GlycA Is a Novel Biomarker of Inflammation and Subclinical Cardiovascular Disease in Psoriasis

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Rationale: GlycA, an emerging inflammatory biomarker, predicted cardiovascular events in population-based studies. Psoriasis, an inflammatory disease associated with increased cardiovascular risk, provides a model to study inflammatory biomarkers in cardiovascular disease (CVD). Whether GlycA associates with psoriasis and how it predicts subclinical CVD beyond high-sensitivity C-reactive protein in psoriasis is unknown.

Objective: To investigate the relationships between GlycA and psoriasis and between GlycA and subclinical CVD.

Methods and Results: Patients with psoriasis and controls (n=412) participated in a 2-stage study. We measured GlycA by nuclear magnetic resonance spectroscopy. National Institutes of Health (NIH) participants underwent 18-F Fluorodeoxyglucose Positron Emission Tomography Computed Tomography (18-FDG PET/CT) scans to assess vascular inflammation (VI) and coronary computed tomographic angiography to quantify coronary artery disease burden. Psoriasis cohorts were young (mean age=47.9), with low cardiovascular risk and moderate skin disease. High-sensitivity C-reactive protein and GlycA were increased in psoriasis compared with controls (GlycA: [PENN: 408.8±75.4 versus 289.4±60.2, P<0.0001; NIH: 415.8±63.2 versus 346.2±46, P<0.0001]) and demonstrated a dose-response with psoriasis severity. In stage 2, VI (β=0.36, P<0.001) and coronary artery disease (β=0.29, P=0.004) associated with GlycA beyond CV risk factors in psoriasis. In receiver operating characteristic analysis, GlycA added value in predicting VI (P=0.01) and coronary artery disease (P<0.01). Finally, initiating anti–tumor necrosis factor therapy (n=16) reduced psoriasis severity (P<0.001), GlycA (463.7±92.5 versus 370.1±78.5, P<0.001) and VI (1.93±0.36 versus 1.76±0.19, P<0.001), whereas GlycA remained associated with VI (β=0.56, P<0.001) post treatment.

Conclusions: GlycA associated with psoriasis severity and subclinical CVD beyond traditional CV risk and high-sensitivity C-reactive protein. Moreover, psoriasis treatment reduced GlycA and VI. These findings support the potential use of GlycA in subclinical CVD risk assessment in psoriasis and potentially other inflammatory diseases. (Circ Res. 2016;119:1242-1253. DOI: 10.1161/CIRCRESAHA.116.309637.)

Key Words: cardiovascular disease ■ coronary artery disease ■ FDG PET CT ■ GlycA ■ inflammation ■ psoriasis ■ risk factors

Therogenesis is an inflammatory process.1,2 High-sensitivity C-reactive protein (hsCRP), an extensively studied inflammatory biomarker, predicts long-term cardiovascular risk in individuals with no previous evidence of cardiovascular disease (CVD).3 However, emerging evidence suggests that elevated hsCRP may not be a universal feature of chronic inflammation4 and may inaccurately predict coronary artery disease (CAD) in patients with chronic inflammatory...
disorders, indicating a need for alternative CV biomarkers in these at-risk populations.

GlycA, a complex heterogeneous nuclear magnetic resonance signal originating from mobile glycan residues on plasma glycoproteins, is a novel composite biomarker of systemic inflammation. Recent studies have demonstrated GlycA to be a strong predictor of future CV events, incident type 2 diabetes mellitus, long-term risk of severe infection, and overall mortality. Moreover, GlycA showed promise in the assessment of disease activity, treatment response, and CAD in patients with inflammatory disorders, such as systemic lupus erythematosus and rheumatoid arthritis.

Psoriasis, a chronic inflammatory skin disease affecting 2% to 3% of US adults, is associated with chronic systemic inflammation, increased vascular inflammation (VI) by 18-F Fluorodeoxyglucose Positron Emission Tomography Computed Tomography (18-FDG PET/CT), and a greater risk of incident CV events and CV mortality. Traditional risk assessment does not accurately capture the increased CV risk among patients with psoriasis, and many patients with CV disease and related events in psoriasis are young with low Framingham Risk Scores (FRSs). As such, psoriasis provides a reliable human model to study the use of novel inflammatory biomarkers for predicting subclinical CVD in chronic inflammatory states.

To understand how GlycA may potentially associate with subclinical CVD and to compare the association between GlycA and subclinical CVD with association between hsCRP and subclinical CVD, we used a 2-stage study design. In the first stage (henceforth PENN cohort), we evaluated patients with psoriasis and healthy controls to determine whether GlycA levels were elevated in psoriasis. In the second stage (henceforth NIH cohort), we wished to confirm the association between GlycA and psoriasis and to characterize potential relationship between GlycA and subclinical CVD by assessing VI by 18-FDG PET/CT and CAD by coronary computed tomographic angiography (CCTA) to estimate coronary plaque burden. We hypothesized that GlycA would be elevated in psoriasis, associate with skin disease severity, and also directly associate with VI by 18-FDG PET/CT and CAD by CCTA beyond traditional risk factors and hsCRP.

Results

Characteristics of the Study Groups
The PENN cohort (Table 1) contained psoriasis patients (n=122) with mild-to-moderate skin disease (median percent body surface area [BSA] 3, interquartile range [IQR]: 1–7) and controls (n=109) with similar age and sex. Participants were middle-aged (mean±SD: psoriasis 45.2±13.6 years and controls 48.3±8.3 years), overweight to obese (body mass index [BMI]: psoriasis 30.6±8.1 versus controls 27.6±4.6), and at low CV risk (FRS median [IQR]: psoriasis 5 [3–9]; controls 5 [3–8]). Patients with psoriasis had lower levels of total cholesterol (psoriasis 191.1±34.4 versus controls 211.6±38.0) and low-density lipoprotein cholesterol (psoriasis 111.8±28.8 versus controls 134.9±35.3), likely corresponding with greater statin use (psoriasis 27% and controls 14%). Finally, patients with psoriasis had higher levels of hsCRP (median [IQR] psoriasis 3.3 [0.8–9.9]; controls 1.1 [0.5–2.3]) and GlycA (psoriasis 408.8±75.4 and controls 289.4±60.2; Figure 1A), which remained significant after adjustment for age, sex, BMI, and traditional CV risk factors.

