Systemic Inflammation and Evidence of a Cardio-splenic Axis in Patients with Psoriasis

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The spleen is thought to play a role in atherosclerosis-associated immunity and cardiovascular research has indicated the existence of a cardio-splenic axis. The aim of this study was to assess splenic 18F-fluorodeoxyglucose uptake as a measure of systemic inflammation in patients with untreated psoriasis compared with historical controls assessed by positron emission tomography-computed tomography. Patients with moderate-to-severe psoriasis (n = 12, age 61.4 ± 4.1 years, 83% men, mean Psoriasis Area Severity Index score of 14.5) and controls (n = 23, age 60.4 ± 4.5 years, 87% men) were included in the study. Splenic inflammation was measured using the background-corrected spleen-liver-ratio (SLR) based on mean standardized uptake values. Mean ± SD SLR was increased in patients with psoriasis compared with controls (0.94 ± 0.11 vs. 0.82 ± 0.08; p = 0.001). SLR was significantly associated with aortic inflammation. These results support the existence of systemic inflammation in patients with psoriasis, and provide the rationale for a mechanistic link between psoriasis-driven inflammation and cardiovascular comorbidity through a spleen-atherosclerotic axis.

Key words: positron emission tomography computed tomography; inflammation; spleen; psoriasis; vascular inflammation; atherosclerosis.

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Psoriasis is a common immune-mediated inflammatory disease that affects the skin, nails and joints. However, in recent years the disease has also been linked (directly or indirectly) to a host of comorbidities, with a strong focus on cardiovascular comorbidities. For example, psoriasis has been associated with an increased prevalence of all traditional cardiovascular risk factors (1), with premature coronary artery disease (2), and an increased risk of major adverse cardiovascular events and cardiac mortality (3, 4). Exploratory studies indicate shared immunological mechanisms in psoriasis and atherosclerosis (5, 6). Furthermore, patients with psoriasis exhibit increased inflammation of the aortic wall (7–9). In addition, it has been hypothesized that an increased systemic inflammatory load in patients with psoriasis, at least in part, causes premature atherosclerotic disease (10). Some studies show evidence of systemic inflammation in psoriasis, whereas other studies rebut these findings (11). A recent meta-analysis of soluble biomarkers of systemic inflammation shows evidence of mild systemic inflammation in patients with psoriasis compared with healthy control subjects (12). Taken together, it remains unclear to which extent psoriasis causes systemic inflammation, whether this is clinically relevant and if it is causally associated with premature development of cardiovascular disease.

Since the approval of the first commercial system in 2001, 18F-fluorodeoxyglucose-positrone emission tomography computed tomography (FDG-PET/CT) has become a valuable imaging method in oncology. In addition, this modality is increasingly being used as an imaging tool for inflammatory conditions in general. Given the focus on inflammation in vascular plaque formation, FDG-PET/CT imaging has been investigated as an imaging tool in atherosclerosis (13), and it has been shown that FDG accumulation correlates with atherosclerotic plaque inflammation (14, 15). Preliminary insights indicate an association between FDG uptake in the vascular wall and increased risk of future cardiovascular events (16, 17). In addition, splenic inflammation can be visualized by FDG-PET/CT. Splenic FDG uptake is increased in inflammatory, malignant and infectious diseases, and the spleen-to-liver ratio (SLR) correlates with the peripheral neutrophil count (18–22). As shown in a human autopsy study, the spleen may play a role in activating and directing monocytes to the heart following ischaemic events (23). Furthermore, it has been shown that the activation state of the spleen may be closely related to proinflammatory gene activation within circulating leukocytes and that splenic FDG uptake independently predicts the risk of cardiovascular events (24). Based on preclinical and clinical data, a central role of the spleen in the progression of atherosclerotic disease has been suggested and conceptualized as the “cardio-splenic axis” (24–26). This concept entertains the hypothesis of a spleen-atherosclerotic plaque crosstalk.

We recently showed that aortic inflammation and subcutaneous adipose tissue inflammation, assessed by FDG-PET/CT, are significantly increased in patients with psoriasis compared with control subjects (9). The primary objective of the present study was to expand on these findings by assessing splenic FDG uptake as a measure of systemic inflammation in the same cohorts of patients with psoriasis and control subjects. A secondary objective was...
to investigate whether splenic inflammation is associated with aortic and subcutaneous adipose tissue inflammation.

