Effect of Poor Glycemic Control Incognitive Performance Inthe Elderly With Type 2 Diabetes Mellitus: The Mexican Health and Aging Study

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Research article

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Abstract

Background

Cognitive impairment is twice more frequent in elderly with type 2 diabetes mellitus (DM). This study was conducted to determine the association between glycemic control and cognitive performance among community-dwelling elderly persons in Mexico.

Methods

Cross-sectional study conducted in individuals aged 60 years or elderly participating in the 2012 Mexican Health and Aging Study. Type 2 DM participants were classified in 3 groups according to their glycated hemoglobin levels (Hb_{A1c}): <7% (intensive control), 7-7.9% (standard control) or ≥ 8% (poor control), and cognitive performance: low (CCCE ≤ 44 points), intermediate (44.1-59.52 points), or high (≥ 59.53 points). Multinomial logistic regression models were constructed to determine this association.

Results

Out of 946 subjects, 216 were selected. Subjects in the low cognitive performance group were older (69.7 ± 6.6 vs 65.86 ± 5.18 years, p < .001) and had a lower educational level (2.5 ± 2.6 vs 7.44 ± 4.15 years, p < .000) when compared to the high cognitive performance participants. Hb_{A1c} ≥8% was associated with having low (OR 3.17, 95% CI 1.17–8.60, p = .024), and intermediate (OR 3.23, 95% CI 1.27–8.20, p = .014) cognitive performance; this trend was not found for Hb_{A1c} 7.0-7.9% group.

Conclusions

Glycemic control with a Hb_{A1c} ≥ 8% was associated with worse cognitive performance.

Background

Numerous reports have shown that patients with type 2 Diabetes Mellitus (DM) are at increased risk of Alzheimer's disease (AD) dementia and vascular dementia[1] An optimal glycemic control is needed to prevent or reduce type 2 DM complications such as nephropathy, retinopathy, neuropathy and cognitive disorder. The increasing prevalence of diabetes in the population will lead to a higher number of people with diabetes-related cognitive impairment. For this reason, efforts to control not only type 2 DM, but hypertension, depression and other risk factors are essential for dementia prevention around the world [2,3]. The Rotterdam study was one of the first population-based studies to examine the relationship between type 2 DM and cognitive impairment. It reported an increased risk of 1.9 (95% CI: 1.3–2.8) for this population [4]. It is currently accepted that worldwide type 2 DM increases 1.5 to 3 times the risk of

dementia [5]. In Mexico, a longitudinal study which included data from the Mexican Health and Aging Study (MHAS) reported a relative risk for cognitive impairment of 2.08 (95% CI: 1.59–2.73) among type 2 DM in elderly [6]. Also, cognitive impairment has been detected as early as 5 years after the initial diagnosis type 2 DM [7].

Although, epidemiologic studies have associated poor type 2 DM control with cognitive decline, clinical evidence about glycemic control goals for type 2 DM in elderly is contradictory and lacking. For instance, excessive control of glycemia using insulin has been associated with increased risk of hypoglycemia and worse cognition than in patient with less strict control [8]. The American Diabetes Association (ADA) 2019 guidelines suggest a reasonable glycated hemoglobin (Hb_{A1c}) goal of < 7% for most patients and a less stringent < 8% for those with limited life expectancy or multiple comorbid conditions [9, 10]. The American Geriatric Society (AGS) recommends a Hb_{A1c} goal < 7.5% for healthy population; while for the complex or comorbid and functional-dependent patient the aim should be a Hb_{A1c} of < 8% [11]. According to these guidelines, Hb_{A1c} goals are based on two variables, which must be considered before a decision: cognitive and functional status. Thus, in both guidelines Hb_{A1c} goal recommendation is < 8% for subjects with mild to moderate cognitive impairment [9,10,11].

Guideline recommendations are based mostly on results from the ACCORD-MIND study, which has been the most influential when concerning glycemic goals. Participants (aged 55–80 years) with higher Hb_{A1c} levels (> 7.5%) were randomly assigned to an intensive treatment goal (Hb_{A1c} < 6.0%) or a standard strategy (Hb_{A1c}: 7.0-7.9). In this trial, authors found no difference when comparing cognitive outcomes between groups, establishing a greater amplitude of therapy goal for patients [12]. Under our impression, ADA 2019 guideline recommendations on a Hb_{A1c} goal below or greater than 8% are lacking on making a clear reference on the risk of adverse effects and cognitive impairment progression.

