An Association Between the Inflammatory Biomarker GlycA and Depressive Symptom Severity

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ABSTRACT

Objective: The underlying mechanisms of depression remain unclear; however, current literature suggests a relationship between inflammation and depression. The association between the inflammatory biomarker high-sensitivity C-reactive protein (hs-CRP) and depression has been previously investigated, but the relationship between GlycA, a novel spectroscopic inflammatory biomarker, and depression does not appear to have been examined.

Methods: Data were obtained from The Dallas Heart Study (DHS, conducted between 2000 and 2002), which consisted of a large community-based sample of Dallas County residents (N = 3,033). Depressive symptom severity was assessed with the Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR). It was hypothesized that the serum GlycA level would be a statistically significant predictor of QIDS-SR scores after control for demographic covariates. Multiple linear regression was used to assess the relationship between GlycA level and QIDS-SR scores. The role of hs-CRP in predicting QIDS-SR scores was also explored.

Results: GlycA level was a statistically significant positive predictor of QIDS-SR score ($\beta = .053$, $P = .038$) with control for sex, age, antidepressant use, ethnicity, smoking status, drinking status, body mass index, and years of education. In a subset of adults with moderate-to-severe depression, GlycA level was not associated with QIDS-SR scores. Additionally, hs-CRP level was not a statistically significant predictor of QIDS-SR scores.

Conclusions: This study found a positive association between the inflammatory biomarker GlycA, but not hs-CRP, and depressive symptom severity in a large multiethnic and multiracial community-based sample. Thus, these results provide the first indication that GlycA may be a potentially useful novel biomarker of depression.

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Depression affects 4.4% of the population worldwide, making it one of the leading causes of disability.[1] Various lines of research have investigated possible underlying mechanisms that cause depression. Current literature suggests that a relationship exists between inflammation and depression, such that depression with inflammation could be interpreted as a vascular depression type.[2,3] Individuals with major depressive disorder have higher levels of inflammatory blood biomarkers, and this relationship is observed in those with (eg, diabetes, rheumatoid arthritis) and without medical conditions.[4,5] For this reason, there is a great interest in determining the relationship between blood biomarkers of inflammation and depression.

The mechanism by which inflammation might increase the risk of depression is not clear. Serum levels of high-sensitivity C-reactive protein (hs-CRP) are associated with basal ganglia levels of glutamate and myoinositol, suggesting glial dysfunction and the potential of glutamate-modulating drugs in the treatment of depressed patients with high levels of inflammation.[6] Dopaminergic changes are also thought to influence the relationship between depression and inflammation.[7] Alternatively, depression and inflammation might be related, at least partly, through other factors. For example, a recent analysis[8] reported that the association between depressive symptom severity and hs-CRP was no longer present after control for body mass index (BMI).

The immune system produces an inflammatory response when introduced to pathogens. On activation, the immune system prompts the release of acute phase proteins via cytokines. Positive acute phase proteins, such as hs-CRP, increase their plasma concentration during inflammation. The biomarker hs-CRP is widely used to assess inflammation levels within the body.[9] Although the association between hs-CRP and depression has been investigated, the findings are somewhat mixed. Some studies[10–15] have found a positive association, meaning a higher level of hs-CRP is associated with a greater expression of depressive symptoms, while others[16–19] found this association to become attenuated when adjusting for covariates. These mixed findings may occur due to various reasons, including the influence of demographic covariates on hs-CRP or the high intraindividual variability of hs-CRP.[20] Specifically, the hs-CRP level may change intermittently with a person, thus making it difficult to accurately determine the average typical hs-CRP level of an individual. Due to this variability and conflicting research findings, it is necessary to find an alternative biomarker to further assess the relationship between the inflammatory response and depressive symptom severity.