The NIH cohort (Table 2) had psoriasis patients (n=151) with mild-to-moderate skin disease (median [IQR]: BSA 3–10.1) and Psoriasis Area Severity Index (PASI) score of 5.8 [3–10.1] and controls (n=30). Both the groups were middle-aged (psoriasis 50.2±12.9 and controls 46.9±10.9, overweight (BMI: psoriasis 29.1±6.0 versus controls 28.2±5.2), and at low CV risk by FRS (median [IQR]: psoriasis 3 [1–6]; controls 3 [1–5]). Patients with psoriasis had higher insulin resistance by homeostatic model assessment of insulin resistance; median [IQR]: psoriasis 2.77 [1.58–4.88] and controls 2.38 [1.74–5.14], despite having a low prevalence of type 2 diabetes mellitus (psoriasis 9% versus controls 10%) and near normal fasting blood glucose levels (psoriasis 100.2±16.6 and controls 97.2±13.4). They also had an equal prevalence of hyperlipidemia (psoriasis 47% versus controls 47%) and a similar prevalence of metabolic syndrome (psoriasis 23% versus controls 17%). hsCRP (median [IQR]: psoriasis 1.80 [0.71–4.22]; controls 1.35 [0.79–2.40]) and GlycA (psoriasis 415.8±63.2 and controls 346.2±46.0; Figure 1B) were elevated in psoriasis similar to that observed in the PENN cohort.

Patients with psoriasis had increased VI by 18-FDG PET/CT (psoriasis 1.70±0.26 and controls 1.59±0.13, P=0.01) and CAD by CCTA (psoriasis 1.12±0.46 and controls 0.99±0.25, P=0.01) compared with controls.

GlycA Associates With hsCRP, Inflammatory Cytokines, Psoriasis Severity, and Cardiometabolic Risk Factors
Correlation analyses revealed a relationship between GlycA and hsCRP in psoriasis in both the cohorts (PENN r=0.73, P<0.01; NIH r=0.50, P<0.001). Furthermore, in the NIH cohort, GlycA correlated with inflammatory cytokines, such as interleukin-6 (IL-6; psoriasis r=0.40, P<0.0001 and controls 0.19, P=0.047) and high-sensitivity C-reactive protein (hsCRP, psoriasis r=0.36, P=0.001 and controls 0.09, P=0.66).}

### Methods

A total of 412 participants were included in a 2-stage, cross-sectional study design: PENN cohort (n=231; 122 patients with psoriasis and 109 controls) and NIH cohort (n=181; 151 patients with psoriasis and 30 controls). A detailed description of methods and materials including inclusion/exclusion criteria, clinical assessment, detailed imaging procedures, and statistical analyses for both the cohorts are available in the online Data Supplement. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed for reporting the findings from both the stages.

### Nonstandard Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>18-F FDG PET/CT</td>
<td>18-F Fluorodeoxyglucose positron emission tomography computed tomography</td>
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<tr>
<td>BMI</td>
<td>body mass index</td>
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<tr>
<td>CAD</td>
<td>coronary artery disease</td>
</tr>
<tr>
<td>CCTA</td>
<td>coronary computed tomographic angiography</td>
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<td>CVD</td>
<td>cardiovascular disease</td>
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<tr>
<td>hsCRP</td>
<td>high-sensitivity C-reactive protein</td>
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<tr>
<td>IL</td>
<td>interleukin</td>
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<tr>
<td>IQR</td>
<td>interquartile range</td>
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<tr>
<td>TNF</td>
<td>tumor necrosis factor</td>
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<td>VI</td>
<td>vascular inflammation</td>
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Table 1. Demographic and Clinical Characteristics of the Study Groups From PENN Cohort

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Psoriasis (n=122)</th>
<th>Control (n=109)</th>
<th>PValue</th>
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<tr>
<td>Demographic and clinical characteristics</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>45.2±13.6</td>
<td>48.3±8.3</td>
<td>0.02*</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>68 (60%)</td>
<td>60 (55%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>39 (34.5%)</td>
<td>31 (29%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Type 2 DM, n (%)</td>
<td>10 (8.8%)</td>
<td>0 (0%)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>8 (7%)</td>
<td>0 (0%)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Statin use, n (%)</td>
<td>33 (27%)</td>
<td>15 (14%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Clinical and laboratory parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>30.6±8.1</td>
<td>27.6±4.6</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>130.2±17.0</td>
<td>127.2±16.2</td>
<td>0.26</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>78.9±10.7</td>
<td>78.4±10.1</td>
<td>0.38</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>191.1±34.4</td>
<td>211.6±30.0</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol, mg/dL</td>
<td>111.8±28.8</td>
<td>134.9±35.3</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol, mg/dL</td>
<td>48.2±15.7</td>
<td>51.5±14.2</td>
<td>0.05</td>
</tr>
<tr>
<td>Triglycerides, mg/dL (Median [IQR])</td>
<td>127 (78–190)</td>
<td>122 (88–156)</td>
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<tr>
<td>Glucose, mg/dL</td>
<td>92.5±37.1</td>
<td>92.3±31.7</td>
<td>0.47</td>
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<tr>
<td>Framingham Risk Score (Median [IQR])</td>
<td>5 (3–9)</td>
<td>5 (3–8)</td>
<td>0.05</td>
</tr>
<tr>
<td>Insulin, μU/mL (Median [IQR])</td>
<td>17.7 (11.6–29.7)</td>
<td>6.7 (4.4–9.8)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>HOMA-IR (Median [IQR])</td>
<td>3.3 (1.3–6.4)</td>
<td>1.5 (0.9–2.2)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Hs-CRP, mg/L (Median [IQR])</td>
<td>3.3 (0.84–9.85)</td>
<td>1.1 (0.5–2.3)</td>
<td>0.02*</td>
</tr>
<tr>
<td>GlycA, μmol/L</td>
<td>408.8±75.4</td>
<td>289.4±60.2</td>
<td>&lt;0.0001*</td>
</tr>
</tbody>
</table>

