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Correlation of global risk assessment with cardiovascular complications in patients with diabetes mellitus living in Puerto Rico

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ABSTRACT

Objective: The objective of this study was to assess the current relationship between certain demographics and chemical factors, and the risk of cardiovascular complications, within a Puerto Rican population with diabetes mellitus.

Research design and methods: A total of 2075 patients with diabetes mellitus were retrospectively evaluated to determine the influence of certain demographics and chemical variables on the appearance of cardiovascular complications. A group of demographic and laboratory variables were analyzed. Our sample was obtained, based on convenience, from an endocrinologist's office in an area of about 250 000 people. All the patients met the American Diabetes Association (ADA) definitions for diabetes mellitus. The study covered a time period of 8 years. The patients signed an informed consent document at their first office visit. Data were obtained by the endocrinologist in charge.

Results: We considered the demographic variables of sex, age, time with diabetes, lipid profile, metabolic control (measured with glycated hemoglobin levels), and microalbumin renal excretion. Cardiovascular complications were more prevalent in patients with poor metabolic control, those with prolonged disease duration, men, and patients who were more than 50 years of age. We found no relationship between cardiovascular disease, systolic blood pressure over 130 mm Hg, body mass index and low-density lipoprotein cholesterol levels over 100 mg/dL.

Conclusions: In Puerto Rican patients with diabetes mellitus, there is a statistically significant relationship between patient's gender, age, disease duration, glycemic control and increased kidney microalbumin excretion with cardiovascular complications.

Key messages

- This study retrospectively evaluated the effect of demographic and chemical variables on cardiovascular complications in a Puerto Rican population with diabetes mellitus.
- Poor metabolic control, prolonged disease duration, male gender and age >50 years were associated with cardiovascular complications.
- Cardiovascular disease was not associated with systolic blood pressure >130 mm Hg, body mass index and low-density lipoprotein cholesterol levels >100 mg/dL.

INTRODUCTION

Diabetes mellitus is one of the most prevalent chronic diseases in Puerto Rico (PR). In 2013, the prevalence of this disease in individuals over 18 years of age was estimated at 14.9% among Puerto Ricans, with an equal gender distribution, using data from the 'Behavioral Risk Factors Surveillance Systems' (BRFSS).[1] The importance of this disease, however, does not lie in its high prevalence rate but rather in the chronic complications and their high mortality rates among Puerto Ricans. Diabetes mellitus has been the third cause of death in PR for the past 20 years, exceeded only by cardiovascular disease (CVD) and cancer.[2]

Findings in previous epidemiological analyses[3] point to disease duration, uncontrolled blood sugar levels measured with the glycated hemoglobin (HbA1c) test, high systolic blood pressure and urine albumin over 30 mg/dL as possible risk factors for chronic complications. Arterial hypertension contributes to the appearance of microangiopathic and macroangiopathic complications in the population with diabetes mellitus.[4] Although changes in the large arterial vessels are not specific to individuals with diabetes mellitus, hypertension contributes to their appearance at an earlier age.

Data from the Chronic Disease Centers in Atlanta report prevalence of 42.3% for arterial hypertension and of 38.5% for hypercholesterolemia in PR for 2013.[5] The estimated figures for Puerto Rican patients with diabetes mellitus for the year 2010 were 72% for arterial hypertension and 51% for hypercholesterolemia.[6]

In this study, we provide data from a selected population with diabetes mellitus

and analyzed the possible association of certain demographic variables and chemical tests with cardiovascular (CV) complications.

Sample and procedure

We retrospectively analyzed the medical data of patients who had visited the office of an endocrinologist with the diagnosis of diabetes mellitus. From these records we selected 2075 patients with type 1 and 2 diabetes with more than two visits to the physician's office. All the patients included in this study met the diagnostic criteria for diabetes mellitus established by the American Diabetes Association.[7] These patients represent a sample from an area with a population of around 250 000 people, predominantly Caucasian, Hispanic and Black. The time period covered was 8 years (2001–2009). Each participant contributed to the study data at different times, because patients' follow-up visits depended solely on their treatment regimen.

