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ORIGINAL RESEARCH

DIABETES STATUS IS ASSOCIATED WITH POOR COGNITIVE PERFORMACE IN SAUDI POPULATION AT HIGH METABOLIC RISK

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Abstract: *Objective:* Previous studies have shown that Diabetes mellitus (DM) is associated with an increased risk of cognitive impairment, but little data is available on Arabic populations, inspite of their remarkably high prevalence of DM. In this study we attempt to study the effect of DM on cognitive performance in middle-aged and elderly patients. *Design:* Observational cross sectional study. *Setting:* Outpatient clinics in King Abdulaziz University Hospital (KAUH) in Jeddah, Saudi Arabia. *Participants:* The study included 241 volunteers aged 59.6 ± 9.2 years; 171 outpatients with DM, matched with 70 controls without. *Measurements:* Volunteers underwent cognitive assessment using the Montreal Cognitive Assessment Test (MoCA) and the Rowland Universal Dementia Assessment Scale (RUDAS). *Results:* RUDAS score was poorer in diabetics (25,25 ± 2,78 vs. 26,71 ± 2,57 in controls; p<0.0001) who are more likely to have cognitive impairment 16% , than those who are not diabetics 3%; p=0.004. This association was confirmed in multivariate analyses and shown to be independent of female gender and low education level, all of which were associated with worse RUDAS cognitive score.The results were not significant when the MoCA was used, as 85 % of the cases and 78 % of the controls had abnormal results;p=0.194.Among diabetics, there was no statistically significant effect found for glycemic control or DM duration on either one of the tests.The prevalence of obesity was similar in the two groups with 63% in diabetics and 62% in controls. *Conclusion:* In our population with an alarming prevalence of obesity, diabetes was associated with poorer cognitive performance independent of female gender or low education level, drawing attention to this under-recognized problem of cognitive impairment that could result in significant health and social problems, particularly in areas with high diabetes prevalence. RUDAS was found to be a very reasonable and convenient test to assess cognition in our sample characterized by a low educational level.

Key words: Diabetes mellitus (DM), cognitive impairment, RUDAS, MoCA, Kingdom of Saudi Arabia (KSA).

Introduction

Diabetes Mellitus (DM) is a prevalent condition worldwide. However, the prevalence of DM in Saudi Arabia is alarmingly high, ranging from 18 to 30% (1, 2).

Moreover, the International Diabetes Federation (IDF) identified 6 countries of the Middle East and North Africa, including Saudi Arabia, among the world's ten highest countries in the prevalence of DM (3).

Previous studies have shown that diabetes is associated with an increased risk of cognitive impairment and the development of dementia (4, 5).

As life expectancy improves in Saudi Arabia (6), the Saudi elderly population is expected to grow resulting in unmasking of more of these age-related complications in the future.

However, most of the existing studies addressing relationship between diabetes and cognitive impairment have been conducted in industrial countries, while few or no data is available in emerging populations and Arabic populations. Moreover, the majority of studies were conducted in the elderly population, however it has been suggested that cognitive decline could begin in midlife in diabetic patients (7).

This study attempts to assess in a tertiary hospital-King Abdulaziz University Hospital (KAUH) in Jeddah, Saudi Arabia, the cognitive performance in middle-aged and elderly diabetic patients with comparison to matched controls.

Patients and methods

A cross sectional study was carried out from June to July 2012 in the outpatient department of King Abdulaziz University Hospital (KAUH), Jeddah, Kingdom of Saudi Arabia. This study included a total of 171 outpatients

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with diabetes, matched with 68 controls without.

The studied patients were consecutively recruited among patients who were approached while they waited for appointments at various hospital clinics. Data collection took place in the Internal medicine clinics.

Participants were included if they were aged ≥ 45 years and had signed an informed consent form. Subjects were excluded if they had documented dementia or in the case of absence of a hospital medical record number.

Volunteers underwent cognitive assessment using two validated tests: the Montreal Cognitive Assessment Test (MoCA), and the Rowland Universal Dementia Assessment Scale (RUDAS).

The Montreal Cognitive Assessment is a brief cognitive screening tool. A score of 30 is obtained when all answers are correct. The MoCA has been found to have a specificity of 87% and a sensitivity of 90-100%for detecting mild cognitive impairment (MCI) with a cutoff score of 26 (25 or below indicating impairment) (8).

