Statin Therapy and Vascular Inflammation Detected by Positron Emission Tomography/Computed Tomography in Patients with Psoriasis

Hannah KAISER[1–3], Amanda KVIST-HANSEN[1–3], Martin KRAKAUER[4,5], Peter Michael GØRTZ[4], Kristoffer Mads Aaris HENNINGSEN[1], Xing WANG[6], Christine BECKER[6,7], Lone SKOV[2,3] and Peter Riis HANSEN[1,3]

[1]Department of Cardiology, [2]Department of Dermatology and Allergy and [4]Department of Clinical Physiology and Nuclear Medicine, Herlev and Gentofte Hospital, DK-2900 Hellerup, [3]Department of Clinical Medicine, University of Copenhagen, [5]Department of Clinical Physiology and Nuclear Medicine, Bispebjerg and Frederiksberg Hospital, Copenhagen, [6]Department of Medicine, Division of Clinical Immunology, Icahn School of Medicine at Mount Sinai, New York, NY, USA and [7]Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA. E-mail: lilian.hannah.kaiser@regionh.dk

Accepted Jan 21, 2021; Epub ahead of print Jan 25, 2021

Psoriasis is associated with increased risk of cardiovascular disease (CVD) and shares inflammatory mechanisms with atherosclerosis, the main contributor to CVD (1). Studies with 18F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) have shown that patients with psoriasis have increased aortic vascular inflammation, an independent predictor of future CVD (2, 3). In addition, psoriasis severity has been associated with aortic inflammation independent of traditional cardiovascular risk factors, including hypercholesterolaemia (4). Statins are lipid-lowering drugs used for prevention of CVD and these agents decrease vascular inflammation in patients at increased risk of CVD (5). However, whether statins are linked with reduced vascular inflammation in patients with psoriasis is not known.

Table I. Characteristics of study patients with or without statin treatment

	Statin treatment ($n=41$)	No statin treatment ($n=42$)	p-value
Age, years, mean±SD	61.1±8.3	58.1±13.0	0.219
Sex, male, *n* (%)	33 (80.5)	27 (64.3)	0.099
PASI, median (IQR)	3.0 (1.5-11.2)	3.6 (0.8-8.9)	0.783
BMI, kg/m^2, mean±SD	30.5±5.3	29.4±6.0	0.371
Psoriasis before 30 years of age, *n* (%)	23 (56.1)	31 (73.8)	0.091
Medically treated hypertension, *n* (%)	24 (58.5)	12 (28.6)	0.006
Medically treated diabetes, *n* (%)	17 (41.5)	3 (7.1)	<0.001
Prior atherosclerotic CVD, *n* (%)	31 (75.6)	8 (19.0)	<0.001
Smoking (current or previous), *n* (%)	34 (82.9)	27 (64.3)	0.054
PsA verified by rheumatologist, *n* (%)	9 (22.0)	11 (26.2)	0.652
Systemic antipsoriatic treatment, *n* (%)[a]	23 (56.1)	21 (50.0)	0.578
HbA1c, mmol/mol, median (IQR)	37.0 (35.0-48.0)	35.0 (33.0-37.0)	0.001
Total cholesterol, mmol/l, mean±SD	3.83±0.85	5.02±0.72	<0.001
LDL-C, mmol/l, mean±SD	1.83±0.55	2.94±0.69	<0.001
hs-CRP, mg/l, median (IQR)	0.94 (0.55-2.84)	2.08 (1.13-5.23)	0.007

[a]Biologic therapy and/or methotrexate.
SD: standard deviation; IQR: interquartile range; PASI: Psoriasis Area and Severity Index; BMI: body mass index; CVD: cardiovascular disease; PsA: psoriatic arthritis; HbA1c: glycated haemoglobin; LDL: low-density lipoprotein; hs-CRP: high-sensitivity C-reactive protein.

