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

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Abstract

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 hsCRP in psoriasis is unknown.

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

Methods and Results—Psoriasis patients and controls (n=412) participated in a two-stage study. We measured GlycA by NMR spectroscopy. NIH participants underwent 18-FDG PET/CT scans to assess vascular inflammation (VI) and coronary CT angiography to quantify coronary artery disease (CAD) burden. Psoriasis cohorts were young (mean age=47.9), with low cardiovascular risk and moderate skin disease. HsCRP and GlycA were increased in psoriasis compared to controls [GlycA: (PENN: 408.8±75.4 vs. 289.4±60.2, p<0.0001, NIH: 415.8±63.2 vs. 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 CAD (β=0.29, p=0.004) associated with GlycA beyond CV risk factors in psoriasis. In ROC analysis, GlycA added value in predicting VI (p=0.01) and CAD (p<0.01). Finally, initiating anti-TNF therapy (n=16) reduced psoriasis severity (p<0.001), GlycA (463.7±92.5 vs. 370.1±78.5; p<0.001) and VI (1.93±0.36 vs. 1.76±0.19; p<0.001), while 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 hsCRP. Moreover, psoriasis treatment reduced GlycA and VI. These findings support the potential utility of GlycA in subclinical CVD risk assessment in psoriasis and potentially other inflammatory diseases.

Keywords

INTRODUCTION

Atherogenesis 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 prior evidence of cardiovascular disease (CVD)[3]. However, emerging evidence suggests that elevated hsCRP may not be a universal feature of chronic inflammation[4] and may inaccurately predict coronary artery disease (CAD) in patients with chronic inflammatory disorders[5–8], indicating a need for alternative CV biomarkers in these at-risk populations.

GlycA, a complex heterogeneous nuclear magnetic resonance (NMR) signal originating from mobile glycan residues on plasma glycoproteins, is a novel composite biomarker of systemic inflammation[9, 10]. Recent studies have demonstrated GlycA to be a strong predictor of future CV events[11, 12], incident type 2 diabetes[13, 14], long-term risk of severe

infection[4], and overall mortality[12]. Moreover, GlycA showed promise in the assessment of disease activity, treatment response, and CAD in patients with inflammatory disorders, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis[15–18].

Psoriasis, a chronic inflammatory skin disease affecting 2–3% of US adults[19], is associated with chronic systemic inflammation, increased vascular inflammation (VI) by 18-FDG PET/CT[20, 21], and a greater risk of incident CV events[22–24] and CV mortality[25]. Traditional risk assessment does not accurately capture the increased CV risk among psoriasis patients[26], and many patients with CVD and related events in psoriasis are young[23, 25] with low Framingham risk scores[26]. As such, psoriasis provides a reliable human model to study the utility of novel inflammatory biomarkers for predicting subclinical CVD in chronic inflammatory states.

To understand how GlycA may potentially associate with subclinical CVD in psoriasis, and to compare the association of subclinical CVD to hsCRP, we used a two-stage study design. In the first stage (henceforth PENN cohort), we evaluated psoriasis patients 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 relationships between GlycA and subclinical CVD by assessing VI by 18-FDG PET/CT and CAD by coronary CT 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.

METHODS

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). 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-only supplement. STROBE guidelines were followed for reporting the findings from both the stages[27].

RESULTS

Characteristics of the study groups

The PENN cohort (Table 1A) contained psoriasis patients (n=122) with mild-to-moderate skin disease (median percent BSA 3, IQR 1–7), and controls (n=109) with similar age and gender. Participants were middle-aged (mean ± S.D.: psoriasis 45.2±13.6 years, controls 48.3±8.3 years), overweight to obese (BMI: psoriasis 30.6±8.1 vs. controls 27.6±4.6), and at low CV risk [Framingham risk score (FRS) median (IQR): psoriasis 5 (3–9); controls 5 (3–8)]. Psoriasis patients had lower levels of total cholesterol (psoriasis 191.1±34.4 vs. controls 211.6±38.0) and LDL cholesterol (psoriasis 111.8±28.8 vs. controls 134.9±35.3), likely corresponding with greater statin use (psoriasis 27%, controls 14%). Finally, psoriasis patients 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, 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 1B) had psoriasis patients (n=151) with mild-to-moderate skin disease [median (IQR): BSA 4.1 (2.1–13.5) and PASI score 5.8 (3–10.1)], and controls (n=30). Both groups were middle aged (psoriasis 50.2±12.9, controls 46.8±8.9), overweight (BMI: psoriasis 29.1±6.0 vs. controls 28.2±5.2), and at low CV risk by FRS [median (IQR): psoriasis 3 (1–6); controls 3 (1–5)]. Psoriasis patients had higher insulin resistance by homeostatic model assessment of insulin resistance (HOMA-IR) [median (IQR): psoriasis 2.77 (1.58–4.88); controls 2.38 (1.74–5.14)], despite having a low prevalence of type-2 diabetes (psoriasis 9% vs. controls 10%) and near normal fasting blood glucose levels (psoriasis 100.2±16.6, controls 97.2±13.4). They also had an equal prevalence of hyperlipidemia (psoriasis 47% vs. controls 47%) and a similar prevalence of metabolic syndrome (psoriasis 23% vs. 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, controls 346.2±46.0) (Figure 1B) were elevated in psoriasis similar to that observed in the PENN cohort.