This study could provide different insights towards the appraisal of cognitive impairment through knowledge of type 2 DM, one of its main risk factors. The aim of the present study was to determine the association between glycemic control and cognitive performance among Mexican rural and urban community-dwelling older adults analyzed in the MHAS round 2012.

Methods

Study Population

Data was obtained from the MHAS, alarge, national representative panel study of older Mexicans (age 50 orolder) and their spouses. Briefly, the aim and design of MHAShas to evaluate its participants' health and cognitive characteristics. The study started in 2001 and has four follow-ups (2003, 2012, 2015 and 2018). Information from a subsample of subjects who participated in 2012 wave was used for the present study. Data was assessed through performance test, anthropometric measures and blood

samples; included HbA_{1c}, among others. [13,14]. Additional information can be found at: http://www.mhasweb.org/[15].

Sample selection

The 2012-MHAS follow-up included 15,723 subjects (aged 50 or older). For the present study, those aged 60 or older with complete cognitive test information(7,469 subjects) were selected; further, available Hb_{A1c} biomarker measurements was required (946 subjects).

Type 2 DM was considered when a positive answer was given to the following question: “Has a doctor ever told or given you a diabetes mellitus diagnosis?”. Also, these subjects had a $Hb_{A1c} \geq 6.5\%$.

Participants included (946 subjects) were classified into 4 mutually exclusive groups according to their blood Hb_{A1c} levels: 141 (14.9%) were considered as healthy (Hb_{A1c}: <5.5%), 407 (43%) with prediabetes (Hb_{A1c}: 5.5-6.4%), 182 (19.2%) had undiagnosed DM ($Hb_{A1c} \geq 6.5\%$) and 216 (22.8%) with DM **(Figure 1)**.

Glycemic Control

Glycemic control was established with the data available in the MHAS database section I, it consists of a single measurement of Hb_{A1c} was measured in the MHAS with the A1c-now test kit, an immunoassay device. This method in comparison to the standard liquid chromatography test has a sensitivity of 91.9% to 100%, and a specificity of 66.7 to 82.4% [16]. Of note,pre-prandial capillary glucose was not available for the analysis.Glycemic control categories were defined based on the cut-off points used in the ADA and ACCORD-MIND studies [9,12]. The following glycemic control groups were defined: intensive (Hb_{A1c}<7%), standard (Hb_{A1c} 7-7.9%), and poor ($Hb_{A1c} \geq 8\%$).

Cognitive Performance

In order to determine the cognitive status, all participants underwent the Cross-Cultural Cognitive Examination (CCCE). The CCCE has a sensitivity and specificity of 99% and 94%, respectively, for detection of dementia [17]. It has the advantage that it isn’t influenced by level of education, language or culture. The CCCE has a score of 0-99 points. Different cognitive domains such as orientation, verbal learning and recall, visual scanning, visuospatial abilities, visual memory, verbal fluency, and numeracy sum up to a total score [18]. In order to determine the association between cognitive performance level and glycemic control and as a strategy for the abnormal distribution of the data, the total CCCE score was classified by tertiles where the highest represents a better cognitive performance and vice versa. Therefore, cognitive performance was defined as low (CCCE ≤44 points), intermediate (44.1-59.52 points), and high (≥59.53 points).

Covariables

Age, sex and level of education were the only sociodemographic variables analyzed. Participants' positive responses to the questions: "Has a doctor ever told you that you have ... [i.e. smoking history, alcoholism, hypertension, cerebrovascular disease (CVD), and ischemic heart disease (IHD), were considered as for the subjects' clinical characteristics.Obesity was considered when the subject's body mass index (BMI) was ≥30 kg/m^2[19]. Further, five cardiovascular comorbidities or categoric variables were grouped as a compound or sum in order to construct a continuous variable. The presence of hypertension, smoking history, CVD, obesity or previous heart disease added one point each to the comorbidity score. A score of 5 represents the highest level of cardiovascular morbidity, while 0 equals no comorbidity.

Depressive symptoms were measured with a 9-item questionnaire previously validated in the MHAS. A positive response to each individual question, adds one point to the total score. A score of 0 represents to depressive symptoms, while 9, the maximum score, equals a high depressive symptom burden [20]. Blood pressure and heart rate measurements, as well as C-reactive protein, total cholesterol, high density cholesterol (HDL), thyroid stimulating hormone (TSH), and vitamin D levels were also analyzed.