**MATERIALS AND METHODS**

**Design and protocol**

The study was designed as an open-label, controlled clinical study. We utilized a previous study cohort, established between January 2015 and May 2016 at a single tertiary dermatology university hospital clinic (9). Imaging investigations were performed at a university hospital nuclear medicine PET centre.

Consecutively enrolled patients with moderate-to-severe psoriasis were examined with FDG-PET/CT and compared with a retrospectively age- and sex-matched control group.

The study was conducted in compliance with the principles of the Declaration of Helsinki. The protocol was reviewed and approved by the Central Denmark Region Committees on Biomedical Research Ethics and by the Danish Data Protection Agency. All consecutively enrolled participants provided written informed consent prior to any study procedures. The Committee on Research Ethics waived the requirement for informed consent regarding the retrospectively matched control group.

**Study population: patients with psoriasis and controls**

Details of the inclusion and exclusion criteria have been described previously (9). Briefly, patients aged between 50 and 70 years with moderate-to-severe psoriasis vulgaris, i.e. a Psoriasis Area Severity Index (PASI) score of at least 10, were eligible for study inclusion if they had no concurrent inflammatory or autoimmune diseases, no history of malignancies within the past 5 years (excluding localized non-melanoma skin cancer) and no contraindications for the clinical use of FDG-PET/CT. Where appropriate, patients with psoriasis were entered into a pre-study washout period, where-in all active anti-psoriatic topical and systemic therapies were discontinued according to pre-specified time frames. The control group comprised age-matched men and women aged ≥ 18 years who were examined at the same centre, using the same technique as that employed for the study cases. The control subjects were either patients with localized melanoma or patients with localized stage 1 melanoma. Additional eligibility criteria and details on clinical assessments are shown in Appendix S1.

**Positron emission tomography acquisition**

Whole-body FDG-PET/CT in patients with psoriasis was performed using a combined PET/CT scanner (GE Discovery 690, General Electric Medical Systems, Milwaukee, WI, USA). Control subjects were either scanned on the same GE Discovery 690 PET/CT or on a Siemens Biograph 64 PET/CT (Siemens, Germany).

A detailed description of the scan parameters is provided in Appendix S1.

**Image analysis**

PET and CT data were fused and analysed with PMOD v3.703 (PMOD Technologies, Zurich, Switzerland). CT and PET images were reviewed for quality, and the images were manually co-registered to ensure optimal anatomical correlation. Image analysis was performed in accordance with recent nuclear medicine imaging guidelines by one expert observer (L.C.G.).

In accordance with previously published methodology the splenic volume was assessed in each CT examination by measuring:

- the maximal width of the spleen, determined as the largest diameter on any transverse section; the maximal thickness, defined as the largest distance between the inner and outer borders of the spleen perpendicular to the plane of the maximal width; and the thickness at the hilum, determined as the distance between the inner and outer borders of the spleen on a plane perpendicular to the splenic width and through the hilum (27).

Splenic inflammation was measured using mean standardized uptake values (SUVmax) and maximal standardized uptake values (SUVmax) and the target-to-background ratio (TBR) of the whole vessel and aortic segments in accordance with recent nuclear medicine imaging guidelines (13) and previously published methodology (9, 28). The TBR was calculated from the ratio of the SUV of the aorta compared with background venous activity, derived from the superior vena cava, for correction of aortic values.

Subcutaneous adipose tissue inflammation was assessed as SUVmax. A detailed description of the aortic wall and subcutaneous adipose tissue image analyses has been published previously (9).

**Statistical analysis**

Summary statistics were expressed as mean ± standard deviation (SD) for normally distributed variables. Patient characteristics were compared using Student’s t-test for continuous variables and Pearson’s χ2 for categorical variables. The primary outcome measure was the mean difference in SLR between the patients with psoriasis and the control group. Between-group differences were compared using the unpaired t-test with equal variances. A multivariate analysis of covariance (ANCOVA) was performed as a secondary analysis to test the effect of the continuous covariates of age and body mass index (BMI) and categorical variable sex on difference in SLR.

Associations were tested using Pearson’s correlation coefficient. Data were tested for normality using the D’Agostino-Pearson normality test (see Appendix S1 for details). The level of statistical significance was set at α = 0.05. Graphs and statistical analyses were made in GraphPad Prism version 7.0 (GraphPad software, San Diego, CA, USA) and STATA/IC ver. 12.1 for Mac (StataCorp LP, College Station, TX, USA).

