005), sE-selectin (P = .001), MMP-9 (P < .0001), MPO (P = .0003), and tPAI-1 (P = .0005) and a tendency toward an increase in sVCAM-1 (P = .07) in patients with psoriasis (Fig 1). None of these markers correlated significantly to PASI (data not shown), suggesting that they indeed represent increased systemic inflammation rather than being elevated as a result of the local inflammation in the skin.

To evaluate whether BMI and WHR influence the observed increase in cardiovascular risk markers, we correlated the levels of the investigated markers with the BMI and WHR of the study participants. This revealed an association between the BMI and sE-selectin (r = 0.68, P < .0001). The correlation was also significant but moderate for tPAI-1 (r = 0.57, P = .0014), sICAM-1 (r = 0.43, P = .02), and MMP-9 (r = 0.41, P = .03). A prominent correlation was seen between WHR and sE-selectin (r = 0.75, P < .0001). There was also a correlation for tPAI-1 (r = 0.65, P = .0002), MMP-9 (r = 0.51, P = .01), and sICAM-1, where the latter was more modest (r = 0.39, P = .04).

Elevation of tPAI-1 in patients with psoriasis when adjusted for BMI and WHR

Because the measured cardiovascular risk markers were at least partly influenced by BMI and WHR, their levels were next compared in patients with psoriasis and BMI- or WHR-matched control subjects. We observed a significant elevation in tPAI-1 in patients with psoriasis compared with both BMI-matched control subjects (P = .01) (Fig 2) and WHR-matched control subjects (P = .05, data not shown).

Reduced levels of cardiovascular markers after systemic TNF-alfa inhibitor treatment but not after UVB treatment

To evaluate the effect of different treatments on the levels of the selected markers, measurements were made on the plasma of patients with psoriasis before and after 12 weeks of NB-UVB treatment and on the serum of patients with psoriasis before and after systemic treatment with the TNF-alfa inhibitor, etanercept.

The treatment with both NB-UVB and the TNF-alfa inhibitor effectively reduced the PASI scores (P < .0001 for both groups, data not shown). There were no significant differences in the magnitude of the PASI score decrement (data not shown).

After 12 weeks of UVB treatment, patients had sustained high levels of the cardiovascular markers (Fig 3). Patients who had undergone therapy with the TNF-alfa inhibitor displayed a considerable reduction in all the investigated risk markers (Fig 4).

