**GlycA: A Composite Nuclear Magnetic Resonance Biomarker of Systemic Inflammation**

James D. Otvos, Irina Shalaurova, Justyna Wolak-Dinsmore, Margery A. Connelly, Rachel H. Mackey, James H. Stein, and Russell P. Tracy

**BACKGROUND:** Nuclear magnetic resonance (NMR) spectra of serum obtained under quantitative conditions for lipoprotein particle analyses contain additional signals that could potentially serve as useful clinical biomarkers. One of these signals that we named GlycA originates from a subset of glycan N-acetylgalactosamine residues on enzymatically glycosylated acute-phase proteins. We hypothesized that the amplitude of the GlycA signal might provide a unique and convenient measure of systemic inflammation.

**METHODS:** We developed a spectral deconvolution algorithm to quantify GlycA signal amplitudes from automated NMR Lipoprofile™ test spectra and assessed analytic precision and biological variability. Spectra of acute-phase glycoproteins and serum fractions were analyzed to probe the origins of the GlycA signal. GlycA concentrations obtained from archived NMR Lipoprofile spectra of baseline plasma from 5537 participants in the Multi-Ethnic Study of Atherosclerosis (MESA) were used to assess associations with demographic and laboratory parameters including measures of inflammation.

**RESULTS:** Major acute-phase protein contributors to the serum GlycA signal are α1-acid glycoprotein, haptoglobin, α1-antitrypsin, α1-antichymotrypsin, and transferrin. GlycA concentrations were correlated with high-sensitivity C-reactive protein (hsCRP) (r = 0.56), fibrinogen (r = 0.46), and interleukin-6 (IL-6) (r = 0.35) (all P < 0.0001). Analytic imprecision was low (intra- and interassay CVs 1.9% and 2.6%, respectively) and intraindividual variability, assessed weekly for 5 weeks in 23 healthy volunteers, was 4.3%, lower than for hsCRP (29.2%), cholesterol (5.7%), and triglycerides (18.0%).

**CONCLUSIONS:** GlycA is a unique inflammatory biomarker with analytic and clinical attributes that may complement or provide advantages over existing clinical markers of systemic inflammation.

Protein glycosylation is the enzyme-mediated posttranslational process responsible for the attachment of diverse glycan structures either to the oxygen of a serine or threonine residue (O-linkage) or nitrogen of an asparagine residue (N-linkage) (1). Virtually all of the abundant proteins in serum, with the exception of albumin, are N-linked glycoproteins, and the great majority of these are acute-phase proteins that rise or fall in response to acute and chronic inflammatory stimuli (2, 3). The major mediator of the acute-phase response is interleukin-6 (IL-6), which induces hepatic synthesis and secretion of positive acute-phase serum proteins such as α1-acid glycoprotein, haptoglobin, and α1-antitrypsin and reduces levels of negative acute-phase proteins such as transferrin (2, 4).

During an acute-phase response, not only are concentrations of serum acute-phase glycoproteins altered, but their glycan structures are also dynamically modified by circulating glycosidases and glycosyltransferases (5, 6). The N-linked acute-phase glycoproteins have carbohydrate structures with 2 to 4 branches (di-, tri- and tetra-antennary). Inflammation- or disease-induced alterations of these structures include changes in the number of antennary branches and the identities of the terminal saccaride residues resulting primarily from addition or removal of sialic acid, galactose, or fucose residues (3, 5, 6). Such modifications of glycosylation microheterogeneity can redirect glycopro-
teins to different cellular and tissue receptors and change their functions (3, 5).

Besides serving as biomarkers of acute inflammation, increases within the reference concentration range of acute-phase proteins, such as C-reactive protein (CRP) and fibrinogen, and proinflammatory cytokines, such as IL-6, are of clinical interest as markers of systemic inflammation. Driving much of this interest is the established role of inflammation in all stages of the atherosclerotic disease process, from lesion initiation to progression to plaque destabilization (7, 8). Epidemiologic studies have confirmed the link between systemic inflammation and adverse clinical outcomes by demonstrating consistent, independent associations of hsCRP, fibrinogen, and IL-6 with both incident cardiovascular disease (CVD) and overall mortality (9–11). Among the many biomarkers that could serve as clinical indicators of the risk associated with inflammation, hsCRP has been favored mainly because of clinical chemistry considerations (7, 12). Among its attributes are stability in fresh and frozen samples, wide dynamic range, and availability of relatively inexpensive, standardized, and precise high-sensitivity immunoassays (7, 8). However, considerable within-individual variability necessitates averaging at least 2 serial hsCRP measurements before making clinical decisions (8, 12–14).

