Lipids

Cholesterol efflux capacity in humans with psoriasis is inversely related to non-calcified burden of coronary atherosclerosis

Taufiq Salahuddin¹, Balaji Natarajan¹, Martin P. Playford¹, Aditya A. Joshi¹, Heather Teague¹, Youssef Masmoudi¹, Mariana Selwaness², Marcus Y. Chen¹, David A. Bluemke², and Nehal N. Mehta^{1*}

¹Cardiovascular and Pulmonary Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, 10 Center Drive, CRC, Room 5-5140, Bethesda, MD 20892, USA; and ²National Institute of Biomedical Imaging and Bioengineering, National Institutes of Health, Bethesda, MD, USA

Received 7 June 2015; revised 26 June 2015; accepted 1 July 2015; online publish-ahead-of-print 18 July 2015

Aims

Cholesterol efflux capacity (CEC) was recently shown to predict future cardiovascular (CV) events. Psoriasis both increases CV risk and impairs CEC. However, whether having poor CEC is associated with coronary plaque burden is currently unknown. We aimed to assess the cross-sectional relationship between coronary plaque burden assessed by quantitative coronary computed tomography angiography (CCTA) with CEC in a well-phenotyped psoriasis cohort.

Methods and results

Total burden and non-calcified burden (NCB) plaque indices were assessed in 101 consecutive psoriasis patients using quantitative software. Cholesterol efflux capacity was quantified using a cell-based *ex vivo* assay measuring the ability of apoB-depleted plasma to mobilize cholesterol from lipid-loaded macrophages. Cholesterol efflux capacity was inversely correlated with NCB (unadjusted β -coefficient -0.33 ; $P < 0.001$), and this relationship persisted after adjustment for CV risk factors ($\beta -0.24$; $P < 0.001$), HDL-C levels ($\beta -0.22$; $P < 0.001$), and apoA1 levels ($\beta -0.19$; $P < 0.001$). Finally, we observed a significant gender interaction ($P < 0.001$) whereby women with low CEC had higher NCB compared to men with low CEC.

Conclusions

We show that CEC is inversely associated with prevalent coronary plaque burden measured by quantitative CCTA. Low CEC may therefore be an important biomarker for subclinical coronary atherosclerosis in psoriasis.

Clinicaltrials.gov NCT01778569.

Keywords

Cholesterol efflux capacity (CEC) • HDL efflux • Non-calcified plaque burden • Coronary plaque burden • Quantitative coronary computed tomography angiography (CCTA) • Psoriasis • Inflammatory atherogenesis • Lipids

Introduction

HDL-cholesterol efflux capacity (CEC) is increasingly recognized as an important determinant of cardiovascular (CV) risk.^{1,2} Randomized controlled clinical trials with drugs such as niacin or cholesterol ester transport protein inhibitors increased HDL-concentration but did not improve CV outcomes, suggesting that steady-state HDL-concentration alone may not capture the complexity of HDL-associated lipid metabolism and its classically protective role in

atherosclerosis.^{3–5} Furthermore, CEC, which estimates HDL's ability to accept cholesterol from peripheral tissues such as macrophages for retrograde transport for excretion into feces, was associated inversely with incident atherosclerotic CV disease recently in a large-scale prospective cohort study¹ independent of circulating HDL-cholesterol concentration, suggesting CEC may better capture the beneficial effect of HDL in atherosclerotic diseases.

Psoriasis is a chronic inflammatory skin disease associated with CV events, presumably due to accelerated atherogenesis.^{6,7}

* Corresponding author. Tel: +1 301 827 0483, Fax: +1 301 451 7093, Email: nehalmehta@nih.gov

Published by Oxford University Press on behalf of the European Society of Cardiology 2015. This work is written by (a) US Government employee(s) and is in the public domain in the US.

Furthermore, CEC is impaired in psoriasis⁸ and is recovered after successful psoriasis treatment,⁹ suggesting a link between the systemic inflammation observed in psoriasis and impaired HDL function. Therefore, psoriasis serves as an *in vivo* model to study CEC and its relation to inflammatory atherogenesis.¹⁰

Coronary computed tomography angiography (CCTA) is validated against intravascular ultrasound¹¹ and provides a reliable framework to understand how emerging biomarkers and biological pathways may relate to *in vivo* coronary plaque. Coronary computed tomography angiography provides a measure of total coronary plaque burden and can delineate plaque composition. Therefore, the aim of our current investigation was to understand whether CEC relates to coronary plaque burden in psoriasis. We hypothesized that the total burden (TB) of coronary plaque, specifically the non-calcified component, would be inversely related to CEC.

