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Elevated GlycA in Severe Obesity is Normalized by Bariatric Surgery

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Abstract

Chronic inflammation drives many obesity-associated conditions, including atherosclerosis. GlycA, a marker of systemic inflammation with lower intraindividual variability than hsCRP, is independently associated with incident cardiovascular events and mortality. Although GlycA is elevated in obesity, correlations with anthropometric measures are modest and the effect of weight loss on GlycA is untested. Obese (BMI 44.6±6.6kg/m²), non-diabetic women (33.7±8.2 years) undergoing Roux-en-Y gastric bypass (n=23) or sleeve gastrectomy (n=31) were prospectively studied at baseline, 6 and 12 months post-procedure. Women with normal BMI (n=14) served as controls. Bariatric surgery significantly reduced GlycA by 6 months (451±47umol/L vs 383±50umol/L; p<0.001) with further reduction at 12 months (348±41umol/L; p<0.001) and no difference between procedures. At 12 months, despite 41% of surgical subjects maintaining BMI >30kg/m², GlycA levels did not differ between surgical and control subjects (p=0.13). Increased HDL particle size was strongly associated with reduced GlycA (r=-0.49; p<0.001) and was found to mediate up to 43% of its weight-loss-associated fall.

This is the first study to demonstrate that surgical weight loss markedly reduces levels of GlycA.

Keywords

inflammation; obesity; GlycA; bariatric surgery; cardiovascular disease; risk

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Introduction

Chronic systemic inflammation is associated with obesity and plays a pathophysiologic role in many of its comorbidities. In particular, inflammation plays a central role in the pathogenesis of cardiovascular disease (CVD) – driving endothelial dysfunction, plaque development, and ultimately plaque rupture.¹

High sensitivity C-reactive protein (hsCRP) is the most widely clinically-employed circulating marker of inflammation.¹ However, its utility in predicting CVD in patients with chronic systemic inflammation is limited, as it is non-specific and may not fully capture all forms of inflammation.^{2, 3} For example, the Multi-Ethnic Study of Atherosclerosis (MESA) demonstrated obesity to be independently associated with subclinical atherosclerosis irrespective of hsCRP, with no additive effect when elevated hsCRP was present.⁴ This finding, among others, suggests the need for other markers of CVD risk that could provide additional risk stratification and potentially guide monitoring and/or treatment of the underlying condition and CVD risk factors in chronic inflammatory states such as obesity.

GlycA is a novel, composite nuclear magnetic resonance (NMR)-measured biomarker that integrates quantities of several abundant acute phase glycoproteins to provide a more global assessment of inflammation with much lower intra-individual variability than hsCRP.⁵ GlycA has been shown to be a strong and independent predictor of CVD, even among patients with concurrent inflammatory diseases.^{6–8} Further, recent data suggest incorporation of GlycA improves the discriminatory capacity of traditional CVD risk models, independent of hsCRP.^{5, 6}

High density lipoprotein (HDL), a traditional measure of CVD risk, is felt to be cardioprotective through several mechanisms including anti-inflammatory activity.⁹ However, impaired HDL function frequently characterizes obesity,¹⁰ possibly contributing to excess inflammation and CVD risk. Notably, both HDL and GlycA (in opposite directions) have been associated with active vascular inflammation.^{6, 11}

Bariatric surgery is the most effective therapy in the management of severe obesity, and generally improves traditional atherosclerosis risk factors. Although bariatric surgery has been shown to reduce adverse cardiovascular outcomes,¹² these data come predominantly from a procedure no longer in use. Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) are currently the most commonly performed bariatric surgeries. Both produce substantial weight loss, but vary somewhat in improvements in specific CVD risk factors.