We describe here an efficient nuclear magnetic resonance (NMR) assay of a composite biomarker of systemic inflammation called GlycA, which is the name we assigned to the prominent resonance in NMR spectra of plasma originating from the N-acetyl methyl group protons of mobile glycan residues of glycoproteins (15). Because, as noted above, most abundant plasma glycoproteins are acute-phase proteins that increase in concentration and glycan complexity in inflammatory states, the measured amplitude of this glycan NMR signal would be expected, and has been observed, to be higher in patients with inflammatory conditions including rheumatoid arthritis (15, 16), cancer (15, 17), and insulin resistance (18).

To enable routine clinical and epidemiologic quantification of the GlycA signal, which is complicated by the overlap of many other NMR resonances, we developed a deconvolution model to extract GlycA concentrations from NMR LipoProfile® test spectra acquired on automated NMR analyzers for the clinical purpose of quantifying lipoprotein particles (19). This approach makes GlycA testing efficient and low cost, and enables retrospective analysis of archived NMR LipoProfile spectra from previous clinical studies. Recent reports from 3 such studies have documented independent associations of GlycA with incident CVD events (20–22). In this report, we describe the GlycA deconvolution algorithm, clarify the signal’s glycoprotein origins, and assess analytic precision and intra-individual variability. In addition, we present initial clinical data from a large, ethnically diverse population study.

Materials and Methods

REAGENTS

We purchased N-acetyl-D-glucosamine, α1-antitrypsin, haptoglobin, transferrin, fibrinogen, and IgG from Sigma-Aldrich and α1-acid glycoprotein, α1-antichymotrypsin, and α2-macroglobulin from Athens Research.

SAMPLE PREPARATION

NMR diluent was composed of 50 mmol/L sodium phosphate, 120 mmol/L KCl, 5 mmol/L Na2EDTA, and 1 mmol/L CaCl2, pH 7.4. Serum pools were adjusted to a density of 1.22 g/mL by addition of sodium bromide and centrifuged at 84 000g for 48 h at 4 °C in an Optima TLX ultracentrifuge (Beckman Coulter) to separate the lipoproteins (top fraction) and proteins (bottom fraction). The 2 fractions were dialyzed against NMR diluent and adjusted to their original concentrations before NMR analysis. We also subjected serum pools to centrifugal passage through a 10-kDa Centricon ultrafilter to obtain the low molecular weight fraction for NMR analysis. We prepared purchased acute-phase glycoproteins for NMR analysis by dissolving in NMR diluent to a final concentration of 5 g/L, except for haptoglobin (2 g/L) and α1-antichymotrypsin (3.3 g/L). A standard sample of 0.01 mol/L N-acetylglucosamine was prepared with NMR diluent.

NMR DATA ACQUISITION AND GlycA DECONVOLUTION ANALYSIS

NMR spectra used for GlycA analysis were those acquired for NMR LipoProfile testing at the CLIA-certified LipoScience (now LabCorp) clinical laboratory in Raleigh, NC (19). For experiment details, see the Data Supplement, which accompanies the online version of this article at http://www.clinchem.org/content/vol61/issue5.

ANALYTICAL CHARACTERISTICS OF GlycA MEASUREMENT

We evaluated assay imprecision according to CLSI EP5-A2 guidelines. We measured intraassay (within-run) precision by analyzing 20 replicates of 8 serum pools and interassay precision by analyzing 8 serum pools daily in duplicate (2 runs per day) for 20 days on 3 NMR analyzers.