MATERIAL AND RESULTS

After informed consent, a total of 83 consecutive adult patients with plaque psoriasis with or without atherosclerotic CVD (myocardial infarction, stroke and/or peripheral artery disease) were recruited at our centre for a multiscale study of the association between CVD and psoriasis (regional ethics committee project ID H-17003458). All patients received intravenous ^{18}F-FDG (3.5 MBq/kg) 120 min prior to whole-body ^{18}F-FDG-PET/CT. Unenhanced low-dose CT images were used for anatomical correlation and 3-mm axial PET slices were manually placed around the external contour of the aorta to outline region of interests (ROIs) and were analysed using MIM 6.9.2 software (MIM Software Inc., Cleveland, OH, USA). The superior vena cava (VCS) was used to correct for background blood activity and vascular inflammation was quantitated in accord with established methods (5, 6). In brief, in each aortic segment a ROI was placed that encompassed both the aortic lumen and wall. The maximal standardized uptake value (SUV_{max}) of each slice of the ROI was divided by the SUV_{mean} of the VCS to achieve the maximal target-to-background ratio (TBR_{max}). Moreover, the mean TBR_{max} was calculated from TBR_{max} values from all slices of each aortic segment. Most-diseased segments (MDSs) were found by detecting slices with the highest FDG uptakes and averages of TBR_{max} values were calculated for the adjacent 1.5 cm segments surrounding these slices. For statistical analyses, Welch 2-sample *t*-test, χ^2 test, exact Wilcoxon-Mann-Whitney test, and multivariable regression models adjusted for sex, age and systemic antipsoriatic treatment were used, as appropriate. All analyses were performed with RStudio version 1.2.5033.

Characteristics of patients with psoriasis with or without statin therapy are shown in **Table I**. Mean age and Psoriasis Area Severity Index were not different between the 2 groups. As expected, patients who received statins were more likely to have a history of atherosclerotic CVD (75.6 vs 19.0%; $p<0.001$), and to receive treatment for hypertension and diabetes. Also, levels of total cholesterol, low-density lipoprotein cholesterol, and the inflammatory biomarker high-sensitivity C-reactive protein (hs-CRP) were lower in the statin group, while glycated haemoglobin (HbA1c) levels were higher. In unadjusted analyses, vascular inflammation measured by FDG uptake (TBR_{max} and MDS) was nominally lower in the entire aorta and all individual aortic segments in patients treated with statins compared with those without statins, although these unadjusted results were not significant (**Table II**). After adjustment for age and sex, however, TBR_{max} was significantly lower in the ascending aorta and the aortic arch, and MDS was lower in the

Table II. Vascular inflammation in patients with or without statin treatment

	Statin treatment ($n=41$) Mean±SD	No statin treatment ($n=42$) Mean±SD	p-value	p-value*	p-value**
TBR_{max} entire aorta	2.19±0.41	2.35±0.36	0.067	0.067	0.072
TBR_{max} ascending aorta	2.36±0.43	2.54±0.45	0.070	0.038	0.046
TBR_{max} aortic arch	2.34±0.46	2.51±0.43	0.090	0.033	0.038
TBR_{max} descending aorta	2.15±0.41	2.31±0.36	0.072	0.086	0.090
MDS ascending aorta	2.55±0.51	2.73±0.50	0.124	0.068	0.082
MDS aortic arch	2.45±0.51	2.62±0.46	0.103	0.032	0.037
MDS descending aorta	2.67±0.55	2.83±0.51	0.166	0.140	0.148

*Adjusted for age and sex. **Adjusted for age, sex and systemic antipsoriatic treatment.
SD: standard deviation; TBR: target-to-background; MDS: most diseased segment.

doi: 10.2340/00015555-3752
Acta Derm Venereol 2021; 101: adv00406

aortic arch, which was also apparent after adding adjustment for systemic antipsoriatic treatment in the model (Table II).

DISCUSSION

This study found that statin therapy was associated with decreased vascular inflammation in patients with psoriasis. Notably, most (75.6%) patients in the statin group had prior atherosclerotic CVD and in patients with psoriasis, favourable effects of statins on atherosclerotic plaque inflammation therefore do not appear to be mitigated by the presence of established CVD. In this regard, *post hoc* analyses from both primary and secondary prevention trials have indicated that statins improve CVD outcomes in patients with psoriasis irrespective of established vascular disease, and psoriasis is perceived as a CVD risk-enhancing factor in assessment of patients for cholesterol-lowering treatment (7, 8). In addition to their lipid-lowering effects, statins display pleiotropic anti-inflammatory actions and reduce hs-CRP levels, as also suggested by the data from the current study, but the role of lipid-independent mechanisms in statin-induced vascular effects remains to be determined (9).

Limitations of this study include that it was not a randomized trial, a control group of individuals without psoriasis was not included, some individuals declined study participation and this self-election may have introduced bias. In addition, there are technical limitations of ^{18}F-FDG-PET/CT. The FDG uptake in inflammatory cells is influenced by, for example, fasting state, blood glucose and insulin levels, as well as the injected ^{18}F-FDG dose. Moreover, imaging protocols and PET/CT scanner properties play a role. In the current study conditions were standardized by measuring blood glucose levels (all were below 11.1 mmol/l (10)), using weight-adjusted ^{18}F-FDG dosing, and observing a fixed time interval between ^{18}F-FDG injection and scanning. This study used TBR in attempt to compensate for individual differences in ^{18}F-FDG excretion rates by correcting for background blood activity. In addition, reduction in vascular inflammation in the statin group was not significant in the unadjusted analyses in the aortic segments. However, significant differences were not least observed when adjusted for age, sex and systemic antipsoriatic treatment in the ascending aorta, where ^{18}F-FDG-PET/CT measurements have shown good reproducibility and where vascular inflammation is predictive of future CVD independent of traditional risk factors (3, 5, 11).