Measures

At every visit, patients were given a physical examination, which included blood pressure, weight and body mass index (BMI) measurements, and a review of the diagnostic tests ordered. Blood pressure was obtained using a sphygmomanometer after 10 min rest in the sitting position, and with the right arm perpendicular to the body. The BMI was calculated using the formula BMI=weight (kg)/body area (m^2). Patient's height was measured while the patient was barefoot.

The data analysis took into account the data obtained from all visits, and the data obtained at the moment of, or nearest to, the debut of the chronic diabetes complication, to assess risk. To determine vascular involvement, we considered the patient's history of CVD, active or chronic cardiac disease, peripheral arterial disease measured by the ankle-brachial index (ABI) or clinical disease (intermittent claudication). Participants with hypertension were identified based on self-reported use of blood pressure-lowering drugs by patients and subsequent verification of the prescribed drug label verification by the physician, or diagnosed by the attending physician during follow-up visits.

Variables such as age, disease duration, weight (BMI), gender, arterial blood pressure, lipids (including non-high-density lipoprotein (non-HDL) cholesterol), glycemic control defined by HbA1c (<7%) and urine albumin excretion (over 30 mg/dL) were analyzed. The prevalence of chronic complications of diabetes was estimated using data from encounters at which the health complication was first detected.

The variables considered in this work were as follows. Two demographic measures were employed in the current analyses: (a) age (18–50, 51–60, 61–70 and >70) and (b) gender: male or female. The number of years with diabetes, (<5, 5–15 and >15), was calculated from the time of diagnosis with diabetes until the time CV complications developed.

Patient history: Different follow-up tests were analyzed, including (a) BMI: ≤24.9, 25–29.9 and ≥30 kg/m^2; (b) systolic blood pressure; (c) diastolic blood pressure; (d) urine microalbumin test; (e) glycemic control defined by HbA1c level and (f) lipids (including non-HDL cholesterol). The pulse pressure was calculated by subtracting the diastolic blood pressure from the systolic blood pressure value. Low-density lipoprotein (LDL) cholesterol level was calculated using the formula: (total cholesterol)—(HDL cholesterol)—(triglycerides×0.20), and was categorized as either >100 or ≤99 mg/dL. Non-HDL cholesterol was calculated by subtracting HDL cholesterol from total cholesterol levels. HDL cholesterol was categorized taking into account gender differences. Low HDL cholesterol is defined as levels of <40 mg/dL for men and <50 mg/dL for women. High HDL cholesterol is defined as levels ≥40 mg/dL for men and ≥50 mg/dL for women. Blood and urine samples were tested by commercial laboratories certified by the Puerto Rico Department of Health and by the Clinical Laboratories Improvement Act (CLIA). Blood and urine test values are presented in milligrams per deciliter (mg/dL).

Statistical analysis

All data management and statistical analyses were performed using the SPSS V.18. Univariate analyses were carried out to describe the overall characteristics of the sample population. For bivariate analysis, χ^2 analysis was used as the measure of association. Finally, multiple logistic regression analyses were used to determine which factors were associated with self-reported CV complications. Multivariate analyses were adjusted for sex, years with diabetes, BMI and pulse pressure. Adjusted ORs and 95% CIs were calculated and reported. Significance level for all analysis was established at $p<0.05$. Interaction, subpopulation analysis and different approaches for pressure indicators and lipid results were conducted but no significant differences were found. Goodness-of-fit was estimated for the final regression model using the Hosmer-Lemeshow test.[8]