The RUDAS is a six item screening test scored out of a total of 30 points. It assesses language, praxis, memory, judgment, construction and fluency. Performance on RUDAS has been shown to be affected by age, but not by education, gender or preferred language. The RUDAS dementia screening cut-off is a score of<23 which yields a specificity of 95.8% and a sensitivity of 81% (9).

Cognitive assessments were carried out by researchers who were trained by experienced geriatricians prior to the study period. Training of researchers took place over several weeks; through sessions in which the tests were explained and performed several times to ensure inter-rater and intra-rater reliability.

As well as undergoing the MoCA and the RUDAS, the Geriatric Depression Scale (GDS) (10) was administered to all subjects and several other variables were collected. These included: age, gender, and marital status, smoking habits, level of education, body mass index (BMI), waist circumference (WC), number of comorbidities and history of hypertension, depression, coronary heart disease (CHD), and stroke or transient ischemic attack (TIA). For diabetic patients, HbA1C results and the duration of diabetes were also collected.

Regarding marital status, subjects were categorized into two groups, married and others (single, window or divorced). Patients were classified into two categories according to smoking habits as never smokers and past smokers or current smokers. Education level was classified into four categories according the years of education: illiterate (<1 year), Fundamental (1-6 years), intermediate (>6-12 years) and Higher Education (>12 years).

Anthropometric measurements were recorded for each subject. Patients' weight in kilograms and height in meters were both measured using a Seca Medical Physician Electronic Scale. BMI was then calculated according to the equation: BMI = Weight (kg)/Height^2 (M^2). The WC was measured for each subject at the umbilicus directly after expiration. Results were recorded in centimeters.

Statistical Analysis

Sample size considerations were based on RUDAS score values established in diabetic patients (11) and in general population previously studies (12), a minimum of 63 diabetic patients and 63 controls was considered as necessary for an alpha risk of 5 % and a beta risk of 20 %.Since our population could be different from the above mentioned studies, it was therefore decided to include more subjects than the minimum indicated above.

The data was analyzed using NCSS 9 statistical software package (Kaysville, UT). Descriptive values are expressed as means ± SD or percentages. The two-tailed significance level was set to $p = 0.05$.

The variables were compared using Student T-test, Chi-Square tests or ANOVA, as appropriate. Pearson's correlation test was performed to examine various correlations.

Analyses of factors associated with RUDAS were performed using multiple regression analyses with an interactive backward selection method. Validity of the model assumption was verified using analysis of model residuals and testing for heteroscedasticity.

Results

Study population characteristics

The present study encompassed 241 participants (171 with diabetes and 70 without) aged 59.6 ± 9.2 years. The age of diabetic patients ranged between 45 and 86 years and 45 and 80 years for controls.

Table 1 shows the characteristics of the studied population. Data are presented according the presence of diabetes. Diabetic patients were older than controls 61.1 ± 9.1 versus 55.7 ± 8.5; $p < 0.0001$. In term of morbidity, hypertension history was increased in diabetic patients in comparison with controls, 65% versus 30%; < 0.0001, and they were more frequently sick with higher number of comorbidities than controls 4.1 ± 2.1 versus 2.8 ± 1.8; $p < 0.0001$.

The prevalence of obesity was similar in the two groups with 63% in diabetics and 62% in controls.

To be noted, no significant difference was found between the two groups in terms of education levels (table I), nor in term of years of education which was found in diabetics and controls to be 6.34 ± 5.885 years and 7.57 ± 6.051 years; $p = 0.220$, respectively. The percentage of illiterate, fundamental, intermediate and high education levels were 31, 28.5, 14.5 and 26 %in diabetics and 26, 29, 14 and 31 % in controls, respectively.

The two groups did not differ significantly in terms of other studied parameters.

Among diabetic patients, the mean HbA1c level was found to be 8.9 ± 2.2 % and the duration of diabetes was 13.8 ± 9.7 years.

Table 1
Clinical and biological characteristics of the population

Characteristics	All	Diabetics	Controls	p*
Number	241	171	70	
Gender (Men %)	50%	51%	47%	0,599
Age (years)	59,6 ± 9,2	61,1 ± 9,1	55,7 ± 8,5	0,000
Marital status (married %)	84%	82%	89%	0,230
Level of Education (Illiterate %)	29%	31%	26%	0,786
Past or current smoker	40%	39%	44%	0,414
Hypertension history (%)	55%	65%	30%	0,000
CHD (%)	23%	25%	17%	0,202
Stroke & TIA (%)	10%	11%	6%	0,195
Depression (%)	9%	7%	13%	0,145
Comorbidities (number)	3,7 ± 2,1	4,1 ± 2,1	2,8 ± 1,8	0,000
BMI (kg/m²)	32,0 ± 6,7	31,9 ± 6,6	32,3 ± 7,0	0,708
WC (cm)	110,8 ± 14,2	111,5 ± 14,5	109,2 ± 13,4	0,265
GDS	4,3 ± 3,1	4,3 ± 3,0	4,2 ± 3,1	0,878
RUDAS	25,67 ± 2,80	25,25 ± 2,78	26,71 ± 2,57	0,000
MOCA	19,97 ± 5,25	19,66 ± 5,09	20,66 ± 5,58	0,192