Psoriasis patients had increased VI by 18-FDG PET/CT (psoriasis 1.70±0.26, controls 1.59±0.13; p=0.01) and CAD by CCTA (psoriasis 1.12±0.46, controls 0.99±0.25; p=0.01) compared to 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 ρ=0.73, p<0.01; NIH ρ=0.50, p<0.001). Furthermore, in the NIH cohort, GlycA correlated with inflammatory cytokines such as IL-6 (psoriasis ρ=0.40, p<0.0001; controls ρ=0.35, p<0.001), IL-16 (psoriasis ρ=0.25, p<0.0001; controls ρ=0.3, p<0.01) and monocyte chemotactic protein-4 (psoriasis ρ=0.12, p<0.05; controls ρ=0.26, p<0.05). GlycA also correlated with psoriasis severity [PENN cohort: BSA (ρ=0.22, p<0.05); NIH cohort: BSA (ρ=0.43, p<0.001) and PASI (ρ=0.57, p<0.001)] (Table 2A&2B, Figure 1 C&D, and Figure 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); NIH cohort: BSA (β=0.40, p<0.001), PASI (β=0.49, p<0.001)] (Table 3 A, B&C). Finally, other cardiometabolic risk factors that significantly correlated with GlycA in psoriasis included metabolic syndrome, waist-to-hip ratio, BMI, LDL-c, HDL-c, FRS, and HOMA-IR (Table 2A&2B).

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, controls β=0.26, p<0.001) (Table 4A). 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 4A). 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, controls β=0.13, p=0.002) (Table 4B) in unadjusted models. After adjustment for traditional CV risk factors these

relationships remained significant in psoriasis (β=0.34, p=0.01), as well as in controls (β=0.13, p=0.04) (Table 4B). Finally, CAD (β=0.05, p=0.30) did not associate with hsCRP in psoriasis, however, 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 (ROC) curves. GlycA provided maximum value in estimation of VI beyond hsCRP, when added to fully adjusted models, in both psoriasis (χ^2=19.59, p<0.0001) and controls (χ^2=8.95, p=0.003) (Table 5A). GlycA also provided incremental value in measuring CAD burden in psoriasis (χ^2=7.88, p=0.008) (Table 5B) beyond hsCRP and traditional CV risk factors. As expected in controls, hsCRP strongly predicted CAD burden (χ^2=7.22, p=0.02) (Table 5B).

ROC 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 (AUC for base model: 0.86, 95% CI 0.85–0.87 vs. 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 vs. 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 3A 3&4). HsCRP did not add value in predicting CAD or VI above the cohort mean in psoriasis (Figure 3B 1&2). Finally, in controls, though 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-TNF therapy decreases GlycA and aortic vascular inflammation 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-TNF therapy and followed them longitudinally for improvement in psoriasis and potentially VI. In these 16 patients, GlycA decreased significantly at follow-up compared to baseline (baseline 463.7±92.5 vs. 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) vs. post-treatment 1.3 (0.6–3.2); p=0.054]. Furthermore, we observed an improvement in both PASI score and VI (baseline vs. post treatment VI: 1.93±0.36 vs. 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 two-stage study design in psoriasis and healthy controls, we demonstrated the following major findings: 1) GlycA levels were elevated in psoriasis compared to 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; 5) successful treatment of psoriatic skin inflammation with anti-TNF therapy decreased GlycA levels and VI with 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, IFN-γ and monocyte chemoattractant protein-1 (MCP-1); mediators of endothelial activation such as VCAM-1, ICAM-1 and E-selectin; and acute phase reactants such as serum amyloid A and hsCRP. HsCRP, a marker of systemic inflammation, has become a promising candidate as it is 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 SLE[6], psoriasis[7], rheumatoid arthritis[5] and HIV[8]. Furthermore, a large population based longitudinal study of >10,000 patients showed evidence to suggest that elevated hsCRP may not be a universal feature of chronic inflammation[4]. 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 populations.

Contemporary studies to identify new inflammatory biomarkers for CV disease, demonstrate the potential for measuring GlycA. GlycA, an NMR 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 >25,000 subjects found GlycA to be predictive of 15-year CV events[11], incident diabetes mellitus[13], and all cause mortality[12, 28]. Fischer et al. also found a 67% and 55% increase in mortality for every standard deviation increase in GlycA, in two independent populations totaling > 17,000 healthy adults[29]. 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[11, 12, 28]. Strikingly, GlycA also showed associations with BMI and fitness among adolescents[30], suggesting its role even in the early stages of cardiometabolic dysfunction. Additionally, in inflammatory states, GlycA associated with disease activity as well as CHD among rheumatoid arthritis patients[15, 18], and was elevated in patients with SLE compared to controls[16]. Finally, GlycA also associated with disease activity in SLE, and revealed improved levels subsequent to treatment[17].

With increased systemic inflammation and VI[20, 21], higher prevalence of diabetes and other traditional CV risk factors[31, 32], and a greater risk of CV disease[33] as well as CV[23, 25] and cerebrovascular events[22] 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 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[10]. 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[4]. However, whether GlycA levels respond to anti-inflammatory treatment is unknown. We found that 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[34, 35], 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 the 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 and hard CV endpoints. 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 multi-modality imaging in an inflammatory state, and also the first study to perform a systematic comparison between GlycA and hsCRP in subclinical CVD assessment. Additionally, both VI by 18-FDG PET/CT[34, 36] and CAD by CCTA[37, 38] 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 upon the previously demonstrated association of GlycA with prospective CV events[11, 12].

