Published in final edited form as:

J Clin Lipidol. 2019 ; 13(1): 186–193. doi:10.1016/j.jacl.2018.09.011.

Decreased GlycA Following Lifestyle Intervention Among Obese, Prediabetic Adolescent Latinos

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Abstract

Background: Obese youth with prediabetes are at increased risk for premature morbidity and mortality through multiple mechanisms, including increased systemic inflammation. GlycA is a novel measure of systemic inflammation that predicts type 2 diabetes, cardiovascular events, and all-cause mortality in adults.

Objective: The purpose of the current study is to examine changes in GlycA following lifestyle intervention among obese, prediabetic Latino youth.

Methods: Obese, prediabetic Latino youth (n=27; 15.5±1.1 years, 13 male/14 female) completed a 12week lifestyle intervention that included weekly nutrition education and three days/week of moderate to vigorous physical activity. Prediabetes was characterized by an expanded definition of impaired glucose tolerance, using 2-hour glucose ≥120 mg/dL after an oral glucose tolerance test. GlycA was assessed at baseline and 12 weeks using nuclear magnetic resonance spectroscopy.

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Author Contributions: All authors contributed to (1) the conception and design of the study, and analysis and interpretation of data, (2) drafting the article, (3) final approval of the version to be submitted.

Conflict of Interest: Margery Connelly is an employee of LabCorp. No other conflict of interests are declared by the authors.

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Results: Following the lifestyle intervention GlycA was significantly reduced (445.3 ± 51.3 $\mu\text{mol/L}$ to 419.0 ± 50.0 $\mu\text{mol/L}$, $p=0.01$) (mean $\pm$ SD). Additional improvements were observed in multiple cardiovascular risk factors, including body mass index (BMI) (34.8 ± 5.0 kg/m^2 to 34.0 ± 5.1 kg/m^2 , $p<0.001$), total cholesterol (154.1 ± 30.3 mg/dL to 143.3 ± 29.1 mg/dL , $p=0.003$), and 2-hour glucose (141.0 ± 13.2 mg/dL to 115.9 ± 31.4 mg/dL , $p<0.001$). Decreases in GlycA were associated with decreases in 2-hour glucose ($r=0.49$, $p=0.008$) and BMI ($r=0.41$, $p=0.03$).

Conclusion: These data are consistent with the hypothesis that lifestyle intervention might improve GlycA levels in obese, prediabetic adolescent Latinos, but randomized trial evidence is needed. Healthy lifestyle modifications among high-risk youth may decrease future risk of cardiometabolic disease through reducing systemic inflammation, in addition to improving traditional cardiovascular risk factors.

Keywords

Pediatric obesity; Inflammation; Latino; Type 2 diabetes; Cardiovascular disease; Impaired glucose tolerance

Introduction:

Obese children have an increased prevalence of traditional cardiovascular disease (CVD) risk factors, including dyslipidemia, hypertension, and insulin resistance.^{1,2} These findings hold true in Latino pediatric populations, where the prevalence of cardiometabolic risk factors increases with severity of obesity.³ Longitudinal studies reveal that the presence of obesity during childhood predicts a higher incidence of cardiovascular events and mortality during adulthood.⁴⁻⁶

In addition to the well-known adverse impact of obesity on traditional CVD risk factors, obesity is also associated with increased systemic inflammation.^{7,8} Adipose tissue is an active endocrine organ that secretes hormones and cytokines that contribute to insulin resistance, dyslipidemia, coagulation, and inflammation.⁹ Chronic low-grade inflammation and activation of the immune system are observed in obesity and may have a causal role in the development of both CVD and type 2 diabetes (T2D). Systemic inflammation is an independent risk factor for CVD and T2D, and markers of inflammation such as C-reactive protein (CRP) independently predict incident CVD¹⁰⁻¹³ and T2D.¹⁴⁻¹⁶ The atherosclerotic process is increasingly seen as not just involving atherogenic lipoproteins, but also requiring a proinflammatory response that includes both the innate and acquired immune systems.¹⁷