RESULTS

Table 1 shows frequencies and proportions for the sociodemographic characteristics, risk factors and chemical laboratory results in the study population. Results show that 54% of the participants were women; 82% were aged >50; more than three-fourths were overweight or obese; and 30% had a pulse pressure >60 mmHg. CVD was diagnosed in 14% of the subjects, with a greater prevalence in men than in women. Patient's average number of visits was 7.8 (data not shown). CV complications were more common in patients over 50 years of age (14.9 vs 2.9), those with disease duration of more than 5 years, those with microalbumin excretion over 30 µg/dL, and those with HbA1c levels >7%. No significant statistical relationship was found when we analyzed

Table 1 Distribution of sample characteristics and association with cardiovascular disease (n=2075)

Characteristics	Total n=2075 (%)	Cardiovascular disease n (%) Yes 293 (14.1)	No 1782 (85.9)	OR (95% CI) p Value
Sex*				
Female	1119 (53.9)	118 (10.5)	1001 (89.5)	—
Male	956 (46.1)	175 (18.3)	781 (81.7)	1.90 (1.48 to 2.44) 0.000
Age (years)*				
18–50	376 (18.1)	11 (2.9)	365 (97.1)	—
51–70	1139 (54.9)		969 (85.1)	5.82 (3.13 to 10.84) 0.000
>70	560 (27.0)	170 (14.9)	448 (80.0)	8.30 (4.40 to 15.65)
Mean (SD)	62.1 (12.8)	112 (20.0)		0.000
Years with diabetes*				
<5	705 (34.0)	59 (8.4)	646 (91.6)	—
5–15	925 (44.6)	123 (13.3)	802 (86.7)	1.68 (1.21 to 2.33) 0.002
>15	445 (21.4)	111 (24.9)	334 (75.1)	3.64 (2.58 to 5.12) 0.000
Mean (SD)	9.9 (8.8)			
BMI (kg/m^2)				
≤24.9	288 (13.9)	46 (16.0)	242 (84.0)	—
25–29.9	827 (39.9)	127 (15.4)	700 (84.6)	0.95 (0.66 to 1.38) 0.804
≥30	960 (46.3)	120 (12.5)	840 (87.5)	0.75 (0.52 to 1.09) 0.129
Mean (SD)	30.0 (5.76)			
Systolic blood pressure†				
≤130	1195 (57.6)	182 (15.2)	1013 (84.8)	—
131–140	366 (17.6)	51 (13.9)	315 (86.1)	0.90 (0.64 to 1.26) 0.543
>140	514 (24.8)	60 (11.7)	454 (88.3)	0.74 (0.54 to 1.00) 0.054
Mean (SD)	132.4 (19.3)			
Diastolic blood pressure†				
<80	1103 (53.2)	142 (12.9)	961 (87.1)	—
80–90	790 (38.1)	126 (15.9)	664 (84.1)	1.28 (0.99 to 1.67) 0.059
>90	182 (8.8)	25 (13.7)	157 (86.3)	1.08 (0.68 to 1.70) 0.749
Mean (SD)	75.0 (9.8)			
Pulse pressure†				
10–60	1456 (70.2)	217 (14.9)	1239 (85.1)	—
>60	619 (29.8)	76 (12.3)	543 (87.7)	0.79 (0.60 to 1.06) 0.117
Mean (SD)	57.4 (18.22)			
Total cholesterol†, ‡				
<200	913 (73.5)	141 (15.4)	772 (84.6)	—
≥200	330 (26.5)	53 (16.1)	277 (83.9)	1.05 (0.74 to 1.48) 0.791
Mean (SD)	177.6 (45.9)			
HDL cholesterol†, ‡, §				
Low HDL	1185 (96.1)	178 (15.0)	1007 (85.0)	—
High HDL	48 (3.9)	9 (18.8)	39 (81.3)	1.31 (0.62 to 2.74) 0.481
Mean (SD)	4.2 (13.3)			

