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Depression is more strongly associated with cognition in elderly women than men with type 2 diabetes

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Abstract

Objective—Depression and cognitive impairment are highly prevalent in type 2 diabetes (T2D) yet little is known about how their relationship varies by sex.

Design—Population-based cross-sectional study.

Setting—Community.

Participants—Eight hundred and ninety seven non-demented elderly with type 2 diabetes aged 65 participating in the Israel Diabetes and Cognitive Decline (IDCD) Study.

Measurements—Cognition was evaluated by a comprehensive neuropsychological battery and depressive symptoms were assessed by the Geriatric Depression Scale (GDS).

Results—In all but the executive function domain, the association of depressive symptoms with poorer cognitive function was stronger in women than men, with a significant interaction for language/semantic categorization and missed significance for episodic memory. Using a cutoff of GDS ≥ 6 for clinical depression, women with depression had significantly poorer language/semantic categorization, memory and overall cognitive function. Inclusion of anti-depressants in the model did not alter substantively the associations.

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Authors Contributions: L.S. researched data, performed statistical analysis, and wrote the manuscript. R.R.-S. designed the study, researched and collected data, reviewed the manuscript, and contributed to the discussion. J.S., performed statistical analysis, reviewed the manuscript, and contributed to the discussion. A.H., E.G.-B., J.M.S., M.S. reviewed the manuscript, and contributed to the discussion. R.P. and R.Z. researched the data. M.S.B. supervised the write up of the manuscript.

Conclusion—Our results suggest that depressed T2D women may have poorer cognitive performance, highlighting the significance of sex-specific personalized management of depression in elderly diabetics.

Keywords

Depression; Diabetes; Cognitive impairment; Sex differences

Introduction

In the USA, about 30 million people suffer from diabetes (Centers for Disease Control and Prevention (CDC) 2017). Thirty percent of this population has significant depressive symptoms and 10% fulfill the criteria for Major Depressive Disorder (Anderson et al., 2001). Co-occurrence of diabetes and depression increases the risk for diabetic complications and poor glycemic control (Dana et al., 2016). Moreover, both type 2 diabetes mellitus (T2D) and depression have been consistently associated with higher risk of cognitive impairment. Large prospective studies have suggested T2D as a risk factor for poor cognitive outcomes with up to 3-fold higher dementia risk (Schneider Beeri et al., 2004). Cognitive deficits including impairment of attention and executive function, both affected by T2D (Kravitz et al., 2013), have long been established as a presentation and diagnostic criteria for depression. In women with T2D, the higher prevalence of depression and lower health and functional status compared to men (Arnetz et al., 2014) raise the question of whether women are more susceptible to cognitive impairment in the presence of depression that could contribute to worse outcomes. There is limited data available on the contribution of sex differences to the association of depression and cognition in T2D patients and the data on non-diabetic patients are conflicting (Cervilla et al., 2000). The objective of this study was to investigate the role of sex differences in the relationship of depression and cognition in a sample of elderly T2D patients who were cognitively normal. Exploring the potential sex-specific susceptibility to lower cognitive functioning in T2D depressed patients may provide clues to neurobehavioral mechanisms linking the two psychopathologies.

Materials and Methods

Subjects

This is a cross-sectional study of baseline data of 897 participants in the Israel Diabetes and Cognitive Decline (IDCD) study, examining cognitive outcomes of long-term T2D-related characteristics. Methods of the IDCD study were described in detail elsewhere (Schneider Beeri, 2014). The IDCD study enrolled T2D elderly, 65 years and older, from the Maccabi Health Services, (the second largest HMO in Israel), who have normal cognitive status at entry and are free of substance abuse and any major neurological or psychiatric conditions affecting cognitive performance. Depression was not an exclusion criterion. The antidepressant treatment was defined as “ever/never used” and based on the data from the computerized Maccabi Health Service medical records and centralized pharmacy. The IDCD research protocol was approved by the Institutional Review Boards at the Sheba Medical Center, Israel, Maccabi, Israel, as well as the Icahn School of Medicine at Mount Sinai,

NY. All study subjects signed informed consent prior to enrollment in the study (Schneider Beeri, 2014).