Psoriasis characteristics

| Affected body surface area (Median [IQR])             | 3 (1–7)           | N/A            | N/A    |
| Systemic or biological treatment, n (%)              | 13 (12%)          | N/A            | N/A    |

Continuous variables are expressed as mean (±SD) unless specified otherwise and categorical variables as %. P values were calculated by Student t test for parametric continuous variables and by Mann-Whitney U test for nonparametric continuous variables, and Pearson χ² test for categorical variables. DM indicates diabetes mellitus; HOMA-IR, homeostasis model assessment of insulin resistance; Hs-CRP, high-sensitivity C-reactive protein; and IQR, interquartile range.

ρ=0.35, P<0.001), IL-16 (psoriasis ρ=0.25, P<0.0001 and controls ρ=0.3, P<0.01), and monocyte chemotactic protein-4 (psoriasis ρ=0.12, P<0.05 and controls ρ=0.26, P<0.05). GlycA also correlated with psoriasis severity (PENN cohort: BSA [ρ=0.22, P<0.05] and NIH cohort: BSA [ρ=0.43, P<0.001], and PASI [ρ=0.57, P<0.001]; Tables 3 and 4; Figures 1C, 1D, and 2). The direct association between GlycA and psoriasis severity remained robust beyond traditional CV risk factors (PENN cohort: BSA [β=0.21, P=0.01] and NIH cohort: BSA [β=0.40, P<0.001], PASI [β=0.49, P<0.001]; Table 5A through 5C). Finally, other cardiometabolic risk factors that significantly correlated with GlycA in psoriasis included metabolic syndrome, waist/hip ratio, BMI, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, FRS, and homeostatic model assessment of insulin resistance (Tables 3 and 4).

GlycA Associates With Vascular Disease Independent of Traditional CV Risk Factors

In unadjusted linear regression models, stage 2 demonstrated that GlycA associated with VI (psoriasis β=0.30 P<0.001 and controls β=0.26, P<0.001; Table 6A). This association remained significant beyond traditional CV risk factors in psoriasis (β=0.26, P=0.004) and in controls (β=0.18, P=0.03; Table 6A). However, similar associations were not found for hsCRP with VI in neither psoriasis (β=−0.02, P=0.76) nor controls (β=−0.02, P=0.93).

GlycA also associated with CAD (psoriasis β=0.31, P<0.001 and controls β=0.13, P=0.002; Table 6B) in unadjusted models. After adjustment for traditional CV risk factors, these relationships remained significant in psoriasis (β=0.34, P=0.01) and in controls (β=0.13, P=0.04; Table 6B). Finally, CAD (β=0.05, P=0.30) did not associate with hsCRP in psoriasis; however, it was strongly associated with hsCRP in controls (β=0.23, P=0.03).

GlycA Provides Value in Assessing VI and CAD Burden Beyond Traditional CV Risk Factors and hsCRP in Psoriasis

The contribution of GlycA in assessing VI and CAD beyond traditional CV risk factors and hsCRP was first determined using likelihood ratio testing in nested models and second by analyzing receiver operating characteristic curves. GlycA provided maximum value in the estimation of VI beyond hsCRP, when added to fully adjusted models, in both psoriasis (χ²=19.59, P<0.0001) and controls (χ²=8.95, P=0.003; Table 7A). GlycA also provided incremental value in measuring CAD burden in psoriasis (χ²=7.88, P=0.008; Table 7B) beyond hsCRP and traditional CV risk factors. As expected in controls, hsCRP strongly predicted CAD burden (χ²=7.22, P=0.02; Table 7B).

Receiver operating characteristic analyses demonstrated that GlycA added value to the base model adjusted for traditional CV risk factors in predicting VI above the cohort mean in psoriasis (area under curve [AUC] for base model: 0.86; 95% CI, 0.85–0.87 versus AUC for model with GlycA: 0.93; 95% CI, 0.91–0.94; P=0.01; Figure 3A1). Similar results were observed in predicting CAD (AUC: 95% CI, 0.89, 0.88–0.89 versus 0.92, 0.91–0.92; P<0.01; Figure 3A2). Furthermore, GlycA also added incremental value in predicting these measures of subclinical CVD in controls (Figure 3A3 and 3A4). hsCRP did not add value in predicting CAD or VI above the cohort mean in psoriasis (Figure 3B1 and 3B2). Finally, in controls, although hsCRP did not add value to predicting VI (Figure 3B3), it provided value in predicting CAD above the cohort mean (Figure 3B4).

