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GlycA is a Novel Marker of Inflammation among Non-Critically Ill Hospitalized Patients with Type 2 Diabetes

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Abstract

Background—GlycA is a nuclear magnetic resonance derived signal that originates from oligosaccharide chains of acute phase proteins. The object of this study is to characterize GlycA levels in hospitalized non-critically ill patients with type 2 diabetes.

Methods—This study evaluated traditional and novel (GlycA) inflammatory markers among 121 patients who were stratified by admission diagnoses: congestive heart failure (CHF), cardiac non-CHF (CARD), infection (INF), and other (OTH).

Results—HbA1c was similar across groups (8.0-9.2%, $p=0.20$). Inflammatory markers were elevated but varied significantly across disease categories, with the highest values of interleukin-6 (IL-6), c-reactive protein (CRP), and GlycA in the INF group and the highest tumor necrosis factor- α and intracellular adhesion molecule-1 levels in CHF group. GlycA was associated with higher IL-6 and CRP, lower hemoglobin and lower glomerular filtration rate. GlycA and other inflammatory markers were not significantly associated with admission glucose or HbA1c.

Conclusions—Among hospitalized non-critically ill patients with type 2 diabetes, GlycA was highest in INF patients and was associated with IL-6 and CRP. None of the markers were significant predictors of glucose control.

Keywords

GlycA; glycoprotein; acute phase response; type 2 diabetes; cytokine

Introduction

Hospital hyperglycemia is common,[1] and is associated with a myriad of poor outcomes, even outside of critical care units,[2,3] and high costs [4]. Diabetes may be a more important predictor of outcomes when combined with some admission diagnoses, such as cardiovascular disease, than others, but the mechanisms are unknown.[5] It is likely that

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patterns of stress responses to illness may differ among admission diagnoses. Type 2 diabetes is known to be a chronic inflammatory state, but the inflammatory milieu has not been well described during acute illness outside of the intensive care unit.[6,7]

The acute phase response to illness is characterized by an increase in hepatic and immune cell production of acute phase proteins, such as C-reactive protein (CRP), and a fall in other proteins such as albumin and transferrin.[8,9] This response is mediated by inflammatory cytokines, particularly interleukin-6 (IL-6). In addition to these changes, there are modifications in glycosylation patterns of circulating proteins which ultimately increase the complexity of their carbohydrate side chains and alter their function.[10,11] Most acute phase proteins are glycosylated and they comprise a large fraction of circulating glycoproteins.

Glyc A is a novel, recently validated assay that quantifies the nuclear magnetic resonance (NMR) signal from *N*-acetylglucosamine and *N*-acetylgalactosamine moieties of plasma glycoproteins.[12] In the Multi-Ethnic Study of Atherosclerosis, GlycA was associated with levels of inflammatory markers, including IL-6 and CRP, and was a predictor of incident cardiac events, diabetes, chronic kidney disease, all-cause mortality, and cancer over a 5.5 year follow-up period.[13] In the Women's Health Study, GlycA was associated with increasing risk of cardiovascular events and incident diabetes; associations were attenuated after adjusting for CRP, suggesting a role in subclinical inflammation leading to disease.[14,15] Other studies have identified associations between the GlycA NMR signal and cardiovascular disease, cancer, and inflammatory diseases.[16]

The objective of this study is to compare GlycA and other markers of inflammation among hospitalized non-critically ill patients with type 2 diabetes according to admission diagnosis groupings and identify relationships with glucose control.

Methods

Patients

Data were obtained from patients with available blood samples from two prospective studies of patients with type 2 diabetes admitted to a single large academic medical center.[19,20] Inclusion criteria for both studies included hospitalized adults with type 2 diabetes and either hyperglycemia or requiring at least 20 units of insulin/day in the 24 hours prior to enrollment. Hyperglycemia was defined as a blood glucose 8.3-22.2 mmol/l on at least 2 occasions separated at least 4 hours apart. Exclusion criteria for both studies included critical illness, major surgery, glucocorticoids, enteral or parenteral nutrition, pregnancy, current intravenous insulin, expected length of stay less than 48 hours, type 1 diabetes, end-stage renal or liver disease, major surgery, inability to give informed consent in English, and sensitive admissions (prisoners, suicidality). In study 1, prolonged *nil per os* status (over 24 hours) was an additional exclusion criterion.[17] Study 2 included only patients with congestive heart failure exacerbation and excluded myocardial infarction within the previous 3 months and isolated right heart failure.[18] This study was approved by the Ohio State University Institutional Review Board and all patients signed informed consent.