Potential confounders

For all study subjects, demographic data (age, sex, years of education), cardiovascular and metabolic variables (creatinine, total cholesterol, triglyceride, Body Mass Index (BMI), systolic and diastolic blood pressure), and T2D-related variables (HbA1c and time in the diabetes registry, a surrogate of duration of T2D) were received from Maccabi. The cardiovascular and metabolic variables, and also HbA1c, were averages of all measures available in the Maccabi diabetes registry for the subject.

Cognitive assessment

The Mini Mental State Examination (MMSE) was used for overall global assessment of cognition. Twelve neuropsychological tests were transformed into z-scores and measured four cognitive domains : episodic memory (Alzheimer's Disease Assessment Scale word list immediate recall, delayed recall and recognition), attention/working memory (Diamond Cancellation, Digit Span forward and backward), executive function (Trails Making Test A and B, Digit Symbol Substitution Test), and language/semantic categorization (Similarities subscale of Wechsler Adult Intelligence Scale-Revised, animal fluency, and Boston Naming test). Overall cognition was the sum of the four domains.

Depressive symptoms

The 15-item Geriatric Depression Scale (GDS) (Yesavage et al., 1982) was used to measure symptoms of depression with clinical depression defined as GDS of 6 and above (Lyness et al., 2014).

Statistical Analysis

Continuous and categorical data were summarized by mean $\pm$ SD and frequencies and percentages, respectively. Comparisons between men and women used *t* test or Pearson chi-square test. Stepwise multiple regression added the interaction of sex and GDS on the five cognitive outcomes, adjusting for the socio-demographic, cardiovascular/metabolic, and T2D-related potential confounders. To describe the direction of the interactions, partial correlations of depression with each cognitive outcome for men and women, controlling for the potential confounders, are presented.

In addition, the interaction of sex and dichotomized GDS (reflecting clinical depression) was assessed by analysis of covariance (ANCOVA) using the same covariates. Effect sizes represent differences between means of depression diagnosed, adjusted for standard deviation.

Of note, the GDS scores were not normally distributed. However, when the analyses were repeated using normalized square root transformation of the GDS, results remained essentially identical to those using the raw GDS scores. Thus, we reported analyses of the non-transformed data to facilitate comparisons with other studies. Sensitivity analysis for

partial correlation and analysis of covariance including antidepressant use as an additional covariate was performed

Results

The demographics of the 897 subjects included in the analysis are summarized in Table 1. The sample averaged 72.0 (± 4.74) years of age, 13.1 (± 3.47) years of education; 40.7% were women. Men and women did not differ in age, duration of T2D, and glycemic control (HbA1C). However, women had higher BMI, cholesterol and triglyceride, and men had higher creatinine, systolic and diastolic blood pressure. Men had higher education and performed better on MMSE, executive function, and attention, while women performed better on episodic memory; they were comparable on the overall summary and language/semantic categorization. Women had more symptoms of depression and accordingly a higher percentage of clinical depression (GDS 6).

Partial correlations in table 1 show that, the interaction of depressive symptoms (using the continuous scores of the GDS) with sex was significant for language/semantic categorization, and missed significance for episodic memory. The language/semantic categorization result was significant after Bonferroni adjustment for the five cognitive outcomes. In all but the executive function domain, the association with the number of depressive symptom was stronger in women.

These patterns were supported by the significant interaction of sex and dichotomized GDS on language/semantic categorization, memory and overall cognitive function; the effect of depression on poorer cognitive function for depressed versus non-depressed women was significantly larger than in men (Table 2).

We had data on history of antidepressant treatment for 788 participants. When conducting sensitivity analysis controlling for the antidepressant use in both partial correlations and the analysis of variance, the sex/ depression interaction with the language/ semantic categorization cognitive domain remained significant both when using GDS as a continuous or as a dichotomous variable. The results for memory and overall cognitive function were attenuated and were no longer statistically significant.