GlycA is a novel marker of systemic inflammation that is strongly associated with other markers of inflammation¹⁸ but exhibits less day-to-day variability and may be less likely confounded by obesity.^{18,19} GlycA is quantified by nuclear magnetic resonance (NMR) spectroscopy through a method that integrates both the protein levels and glycosylation states of the most abundant acute phase proteins in the circulation.¹⁸ Cross-sectional adult studies demonstrate higher GlycA among those with metabolic syndrome and T2D.²⁰ GlycA is predictive of incident CVD events²¹⁻²³ and T2D,²⁴⁻²⁶ independent of traditional risk factors, in longitudinal adult cohorts. A pediatric cross-sectional study reported that higher body mass index (BMI) and lower fitness level were associated with higher GlycA.²⁷

Lifestyle interventions reduce markers of inflammation in obese adults^{28–30} and children.^{31,32} While it has been shown that exercise is able to reduce GlycA in an adult population,³³ it is not known whether lifestyle interventions are effective in reducing GlycA levels in a pediatric population. The purpose of this study is to examine changes in GlycA following lifestyle intervention among obese, prediabetic Latino youth.

Methods:

Participants

Participants were selected for the following inclusion criteria, Latino ancestry by self-report; age 14–16 years old at time of enrollment; obesity defined as BMI percentile ≥95th percentile for age and sex or BMI ≥30 kg/m²; and an expanded definition of impaired glucose tolerance (IGT). For the purpose of the current report, IGT was defined using 2-hour glucose ≥120 and <200 mg/dL after an oral glucose tolerance test. This expanded definition was based on literature demonstrating that among obese adolescents, subjects with a 2-hour glucose level of 120–139 mg/dL had measures of insulin sensitivity and pancreatic β -cell function that closely approximated those with traditional IGT (i.e. 2-hour glucose ≥140 and <200 mg/dL).³⁴

The participant data and samples included in this report represent a subset analysis derived from a larger community-based diabetes prevention study of obese Latino youth conducted in a large urban metropolitan center in the Southwestern United States. The parent study was a randomized, controlled trial designed to test the effects of a culturally-grounded lifestyle intervention on T2D risk factors among 160 obese Latino youth. Participants in the parent study who met the American Diabetes Association criteria for prediabetes were automatically assigned to the intervention group as this population can rapidly decompensate and develop T2D in a short timeframe. Given that the parent study followed children for 12-months, it was deemed inappropriate from a medical and ethical perspective to randomize participants with prediabetes to the control arm of the parent study. Therefore, the current report represents a single-group, longitudinal cohort sub-study of youth from the larger parent trial.

Details of the parent study³⁵ along with the effects of the intervention on the primary outcomes of insulin sensitivity and quality of life have been reported elsewhere.³⁶ The 12-week lifestyle intervention included weekly nutrition and health classes delivered by promotores (bilingual, bicultural health educators) along with three days / week of moderate to vigorous physical activity. All intervention sessions were delivered at a local YMCA and a parent or guardian was required to attend the nutrition and health classes with their participating child. The classes discussed obesity-related health risks, healthy eating (focusing on portion control, reducing added sugar and saturated fat intake, and unhealthy snacking), family roles and responsibilities, physical activity and inactivity, and emotional well-being. In addition to these topics, behavior modification strategies of goal setting and self-monitoring were leveraged to support health behavior changes. The physical activity sessions were delivered by YMCA fitness instructors to groups of 8–10 youth and included three days per week of structured and unstructured exercise for 60 minutes. Structured components included aerobic activities (e.g. running, spinning), anaerobic activities (e.g. athletic drills), and resistance exercises. Unstructured components included team sports and

games that promoted social support and bonding among youth. Physical activity sessions were designed to elicit an average heart rate 150 beats per minute for the majority of the session. The study protocol and all study-related documents were approved and monitored by the Institutional Review Board at Arizona State University. Written parental consent and child assent were obtained by study staff prior to any data collection procedures.

