SUPPLEMENTAL MATERIAL

Methods and Materials

Design

A total of 412 participants were included in a two-stage, cross-sectional study design: PENN cohort (n=231; 122 psoriasis patients and 109 controls) and NIH cohort (n=181; 151 psoriasis patients and 30 controls).

PENN Cohort

In the PENN cohort, psoriasis patients (n=122) with no history of clinical CV disease were consecutively enrolled over a six-month period. Absence of CV disease was defined as no CV symptoms, absent electrocardiographic findings consistent with ischemia or infarction, and no history of positive stress test or revascularization. Control cohort (n=109) without psoriasis was chosen from a study of healthy participants in Philadelphia matched by age and sex to the psoriasis cohort from the SIRCA study[1] (Study of Inherited Risk of Coronary Atherosclerosis) and was purposely larger to understand the association of GlycA with psoriasis. All patients underwent clinical assessment at the University of Pennsylvania Clinical and Translational Research Center and psoriasis severity assessment using body surface area (BSA) measurement by a dermatologist. Plasma Hs-CRP levels were assayed with the use of a high-sensitivity latex turbidimetric immunoassay (Wako Ltd) and GlycA levels were derived from NMR spectroscopy (LabCorp). Study approval was obtained from the University of Pennsylvania Institutional Review Board.

NIH Cohort

The NIH cohort included consecutively enrolled psoriasis patients (n=151) from the Psoriasis, Atherosclerosis and Cardiometabolic Disease Initiative (NCT01778569), from January 2013 until October 2015, as well as 30 healthy controls, who were matched to psoriasis patients by age and sex at an apriori decided ratio of 5:1. Psoriasis patients were required to have a formal diagnosis of psoriasis confirmed by an internist, dermatologist or rheumatologist. Psoriasis patients were excluded from the study if they had any comorbid condition known to promote cardiovascular disease (CVD) or systemic inflammation, such as known CV disease, defined as any major adverse cardiovascular event, including Myocardial Infarction, stroke, unstable angina within 5 years from their enrollment in the study, uncontrolled hypertension, malignancy within 5 years, HIV, active infection within the past 72 hours, and major surgery within 3 months. Healthy controls were excluded by any of the following conditions: pregnancy, breastfeeding, malignancy (excluding non-melanoma skin cancer), active infection within 3 months requiring antibiotics, CV disease, diabetes, liver disease, collagen vascular diseases, body mass index >40kg/m^2 or glomerular filtration rate <60mL/min. A dermatologist assessed psoriasis severity by both the Psoriasis Area Severity Index (PASI) score and BSA affected. Both groups underwent the same clinical assessment and testing. Clinical parameters including blood pressure, height, weight, waist and hip circumferences were measured. Laboratory parameters including fasting blood glucose, fasting lipid panel, white blood count with differential, and systemic inflammatory markers including hsCRP and erythrocyte sedimentation rate were evaluated in an accredited clinical laboratory. Similar criteria for inclusion and exclusion of healthy volunteers are published in our earlier work[2]. GlycA was measured by NMR Spectroscopy (LabCorp).

18-FDG PET/CT scans were analyzed to derive target-to-background ratio values to quantify VI. Furthermore, CAD was assessed using dedicated software to quantify total coronary plaque burden from CCTA scans as previously described[3]. Study approval was obtained from the National Heart, Lung, and Blood Institute Institutional Review Board in accordance with the Declaration of Helsinki. All guidelines for Good Clinical Practice and those set forth by the NIH Radiation Safety Commission and in the Belmont Report (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research) were followed. All study participants provided written informed consent. Other

details of materials and methods, including inclusion/exclusion criteria, clinical assessment, detailed imaging procedures, and statistical analyses are available in the online-only supplement. STROBE guidelines were followed for reporting the findings from both the stages[4].

18-FDG PET/CT Image Acquisition and Analysis

Patients underwent 18F-Fluorodeoxyglucose positron emission tomography computed tomography (FDG PET/CT) scans following overnight fast. Images were obtained approximately 60 minutes after administration of a 10mCi dose of 18-FDG. All scans were completed using a 64-slice scanner (Siemens Biograph mCT PET/CT 64-slice scanner, Malvern, PA, USA) with 1.5mm axial slices of the aorta obtained. We analyzed the uptake of 18-FDG within the aorta using a dedicated PET/CT image analysis program (Extended Brilliance Workspace, Phillips Healthcare, Andover, MA, USA) to measure vascular inflammation (VI) calculated as target-to-background ratio as previously described[2].

Coronary CT Angiography Image Acquisition and Analysis

Psoriasis patients and healthy controls underwent coronary computed tomography angiography (CCTA) scans (320-detector row Aquilion ONE ViSION, Toshiba, Japan) to assess and quantify total burden of coronary artery disease (CAD)[3] in each coronary artery (left anterior descending, left circumflex and right coronary artery) using dedicated research software, QAngio CT (Medis, The Netherlands).

Statistical Analysis

Summary statistics were generated and expressed as mean and standard deviation for normally distributed variables, median and interquartile range for non-normally distributed continuous variables and frequencies for categorical variables. Normality was assessed by skewness and kurtosis. Parametric variables were compared between groups using Student's t-test while Mann-Whitney U test was performed for non-parametric variables. Dichotomous variable comparisons were done using Pearson's chi-square test. Spearman correlation analyses were performed to evaluate for potential relationships between cardiometabolic variables and GlycA in both PENN and NIH cohorts. We conducted multivariable linear regression analyses to evaluate the associations of VI and CAD with GlycA. These analyses were performed with adjustment for potential confounders including age, sex, Framingham risk score, body mass index, Homeostatic Model Assessment-Insulin Resistance (HOMA-IR) and other traditional CV risk factors. Likelihood-ratio testing was performed in nested Tobit models to determine the incremental value of GlycA in assessing VI and CAD beyond hsCRP and traditional CV risk factors. To further understand the value added by GlycA in predicting VI and CAD in psoriasis patients, receiver operating characteristics (ROC) curves were generated. To identify psoriasis patients with higher burden of subclinical CVD, we converted the continuous variables of VI and CAD burden into dichotomous variables for ROC analyses; mean values in psoriasis were used such that any variable value $\geq$ mean was designated as 1 and variable value $<$ mean was designated as 0. Logistic multivariable regression analyses were then performed to compare the area under curves for base model to model with GlycA, and to model with hsCRP. Base model was adjusted for age, sex, Framingham risk score, body mass index, HOMA-IR, systolic BP, LDL-C, HDL-cholesterol, statins, smoking and any systemic or biologic psoriasis treatment. Sample size in both cohorts had more than 95% power to significantly detect difference in GlycA between psoriasis and controls. Additionally, in order to justify the sample size in NIH cohort to derive associations between GlycA and vascular outcomes, we hypothesized that addition of GlycA would augment adjusted R^2 value by 5% in linear regression models, based on which our sample size had more than 90% power to detect these associations with significance. STATA 12 (StataCorp, College Station, TX, USA) was utilized for all analyses. P values < 0.05 were considered statistically significant.

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