Materials and methods

The study population included 101 consecutive patients recruited for measurement of coronary plaque burden by CCTA as part of a 4-year prospective cohort study of cardiometabolic diseases in psoriasis at the National Institutes of Health (NIH) Clinical Center (NCT01778569). Data presented here are from the baseline visit of this study of the first 101 patients.¹² All patients provided written informed consent, and the study protocol is in compliance with the Declaration of Helsinki. In brief, study participants were >18 years of age with diagnostic confirmation of plaque psoriasis by a dermatologist. Exclusion criteria included pregnancy and lactating women or estimated glomerular filtration rate <30 mL/min/1.73 m².

Patients underwent CCTA (320-detector row Aquilion ONE ViSION, Toshiba, Japan) and fasting blood draw on the same day. Coronary plaque was separately assessed in each of the main coronary arteries (left anterior descending, left circumflex, and right coronary artery) using QAngio CT (Medis, The Netherlands). Total burden and non-calcified burden (NCB) plaque indices were calculated by dividing total vessel plaque volume by total vessel length (Figure 1).

Cholesterol efflux capacity was measured in duplicate using a validated cell-based *ex vivo* assay involving the incubation of J774 macrophages with apoB-depleted serum from psoriasis subjects as previously described.⁸

Spearman correlation testing, unadjusted, and multivariable linear regression were used to assess the relationship between non-calcified coronary plaque burden and CEC beyond traditional CV risk factors (age, sex, LDL-cholesterol, systolic blood pressure, fasting blood glucose, and tobacco use), HDL, and apoA1 concentrations. Standardized β coefficients are reported. Plaque indices were adjusted for lumen intensity. We also performed stratified analyses, adjusted analyses, and sensitivity analyses to understand whether psoriasis treatment or statin medication modified our primary results. Finally, we tested for interaction by gender in fully adjusted models. All reported *P* values are two-tailed, with *P*-value <0.05 indicating statistical significance.

Results

The study population (Table 1) included 101 psoriasis patients [median psoriasis area severity index (PASI) score 6.2 indicating moderate skin disease severity] with low 10-year pooled cohort equation risk score (median 2.7%). Traditional lipid profiles were within normal limits, and the median CEC was 0.94. We found

Figure 1 Multiplanar reconstruction of coronary artery for plaque volume quantification. (A) Reconstruction of the left anterior descending artery in four views to measure plaque burden. The orange line and the yellow line represent the outer border (total volume) and the inner border (lumen volume) respectively. These boundaries permit measurement of plaque volume. (B) Schematic of what plaque volume represents and the equation used to derive the plaque index.

Table 1 Demographics and clinical characteristics of study group

Variable	Psoriasis patients (n = 101)
Demographics	
Age (years)	49.9 ± 13.2
Male sex, n (%)	59 (57.3)
Psoriasis severity	
PASI score	6.2 (3.2–10.8)
BSA score	4.0 (1.6–10.8)
On systemic PSO treatment, n (%)	10 (38.8)
Cardiometabolic variables	
Body mass index (kg/m ²)	29.4 ± 6.1
Waist-to-hip ratio	0.94 ± 0.09
Systolic blood pressure (mmHg)	124.8 ± 14.0
Diastolic blood pressure (mmHg)	73.1 ± 9.6
HOMA-IR	4.41 ± 4.89
Cardiovascular risk factors	
Current smoking, n (%)	8 (7.9)
Hypertension, n (%)	27 (26.7)
Diabetes, n (%)	10 (9.9)
Hyperlipidaemia, n (%)	50 (49.5)
Lipid treatment, n (%)	33 (32.7)
Pooled cohort equation risk estimate (%)	2.7 (1.1–6.6)
Lipid panel	
Total cholesterol (mg/dL)	182.7 ± 39.2
LDL (mg/dL)	100.0 ± 32.0
HDL (mg/dL)	56.6 ± 19.2
Triglycerides (mg/dL)	126.7 ± 84.3
Cholesterol efflux capacity (CEC)	0.94 (0.84–1.07)
Coronary plaque burden	
Total burden (mm ²)	0.01184 ± 0.00468
Non-calcified burden (mm ²)	0.01140 ± 0.00452

PASI, psoriasis area and severity index; BSA, body surface area; PSO, psoriasis; HOMA-IR, homeostatic model assessment for insulin resistance. Mean ± standard deviation or median (interquartile range) reported.

relationships between CEC and PASI score ($\rho = -0.15$, $P = 0.01$), body surface area affected by psoriasis ($\rho = -0.15$, $P = 0.01$), and HDL-C ($\rho = 0.51$, $P < 0.0001$). Furthermore, there was a correlation between NCB and: (i) CEC ($\rho = -0.38$, $P < 0.0001$); (ii) psoriasis severity measured by the PASI score ($\rho = 0.16$, $P < 0.01$); (iii) body surface area affected by psoriasis ($\rho = 0.16$, $P < 0.01$); and (iv) HDL-C ($\rho = -0.33$, $P < 0.0001$).