Data Collection

Height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively, and were used to calculate BMI and BMI percentile. Waist circumference at the umbilicus was measured to the nearest 0.1 cm. Body fat percentage was determined using bioelectrical impedance analysis (TBF-300A, Tanita Corp of America, Arlington Heights, Illinois). This measure partitions the body into two compartments (fat mass and fat-free mass) and provides estimates of total fat mass, percent fat, and fat-free mass.

Fasting serum insulin, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglyceride were collected and low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald calculation. Glucose tolerance (fasting and 2-hour glucose) was assessed via a 75 gram, 2-hour oral glucose tolerance test. Insulin resistance was calculated by the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) using the formula: $\text{HOMA-IR} = [(\text{fasting insulin in } \mu\text{U/ml}) \times (\text{fasting glucose in mg/dl})] / 405$. Lipoprotein particle profiles and GlycA were measured in fasting samples by NMR spectroscopy with the LipoProfile-3 algorithm at LabCorp, Inc. (formerly LipoScience; Morrisville, NC, USA) according to previously described procedures.^{18,37,38}

Statistical Analysis

Descriptive statistics, including means, standard deviations, and percentages were calculated at baseline. Pearson correlation and partial correlation (adjusting for BMI) coefficients were used to evaluate baseline associations between GlycA and anthropometric measures, fasting and two-hour glucose, HOMA-IR, standard lipid profile and lipoprotein particles. Baseline to post-intervention changes were tested using a paired-samples t-test. Within-subjects correlation coefficient with repeated measures³⁹ was used to measure how changes in GlycA correlated with changes in BMI, triglyceride, 2-hour glucose, HOMA-IR, and LDL particle size. Independent sample t-tests were used to compare changes in BMI, HOMA-IR, and 2-hour glucose between those who did and did not reduce GlycA after the intervention and Cohen's d effect sizes were calculated. Statistical analyses were performed using SPSS version 23 (IBM Corp., Armonk, NY) and SAS 9.4 (SAS Institute Inc., Cary, NC). Significance was set at $P = 0.05$.

Results:

Twenty seven obese, prediabetic Latino youth (average age 15.5 ± 1.1 years, 13 male/14 female) participated in the 12-week lifestyle intervention. At baseline, 52% (14/27) met the ADA definition of IGT (13/27), while the other 48% (13/27) met the expanded definition of IGT. GlycA at baseline was not associated with any anthropometric or biochemical variables (Table 1).

Over the 12-week intervention program, participants attended 88.1% of all nutrition and physical activity sessions. Changes in anthropometric and cardiometabolic risk factors following the intervention are presented in Table 2 and show significant reductions in BMI (2.3%), body fat percentage (7.5%), and waist circumference (1.7%) as well as several biochemical markers including total cholesterol (7.0%), non-HDL-C (7.5%), HOMA-IR (23.9%) and 2-hour glucose (17.8%). Changes in lipoprotein particle parameters including total and small LDL particle numbers were not significant. In addition to these changes, GlycA levels decreased by 6% after the intervention (Figure 1), and this change remained significant after controlling for changes in BMI ($p=0.012$).

Changes in GlycA in relation to changes in select cardiometabolic risk factors (within-subjects repeated measures correlation) are presented in Figure 2a-c. Following the intervention, changes in GlycA were significantly associated with changes in BMI and 2-hour glucose but not correlated with changes in HOMA-IR. An additional observation from the within-subjects analysis is a fair degree of heterogeneity in change in GlycA following the intervention. To follow-up on this observation, we divided participants into those who exhibited a decrease in GlycA concentrations post intervention (responders $n=19$) and those who exhibited an increase in GlycA concentrations (non-responders $n=9$). Although not statistically significant, GlycA responders exhibited larger reductions in BMI, 2-hour glucose, and HOMAIR compared to non-responders (Table 4) with Cohen's d indicating small to medium effect sizes.