Laboratory Analyses

Admission serum glucose and HbA1c (HPLC method) were the primary measures of acute and chronic glycemic control respectively. Blood draws were performed at enrollment in both studies. Laboratory analyses were performed at the OSU Clinical Research Center using standard commercial kits. Interleukin-6 (IL-6, range 0.3-2500 pg/ml), and tumor necrosis factor- α (TNF- α range 0.3-2500 pg/mL) were performed using Meso Scale Discovery kits (Rockville, MD), and CRP (range 0-15 mg/L) was performed using Immulite 1000 assay (Siemens; Erlangen, Germany). The GlycA signal was obtained using nuclear magnetic resonance spectroscopy (Liposcience, Raleigh, NC). The GlycA signal was quantified using proprietary software developed by LipoScience, Inc. (Raleigh, NC). The GlycA assay has been validated, and showed intra-assay (within run) and inter-assay (within lab) coefficients of variation of 1.9% and 2.1%, respectively.[14] Glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease equation.[19]

Statistical Analysis

In order to facilitate analysis, patients in Study 1 were classified into one of four categories (CHF exacerbation, cardiac-non-CHF [including arrhythmia, myocardial infarction, unspecified chest pain], infection, or other) based upon the primary reason for admission. Continuous variables were reported as mean (standard deviation) for normal distributions or median (interquartile range) for non-normal distributions. Differences between groups were determined with analysis of variance (ANOVA) or Wilcoxon rank-sum as appropriate. Dichotomous variables were reported as number (percentage) and differences between groups were determined using Fisher's exact test was used. P-values less than 0.05 were considered statistically significant. Relationships were evaluated with simple linear regression with log transformation of variables failing to meet the normality assumption. Analyses were performed using JMP 9.0 software.

Results

A total of 121 patients had available data (71, 21, 18, and 11 in the CHF, cardiac-non-CHF, infection, and other categories respectively). Characteristics are shown in Table 1. Of the cardiac-non-CHF diagnoses, 8 were admitted with non-ST elevation myocardial infarction, 3 with unstable angina, 2 with arrhythmia, 5 with non-cardiac chest pain, and the remainder included presyncope, pericarditis, and hypertensive urgency. There were no patients with ST elevation myocardial infarction. The infection group consisted of 12 skin/soft tissue infections, 2 cases of urosepsis, 3 cases of osteomyelitis, and one patient with fever of unknown origin. Primary diagnoses in the "other" category included neurologic (N=3), gastrointestinal (N=3), renal/metabolic (N=3), pulmonary (N=2) or oncologic (N=1), conditions. Demographics were similar across disease categories. Patients with heart failure and infection had the longest duration of diabetes ($p<0.05$ across groups by ANOVA). HbA1c ranged from 8.0-9.2% across groups ($p=0.20$ by ANOVA), while 1,5-anhydroglucitol (1,5-AG), a short-term, inverse marker of glucose control, was highest among CHF patients (3.4-9.8 $\mu\text{g/ml}$, $p=0.002$ by ANOVA). Glucose levels were high at

admission and were highest in the cardiac-non-CHF and infection groups ($p=0.002$ across groups by ANOVA, Table 1).

GlycA varied significantly across diagnostic categories (Table 1, $p=0.006$, ANOVA) and values were highest in patients with infectious disease ($630 \pm 158 \mu\text{mol/L}$). IL-6 and CRP were also highest in patients with infectious disease (for IL-6, $p=0.049$ across groups by ANOVA; for CRP, $p=0.13$ by ANOVA, $p=0.04$ infection vs. CHF group). In contrast, TNF- α and intracellular adhesion molecule-1 (ICAM-1) were highest in the CHF group, ($p=0.003$, $p<0.001$ for differences across groups [ANOVA], respectively).

