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Caribbean female patients with type 2 diabetes mellitus have lower serum levels of adiponectin than nondiabetic subjects

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ABSTRACT

Background: Previous studies in other populations suggest that low levels of serum adiponectin may be a cardiovascular risk factor. We aimed to determine the baseline concentration of serum adiponectin and its relationship with selected biochemical risk factors for coronary artery disease (CAD) in a cross-section of Caribbean patients with type 2 diabetes.

Methods: Anthropometric indices and fasting plasma concentrations of glucose, insulin, adiponectin, triglyceride, and total and HDL cholesterol were measured in 56 type 2 diabetic patients and 33 nondiabetic subjects. Insulin resistance (IR) was determined using the homeostatic model assessment (HOMA) method.

Results: Consistent with previous reports, Caribbean type 2 diabetic patients had significantly lower fasting serum adiponectin levels and higher mean levels of glucose, triglyceride and IR than the nondiabetic subjects (all, $p<0.01$). The nondiabetic female subjects had significantly higher serum adiponectin levels than did the female diabetics or nondiabetic males ($p<0.01$). Serum adiponectin level was negatively correlated with triglyceride or LDL cholesterol and positively related with HDL cholesterol among nondiabetic subjects, and the latter relationship persisted after adjusting for the effects of age, sex and BMI ($r=0.70$, $p<0.01$).

Conclusion: Similar to reports from other populations, Caribbean patients with type 2 diabetes, particularly the females, have lower levels of serum adiponectin than their nondiabetic counterparts and this is an additional CVD risk factor for the patients.

INTRODUCTION

Trinidad and Tobago is a multiethnic population compromising mainly peoples of African (40.8%) and East Indian (40.7%) origin.[1] While the prevalence of type 2 diabetes mellitus is higher in people of East Indian descent, the people of African origin had a higher prevalence rate of hypertension.[2,3] Recent reports from Trinidad and Tobago have shown increased risk of cardiovascular disease (CVD) among type 2 diabetic patients at the primary care setting;[4-6] this was thought to be related to poor postprandial hyperglycaemic control especially after consuming some ethnic carbohydrate foods.[7,8] The high CVD risk in this population has also been reported in other developing countries undergoing socioeconomic transformations such as Taiwan,[9] Mexico,[10] and countries in the Arabian Gulf.[11,12]

Thus, studies are warranted to identify modifiable and nonmodifiable CVD risk factors that may have accounted for its recent increase in developing countries. For example, although nonmodifiable, low serum concentration of the newly identified adipose tissue derived cytokine, adiponectin, has been shown to increase the risk of developing diabetes in both Japanese and Pima Indian populations.[13,14] Similarly, other studies in Caucasian and Pima Indian populations have shown that patients with type 2 diabetes and/or obesity have low serum concentrations of adiponectin.[15] Thus, given that low serum adiponectin level is now considered a CVD risk factor,[16-18] type 2 diabetic patients with low concentrations of this protein would have increased risk of developing premature arteriosclerosis. We therefore considered it important to determine the baseline concentration of adiponectin in this population where a cross-section of diabetic patients has previously been shown to

have increased risk of CVD.[4-6] Furthermore, this study is warranted considering a recent report from this population, which showed significant relationships between serum adiponectin levels and selected biochemical risk factors for developing diabetes in the offspring of patients with type 2 diabetes.[19] It is believed that the determination of the baseline value of this important adipocytokine in patients at increased risk for CVD would assist in early identification and management of the patients with high propensity of developing heart disease.

SUBJECTS AND METHODS

The recruitment strategies for diabetic and nondiabetic subjects were the same as has recently been published.[7,8] Briefly, type 2 diabetic patients were recruited from a database of 244 type 2 diabetic patients. The patients were randomly contacted by telephone and the study protocol and objectives of the study were thoroughly explained to them. Patients who expressed interest in participating in the study were required to visit our laboratory for registration and signing of the consent forms. The nondiabetic subjects were recruited through posters and flyers. Interested persons were required to contact our laboratory for thorough explanations of the study protocol and objectives and to perform a standard oral glucose tolerance test (OGTT), which was compulsory to exclude healthy subjects who might have undiagnosed diabetes. Thus, after collecting a fasting blood sample each nondiabetic subject consumed 75 g of anhydrous glucose (Cow & Gate Glucose, Nutricia, Rokkeveenseweg 49, Zoetermeer, the Netherlands) dissolved in 250 ml of water and a blood sample was collected at 120 minutes. Subjects with fasting and two-hour postprandial plasma glucose >7.0 and 11.1 mmol/l respectively were excluded from the study.[20]

Study protocol

The study protocol was reviewed and approved by our institutional Ethics Review Committee. All subjects were studied in our laboratory the morning after an overnight (12 to 14 hour) fast. During the visit, details of ethnic origin and age were directly ascertained from the subjects and recorded. Then, waist (cm), at the level of the umbilicus with the patient standing and breathing normally, and hip circumferences (cm), at the level of the largest projection of the buttocks, were obtained by tape measure while weight (kg), with standard hospital scales, and height (m), with a metal rule, were measured (in light clothing, without shoes). Then a fasting blood sample was collected from each subject. The blood samples were preserved in fluoride oxalate and plain tubes and plasma and serum specimens, respectively, were removed after centrifugation within 30 minutes of collection and stored at -20°C.