Successful Treatment of Psoriasis With Anti–Tumor Necrosis Factor Therapy Decreases GlycA and Aortic VI by FDG PET/CT

Given the association between GlycA and systemic inflammation, we hypothesized that the treatment of psoriasis would...
lead to a reduction in GlycA. We initiated 16 treatment-naïve patients on anti–tumor necrosis factor (TNF) therapy and followed them longitudinally for improvement in psoriasis and potentially VI. In these 16 patients, GlycA decreased significantly at follow-up compared with baseline (baseline 463.7±92.5 versus post treatment 370.1±78.5, P<0.001), whereas hsCRP reduction did not achieve statistical significance (median [IQR]: baseline 2.3 [0.8–9.3] versus post treatment 1.3 [0.6–3.2]; P=0.054). Furthermore, we observed an improvement in both PASI score and VI (baseline versus post treatment VI:
1.93±0.36 versus 1.76±0.19; P<0.001). Strikingly, the strong association between VI and GlycA persisted post treatment beyond traditional CV risk (β=0.56, P<0.001), whereas hsCRP was not associated with VI post treatment (β=0.01, P=0.95).

**Discussion**

Using a 2-stage study design in psoriasis and healthy controls, we demonstrated the following major findings: (1) GlycA levels were elevated in psoriasis compared with healthy controls...
with a dose–response relationship between GlycA and psoriasis skin disease severity; (2) GlycA significantly correlated with hsCRP, inflammatory cytokines, and markers of cardiometabolic disease; (3) GlycA associated with VI by 18-FDG PET/CT and CAD by CCTA beyond traditional CV risk factors in psoriasis; (4) GlycA provided maximum value in the assessment of VI and CAD beyond hsCRP in models adjusted for traditional CV risk in psoriasis; and (5) successful treatment of psoriatic skin inflammation with anti-TNF therapy decreased GlycA levels and VI with the persistence of the association between VI and GlycA post-treatment. Collectively, these findings support the value of GlycA as a promising biomarker of inflammation and subclinical CVD risk in psoriasis.

In recent years, the inflammatory hypothesis of atherosclerosis has generated interest in several potential inflammatory biomarkers for CV disease. These include cytokines, such as IL-6, TNF-α, interferon-γ, and monocyte chemotactractant protein-1); mediators of endothelial activation, such as VCAM-1 (vascular cell adhesion molecule-1), ICAM-1 (intercellular adhesion molecule-1), and E-selectin; and acute phase reactants, such as serum amyloid A and hsCRP. hsCRP, a marker of systemic inflammation, has become a validated prognostic biomarker of CV disease. However, recent evidence demonstrates that hsCRP may not accurately predict CV disease in patients with inflammatory conditions, such as systemic lupus erythematosus,6 psoriasis,7 rheumatoid arthritis,8 and HIV.9 Furthermore, a large population–based longitudinal study of >10000 patients showed evidence to suggest that elevated hsCRP may not be a universal feature of chronic inflammation.9 Collectively, these findings indicate that hsCRP may perform suboptimally in CV risk prediction in patients with chronic inflammatory diseases and suggest a need for alternative CV biomarkers in these vulnerable population.

Contemporary studies to identify new inflammatory biomarkers for CV disease demonstrate the potential for measuring GlycA. GlycA, a nuclear magnetic resonance signal originating from a subset of glycan N-acetylglucosamine residues on enzymatically glycosylated acute-phase proteins, is a biomarker of systemic inflammation.9,10 Recent studies involving >25000 subjects found GlycA to be predictive of 15-year CV events,11 incident diabetes mellitus,13 and all-cause mortality.12,28 Fischer et al29 also found a 67% and 55% increase in mortality for every SD increase in GlycA, in 2 independent populations totaling >17000 healthy adults. Furthermore, these large population studies in subjects without pre-existing inflammatory diseases have revealed that GlycA either conferred additional value beyond traditional biomarkers of inflammation, such as hsCRP, IL-6, ICAM-1, and fibrinogen, or that it was equivalent to these traditional biomarkers in predicting long-term CV and all-cause mortality.12,28 Strikingly, GlycA also showed associations with

Table 3. Correlation Analyses of GlycA With Various Demographic and Cardiometabolic Variables in Both Cohorts (Spearman Correlation Analyses of GlycA in the PENN Cohort)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total Cohort (N=231)</th>
<th>Psoriasis (N=122)</th>
<th>Control (N=109)</th>
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<tr>
<td>Demographic and clinical characteristics</td>
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<td></td>
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<tr>
<td>Age</td>
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<td>0.08 (NS)</td>
<td>0.09 (NS)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.08 (NS)</td>
<td>0.14 (NS)</td>
<td>0.04 (NS)</td>
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<td>0.19 (&lt;0.001)*</td>
<td>0.18 (NS)</td>
<td>No correlation</td>
</tr>
<tr>
<td>Smoker</td>
<td>0.23 (&lt;0.001)*</td>
<td>0.10 (NS)</td>
<td>0.01 (NS)</td>
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<td>Statin use</td>
<td>0.07 (NS)</td>
<td>−0.07 (NS)</td>
<td>0.06 (NS)</td>
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<td>Clinical and laboratory values</td>
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</tr>
<tr>
<td>Body mass index</td>
<td>0.33 (&lt;0.001)*</td>
<td>0.43 (&lt;0.001)*</td>
<td>0.29 (&lt;0.001)*</td>
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<tr>
<td>Systolic blood pressure</td>
<td>0.21 (&lt;0.001)*</td>
<td>0.14 (NS)</td>
<td>0.22 (&lt;0.001)*</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
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<td>0.11 (NS)</td>
<td>0.21 (&lt;0.001)*</td>
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<tr>
<td>Total cholesterol</td>
<td>0.09 (&lt;0.05)*</td>
<td>0.27 (&lt;0.01)*</td>
<td>0.23 (&lt;0.001)*</td>
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<tr>
<td>Low-density lipoprotein cholesterol</td>
<td>−0.01 (NS)</td>
<td>0.27 (&lt;0.01)*</td>
<td>0.11 (&lt;0.05)*</td>
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<td>High-density lipoprotein cholesterol</td>
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<td>−0.16 (NS)</td>
<td>−0.01 (NS)</td>
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<td>Triglycerides</td>
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<td>0.35 (&lt;0.001)*</td>
<td>0.36 (&lt;0.001)*</td>
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<td>Framingham Risk Score</td>
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<td>0.27 (&lt;0.01)*</td>
<td>0.12 (&lt;0.05)*</td>
</tr>
<tr>
<td>Glucose mg/dL</td>
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<td>0.01 (NS)</td>
<td>0.05 (NS)</td>
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<tr>
<td>Insulin</td>
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<td>0.17 (NS)</td>
<td>0.25 (&lt;0.001)*</td>
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<td>hsCRP</td>
<td>0.45 (&lt;0.001)*</td>
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<td>0.44 (&lt;0.001)*</td>
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<td>Body surface area</td>
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<td>Systemic or biological therapy</td>
<td>N/A</td>
<td>0.05 (0.58)</td>
<td>N/A</td>
</tr>
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</table>