Continued

Table 1 Continued

Characteristics	Total n=2075 (%)	Cardiovascular disease n (%) Yes 293 (14.1)	No 1782 (85.9)	OR (95% CI) p Value
LDL cholesterol†, ‡				
<100	40 (3.2)	7 (17.5)	33 (82.5)	—
≥100	1193 (96.8)	180 (15.1)	1013 (84.9)	0.84 (0.37 to 1.92) 0.676
Mean (SD)	680.9 (371.8)			
Non-HDL†, ‡				
<130	185 (15.0)	24 (13.0)	161 (87.0)	—
≥130	1048 (85.0)	163 (15.6)	885 (84.4)	1.24 (0.78 to 1.96) 0.368
Mean (SD)	173.4 (46.8)			
Triglyceride†, ‡, ¶				
<150	1227 (99.2)	189 (15.4)	1038 (84.6)	—
≥150	10 (0.8)	1 (10.0)	9 (90.0)	0.61 (0.08 to 4.85) 1.000
Mean (SD)	4.97 (23.0)			
Urine microalbumin*, †				
≤30	541 (81.0)	48 (8.9)	493 (91.0)	—
>30	127 (19.0)	29 (22.8)	98 (77.2)	3.04 (1.83 to 5.06) 0.000
Mean (SD)	36.5 (148.8)			
HbA1c (%)*				
<7	822 (47.3)	65 (7.9)	757 (92.1)	—
≥7	915 (52.7)	158 (17.3)	757 (82.7)	2.4 (1.80 to 3.30) 0.000
Mean (SD)	7.6 (1.8)			

*p value <0.05.
†The units are mg/dL.
‡Sample size variation due to missing data.
§Low HDL cholesterol: males <40; females <50; high HDL cholesterol: males ≥40; females ≥50.
¶Expected count <5. Fisher's exact test used.
BMI, body mass index; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

systolic blood pressure or LDL cholesterol levels in patients with and without CV complications.

In the laboratory report analysis, we found that among the 1826 patients for whom a lipids report was available, 17.5% had LDL cholesterol levels at goal. No statistical differences were observed between patients with and without CV complications in the group with high LDL cholesterol. Similar results were observed in the HDL and non-HDL cholesterol patient groups.

With respect to microalbumin levels, a statistically significant difference was observed in the association between patients with values below and those with values over 30 µg/dL of microalbumin renal excretion, and the emergence of CV complication (OR of 3.04, p value <0.05).

Analysis of HbA1c reports also revealed a statistically significant difference in the association between the groups with HbA1c levels below and over 7%, and CV complications. In this population, the odds of developing CV complications increased when HbA1c was >7% (OR=2.4, p value <0.05).

Table 1 also includes bivariate logistic regression analyses describing the association between CV and sociodemographic characteristics, risk factors and chemical laboratory results. Unadjusted ORs show that associations with CV were found for gender, age, years with diabetes, urine microalbumin and HbA1c. The odds of having CV increased with age (participants between 51 and 70 years of age had six-fold higher odds of developing CV, and the odds increased eight-fold for participants >70 years old). Participants with diabetes mellitus for more than 15 years had 3.5-fold higher odds of developing CV than did people with diabetes mellitus for <5 years. With respect to chemical laboratory results, the odds of having CV were three times higher in participants with microalbuminuria than in individuals with normal levels of microalbumin. Compared with participants with low levels of HbA1c, participants with high levels of HbA1c had odds of more than two of having CV.

Table 2 shows the results from multiple logistic regression analysis. Analyses were conducted for variables that were theoretically important and those found to be associated with CV. Different models are presented to measure the effect of different predictors when entered. For model 1 (controlling for BMI, pulse

pressure and HDL cholesterol), the odds of men having CV were more than 1.5-fold higher than for women. The odds of having CV for participants who had diabetes for 5–15 years were 1.5-fold higher than participants with disease duration of <5 years. In participants who had diabetes for more than 15 years, the odds were >2.5-fold compared with participants who had the condition for <5 years. For a 1-unit increase of HbA1c levels, we expected a 21% increase in the odds of having CV.