Data on the modulation of GlycA are very limited. Although statins reduce hsCRP levels, this therapy does not affect GlycA.¹³ However, anti-tumor necrosis factor- α (TNF α) therapy in the chronic inflammatory condition, psoriasis, reduced GlycA in close parallel with reductions in demonstrated atherosclerotic CVD activity.⁶ Some data show an association of GlycA with body mass index (BMI), but are limited to children.^{14, 15} Further, it remains unknown if any weight loss intervention affects GlycA levels in obesity. We thus sought to explore the effect of bariatric surgery on GlycA in severely obese adults.

Methods

Nonsmoking, non-diabetic, premenopausal Hispanic women, age 18 years, undergoing RYGB or SG at Bellevue Hospital (New York, NY) were recruited for a prospective observational study approved by the NYU School of Medicine IRB (S13–00746). To reduce confounding, patients taking medications affecting lipid levels or blood glucose, chronic use of anti-inflammatory medications, or with chronic inflammatory conditions were excluded. 77 subjects enrolled and presented for pre-operative anthropometric and clinical measurements and blood sampling. 54 subjects subsequently underwent laparoscopic RYGB or SG and follow-up testing at 6 and 12 months post-operatively.

Nonsmoking, premenopausal Hispanic women, age 18 years, with BMI 18.5–24.9 kg/m², not taking exclusionary medications nor with chronic inflammatory conditions, recruited from the same medical center served as controls.

GlycA levels and high density lipoprotein (HDL) particles were measured by NMR (LabCorp Inc., Raleigh, NC). Lipid profiles, hsCRP and hemoglobin A1c (HbA1c – a measure of three-month average blood glucose concentration) were measured on a Beckman-Coulter AU5832 chemistry analyzer. Plasma adiponectin was measured via multiplex immunoassay (Millipore, Germany). Elevated GlycA was defined as >2 standard deviations above the mean of control subjects (410 μmol/L).

Comparisons of baseline and post-operative variables were performed as described in the Figure legend. Pearson correlation testing was used to assess associations between GlycA and anthropometric and blood measures, as well as 12 month changes in GlycA with changes in these same variables: body weight, BMI, waist and hip circumferences, waist:hip, triglycerides, HDL-cholesterol, HDL-particles (as well as small, small+medium, and large HDL particles), HDL particle size, glucose, HbA1c, LDL-cholesterol, adiponectin and hsCRP. These measures were further used as independent variables in univariate linear regression analyses to predict post-operative changes in GlycA. Variables associated with the outcome in univariate modeling ($p \leq 0.1$) were included as candidates in multivariable regression analyses. The final model included all predictors with $p < 0.05$. For each selected predictor in the multivariable model separately, we performed a mediation analysis employing boot strapping (5000 samples) to assess its mediator effect on the effect of body weight loss on the outcome of post-operative changes in GlycA. SPSS (Armonk, NY), with the PROCESS plug-in for mediation analyses, was used for statistical analyses.

Results

The 77 subjects enrolled in this study were young (32.4 ± 7.7 years) and severely obese (44.1 ± 6.4 kg/m²). They did not differ from the 54 subjects who underwent surgery and completed all study procedures whose data are presented in the Table. Although, by design, subjects did not exhibit insulin resistance or dyslipidemia necessitating medications, 28/54 subjects met International Diabetes Federation metabolic syndrome diagnostic criteria¹⁶ pre-operatively. Obese subjects also exhibited very elevated levels of inflammatory markers (Table). Pre-operatively, 44/54 subjects had elevated GlycA (> 410 μmol/L) and 47/54

subjects had hsCRP >3mg/L. No normal-BMI subject exhibited elevated inflammatory markers.