We assessed intra-individual biological variability of GlycA, as well as hsCRP, total cholesterol, and triglycerides, by obtaining fasting serum samples at weekly intervals for 5 weeks from 23 healthy individuals: 11 male (ages 35–51 years) and 12 female (ages 29–52 years). All samples were frozen at –80 °C and subsequently thawed for NMR and chemistry analysis on the same day. hsCRP was measured turbidimetrically on a Beckman Coulter
AU680 analyzer. The clinical reportable range was 0.2–160 mg/L with a within-laboratory (interassay) CV of 1.9% derived from QC material. Total cholesterol and triglycerides were measured on a Beckman Coulter AU680 analyzer. Total laboratory CVs were 1.4% and 1.8%, respectively.

We studied the potential influence of sample type on GlycA measurement by drawing blood from 30 volunteers into serum, lithium heparin–containing, and K2EDTA-containing tubes (Becton Dickinson). To assess storage stability, serum aliquots obtained from 30 ducted NMR measurements daily for 12 days. To conduct NMR plasma samples from 10 volunteers and assess storage stability at 4 °C, we obtained serum and EDTA plasma samples from 10 volunteers and conducted NMR measurements daily for 12 days. To assess frozen sample stability, serum aliquots obtained from 30 volunteers were stored at −80 °C and measured after 4, 6, 9, 12, and 24 months. Possible postprandial influences were studied in 23 volunteers from whom serum was obtained in the fasting state and 1, 2, and 4 h after consuming a high-fat or high-carbohydrate test meal.

**POPULATION STUDY**

We sought initial insights into the population and clinical characteristics of GlycA by using archived NMR LipoProfile spectra from participants in the Multi-Ethnic Study of Atherosclerosis (MESA). A detailed description of the design and objectives of this NIH-sponsored community-based study have been published (23). Briefly, MESA is a prospective cohort study begun in 2000 to investigate the prevalence, correlates, and progression of subclinical CVD in individuals without a history of clinical CVD. The cohort included 6814 women and men 45–84 years old of African American, Hispanic, white, and Chinese American ethnicity. Analysis was restricted to 5537 participants who provided informed consent for this ancillary study and were not missing inflammation marker information. Demographics, anthropomorphic, and laboratory data were obtained at the baseline MESA examination (2000–2002), and NMR LipoProfile spectra of frozen baseline EDTA plasma samples were acquired in June–October 2003 by use of a single NMR analyzer (24). This analyzer was later found to have a fluidics defect, corrected in January 2004, that transiently exposed MESA samples to a higher-than-specified temperature, causing a systematic minor alteration in the shape of the protein baseline signal. Retrospective analysis of daily serum control spectra run on this instrument from 2003 to 2004 plus data from large batches of random clinical samples analyzed over the same time period revealed that GlycA concentrations were uniformly 15% (±5%) higher after the fluidics defect was corrected. MESA GlycA values reported here have therefore been increased by 15% to minimize potential bias with GlycA concentrations measured after 2004. hsCRP, intra- and interassay CVs from QC material ranged from 2.3% to 4.4% and 2.1% to 5.7%, respectively. For fibrinogen, intra- and interassay CVs were 2.7% and 2.6%, respectively. IL-6 was measured by ultrasensitive ELISA (Quantikine HS human IL-6 immunoassay; R&D Systems). The interassay CV was 6.3%.

**STATISTICAL ANALYSES**

Analyses were performed by use of SAS version 9.2 (SAS Institute). We used means (SD) to summarize characteristics of the MESA population by GlycA quartile. All P values were 2-tailed. Spearman rank correlation coefficients were calculated to evaluate interrelations between the inflammation markers and other variables. We analyzed biovariability data as described by Fraser and Harris (25) to give within-subject (CVI) and between-subject (CVB) CVs, and intraclass correlation coefficients were also calculated (14).

**Results**

**QUANTIFICATION OF GlycA**

The NMR signal we named GlycA is centered at 2.00 ppm in NMR LipoProfile spectra of serum or plasma (Fig. 1A). It is not a homogeneous signal from a single molecular species, but rather a composite signal arising from the superposition of slightly offset N-acetyl methyl group resonances from a subset of mobile N-acetylgalactosamine (GlcNAc) residues on the glycans branches of abundant glycoproteins (15). Only the GlcNAc units depicted in Fig. 1B in β(1→2) or β(1→6) linkage with a preceding mannose residue give rise to N-acetyl methyl resonances at 2.00 (±0.01) ppm GlycA position (26, 27). The methyl signals of GlcNAc residues at other positions in the bi-, tri-, and tetraantennary structures as well as on sialic acid residues are generally located 0.02–0.05 ppm downfield (15, 26, 27). We focused on the large 2.00 ppm signal not because of data suggesting it might be more clinically informative than neighboring peaks, but because it is able to be measured with greater precision.