In model 2 (controlling for sex, years with diabetes, BMI, pulse pressure, HDL cholesterol and HbA1c), the odds of participants having CV were 2.5-fold greater in participants with microalbuminuria than in persons with normal levels of microalbumin renal excretion (≤30 mg/dL).

DISCUSSION

Diabetes mellitus and arterial hypertension are two highly prevalent health conditions in the US and Puerto Rican population.[1] Both are more frequent after the age of 50 and, therefore, are frequently identified as concomitant conditions. Arterial hypertension occurs concurrently with diabetes mellitus in 62% of the cases.[1] From previous studies, we know that systolic hypertension increases the risks of retinopathy, nephropathy, vasculopathy and neuropathy in patients with diabetes.[8 9] Epidemiological studies indicate that blood pressure >120 mm Hg is associated with an increase in CV events and death in patients with diabetes.[9] The ADVANCE Collaborative Group found a 38% increase in macrovascular complications in patients with type 2 diabetes mellitus.[10]

On the other hand, other reports show no benefit of lowering systolic blood pressure to under 130 mm Hg,[11] although we must point out that bringing arterial pressure values down to normal in patients with diabetes mellitus and hypertension increases the cost and the risk of undesirable events.

In the UK Prospective Diabetes Study (UKPDS) study, it was found that the risk of having microangiopathy decreased in 37% among patients whose arterial blood pressure was treated intensively.[4] Systolic blood pressure went down to 144/83 mm Hg in the group taking captopril and to 143/81 mm Hg in the atenolol group. Both groups showed similar incidence of retinopathy (31% vs 37%). The same study showed a similar decrease in CV risk in the group receiving intensive treatment (with a reduction of only 1 and 2 mm Hg in systolic and diastolic blood pressures).

The Appropriate Blood Pressure Control in Diabetes (ABCD) trial[12] did not find any difference between the intensive treatment groups and the moderate treatment groups. In both groups, blood pressure went down to 132/78 mm Hg (intensive treatment) and to 138/76 mm Hg (moderate treatment). The impact of arterial blood pressure in patients with diabetes mellitus with hypertension was also evaluated by Cooper-DeHoff *et al*.[13] This analysis demonstrated that strict control (systolic blood pressure <130 mm Hg) in patients with diabetes mellitus and coronary artery disease was not related to better CV outcomes when compared with the non-control group (systolic blood pressure >140 mm Hg).

In this analysis, we found that the time living with diabetes is a strong risk factor for the development of macrovascular complications as well as HbA1c, with a cut-off value of 130 mm Hg for systolic blood pressure and 7% for HbA1c. This means that long-term diabetes control, as measured by HbA1c level, is a strong predictor of CV complications accompanying diabetes mellitus. Data from the Framingham Heart Study,[14] showed a 1.38-fold increased risk for CV events for every 10 years of diabetes duration.

Arterial hypertension was more prevalent among women (60%); however, CV complications were 1.5-fold more prevalent in men than in women (18% vs 10.5%). We found higher levels of HDL cholesterol among women, and this can explain the lower prevalence of CV complications. Estrogen has long been advocated as a

Table 2 Adjusted ORs, 95% CI, and p values for CV (n=2705)

	Adjusted OR (95% CI) p Value	
Covariates	**Model 1**	**Model 2**
Sex		
Female	—	—
Male	1.72 (1.21 to 2.45) 0.002	1.62 (0.86 to 3.04) 0.134
Years with diabetes		
<5	—	—
5–15	1.55 (0.99 to 2.45) 0.057	1.74 (0.78 to 3.86) 0.174
>15	2.52 (1.55 to 4.11) 0.000	1.99 (0.81 to 4.91) 0.134
BMI (kg/m^2)		
≤24.9	—	—
25–29.9	0.85 (0.49 to 1.46) 0.553	1.28 (0.45 to 3.62) 0.647
≥30	0.76 (0.44 to 1.30) 0.316	0.97 (0.35 to 2.73) 0.955
Pulse pressure (mmHG)		
≤60	—	—
>60	0.84 (0.56 to 1.24) 0.377	1.26 (0.63 to 2.51) 0.511
HDL cholesterol		
Low HDL	—	—
High HDL	1.60 (0.70 to 3.62) 0.262	2.17 (0.48 to 9.8) 0.315
HbA1c (%)	1.21 (1.11 to 1.31) 0.000	1.16 (0.99 to 1.35) 0.062
Urine microalbumin (mcg/dL)		
≤30		—
>30		2.46 (1.24 to 4.88) 0.010

