Clinica Chimica Acta 475 (2017) 56–63

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Palestinian Arab ethnicity is associated with an adverse metabolic phenotype☆

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ARTICLE INFO

Keywords:
GlycA
Obesity
Inflammation
Arabs
Cardio-metabolic phenotype

ABSTRACT

Urban-dwelling Palestinians have been shown to have higher cardiovascular morbidity and mortality and prevalence of diabetes than urban Israelis. Inflammation is implicated in the etiology of these conditions. We hypothesized that increased inflammatory activation, manifested as increased GlycA, a novel biomarker of global inflammation, would be evident in Palestinians.

We compared GlycA concentrations between Palestinians and Israelis and assessed the associations of GlycA with anthropometric, health behavioral and clinical variables in a sample of 1674 Palestinians and Israelis aged 25–74, residing in Jerusalem. The main outcome measure was GlycA concentration.

GlycA was higher in Palestinians than Israelis ($p < 0.001$). This finding persisted in young Palestinians with normal glucose tolerance. GlycA, total white blood cell count, the triglyceride to HDL-cholesterol ratio and small LDL-cholesterol particles were all significantly higher in Palestinians compared to Israelis across obesity and glucose tolerance categories. Palestinian women had greater GlycA compared to Israeli women and men of both ethnicities.

GlycA as well as adverse cardiovascular biomarkers are all higher in Palestinian Arabs than Israeli Jews, even in young healthy adults. This propensity to inflammation may be a driver of the higher risk of cardiovascular disease, insulin resistance and diabetes observed in this population.

1. Introduction

A global epidemic of obesity and its associated comorbidity is affecting the world in general and the Middle East specifically [1]. Israeli Arabs have been shown to have a higher prevalence of obesity [2] and type 2 diabetes (T2DM) manifesting at an earlier age than Israeli Jews [3]. Similarly, urban Palestinians tend to suffer from a greater incidence of coronary heart disease (CHD) [4] and higher CHD mortality than Israeli Jews [5]. These observations suggest that there may be an additional factor, specific to the Arab population, driving these findings. Indeed, subclinical inflammation, detected by molecules such as increased C-reactive protein, has been suggested to be mechanistically related to increased cardiometabolic risk [6,7].

Plasma protein glycosylation is a hallmark of activation of immune system proteins[8,9]. Most activated inflammatory proteins are glycosylated while others undergo differential glycosylation as a function of inflammatory stimuli [10]. Amplification of protein function via structural changes of glycan residues makes glycans potential early biomarkers of sub-clinical disease conditions [11]. Because markers of subclinical chronic inflammation have been recognized as cardiovascular disease (CVD) and diabetes risk predictors [12–14], it is reasonable to assume that measurement of global glycosylation of plasma proteins may serve as a nonspecific marker of inflammation and thus be associated with diabetes and CVD risk. The nuclear magnetic resonance (NMR) spectrum used for lipoprotein analysis detects a signal originating from methyl group protons of carbohydrate elements of glycosylated (not glycated) proteins [15]. The signal, named GlycA, is derived from the *N*-acetyl groups of the *N*-acetylglucosamine and *N*-acetylgalactosamine moieties of protein glycans [16]. This signal correlates well with C-reactive protein concentrations [17] and has been

☆ Conflict of interest statement: RW, HN, RS, WAA and JDK declare no conflict of interest. JO is employed by, is a stockholder of, and serves on the board of directors of LipoScience, Inc., a diagnostic laboratory company that performed the blinded GlycA analyses described in this manuscript. The work was supported by the USAID MERC Program (Grant # TA-MOU-01-M21-002) and by a research grant from DCURE Israel.

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http://dx.doi.org/10.1016/j.cca.2017.10.004
Received 23 September 2017; Accepted 3 October 2017
Available online 04 October 2017
0009-8981/

shown to predict CVD in general [16] and to be associated with risk for total death, CVD, and total cancer after adjustment for CRP, IL-6, and d-dimer concentrations. [18] The measured amplitudes of this signal reflect the extent of plasma protein glycosylation. One may therefore infer that GlycA levels can serve as a nonspecific measure of global inflammation status.

The Jerusalem Palestinian-Israeli Risk Factor Study was designed to assess differences in the distribution of risk factors for cardiovascular disease (CVD) and diabetes between Palestinian Arabs and Israeli residents of Jerusalem, in view of evidence for a substantial disparity in the incidence of CHD[4,19] between these two populations and the high prevalence of diabetes in east Jerusalem Arabs[20]. The aim of this analysis was to analyze, in relation to ethnic background, this novel biomarker along with other adverse metabolic biomarkers, anthropometric measures and the presence of type 2 diabetes. We postulated that GlycA, as well as markers of inflammation (such as the white blood cell count) and surrogates of insulin resistance, would be increased in Palestinians compared to Israelis and associated with the degree of obesity and the presence of diabetes.

2. Methods

Methods of the Jerusalem Palestinian-Israeli Risk Factor Study have been previously described[21]. The study consists of a population-based sample of the city of Jerusalem which since 1967 has been unified under Israeli rule. The Palestinians of east Jerusalem have a status of permanent Israeli residents with full access to the Israeli national health system and are recorded in the Israeli national population registry. Recruitment for this study was performed using an age-sex-stratified random sample drawn from the population registry of 2000 Palestinian residents of east Jerusalem and 2000 Israeli residents from west Jerusalem sampled at age 25–74 years (comprising 200 individuals in each sex-age decile per population group). Of the Palestinian sample 29.5% could not be located and of those contacted 89.6% were eligible for the study. The corresponding figures for the Israelis were 25.1% and 88.4%. The response rates for all located eligible residents were 76.7% for Palestinians and 53.7% for Israelis. Between 2004 and 2008 1682 participants (970 Palestinians and 712 Israelis) attended two study centers in east and west Jerusalem for a face-to-face interview and for clinical evaluation. All participants provided signed language-specific informed consent. The study was authorized by the St Joseph Hospital (in east Jerusalem) and Hadassah-Hebrew University Medical Center Ethics (Helsinki) Committees.

