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Geriatric Syndromes and Not Cardiovascular Risk Factors are Associated with Cognitive Impairment among Mexican Community-Dwelling Elderly with Type 2 Diabetes

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ABSTRACT

Background: The association of cognitive impairment and type 2 diabetes has been consistently shown in several studies, yet its association with geriatric syndromes has not been fully explored. **Objective:** To study the correlates of cognitive impairment among community-dwelling elderly with type 2 diabetes. **Methods:** Cross-sectional study of 135 diabetic persons aged 70 years or older participating in the Coyoacán Cohort Study in Mexico City. Baseline data included chronic illnesses, geriatric syndromes, and diabetes-related variables. The lowest quartile in both the Mini-Mental State Examination and the Isaacs Set Test, according to age and schooling, was used to identify participants with cognitive impairment. Multivariate logistic regression analyses were used to identify the correlates of cognitive impairment. **Results:** Mean age of participants was 77.7 ± 5.8 years. The prevalence of cognitive impairment was 14.1%. Univariate logistic regression analyses showed that diabetic nephropathy, depression symptoms, falls, and frailty were associated with cognitive impairment. Multivariate logistic regression analyses showed that urinary incontinence and frailty were independently associated with cognitive impairment. Cardiovascular risk factors and diabetes-related variables did not show significant association to cognitive impairment. **Conclusions:** Geriatric syndromes, but not cardiovascular risk factors, were independently associated with cognitive impairment among diabetic elderlies. Intentional evaluation of these conditions may be important to improve management of the elderly patient with type 2 diabetes and cognitive impairment. (REV INVES CLIN. 2017;69:166-72)

Key words: Geriatric syndrome. Cognitive impairment. Frailty. Urinary incontinence. Diabetes.

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INTRODUCTION

Type 2 diabetes mellitus (DM) is a significant public health burden worldwide, particularly in countries under epidemiological transition[1-3]. Care and management in elderly DM patients is complicated, especially given the simultaneous presence of comorbidity and geriatric syndromes. Of special importance is cognitive impairment (CIM), which is associated with reduced self-care and monitoring of DM as well as higher hospitalization records, among others[3]. The association between DM and CIM has been persistently reported in several studies. In comparison with non-diabetic populations, those with DM have more frequent cognitive impairment[4,5]. In addition, factors such as long evolution of DM, elevated HbA1c levels, or history of insulin treatment are considered risk factors for the development of CIM. Previous work has demonstrated that Mexican-American participants with DM had a greater risk of dementia and CIM in comparison with non-diabetic participants[6-8]. Similarly, DM patients also have a higher risk of geriatric conditions, including dementia, disability, falls, and urinary incontinence[9]. Despite the large evidence supporting these associations, the relation of geriatric conditions with the presence of CIM in DM patients is still largely unknown; furthermore, previous work suggests that cardiovascular risk factors have a more established role in association with CIM[10]. Therefore, this study aimed to determine the geriatric and cardiovascular correlates of CIM among community dwelling elderly diabetics.

METHODS

Study population

This is a cross-sectional analysis of a subset of participants from the Coyoacán Cohort, an observational study conducted in Mexico City. Specific details for the design of this study have been published elsewhere[10]. Briefly, to be eligible for recruitment, participants had to meet the following criteria: age 70 years or older, established residence in Coyoacán, not being institutionalized, and being registered at the Food Support, Medical Care and Free Drugs Program, which is a government program that includes 95% of the community dwelling elderly (≥ 70 years of age) in Mexico City. The first phase was composed of a face-to-face interview during which a wide range of information was collected, including self-reported data regarding sociodemographic characteristics, general health-related information, medication use, oral health (self-reported and clinically evaluated), and mental health. Each participant underwent a comprehensive geriatric assessment that included physical performance tests, cognitive tests, and nutrition and medical assessment as well. The Human Research Local Ethics Committee approved all proceedings regarding this study.