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**Fig. 1. Coronal and transverse PET images with volume of interests drawn in the spleen and the liver in a representative patient with psoriasis. Arrows indicate the region of interest in the spleen, liver, and aorta.**

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RESULTS

Included in the study were 12 subjects with moderate-to-severe psoriasis and 23 controls. Table I shows the characteristics of the included study subjects. The mean ± SD splenic total volume was slightly higher, albeit insignificantly so, among psoriasis patients compared with controls (269.5 ± 95.6 cm³ vs. 224.5 ± 62.8 cm³; p = 0.11).

Further imaging analyses are shown in Table II. FDG uptake in aortic segments and subcutaneous adipose tissue has been published previously (9). Mean SLRmean was increased in patients with psoriasis compared with controls (mean ± SD SLR 0.94 ± 0.11 vs. 0.82 ± 0.08; p = 0.001 (Fig. 2).

A significant association between SLR and aortic mean whole vessel TBRmax was found in the populations overall (Pearson r = 0.51; p = 0.002) and in the subjects with psoriasis (Pearson r = 0.65; p = 0.02) (Fig. 3A). No significant association between SLR and aortic mean whole vessel TBRmax was found in the control subjects (Pearson r = 0.16; p = 0.48). Comparable results were seen when assessing SLRmax based on spleen and liver SUVmax (see results in Appendix S2).
or between psoriatic disease duration and SLR (Pearson
\( r = 0.40; p = 0.20 \)).

After adjusting for BMI, age and sex using a multi-
variate ANCOVA regression model, psoriasis remained
significantly associated with elevated SLR levels (\( F = 3.79,\)
\( p = 0.01 \)). Furthermore, no difference was seen between
PET investigations in controls using GE Discovery 690
PET/CT vs. Siemens Biograph 64 PET/CT (mean ± SD
SLR\(_{\text{mean}} \) 0.81 ± 0.07 vs. 0.83 ± 0.09; \( p = 0.60 \)).

**DISCUSSION**

This is the first clinical study to show increased splenic
inflammation in patients with moderate-to-severe psoriasis
compared with control subjects. It also shows that splenic
inflammation is associated with aortic inflammation in
patients with psoriasis. Taken together with our previous
findings of increased global arterial and subcutaneous
adipose tissue inflammation in this cohort, these data pro-
vide evidence to support a role of systemic inflammation
and a likely role of an interplay between the spleen and
atherosclerotic plaque in patients with psoriasis.

The hypothesis that psoriasis may be a systemic in-
flammatory disease rather than a localized disease of the
skin and nails has gained much attention in recent years,
but the concept rests mainly on evidence from soluble
blood biomarker studies and on deductive reasoning ba-
ased on observational registry data (29). Most published
studies on soluble biomarkers indicate a moderate role
of systemic inflammation in psoriasis (1, 12). However,
these studies have a number of limitations in addition to
unknown predictive values and the non-specificity of
certain biomarkers. Nevertheless, systemic inflammation
in psoriasis has become a key suspected culprit in the
link between psoriasis and cardiovascular comorbidities,
as well as in the reasoning on the role of psoriasis as an
independent risk factor for future cardiovascular events
that is seemingly unrelated to the traditional cardiovas-
cular risk factors. Although this hypothesis has gained
considerable momentum, the reported cardiovascular
effects of dampening the systemic inflammation with

tumour necrosis factor-alpha (TNF-\( \alpha \) inhibitors have been
somewhat conflicting (30, 31).

FDG-PET/CT provides a direct measure of metabolic
activity in vessels and other tissues. FDG is a radiolabel-
led glucose analogue that is taken up by tissues with high
metabolic activity, such as inflammatory active tissue and
tumour cells. Accumulation of FDG in the arterial wall
localizes to macrophage-rich regions and correlates with
immunohistochemical staining and gene expression for
macrophage-specific markers, as well as with soluble
markers of inflammation (32, 33). Furthermore, arterial
FDG uptake increases in proportion to atherosclerotic
risk factors, with plaque morphological complexity, and
after atherothrombotic events (34). It has been shown
that FDG-PET/CT significantly improves cardiovascular
disease prediction beyond that of traditional risk factor
scoring, and that FDG-PET/CT imaging provides prog-
nostic information adding to that which may be obtained
using soluble biomarkers (16, 17, 35, 36).

The spleen is a key organ in erythrocyte homeostasis
and plays important roles in the immunological system.
Leukocytes in the spleen include various subsets of T and
B cells, dendritic cells and macrophages that initiate and
control innate and adaptive immune functions.

It has been shown that splenic inflammation assessed
by FDG-PET/CT is increased in patients with autoim-
mune and inflammatory diseases, and that the splenic
FDG uptake correlates with measures of systemic inflam-
mation (18–22). Furthermore, studies in murine models
indicate a role of the spleen in atherosclerosis-associated
immunity (25, 37). Human proof-of-concept studies show
increased levels of splenic FDG uptake in patients with
recent myocardial infarction and an association between
splenic and arterial inflammation (38, 39). Emami et al.
showed that aortic wall FDG uptake correlated with spon-
ch NF FDG uptake in a large number of patients (\( n = 464 \)).
Moreover, in this study splenic FDG uptake appeared
to be a predictor of future cardiovascular events. Taken
together with the correlation between splenic and aortic
inflammation, this entails that not only does the spleen
react acutely to myocardial infarction, but it also appears
to drive cardiovascular inflammation in a stable setting
(24, 26). Thus, the results of the current study corrobora-
the existence of systemic inflammation in psoriasis beyond
that ascertained in previous biomarker studies, and the
current study provides the rationale for a mechanistic link
between psoriasis-driven inflammation and cardiovascular
comorbidity through a spleen-atherosclerotic axis.

In addition, we observed an increased volume of the
spleen in patients with psoriasis compared with controls,
albeit insignificantly so. Thus, a recent publication de-
cribed increased spleen longitudinal diameter in patients
with psoriasis compared with non-psoriatics, as well as an
association between disease duration and splenic diameter
(40). While this publication provided important quantative
analyses of the spleen in psoriasis, our study extends these
findings by providing functional imaging analysis, which
quantifies the metabolic activity of the spleen.

Interestingly, we found no association between PASI
scores and splenic inflammation. Hypothetically, a dose-
response relationship between psoriasis severity and the
inflammatory activation state of the spleen would be
plausible. The absence of such correlation in our data may
de be due to the low variation in PASI scores and the limited
number of subjects investigated. Another reason may be
that PASI is not an optimal instrument for assessment of
systemic inflammation in patients with psoriasis (41).
This viewpoint is supported by the fact that studies with
cardiovascular and systemic inflammatory outcomes show
conflicting results when assessing the association with
PASI (2, 8, 9, 31, 42, 43).
These findings are strengthened by the use of background-corrected ratios TBR and SLR rather than SUV. Thus, the use of a ratio between 2 measurements limits the effects on signal quantification of errors in patient weight and in the dose of radiotracer injected and of the imaging time-point (13). It has been shown that exclusive use of SUV does not reliably reflect tissue metabolic activity and that, especially, correlations between SUV in various tissues should be interpreted with caution due to a positive correlation between SUV and body weight (26, 44). Thus, and in agreement with recent literature (26), SLR and not SUV was the primary outcome measure in this study. Further methodological strengths of the present study include our use of robust splenic and liver SUV mean values, which reduces the risk of measurements based on single high pixel values; the analysis of the entire aorta without sampling of slices; the inclusion of untreated psoriasis patients with moderate-to-severe disease activity only; and the use of semi-automatic software for image analysis, which makes the results reproducible with a low risk of biased assessments. The findings remained significant after adjusting for age, sex and BMI.

The main limitations of the study include the small sample size, the open-label design, restricted age groups due to radiation exposure, and the use of historical control subjects for whom only limited medical data were available.

It is well known that psoriasis is associated with an increased risk of non-alcoholic fatty liver disease (NAFLD) (45). As the presence of NAFLD was not specifically assessed it cannot be ruled out that some patients with NAFLD may have been included in our study. Although contradictory results have been published, recent studies indicate that NAFLD may increase the liver FDG uptake, which may have caused us to underestimate the SLR in such patients (46, 47). In addition, 2 PET/CT systems were used. Comparable protocols were used, however, and no significant differences between results obtained from the 2 systems were noted.

Finally, although compelling interrelationships were observed between splenic activation and arterial inflammation, these relationships do not necessarily indicate causality.

In conclusion, our data provide evidence of increased splenic inflammation in subjects with moderate-to-severe psoriasis. Furthermore, we show that splenic activity correlates with aortic wall inflammation in subjects with psoriasis. These findings indicate clinically relevant systemic inflammation in patients with moderate-to-severe psoriasis. The cardio-splenic axis may mechanistically, at least in part, explain the epidemiological observation that patients with psoriasis have an increased risk of heart disease.

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