Accurate quantification of the GlycA signal amplitude by simple integration is not possible, because a variable amount of its intensity comes from the overlapping signals from the allylic protons of unsaturated fatty acyl chains on lipoprotein lipids (Fig. 1A). We therefore used a linear least-squares deconvolution approach similar to that used in NMR LipoProfile testing to derive lipoprotein particle concentrations from the methyl signal envelope at approximately 0.8 ppm (19). The particular challenge in this case was accounting completely for the contributions from the allylic lipid protons from VLDL, LDL, and HDL subclasses, each of which generates a signal of slightly different frequency dependent on particle diameter (19). The necessity for such a complex
Fig. 1. GlycA NMR signal and its glycoprotein glycan origins.

(A), A representative plasma NMR LipoProfile spectrum showing in the upper expansion the GlycA signal and deconvolution model used for its quantification. The red line is the measured plasma signal envelope, and the virtually superimposed black line is the calculated sum of the deconvolution-derived amplitudes of the lipoprotein and protein (purple) and N-acetyl methyl (blue) reference signals. (B), Locations of the N-acetylglucosamine moieties in the major forms of the branched glycans of acute-phase glycoproteins that give rise to the GlycA signal.
lineshape-fitting model is illustrated in Fig. 2, which shows the GlycA spectral region of plasma from 4 individuals with varying concentrations of triglycerides. The higher the triglyceride concentration, the greater the overlap of the GlycA signal by resonances from the allylic protons of (mainly) VLDL subclasses.

What we define as GlycA is all of the measured plasma signal amplitude between 1.99–2.01 ppm that is not accounted for in the deconvolution model by overlapping lipoprotein lipid signals and the broad underlying protein background signal coming mainly from albumin. The chemical shift heterogeneity of the glycan \( N \)-acetyl methyl signals arising from differences in local environment is accounted for in the fitting model by a set of slightly offset narrow Lorentzian-shaped reference signals (depicted in blue in Figs. 1A and 2). The sum of the deconvolution-derived amplitudes of these signals gives the GlycA concentration after conversion to micromoles per liter of glycoprotein \( N \)-acetyl methyl group concentration units.

**GLYCOPROTEIN ORIGINS OF THE GlycA NMR SIGNAL**

Although the plasma GlycA signal comes predominantly from glycan \( N \)-acetyl methyl groups on acute-phase glycoproteins (15), there may be some contribution from free circulating \( N \)-acetylated sugars and glycosylated apolipoproteins on lipoprotein particles. The former possibility was investigated by examining NMR spectra of the small-molecule filtrate obtained by passing serum through a 10-kDa ultrafilter. As shown in Fig. 3D, this filtrate contributed no observable NMR signal to the GlycA position. The possibility that lipoproteins make a significant contribution to the GlycA signal was investigated by obtaining NMR spectra of serum separated by ultracentrifugation into the <1.22 g/L density fraction containing the lipoproteins (Fig. 3B) and the >1.22 g/L protein-containing bottom fraction (Fig. 3C). As expected, the protein fraction produced a prominent GlycA signal, but we also observed in the lipoprotein fraction of this and similar experiments a small peak at 2.00 ppm that by deconvolution analysis never accounted for >10% of the measured serum/plasma GlycA signal. We presume that the small lipoprotein GlycA signal originates from the glycan attached to the apolipoprotein B (apoB) and/or apo(a) proteins on LDL and lipoprotein(a) particles, since both of these apolipoproteins are glycosylated (28, 29).

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**Fig. 2.** GlycA deconvolution analysis of plasma from 4 individuals with varying triglyceride (TG) concentrations.
Because the GlycA signals originating from different plasma glycoproteins are not distinguishable, and the glycan on each is heterogeneous and varies dynamically, only a rough estimate can be made of how much each contributes to measured plasma GlycA concentrations.