BMI, body mass index; CV, cardiovascular; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein.

protective factor against CVD in women. Nevertheless, results from the Women's Health Initiative (WHI) trial,[15] as well as those from our study are against this assumption, since most of our female participants were going through menopause.

After the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, the role of HbA1c in the genesis of CV events was degraded, and there was doubt of whether tight glycemic control would have a major impact on diabetes-related CV events. Prospective population studies such as the EPIC-Norfolk study suggest that HbA1c concentration can explain the high prevalence of CV events in men. It is not clear how aggressively HbA1c levels should be reduced in order to reduce the risk of CV events in people with type 2 diabetes who are at particularly high risk for a CV event.[16] In our analysis we observed that there is strong relationship between high levels of HbA1c and CV complications in diabetes mellitus. We cannot set a cut-off point, but for a 1-unit increase in HbA1c over 7%, we expect a 21% increase in the odds of having a CV event.

Normally, the endothelium is not permeable to albumin molecules. In patients with diabetes mellitus, the presence of small amounts of albumin (microalbumin) is an indicator of renal (or endothelial) disease, and of increased CV mortality in this population. There is no doubt that this is one of the most important markers of vascular damage. Albuminuria seems to be an independent and strong predictor of CVD. We found in our analysis that microalbumin kidney excretion levels are strongly correlated (2.5-fold increase) with CVD.

It is important to note that our population received appropriate treatment for their comorbid conditions during the study, thereby causing a possible risk underestimation. We must take into account the fact that the first event could have occurred before entering the study, and that the patient had not been receiving antihypertensive treatment at the time of developing the complication, but was receiving such treatment by the time of the endocrinologist's visit.

In addition, lipid calculations were made in a population that was receiving lipid treatment in 86% of the cases; therefore, risk calculations were performed using treatment-altered lipid data. Only the HDL cholesterol variable can be considered valid, since this value is not greatly altered by the statin therapy used to lower LDL cholesterol. In the case of non-HDL cholesterol, we can assume that values over 130 mg/dL can be used as valid, but not those <130 mg/dL because these values are altered by the use of statins. Taking this as a valid base, we found that non-HDL cholesterol does not have a statistically significant effect in the genesis of CV complications in patients with diabetes.

We must point out that our participants were attended by different specialists for the treatment of their health conditions who were not necessarily located at endocrinologist clinics. This could cause an underestimation due to loss of information and patients lost during follow-up.

In spite of these limitations, this study provides information pertinent to the relationship between systolic blood pressure and CV complications in patients with diabetes mellitus. Metabolic control appears to be more important in the genesis of the atherosclerotic process in the Puerto Rican population. If we consider the atherosclerotic process as an inflammatory one, medication that reduces endothelium inflammatory process (ACE inhibitors, statins) should be our first line of therapy when dealing with patients with diabetes mellitus. To prevent chronic complications in diabetes, we should maintain the variables that account for the metabolic process to levels as normal as possible.

Collaborators Migdalia Rodríguez-Chacón and José J Ruiz Valcarcel.

Contributors ER-V wrote the manuscript and researched data. JJRV performed statistical analysis and reviewed/edited the manuscript. MR-C contributed to the discussion and reviewed/edited the manuscript.

Competing interests None declared.

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