As GlycA NMR signal is composed of several acute phase reactant glycoproteins, deeper physiologic studies to enhance our understanding of GlycA pathophysiology are warranted. Furthermore, from the emerging evidence and findings of our study, GlycA may be utilized as a risk factor in epidemiologic studies as well as a potential surrogate endpoint in clinical trials of anti-inflammatory treatment. However, larger studies will be needed to confirm these findings before broad scale use of GlycA in trials. Moreover, GlycA measurement may become more widespread with the recent FDA-approval of NMR-based lipoprotein measurement such as LDL-particle number in clinical laboratories. Finally, though 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 utility as a clinical biomarker of cardiovascular outcomes.

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, following anti-TNF treatment, we found a decrease in

GlycA levels and VI with 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 psoriasis patients in addition to hsCRP for CVD assessment, however, larger studies are needed to further confirm these findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Nonstandard Abbreviations and Acronyms

VI   Vascular Inflammation

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Novelty and Significance

What Is Known?

- GlycA is a nuclear magnetic resonance (NMR)-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 18-F Fluorodeoxyglucose Positron Emission Tomography Computed Tomography (18-FDG PET/CT) and coronary artery disease (CAD) burden by coronary CT angiography (CCTA) provide surrogate markers of future cardiovascular events.

What New Information Does This Article Contribute?

- GlycA was associated with 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 vascular inflammation by 18-FDG PET/CT and coronary artery disease burden by CCTA beyond traditional cardiovascular risk factors, and added incremental value beyond high-sensitivity C-reactive protein (hsCRP) in psoriasis.

- Treatment of psoriasis with anti-TNF therapy led to a decrease in GlycA levels and VI, and GlycA maintained a strong relationship with VI following treatment.

Recent studies have suggested that hsCRP, a biomarker of systemic inflammation which 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 vascular inflammation by 18-FDG PET/CT and burden of coronary artery disease by CCTA. Moreover, treatment of skin disease with anti-TNF therapy was associated with reduction in GlycA levels and VI, with GlycA maintaining its association with vascular inflammation following therapy. This study provides novel insights into the potential utility of GlycA in assessing subclinical CVD, as well as to follow the effects of anti-inflammatory therapy. These findings pave the way for future studies to examine the use of GlycA in studying other inflammatory disease states and in large studies of anti-

inflammatory therapy to investigate whether the use of GlycA translates into clinical outcomes.
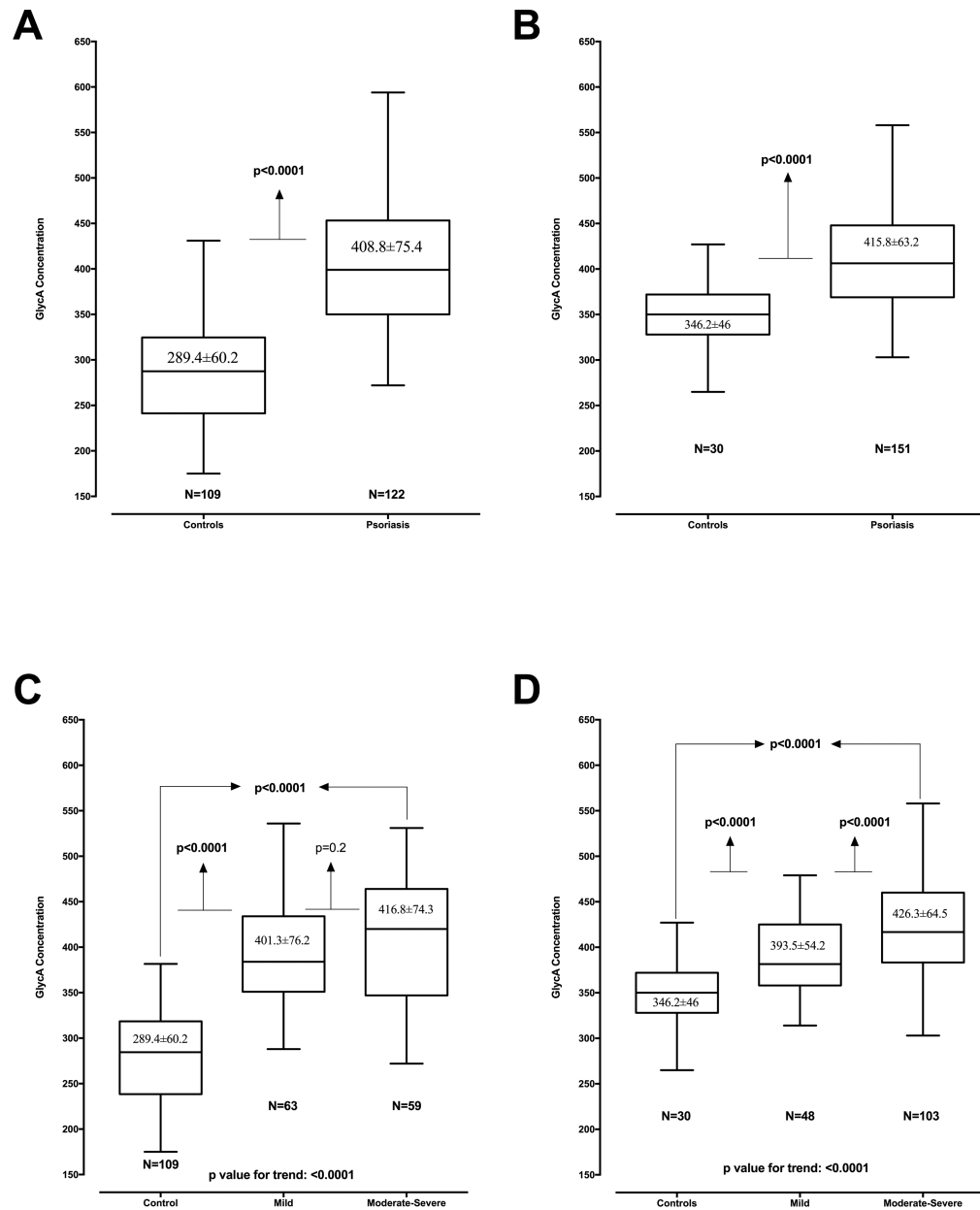
Mild Psoriasis: BSA < 3%; Moderate-to-Severe Psoriasis: BSA ≥ 3%