Discussion

Our results suggest that the association of the number of depressive symptoms with language/semantic categorization was stronger for women, with results in the same direction for additional cognitive domains after adjusting for potential demographic and clinical confounders. Clinical depression had stronger associations for overall cognition, episodic memory and language/semantic categorization in women than in men, such that cognitive performance was poorer for depressed women compared to depressed man, while it was better for non-depressed women compared to non-depressed men. Including history of anti-depressants use in the model attenuated only slightly these differences. Although our study is observational and thus we must be careful when extrapolating its results to clinical practice, the effects sizes for the interactions of depression with cognition were substantially

larger than those for men (Table 2) highlighting the role of depression in diabetic elderly women when assessing for cognitive impairment.

Among non-diabetics, the evidence for sex stratified differences in the relationship of depression and cognition is inconsistent. A cross-sectional study on a community sample of 2792 non-institutionalized non-demented elderly patients over 65 showed significant association between depression and changes in cognitive score in women, but not in men (Fuhrer et al., 1992). Conversely, in a prospective study conducted on 1083 subjects (65–74 years), depression was shown to predict MMSE 9 to 12 years later. Sex was noted to modify the association between depression and poorer cognition so that the association was statistically significant only among men (Cervilla et al., 2000). Another prospective study on 2584 subjects from the same cohort followed up for 54 months, showed that cognitive decline was modified by sex and premorbid intelligence and was only apparent in women of below median intelligence and men of above median intelligence (Prince et al., 1996). Interestingly, in an animal model study of T2D, female mice showed more marked cognitive impairment compared to males as measured by the shuttle avoidance test and Morris water maze test (Sataka et al., 2010).

Our results suggest diabetic women's brains may be more susceptible to the additional brain pathology related to depression and possibly resulting in poorer cognitive function. Biological correlates of sex-specific effect of depression on cognitive outcomes in T2D patients are yet to be elucidated. Higher risk of vascular abnormalities in late life depression, as evidenced by neuroimaging and postmortem neuropathological studies (Thomas et al., 2002), may be one of the factors contributing to this susceptibility. Our study is limited by its cross-sectional design so causation cannot be implied by our results and we cannot rule out the possibility of “reverse causality” where cognitive impairment may be leading to depression. The ongoing longitudinal data collection of the IDCD study will shed light into the directionality of the association. Moreover, since the study does not include non-diabetic subjects, we cannot conclude whether our results are specifically relevant to T2D or can be generalized to the elderly as a whole. In addition, the absence of brain imaging information restrains our ability to investigate whether cerebrovascular disease, associated with depression, T2D, and dementia, underlies the stronger associations found in women. Yet, the study is strengthened by a relatively large sample size with well-defined diagnosis of T2D, a plethora of directly measured covariates available through Maccabi, and a broad neuropsychological battery, which allowed us to examine different cognitive domains.

There is substantial evidence suggesting that higher depression in women with T2D is associated with lower health and functional status compared to men (Arnetz et al., 2014). Our results suggest that these negative outcomes may extend to cognitive impairment. Clinically, these results highlight the significance of sex specific personalized management of depression in elderly with T2D.

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We certify that this work is novel clinical research, highlighting the significance of sex-specific personalized management of depression in elderly with diabetes.

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Table 1

Summary of the demographics, cardiovascular, T2D-related, and cognitive performance variables, stratified by sex; partial correlations and interaction analyses.