To further investigate the relationship between inflammation and depression, the current study pursued an alternative

Clinical Points

- Past research has largely focused on the role of the inflammatory biomarker high-sensitivity C-reactive protein in depression. Other inflammatory biomarkers, such as GlycA, may be useful novel biomarkers of depression. This study examined the association between GlycA and depressive symptom severity in a large, multiethnic, community-based population.
- The findings of this study suggest that higher GlycA levels are associated with higher depressive symptom scores. Clinicians may benefit from considering the level of inflammation based on GlycA to evaluate depression severity.

inflammatory biomarker, GlycA. The formulation of GlycA results from *N*-acetyl glucosamine residues on acute phase proteins, whereupon levels increase during inflammation.[21] A high level of blood GlycA, as measured by spectroscopy, indicates inflammation within the body.[22] Increased level of GlycA may be also associated with coronary artery disease, all-cause mortality and both cardiovascular disease and non-cardiovascular disease mortality,[23] autoimmune diseases,[21] and type 2 diabetes.[24] GlycA has a lower intraindividual variability and may serve as a more stable indicator of inflammation compared to hs-CRP.[21] However, to our knowledge, no studies to date have examined the relationship between GlycA and depression. Thus, the aim of this study was to determine the relationship between GlycA level and depressive symptom severity using data obtained from a large, diverse, community-based sample. In an exploratory analysis, levels of hs-CRP were also examined as a predictor of depressive symptom severity.

METHODS

Population

The Dallas Heart Study (DHS) is a community-based study initially conducted in 2000–2002 (DHS-1) and subsequently during 2007–2009 (DHS-2).[25] The DHS data collection involved a probability-based population sample of Dallas County residents between the ages of 18 and 65 years.[25] All participants completed a comprehensive health interview that included information about cardiovascular risk factors. A subsample of adults between 30 and 65 years old also provided biomarker, neuroimaging, and cardiac imaging data.[25] The data collected during the second phase were obtained in a single visit from participants from phase 1 (DHS-1) that elected to continue on to phase 2 (DHS-2) or from newly acquired participants. The University of Texas Southwestern Medical Center Institutional Review Board approved the study, and written informed consent was obtained from all participants. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki.

In the current analysis, the association between GlycA level and depression was examined using the cross-sectional data obtained from DHS-2 (depressive symptom severity was assessed only at DHS-2). Due to the Dallas Heart Study's objective to examine racial differences in cardiovascular disease risk, the study oversampled for African Americans.

The Quick Inventory of Depressive Symptomatology–Self-Report

Depressive symptom severity was assessed using the 16-item Quick Inventory of Depressive Symptomatology–Self-Report scale (QIDS-SR), a shortened form of the 30-item clinician-administered assessment.[26] The psychometric properties of the QIDS-SR indicate that the assessment has high internal consistency as well as high inter-item correlations with its clinical-rated counterpart.[26] The 16-item questionnaire assesses depression symptoms in accordance with *DSM-IV* criteria domains, including depressed mood, loss of interest, sleep problems, appetite/weight changes, concentration difficulties, self-criticism, fatigue/lack of energy, psychomotor agitation/retardation, and suicidal ideation. The QIDS-SR total score ranges from 0 to 27, with higher score indicative of greater depressive symptom severity.

Biomarker Collection

Venous blood was collected in EDTA tubes during DHS-2. The samples were maintained at 4°C for < 4 hours and, following plasma removal, the serum for assay was frozen at −80°C. GlycA levels were processed and analyzed by LabCorp. The nuclear magnetic resonance (NMR) signal of GlycA was obtained from glycosylated acute phase proteins. This signal was then analyzed via LP4 algorithm to perform a metaboprofile analysis.[27] The level of inflammation (proteins) was indicated by the proteins' differential glycosylation, as shown by the amplitude of the GlycA signal. During an inflammatory response, the majority of the acute phase proteins are glycosylated and greatly influence the GlycA signal, which is predominately composed of the detection of glycosylation of *N*-acetyl methyl groups of α_1-acid glycoprotein, haptoglobin, α_1-antitrypsin, α_1-antichymotrypsin, and transferrin.