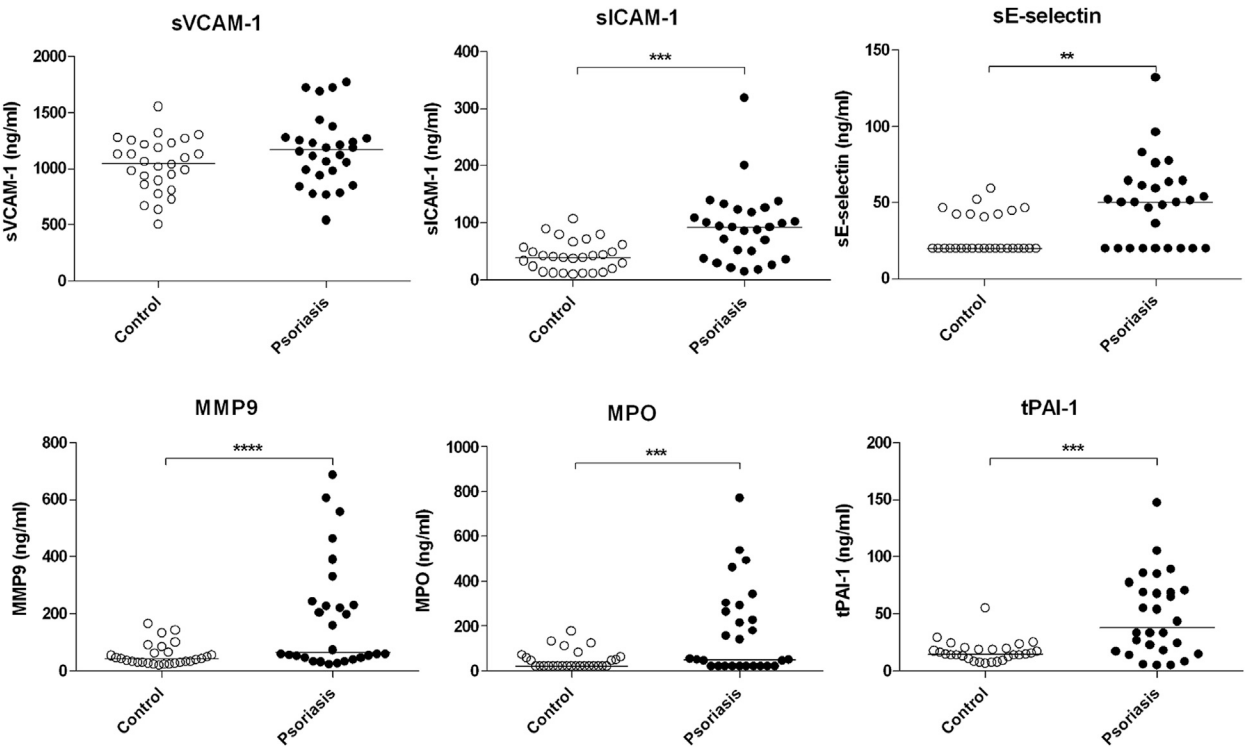

Fig 1. The levels of cardiovascular risk markers soluble vascular cell adhesion molecule (*sVCAM*)-1, soluble intercellular adhesion molecule (*sICAM*)-1, soluble E (*sE*)-selectin, matrix metalloproteinase (*MMP*)-9, myeloperoxidase (*MPO*), and total plasminogen activator inhibitor (*tPAI*)-1 measured in the plasma of age- and gender-matched patients with psoriasis and control subjects, n = 28. The line shows the median. The mean age of the patients was 48.1 years (range 16-78 years) and the median Psoriasis Area and Severity Index (PASI) score was 7.55 (range 2.0-25.3), $^{**}P < .01$, $^{***}P < .001$, $^{****}P < .0001$.

DISCUSSION

The characterization of the cardiovascular biomarkers in psoriasis is an important step toward understanding the association between psoriatic and cardiovascular disease. In this study, we have investigated the systemic levels of 6 risk markers for cardiovascular disease in patients with psoriasis.

There is accumulating evidence of an ongoing systemic inflammation in psoriasis that is believed to be a pivotal link to the cardiovascular comorbidities associated with the disease. Psoriasis is associated with obesity and proinflammatory cytokines and adipokines derived from the adipose tissue can be detected systemically in patients with psoriasis. Insulin resistance, which correlates with PASI score,[13] contributes to endothelial dysfunction, manifested by an imbalance in the release of vasodilating and vasoconstricting factors. This imbalance predisposes patients to development of atherosclerosis.[14] A mechanistic link between the systemic inflammation and cardiovascular risk has been suggested by the anti-inflammatory and cardioprotective effect of statins in patients with normal lipid levels.[15]

Psoriasis shares many features with atherosclerosis in terms of immunoactivation, cytokine network, and angiogenesis.[16,17] Both conditions are characterized by infiltration of activated T cells and atherosclerosis macrophages, whose migration from the blood vessels is mediated by the interaction of adhesion molecules with selectins. The membrane-bound forms of intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 are located on the endothelial surface and facilitate the adhesion and transendothelial migration of leukocytes into the extravascular space to enable the interaction of immune cells and promote inflammation, resulting in the formation of plaque in both conditions.

In this study, the inflammatory markers were selected as being indicative of cardiovascular risk (Table I). Adhesion molecules, including ICAM-1, VCAM-1, and E-selectin, are recognized as mediators of inflammation in cardiovascular disease[18] and the levels of their soluble forms correlate to various cardiovascular risk factors, such as hypercholesterolemia, hypertension, and diabetes.[19] sICAM-1 predicts future coronary artery disease,