To make this estimate, we multiplied the typical plasma concentration of each abundant glycoprotein by the number of N-glycosylation sites they contain. The results of these calculations (see online Supplemental Table 1) indicate that significant contributions to the plasma GlycA signal would be anticipated from α₁-acid glycoprotein, haptoglobin, α₁-antitrypsin, α₁-antichymotrypsin, transferrin, α₂-macroglobulin, IgG, and fibrinogen. It is known, however, that structurally immobilized glycan will not give rise to narrow detectable NMR signals (15, 30). To check whether any of the above 8 glycoproteins might produce less GlycA signal than anticipated because of constrained glycan mobility, we measured NMR spectra of each (Fig. 4). IgG, as expected (30), and also fibrinogen gave rise to no detectable GlycA NMR signal, and the signal from α₂-macroglobulin was attenuated from what is expected. The other 5 acute-phase glycoproteins appear to have mobile glycan chains that would produce GlycA signal in proportion to their glycan GlcNAc concentrations. Because plasma concentrations of CRP and other acute-phase glycoproteins are much lower by comparison, they contribute negligibly to the measured GlycA signal.

**PERFORMANCE CHARACTERISTICS OF THE GlycA ASSAY**

We assessed intrasay variability by analyzing 20 replicates of 8 serum pools; the mean GlycA concentration was 441 μmol/L (range 286–539 μmol/L) and the CV was 1.9%. We measured interassay variability by assaying the same 8 serum pools daily (2 runs per day) for 20 days.
Women have higher hsCRP concentrations than men. Just as the prevalence of smoking, diabetes, and metabolic syndrome increases, so does the prevalence of inflammation, as concentrations of GlycA increase. Consistent with observations for hsCRP and other markers of chronic inflammation, as concentrations of GlycA increase, so do the prevalence of smoking, diabetes, hypertension, obesity, and metabolic syndrome. The same is true for GlycA [mean (SD) 365 (57) μmol/L for men; 394 (62) μmol/L for women].

### Discussion

NMR spectroscopy has proven to be a versatile and efficient research tool with which to quantify numerous metabolites in blood samples (18, 31) and has long held the promise of making important contributions to clinical laboratory medicine (32), but until now the only application in routine clinical use is lipoprotein particle analysis by NMR LipoProfile testing (19). Serum NMR spectra acquired for this purpose are measured with automated instrumentation calibrated to ensure that amplitudes of all signals, not just those used for lipoprotein quantification, are proportional to concentration. The opportunity therefore exists to add value to clinical NMR testing by using the measured amplitudes of these numerous “byproduct” signals to achieve simultaneous quantification of multiple analytes.

We report here that quantification of 1 such NMR signal, named GlycA, provides a unique measure of systemic inflammation that might offer advantages for clinical use. Unlike existing biomarkers of inflammation that are discrete molecular species, such as acute-phase proteins or inflammatory cytokines, GlycA is a composite biomarker that senses the integrated concentrations and glycosylation states of several of the most abundant acute-phase proteins in serum. We speculate that GlycA concentrations may therefore provide a more stable measure of low-grade systemic inflammation and respond more uniformly to diverse inflammatory stimuli than individual acute-phase reactants that are each regulated differentially and vary in response to inflammation site and intensity (2, 3).

The GlycA NMR signal is chemically nonspecific in origin, coming from the N-acetyl methyl groups of GlcNAc residues on the antennary branches of serum glycoproteins (15, 26, 27). Although in theory all N-linked glycoproteins are responsible for producing the GlycA signal, in practice only a small subset of acute-phase glycoproteins make meaningful contributions to

### Table 1. Variability of GlycA, hsCRP, cholesterol, and triglycerides measured weekly for 5 weeks (n = 23).

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Mean</th>
<th>SD</th>
<th>CVp, %</th>
<th>CVG, %b</th>
<th>ICC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GlycA, μmol/L</td>
<td>399.5</td>
<td>17.3</td>
<td>4.3</td>
<td>15.3</td>
<td>0.92 (0.90–0.94)</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>3.6</td>
<td>1.2</td>
<td>29.2</td>
<td>133.9</td>
<td>0.77 (0.72–0.83)</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>181.9</td>
<td>10.6</td>
<td>5.7</td>
<td>16.4</td>
<td>0.85 (0.81–0.89)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>118.4</td>
<td>20.0</td>
<td>18.0</td>
<td>55.6</td>
<td>0.89 (0.86–0.92)</td>
</tr>
</tbody>
</table>

*a To convert cholesterol concentrations to mmol/L, multiply by 0.02586. To convert triglycerides concentrations to mmol/L, multiply by 0.01129.