Statistical Analysis

In the current study, we analyzed cross-sectional data from participants who completed the QIDS-SR during DHS-2, yielding a total sample size of 3,033. A multiple regression analysis was performed using GlycA level as a predictor and QIDS-SR total score as the outcome variable. The model adjusted for the following covariates: sex, ethnicity (African American, White, Hispanic), age, BMI, years of education, drinking status, smoking status, and antidepressant use. Smoking status categories were defined as current smoker, past smoker, and never smoker. For drinking status, participants defined their drinking habits as current drinking, recent abstainer, and lifetime abstainer. Categorical variables were dummy coded prior to analyses with the following reference categories: female (sex), African American (race/ethnicity), never smoker (smoking status), current drinker (drinking status), and antidepressant use

(yes). Dummy coding is a coding system that transforms a categorical variable with multiple levels into a series of dichotomous variables with 2 levels. This procedure allows to compare each level of a variable to the reference (omitted) level.[28] To create interaction terms, the continuous variables (GlycA and age) were mean-centered and multiplied by the categorical variables of interest. Four interactions were tested: GlycA × age, GlycA × sex, GlycA × African American, and GlycA × antidepressant use. All analyses were conducted using IBM SPSS Statistics Version 26.0.[29] Statistical significance was defined as $P < .05$.

RESULTS

The descriptive statistics that list the study sample's demographics are found in Table 1. The overall regression model was statistically significant ($F_{12,1579} = 17.12$, adjusted $R^2 = 0.108$), suggesting that the predictors accounted for 10.8% of variance in the QIDS-SR score after adjusting for the number of predictors in the model. After adjusting for the covariates of interest, GlycA level was a statistically significant positive predictor of QIDS-SR score ($\beta = .053$, $r_s = 0.398$, $r_s^2 = 0.158$, $P = .038$). The squared structure coefficient (r_s^2) of 0.158 suggests that GlycA level uniquely explains 15.8% of the R^2 effect in the QIDS-SR score. Several covariates were also statistically significant, including sex ($\beta = .117$, $P < .001$), antidepressant use ($\beta = -.155$, $P < .001$), age ($\beta = -.073$, $P = .004$), ethnicity (White vs African American, $\beta = -.077$, $P = .004$), ethnicity (Hispanic vs African American, $\beta = -.062$, $P = .023$), smoking status (current vs never smoker, $\beta = .092$, $P < .001$), education years ($\beta = -.159$, $P < .001$), and BMI ($\beta = .081$, $P = .001$) (Table 2). GlycA level also remained statistically significant after adding the interaction terms to the model. However, none of the interaction terms was a statistically significant predictor of QIDS-SR score, suggesting that there is no differential effect of GlycA level on depressive symptom severity based on sex, age, ethnicity, or antidepressant use.

We also evaluated the relationship between GlycA level and QIDS-SR score in a subset of adults (n = 156) with moderate-to-severe depressive symptoms (defined as QIDS-SR score ≥ 11) while controlling for the same covariates included in the analysis of the overall sample. In this subset, GlycA level was not a statistically significant predictor of QIDS-SR score ($\beta = .074$, $P = .391$). This relationship between GlycA level and QIDS-SR score was also not observed in a subset of adults with mild depressive symptoms (QIDS-SR score < 11, n = 1,436; $\beta = .015$, $P = .584$).

Exploratory Analysis of CRP and QIDS-SR

To investigate the role of another inflammatory biomarker, hs-CRP, in predicting depressive symptom severity, we added hs-CRP as a predictor of QIDS-SR score in the multiple regression model. When controlling for GlycA level, age, ethnicity, education years, BMI, smoking status, and drinking status, hs-CRP level was not a statistically significant predictor of QIDS-SR ($\beta = .015$, $r_s = 0.459$, $P = .543$). However, GlycA level remained a significant positive predictor of QIDS-SR score ($\beta = .073$, $r_s = 0.257$, $P = .004$), even in the presence of hs-CRP. The structure coefficients suggest that GlycA level uniquely explained 45.9% of the R^2 effect in the QIDS-SR score

Table 1. Demographic Characteristics of the Sample[a]