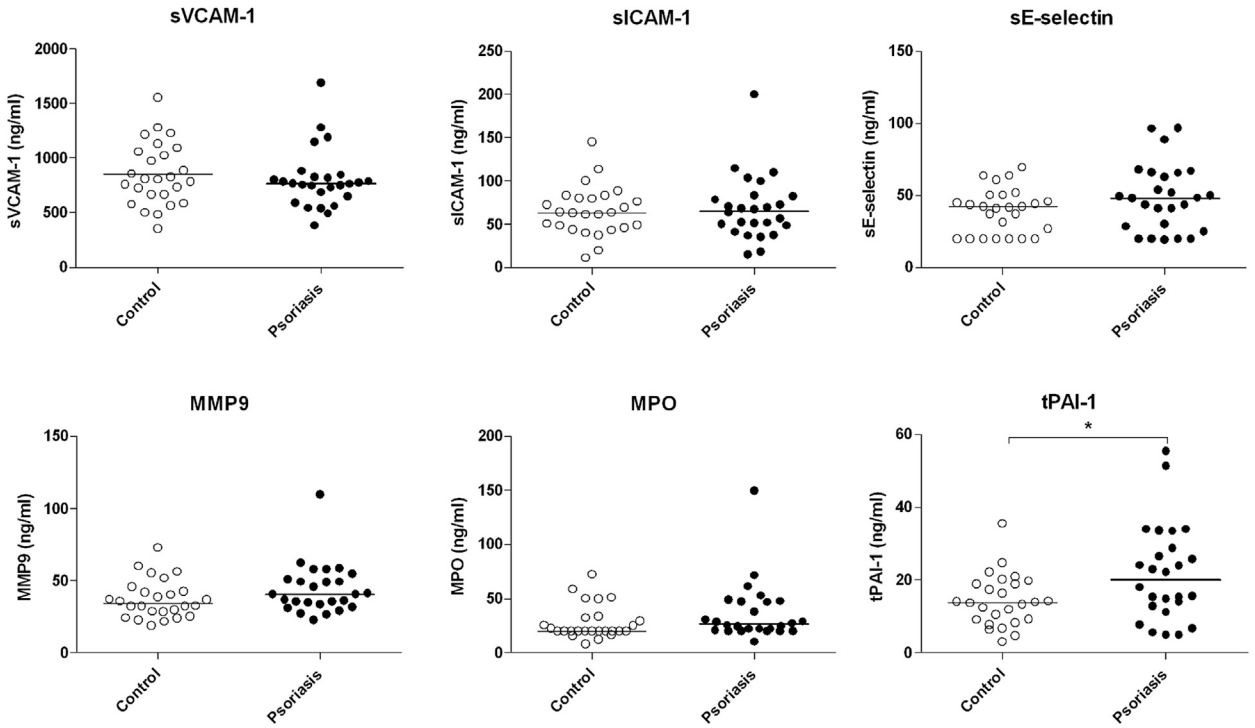

Fig 2. The levels of cardiovascular risk markers soluble vascular cell adhesion molecule (*sVCAM*)-1, soluble intercellular adhesion molecule (*sICAM*)-1, soluble E (*sE*)-selectin, matrix metalloproteinase (*MMP*)-9, myeloperoxidase (*MPO*), and total plasminogen activator inhibitor (*tPAI*)-1 measured in the plasma of age-, gender-, and body mass index (BMI)-matched patients with psoriasis and control subjects, n = 26. The line shows the median. The mean age and BMI of the patients were 50.7 years (range 27-79) and 26.0 kg/m^2 (range 22.0-34.7). The median Psoriasis Area and Severity Index (PASI) score was 6.7 (range 0.6-17.1), *$P < .05$.

whereas sVCAM-1 is a marker of the severity of atherosclerosis in patients with established disease.[20] In the psoriatic lesion, membrane-bound ICAM-1 has been detected in keratinocytes[21] and ICAM-1 and VCAM-1 are expressed in T cells and Langerhans cells of the inflammatory infiltrate. ICAM-1, VCAM-1, and E-selectin have also been demonstrated in dermal vessels of psoriatic lesions.[21,22] In a meta-analysis comprising 78 studies, increased levels of sICAM-1 and sE-selectin were detected in the serum of patients with psoriasis.[23]

MMPs degrade extracellular matrix components and are regarded as key regulatory molecules in the pathogenesis of cardiovascular disease.[24] MMP-9 levels are independently associated with adverse cardiovascular outcomes.[25] The MMP-9 protein is induced by TNF-alfa and is in psoriatic lesions produced by macrophages and neutrophils.[26] In a study of psoriatic arthritis, infliximab treatment led to a reduction in the MMP-9 and sE-selectin serum levels, together with a reduction in the spontaneous release of MMP-9 and sE-selectin from lesional skin.[27] Therapy with TNF-alfa inhibitor also leads to a reduction in MMP-9 in peripheral blood mononuclear cells, plasma, and psoriatic lesions.[28] Moreover, methotrexate down-regulates these molecules in psoriatic skin.[21]