Figure 1.
GlycA levels are increased in psoriasis vs. controls in a two-stage study design (A: PENN Cohort, B: NIH Cohort), GlycA levels and relationship to psoriasis skin disease severity by body surface area in a two-stage study design (C: PENN cohort, D: NIH Cohort).
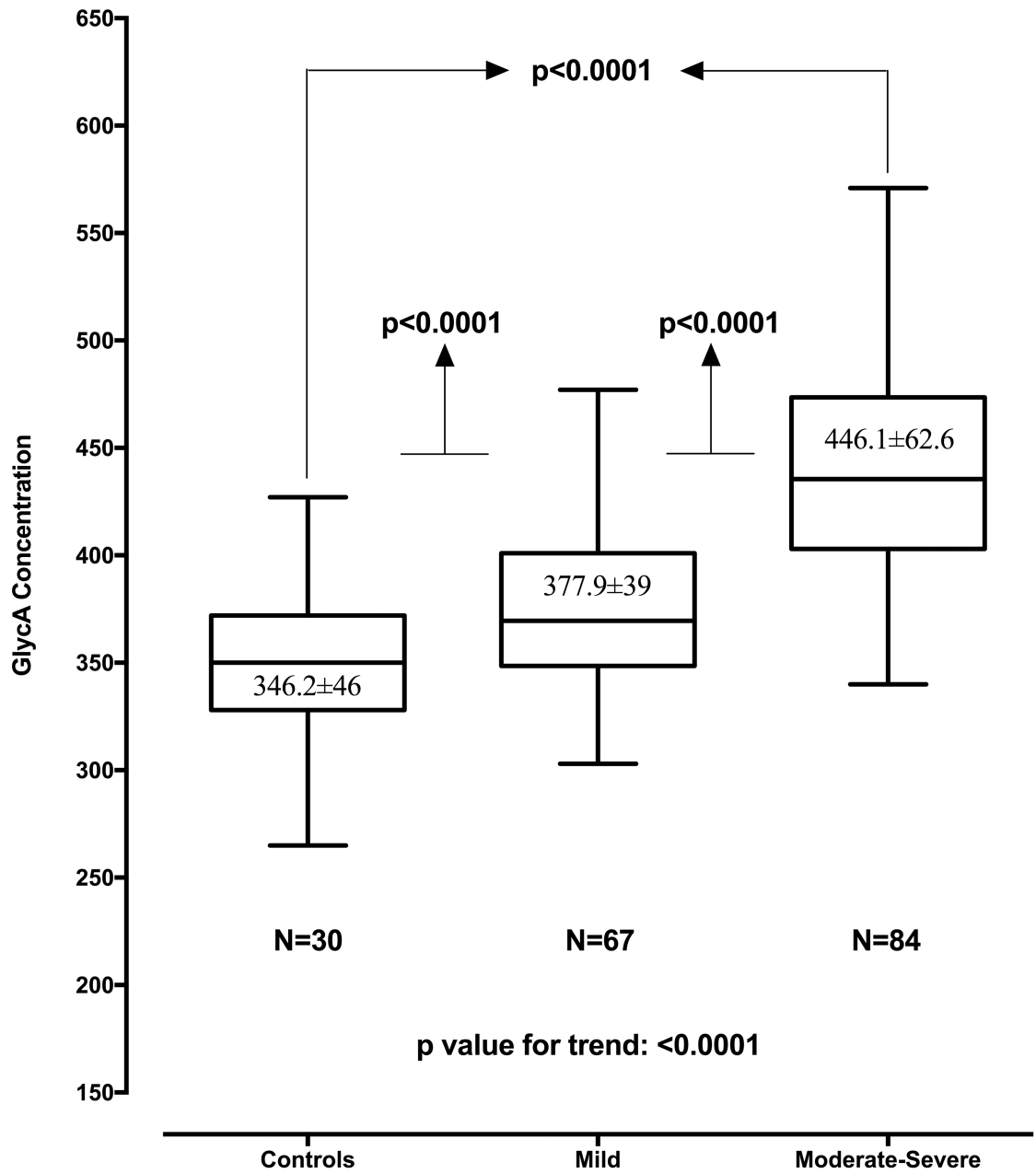
Mild Psoriasis: PASI Score < 5; Moderate-to-Severe Psoriasis: PASI Score ≥ 5