2.1. Laboratory analyses

All participants had fasting venous blood drawn into plain and EDTA-containing vacuum containers. Those without known diabetes underwent a 2-h glucose challenge. Blood was immediately separated in a refrigerated centrifuge, aliquoted and stored at − 80 °C until analysis. Plasma cholesterol, HDL-cholesterol (after precipitation of the apoB-containing lipoproteins with magnesium chloride and phosphotungstic acid) and triglycerides (TG) were measured by enzymatic methods using Roche reagents in the Hadassah University Medical Center lipid research laboratory (that met US-CDC quality control standards). *NMR LipoProfile®* spectra of plasma were acquired at LipoScience, Inc. (Raleigh, NC) using automated 400 MHz NMR analyzers. Lipoprotein particle subclasses were quantified by deconvolution of the lipid methyl signal envelope at ~0.8 ppm. The glycan *N*-acetyl methyl signal at 2.00 ppm referred to as GlycA was quantified by deconvolution analysis and reported in methyl group concentration units of μmol/L. The GlycA signal originates from a subset of *N*-acetylglucosamine and *N*-acetylgalactosamine residues on the bi-, tri-, and tetra-antennary glycan branches of abundant serum acute phase glycoproteins, mainly α1-acid glycoprotein, haptoglobin, α-antitrypsin, α1-antichymotrypsin, and transferrin[15].

2.2. Variable definitions

Height and weight (in light clothing) were measured to the nearest 0.1 cm and 100 g, respectively, and body mass index (BMI) was calculated[9]. Waist circumference was measured to the nearest 0.1 cm at the midpoint between the upper margin of the iliac crest and the lower rib margin as determined in the mid-axillary line. Glucose tolerance status was defined as follows: Normal glucose tolerance (NGT) was defined as a fasting glucose < 100 mg/dl and a 2-h glucose < 140 mg/dl, and not on anti-hyperglycemic treatment; pre-diabetes was defined as a fasting glucose ≥100 mg/dl yet < 126 mg/dl or a 2-h glucose ≥140 mg/dl yet < 200 mg/dl, and not on anti-hyperglycemic treatment; diabetes was defined as having a documented diagnosis and anti-hyperglycemic treatment or as having a fasting glucose ≥126 mg/dl or a 2-h glucose ≥200 mg/dl. Current smoking was grouped as 0, 1–10, 11–20, 21–30 and 31 + cigarettes per day.

2.3. Statistical analysis

Variables are described by means ± standard deviation or as percentages. Variables that were not normally distributed (such as plasma TG) underwent natural logarithmic transformation. Pearson correlations were used to assess bivariate associations. Multivariable linear regression was performed with GlycA as the dependent variable and the ethnic, anthropometric and biochemical measures as independent variables. Correction for multiple comparisons was performed using the post-hoc Bonferroni procedure. Standardized Betas are presented. Analyses were performed using SPSS20.0 for Windows.

3. Results

3.1. Study participants and their characteristics (Table 1)

964 Palestinian Arabs (512 M/452F) and 710 Israelis (374 M/336F) with GlycA measures participated in this analysis. As shown in Table 1, Palestinian men and particularly women had a greater mean BMI than their Israeli counterparts ($p = 0.02$ and $p < 0.001$ for males and females, respectively). Mean waist circumference was comparable among men yet was considerably larger in Palestinian women ($p < 0.001$). Palestinian females had higher systolic blood pressure than their Israeli counterparts ($p = 0.04$). Prevalence of type 2 diabetes was higher in Palestinians than Israelis of both sexes ($p_{\chi 2} < 0.001$ for both). Use of statins was generally similar between the two population groups who are served by the Israeli health system. Mean plasma total cholesterol and LDL-cholesterol concentrations were similar between both groups, whereas triglycerides were higher and HDL-cholesterol was substantially lower in Palestinian men and women alike. The TG/HDL-cholesterol ratio was strongly elevated in Palestinian men and women compared to their Israeli counterparts ($p < 0.001$ for both). Smoking was far more common in Palestinian men and Israeli women than their counterparts ($p\chi^2 < 0.001$ for both). Palestinian women and men had higher white blood cell (WBC) counts than Israelis ($p < 0.001$ and $p = 0.07$, respectively). Of note, women of both population groups had higher WBC counts than men.

3.2. GlycA concentrations among Palestinian Arabs and Israelis (Fig. 1)

Palestinian men and women had greater mean concentrations of GlycA compared to their Israeli counterparts ($p < 0.001$ for each sex). Notably, among Palestinians and Israelis alike, women exhibited consistently higher concentrations of GlycA than men ($p < 0.001$). Upon adjustment for age, sex, waist circumference, glucose tolerance, use of statins, use of anti-hypertensives, smoking status, triglyceride, HDL-cholesterol and total white blood cell count, Palestinians still had significantly greater concentrations of GlycA in comparison to their Israeli counterparts ($p < 0.001$) as did women compared to men