MPO is an enzyme present in leukocytes and in arteriosclerotic plaques, where it oxidizes low-density lipoprotein in the artery wall. Elevated levels of MPO are linked to an increased risk of coronary disease and MPO has been proposed as a prognostic factor.[29] Thrombus-related cardiovascular markers have also been implicated in psoriasis. The most common abnormality of fibrinolysis is a result of increased levels of plasminogen activator inhibitor (PAI)-1. PAI-1 is the main inhibitor of tissue-type plasminogen activator and is therefore a potent inhibitor of fibrinolysis. Elevated plasma levels are noted in abdominal obesity, insulin resistance, hypertriglyceridemia, thrombosis, and cardiovascular disease[30] and may be a link among obesity, insulin resistance, and a risk of cardiovascular events.[31] Previous data on PAI-1 expression in psoriasis are limited. In a study by Gissler et al,[32] which investigated PAI-1 expression in skin, PAI-1 was not detected in normal epidermis and was only present in a fraction of the psoriatic lesions investigated. Another study revealed increased levels

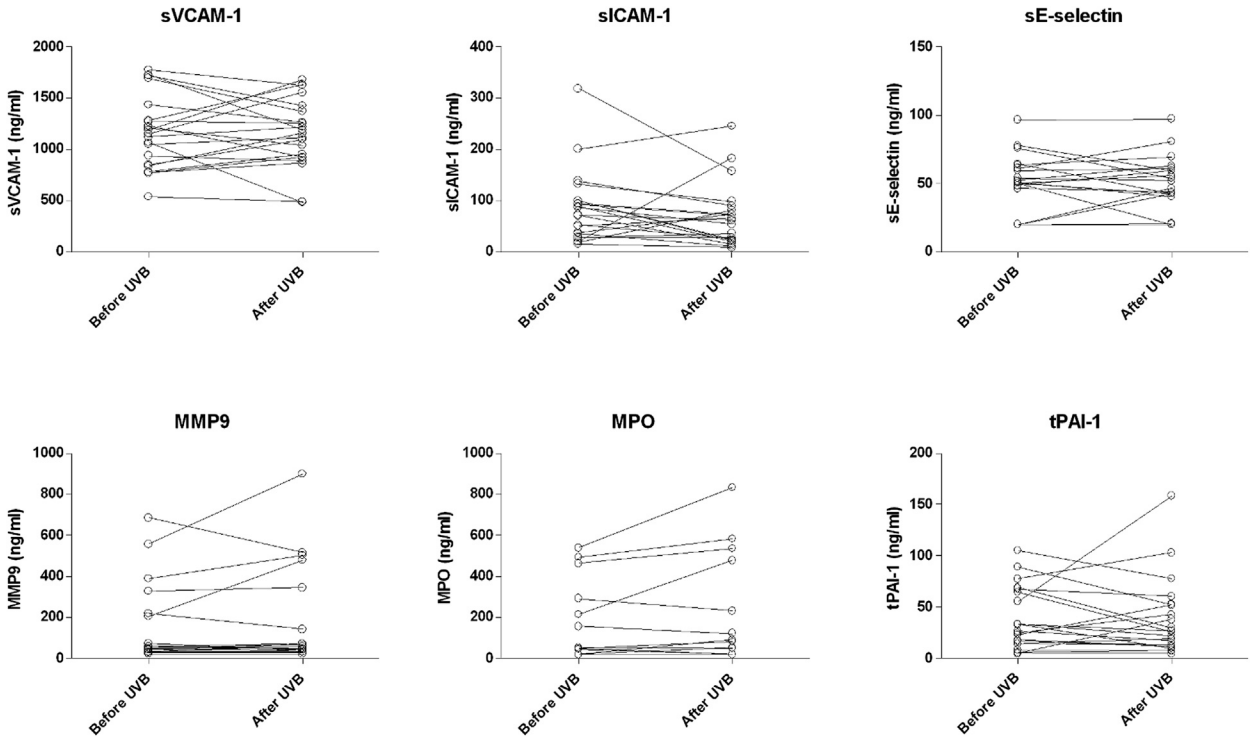

Fig 3. The levels of cardiovascular risk markers soluble vascular cell adhesion molecule (*sVCAM*)-1, soluble intercellular adhesion molecule (*sICAM*)-1, soluble E (*sE*)-selectin, matrix metalloproteinase (*MMP*)-9, myeloperoxidase (*MPO*), and total plasminogen activator inhibitor (*tPAI*)-1 in the plasma of patients with psoriasis before and 12 weeks after narrowband ultraviolet (UV)B therapy, n = 21. The mean age of the patients was 50.2 years. The median Psoriasis Area and Severity Index (PASI) score was 8.3 (range 2.20-17.2) at week 0 and 1.8 (range 0.0-5.6) at week 12.

of PAI-1 in the plasma of psoriatic patients compared with control subjects, followed by a reduction during treatment.[33]

Although these markers are strongly associated with cardiovascular risk, it should be remembered that additional mediators may contribute.