Subjects lost significant weight at six ($-27.4 \pm 5.0\%$) and 12 months ($-33.3 \pm 7.4\%$). GlycA levels significantly decreased at six months and were further reduced at 12 months after surgery (Figure A). hsCRP also significantly decreased post-operatively. At 6 months, average hsCRP did not differ between post-operative and normal-BMI subjects, while GlycA remained elevated in the surgical group (Figure B). At 12 months, average GlycA did not differ between post-operative obese subjects and normal-BMI control subjects, despite 22/54 post-operative subjects remaining obese ($\text{BMI} > 30 \text{ kg/m}^2$) at this time point. The response in GlycA did not differ by surgical procedure (RYGB: $-24.6 \pm 8.2\%$ vs SG: $-21.2 \pm 7.7\%$; $p=0.32$). At one year after surgery, five subjects had persistently elevated GlycA levels, but only one also exhibited hsCRP >3mg/L.

In pre-operative obese subjects, GlycA significantly correlated with hsCRP ($r=0.68$; $p<0.001$, Supplemental Figure 1), but not body weight ($r=0.24$; $p=0.08$), BMI ($r=0.14$; $p=0.33$), waist circumference ($r=0.18$; $p=0.20$) or waist:hip ($r=0.17$; $p=0.22$). One year post-operatively, GlycA was no longer associated with hsCRP ($r=0.24$; $p=0.09$). Post-operative changes in GlycA were strongly positively associated with changes in body weight ($r=0.41$; $p=0.002$, Figure C), hsCRP ($r=0.36$; $p=0.008$) and HbA1c ($r=0.31$; $p=0.03$, Figure D), and inversely with changes in mean HDL particle size ($r=-0.49$; $p<0.001$, Figure E) and adiponectin ($r=-0.47$; $p=0.002$). Post-operative changes in HbA1c and HDL size are displayed in Supplemental Figure 2. Multivariable linear regression analyses for the outcome of change in GlycA at 12 months demonstrated that only changes in HDL particle size ($B=-0.62$ (0.21); $p=0.006$) and HbA1c ($B=0.28$ (0.11); $p=0.01$) contributed to the model. Mediation analyses revealed that the effect of body weight loss on GlycA occurred partly through increased HDL size ($ab=0.19$ [0.04, 0.38]) which accounted for 43% of the effect of body weight loss on GlycA.

As GlycA is associated with incident diabetes¹⁷ and insulin resistance may influence HDL particles, we investigated whether reductions in HbA1c were related to increased HDL particle size in our subjects. Changes in HbA1c did not correlate with changes in HDL size ($r=-0.17$, $p=0.24$), nor was HbA1c one of several predictors of post-operative HDL particle size change identified with multivariable linear regression modeling (Supplemental Table).

Conclusions

This is the first study of the effect of weight loss or bariatric surgery on the novel composite inflammatory marker, GlycA. In this study of 54 Hispanic women followed for over one year, we showed that obesity, even in predominantly metabolically healthy individuals, is characterized by markedly elevated GlycA. We demonstrate that bariatric surgery is largely effective in normalizing GlycA levels, even in patients who remain obese, and that weight-loss-associated reduction in GlycA may be partly mediated by HDL particle size increases.

The pathophysiologic link between systemic inflammation and atherosclerosis is well established and interventions aimed specifically at reducing inflammation can reduce

adverse CVD outcomes.¹⁸ The precise nature of the association between obesity, inflammation and CVD is less clearly understood. Many inflammatory markers associated with CVD^{3, 18} are also elevated in obesity, including interleukin-6, TNF α , interleukin-1 β and hsCRP.¹ hsCRP is the most widely studied and clinically validated marker of systemic inflammation in CVD and obesity.¹ However, chronic inflammation is heterogeneous in nature and as a single marker of inflammation with sizable intra-individual variability, hsCRP may incompletely represent an individual's inflammatory status.² The relevance of this to CVD risk, specifically in obesity, is highlighted by the analysis of MESA described above.⁴

GlycA has been associated with CVD and all-cause mortality, even after adjusting for hsCRP, suggesting that GlycA captures different aspects of inflammation than hsCRP.^{2, 4-8} Supporting this, in several studies of patients undergoing coronary angiography, GlycA and hsCRP were shown to be independent and additive markers of CV event risk.^{5, 19} Therefore, GlycA may serve to augment and better risk-stratify patients experiencing the cardiovascular sequelae of inflammation compared to traditional inflammatory markers.