Variable	Value
QIDS-SR score, mean (SD)	5.56 (3.92)
Serum GlycA level, mean (SD), μmol/L	431.96 (83.08)
Serum hs-CRP level, mean (SD), μmol/L	5.65 (19.40)
Age, mean (SD), y	49.78 (11.14)
Education, mean (SD), y	12.67 (2.15)
BMI, mean (SD), kg/m^2	31.25 (7.43)
Sex	
Female	1,233 (40.7)
Male	1,800 (59.3)
Ethnicity	
African American	1,535 (50.6)
White	1,005 (33.1)
Hispanic	417 (13.7)
Missing	76 (2.5)
Drinking status	
Current drinker	2,092 (69.0)
Recent abstainer	642 (21.2)
Lifetime abstainer	261 (8.6)
Missing	38 (1.3)
Smoking status	
Current smoker	685 (22.6)
Past smoker	673 (22.2)
Never smoker	1,641 (54.1)
Missing	34 (1.1)
Antidepressant use	
Yes	178 (5.9)
No	1,619 (53.4)
Missing	1,236 (40.8)

[a]Values are shown as n (%) unless otherwise noted. The initial sample included participants with available QIDS-SR scores (N = 3,033). The score cut-off ranges for the QIDS-SR are as follows: Not Depressed: 0–5; Mild Depression: 6–10; Moderate Depression: 11–15; Severe Depression 16–20; Very Severe Depression: 21–27. The suggested level of GlycA is < 399 μmol/L (ie, low risk for cardiovascular disease).
Abbreviations: BMI = body mass index, hs-CRP = high-sensitivity C-reactive protein, QIDS-SR = Quick Inventory of Depressive Symptomatology–Self-Report.

Table 2. Results of Multiple Regression Analysis With GlycA Predicting QIDS-SR Scores[a]

Predictor	β	SE	*P*	Correlation (*r*) With QIDS-SR Score
Serum GlycA level (μmol/L)*	.05	0.00	.038	0.14
Sex*	.12	0.19	< .001	0.17
Age*	−.07	0.01	.004	−0.08
Education years*	−.16	0.05	< .001	−0.18
Antidepressant use (yes/no)*	−.16	0.30	< .001	−0.16
White versus African American*	−.08	0.21	.004	−0.12
Hispanic versus African American*	−.06	0.29	.023	0.02
Recent abstainer versus current drinker	−.01	0.23	.775	0.02
Lifetime abstainer versus current drinker	.00	0.38	.99	0.02
Past smoker versus never smoker	.00	0.23	.986	−0.07
Current smoker versus never smoker*	.09	0.24	< .001	0.12
BMI*	.08	0.02	.001	0.12

[a]Age, sex, ethnicity, BMI, education, smoking status, drinking status, and antidepressant use represent covariates in the multiple linear regression analysis of the relationship between GlycA and QIDS-SR scores.
*The variables are statistically significant at $P < .05$.
Abbreviations: BMI = body mass index, QIDS-SR = Quick Inventory of Depressive Symptomatology–Self-Report.

compared to 25.7% explained by hs-CRP level. When examined by itself (without the influence of GlycA level in the regression equation), hs-CRP level was not statistically significant (β = .042, *P* = .054).

DISCUSSION

This study is, to the best of our knowledge, the first examining the relationship between depression and GlycA, a novel inflammatory biomarker. The results of the current study suggest that higher GlycA levels are associated with higher depressive symptoms scores (QIDS-SR) after controlling for sex, age, BMI, years of education, antidepressant use, and drinking and smoking status. The GlycA level was operationalized based on the risk for cardiovascular disease, with low risk defined as GlycA level < 399 μmol/L and high risk defined as GlycA level ≥ 399 μmol/L.[22] The mean GlycA level in the study was 431.96 μmol/L, suggesting that the study participants were, on average, in the higher risk group for cardiovascular disease based on the mean GlycA level. These findings suggest that GlycA may be a useful peripheral inflammatory biomarker of depression.