In pooled analyses, GlycA was associated with higher IL-6 ($\rho=0.27$, $p=0.04$) and CRP ($\rho=0.35$, $p=0.01$) and lower hemoglobin ($\rho=-0.27$, $p=0.02$) and estimated GFR ($\rho=-0.30$, $p=0.01$, Table 2). GlycA was not associated with hospital length of stay. By comparison, increasing IL-6 was associated with increasing hospital length of stay ($\rho=0.22$, $p=0.03$), TNF- α ($\rho=0.28$, $p=0.01$), ICAM-1 ($\rho=0.35$, $p=0.001$), and CRP ($\rho=0.56$, $p<0.0001$). Increasing CRP was associated with increasing IL-6 ($\rho=0.56$, $p<0.0001$) and TNF- α ($\rho=0.23$, $p=0.03$).

GlycA was not associated with HbA1c or 1,5-AG and was only weakly associated with admission glucose ($\rho=0.20$, $p=0.08$, Table 2,3). Other inflammatory markers were not associated with acute or chronic glucose control, except for IL-6, which was *inversely* associated with admission glucose ($\rho=-0.24$, $p=0.02$, Table 3).

In multi-variable analyses adjusting for race, CHF, ID, GFR, hemoglobin level, and admission glucose, only GFR and ID were significant predictors of GlycA (Table 4). After backwards linear regression, ID, GFR, and hemoglobin were significant predictors of GlycA in the final model (Table 4). The addition of IL-6 to the final model resulted in similar model performance (adjusted R^2 0.24 without IL-6 vs. 0.25 with IL-6, 0.23 with log-transformed IL-6), while the addition of CRP worsened model performance (adjusted R^2 0.20, and 0.21 without and with log transformation).

Discussion

In this study, there were differences in inflammatory markers across disease states among hospitalized non-critically ill patients with type 2 diabetes. Patients with infectious disease had the highest GlycA, IL-6, and CRP levels. In contrast, CHF patients had the highest TNF- α and ICAM-1 levels.

GlycA was associated positively with IL-6 and CRP and negatively with hemoglobin and GFR, which is consistent with the acute phase response. GlycA is a particularly attractive marker of the acute phase response in that it captures plasma levels of multiple acute phase proteins, and thus may provide a more complete or complementary picture than other markers.[13-15] GlycA measures glycan content, not protein levels, and since NMR signals are concentration dependent, likely components include glycoproteins that circulate at 20-50 μM , such as α -1 acid glycoprotein, α -1 antitrypsin, and haptoglobin.[14] Other glycoproteins that circulate at low concentrations (such as cytokines) or proteins that have low or no carbohydrate content (such as CRP) are unlikely to be represented. GlycA was a

significant predictor of mortality in large prospective longitudinal studies.[14,16] Therefore, it may have prognostic value in addition to diagnostic uses.

The etiology of differences in inflammatory markers among various disease categories is related to known pathophysiologic mechanisms, though these are probably multi-factorial in an acutely ill population with diabetes. Chronic abnormalities in inflammation (including the traditional markers presented here) are have been characterized in various disease states. In patients with CHF, inflammation and neuroendocrine dysfunction are well characterized, [20,21] and may be more pronounced in patients with comorbid diabetes.[24] Such alterations have prognostic value and are reported to be interrelated.[25] Following myocardial infarction, IL-6 and CRP are higher among patients with diabetes compared to those without, and the response is more pronounced with ST elevation compared to less severe presentations.[24,25] Like CHF, chronic kidney disease may be associated with important aberrations in metabolism and increased inflammation (including increased levels of circulating CRP, TNF- α , and IL-6.[26] While patients with advanced renal failure were excluded from this analysis; less advanced kidney disease is still represented. Finally, while excluded from this study, diabetic ketoacidosis is associated with marked elevations in inflammatory cytokines, including IL-6 and CRP, which are dependent on the severity of presentation.[27]