Figure 2.
GlycA levels and relationship with psoriasis skin disease severity measured by Psoriasis Area Severity Index (PASI) score in the NIH cohort.
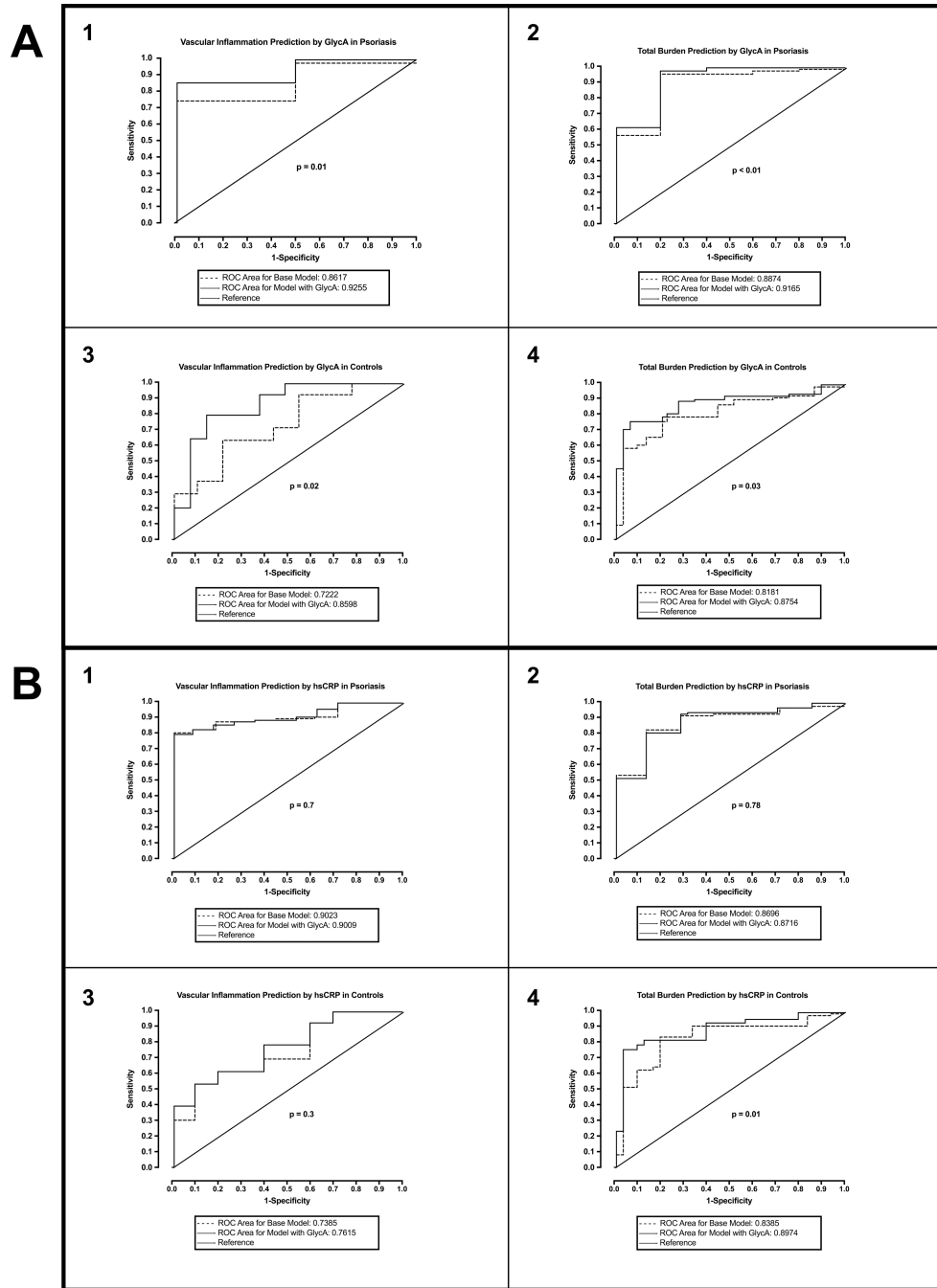
Figure 3.
Receiver operating characteristic (ROC) curves demonstrating incremental values added by GlycA and hsCRP: (A) ROC analyses demonstrate that GlycA adds value in predicting higher vascular inflammation and greater total burden of coronary artery disease in both psoriasis (1 and 2) and controls (3 and 4); (B) ROC analyses demonstrate that hsCRP adds value in predicting greater total burden of coronary artery disease (4) but not vascular inflammation (3) in controls, however, it fails to add any value in predicting vascular inflammation and coronary artery disease in psoriasis (1 and 2). Mean values of vascular

inflammation and coronary artery disease burden were used to convert these continuous variables into dichotomous variables, such that values ≥ mean were designated as 1 and values < mean were designated as 0.