Data are expressed as: Mean ± SD and Percentage (%), *: Probability of the Student's t-test (continuous variables) or Chi-Square test (categorical variables), CHD: coronary heart disease; TIA: transient ischemic attack; GDS: geriatric depression scale; WC: waist circumference; BMI: body mass index.

Cognitive performance

Both cognitive tests (RUDAS and MoCA) demonstrated a direct and significant correlation with the subjects' level of education (r=0.437, p<0.0001 and r=0.661, p<0.0001) and BMI score (r= 0.172, p=0.009 and r= 0.139, p=0.041), and an inverse relation with advancing age (r=-0.241; p = 0.0004 and r=-0.162; p=0.023).

MoCA score was better in men (18.8 ± 5.5) than in women (21.1 ± 4.8); p= 0,001, and also in married patients (20.3 ± 5.1) than in others (20.3 ± 5.1); p= 0,016, whereas no difference of RUDAS score was found in the distribution of gender or marital status.

Nevertheless, a highly significant correlation was observed between RUDAS and MoCA (r= 0,523; p < 0.000).

Association between diabetes andcognitive function

Diabetic patients are more likely to have less performance than controls in term of RUDAS score (Table 1), and this association persists after adjustment for age, gender, education level, GDS, BMI, hypertension history and number of comorbidities (26.7 ± 0.31 in diabetics versus 25.3 ± 0.19 in controls; p= 0,0007).

As we divided the RUDAS score into normal for these who scored ≥23 and abnormal for those scoring less, we found that among diabetics 16% had abnormal scores compared to 3% for controls (p = 0.004).

Table 2
Analysis of factors associated with RUDAS score using multiple regression models

Source	Regression coefficient	p
Intercept	24.40 ± 0.45	< 0.0001
Female gender	-1.17 ± 0.33	0,0004
Diabetes	-1.21 ± 0.34	0,0005
High level of education	3.30 ± 0.43	0,0297
R^2	0,2762	

Regarding MoCA Scores, there was no significant difference between diabetics and controls (Table 1), as when MoCA was used as categorical score (abnormal if < 26), 85 % of the diabetics and 78% of the controls had abnormal results; p=0.194.

In order to further investigate our primary finding that RUDAS score was worse in diabetics, additional multiple regression analyses were performed, adjusting for age, gender, education level, marital status, smoking, hypertension history, number of comorbidities, GDS, and BMI. The analyses show that the RUDAS scores decreased in females and with a history of diabetes, and increased when education level was high (Table 2). The model accounted for 28 % of the total variance in RUDAS score.

Among diabetics, no statistically significant effect was foundfor neither the duration of diabetes on RUDAS (r= -0,039; p=0.607) or MoCA (r= -0,096; p= 0.235), nor for glycemic control (HbA1C) on RUDAS (r= 0,116; p=0.194) or MoCA (r= -0.027; p= 0.776).

Discussion

The present case-control study conducted in a population sample from Saudi Arabia provides some elements of an effect of diabetes on cognition. Notably, the cognitive performance, as assessed by RUDAS, is poorer in diabetes, who are more likely to have cognitive impairment , than those who are not diabetics. This association was confirmed in multivariate analyses and shown to be independent of female gender and low education level all of which were associated with worse RUDAS cognitive score.

These results corroborate and extend results obtained in different populations reporting that diabetic patients are at an increased risk for development of cognitive performance or dementia (4, 13, 14).

Although the design of the present study cannot provide an ascertain causality, it is of note that there are many direct mechanism linking diabetes and cognitive impairment such as insulin dysregulation (15-17) and chronic exposure to glucose (18-20). In the present study, we did not find a role for the duration of diabetes or glycemic control on cognitive performance. This was contrary to our expectation, but the observational study design with one assessment of HbA1C does not allow ascertaining causality. Nevertheless, the landmark ACCORD MIND trial did not show a benefit for strict glycemic control on cognition as well (21).