Biochemical analysis

Plasma glucose and serum triglyceride (TG), total cholesterol (TC) and high-density lipoprotein (HDL) cholesterol were measured in multichannel auto-analysers using dry slide kits (Johnson & Johnson Vitros 250, Ortho-Clinical Diagnostics Inc., Rochester NY 14626, USA) while low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation.[21] HbA_{1c} was determined using a nonenzymatic reaction kit for DCA 2000 (Bayer Corp., Elkhart, IN 46515, USA). The serum insulin (Mercodia AB, Sylveniusgatan 8A, SE-754 50 Uppsala, Sweden) and adiponectin (B-Bridge International, Inc, BioCat GmbH, Im Neuenheimer Feld 581, 69120 Heidelberg, Germany) levels were determined by enzyme linked immunoabsorbent assay (ELISA). The intra- and inter-assay coefficients of variation for insulin were 3.7 and 6.4%, respectively.

Statistics and calculations

The results are expressed as mean ± SE. The Statistical Package for the Social Sciences (SPSS Inc., 233 South Wacker Drive, Chicago IL 60606-6307, USA) software was used in all analyses. Insulin resistance (IR), defined as the product of fasting serum insulin and plasma glucose divided by 22.5, was assessed using fasting serum insulin and plasma glucose concentrations in homeostasis model assessment (HOMA).[22] Comparisons of the mean differences in biochemical parameters between diabetic and nondiabetic subjects were performed using Students' t-tests while χ^2 was used for nonparametric tests. The relationships between adiponectin and selected biochemical parameters were explored using Pearson's correlation technique. Multiple linear regression analysis was employed to determine the influence of age, sex, BMI, waist circumference, ethnicity and diabetes status on serum levels of adiponectin. A p value <0.05 was considered statistically significant on two-tailed testing for all analysis.

RESULTS

Table 1 shows the background characteristics of the diabetic and nondiabetic subjects studied. The diabetic patients were older than nondiabetic control subjects. Although both groups had similar body mass indexes, the diabetic patients had significantly higher waist circumference ($p<0.05$, *table 1*). The diabetic patients had significantly lower fasting serum adiponectin levels and higher mean levels of HbA_{1c}, glucose, triglyceride and HOMA-derived insulin resistance (IR) than the nondiabetic subjects ($p<0.01$, *table 2*). The nondiabetic female subjects had significantly higher mean serum adiponectin levels than did diabetic females or nondiabetic males ($p<0.01$, *table 2*). However, serum adiponectin levels did not differ between subjects of African and East Indian origin irrespective of gender (data not

Table 1
Clinical characteristics and anthropometric indices of the diabetic and nondiabetic subjects studied

CHARACTERISTICS	DIABETIC PATIENTS N=56	NONDIABETIC SUBJECTS N=33
Male/female ratio	23/33	11/22
Drinkers of alcoholic beverages‡ (%)	30 (53.6)	15 (46.9)
Cigarette smokers (%)	6 (10.7)	2 (6.3)
Ethnicity		
African origin (%)	23 (41.1)	15 (45.5)
East-Indian origin (%)	33 (58.9)	18 (54.5)
Diabetes management		
Diet/exercise (%)	2 (3.6)	-
Tablets/insulin‡ (%)	14 (25.9)	-
Tablets (metformin, sulphonylurea or combination therapy) (%)	40 (71.4)	-
Age (years)	55.5 ± 1.1*	50.1 ± 1.9
Weight (kg)	77.6 ± 2.3	73.8 ± 2.2
Body mass index (kg/m²)	29.5 ± 0.8	27.4 ± 0.8
Waist circumference (cm)	100.1 ± 1.8*	93.8 ± 1.8

**p<0.05 for comparisons between the healthy control subjects and the patients; ‡units of alcohol or insulin was not ascertained.*

Table 2
Baseline serum adiponectin levels and some selected biochemical parameters in all subjects, and in male and female diabetic and nondiabetic subjects