Table 1

A: Demographic and clinical characteristics of the study groups from PENN cohort			
Parameter	**Psoriasis (N=122)**	**Control (N=109)**	**P value**
Demographic and Clinical Characteristics			
Age, years	45.2±13.6	48.3±8.3	**0.02**
Male Gender, N (%)	68 (60%)	60 (55%)	0.49
Hypertension, N (%)	39 (34.5%)	31 (29%)	0.35
Type 2 DM, N (%)	10 (8.8%)	0 (0%)	**<0.01**
Current Smoker, N (%)	8 (7%)	0 (0%)	**<0.01**
Statin use, N (%)	33 (27%)	15 (14%)	0.12
Clinical and Lab Parameters			
Body Mass Index, kg/m^2	30.6±8.1	27.6±4.6	**<0.0001**
Systolic blood pressure, mm Hg	130.2±17.0	127.2±16.2	0.26
Diastolic blood pressure, mm Hg	78.9±10.7	78.4±10.1	0.38
Total Cholesterol, mg/dL	191.1±34.4	211.6±38.0	**<0.0001**
Low-Density Lipoprotein cholesterol, mg/dL	111.8±28.8	134.9±35.3	**<0.0001**
High-Density Lipoprotein cholesterol, mg/dL	48.2 ±15.7	51.5±14.2	0.05
Triglycerides, mg/dL [Median (IQR)]	127 (78–190)	122 (88–156)	0.34
Glucose, mg/dL	92.5±37.1	92.3±11.7	0.47
Framingham Risk Score [Median (IQR)]	5 (3–9)	5 (3–8)	0.05
Insulin, µU/mL [Median (IQR)]	17.7 (11.6–29.7)	6.7 (4.4–9.8)	**<0.0001**
HOMA-IR [Median (IQR)]	3.3 (1.3–6.4)	1.5 (0.9–2.2)	**<0.0001**
Hs-CRP, mg/L [Median (IQR)]	3.3 (0.84–9.85)	1.1 (0.5–2.3)	**0.02**
GlycA, µmol/L	408.8±75.4	289.4±60.2	**<0.0001**
Psoriasis Characteristics			
Body Surface Area affected [Median (IQR)]	3 (1–7)	-	-
Systemic or Biologic Treatment, N (%)	13 (12%)	-	-

B: Demographic and clinical characteristics of the study groups from NIH cohort.			
Parameter	**Psoriasis (N=151)**	**Control (N=30)**	**P value**
Demographic and Clinical Characteristics			
Age, years	50.2±12.9	46.8±8.9	0.15
Male Gender, N (%)	85 (56%)	20 (67%)	0.73
Hypertension, N (%)	40 (27%)	7 (23%)	0.72
Type 2 DM, N (%)	14 (9%)	3 (10%)	0.9
Hyperlipidemia, N (%)	71 (47%)	14 (47%)	0.98
Metabolic Syndrome, N (%)	35 (23%)	5 (17%)	0.5

B: Demographic and clinical characteristics of the study groups from NIH cohort.			
Parameter	**Psoriasis (N=151)**	**Control (N=30)**	**P value**
Current Smokers, N (%)	13 (9%)	1 (3%)	0.32
Statin Use, N (%)	48 (32%)	9 (30%)	0.9
Clinical and Laboratory Values			
BMI, kg/m^2	29.1±6.0	28.2±5.2	0.21
SBP, mm Hg	123.7±14.5	112.4±11.8	**<0.001**
DBP, mm Hg	72.9±10	70.3±8.2	0.1
Total Cholesterol, mg/dL	182.4±36.5	188.3±38.7	0.21
Low-Density Lipoprotein cholesterol, mg/dL	101.7±29.8	105.3±33.3	0.29
High-Density Lipoprotein cholesterol, mg/dL	56.5±18.3	53.2±18.2	0.18
Triglycerides, mg/dL	100.5 (76–138)	108.5 (83–173)	0.17
Apolipoprotein A1, mg/dL	158±30.7	150±29.1	0.1
Apolipoprotein B, mg/dL	90±19.6	87.6±22	0.33
Framingham Risk Score, Median (IQR)	3 (1–6)	3 (1–5)	0.87
Glucose, mg/dL	100.2±16.6	97.2±13.4	0.17
Insulin, μU/mL [Median (IQR)]	11.1 (7.2–19.3)	9.9 (8.2–15.9)	0.72
HOMA-IR, Median (IQR)	2.77 (1.58–4.88)	2.38 (1.74–5.14)	0.67
Hs-CRP, mg/L [Median (IQR)]	1.80 (0.71–4.22)	1.35 (0.79–2.40)	0.24
GlycA, μmol/L	415.8±63.2	346.2±46	**<0.0001**
Psoriasis Characteristics			
Disease duration, years [Median (IQR)]	20 (8–30)	N/A	
Body Surface Area affected, Median (IQR)	4.1 (2.1–13.5)	N/A	
PASI score, Median (IQR)	5.8 (3–10.1)	N/A	
Systemic or Biologic Treatment, N (%)	55 (37%)	N/A	
Vascular Inflammation by FDG PET/CT			
Aortic Vascular Inflammation	1.70±0.26	1.59±0.13	**0.01**
Coronary Artery Disease by CCTA			
Total Burden of Coronary Artery Disease	1.12±0.46	0.99±0.25	**0.01**

Continuous variables are expressed as Mean ±S.D unless specified otherwise and categorical variables as %. P values were calculated by Student's t-test for continuous variable and Pearson's chi-square test for categorical variables.

DM: Diabetes Mellitus, HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, Hs-CRP: High-sensitivity C-reactive protein, PASI: Psoriasis area and severity index

Table 2

Correlation Analyses of GlycA with various demographic and cardiometabolic variables in both cohorts