*b ICC, intraclass correlation coefficient.
measured GlycA concentrations. The reason is the relatively low detection sensitivity of NMR, which renders species present at concentrations less than about 20 μmol/L effectively undetectable under the conditions of measurement. Constrained glycan chain mobility is another reason N-acetyl methyl signals may not be seen even when glycoprotein concentrations are in the detectable range (30), as our evidence suggests is true for IgG and fibrinogen. Our estimates taking these considerations into account suggest that measured GlycA concentrations are due in aggregate primarily to contributions from 1-acid glycoprotein, haptoglobin, 1-antitrypsin, 1-antichymotrypsin, and transferrin. Because the latter is a negative acute-phase protein, GlycA elevations in inflammatory states are presumed to reflect increased concentrations of the former 4 proteins. The extent to which GlycA signal intensity is additionally modulated by inflammation-induced increases in glycan complexity is unknown and warrants investigation (3, 5, 6).

Our finding that the intraindividual variability of GlycA was much lower than that of hsCRP may have clinical relevance. Because hsCRP in epidemiologic studies has prognostic value beyond traditional CVD risk factors, guidelines recommend for certain patients that hsCRP concentrations be used to refine risk assessment (8, 12). However, concern has arisen that hsCRP may have insufficient within-person stability to provide reliable risk stratification from 1 or even 2 serial determinations (14, 36–38). Although some studies have come to a different conclusion (34, 35), most have found the within-individual variability of hsCRP to be considerably greater than that of cholesterol (13, 14, 37, 38). Our results for short-term repeated assessments agree with the latter reports, showing 5-fold greater CVI values for hsCRP compared with cholesterol (29.2% vs 5.7%). In marked contrast, serial measurements of GlycA appear to be at least as stable as those of cholesterol (CVI 4.3%). If these initial findings are borne out in more diverse populations studied over wider time intervals, GlycA for biological stability reasons might prove useful as an adjunct or alternative to hsCRP for helping stratify risk associated with inflammation.

Much remains to be learned about GlycA before its potential as a clinical marker of systemic inflammation is known.