Values are expressed as \( \rho \) (P-value) for all variables. DM indicates diabetes mellitus; hs-CRP, high-sensitivity C-reactive protein; and NS, nonsignificant.
BMM and fitness among adolescents, suggesting its role even in the early stages of cardiometabolic dysfunction. In addition, in inflammatory states, GlycA associated with disease activity and CHD among rheumatoid arthritis patients, and it was elevated in patients with systemic lupus erythematosus compared with controls. Finally, GlycA also associated with disease activity in systemic lupus erythematosus and revealed improved levels subsequent to treatment.

With increased systemic inflammation and VI, higher prevalence of diabetes and other traditional CV risk factors, and a greater risk of CV disease as well as CV and cerebrovascular events, psoriasis provides a reliable human model to understand how inflammatory biomarkers perform in CV risk assessment in an inflammatory disease state. In the present study, we demonstrated that GlycA associated with VI and CAD beyond hsCRP and traditional risk in psoriasis, and

Table 4. Spearman Correlation Analyses of GlycA in the NIH Cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Cohort (n=181)</th>
<th>Psoriasis (n=151)</th>
<th>Controls (n=30)</th>
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<tr>
<td>Demographic and clinical characteristics</td>
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</tr>
<tr>
<td>Age</td>
<td>0.08 (0.31)</td>
<td>−0.003 (0.95)</td>
<td>0.24 (0.19)</td>
</tr>
<tr>
<td>Sex</td>
<td>0.05 (0.49)</td>
<td>0.09 (0.06)</td>
<td>−0.23 (0.22)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.01 (0.86)</td>
<td>−0.03 (0.52)</td>
<td>0.21 (0.28)</td>
</tr>
<tr>
<td>Type 2 DM</td>
<td>0.03 (0.67)</td>
<td>0.01 (0.81)</td>
<td>0.19 (0.31)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.28 (0.08)</td>
<td>0.08 (0.08)</td>
<td>0.24 (0.2)</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>0.14 (0.009)*</td>
<td>0.11 (0.02)*</td>
<td>0.15 (0.46)</td>
</tr>
<tr>
<td>Waist/Hip ratio</td>
<td>0.16 (0.03)*</td>
<td>0.23 (&lt;0.001)*</td>
<td>0.1 (0.36)</td>
</tr>
<tr>
<td>Tobacco</td>
<td>0.12 (0.11)</td>
<td>0.11 (0.07)</td>
<td>0.18 (0.3)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>0.08 (0.06)</td>
<td>0.06 (0.20)</td>
<td>0.25 (0.19)</td>
</tr>
<tr>
<td>Statin use</td>
<td>0.01 (0.9)</td>
<td>0.01 (0.89)</td>
<td>No correlation</td>
</tr>
<tr>
<td>Clinical and laboratory values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.29 (0.001)*</td>
<td>0.32 (0.001)*</td>
<td>0.20 (0.03)*</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.15 (0.04)*</td>
<td>−0.01 (0.91)</td>
<td>0.24 (0.2)</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.07 (0.37)</td>
<td>−0.02 (0.65)</td>
<td>0.29 (0.12)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>0.06 (0.16)</td>
<td>0.01 (0.75)</td>
<td>0.29 (0.12)</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol</td>
<td>0.12 (0.09)</td>
<td>0.16 (&lt;0.001)*</td>
<td>0.17 (0.37)</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol</td>
<td>−0.14 (&lt;0.007)*</td>
<td>−0.17 (&lt;0.001)*</td>
<td>−0.11 (&lt;0.01)*</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>−0.02 (0.78)</td>
<td>−0.02 (0.70)</td>
<td>0.36 (0.04)*</td>
</tr>
<tr>
<td>Apolipoprotein A1</td>
<td>−0.13 (&lt;0.001)*</td>
<td>−0.20 (&lt;0.001)*</td>
<td>−0.14 (0.02)*</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>0.17 (0.02)*</td>
<td>0.17 (0.002)*</td>
<td>0.23 (0.2)</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.13 (0.09)</td>
<td>0.06 (0.19)</td>
<td>0.20 (0.3)</td>
</tr>
<tr>
<td>Framingham Risk Score</td>
<td>0.12 (0.1)</td>
<td>0.11 (0.04)*</td>
<td>0.18 (0.42)</td>
</tr>
<tr>
<td>Insulin</td>
<td>0.24 (&lt;0.001)*</td>
<td>0.25 (&lt;0.001)*</td>
<td>0.28 (0.02)*</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.24 (&lt;0.001)*</td>
<td>0.23 (&lt;0.001)*</td>
<td>0.28 (0.03)*</td>
</tr>
<tr>
<td>hsCRP</td>
<td>0.46 (&lt;0.001)*</td>
<td>0.50 (&lt;0.001)*</td>
<td>0.51 (0.01)*</td>
</tr>
<tr>
<td>Psoriasis details</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PASI score</td>
<td>0.57 (&lt;0.001)*</td>
<td>0.57 (&lt;0.001)*</td>
<td>N/A</td>
</tr>
<tr>
<td>Affected body surface area</td>
<td>0.43 (&lt;0.001)*</td>
<td>0.43 (&lt;0.001)*</td>
<td>N/A</td>
</tr>
<tr>
<td>Systemic or biological treatment</td>
<td>−0.12 (0.04)*</td>
<td>−0.12 (0.04)*</td>
<td>N/A</td>
</tr>
<tr>
<td>Vascular inflammation by FDG PET/CT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic vascular inflammation</td>
<td>0.33 (&lt;0.001)*</td>
<td>0.32 (&lt;0.001)*</td>
<td>0.27 (0.008)*</td>
</tr>
<tr>
<td>Coronary plaque burden by CCTA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total burden of coronary artery disease</td>
<td>0.20 (&lt;0.001)*</td>
<td>0.30 (&lt;0.001)*</td>
<td>0.19 (&lt;0.001)*</td>
</tr>
</tbody>
</table>