In addition, the impact of the cardiovascular risk factors, which are increased in diabetic patients, could contribute to explain this association between diabetes and cognitive impairment (14). Indeed, several studies have indicated that individuals with cardiovascular risk factors and vascular alterations are at increased risk of developing cognitive disorders (22-24). In the present study, the prevalence of hypertension and the number of comorbidities were significantly higher in diabetic patient, but without significant direct association with cognitive performance as assessed by the both cognitive tests.

Our findings indicated a positive effect of increasing BMI on cognition (evident in both tests). This is in accordance with the results of some previous studies (25), but in contrast to others (26). However, the effect of BMI did not remain significant in the regression analyses (Table 2). Moreover, we have to mention that the prevalence of obesity is quite alarming in our sample. This however does reflect the unfortunate fact of the widespread of this problem in our society (1). Indeed, this high prevalence of obesity could make minimize the significance of the BMI when entered as covariable in the regression model.

As expected and shown in many previous studies (27, 28), cognitive tests scores herein were superior in those individuals that were more educated. Although education levels were similar in diabetics and controls in our study, it could be considered as a shared risk factor for cognitive impairment and diabetes since there is evidence that low educational levels increase the risk of diabetes (29) given the overall low education level among our study population. This last observation could contribute to explain our results demonstrating the cognitive impairment in diabetics using the RUDAS, but not the MOCA. Although MOCA is validated, quick, and easy to administer, it requires a certain level of education and therefore can lose its sensitivity in a low-education population. The MoCA was reported to be more sensitive in individuals with a high level of education (30), whereas the RUDAS has been found to be particularly helpful in populations with limited education (31, 32). Moreover, We have found RUDAS easy to administer, both for the testerand the tested, which is very important in an ethnically and educationally diverse population like ours. This also carries important implications infuture research in our region given the dearth of cognitive research in our region, perhaps due to the difficulty of administering the more popular cognitive tests.

Beyond diabetes and low education level, female gender was also independently associated with lower score son RUDAS. Indeed, it was reported that there is gender-difference in term of cognitive function in the developing countries (33). Since it was observed that the combining between socio-cultural factors with gender has more effect on cognition rather than sex alone (34), this negative effect of female gender on cognitive performance could also be explained by lesser levels of education in females who could for example lose their sex-advantage in terms of cardiovascular profile relating to socio-cultural factors (35).

To our knowledge, this is the first study that addresses cognitive impairment in diabetics in an Arabic country. In addition, it is important to mention that our population included not only elderly but middle-aged as well as there is evidence of the role of mid-life rather than late-life diabetes in the development of cognitive impairment (36).

Our results could draw attention to this under-recognized problem of cognitive impairment that can lead to significant health and social outcomes, especially that diabetes in KSA is now a national health problem. Indeed, diabetics with cognitive impairment are more likely to experience poor compliance to medications, are more susceptible to medication errors, and less likely to measure blood sugars and adjust their medications properly. Moreover, the functional disability that could result from cognitive impairment adds up to the burden of diabetes on the person, caregivers, and the community as a whole.

Certain limitations in this study should be noted. The controlswere determined based on their self-reported health, raising the possibility of underreporting in the control group. Indeed, many reports highlight educational levels and ethnicity as biases in disease under-reporting in self-assessed health (37). Moreover, the observational study design does not allow ascertaining causality, and the cross sectional design does not allow testing for temporal changes in cognitive performance.

We believe that largerlongitudinal studiesare needed to furtheridentify possible modifiable risk factors for cognitive impairment in diabetes taking into account life style, education, contextual, social and metabolic proprieties of our population. Moreover, new cognitivemarkers such as advanced neuroimaging could be utilized to shed light on the possible underlying pathology and the potential relationship between diabetes and cognitive impairment.

However, in keeping with the present study results, diabetes and female gender increased the likelihood of classifying patients as cognitively impaired while high education level may protect them from cognitive impairment.

Conclusion

In our population with an alarming prevalence of obesity, diabetes was associated with poorer cognitive performance independent of female gender and low education levels, drawing attention to this under-recognized problem of cognitive impairment that can lead to significant health and social outcomes, particularly in areas with high prevalence of DM. RUDAS was found to be a very reasonable and convenient test to assess cognition in our sample characterized by a low educational level.

Ethical standards: The research was conducted in accordance withthe current laws of KSA and obtained the approval from KAUH. The investigators undertook to respect the protocol in all respects.

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Conflict of interest: No

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