	DIABETIC SUBJECTS			NONDIABETIC SUBJECTS		
	ALL	MALES	FEMALES	ALL	MALES	FEMALES
Age (years)	55.5 ± 1.1	58.3 ± 1.7‡	53.5 ± 1.4	50.1 ± 1.9‡	52.2 ± 3.3	49.1 ± 2.4
Body mass index (kg/m²)	29.5 ± 0.8	26.4 ± 0.7‡	31.6 ± 1.1*	27.4 ± 0.8	26.1 ± 0.9	28.1 ± 1.1
Adiponectin (µg/ml)	5.2 ± 0.5	4.9 ± 0.9	5.3 ± 0.6**	10.4 ± 1.4‡‡	4.5 ± 0.7	12.8 ± 1.7‡‡
Insulin (mU/l)	13.3 ± 2.4	16.3 ± 5.3	11.1 ± 1.8	8.5 ± 1.3	7.1 ± 1.5	9.2 ± 1.8
Glucose (mmol/l)	8.7 ± 0.5	7.9 ± 0.7	9.3 ± 0.6	5.5 ± 0.1‡‡	5.7 ± 0.2	5.5 ± 0.1
Glycated haemoglobin (%)	8.7 ± 0.5	8.1 ± 0.3‡	9.1 ± 0.4	5.6 ± 0.1‡‡	5.5 ± 0.2	5.6 ± 0.1
Triglyceride (mmol/l)	1.8 ± 0.1	2.0 ± 0.3	1.7 ± 0.2**	1.3 ± 0.1‡	1.9 ± 0.4	1.1 ± 0.01‡
HDL cholesterol (mmol/l)	1.5 ± 0.01	1.4 ± 0.1	1.6 ± 0.1	1.6 ± 0.01	1.3 ± 0.1	1.7 ± 0.1
LDL cholesterol (mmol/l)	3.3 ± 0.2	3.3 ± 0.3	3.4 ± 0.2	3.0 ± 0.2	3.6 ± 0.2	2.8 ± 0.2‡
Total cholesterol (mmol/l)	5.2 ± 0.2	5.1 ± 0.3	5.3 ± 0.2	4.9 ± 0.2	5.3 ± 0.2	4.7 ± 0.2
Insulin resistance (pmol/mmol/l)	37.8 ± 6.9	41.3 ± 15.5	35.4 ± 5.0**	15.5 ± 2.6‡‡	13.3 ± 3.3	16.7 ± 3.6

**p<0.05 and **p<0.01 for within gender (diabetic females vs nondiabetic females) comparisons; ‡p<0.05 and ‡‡p<0.01 for all, and between gender (male vs female) comparisons in both diabetic and nondiabetic groups.*

shown). There was a significant inverse relationship between adiponectin and triglyceride or LDL cholesterol in nondiabetic subjects but not in diabetic patients. Again, a significant positive correlation was observed between adiponectin levels and HDL cholesterol in nondiabetic subjects, but not in diabetic patients, and the relationship persisted after adjusting for the effects of age, sex and BMI (r = 0.70, p<0.01, *table 3*). However, multiple linear regression analysis suggests that sex, BMI and diabetes status are the major determinants of serum adiponectin levels in the subjects studied (*table 4*).

DISCUSSION

The present study has shown that in a Caribbean population (i) serum adiponectin levels are lower in type 2 diabetic patients than in nondiabetic subjects, (ii) serum adiponectin

Table 3

Relationship between adiponectin and selected biochemical variables before and after controlling (partial correlation) for age, sex and BMI in diabetic and nondiabetic subjects

	DIABETIC PATIENTS N=56		NONDIABETIC SUBJECTS N=33	
ADIPONECTIN (MG/ML) VS	BIVARIATE CORRELATION	PARTIAL CORRELATION	BIVARIATE CORRELATION	PARTIAL CORRELATION
Insulin (mU/ml)	-0.23	-0.17	-0.16	-0.25
Glucose (mmol/l)	-0.11	-0.03	0.02	0.14
Triglyceride (mmol/l)	-0.26	-0.23	-0.39*	-0.20
HDL cholesterol (mmol/l)	0.07	-0.03	0.67**	0.70**
LDL cholesterol (mmol/l)	-0.08	-0.04	-0.47**	-0.37
Insulin resistance (pmol/mmol/l)	-0.26	-0.21	-0.16	-0.23
Body mass index (kg/m²)	-0.21	-	0.05	-

**p<0.05 and **p<0.01 for levels of significance of correlation coefficient at two-tailed testing.*

Table 4

Multiple linear regression analysis showing the influence of independent variables (age, sex, ethnicity, BMI, waist circumference and diabetes status) on serum adiponectin levels in all subjects, and diabetic and nondiabetic subjects studied

	ALL SUBJECTS N=89		NONDIABETIC SUBJECTS N=33		DIABETIC PATIENTS N=56	
	B-COEFFICIENT	SE	B-COEFFICIENT	SE	B-COEFFICIENT	SE
Age	0.1	0.07	0.17	0.13	0.14	0.07
Sex	0.33**	1.41	0.48*	3.29	0.29	1.18
Ethnic group	-0.14	1.2	-0.13	2.75	-0.15	1.06
Body mass index	-0.29	0.24	0.05	0.53	-0.78*	0.20
Waist circumference	0.11	0.1	-0.13	0.23	0.50	0.08
Diabetes status	0.38**	1.28	_	_	_	_

**p<0.05 and **p<0.01 for levels of significance of β-coefficient at 2-tailed testing. SE = standard error.*

level has a significant positive relationship with HDL cholesterol in nondiabetic subjects but not in diabetic patients, (iii) nondiabetic females had higher levels of serum adiponectin than did diabetic females or nondiabetic males. The implications of these findings in diabetes management in this population are further discussed.