Values are expressed as ρ (P value) for all variables. CCTA indicates coronary computed tomographic angiography; DM, diabetes mellitus; FDG PET/CT, Fluorodeoxyglucose Positron Emission Tomography Computed Tomography; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; Hs-CRP, high-sensitivity C-reactive protein; NIH, National Institutes of Health; and PASI, Psoriasis Area Severity Index.
GlycA, Inflammation, and CV Disease in Psoriasis

Table 5. Relationship Between GlycA Levels and Psoriasis
Skin Disease Severity Assessed by Multivariable Linear Regression Analysis

<table>
<thead>
<tr>
<th>Model</th>
<th>β (PValue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. GlycA vs body surface area in the PENN Cohort</td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.29 (0.002)</td>
</tr>
<tr>
<td>Adjusted for age and sex</td>
<td>0.34 (0.001)</td>
</tr>
<tr>
<td>Adjusted for age, sex, and FRS</td>
<td>0.26 (0.007)</td>
</tr>
<tr>
<td>Adjusted for age, sex, FRS, and BMI</td>
<td>0.25 (0.01)</td>
</tr>
<tr>
<td>Adjusted for age, sex, FRS, BMI, SBP, LDL-C, HDL-C, and HOMA-IR</td>
<td>0.21 (0.01)</td>
</tr>
<tr>
<td>B. GlycA vs body surface area in the NIH Cohort</td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.42 (&lt;0.001)</td>
</tr>
<tr>
<td>Adjusted for age and sex</td>
<td>0.42 (&lt;0.001)</td>
</tr>
<tr>
<td>Adjusted for age, sex, and FRS</td>
<td>0.42 (&lt;0.001)</td>
</tr>
<tr>
<td>Adjusted for age, sex, FRS, and BMI</td>
<td>0.41 (&lt;0.001)</td>
</tr>
<tr>
<td>Adjusted for age, sex, FRS, BMI, SBP, LDL-C, HDL-C, and HOMA-IR</td>
<td>0.40 (&lt;0.001)</td>
</tr>
<tr>
<td>C. GlycA vs Psoriasis Area and Severity Index Score in the NIH Cohort</td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.52 (&lt;0.001)</td>
</tr>
<tr>
<td>Adjusted for age and sex</td>
<td>0.53 (&lt;0.001)</td>
</tr>
<tr>
<td>Adjusted for age, sex, and FRS</td>
<td>0.52 (&lt;0.001)</td>
</tr>
<tr>
<td>Adjusted for age, sex, FRS, and BMI</td>
<td>0.50 (&lt;0.001)</td>
</tr>
<tr>
<td>Adjusted for age, sex, FRS, BMI, SBP, LDL-C, HDL-C, and HOMA-IR</td>
<td>0.49 (&lt;0.001)</td>
</tr>
</tbody>
</table>

All values reported as standardized β (P value). BMI indicates body mass index; FRS, Framingham Risk Score; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; NIH, National Institutes of Health; and SBP, systolic blood pressure.

GlycA provided value in the assessment of subclinical CVD independent of traditional risk factors. Since GlycA provides a composite measurement of human inflammatory glycoproteins, it may capture a broader, summative profile of systemic inflammation. Together, these findings suggest that GlycA may assess both systemic inflammation and CVD risk more accurately when compared to hsCRP in chronic inflammatory conditions.

GlycA levels recently were shown to be stable in healthy individuals for >10 years, barring a clinical change. However, whether GlycA levels respond to anti-inflammatory treatment is unknown. We found that the treatment of skin disease with anti-TNF therapy led to reductions in GlycA and VI, suggesting that GlycA may be a reliable biomarker for disease severity, subclinical CVD risk, and treatment response in psoriasis. Furthermore, the association between VI and GlycA persisted post-treatment suggesting that it may be a robust biomarker of CVD. Given the known relationship between VI by 18-FDG PET/CT and prospective CV events, our results suggest that this achieved reduction in GlycA may correspond with a concomitant reduction in CV risk; however, randomized interventional trials are required to answer this question.

There are limitations to this current study, which warrant mention. First, the sample size of controls in the second stage of the study was limited, as was the sample size of the treatment cohort. Furthermore, given the cross-sectional design, our study cannot assess causality. Finally, we did not examine the association of GlycA with hard CV end points. Despite these limitations, this is the first study, to our knowledge, of GlycA in psoriasis, to show an association between GlycA and subclinical CVD using multimodality imaging in an inflammatory state, and also the first study to perform a systematic comparison between GlycA and hsCRP in subclinical CVD assessment. In addition, both VI by 18-FDG PET/CT and CAD by CCTA are validated surrogates for prospective CV outcomes. Utilizing these markers in deeply phenotyped cohorts, we provide novel insight into the value of GlycA for assessing subclinical CVD, building on the previously demonstrated association of GlycA with prospective CV events.