Despite the acute illness, inflammatory markers were not significantly associated with acute or chronic glucose control or other measures of diabetes burden. The data suggest that the patterns of inflammatory markers reflect the underlying acute illness rather than diabetes or hyperglycemia per se. This is in contrast to other studies, mainly but not exclusively from acutely ill patients. [28, 29] One potential explanation for this may be that the stress hyperglycemic response is negligible in non-critically ill patients. Alternatively, stress hyperglycemia may depend upon patient characteristics. In particular, it would be of interest to know if associations are more apparent among patients who are not insulin-requiring at admission. In addition, while important differences in GlycA and other inflammatory markers are evident in ambulatory patients with or without diabetes, it would be important to determine if such differences persist in hospitalized patient populations. Finally, inflammatory markers were typically drawn on the day after admission, potentially missing an important window of peak stress. While clearance of GlycA has not been well described, it would be expected to reflect that of the major protein glycans that are most likely to contribute to the NMR signal, such as α -1 acid glycoprotein (2-3 days) [29], α -1 antitrypsin (4-5 days) [30], and haptoglobin (5 days) [31]. Therefore, the GlycA signal at the time of the blood draw should reflect the time of admission, since patients were generally enrolled within one day of admission. In contrast, the half-life for CRP and serum cytokines is notably shorter and would be more likely to exhibit dynamic changes within this timeframe. [32-34] Nevertheless, cytokines were still markedly elevated overall.[14]

The study is novel in that it is the first to compare inflammatory markers among common admission diagnoses in hospitalized noncritically ill patients with type 2 diabetes. Furthermore, the study adds to the literature describing the novel inflammatory marker GlycA. It should be noted that this was a post-hoc analysis, and while data were collected prospectively, it is difficult to assess causality to remove residual confounding. In particular,

there was a small, heterogeneous population of patients with infections. While differences between groups were highly statistically significant, the findings will necessitate larger prospective studies to evaluate further.

In conclusion, the recently described protein glycan GlycA, differed across comorbidities of hospitalized non-critically ill patients with type 2 diabetes, consistent with patterns for CRP and IL-6. However, inflammatory markers were not associated with acute or chronic glucose control.

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Abbreviations

CRP	C-reactive protein
IL-6	interleukin-6
NMR	nuclear magnetic resonance
TNF-α	tumor necrosis factor- α
GFR	Glomerular filtration rate
ANOVA	analysis of variance
CHF	congestive heart failure

Table 1

Baseline and Study Characteristics by Diagnostic Category

	CHF (N=71)	Other Cardiac (N=21)	Infection (N=18)	Other (N=11)	P-value
Age (years)	62 (11)	55 (11)	57 (9.2)	58 (14)	0.13
Female	25 (37)	11 (55)	9 (50)	5 (45)	0.44
Caucasian	48 (71)	17 (85)	13 (72)	8 (73)	0.66
Diabetes duration (years)	13 (10-20)	10 (6.3-11.5)	14.5 (9.25-16.5)	5 (2.5-16)	0.0496
BMI (kg/m ²)	39 (9.7)	38 (11)	31 (7.4)	40 (15)	0.04
Admit Insulin	63 (89)	13 (62)	17 (94)	11 (100)	0.008
Hemoglobin g/dl	11.3 (1.90)	11.7 (2.11)	10.8 (1.26)	9.8 (1.24)	0.07
Estimated GFR (MDRD)	53 (36-73)	82 (64-130)	62 (48-116)	51 (36-100)	0.02
HbA1c					
%	8.0 (1.7)	9.2 (2.0)	8.5 (1.9)	8.7 (2.8)	
mmol/mol	64 (18.6)	77 (21.9)	69 (20.8)	72 (30.6)	0.20
1,5-AG (µg/ml)	9.8 (4.8-16)	3.4 (2.3-8.6)	6.1 (2.9-13)	4.3 (2.7-12)	0.002
Admission glucose (mmol/l)	9.83 (3.44)	12.8 (5.61)	11.4 (5.72)	15.0 (6.56)	0.002
Enrollment Glucose	8.56 (3.63)	6.61 (2.10)	7.16 (2.83)	8.66 (3.12)	0.16
IL-6 (pg/ml)	8.5 (5.3-13.2)	6.6 (2.1-33.4)	21.4 (8.1-50.7)	4.4 (2.7-13.3)	0.049
TNF-α (pg/ml)	13 (10-17)	7.25 (5.5-15)	9.1 (7.9-21.9)	8.9 (7.4-10.9)	0.003
ICAM-1	384 (304-494)	247 (181-339)	272 (226-344)	251 (205-294)	<0.0001
CRP (mg/L)	19 (7.0-38)	15 (4.4-64)	52 (16-144)	9.8 (5.4-37)	0.13
GlycA A (µmol/L)	514 (93)	492 (147)	630 (158)	530 (80)	0.008
Hospital length of stay (days)	8.5 (5-12)	6 (4-8.5)	7.5 (5-9.5)	6 (5-9)	0.07