Sample

Patients with type 2 DM were selected from the Coyoacán Cohort and included in this study. Diabetes was defined as the self-report of previously diagnosed DM or self-report of taking DM medications. All considered participants underwent a Mini-Mental State Examination (MMSE) and a semantic verbal fluency test (Isaacs Set Test, IST). Cognitive impairment was defined as a score below the 25th percentile for this specific population, according to age and schooling in both tests, without functional impairment[10]. Patients who only completed either the MMSE or the IST were excluded from the study; no significant differences were found between patients included and excluded from the analysis.

Definition of potential correlates

Participants were categorized as "frail" if they fulfilled three or more frailty criteria; otherwise if they fulfilled one or two, they were considered to be pre-frail or non-frail if none[11]:

– Unintentional weight loss of 5 kg or more in the last 12 months;

– Exhaustion was assessed by the positive answer to two questions from the Center for Epidemiologic Studies-Depression scale (CES-D) :"I felt that everything I did was an effort" and "I could not get going";

– Low physical activity was defined according to the lowest quintile (adjusted by sex) on the Physical Activity Scale for the Elderly questionnaire (PASE);

– Slowness was defined if participants answered "yes" or "can't do" to any of the following two questions: Because of a health problem, "do you have difficulty

walking one block?" or alternatively, "Do you have difficulty with climbing several flights of stairs without resting?"; and

– Weakness was determined among participants who answered "yes" to the question, "Because of a health problem, do you have difficulty with lifting or carrying objects weighting over 5 kg, like a heavy bag of groceries?".

These definitions have previously been validated for this population[12].

Fall syndrome was defined as having > 2 fall episodes in the previous 12 months[13].

Depressive symptoms were determined when participants had a Geriatric Depression Scale score > 5 (15-item version)[14].

Polypharmacy was defined as taking > 3 different medications at the time of the study[15].

Urinary incontinence, visual deficit, myocardial infarction, stroke, hypertension, hypercholesterolemia, hypertriglyceridemia, osteoporosis, and smoking were determined by the self-report of each entity and considered individually as binary outcomes.

For diabetes-related variables, duration of DM from diagnosis in years as well as age at diagnosis were each individually assessed; self-report of diabetic nephropathy and diabetic retinopathy was assessed independently and then combined under "Any microvascular complications" for purposes of the analysis. Previous history of insulin use was treated as a binary variable according to self-report by the patient. Macrovascular complications include self-report of diabetic foot or peripheral vascular disease.

Body mass index (BMI; weight/height^2) was also calculated and included as a correlate.

Sociodemographic variables included age (years), sex, and schooling (education grade).

Statistical analysis

Characteristics of participants were described using arithmetic means and standard deviations (SD) or frequencies and proportions where appropriate. The following statistical procedures were used according to analyzed variables: chi-squared test for qualitative variables, Student *t*-test, and the *U* of Mann-Whitney tests were used where applicable for quantitative variables. In order to develop an explanatory model for CIM, we fitted multivariate logistic regression models, including several variable-blocks: sociodemographic variables, diabetes-related variables, cardiovascular risk factors, and geriatric conditions. Wald tests were used to eliminate from every model those variables judged not significant at the 20% level, and then the variables considered significantly associated with CIM were retained. Secondly, a new model including the variables significantly associated with CIM from previous models was run and the cut-off level at this time was 5% in order to select a set of variables to be included in a last full model. All comparisons were evaluated using 95% confidence intervals (CI) and the Nagelkerke R^2 was also reported. Statistical analyses were performed in SPSS software for Windows® (SPSS Inc., Chicago, IL, version 19.0).

RESULTS

The study sample included 135 participants. Mean age was 77.7 years (SD: 5.8) and 54.1% were female. Mean age of DM onset was 62.4 years (SD: 12.5), with a mean DM duration of 14.7 years (SD: 11.3), 19.3% were using insulin treatment, and 57% reported having at least one microvascular complication (28.1% diabetic nephropathy and 44.1% diabetic retinopathy). Of the participants, 18% had urinary incontinence, 46.7% had at least two falls in the last year, 20% reported depressive symptoms, 14% were frail, and 57.8% reported currently taking > 3 medications. Only 19 participants (14.1%) had CIM.