Statistical Analysis

Results

From a total of 946 participants, the mean age was 68.11 (± 6.4) years, 57.9% were female, and the mean education level was 4.72 (± 3.9) years. Type 2 DM participants also had a high prevalence of hypertension (69%) and IHD (7.9%). Obesity was reported in 40% of the participants. Smoking history was present in 9.7% and alcohol history in 18.1%. The mean score for depressive symptoms was 4.76 (± 1.9) points. Mean Hb_{A1c} blood level value was 8.34 ± 2.05%. When divided by glycemic control groups, no differences were found in any of the variables analyzed **(Table 1)**.

As shown in **Table 2**, the 216 participants with type 2 DM were classified as having low (35.1%), intermediate (31.4%) or high (33.3%) cognitive dysfunctions. Subjects in the lower cognitive performance group were older (69.7 ± 6.6 years vs 65.86 ± 5.18 $p < .001$) and had a lower educational level (2.5 ± 2.6 years vs 7.44 ± 4.15; $p < .000$) when compared to the high cognitive performance participants. No significant differences between the three groups were found for any of the other clinical variables, except for alcoholism, which was more frequent in the intermediate cognitive performance group (27.9%, $p = .023$).

When compared to the intensive glycemic control group those with poor glycemic control had a borderline association with worse cognitive performance in the unadjusted regression model. After adjusting for confounding variables, the multinomial regression analysis showed that the presence of Hb_{A1c} ≥8% (poor glycemic control) was associated with low (Odds Ratio (OR) 3.17, 95% CI = 1.17–8.60, $p = .024$), and intermediate (OR 3.23, 95% CI = 1.27–8.20, $p = .014$) cognitive performance. This trend was not found for the standard glycemic control (Hb_{A1c} 7-7.9%) (**Table 3**).

Discussion

In our study of community-dwelling older Mexican adults with type 2 DM, a poor glycemic control (Hb_{A1c} ≥ 8%) was associated with worse cognitive performance when compared to intensive control group. The uncontrolled type 2 DM group had a positive association with overall low cognitive performance, while the standard controlled population (Hb_{A1c} 7-7.9%) did not show an association.

A high Hb_{A1c} level (> 10%) is associated with an increased risk of all type dementia (HR 1.20, 95% CI 1.07–1.35) [21]. However, studies that analyze glycemic control, specifically, Hb_{A1c} levels ≥ 8% and their association with cognitive performance, are scarce. After a sub-analysis, a US prospective study of 5,099 participants showed an association between Hb_{A1c} levels (≥ 8% and 7-7.9%) and mild cognitive impairment (MCI) measured by proxy (Hazzard Risk (HR) 1.89, CI 95% 1.14–3.14, $p < 0.05$ and HR 1.65, CI 95% 1.13–2.42, $p < 0.01$, respectively) in an older adult population [22]. Our results support these association, as an Hb_{A1c} ≥8% was associated with worse cognitive performance.

Multiple studies have identified that an intensive vs a standard glycemic treatment had no beneficial or detrimental effects on cognition [12,23,24]. As previously mentioned in the ACCORD-MIND study, a North American randomized trial, there were no differences on cognitive outcomes when an intensive (Hb_{A1c} < 6.0%) or a standard (Hb_{A1c} 7.0-7.9%) glycemic control was used in 2,977 participants after 40-week treatment [12]. We were not able to find an association between standard glycemic control (Hb_{A1c} 7-7.9%) and low cognitive performance, supporting the previously reported analysis.

Several studies have evaluated the impact of type 2 DM on cognition; however, methodological differences are noted [25]. Data from the English Longitudinal Study of Ageing (ELSA) showed in 5,189 participants, a longitudinal association between Hb_{A1c} levels and a rate of change in cognitive scores, where 1 mmol/mol increment in Hb_{A1c} was significantly associated with increased rate of decline in global cognitive z scores (-0.0009 SD/ year, 95% CI -0.0014, -0.003, p 0.002) [26]. Our study provides an association of glycemic control levels and global cognitive performance supporting the data mentioned above; unlike other studies, additional specific Hb_{A1c} goals are analyzed and type 2 DM is not taken as a single entity.