Despite GlycA's association with clinical end points, there are few reports demonstrating GlycA to be responsive to therapeutic intervention. Notably, statins do not affect GlycA,¹³ although they are known to reduce hsCRP. Recently, two groups showed that treatment of psoriasis⁶ and HIV²⁰ significantly reduced GlycA levels. The former demonstrated that GlycA (but not hsCRP) level was strongly associated with vascular inflammation measured by positron emission tomography (PET) before and after anti-TNF α therapy.⁶ In our study, bariatric surgery reduced mean GlycA from 447 μ mol/L to 345 μ mol/L, with levels only slightly higher (364 μ mol/L) in women remaining obese at one year. These post-operative levels are comparable to median GlycA values of normal weight healthy girls and women in other published studies (351 – 379 μ mol/L).^{8, 14} While studies of bariatric surgery have inadequate power to evaluate cardiovascular outcomes, these post-surgery levels of GlycA suggest a possible decrease in long-term risk related to atherosclerotic CVD, as a study of GlycA and coronary artery calcium (CAC) in patients with rheumatoid arthritis found patients with CAC (415 μ mol/L) had higher GlycA levels than those without CAC (379 μ mol/L).⁷ Ours is the first study demonstrating the ability of surgical weight loss intervention to reduce, and largely normalize, systemic inflammation as measured by GlycA, even in patients who remain overweight and obese.

GlycA remained elevated in a small number of subjects at 12 months after surgery in spite of improvements in typical CVD risk factors. Notably, these subjects exhibited minimal CVD risk by traditional models, were absent a metabolic syndrome diagnosis, and only one had elevated hsCRP. Others have demonstrated that GlycA adds additional risk stratification capacity in moderate-to-high risk cohorts,^{5, 19} and levels 417 μ mol/L were associated with 29% greater odds of incident CVD in the Women's Health Study.⁸ Although they require validation in larger diverse cohorts, our data suggest that GlycA may be useful for further risk stratification in patients with a history of obesity who have lost substantial weight.

Finally, we found that reductions in GlycA following bariatric surgery were strongly related to reductions in body weight and HbA1c, as well as increased HDL particle size. In further

modeling, changes in HDL particle size appeared to explain much of the association with reduced body weight. Anti-inflammatory activity is one mechanism by which HDL is felt to be atheroprotective⁹ and HDL size has been inversely associated with vascular inflammation on PET,¹¹ a measure of atherosclerotic CVD that also strongly correlates with GlycA.⁶ Although some recent work suggests small, rather than large, HDL particles may be most associated with reduced CVD risk,^{5, 13} these researchers also found that the associations of HDL with outcomes are altered in the setting of elevated GlycA.⁵ While the current study does not allow determination of causation, the sizable mediation effect by HDL particle size presents a potential plausible mechanism to evaluate in future studies.

This study has a number of limitations. In order to reduce confounding in our limited sample, our cohort was quite homogenous. Thus, it is not known if our findings can be extrapolated to men, older individuals, other ethnicities, or how common medications may influence GlycA in obesity. Further, findings from our 12 month time point may not reflect changes that occur with additional weight loss or alternative weight loss techniques.