As expected, many of the covariates, such as sex, BMI, antidepressant use, and smoking status, were also associated with QIDS-SR scores. Alcohol use was not associated with QIDS-SR scores. The existing literature is mixed on whether abstinence and moderate alcohol use demonstrate different rates of depression.[30–33] Thus, the limited amount of problem drinking in this community sample may have limited the ability to observe a relationship between depression and alcohol consumption in this analysis. The difference in QIDS-SR score between African Americans and White individuals is consistent with a reported lower rate of lifetime depression in African Americans compared to White individuals.[34] The mean (SD) BMI in the study was 31.14 (7.40) kg/m^2, suggesting that, on average, the study participants were in the obese BMI range. A positive association between BMI and depression has been observed in prior research, particularly in adults with low-grade systemic inflammation as measured by hs-CRP and interleukin-6.[35] Some studies also point to GlycA elevation in obesity and normalization of GlycA to baseline following bariatric surgery; however, no studies, to our knowledge, have specifically examined both GlycA and obesity as predictors of depression.[36]

The study has several strengths. First, we examined the relationship between the inflammatory biomarker GlycA and depressive symptom severity scores in a large, multiethnic, community-based sample. Second, the QIDS-SR is a validated and reliable instrument for assessing the severity of depressive symptoms, with good psychometric measure properties derived from the clinician administered assessment.[37] Third, GlycA may serve as a feasible and useful measurement of inflammation when compared to other inflammatory biomarkers. GlycA has a low intraindividual variability when compared to hs-CRP[21]; hs-CRP levels can fluctuate greatly across time, making a singular reading less useful.[38] However, the need for NMR for GlycA analysis, and generally higher costs than for hs-CRP analysis, may slow its widespread use as an inflammatory biomarker.

The study also has limitations. Depressive symptom severity at a single point in time was assessed. Thus, a diagnosis of a depressive disorder was not made. Although a validated instrument was used to assess depressive symptom severity, it relied upon participant self-report. The cross-sectional nature of the analysis does not allow for a clear determination of causation. This sample was not a clinical population (ie, depression clinic patients); thus, the study findings may not be generalizable to a clinical population with higher depressive symptom severity. The mean QIDS-SR score was 5.56, suggesting that, on average, the sample had mild depressive symptom severity. QIDS-SR scores between 0 and 10 typically indicate no to mild depressive symptomatology, with higher scores suggesting greater severity.[39] Blood draws in the DHS were not scheduled at a consistent time of day. Diurnal variation in GlycA level has not been specifically examined. However, variability of GlycA over a 5-week period within individual participants was less than for hs-CRP (coefficient of variation [CV] was 4.3% vs 29.2%, respectively) and similar to that for cholesterol (CV = 5.7%).[22] Furthermore, in the postprandial state over 4 hours, no significant change in GlycA levels were observed. The multiethnic sample with a broad age range and inclusion of both sexes increases the generalizability of the findings but could also add variability to the data, which might limit statistical power.

The mechanisms linking GlycA with depression are not entirely clear. A common finding within the literature is that inflammation is an immunologic response to outside biological and psychological stressors. Specifically, inflammation occurs via proinflammatory cytokines, which in turn promote serotonin transporter activity, thus increasing serotonin reuptake. This process lowers the overall amount of extracellular serotonin available within the system.[40] Lower amounts of serotonin are associated with depression,[41] which may explain why several proinflammatory cytokines have been found to be depressogenic or why depressed individuals tend to have a higher concentration of proinflammatory cytokines.[42] External factors that contribute to depression such as chronic daily stress or psychosocial stressors, may also increase levels of proinflammatory cytokines.[43] Although speculative, the association between GlycA, a proinflammatory biomarker, and depression could be explained by the aforementioned mechanisms. In conclusion, our study found a positive association between the inflammation biomarker GlycA and depressive symptom severity, and this relationship held after controlling for multiple demographic variables. Further research is needed to further investigate this relationship. Ideally, future studies should assess this relationship longitudinally, comparing healthy and depressed populations to determine differences in inflammation levels. In addition, studies to determine if GlycA, as does hs-CRP,[44,45] predicts antidepressant response are needed.

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