Because GlycA nuclear magnetic resonance signal is composed of several acute phase reactant glycoproteins, deeper physiological studies to enhance our understanding of GlycA pathophysiology are warranted. Furthermore, from the emerging evidence and findings of our study, GlycA may be used as a risk factor in epidemiological studies and a potential surrogate end point in clinical trials of anti-inflammatory treatment. However, larger studies will be needed to confirm these findings before the broad scale use of GlycA in trials. Moreover, GlycA measurement may become more widespread with the

Table 6. Relationship Between GlycA and Vascular Disease

<table>
<thead>
<tr>
<th>Model</th>
<th>Total Cohort</th>
<th>Psoriasis</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Multivariable regression analyses show a direct relationship between vascular inflammation and GlycA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.30 (&lt;0.001)</td>
<td>0.30 (&lt;0.001)</td>
<td>0.26 (&lt;0.001)</td>
</tr>
<tr>
<td>Adjusted for age and sex</td>
<td>0.29 (&lt;0.001)</td>
<td>0.28 (&lt;0.001)</td>
<td>0.22 (&lt;0.001)</td>
</tr>
<tr>
<td>Adjusted for age, sex, and FRS</td>
<td>0.25 (&lt;0.001)</td>
<td>0.25 (&lt;0.001)</td>
<td>0.22 (&lt;0.001)</td>
</tr>
<tr>
<td>Adjusted for age, sex, FRS and BMI</td>
<td>0.26 (&lt;0.001)</td>
<td>0.22 (&lt;0.001)</td>
<td>0.17 (0.045)</td>
</tr>
<tr>
<td>Adjusted for age, sex, FRS, BMI, SBP, LDL-C, HDL-C, HOMA-IR, smoking, and statins</td>
<td>0.21 (0.002)</td>
<td>0.26 (0.004)</td>
<td>0.18 (0.03)</td>
</tr>
<tr>
<td>B. Multivariable regression analyses show a direct relationship between total burden of coronary artery disease quantified by CCTA and GlycA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.17 (&lt;0.001)</td>
<td>0.31 (&lt;0.001)</td>
<td>0.13 (0.002)</td>
</tr>
<tr>
<td>Adjusted for age and sex</td>
<td>0.15 (&lt;0.001)</td>
<td>0.25 (0.005)</td>
<td>0.12 (0.003)</td>
</tr>
<tr>
<td>Adjusted for age, sex, and FRS</td>
<td>0.16 (0.003)</td>
<td>0.26 (0.004)</td>
<td>0.15 (0.007)</td>
</tr>
<tr>
<td>Adjusted for age, sex, FRS, and BMI</td>
<td>0.12 (0.007)</td>
<td>0.24 (0.002)</td>
<td>0.10 (0.02)</td>
</tr>
<tr>
<td>Adjusted for age, sex, FRS, BMI, SBP, LDL-C, HDL-C, HOMA-IR, smoking, and statins</td>
<td>0.14 (0.001)</td>
<td>0.34 (0.01)</td>
<td>0.13 (0.04)</td>
</tr>
</tbody>
</table>

All values reported as standardized β (P value). BMI indicates body mass index; CCTA, coronary computed tomographic angiography; FRS, Framingham Risk Score; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; and SBP, systolic blood pressure.
recent Food and Drug Administration approval of nuclear magnetic resonance-based lipoprotein measurement, such as low-density lipoprotein particle number in clinical laboratories. Finally, although large population studies have shown GlycA as a marker of prospective cardiovascular events, prospective cardiovascular event studies with large sample size will be needed to determine its use as a clinical biomarker of cardiovascular outcomes.

Table 7. Incremental Value of GlycA Beyond Traditional Cardiovascular Risk Factors and Hs-CRP in Assessing Both Vascular Inflammation and Coronary Artery Disease

<table>
<thead>
<tr>
<th>Model</th>
<th>Total Cohort, $\chi^2$ (P value)</th>
<th>Psoriasis, $\chi^2$ (P value)</th>
<th>Control, $\chi^2$ (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. GlycA added to model 1</td>
<td>23.47 (0.0007)*</td>
<td>24.83 (&lt;0.0001)*</td>
<td>5.8 (0.02)*</td>
</tr>
<tr>
<td>Hs-CRP added to model 1</td>
<td>0.96 (0.33)</td>
<td>0.1 (0.8)</td>
<td>1.01 (0.32)</td>
</tr>
<tr>
<td>GlycA added to Hs-CRP in model 1</td>
<td>20.06 (&lt;0.0001)*</td>
<td>19.59 (&lt;0.0001)*</td>
<td>8.95 (0.003)*</td>
</tr>
<tr>
<td>Hs-CRP added to GlycA in model 1</td>
<td>2.54 (0.11)</td>
<td>0.7 (0.4)</td>
<td>0.22 (0.64)</td>
</tr>
<tr>
<td>B. GlycA added to model 1</td>
<td>15.80 (0.0003)*</td>
<td>8.8 (0.003)*</td>
<td>7.78 (0.003)*</td>
</tr>
<tr>
<td>Hs-CRP added to model 1</td>
<td>1.09 (0.3)</td>
<td>0.64 (0.42)</td>
<td>8.12 (0.04)*</td>
</tr>
<tr>
<td>GlycA added to Hs-CRP in model 1</td>
<td>14.34 (0.0003)*</td>
<td>7.88 (0.008)*</td>
<td>6.49 (0.01)*</td>
</tr>
<tr>
<td>Hs-CRP added to GlycA in model 1</td>
<td>0.63 (0.43)</td>
<td>0.4 (0.55)</td>
<td>7.22 (0.02)*</td>
</tr>
</tbody>
</table>

Model 1 is adjusted for age, sex, FRS, BMI, HOMA-IR, SBP, LDL-C, HDL-C, smoking, and statin use. 18-FDG PET/CT indicates 18-F Fluorodeoxyglucose Positron Emission Tomography Computed Tomography; BMI, body mass index; CCTA, coronary computed tomographic angiography; FRS, Framingham Risk Score; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; Hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; and SBP, systolic blood pressure.