Stratified by the sample's median CEC value (0.94), patients with low CEC had greater TB of coronary plaque and greater NCB than did patients with high CEC (0.0131 and 0.0127 mm² in low CEC vs. 0.0106 and 0.0103 mm² with high CEC; $P < 0.0001$). Furthermore, CEC was inversely correlated with NCB (Table 2) even after adjustment for CV risk factors ($\beta = -0.21$; $P < 0.001$), HDL levels ($\beta = -0.19$; $P < 0.001$), apoA1 levels ($\beta = -0.20$; $P < 0.001$), and

body mass index (BMI). We found no difference by psoriasis treatment status or statin use, although systemic/biological therapy was associated with reduction in NCB in psoriasis ($\beta = -0.11$, $P = 0.04$). Interestingly, this relationship between CEC and NCB was stronger in women compared with men in fully adjusted models ($\beta = -0.31$; $P = 0.001$ and $\beta = -0.22$; $P = 0.01$ for women and men, respectively) with a statistically significant gender interaction ($P < 0.001$).

Discussion

Here, we demonstrate that in psoriasis, an inflammatory disease associated with increased atherosclerosis and CV events, poor HDL function is associated with an increased TB of coronary atherosclerosis and non-calcified plaque. This relationship remained significant even after adjustment for traditional CV risk factors, HDL-concentration, apoA1 levels, and BMI and displayed a stronger relationship in women compared with men. To our knowledge, this is the first study to examine the relationship of CEC with characterized coronary plaque burden quantitatively. Our findings in psoriasis are consistent with previous reports demonstrating inverse association between HDL function and subclinical atherosclerosis in non-psoriasis patients.²

Cholesterol efflux capacity is increasingly recognized as a promising marker of HDL activity, and recently was inversely associated with adverse CV outcomes independent of HDL-concentration.¹ Our finding that non-calcified coronary plaque burden is inversely associated with CEC independent of HDL-concentration supports CEC as an important metric in understanding the relationship between HDL and coronary atherosclerosis. A relationship between CEC and NCB suggests that higher CEC may promote reverse cholesterol transport from earlier, more lipid-rich plaques. Others have found this non-calcified plaque to be the culprit lesions in acute coronary syndromes.^{13,14} Therefore, in the context of our study, there is strong biological plausibility for observing a relationship between CEC and NCB; psoriasis is associated with both increased future CV events and impaired HDL function, and our findings suggest that this may be due to predisposition towards formation of non-calcified plaque.

Our results are in line with report of an inverse association between CEC and carotid intima media thickness and coronary stenosis by coronary angiography. Another study did not find an association between CEC and incident MI, stroke, or MACE.¹⁵ However, in line with our observation, the study did demonstrate that CEC was inversely associated with the risk of prevalent CAD in two cohorts.

Finally, we observed a significant gender interaction whereby women with psoriasis who have lower CEC had higher non-calcified plaque compared with men beyond HDL-C adjustment. Although the mechanism of this interaction remains to be elucidated, these findings may suggest that greater CEC may be more protective against non-calcified plaque in women than it is in men. Despite the cross-sectional nature of this study, ongoing follow-up of these patients will inform whether aggressive treatment of psoriasis and lifestyle measures improve CEC and ultimately non-calcified burden within the coronary arteries in psoriasis. Future studies should focus

Table 2 Univariable and multivariable analysis of lumen intensity-adjusted non-calcified burden vs. cholesterol efflux capacity

Model	Std β^a	Coefficient	Intercept	P-value
Unadjusted	−0.33	−0.010	0.021	<0.001
Model 1	−0.24	−0.007	0.016	<0.001
Model 2	−0.21	−0.006	0.004	<0.001
Model 2 + HDL-concentration adjustment	−0.19	−0.005	0.006	0.001
Model 2 + ApoA1 adjustment	−0.20	−0.006	0.005	0.001
Model 2 + body mass index adjustment	−0.11	−0.003	0.001	0.05
Model 2 + lipid treatment adjustment	−0.20	−0.006	0.005	<0.001
Model 2 + psoriasis treatment adjustment	−0.21	−0.006	0.004	<0.001

Model 1: age, sex-adjusted; Model 2: model 1 + LDL, systolic blood pressure, glucose, and tobacco use adjustment.

^aStandardized β values.

on providing mechanistic insights into the association between CEC and NCB.