After several studies of diabetes and cognitive impairment, authors have gone as far as proposing the possibility of type 3 of DM. Chronic hyperglycemia contributes to conditions such as inflammation, accumulation of advanced glycation end products, and oxidative stress, which in turn lead to cognitive impairment [27]. Studies have shown that persons with DM experience a progressive cognitive decline, particularly characterized by a lower psychomotor speed and alterations in cognitive domains such as attention and executive function [28]. Disruption in glucose metabolism leads to lower cognitive dysfunctions through different mechanisms; a) GLUT transporter altered sensitivity, b) insulin resistance, and c) vascular dysfunction. Chronic hyperglycemia is a phenomenon that inhibits brain autoregulation since GLUT transporters diminish their function in order to protect neurons from an increased glucose

influx. When glucose is restored to a normal level, GLUT transporters fail to recover, causing an absence of intraneuronal glucose in a process called neuroglycopenia [29]. Insulin resistance could lead to apoptosis by disruption of a secondary pathway; insulin receptor phosphorylation which disrupts long term potentiation, thus increasing inflammation and generating oxidative stress [30]. Vascular homeostasis is also affected by type 2 DM. The presence of atherosclerotic plaques, endothelial dysfunction, increased shear stress, inflammation, impaired vasodilation, and increased vasoconstriction, are some of the mechanisms that lead to vascular injury. The theories presented above, often converge into a type 3 DM diagnosis [31,32].

The combination of factors seen in the type 2 DM population (hypertense, obese, IHD) mirrors the population's clinical characteristics that physicians are set to treat in the present and near future. As type 2 DM control is one of the strongest modifiable comorbidities that affect brain function, hypertension and obesity are equally relevant risk factors to target. Since currently there are no therapies to cure dementia, the treatment of modifiable risk factors should be emphasized [2,3].

Some other factors may impact the glycemic control in older adults. In our study, type 2 DM participants with low cognitive performance were older and had a lower educational level. Studies have shown that age is the most important and non-reversible risk factor for the development of cognitive dysfunctions [33]. In elderly adults, pharmacologic management with multiple drugs leads to a low treatment adherence, given a higher number of side effects. Besides, non-pharmacologic treatments such as a diet and lifestyle interventions are generally less effective, since the modification of eating and physical activity habits is usually a difficult task [34,35]. Education has previously been described as a protective factor for cognitive impairment, as higher education allows the development of "cognitive reserve" and a lower educational level is associated with a 5.6 greater risk of dementia [36]. Also, a lower educational level could influence glycemic control. Adherence to treatment and lifestyle recommendations, disease complications, and awareness are some of the variables in which a lower educational level, over time, has a negative impact [37].

Our study has several limitations. The cross-sectional nature of this study is a major limitation for making cause-effect statements. Also, since the MHAS data was gathered through a survey, many subjects were excluded because there was a lack of biomarker availability. Regarding type 2 DM, diagnosis was limited to one Hb_{A1c} measurement. A history of duration in years and information on previous control strategies was not obtained. Nevertheless, our study has several strengths. The MHAS is a large representative sample of community older adults; considering that control of cognitive impairment risk factors is a primary prevention strategy that should be prioritized.

Conclusions

Our study shows a Hb_{A1c} value $\geq$ 8% in older adults with diabetes is associated with a worse cognitive performance.

Abbreviations

ACCORD-MIND The Memory in Diabetes (MIND) sub study of the Action to Control

Cardiovascular Risk in Diabetes (ACCORD)

ADA American Diabetes Association

CCCE Cross-Cultural Cognitive Examination

CVD Cerebrovascular disease

DM Diabetes Mellitus

ELSA English Longitudinal Study of Ageing

GLUT Glucose transporter

Hb_{A1c} Glycated Hemoglobin

HDL High Density Cholesterol

IHD Ischemic Heart Disease

MCI Mild Cognitive Impairment

MHAS Mexican Health and Aging Study

TSH Thyroid stimulating hormone

Declarations

Ethics Approval and consent to participate:

The Institutional Review Boards or Ethics Committees of the University of Texas Medical Branch in the United States, the Instituto Nacional de Estadística y Geografía, the Instituto Nacional de Salud Publica and the Instituto Nacional de Geriatría in Mexico approved the study. All study subjects signed an informed consent form.

Consent for publications:

All authoragree with the publication of the article.

Availability of data and materials:

The data reported in this manuscript are available within the article and/or its supplementary data. Additional data will be shared by request from any qualified investigator.

Competing interests:

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.There was no founding for this work, and we declare that there was no conflict of interest.

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Authors' contributions

AJMA, SGAN, and JGJC designed the study. AJBB and JGJC searched the literature. AJMA, SGAN, SGYC collected and analysed the data. MUPZ, JAAF y SGAN interpreted the data. JGJC and SGYC wrote the manuscript draft. All authors (AJMA, JGJC, SGYC, AJBB, MUPZ, JAAF, SGAN)revised the manuscript and approved it for submission.

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