Figure 2. GlycA levels and relationship with psoriasis skin disease severity measured by Psoriasis Area Severity Index (PASI) score in the National Institutes of Health [NIH] Cohort.
Figure 3. Receiver operating characteristic (ROC) curves demonstrating incremental values added by GlycA and high-sensitivity C-reactive protein (hsCRP). A, ROC analyses demonstrate that GlycA adds value in predicting higher vascular inflammation and greater total burden of coronary artery disease in both psoriasis (1 and 2) and controls (3 and 4). B, ROC analyses demonstrate that (Continued)
In conclusion, our study provides strong evidence for an association between GlycA and psoriasis as well as GlycA and subclinical CVD in psoriasis. Furthermore, GlycA predicted VI and CAD beyond hsCRP. Finally, after anti-TNF treatment, we found a decrease in GlycA levels and VI with the persistence of the relationship between GlycA and VI. Taken together, these findings support a potential role of GlycA in CV risk assessment in an inflammatory state beyond hsCRP. Eventually, GlycA may be considered in patients with psoriasis in addition to hsCRP for CVD assessment; however, larger studies are needed to further confirm these findings.

Acknowledgments
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Disclosures
Dr Gelfand served as a consultant for AbbVie, AstraZeneca, Celgene Corp, Coherus, Eli Lilly, Janssen Biologics (formerly Centocor), Sanofi, Merck, Novartis Corp, Valeant, and Pfizer Inc, receiving honoraria; received research grants (to the Trustees of the University of Pennsylvania) from AbbVie, Amgen, Eli Lilly, Janssen, Novartis Corp, Regeneron, and Pfizer Inc; and received payment for continuing medical education work related to psoriasis. Dr Gelfand is a coparent holder of resiquimod for the treatment of cutaneous T-cell lymphoma. Dr Gelfand has also received a grant from the National Institute of Arthritis and Musculoskeletal Diseases (5K24AR064310-03). Dr Nehal Mehta is a full-time US Government employee. The other authors report no conflicts.

References
Recent studies have suggested that high-sensitivity C-reactive protein, a biomarker of systemic inflammation that provides value in CV risk prediction, may not accurately capture risk in patients with chronic inflammatory disorders. GlycA is an emerging biomarker of systemic inflammation associated with CV events in population-based studies but has not been systematically characterized in an inflammatory disease state. Therefore, we examined whether in psoriasis, a chronic inflammatory skin disease, GlycA is associated with skin inflammation and vascular diseases. We found that GlycA was associated with psoriasis severity and also with VI by 18F-FDG PET/CT and burden of coronary artery disease by coronary computed tomographic angiography. Moreover, the treatment of skin disease with anti–tumor necrosis factor therapy was associated with reduction in GlycA levels and VI, with GlycA maintaining its association with VI after therapy. This study provides novel insights into the potential use of GlycA to predict future acute coronary events. J Am Coll Cardiol. 2013;61:2296–2305. doi: 10.1016/j.jacc.2013.02.065.

Novelty and Significance

What Is Known?

- GlycA is a nuclear magnetic resonance–derived signal, originating from mobile glycan residues on plasma glycoproteins, is an emerging biomarker of systemic inflammation associated with all-cause mortality and future cardiovascular events.
- Psoriasis is a chronic inflammatory skin disease associated with greater risk of myocardial infarction and provides a reliable human inflammatory model to understand how GlycA may associate with subclinical vascular diseases.
- Vascular inflammation (VI) quantitatively assessed by 18F Fluorodeoxyglucose Positron Emission Tomography Computed Tomography (18F-FDG PET/CT) and coronary artery disease burden by coronary computed tomographic angiography provides surrogate markers of future cardiovascular events.

What New Information Does This Article Contribute?

- GlycA was associated with the severity of psoriasis skin disease in a dose-dependent fashion measured by body surface area and Psoriasis Area Severity Index (PASI).
- GlycA was associated with both VI by 18F-FDG PET/CT and coronary artery disease burden by coronary computed tomographic angiography beyond traditional cardiovascular risk factors and added incremental value beyond high-sensitivity C-reactive protein in psoriasis.
- Treatment of psoriasis with anti–tumor necrosis factor therapy led to a decrease in GlycA levels and VI, and GlycA maintained a strong relationship with VI after treatment.

GlycA, Inflammation, and CV Disease in Psoriasis

Joshi et al

What Is New Information Does This Article Contribute?
GlycA Is a Novel Biomarker of Inflammation and Subclinical Cardiovascular Disease in Psoriasis

Aditya A. Joshi, Joseph B. Lerman, Tsion M. Aberra, Mehd Acfar, Heather L. Teague, Justin A. Rodante, Parasuram Krishnamoorthy, Qimin Ng, Tarek Z. Aridi, Taufiq Salahuddin, Balaji Natarajan, Benjamin N. Lockshin, Mark A. Ahlman, Marcus Y. Chen, Daniel J. Rader, Muredach P. Reilly, Alan T. Remaley, David A. Bluemke, Martin P. Playford, Joel M. Gelfand and Nehal N. Mehta

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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 study1 (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 a priori 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/m² 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 work2. 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 described3. 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\textsuperscript{4}.

\textbf{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\textsuperscript{2}.

\textbf{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)\textsuperscript{3} in each coronary artery (left anterior descending, left circumflex and right coronary artery) using dedicated research software, QAngio CT (Medis, The Netherlands).

\textbf{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.
REFERENCES:


