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Research article

TOTAL AND PROTEIN-BOUND SIALIC ACID SERUM LEVELS IN PREDIABETES

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ABSTRACT

Background: Prediabetes is the main risk factor of Type 2 diabetes mellitus (T2DM), which is a low-grade systemic chronic inflammation disease. Sialic acid is a marker of systemic inflammation as well as significantly associated with new T2DM. Previous studies are scarce and have yielded contrasting results about sialic acid levels in prediabetes. The aim of this study was to assess sialic acid serum levels (total sialic acid and its fractions) innewly diagnosed prediabetes.

Materials and Methods: Potential confounding variables were controlledto search for the association of newly diagnosed prediabetes with total sialic acid (TSA), protein-bound sialic acid (BSA), and free sialic acid (FSA) serum levels; 28 cases of adults with prediabetes and 31 normoglycemic controls, matched for BMI, sex and age were included.

Results: Compared to controls, only TSA and BSA were elevated in subjects with prediabetes ($p < 0.0001$ and $p < 0.0001$, respectively). A positive association between prediabetes and both, TSA and BSA, was observed ($\beta = 11.9$, $p < 0.0001$ and $\beta = 12.0$, $p < 0.0001$, respectively).

Conclusions: Our results showed increased TSA and BSA levels in adults with newly diagnosed prediabetes. Increased TSA relied on the increment of BSA, and both, TSA and BSA were associated with pre diabetic state independently of the C-reactive protein. Further studies are needed to support this evidence.

Key words: Prediabetic state; impaired glucose tolerance; impaired fasting glucose; serum sialic acid; protein-bound sialic acid

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INTRODUCTION

Prediabetes is the term used for individuals with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) and is the main risk factor for the development oftype 2 diabetes mellitus (T2DM) (ADA, 2015, Bergman M, 2013, Eikenberg JD, Davy BM, 2013). Total serum sialic acid (TSA) is a marker of low-grade systemic inflammation as well assignificantly associated with new T2DM (Schmidt MI et al, 1999). However, studies on TSA in those with prediabetes have shown discrepant results. For instance, while sialic acid was not elevated in Melanesians from Fiji with IFG and IGT (Crook MA et al, 2002), an increased TSA in subjects with IGT indicated thatTSA measurement could be valuable as an independent parameter in identifying subjects at higher risk of developing T2DM (Gavella M et al, 2003).

Acylated derivatives of neuraminic acid, called sialic acidare present as terminal components of non-reducing ends of oligosaccharide chains of glycoproteins and glycolipids. Also, sialic acid is localized at the end of many acute phase proteins, asprotein-bound sialic acid (BSA) fraction (Crook MA et al, 2002). However, only small amounts of free sialic acid (FSA) are normally present in serum (Sillanaukee P et al, 1999). Elevated levels of inflammatory markersmay play an important role in prediabetes (Bardini G et al, 2010) consequently, an increased BSA could be expected. Studies on the relationship of both TSA and BSA with metabolic parameters in subjects with prediabetes are scarce (Crook MA et al, 2002, Gavella M et al, 2003, Rajappa M et al, 2013).

The Mexican population has a high prevalence of pre diabetes (Ureña-Bogarín EL et al, 2015), and diabetes (Villalpando S et al, 2010, Aguilar-Salinas CA et al, 2003). In fact, the incidence of T2DMin Mexico is among the highest reported worldwide (González-Villalpando C et al, 2014). Further, diabetes is the number one cause of disability adjusted life years lost in Mexico (Vos T et al, 2013) and fasting and 2h plasma glucose valuesare independent predictors of incident T2DM in Mexican people (Ferrannini E et al, 2009).Therefore, the study of inflammatory markers inMexican subjects with prediabetesis of outmost importance. Toour knowledge, no previous studies have investigated whether there is an increased TSA levelin Mexican adults and/or those with prediabetesor the role that BSA and FSA fractions play.Theaim of the present study was to investigate the sialic acidlevels (TSA, BSA, and FSA) in Mexican adults, and to assess their association with newly diagnosed prediabetes.

MATERIALS AND METHODS

Subjects

The participants were selected from 176 adultswho were referred to the outpatient clinic for diabetes of the Dr. Ignacio Chavez Hospital, in Hermosillo, Sonora, Mexico, throughout six months (January to August 2015). As part of their visit to the clinic, all subjects had a medical and biochemical assessment. Participants avoided strenuous exercise and any alcohol intake for two days before the medical and biochemical assessment. From the source population of 176 subjects, 28 were newly diagnosed with prediabetes (15 women and 13 men) and agreed to participate in the study. Diagnosis of prediabetes was based on the American Diabetes Association (ADA) criteria (ADA, 2015). Another 31 subjects matched for BMI, sex and age, were selected as controls (18 women and 13 men). Subjects with T2DM, hypochromic microcyticanemia, hemoglobinopathies, cancer, hypothyroidism, acute vascular events, hepatic or renal disease, autoimmune diseases or any infection, alcoholism or pregnancywere excluded from the study. In addition, none of them were on anti-hypertensive, lipid-lowering medication, non-steroid anti-inflammatories, steroids, oral contraceptive and hormone replacement therapy, pioglitazone, thyroglobulin or fibrates at the time of the study.Thus, 59 subjects with a mean age of 46.15 ± 12.01 years met the inclusion criteria for the study and agreed to participate. Written informed consent was obtained from all participants before being included in the study.

This study was approved by the institutional bioethics committee of the Department of Medicine and Health Sciences, University of Sonoraand the bioethics committee of the Dr. Ignacio Chavez Hospital (Dated 13th June 2014). All procedures followed were in accordance with the Declaration of Helsinki 1975, as revised in 2008.

Analytical methods

The same blood sample used for the biochemical assessment for all 176 subjects was used for this study to measure insulin, PCR and sialic acid in the 59 study participants. Fasting serumlipid profile (total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglyceride), total protein, albumin, creatinine, uric acid, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyltransferase (GGT) were spectrophotometrically quantified by standardized commercially available diagnostic testsin aHitachi Modular P800 Analyzer (Roche Diagnostics Co., Indiana, USA).LDL-cholesterol was calculated using the Friedewald et al, 1972 formula.

An oral glucose tolerance test (OGTT) was performed after 10-12 h of overnight fasting by using 75 g of glucose as the oral load over a 2min period, followed by collection of blood samples at baseline and 2 h after the glucose load formeasurement of serum glucose. Results from OGTT were used to define normal glucose tolerance, impaired glucose tolerance or T2DMaccording to ADA criteria (ADA, 2015).

Duplicate HbA_{1c} determinations were performed in a DCA Vantage Analyzer (Siemens DCA Vantage™ Analyzer, Tarrytown, NY, USA). Fasting serum insulin was determined using a Cal biotech insulin immuno enzymatic assay (Catalog No. IS130D, Spring Valley, CA, USA).Fasting serum glucose was determined using a glucose oxidase assay (Hitachi Modular P800 Analyzer, Roche Diagnostics Co., Indiana, USA). Both measures were combined to calculate the homeostasis model assessment of insulin resistance (HOMA-IR) (Matthews DR, 1985).

Serum C-reactive protein (CRP) was measured in duplicate using a high sensitivity assay by the nephelometric Minineph human CRP assay (hsCRP) (ZK044.L.R, Binding Site Ltd, Birmingham, UK).Duplicate measurements of total serum sialic acid (TSA) and free sialic acid (FSA) were performed using the Quantichrom TM Sialic Acid assay (BioAssay Systems, Hayward, CA). This assay uses an improved Warren method (Warren L, 1959).

Anthropometric and blood pressure measurements

To obtain body mass index (BMI, kg/m^2) weight was measured using an electronic balance (Defender 3000 series, Ohaus, Pine Brook, NJ, U.S.A.) and height was measured with a wall-mounted stadiometer (Holtain Ltd., Dyfed, UK). Waist circumference was measuredusing a flexible tape measure directly on the skin. Participants stood relaxed, with arms folded comfortably across the chest. Measures were made at the end of normal expiration, making sure the tape was positioned perpendicular to the vertical (Y) axis of the body and parallel to the floor.The site was measured twice and the average was used for analysis. Blood pressure was measured using a manual sphygmomanometer, afterthe subject rested for 5 min in a seated position. Systolic and diastolic values were taken as the average of two readings. High blood pressure was defined as a systolic blood pressure at or above 140 mmHg and/or a diastolic blood pressure at or above 90 mmHg, and/or known established hypertension requiring medical treatment.

Statistical analysis

Either the independent t-test or the Mann-Whitney U-test was used to analyze differences between subjects with prediabetes vs. controls for the clinical, biochemical and anthropometric variables, depending whether the variable was normally distributed or not. Data are presented as the arithmetic mean ± standard deviation (SD), geometric means (95% confidence interval,CI), ormedians (interquartile range, IR), depending on the distribution of the variable. Associations between TSA, BSA and FSA concentrations and prediabetes state were examined using multiple linear regression analysis in separate regression models. Models were constructed using a combination of univariate ($p<0.2$) and stepwise ($p<0.05$) analyses. Interactions of prediabetes state with selected covariates were tested in the models but these were not significant. Collinearity of selected variables was also tested. Model assumptions were tested using a graph of residuals. Statistical analyses were performed using the NCSS 9 statistical software (NCSS 9 Statistical Software 2013, NCSS LCC, Kaysville, UT, USA).

RESULTS

Clinical, biochemical and anthropometric characteristics of study groups

Twenty eight subjects (15.9%) among 176 adultswere identified as newly diagnosed cases of pre diabetes. These subjects shared similar gender and age distributions with the normoglycemic subjects of the control group (Table-1). Significant differences in HbA_{1c}, fasting blood glucose and 2-h post-load glucose levels were foundfor the two groups, as expected.Similar body mass index (BMI)($p=0.076$) and waist circumference($p=0.075$) wereobserved between the two groups. Blood pressure at or above 140/80 mmHg was observed in 10.7% of the subjects with prediabetes and 9.7% of the control subjects, with no significant difference between the two groups (Table 1).

Insulin concentration was higher ($p<0.0001$) in subjects with prediabetes when compared tocontrols. HOMA-IR indexwas also increased in subjects with prediabetes ($p<0.0001$).

Levels of GGT and ALT were within normal ranges (20) in both groups. However, subjects with pre diabetes showed higher concentrations of both enzymesthan controlsubjects ($p<0.0001$). No differences in HDL-cholesterol ($p = 0.223$) and triglyceride ($p = 0.676$) were observed between groups, although LDL-cholesterol was higher in the control group ($p = 0.007$).

Compared to control individuals, subjectswith prediabetes had a lower albumin/globulin ratio ($p= 0.007$).Also, higher levels of hs CRP were found in subjectswith prediabetes when compared to controls ($p = 0.035$) (Table 1).

Table 1. Clinical, biochemical and anthropometric variables of the subjects with prediabetes and control subjects at baseline.

Variable	Subjects with prediabetes (n=28)	Control subjects (n=31)	*P* value
Gender (%Men)	44.8	43.3	0.799
Age (years)	46.4 ± 11.3	45.9 ± 12.8	0.854
Altered blood pressure (%)	10.7	9.7	0.1500
HbA1c, % (mmol/mol)	6.0 ± 0.3 (42.6 ± 3.3)	5.2 ± 0.3 (33.5 ± 3.5)	<0.0001
Fasting glucose (mg/dL)	99.8 ± 11.1	84.7 ± 5.6	<0.0001
2-h glucose (mg/dL)	140.5 ± 30.1	112.1 ± 22.6	<0.0001
Fasting insulin (µIU/mL)[a]	5.0 (4.1, 6.3)	3.17 (2.7, 3.8)	<0.0001
HOMA-IR[a]	5.0 (4.1, 6.3)	3.17 (2.7, 3.8)	<0.0001
Total sialic acid (mg/dL)	76.8 ± 10.3	61.9 ± 9.0	<0.0001
Bound sialic acid (mg/dL)	76.3 ± 10.2	61.4 ± 9.0	<0.0001
Free sialic acid (mg/dL)[b]	0.5 (0.1, 0.5)	0.5 (0.2, 0.7)	0.443
Total cholesterol (mg/dL)[b]	187.0 (47.0, 141.0)	201.0 (24.3, 162.0)	0.096
Triglyceride (mg/dL)	142.9 (57.6)	137.5 (37.7)	0.676
HDL-cholesterol (mg/dL)	47.3 ± 9.4	50.5 ± 10.8	0.223
LDL-cholesterol (mg/dL)	106.8 ± 34.7	131.2 ± 33.0	0.007
Total proteins (g/dL)	7.0 ± 0.4	6.9 ± 0.5	0.448
Globulins (g/dL)	3.1 ± 0.5	2.8 ± 0.8	0.039
Albumin/Globulin ratio (g/dL)[a]	1.2 (1.1, 1.3)	1.5 (1.3, 1.8)	0.007
hsCRP (mg/L)[b]	1.6 (3.2, 10.1)	1.0 (1.1, 7.1)	0.035
Gamma-glutamyltransferase (IU/L)[a]	20.6 (16.3, 26.1)	9.4 (7.8, 11.2)	<0.0001
Aspartateaminotransferase (IU/dL)[a]	15.3 (13.7, 17.1)	13.5 (11.9, 15.4)	0.431
Alanineaminotransferase (IU/dL)[b]	18.5 (12.9, 41.0)	12.6 (5.5, 57.6)	<0.0001
Height (cm)[b]	161.1 (13.0, 32.2)	164.4 (18.2, 180.5)	0.933
Weight (kg)	85.8 ± 17.7	80.3 ± 13.3	0.176
Body mass index (kg/m^2)	31.7 ± 5.2	29.57 ± 3.8	0.076
Waist circumference (cm)	107.4 ± 12.6	101.7 ±11.4	0.075

A t test was done for independent samples. Non-normal distribution data were tested with the Mann-Whitney U-test.
[a] Geometric means (95% CI)
[b] Medians (IR)
[c] All other data are presented as mean ± SD
* Altered blood pressure >130/90 mmHg
hs CRP, high sensitive C-reactive protein

Quantification of the different forms of sialic acid

Mean TSA and BSAlevelswere higher in subjects with pre diabetes than control subjects (p<0.0001 and p<0.0001, respectively). However, no significant differences between groups were observed for serum FSA level (p=0.443) (Table 1).

Univariate analysis of serum sialic acid forms

Univariate regression analyses were performed with TSA, BSA or FSA as the dependent variables. Results showed positive association of serum TSA with fasting insulin (p=0.0031), HOMA-IR (p=0.0018), GGT (p<0.0001), hs CRP (p=0.0008), total proteins (p=0.0058), globulins (p=0.0070), BMI (p=0.0019), and waist circumference (p=0.0464); and a negative association withthe albumin/globulin ratio (p=0.0143)(Table 2).Likewise,results showed a positive association of BSAwith fasting insulin (p=0.0033), HOMA-IR (p=0.0019), GGT (p<0.0001), hs CRP (p=0.0009), total proteins (p=0.0058), globulins (p=0.0067), BMI (p=0.0019), and waist circumference (p=0.0473); and a negative association with the albumin/globulin ratio (p=0.0137) (Table 2). FSA was positively associated only with triglyceride (p=0.0088), LDL cholesterol (p=0.0118), tri/HDL ratio (p=0.0230) and creatinine (p=0.0098) (Table 3).

Multiple linear regression analysis of serum sialic acid and associated variables

Multiple regression models confirmed the association of TSA and BSA with prediabetes state (TSA: β = 11.9, p<0.0001; BSA: β = 12.0, p<0.0001) (Table 4). Subjects with prediabetes showedhigher levels of TSA and BSA than those with normal glucose levels after adjusting for hs CRP, total proteins and AST.

Table 2.Univariate relationships between total sialic acid and bound sialic acid with clinical, biochemical and anthropometric characteristics in the whole group (n = 59).

Variable	Total Sialic Acid			Bound Sialic Acid		
	β	Standard Error	*p*	β	Standard Error	*p*
Prediabetes (yes)	14.9	2.5	<0.0001	14.9	2.5	<0.0001
Gender (men)	-4.1	3.2	0.1966	-4.2	3.1	0.1904
Altered blood pressure (%)	7.2	3.7	0.0581	7.2	3.7	0.0585
HbA_{1c} % (mmol/L)	1.5	0.2	<0.0001	1.5	0.2	<0.0001
Fasting glucose (mg/dL)	0.5	0.1	0.0003	0.5	0.1	0.0003
2-h glucose (mg/dL)	0.1	0.1	0.0393	0.1	0.1	0.0403
Fasting insulin (µIU/mL)	1.6	0.5	0.0031	1.6	0.5	0.0033
HOMA-IR	6.2	1.9	0.0018	6.2	2.0	0.0019
HDL-cholesterol (mg/dL)	-0.3	0.6	0.0829	-0.3	0.2	0.0850
Total proteins (g/dL)	9.5	3.3	0.0058	9.5	3.3	0.0058
Globulins (g/dL)	6.4	2.3	0.0070	6.5	2.3	0.0067
Albumin/Globulin ratio (g/dL)	-7.1	2.8	0.0143	-7.2	2.8	0.0137
hsCRP (mg/L)	2.2	0.6	0.0008	2.2	0.6	0.0009
Gamma-glutamyltransferase (IU/L)	0.5	0.1	<0.0001	0.5	0.1	<0.0001
Aspartateaminotransferase (IU/dL)	0.5	0.2	0.0714	0.5	0.2	0.0729
Alanineaminotransferase (IU/dL)	0.4	0.1	0.0121	0.4	0.1	0.0121
Weight (kg)	0.2	0.1	0.1199	0.1	0.1	0.1236
Body mass index (kg/m^2)	1.1	0.3	0.0019	1.1	0.3	0.0019
Waist circumference (cm)	0.3	0.1	0.0464	0.3	0.1	0.0473

Table 3. Univariate relationship between free sialic acid and clinical, biochemical and anthropometric characteristics of the study groups (n=59).

	Free Sialic Acid		
Variable	β	Standard Error	p
Group (prediabetic group yes)	-0.0494	0.0358	0.1738
Gender (men)	0.0613	0.0357	0.0915
Cholesterol (mg/dL)	0.0008	0.0005	0.1109
Triglyceride (mg/dL)	0.001	0.0004	0.0088
LDL cholesterol (mg/dL)	0.0013	0.0005	0.0118
Triglyceride/HDL ratio (mg/dL)	0.0317	0.0136	0.0230
Creatinine (mmol/L)	0.3175	0.1188	0.0098

Table 4.Multiple regression models for total sialic acid, bound sialic acid and free sialic acid inthe study groups (n =59).

	Total Sialic Acid		Bound Sialic Acid		Free Sialic Acid	
	β	*p*	β	*p*	β	*p*
Prediabetes (Yes)	11.9	<0.0001	12.0	<0.0001	- 0.04	0.1591
C reactive protein (mg/L)	1.1	0.0267	1.1	0.0275	-	-
Total proteins (g/dL)	8.1	0.0017	8.1	0.0017	-	-
Aspartate aminotransferase (IU/dL)	0.4	0.0230	0.4	0.0238	-	-
Cholesterol (mg/dL)	-	-	-	-	-0.002	0.0028
Triglycerides (mg/dL)	-	-	-	-	0.001	0.0001
LDL-Choleterol (mg/dL)	-	-	-	-	0.0031	0.0012
Creatinine (mmol/L)	-	-	-	-	0.3	0.0007

DISCUSSION

In this study, prediabetes was detected in 15.9% of 176adults who participated as the source group. Similar results were reported from a cross-sectional study on Mexican adult population (Ureña-Bogarín EL et al, 2015).