Table 1 presents the comparative analysis between participants according to the presence or absence of CIM. In comparison to subjects without CIM, those cognitively impaired had more diabetic nephropathy ($p = 0.014$) or the presence of any microvascular complication ($p = 0.046$), falls ($p = 0.047$), depressive symptoms ($p = 0.013$), and frailty ($p = 0.011$). The frequency of cardiovascular risk factors, including myocardial infarction, stroke, systemic hypertension, and hypercholesterolemia were not different between groups.

Table 1. Comparative analysis among participants without or with cognitive impairment

Variable	Overall (n = 135)	Without cognitive impairment (n = 116) (%)	With cognitive impairment (n = 19) (%)	p value
Women (%)	73 (54.1)	63 (54.3)	10 (52.9)	0.892
Age (Mean ± SD)	77.7 ± 5.8	77.7 ± 5.7	77.5 ± 7.1	0.414
Years of schooling (Median ± IQR)	6.0 ± 4.0	5.0 ± 4.0	6.0 ± 2.5	0.849
BMI (Mean ± SD)	26.3 ± 4.4	26.9 ± 4.3	24.6 ± 4.3	0.073
Myocardial infarction	15 (11.1%)	12 (10.3)	3 (15.8)	0.444
Stroke	14 (10.4)	12 (10.3)	2 (10.5)	0.999
Systemic hypertension	85 (63.0)	74 (63.3)	11 (57.9)	0.618
Hypercholesterolemia	58 (43.0)	51 (44)	7 (36.8)	0.561
Hypertriglyceridemia	35 (25.9)	19 (25)	6 (31.6)	0.544
Smoking	65 (48.1)	56 (48.3)	9 (47.4)	0.942
Osteoporosis	20 (14.8)	17 (14.7)	3 (15.8)	0.999
Previous diabetes treatment	127 (94.1)	111 (95.7)	16 (84.3)	0.084
Age at onset (Mean ± SD)	62.4 ± 12.3	62.6 ± 12.7	61.5 ± 11.3	0.742
Years of T2D duration (Mean ± SD)	14.7 ± 11.3	14.6 ± 11.2	15.5 ± 12.3	0.714
Insulin use	23 (19.3)	19 (18.6)	4 (23.5)	0.494
Diabetic nephropathy	38 (28.1)	28 (24.1)	10 (52.6)	0.010
Diabetic retinopathy	60 (44.4)	50 (43.1)	10 (52.6)	0.438
Any microvascular complication	77 (57.0)	62 (53.4)	15 (78.9)	0.037
Vascular problems	58 (43.0)	48 (41.4)	10 (52.6)	0.358
Urinary incontinence	24 (18.0)	18 (15.7)	6 (33.3)	0.070
Visual deficit	34 (54.0)	31 (57.4)	3 (33.3)	0.280
Falls	63 (46.7)	50 (43.1)	13 (68.4)	0.040
Depression symptoms	27 (20.0)	19 (16.4)	8 (42.1)	0.009
Frailty	16 (14.0)	11 (10.6)	5 (50.0)	0.001
Polypharmacy	78 (57.8)	67 (57.8)	11 (57.9)	0.991

BMI: body mass index; IQR: interquartile range; SD: standard deviation; T2D: type 2 diabetes.

Table 2 presents the univariate logistic regression analyses of CIM. The models found that diabetic nephropathy (p = 0.014), having any microvascular complication (p = 0.046), previous falls (p = 0.047), depression symptoms (p = 0.013), and frailty (p = 0.011, pre-frailty was non-significant) were associated with CIM, whereas urinary incontinence did not reach statistical significance (p = 0.070). Conversely, variables such as previous history of myocardial infarction or stroke, hypercholesterolemia, hypertension, hypertriglyceridemia, or smoking were not associated with CIM.