Data are reported as mean (SD) or median (interquartile range: 27%-75%). BMI=body mass index, GFR= glomerular filtration rate, MDRD=Modification of Diet in Renal Disease method, 1,5-AG=1,5-anhydroglucitol, IL-6=interleukin-6, TNF-α=tumor necrosis factor-α, ICAM-1=intracellular adhesion molecule-1, CRP=high sensitivity c-reactive protein, GlycA = NMR signal arising from glycosylated acute phase proteins.

Table 2

Correlations with GlycA, IL-6, and CRP

	Glyc A		IL-6		CRP	
	Spearman ρ	P-value	Spearman ρ	P-value	Spearman ρ	P-value
Age	0.03	0.83	0.01	0.90	0.07	0.52
Caucasian	-0.16	0.17	-0.11	0.29	-0.02	0.85
Female	0.04	0.71	0.09	0.37	0.03	0.81
Diabetes Duration	0.04	0.73	0.09	0.44	0.03	0.80
Insulin Admit	0.08	0.46	0.04	0.68	0.10	0.33
Hemoglobin	-0.27	0.02	-0.05	0.66	-0.07	0.51
GFR (MDRD)	-0.30	0.01	-0.11	0.31	-0.08	0.44
BMI	0.04	0.75	0.12	0.26	0.03	0.75
1,5-AG	-0.10	0.43	0.08	0.44	0.00	0.99
Hospital length of stay	0.13	0.27	0.22	0.03	0.13	0.20
IL-6	0.27	0.04	*	*	0.56	<0.0001
TNF- α	0.18	0.18	0.28	0.01	0.23	0.03
ICAM-1	-0.09	0.50	0.35	0.001	0.20	0.06
CRP	0.35	0.01	0.56	<0.0001	*	*

BMI=body mass index, GFR= glomerular filtration rate, MDRD=Modification of Diet in Renal Disease method, 1,5-AG=1,5-anhydroglucitol, IL-6=interleukin-6, TNF- α =tumor necrosis factor- α , ICAM-1=intracellular adhesion molecule-1, CRP=high sensitivity c-reactive protein.

Table 3
Correlations between Inflammatory Markers and Glucose Control

	HbA1c		Admission Glucose		Enrollment Glucose	
	Spearman ρ	P-value	Spearman ρ	P-value	Spearman ρ	P-value
GlycA	-0.07	0.59	0.20	0.08	-0.06	0.59
IL-6	-0.16	0.21	-0.24	0.02	-0.06	0.58
TNF-α	-0.22	0.08	-0.14	0.17	-0.04	0.73
ICAM-1	0.06	0.65	-0.16	0.13	-0.06	0.57
CRP	0.09	0.50	-0.06	0.56	-0.10	0.37

IL-6=interleukin-6, TNF-α=tumor necrosis factor-α, ICAM-1=intracellular adhesion molecule-1, CRP=high sensitivity c-reactive protein.

Table 4
Multivariable Analysis of GlycA

Initial Model			
Term	Estimate	SE	P-value
Intercept	780.7	96.3	<.0001
Admission for Infection	49.8	22.7	0.03
Admission for Heart Failure	-5.07	18.44	0.78
Hemoglobin	-14.6	7.6	0.06
Estimated GFR (MDRD)	-0.82	0.36	0.03
Caucasian	-9.75	15.81	0.54
Admission Glucose	0.06	0.16	0.72
Final Model			
Term	Estimate	SE	P-value
Intercept	809.9	81.9	<.0001
Admission for Infection	56.0	17.6	0.002
Hemoglobin	-16.2	7.1	0.027
Estimated GFR (MDRD)	-0.85	0.32	0.011

GFR= glomerular filtration rate, MDRD=Modification of Diet in Renal Disease