Funding

This work was supported by National Institutes of Health (NIH) Intramural grant by the National Heart, Lung, and Blood Institute (NHLBI DIR grant HL006193-01) and the NIH Clinical Center. This research was made possible in part through the NIH Medical Research Scholars Program, a public–private partnership supported jointly by the NIH and generous contributions to the Foundation for the NIH from Pfizer Inc., The Doris Duke Charitable Foundation, The Newport Foundation, The American Association for Dental Research, The Howard Hughes Medical Institute, and the Colgate-Palmolive Company, as well as other private donors.

Conflict of interest: none declared.

References

- Rohatgi A, Khera A, Berry JD, Givens EG, Ayers CR, Wedin KE, Neeland IJ, Yuhanna IS, Rader DR, de Lemos JA, Shaul PW. HDL cholesterol efflux capacity and incident cardiovascular events. *N Engl J Med* 2014;**371**:2383–2393.
- Khera AV, Cuchel M, de la Llera-Moya M, Rodrigues A, Burke MF, Jafri K, French BC, Phillips JA, Mucksavage ML, Wilensky RL, Mohler ER, Rothblat GH, Rader DJ. Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. *N Engl J Med* 2011;**364**:127–135.
- Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M, Lopez-Sendon J, Mosca L, Tardif JC, Waters DD, Shear CL, Revkin JH, Buhr KA, Fisher MR, Tall AR, Brewer B, Investigators I. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med* 2007;**357**:2109–2122.
- Investigators A-H, Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, McBride R, Teo K, Weintraub W. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011;**365**:2255–2267.
- Schwartz GG, Olsson AG, Abt M, Ballantyne CM, Barter PJ, Brumm J, Chaitman BR, Holme IM, Kallend D, Leiter LA, Leitersdorf E, McMurray JJ, Mundt H, Nicholls SJ, Shah PK, Tardif JC, Wright RS, dal Ol. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med* 2012;**367**:2089–2099.
- Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. *JAMA* 2006;**296**:1735–1741.
- Mehta NN, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM. Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database. *Eur Heart J* 2010;**31**:1000–1006.
- Mehta NN, Li R, Krishnamoorthy P, Yu Y, Farver W, Rodrigues A, Raper A, Wilcox M, Baer A, DerOhannessian S, Wolfe M, Reilly MP, Rader DJ, VanVoorhees A, Gelfand JM. Abnormal lipoprotein particles and cholesterol efflux capacity in patients with psoriasis. *Atherosclerosis* 2012;**224**:218–221.
- Holzer M, Wolf P, Inzinger M, Trieb M, Curcic S, Pasterk L, Weger W, Heinemann A, Marsche G. Anti-psoriatic therapy recovers high-density lipoprotein composition and function. *J Invest Dermatol* 2014;**134**:635–642.
- Boehncke WH, Boehncke S, Tobin AM, Kirby B. The 'psoriatic march': a concept of how severe psoriasis may drive cardiovascular comorbidity. *Exp Dermatol* 2011;**20**:303–307.
- Fischer C, Hultén E, Belur P, Smith R, Voros S, Villines TC. Coronary CT angiography versus intravascular ultrasound for estimation of coronary stenosis and atherosclerotic plaque burden: a meta-analysis. *J Cardiovasc Comput Tomogr* 2013;**7**:256–266.
- Rose S, Dave J, Mollo C, Naik HB, Siegel EL, Mehta NN. Psoriatic arthritis and sacroiliitis are associated with increased vascular inflammation by 18-fluorodeoxyglucose positron emission tomography computed tomography: baseline report from the Psoriasis Atherosclerosis and Cardiometabolic Disease Initiative. *Arthritis Res Ther* 2014;**16**:R161.
- Hoffmann U, Moselewski F, Nieman K, Jang IK, Ferencik M, Rahman AM, Cury RC, Abbasa S, Joneidi-Jafari H, Achenbach S, Brady TJ. Noninvasive assessment of plaque morphology and composition in culprit and stable lesions in acute coronary syndrome and stable lesions in stable angina by multidetector computed tomography. *J Am Coll Cardiol* 2006;**47**:1655–1662.
- Nance JW Jr, Bamberg F, Schoepf UJ, Kang DK, Barraza JM Jr, Abro JA, Bastarrika G, Headden GF, Costello P, Thilo C. Coronary atherosclerosis in African American and white patients with acute chest pain: characterization with coronary CT angiography. *Radiology* 2011;**260**:373–380.
- Li XM, Tang WH, Mosior MK, Huang Y, Wu Y, Matter W, Gao V, Schmitt D, Didonato JA, Fisher EA, Smith JD, Hazen SL. Paradoxical association of enhanced cholesterol efflux with increased incident cardiovascular risks. *Arterioscler Thromb Vasc Biol* 2013;**33**:1696–1705.