The effect of TNF-alfa inhibitor treatment on the levels of these mediators is not surprising. TNF-alfa is a key proinflammatory cytokine in psoriasis and induces the expression of several inflammatory adipokines and adhesion molecules, such as ICAM-1, VCAM-1, and E-selectin.[34]

NB-UVB phototherapy is a standard treatment for psoriasis. It is often the prior intervention before systemic treatment is considered in patients with moderate to severe psoriasis. UVB is considered primarily to affect the epidermis, where a major part of the UVB radiation is absorbed. NB-UVB suppresses the interferon and Th17-signaling pathways in the skin.[35] Moreover, keratinocyte apoptosis is a mechanism of action of NB-UVB in psoriatic epidermis.[36]

We demonstrate that, in spite of clinical improvements in psoriasis skin symptoms, patients receiving NB-UVB treatment display continuously high levels of circulating cardiovascular risk markers, supporting the hypothesis that the effect of the treatment is localized to the skin. This is in contrast to the patients treated with TNF-alfa inhibitor, where we detected highly significant reductions in the studied risk markers after treatment.

This study was a nonrandomized study. As such, it cannot be fully excluded that other factors present in the etanercept group could influence the responsiveness to treatment. However, the reduction we observe in the etanercept group is very pronounced, and the notion of a decreased cardiovascular risk by use of TNF-alfa inhibitors is supported by findings of a decreased occurrence of myocardial infarction in patients with psoriasis upon treatment.[37] Systemic therapy has an effect on cardiovascular risk in both rheumatoid arthritis and psoriasis, both with systemic biological therapy and methotrexate.[38,39] In psoriasis, methotrexate down-regulates the expression of the membrane-bound isoforms of ICAM-1, VCAM-1, and E-selectin in the skin.[21] Furthermore, the therapy decreases the soluble form of E-selectin in serum from patients with the autoimmune skin