Some studies have shown increased TSA in subjects with IGT (Gavella M et al, 2003). However, studies on the relationship between TSA fractions and prediabetes are scarce (Rajappa M et al, 2013). Data from the present study showed significantly increased serum TSA and BSA concentrations in subjects with prediabetes, compared to control subjects. The lack of differences in FSA concentrations between groups suggests this fraction of sialic acid does not contribute to the increase of TSA.In addition, a direct association between BSA and prediabetes was also demonstrated.

In this context, Rajappa et al. 2013 showed that BSA is elevated in non-diabetic obese subjects, and concluded that BSA levels are associated with insulin resistance and obesity. An association between BSA and prediabetes was not found (Rajappa M et al, 2013). This is important because when analyzing data using the ADA, 2015 criteria in the aforementioned study, it wasobserved that several individuals had altered fasting plasma glucose.

As elevation in serum sialic acid occurs in low-grade systemic inflammation, the increment of acute phase proteins would be associated with BSAlevelsin subjects with prediabetes. In human beings the most derivative (90%) sialic acid is linked to globulins (Carter A et al, 1962) in the form of BSA. Accordingly, in our study asignificant rise inCRPin subjects with prediabetes was observed when compared to control subjects. These results are similar to those reported by (Sabanayagam et al.2011), who demonstrated that CRP levels are associated with prediabetes.Also, in the presentstudyonlythe subjects with prediabetes showed CRP levels above the low risk referent of 1 mg/L (Pearson TA et al, 2003), which suggest they have a higher risk for chronic subclinical inflammation than control subjects.

Differences in CRP concentrations between subjects with prediabetes and controlsubjects could be associated to the increased sialic acid concentrations, due to the fact that CRP is part of the acute-phase response. Since CRP is a non-glycosylated protein (Schultz DR, Arnold PI, 1990) and sialic acid is bound to most acute-phase glycoproteins (Sillanaukee P et al, 1999), differences in concentrations of CRP in the current study could partiallyexplain the rise of BSA levels in subjectswith prediabetes.

In the present work, the association between sialic acid concentration andprediabetes proved to be independent ofCRP levels.It has been reported that, compared to CRP, TSA is a more robust inflammatory marker and a better predictor of metabolic-associated inflammation (Browning et al. 2004). An explanation could be that CRP is subject to greater individual variation. Furthermore, serum TS Amay reflect the global acute-phase responseproduced by the increased synthesis of glycoproteins (Pepys MB, 2003) whereas CRP represents the response of only one protein that is not sialylated (Pepys MB, 2003).

At the same time,subjectswith prediabetes had higher HOMA-IR than controls.However, HOMA-IR was not independently associated with sialic acidlevels.In contrast, (Browning et al. 2004) demonstrated that TSA was directly associated with insulin resistance and BMI but also with dislypidemia and the hypertensive state of patients with metabolic syndrome. This discrepancycould be explained by the fact that subjects and controls in our study had similar BMI, waist circumference, and blood pressure.

In conclusion, the present studyshowed increased TSA and BSA levels in Mexican adults with newly diagnosed prediabetes. Increased TSA relied on the increment of BSA, and both TSA and BSA were associated with prediabetes independently of the CRPlevel. Further research is required to elucidate the reason for the increased BSA levels in subjects with prediabetes. Since BSA may increase as a result of an increased acute-phase response, additional studies are required to look for alterations inother hepatic glycoproteins, besides CRP. Overall, the results and the evidence created from this study may be considered reliable from the point of view of its design. However it has the limitation of the relatively low number of participants. Therefore, further studies are needed to support this evidence.

Conflicts of interest

No potential conflicts of interest relevant to this article were reported.

M. C. Candia-Plata designed the study, oversaw the conduct of the study, conducted the clinical and biochemical assessment, wrote the paper, and is the guarantor. A.L. Mata-Pineda and H. Valdez-Salazarrecruited subjects and conducted clinical assessment. Also A.L. Mata-Pineda performed the anthropometric and biochemical measurements. M.L. González-Félix assisted the study and writing the manuscript. J. Esparza-Romero, G. Alvarez and E. Valencia assisted the design of the study and carried out the statistical analysis and contributed to writing the paper. The authors thank the patients who volunteered to participate in this study.

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