A: Spearman correlation Analyses of GlycA in the PENN Cohort.			
Parameter	**Total Cohort (N=231)**	**Psoriasis (N=122)**	**Control (N=109)**
Demographic and Clinical Characteristics			
Age	0.004 (NS)	0.08 (NS)	0.09 (NS)
Hypertension	0.08 (NS)	0.14 (NS)	0.04 (NS)
Type 2 DM	**0.19 (<0.001)**	0.18 (NS)	No correlation
Smoker	**0.23 (<0.001)**	0.10 (NS)	0.01 (NS)
Statin use	0.07 (NS)	−0.07 (NS)	0.06 (NS)
Clinical and Laboratory Values			
Body Mass Index	**0.33 (<0.001)**	**0.43 (<0.001)**	**0.29 (<0.001)**
Systolic blood pressure	**0.21 (<0.001)**	0.14 (NS)	**0.22 (<0.001)**
Diastolic blood pressure	**0.17 (<0.001)**	0.11 (NS)	**0.21 (<0.001)**
Total Cholesterol	**0.09 (<0.05)**	**0.27 (<0.01)**	**0.23 (<0.001)**
Low-Density Lipoprotein cholesterol	−0.01 (NS)	**0.27 (<0.01)**	**0.11 (<0.05)**
High-Density Lipoprotein cholesterol	−0.08 (NS)	−0.16 (NS)	−0.01 (NS)
Triglycerides	**0.30 (<0.001)**	**0.35 (<0.001)**	**0.36 (<0.001)**
Framingham risk score	**0.14 (<0.01)**	**0.27 (<0.01)**	**0.12 (<0.05)**
Glucose mg/dl	−0.03 (NS)	0.01 (NS)	0.05 (NS)
Insulin	**0.48 (<0.001)**	0.17 (NS)	**0.25 (<0.001)**
hsCRP	**0.45 (<0.001)**	**0.73 (<0.01)**	**0.44 (<0.001)**
Psoriasis Characteristics			
Body Surface Area	N/A	**0.22 (<0.05)**	N/A
Systemic or Biologic therapy	N/A	0.05 (0.58)	N/A

B: Spearman correlation Analyses of GlycA in the NIH Cohort.			
Variable	**Total Cohort (N=181)**	**Psoriasis (N=151)**	**Controls (N=30)**
Demographic and Clinical Characteristics			
Age	0.08 (0.31)	−0.003 (0.95)	0.24 (0.19)
Gender	0.05 (0.49)	0.09 (0.06)	−0.23 (0.22)
Hypertension	0.01 (0.86)	−0.03 (0.52)	0.21 (0.28)
Type 2 DM	0.03 (0.67)	0.01 (0.81)	0.19 (0.31)
Hyperlipidemia	0.28 (0.08)	0.08 (0.08)	0.24 (0.2)
Metabolic Syndrome	**0.14 (0.009)**	**0.11 (0.02)**	0.15 (0.46)
Waist-to-Hip ratio	**0.16 (0.03)**	**0.23 (<0.001)**	0.1 (0.36)

B: Spearman correlation Analyses of GlycA in the NIH Cohort.			
Variable	Total Cohort (N=181)	Psoriasis (N=151)	Controls (N=30)
Tobacco	0.12 (0.11)	0.11 (0.07)	0.18 (0.3)
Current Smokers	0.08 (0.06)	0.06 (0.20)	0.25 (0.19)
Statin use	0.01 (0.9)	0.01 (0.89)	No correlation
Clinical and Laboratory Values			
Body mass index	**0.29 (0.001)**	**0.32 (0.001)**	**0.20 (0.03)**
Systolic blood pressure	**0.15 (0.04)**	−0.01 (0.91)	0.24 (0.2)
Diastolic blood pressure	0.07 (0.37)	−0.02 (0.65)	0.29 (0.12)
Total Cholesterol	0.06 (0.16)	0.01 (0.75)	0.29 (0.12)
Low-Density Lipoprotein cholesterol	0.12 (0.09)	**0.16 (<0.001)**	0.17 (0.37)
High-Density Lipoprotein cholesterol	**−0.14 (<0.007)**	**−0.17 (<0.001)**	**−0.11 (<0.01)**
Triglycerides	−0.02 (0.78)	−0.02 (0.70)	**0.36 (0.04)**
Apolipoprotein A1	**−0.13 (<0.001)**	**−0.20 (<0.001)**	**−0.14 (0.02)**
Apolipoprotein B	**0.17 (0.02)**	**0.17 (0.002)**	0.23 (0.2)
Glucose	0.13 (0.09)	0.06 (0.19)	0.20 (0.3)
Framingham risk score	0.12 (0.1)	**0.11 (0.04)**	0.18 (0.42)
Insulin	**0.24 (<0.001)**	**0.25 (<0.001)**	**0.28 (0.02)**
HOMA-IR	**0.24 (<0.001)**	**0.23 (<0.001)**	**0.28 (0.03)**
hsCRP	**0.46 (<0.001)**	**0.50 (<0.001)**	**0.51 (0.01)**
Psoriasis Details			
PASI score	**0.57 (<0.001)**	**0.57 (<0.001)**	N/A
Body Surface Area affected	**0.43 (<0.001)**	**0.43 (<0.001)**	N/A
Systemic or Biologic Treatment	**−0.12 (0.04)**	**−0.12 (0.04)**	N/A
Vascular Inflammation by FDG PET/CT			
Aortic Vascular Inflammation	**0.33 (<0.001)**	**0.32 (<0.001)**	**0.27 (0.008)**
Coronary Plaque Burden by CCTA			
Total Burden of Coronary Artery Disease	**0.20 (<0.001)**	**0.30 (<0.001)**	**0.19 (<0.001)**

Values are expressed as Rho (p value) for all variables.

DM: Diabetes Mellitus, HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, Hs-CRP: high-sensitivity C-reactive protein, PASI: Psoriasis Area Severity Index.

Table 3

Relationship between GlycA levels and psoriasis skin disease severity assessed by multivariable linear regression analysis.