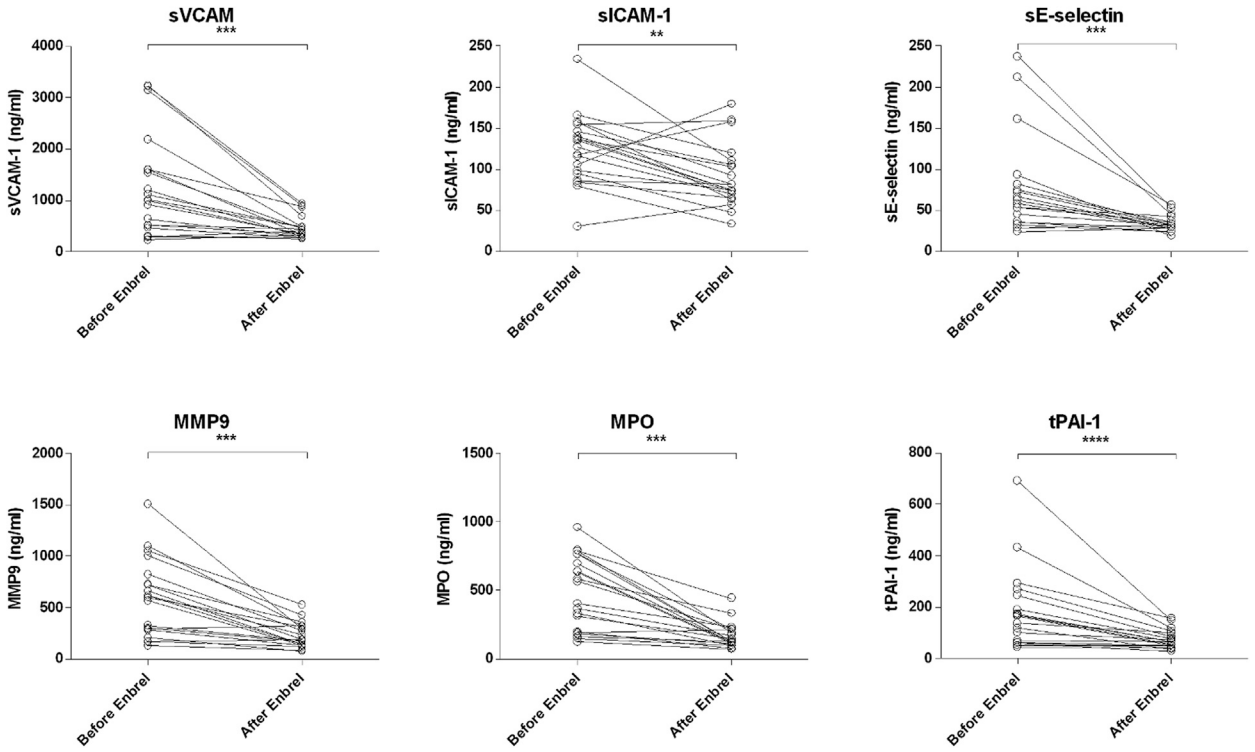

Fig 4. The levels of cardiovascular risk markers soluble vascular cell adhesion molecule (*sVCAM*)-1, soluble intercellular adhesion molecule (*sICAM*)-1, soluble E (*sE*)-selectin, matrix metalloproteinase (*MMP*)-9, myeloperoxidase (*MPO*), and total plasminogen activator inhibitor (*tPAI*)-1 in the serum of patients with psoriasis before and after treatment with etanercept (Enbrel), n = 20. The mean age of the patients was 46.4 years. The median Psoriasis Area and Severity Index (PASI) score was 12.0 (range 5.0-22.4) before treatment and 4.0 (0.6-11.4) after treatment, $^{**}P < .01$, $^{***}P < .001$, $^{****}P < .0001$.

Table I. Inflammatory markers analyzed

Inflammatory marker	Indicated cardiovascular risk	References
Vascular cell adhesion molecule-1	- Inflammatory mediators in cardiovascular disease	17
Intercellular adhesion molecule-1	- The levels correlate to various cardiovascular risk factors,	18
E-selectin	such as hypercholesterolemia, hypertension, and diabetes	
Matrix metalloproteinase-9	- Associated with increased risk for stroke or cardiovascular death	24
Myeloperoxidase	- Present in arteriosclerotic plaques	28
	- Associated with increased risk of coronary disease	28
Total plasminogen activator inhibitor-1	- Elevated levels in thrombosis and cardiovascular disease	29
	- Increased levels are suggested as a link among obesity,	30
	insulin resistance, and a risk of cardiovascular events	30
	- Elevated levels in atherosclerotic vessel walls and	
	atherosclerotic lesions	

disease bullous pemphigoid.[40] The cardiovascular risk biomarkers high-sensitivity C-reactive protein (hs-CRP), vascular endothelial growth factor (VEGF) and resistin decrease similarly in psoriasis both after biological therapy and methotrexate.[10]

Our results are also supported by the data from Romaní et al,[41] who observed increased systemic levels of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein (Apo) B in patients with psoriasis, levels that were unaffected by phototherapy. Signs of a persistent inflammatory process after UV therapy were also established by Coimbra et al.[42] In contrast, UV therapy led to a decrease in interleukin (IL)-22, IL-17, IL-23, IL-8, TNF-alfa, and VEGF serum levels,[43] suggesting that the skin is the major source of these

cytokines in psoriasis. However, the literature is controversial and both we and others have shown a lack of effect by UV therapy on the studied cytokines.[35,44,45] It should be remembered that the relationship between local inflammation and systemic inflammation is complex, and that an influence from the skin inflammation may affect the systemic cardiovascular risk. This is demonstrated by hs-CRP, which is a systemic marker of cardiovascular risk but that strongly correlates to disease severity measured by PASI and is reduced along with skin symptoms, for example upon UVB treatment.[46]

In conclusion, we observe an increase in the plasma levels of several markers associated with cardiovascular risk. Several of these markers correlate with BMI and WHR and are therefore most likely the result of the increased prevalence of the metabolic syndrome in patients with psoriasis. The levels of the markers were effectively diminished by treatment with the TNF-alfa inhibitor but they were not reduced by UVB treatment. This lack of reduction in cardiovascular risk markers after UV therapy suggests that this commonly used treatment might have a limited effect on the systemic inflammation and risk of cardiovascular comorbidities in psoriasis. It also suggests that, in addition to alleviating psoriasis symptoms, systemic treatment with TNF-alfa inhibitors might also serve to reduce the risk of cardiovascular comorbidities seen in patients with psoriasis. Patients with psoriasis and the metabolic syndrome may therefore benefit from systemic treatment rather than UV therapy.

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