However, the multivariate logistic regression model showed that only urinary incontinence (OR: 13.9; 95% CI: 2.12-80.84; p < 0.001) and frailty (OR: 4.2; 95% CI: 0.75-22.74; p = 0.019) were independently associated with CIM among DM participants (Table 3). The model explained 31% of the variability observed in the composite measure of CIM (R^2= 0.319).

Table 2. Univariate regression analysis of variables associated to cognitive impairment in type 2 diabetes participants

Variable	OR	95% CI	p value
BMI	0.89	0.79-1.01	0.077
Previous myocardial infarction	0.61	0.16-2.42	0.487
Previous stroke	0.98	0.20-4.77	0.981
Systemic hypertension	1.28	0.48-4.44	0.622
Hypercholesterolemia	1.34	0.49-3.66	0.562
Diabetic nephropathy	3.49	1.29-9.54	0.014
Any microvascular complication	3.27	1.02-10.44	0.046
Falls	2.86	1.02-8.05	0.047
Depression symptoms	3.71	1.32-10.45	0.013
Frailty	4.89	1.12-21.30	0.011
Polypharmacy	1.01	0.38-2.69	0.991
Urinary incontinence	2.69	0.90-8.11	0.078

BMI: body mass index; OR: odds ratio.

Table 3. Multivariate regression analysis of variables associated to cognitive impairment in type 2 diabetes participants

Model	Variable	OR (95% CI)	p value
1 R2 = 0.363	BMI	0.93 (0.74-1.17)	0.538
	Diabetic nephropathy	1.57 (0.25-9.70)	0.627
	Urinary incontinence	10.22 (1.52-68.82)	0.017
	Frailty	3.27 (0.38-28.38)	0.047
	Depression	1.21 (0.11-13.67)	0.879
	Falls	1.86 (0.30-11.39)	0.503
2 R2 = 0.313	Frailty	4.12 (0.75-22.74)	0.019
	Urinary incontinence	13.09 (2.12-80.84)	0.006

BMI: body mass index; OR: odds ratio.

DISCUSSION

In this sample of community dwelling diabetic elderly persons, urinary incontinence and frailty were independently associated with cognitive impairment. Given that the adequate management of elderly DM patients is dependent on their functional status, investigating the presence of cognitive decline and additional geriatric syndromes within this population is of the utmost importance.

A previous study in elderly Mexican Americans with DM reported that the prevalence of CIM, urinary incontinence, and individual components of the frailty syndrome (muscle strength, slowness) was lower, which contrasts with the data herein reported[16]. However, its definition of cognitive impairment could potentially overestimate the prevalence of CIM (MMSE scores), especially considering that the scores were not adjusted for confounders such as age and schooling in comparison to the present study.

The association of DM and CIM has been consistently shown in several studies; the reported associations suggest a potential role of vascular and non-vascular mechanisms for CIM in DM patients[17,18]. Although the mechanisms of cognitive dysfunction associated to DM are still unclear, combined neurological dysfunction, inflammation, hyperglycemia, insulin resistance, and vascular dysfunction have been proposed to be either causal or contributing elements to the development of both Alzheimer's disease and vascular dementia. Additionally, DM-associated microvascular complications, especially diabetic nephropathy and retinopathy, have also been linked to brain stroke and small-vessel disease associated with cognitive dysfunction[19,20].

The association of frailty with CIM has been described in other studies[21,22]; however, the association of frailty and CIM in elderly DM patients has not previously been reported. Avila-Funes, et al. proposed that frailty is a major risk factor for the development of cognitive impairment and a possible prodromal stage of vascular dementia[21]. This suggests that, despite the lack of association between the traditional cardiovascular risk factors and CIM in our study, the presence of frailty may account as a mechanism for vascular-mediated cognitive decline. It is important to consider that in other studies, DM has also been associated to an increase in the risk of frailty[23]; moreover, frail DM patients have an increased risk of complications when compared to patients with comorbidities[24-27]. These may play a role as potential confounders to the established association in our study.