### Table 2. Baseline characteristics of MESA participants by GlycA quartile.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All</th>
<th>Q1 (&lt;336)</th>
<th>Q2 (336–373)</th>
<th>Q3 (374–417)</th>
<th>Q4 (&gt;417)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>5537</td>
<td>1365</td>
<td>1383</td>
<td>1398</td>
<td>1391</td>
</tr>
<tr>
<td>Age, years</td>
<td>62 (10.3)</td>
<td>62 (10.5)</td>
<td>63 (10.2)</td>
<td>63 (10.3)</td>
<td>62 (10.2)</td>
</tr>
<tr>
<td>Men</td>
<td>48.5</td>
<td>63.6</td>
<td>53.1</td>
<td>46.5</td>
<td>31.1c</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>39.7</td>
<td>38.1</td>
<td>41.6</td>
<td>37.9</td>
<td>41.1</td>
</tr>
<tr>
<td>Chinese American</td>
<td>13.3</td>
<td>21.1</td>
<td>14.8</td>
<td>12</td>
<td>5.2c</td>
</tr>
<tr>
<td>African American</td>
<td>24.2</td>
<td>22.4</td>
<td>21.9</td>
<td>25.5</td>
<td>27.1c</td>
</tr>
<tr>
<td>Hispanic</td>
<td>22.8</td>
<td>18.4</td>
<td>21.6</td>
<td>24.6</td>
<td>26.5c</td>
</tr>
<tr>
<td>Current smoking</td>
<td>12.4</td>
<td>8.7</td>
<td>10.5</td>
<td>13.2</td>
<td>17.0c</td>
</tr>
<tr>
<td>Diabetes</td>
<td>12.5</td>
<td>8.4</td>
<td>10.2</td>
<td>12.7</td>
<td>18.7c</td>
</tr>
<tr>
<td>Hypertension</td>
<td>44.3</td>
<td>32.9</td>
<td>42.1</td>
<td>46.4</td>
<td>55.5c</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>36</td>
<td>20.7</td>
<td>29.6</td>
<td>40.6</td>
<td>52.8c</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.2 (5.4)</td>
<td>26.4 (4.7)</td>
<td>27.4 (4.9)</td>
<td>28.7 (5.1)</td>
<td>30.4 (6.1)c</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>133 (80)</td>
<td>105 (63)</td>
<td>124 (67)</td>
<td>140 (77)</td>
<td>160 (96)c</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>117 (31)</td>
<td>113 (29)</td>
<td>118 (30)</td>
<td>120 (32)</td>
<td>119 (34)c</td>
</tr>
<tr>
<td>LDL particles, nmol/L</td>
<td>1250 (338)</td>
<td>1169 (310)</td>
<td>1245 (321)</td>
<td>1281 (335)</td>
<td>1303 (368)c</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>51 (15)</td>
<td>52 (15)</td>
<td>51 (15)</td>
<td>50 (15)</td>
<td>50 (14)c</td>
</tr>
<tr>
<td>HDL particles, μmol/L</td>
<td>34.1 (6.7)</td>
<td>32.9 (5.8)</td>
<td>34.0 (6.5)</td>
<td>34.3 (6.8)</td>
<td>35.2 (7.3)c</td>
</tr>
<tr>
<td>GlycA, μmol/L</td>
<td>380 (61)</td>
<td>307 (23)</td>
<td>356 (11)</td>
<td>395 (12)</td>
<td>462 (39)c</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>3.6 (5.3)</td>
<td>1.3 (1.6)</td>
<td>2.2 (2.6)</td>
<td>3.6 (4.3)</td>
<td>7.1 (8.0)c</td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
<td>1.6 (1.2)</td>
<td>1.2 (1.0)</td>
<td>1.4 (1.1)</td>
<td>1.6 (1.1)</td>
<td>2.1 (1.4)c</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>345 (73)</td>
<td>303 (54)</td>
<td>330 (58)</td>
<td>354 (65)</td>
<td>391 (80)c</td>
</tr>
</tbody>
</table>

* Values are % or mean (SD). To convert cholesterol concentrations to mmol/L, multiply by 0.02586. To convert triglycerides concentrations to mmol/L, multiply by 0.01129.  
* P for trend < 0.0001.
can be evaluated. Nothing is yet known, for example, about the magnitude and duration of the GlycA response to acute inflammation, or how GlycA concentrations relate to the presence and severity of inflammatory diseases such as rheumatoid arthritis and psoriasis. Future research as well as the rate of clinical translation is likely to progress quickly, however, since rapid and automated GlycA measurements can be performed on FDA-cleared NMR analyzers already deployed in clinical laboratories, and many previously obtained NMR LipoProfile research datasets are available for interrogation. Adding to the evidence from MESA that GlycA is indeed a marker of systemic inflammation are recent results from the Women’s Health Study showing that GlycA and hsCRP measured in 27,491 participants were similarly associated with incident CVD events (n = 1648) during 17 years of follow-up, each attenuating the others’ association with risk when included in the same regression model (20). Increased GlycA appeared to confer short- to medium-term CVD risk (up to 6 years) independent of hsCRP, but longer-term risk relations were stronger for hsCRP (20). Higher GlycA concentrations were also reported to be associated with increased risk of future CVD independent of traditional risk factors in Justification for the Use of Statin in Prevention, an Intervention Trial Evaluating Rosuvastatin (JUPITER) (21) and in HIV patients in the Strategies for Management of Anti-Retroviral Therapy (SMART) study (22). Future analyses in MESA and other cohort studies will be needed to determine the comparative prognostic value of GlycA as a clinical indicator of the risk of cardiovascular disease, diabetes, and other inflammation-related diseases.

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