Nonetheless, our study is the first to demonstrate the ability of bariatric surgery to reduce inflammation as indicated by elevated GlycA. Our data also suggest that GlycA may be an attractive inflammatory marker to discriminate CVD risk in metabolically-healthy obesity. Additional studies are needed to further evaluate mechanisms underlying GlycA reduction with weight loss in obesity and if reduction of GlycA in this patient population correlates with clinically relevant endpoints.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Rocha VZ, Libby P. Obesity, inflammation, and atherosclerosis. *Nat Rev Cardiol.* 2009;6:399–409. [PubMed: 19399028]
2. Ritchie SC, Wurtz P, Nath AP, et al. The biomarker GlycA is associated with chronic inflammation and predicts long-term risk of severe infection. *Cell Syst.* 2015;1:293–301. [PubMed: 27136058]
3. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation.* 2003;107:499–511. [PubMed: 12551878]
4. Blaha MJ, Rivera JJ, Budoff MJ, et al. Association between obesity, high-sensitivity C-reactive protein 2 mg/L, and subclinical atherosclerosis: implications of JUPITER from the Multi-Ethnic Study of Atherosclerosis. *Arterioscler Thromb Vasc Biol.* 2011;31:1430–1438. [PubMed: 21474823]
5. McGarrah RW, Kelly JP, Craig DM, Haynes C, Jessee RC, Huffman KM, Kraus WE, Shah SH. A novel protein glycan-derived inflammation biomarker independently predicts cardiovascular disease

and modifies the association of HDL subclasses with mortality. *Clin Chem*. 2017;63:288–296. [PubMed: 27811210]

6. Joshi AA, Lerman JB, Aberra TM, et al. GlycA is a novel biomarker of inflammation and subclinical cardiovascular disease in psoriasis. *Circ Res*. 2016;119:1242–1253. [PubMed: 27654120]
7. Ormseth MJ, Chung CP, Oeser AM, Connelly MA, Sokka T, Raggi P, Solus JF, Otvos JD, Stein CM. Utility of a novel inflammatory marker, GlycA, for assessment of rheumatoid arthritis disease activity and coronary atherosclerosis. *Arthritis Res Ther*. 2015;17:117. [PubMed: 25956924]
8. Akinkuolie AO, Buring JE, Ridker PM, Mora S. A novel protein glycan biomarker and future cardiovascular disease events. *J Am Heart Assoc*. 2014;3:e001221. [PubMed: 25249300]
9. Kontush A HDL particle number and size as predictors of cardiovascular disease. *Front Pharmacol*. 2015;6:218. [PubMed: 26500551]
10. Osto E, Doytcheva P, Corteville C, et al. Rapid and body weight-independent improvement of endothelial and high-density lipoprotein function after Roux-en-Y gastric bypass: role of glucagon-like peptide-1. *Circulation*. 2015;131:871–81.10. [PubMed: 25673670]
11. Yu Y, Sheth N, Krishnamoorthy P, et al. Aortic vascular inflammation in psoriasis is associated with HDL particle size and concentration: a pilot study. *Am J Cardiovasc Dis*. 2012;2:285–292. [PubMed: 23173102]
12. Sjostrom L, Peltonen M, Jacobson P, et al. Bariatric surgery and long-term cardiovascular events. *JAMA*. 2012;307:56–65. [PubMed: 22215166]
13. Otvos JD, Guyton JR, Connelly MA, Akapame S, Bittner V, Kopecky SL, Lacy M, Marcovina SM, Muhlestein JB, Boden WE. Relations of GlycA and lipoprotein particle subspecies with cardiovascular events and mortality: A post hoc analysis of the AIM-HIGH trial. *J Clin Lipidol*. 2018;12:348–355. [PubMed: 29409728]
14. Jago R, Drews KL, Otvos JD, Willi SM, Buse JB. Novel measures of inflammation and insulin resistance are related to obesity and fitness in a diverse sample of 11–14 year olds: The HEALTHY Study. *Int J Obes*. 2016;40:1157–63
15. Jin R, Otvos J, Le NA, Vos M. Evaluation of novel inflammation biomarkers GlycA and GlycB in overweight and obese adolescents with NAFLD. *FASEB J*. 2014;28:11169.
16. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome--a new worldwide definition. *Lancet*. 2005;366:1059–62. [PubMed: 16182882]
17. Akinkuolie AO, Pradhan AD, Buring JE, Ridker PM, Mora S. Novel protein glycan side-chain biomarker and risk of incident type 2 diabetes mellitus. *Arterioscler Thromb Vasc Biol*. 2015;35:1544–155. [PubMed: 25908766]
18. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *New Engl J Med*. 2017;377:1119–1131. [PubMed: 28845751]
19. Muhlestein JB, May HT, Galenko O, Knowlton K, Otvos JD, Connelly MA, Lappe DL, Anderson JL. GlycA and hsCRP are independent and additive predictors of future cardiovascular events among patients undergoing angiography: The intermountain heart collaborative study. *Am Heart J*. 2018;202:27–32. [PubMed: 29803983]
20. Kelesidis T, Tran TT, Stein JH, Brown TT, Moser C, Ribaldo HJ, Dube MP, Murphy R, Yang OO, Currier JS, McComsey GA. Changes in inflammation and immune activation with atazanavir-, raltegravir-, darunavir-based initial antiviral therapy: ACTG 5260s. *Clin Infect Dis*. 2015;61:651–660. [PubMed: 25904376]