A: GlycA vs. body surface area in the PENN Cohort	
Model	**β (p value)**
Unadjusted	**0.29 (0.002)**
Adjusted for age and gender	**0.34 (0.001)**
Adjusted for age, gender and FRS	**0.26 (0.007)**
Adjusted for age, gender, FRS and BMI	**0.25 (0.01)**
Adjusted for age, gender, FRS, BMI, SBP, LDL-C, HDL-C, HOMA-IR	**0.21 (0.01)**

B: GlycA vs. body surface area in the NIH Cohort	
Model	**β (p value)**
Unadjusted	**0.42 (<0.001)**
Adjusted for age and gender	**0.42 (<0.001)**
Adjusted for age, gender and FRS	**0.42 (<0.001)**
Adjusted for age, gender, FRS and BMI	**0.41 (<0.001)**
Adjusted for age, gender, FRS, BMI, SBP, LDL-C, HDL-C, HOMA-IR	**0.40 (<0.001)**

C: GlycA vs. Psoriasis Area and Severity Index score in the NIH Cohort	
Model	**β (p value)**
Unadjusted	**0.52 (<0.001)**
Adjusted for age and gender	**0.53 (<0.001)**
Adjusted for age, gender and FRS	**0.52 (<0.001)**
Adjusted for age, gender, FRS and BMI	**0.50 (<0.001)**
Adjusted for age, gender, FRS, BMI, SBP, LDL-C, HDL-C, HOMA-IR	**0.49 (<0.001)**

All values reported as 'Standardized β (p value)'.

FRS: Framingham Risk Score, BMI: Body Mass Index, SBP: Systolic Blood Pressure, HOMA-IR: Homeostasis Model Assessment of Insulin Resistance.

Table 4

Relationship between GlycA and Vascular disease

A: Multivariable regression analyses show a direct relationship between vascular inflammation and GlycA.			
Model	**Total Cohort**	**Psoriasis**	**Control**
Unadjusted	0.30 (<0.001)	0.30 (<0.001)	0.26 (<0.001)
Adjusted for age and gender	0.29 (<0.001)	0.28 (<0.001)	0.22 (<0.001)
Adjusted for age, gender and FRS	0.25 (<0.001)	0.25 (<0.001)	0.22 (<0.001)
Adjusted for age, gender, FRS and BMI	0.26 (<0.001)	0.22 (<0.001)	0.17 (0.045)
Adjusted for age, gender, FRS, BMI, SBP, LDL-C, HDL-C, HOMA-IR, Smoking and Statins	0.21 (0.002)	0.26 (0.004)	0.18 (0.03)

B: Multivariable regression analyses show a direct relationship between total burden of coronary artery disease quantified by CCTA and GlycA.			
Model	**Total Cohort**	**Psoriasis**	**Control**
Unadjusted	0.17 (<0.001)	0.31 (<0.001)	0.13 (0.002)
Adjusted for age and gender	0.15 (<0.001)	0.25 (0.005)	0.12 (0.003)
Adjusted for age, gender and FRS	0.16 (0.003)	0.26 (0.004)	0.15 (0.007)
Adjusted for age, gender, FRS and BMI	0.12 (0.007)	0.24 (0.002)	0.10 (0.02)
Adjusted for age, gender, FRS, BMI, SBP, LDL-C, HDL-C, HOMA-IR, Smoking and Statins	0.14 (0.001)	0.34 (0.01)	0.13 (0.04)

All values reported as 'Standardized β (p value)'.

CCTA: Coronary Computed Tomography Angiography, FRS: Framingham Risk Score, BMI: Body Mass Index, SBP: Systolic Blood Pressure, HOMA-IR: Homeostasis Model Assessment of Insulin Resistance.

Table 5

Incremental Value of GlycA beyond traditional cardiovascular risk factors and Hs-CRP in assessing both Vascular Inflammation and Coronary Artery Disease

A: Incremental value provided by GlycA in assessing aortic vascular inflammation by 18-FDG PET/CT.			
	Total Cohort	Psoriasis	Control
Model	Chi-square (p value)	Chi-square (p value)	Chi-square (p value)
GlycA added to Model 1	**23.47 (0.0007)**	**24.83 (<0.0001)**	**5.8 (0.02)**
Hs-CRP added to Model 1	0.96 (0.33)	0.1 (0.8)	1.01 (0.32)
GlycA added to Hs-CRP in Model 1	**20.06 (<0.0001)**	**19.59 (<0.0001)**	**8.95 (0.003)**
Hs-CRP added to GlycA in Model 1	2.54 (0.11)	0.7 (0.4)	0.22 (0.64)

B: Incremental value provided by GlycA in assessing total burden of coronary artery disease by CCTA.			
	Total Cohort	Psoriasis	Control
Model	Chi-square (p value)	Chi-square (p value)	Chi-square (p value)
GlycA added to Model 1	**15.80 (0.0003)**	**8.8 (0.003)**	**7.78 (0.003)**
Hs-CRP added to Model 1	1.09 (0.3)	0.64 (0.42)	**8.12 (0.04)**
GlycA added to Hs-CRP in Model 1	**14.34 (0.0003)**	**7.88 (0.008)**	**6.49 (0.01)**
Hs-CRP added to GlycA in Model 1	0.63 (0.43)	0.4 (0.55)	**7.22 (0.02)**

Model 1 is adjusted for age, gender, FRS, BMI, HOMA-IR, SBP, LDL-C, HDL-C, smoking and Statin use.

Hs-CRP: High-sensitivity C-reactive protein, FRS: Framingham Risk Score, BMI: Body Mass Index, SBP: Systolic Blood Pressure, HOMA-IR: Homeostasis Model Assessment of Insulin Resistance.