In conclusion, the results of this study suggest that statins may be linked with reduced vascular inflammation in patients with psoriasis, and the results may support the case for use of statins in patients with psoriasis who are at increased risk of CVD.

ACKNOWLEDGEMENTS

Joel Dudley, PhD, and Brian Kidd, PhD, are acknowledged for support.

Funding: HK, AKH, XW, CB and PRH were supported by the LEO Foundation (grant no. LF16115).

Conflicts of interest: PRH is a recipient of a Borregaard Clinical Scientist Fellowship from the NOVO Nordisk Foundation and chairs a clinical academic group supported by the Greater Region of Copenhagen. CB is a consultant for Onegevity Health. LS has been a paid speaker for AbbVie, Eli Lilly and LEO Pharma, and has been a consultant or served on Advisory Boards with AbbVie, Janssen Cilag, Novartis, Eli Lilly, LEO Pharma, UCB, Admirall and Sanofi. She has served as an investigator for AbbVie, Janssen Cilag, Boehringer Ingelheim, AstraZenica, Eli Lilly, Novartis, Regeneron and LEO Pharma and received research and educational grant from Pfizer, AbbVie, Novartis, Sanofi, Janssen Cilag and Leo Pharma.

REFERENCES

1. Alexandroff AB, Pauriah M, Camp RD, Lang CC, Struthers AD, Armstrong DJ. More than skin deep: atherosclerosis as a systemic manifestation of psoriasis. Br J Dermatol 2009; 161: 1–7.
2. Hjuler KF, Gormsen LC, Vendelbo MH, Egeberg A, Nielsen J, Iversen L. Increased global arterial and subcutaneous adipose tissue inflammation in patients with moderate-to-severe psoriasis. Br J Dermatol 2017; 176: 732–740.
3. Figueroa AL, Abdelbaky A, Truong QA, Corsini E, MacNabb MH, Lavender ZR, et al. Measurement of arterial activity on routine FDG PET/CT images improves prediction of risk of future CV events. JACC Cardiovasc Imaging 2013; 6: 1250–1259.
4. Naik HB, Natarajan B, Stansky E, Ahlman MA, Teague H, Salahuddin T, et al. Severity of psoriasis associates with aortic vascular inflammation detected by FDG PET/CT and neutrophil activation in a prospective observational study. Arterioscler Thromb Vasc Biol 2015; 35: 2667–2676.
5. Tawakol A, Fayad ZA, Mogg R, Alon A, Klimas MT, Dansky H, et al. Intensification of statin therapy results in a rapid reduction in atherosclerotic inflammation: results of a multicenter fluorodeoxyglucose- positron emission tomography/computed tomography feasibility study. J Am Coll Cardiol 2013; 62: 909–917.
6. Bucerius J, Hyafil F, Verberne HJ, Slart RHJA, Lindner O, Sciagra R, et al. Position paper of the cardiovascular committee of the european association of nuclear medicine (EANM) on PET imaging of atherosclerosis. Eur J Nucl Med Mol Imaging 2016; 43: 780–792.
7. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the american college of cardiology/american heart association task force on clinical practice guidelines. Circulation 2019; 139: E1082–1143.
8. Ports WC, Fayyad R, DeMicco DA, Laskey R, Wolk R. Effectiveness of lipid-lowering statin therapy in patients with and without psoriasis. Clin Drug Investig 2017; 37: 775–785.
9. S. Antonopoulos A, Margaritis M, Lee R, Channon K, Antoniades C. Statins as anti-inflammatory agents in atherogenesis: molecular mechanisms and lessons from the recent clinical trials. Curr Pharm Des 2012; 18: 1519–1530.
10. Reddy AS, Uceda DE, Al Najafi M, Dey AK, Mehta NN. PET scan with fludeoxyglucose/computed tomography in low-grade vascular inflammation. PET Clinics 2020; 15: 207–213.
11. Rudd JHF, Myers KS, Bansilal S, Machac J, Rafique A, Farkouh M, et al. 18Fluorodeoxyglucose positron emission tomography imaging of atherosclerotic plaque inflammation is highly reproducible. Implications for atherosclerosis therapy trials. J Am Coll Cardiol 2007; 50: 892–896.