Figure.

A) GlycA (mean $\pm$ standard deviation) and **B)** hsCRP (median $\pm$ interquartile range) in normal-BMI women and obese women before and at 6 and 12 months following bariatric surgery. Comparisons with baseline inflammatory marker values were performed using RMANOVA and post-hoc paired sample t-tests (GlycA) or the Friedman test and post-hoc Wilcoxon signed rank tests (hsCRP). Comparisons of obese subjects with normal-BMI control subjects were performed using independent two-sample t-tests (GlycA) or Mann-Whitney U tests (hsCRP).

* indicates $p < 0.001$ vs baseline

Pairwise Pearson correlations between changes in GlycA from before to 12 months following bariatric surgery with **C)** body weight, **D)** HbA1c and **E)** HDL size.

Baseline characteristics of obese and normal-BMI control subjects [Mean $\pm$ standard deviation or Median (interquartile range)]

Table.

	Obese subjects (n = 54)	Normal-BMI subjects (n = 14)	P-value
Age (years)	33.7 $\pm$ 8.2	31.7 $\pm$ 3.3	0.38
BMI (kg/m ²)	44.6 $\pm$ 6.6	23.3 $\pm$ 2.1	<0.0001
Weight (kg)	113.1 $\pm$ 17.1	58.0 $\pm$ 3.4	<0.0001
Waist circumference (cm)	117 $\pm$ 12	80 $\pm$ 5	<0.0001
Blood pressure (mm Hg)	122 $\pm$ 9/74 $\pm$ 8	101 $\pm$ 6/60 $\pm$ 6	<0.0001
Total Cholesterol (mg/dL)	174 $\pm$ 34	174 $\pm$ 32	0.99
Triglycerides (mg/dL)	102 (77, 149)	77 $\pm$ 28	<0.001
HDL-cholesterol (mg/dL)	46.4 $\pm$ 9.8	57.2 $\pm$ 10.4	<0.001
HDL particle size (nm)	9.16 $\pm$ 0.37	9.64 $\pm$ 0.46	<0.0001
Adiponectin (ug/mL)	11.6 (6.2, 16.0)	31.0 (12.8, 94.8)	<0.01
Glucose (mg/dL)	105 $\pm$ 17	82 $\pm$ 7	<0.001
HbA1c (%)	5.6 $\pm$ 0.6	4.8 $\pm$ 0.2	<0.001
Insulin (uIU/mL)	21.9 $\pm$ 10.5		
GlycA (umol/L)	451 $\pm$ 47	326 $\pm$ 36	<0.0001
hsCRP (mg/L)	8.9 (4.6, 14.3)	1.3 (0.7, 1.5)	<0.0001

P-values derived from comparisons using independent two-sample t-tests for normally distributed variables and Mann-Whitney U tests for hsCRP, triglycerides and adiponectin. Blood pressure is represented as systolic blood pressure/diastolic blood pressure.