The finding of lower serum adiponectin levels in type 2 diabetic patients (particularly female subjects) in comparison with nondiabetic subjects is absolutely consistent with previous reports from other populations.[15,23] A possible explanation for the observed differences in serum adiponectin levels might be related to the levels of fasting insulin and insulin resistance. Indeed, the diabetic patients have higher basal insulin and HOMA-derived insulin resistance levels, and a previous report has shown that adiponectin levels were suppressed below basal levels in both diabetic and nondiabetic subjects during hyperinsulinaemic euglycaemic clamp study.[24] Again, the comparatively higher waist circumference, an index of abdominal obesity and intra-abdominal fat deposition,[25,26] among the type 2 diabetic patients might have contributed to the lower serum adiponectin levels given that plasma adiponectin concentration decreases with increasing adiposity.[27] Interestingly, multiple linear regression analysis of the current data suggested that body mass index, but not waist circumference, is a significant determinant of serum adiponectin levels in the diabetic patients. Indeed, the female diabetic patients that constituted the majority of patients (59%) had higher BMIs than female nondiabetic subjects. It should be noted that in this population, patients of East Indian origin have higher prevalence of diabetes[2,3] and are at greater risk of CVD than patients of African descent.[4-6] However, univariate analysis of the current data (not shown) did not indicate any differences in the serum adiponectin levels of the patients of the two ethnic groups irrespective of gender. Indeed, multiple linear regression analysis confirmed that ethnicity is not a cofounder in serum adiponectin levels in this study (*table 4*).

Several previous studies have shown that plasma adiponectin is positively related to HDL-cholesterol levels and maybe protective against CVD.[16-18] Thus, the findings of the present study agreed with the previous observation at least among the nondiabetic subjects where the observed relationship between serum adiponectin levels and HDL cholesterol was not influenced by age, sex or BMI on partial correlation. Interestingly, the present finding in the nondiabetic subjects is consistent with a recent report in Caribbean subjects with and without positive family history of diabetes.[19] However, the finding that the relationship between serum adiponectin level and HDL cholesterol in type 2 diabetic patients was not significant in this study is not completely clear and is in contrast to previous reports where strong relationships between plasma adiponectin and HDL-cholesterol levels were documented.[16-18] Perhaps it is important to note that diabetes is a disorder of metabolic function, meaning that the anti-inflammatory and antiatherogenic activities of adiponectin are not restricted to its relationship with HDL cholesterol, hence certain activities of adiponectin are independent of HDL-cholesterol levels.[28,29] Indeed, experimental cell studies, for example, have shown that adiponectin is involved in modulating nuclear factor-kB signalling through a CAMP-dependent pathway and also act as an endogenous regulator of endothelial cells in response to inflammatory stimuli.[30,31] The finding of gender-related differences in plasma adiponectin concentration has previously been reported in Japanese diabetic patients without coronary artery disease.[23] Similarly, other studies in nondiabetic subjects in Japanese, Caribbean, North American and Canadian populations have shown that women have higher adiponectin levels than men.[19,32-34] Other workers have speculated that sex hormones such as oestrogen, progesterone and androgen might have an affect on plasma adiponectin levels.[23] It should, however, be noted that previous studies where sexual dimorphism in adiponectin concentration have been reported included postmenopausal[23,34] and premenopausal[19] women indicating that the reported differences may not be entirely related to the possible effect of sex hormones. It is therefore suggested that further studies aimed at addressing sexual dimorphism in plasma adiponectin levels and its role in insulin and glucose metabolism are warranted.

We acknowledge that the type 2 diabetic patients studied here might have included patients with latent atherosclerotic vascular diseases considering that diabetic patients with coronary artery disease are often asymptomatic.[23] Although none of the patients reported or admitted a case of CAD, the patients were not clinically examined for CAD and the presence of latent atherosclerotic disorder would worsen the plasma adiponectin levels among the diabetic patients, especially the males.[34] This limitation notwithstanding, our findings are consistent with previous reports from other populations. Thus, we conclude that Caribbean patients with type 2 diabetes, particularly the females, have lower levels of serum adiponectin than their nondiabetic counterparts or male subjects, and this is an additional CVD risk factor for the patients.

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