Additionally, we show that urinar incontinence was also independently associated with CIM in DM patients; however, a causal link cannot be established to be precise on its association, given that DM is also a known risk factor for the development of urinary incontinence and the latter may already be present before CIM onset. A recent study suggests that biochemical measures, mainly hyperglycemia, are not independent predictors of the presence of urinary incontinence in DM patients[28]. Hsu, et al. investigated the association of risk factors related to the presence of urinary incontinence in elderly DM subjects[29]. They concluded that dependence on ambulation and transferring as well as the presence of CIM is associated with the presence of urinary incontinence in patients with DM, which is consistent with our findings.

Among the correlates that were associated, though not independently with CIM, microvascular complications are the most extensively studied. Despite evidence of microvascular complications leading to CIM, glucose control has not shown significant benefit on cognitive outcomes[19]. The ACCORD-MIND trial evaluated the cross-sectional and longitudinal association of diabetic retinopathy on cognitive function and brain volume, suggesting that retinal microvascular damage leads to decreased gray matter and cognitive function in diabetic patients, but is not necessarily predictive of vascular-mediated cognitive dysfunction[30]. Our results imply that microvascular complications, in particular diabetic nephropathy, are more frequent in patients with CIM, but their association is not independent. Additionally, microvascular complications are related to age of DM onset and years of DM exposure, both of which were not different between the group with and without CIM. The role of diabetic nephropathy has not been extensively studied and thus requires further longitudinal confirmation.

In DM patients, vascular complications are an important cause of morbidity, and individuals with cardiovascular risk factors are traditionally at higher risk. A large recent study[31] suggested that metabolic syndrome, central obesity, diabetes mellitus, and other cardiovascular risk factors were associated to incident mild cognitive impairment and dementia; however, this observation is true for patients under the age of 75 years as those included in the population of the study. In populations older than 75 years, such as the mean age of our population, the association of cardiovascular risk factors, including metabolic syndrome, dyslipidemia, central obesity, and hypertension with incident cognitive impairment, has been inconsistent[31-33]. This observation is also supported by the observation that carotid stiffness is associated with cognitive impairment in individuals with diabetes, but was not the mechanism of cognitive dysfunction[34]. In our study, we did not find a significant association of cardiovascular risk factors and cognitive impairment, as has been shown for individuals over 75 years. This suggests that CIM in DM patients is not exclusively vascular-mediated and implies that other factors, such as frailty and urinary incontinence, may contribute to the presence of CIM. Nonetheless, these associations must be confirmed in longitudinal follow-up.

Our study had some limitations. First, this study is a cross-sectional analysis, thus limiting our ability to establish causal associations because we lack the possibility to establish a temporal relation between variables. Furthermore, because only a subset of the studied population completed cognitive evaluation, our study population was reduced and the group with confirmed CIM was relatively small. However, no significant differences were found between the initial sampled group and the analyzed group. Additionally, because our model only explains 31% of the variability observed in CIM, other variables may contribute as correlates to CIM that were not included in the present model for this work. Subjects classified in the cognitive outcome were not assessed according to the standardized method for CIM. Instead, normative data for performance below the 25th percentile in both the MMSE and in IST were used to identify subjects with CIM. We consider that this global assessment is sufficient for the evaluated spectrum, but the results must be interpreted with caution. Nevertheless, the considered correlates have previously been defined or analyzed in other studies involving the Coyoacán cohort, which makes their definition consistent.

In conclusion, in this cohort of community-dwelling elderly, frailty and incontinence, but not cardiovascular risk factors, are associated with a higher frequency of CIM. Geriatric assessment is not usually sought out during a routine examination by an endocrinologist in an elderly patient with DM. Furthermore, given the strong links of DM and vascular complications, cardiovascular risk factors are classically attributed as the cause of CIM in this population, largely overlooking the effect of geriatric comorbidities. This suggests that the contribution of geriatric conditions to the presence CIM in DM patients should be further investigated. Intentional evaluation of these conditions might be of importance to improve patient care and management of the elderly patient with DM and cognitive decline.

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