Discussion:

With the epidemics of obesity and T2D among youth, understanding the mechanisms by which adiposity contributes to future CVD, and how best to reduce CVD risk among obese youth, remains an important topic. Systemic inflammation is hypothesized as a central mechanism linking obesity to both CVD and T2D and our data demonstrate that a 12-week lifestyle intervention can reduce systemic inflammation, as measured by GlycA level, among a very high risk pediatric population. Participants also experienced improvements in several traditional risk factors for CVD and T2D that were significantly associated with reductions in GlycA.

Our data demonstrate a high degree of inflammation present at baseline in our cohort compared to other pediatric and adult studies. The mean pre-intervention GlycA in our cohort was 445.3 ± 51.3 $\mu\text{mol/L}$. In the Multi-Ethnic Study of Atherosclerosis, a large longitudinal study of generally healthy adults, the mean baseline GlycA was 381 $\mu\text{mol/L}$.⁴⁰ To our knowledge, GlycA has only been reported in one other pediatric study of healthy 8th grade children where median GlycA levels were 397 $\mu\text{mol/L}$ and 365 $\mu\text{mol/L}$, among females and males, respectively.²⁷ The high baseline GlycA noted in our cohort is consistent with previous studies demonstrating increased systemic inflammation in obese populations,^{7,8} and demonstrates that increased inflammation associated with obesity is present in the pediatric age group and may be exacerbated by insulin resistance and hyperglycemia.

While it is typically thought that excessive weight gain causes inflammation, there is evidence that a bidirectional relationship may be present. In a longitudinal study of Brazilian

children, those with highest baseline CRP levels experienced the highest degree of BMI percentile increase over a 5-year period.⁴¹ Furthermore, a longitudinal study of Spanish adults revealed that participants with the highest inflammatory diets at baseline experienced higher average yearly weight gain than those with less inflammatory diets. Participants who were normal-weight at baseline but consumed a proinflammatory diet experienced a significantly greater relative risk (RR=1.32, p=0.004) for developing overweight or obesity over an 8 year follow-up period.⁴²

These findings raise important questions regarding the causal mechanisms underlying pediatric obesity, insulin resistance, and inflammation, as well as the pathogenesis of T2D and CVD. While our study revealed that obese, prediabetic, Latino youth have a high degree of inflammation relative to published population averages, our study design does not allow us to identify the degree to which obesity is driving inflammation, or vice-versa. An additional factor to consider in our study population is the presence of prediabetes. Baseline GlycA levels predict incident type 2 diabetes in adults,^{14–16} and while the presence of prediabetes at baseline is likely an additional factor explaining the high degree of inflammation seen in our cohort, it remains an open question of whether our cohort's increased inflammation was a causal factor in the development of their prediabetes, or whether the presence of prediabetes exacerbated their inflammation.

The within-subjects correlation coefficients with repeated measures analysis (Figure 2) may provide some insight in the relationship between inflammation and markers of cardiometabolic disease. Changes in GlycA following the 12-week intervention were associated with changes in BMI and 2-hour glucose. This is an intriguing relationship that raises the possibility that targeting decreases in systemic inflammation in youth may help reduce the risk of developing obesity and T2D. Behavioral changes that were targeted in the intervention included reductions in dietary consumption of sugar and saturated fat, increases in fiber through whole grains, and increases in fruits and vegetables. Of these dietary factors, higher consumption of whole grains,^{43–46} and fruit and vegetables,^{47–50} and lower consumption of sugar,^{51–53} have been associated with reductions in inflammatory markers. In addition to diet, youth engaged in 3 days per week of moderate to vigorous exercise. Several studies support the notion that exercise training can reduce the chronic inflammation associated with obesity and insulin resistance in adults and children.^{54–56} Although the mechanisms are unclear, there is evidence that skeletal muscle contraction during exercise stimulates the production and release of anti-inflammatory myokines that in turn inhibit the production of pro-inflammatory cytokines.⁵⁷

An interesting post-hoc observation was the degree of heterogeneity of change in GlycA among participants following the intervention. We found that participants whose GlycA levels improved over the course of the intervention (GlycA responders) exhibited larger reductions in BMI, 2-hour glucose, and insulin resistance compared to those whose GlycA levels did not improve (GlycA non-responders). Although the small sample size limits any ability to detect statistical significance, this observation raises the possibility that improvements in systemic inflammation are linked to improvements in other cardiometabolic risk factors following lifestyle intervention. Future studies that are sufficiently powered will be able to employ formal mediation analysis to better determine

whether changes in systemic inflammation are mechanistically tied to changes in cardiometabolic disease risk.

Strengths of our study include the focus on a high-risk population of obese Latino prediabetic adolescents, the evaluation of a robust lifestyle intervention, and the inclusion of GlycA as a novel marker of systemic inflammation. GlycA reference ranges in pediatric populations do not exist, and very little is known about GlycA status in pediatric populations at high risk for cardiometabolic disease. Furthermore, longitudinal GlycA data are limited in adult populations, nor are we aware of any longitudinal data in pediatric populations, and therefore these data make a unique contribution to the field.

Despite these strengths, the lack of a control group in order to compare the change in GlycA level and other CVD markers without intervention is a limitation. Without a control group, it is impossible to determine whether the observed changes were due to the actual intervention, the specific behavioral targets of the intervention (i.e. changes in nutrition or exercise patterns), or simply participating in a group intervention in a community setting. Therefore, the changes in GlycA should be taken in the context of hypothesis generation rather than definitively the result of the intervention. The absence of a control group, combined with the study's small sample size, limit the generalizability of our findings. Unfortunately, GlycA levels were not obtained in participants who did not have prediabetes at baseline, thus baseline comparison cannot be made between those with normal glucose tolerance and those with prediabetes. In addition, other markers of systemic inflammation were not available in our study cohort, thus no comparison between GlycA and other common markers of inflammation can be made. While GlycA levels correlate well with other commonly used markers of systemic inflammation, including interleukin-6, fibrinogen, and CRP, the glycans on these proteins contribute minimally to the GlycA NMR signal.¹⁸ Longitudinal adult cohorts demonstrate that baseline GlycA is associated with incident CVD events, after adjustment for traditional risk factors, and these associations are only slightly attenuated by CRP, suggesting that GlycA measures CVD risk independently of CRP.^{21–23} Lastly, body composition data derived from bioelectrical impedance are known to fluctuate with hydration status, which was not controlled for in the study. As such, the reliability of these data should be interpreted with caution.

Conclusion

Intensive lifestyle intervention in obese, prediabetic Latino youth was associated temporally with improvements in CVD risk factors, including systemic inflammation as measured by GlycA. Changes in GlycA were associated with changes in BMI and 2-hour glucose. Further studies, including randomized controlled trials, are needed to identify causal mechanisms regarding the interplay between obesity, inflammation, and the development of T2D and CVD among high-risk pediatric populations.

Acknowledgments

Funding: This research was funded by the National Institutes of Health/National Institute on Minority Health and Health Disparities (P20MD002316; U54MD002316). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIMHD or the NIH. Drs. Olson, Soltero, and Shaibi were

also supported by a grant from the National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Disease (R01 DK10757901).

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Highlights

- Systemic inflammation predicts incident cardiovascular disease and type 2 diabetes
- We evaluated effects of a 12-week lifestyle program among obese Latino adolescents
- GlycA levels fell by 6% following lifestyle intervention over 12 weeks
- Improvements in GlycA were associated with improvements in diabetes risk factors

Figure 1. Mean ($\pm$ standard deviation) GlycA concentrations before (Pre) and after (Post) a 12-week lifestyle intervention among 27 obese Latino adolescents with prediabetes.

Figure 2.

Within participant repeated measures correlation between changes in GlycA and BMI (A), 2-hour glucose (B), and HOMA-IR (C) following a 12-week intervention. Each participant is represented by two dots of the same color that correspond pre and post values for GlycA and the respective cardiometabolic risk factor. Each line represents the repeated measures correlation fit for each participant across the two time points. BMI, Body Mass Index; HOMA-IR.

Table 1.

Relationship between Baseline GlycA and CVD Risk Factors by Pearson Correlation

	Unadjusted Pearson Correlation (r)	P-Value	Pearson Partial Correlation ^b (r)	P-Value
BMI	0.29	0.14	-	-
Body Fat	0.30	0.12	0.14	0.50
Waist circumference	0.31	0.11	0.16	0.5
Total cholesterol	-0.08	0.69	-0.08	0.72
Triglyceride	0.02	0.92	0.25	0.23
HDL cholesterol	-0.20	0.30	-0.13	0.54
LDL cholesterol	-0.19	0.35	-0.21	0.32
Non-HDL cholesterol	-0.03	0.90	-0.05	0.83
Fasting glucose	0.01	0.98	-0.06	0.77
Two-hour glucose	-0.08	0.67	-0.10	0.65
HOMA-IR	0.30	0.14	0.20	0.35
Total LDL Particles	0.03	0.87	-0.05	0.81
Small LDL Particles	0.33	0.10	0.27	0.20
LDL Size	-0.28	0.15	-0.23	0.25

N=27 for all variables except HOMA-IR (N=25)

^b Pearson partial correlation adjusted for BMI.

Table 2.**CVD Risk Factors Pre and Post Lifestyle Intervention**

	Pre	Post	Change	P-Value
BMI (kg/m ²)	34.8 ± 5.0	34.0 ± 5.1	-0.8 ± 1.0	< 0.001
Body Fat (%)	45.5 ± 7.3	42.1 ± 6.6	-3.4 ± 5.1	0.002
Waist circumference (cm)	109.6 ± 10.4	107.7 ± 11.8	-1.9 ± 4.7	0.046
Total cholesterol (mg/dL)	154.1 ± 30.3	143.3 ± 29.1	-10.7 ± 16.7	0.003
Triglyceride (mg/dL)	151.0 ± 73.0	131.0 ± 70.3	-20.0 ± 58.1	0.01
HDL-C (mg/dL)	38.7 ± 8.0	36.6 ± 6.9	-2.0 ± 3.9	0.01
Non-HDL-C (mg/dL)	115.4 ± 30.2	106.7 ± 27.5	-8.7 ± 16.2	0.01
LDL-C (mg/dL)	85.2 ± 24.4	80.4 ± 21.8	-4.7 ± 11.5	0.04
Fasting Glucose (mg/dL)	85.3 ± 7.7	84.0 ± 6.8	-1.3 ± 6.4	0.30
2-hour Glucose (mg/dL)	141.0 ± 13.2	115.9 ± 31.4	-25.0 ± 30.3	< 0.001
HOMA-IR	6.9 ± 3.6	5.4 ± 2.9	-1.6 ± 2.7	0.008
Total LDL Particles (nmol/L)	1007.7 ± 253.8	952.9 ± 219.4	-54.8 ± 163.4	0.09
Small LDL Particles (nmol/L)	689.2 ± 255.3	637.4 ± 181.2	-51.9 ± 172.8	0.13
LDL Size (nmol)	20.2 ± 0.4	20.3 ± 0.5	0.1 ± 0.4	0.37
GlycA (μmol/L)	445.3 ± 51.3	419.0 ± 50.0	-26.4 ± 50.2	0.01

^aN=27 for all variables except HOMA-IR. N=25 for HOMA-IR.

Data are means ± standard deviation

Table 3.

Percent Change Cardiometabolic Risk Factors between GlycA Responders vs. Non-responders

Variable	Responders (n=19)	Non-Responders (N=8)	P-value	Effect Size (Cohen's d)
BMI	-2.9 ± 2.4%	-1.0 ± 3.2%	0.11	0.67
HOMA-IR	-19.5 ± 38.9%	-10.1 ± 30.2%	0.57	0.27
2-Hr Glucose	-19.6 ± 20.6%	-12.9 ± 25.3%	0.47	0.29

Data are means ± standard deviation