Variable	Men	Women	
Demographics	Mean (SD) (n= 532)	Mean (SD) (n=365)	p-value for difference ¹
Age last seen at baseline (years)	71.97 (4.68)	72.05(4.38)	0.82
Education (years)	13.34 (3.54)	12.72 (3.33)	0.008 **
Duration of T2D	10.43 (1.38)	10.47(1.40)	0.70
Metabolic and Cardiovascular covariates	Mean (SD) (n=513)	Mean (SD) (n=335)	p-value for difference ¹
HbA1c	6.78(0.84)	6.79(0.66)	0.83
Cholesterol	172.24(22.29)	192.44(23.10)	<0.001 ***
Triglyceride	152.54(65.91)	165.49(58.20)	0.004 **
Creatinine	1.09(0.24)	0.84(0.16)	<0.001 ***
Diastolic Blood pressure	86.94(14.16)	78.10(14.67)	<0.001 ***
Systolic blood pressure	170.84(7.57)	158.32(6.44)	<0.001 ***
BMI	27.98 (3.89)	28.96(4.89)	0.002 **
Cognitive Outcome	Mean (SD) (n=513)	Mean (SD) (n=333)	p-value for difference ¹
MMSE total	28.16(1.65) ^a	27.77(1.95)	0.001 ***
Overall summary	0.17 (7.31)	- 0.33 (7.57)	0.34
Language/Semantic Categorization	-0.049 (2.37)	0.06(2.43)	0.50
Episodic Memory	-0.23(2.11)	0.33(2.38)	<0.001 ***
Executive Function	0.17 (3.00) ^b	- 0.29 (3.05)	0.03 *
Attention/Working Memory	-0.28 (2.14)	-0.44(2.08)	<0.001 ***
Depression	Mean (SD) (n=530)	Mean (SD) (n=363)	p-value for difference ¹
Total GDS score	1.92(2.05)	2.54(2.53)	<0.001 ***
% subjects with GDS>6	6.22	14.87	<0.001 **
Partial correlation of Depression (GDS score) with Cognitive Outcome	Partial correlation (p-value)	Partial correlation (p-value)	p-value for interaction ²
Overall Cognition	-0.13 (0.004 **)	-0.26 (<0.001 ***)	0.13
Language/Semantic Categorization	-0.11(0.02 *)	-0.32 (<0.001 ***)	0.008 **
Episodic Memory	0.001(0.97)	-0.14 (0.01 **)	0.06
Executive Function	-0.21(<0.001 ***)	-0.20 (<0.001 ***)	0.56
Attention/Working Memory	-0.02(0.69)	-0.08 (0.17)	0.60

¹ - Comparisons of man and women using t-test or Pearson chi-square test.

² - Interaction of sex with depressive symptoms (continuous GDS) on cognition using Stepwise Multiple Regression.

Note:

*
 P 0.05,

**
0.01,

 P 0.001,

^a531 men and 365 women,

^bn for executive function in women were 333.

Abbreviations: Standard deviation (SD), Mini Mental State Examination (MMSE), Geriatric Depression Scale (GDS).

Table 2

Adjusted means (standard Error of Mean; SEM) for each cognitive domain in men and women by depression diagnosis (* $P < 0.05$).

Adjusted means for each Cognitive Domain	Men		Women		Effect Size	p-value for Interaction F(1, 818) (P) ^I
	GDS < 6 Mean (SEM) (n=473)	GDS 6 Mean(SEM) (n=33)	GDS < 6 Mean (SEM) (n=277)	GDS 6 Mean (SEM) (n=49)		
Overall Cognition	-0.53 (0.33)	-1.55(1.08)	1.47(0.46)	-2.55 (0.92)	0.57	0.04 *
Language/Semantic Categorization	-0.25 (0.11)	-0.56(0.37)	0.65(0.16)	-0.90(0.31)	0.64	0.01 **
Episodic Memory	-0.29(0.12)	-0.09(0.37)	0.52 (0.16)	-0.29 (0.32)	0.33	0.05 *
Executive Function	-0.12(0.14)	-0.99 (0.45)	0.45(0.19)	-0.93 (0.38)	0.47	0.39
Attention/Working Memory	0.12(0.11)	0.09(0.35)	-0.16(0.15)	-0.43(0.30)	0.12	0.62

^I Interaction of sex with depression (dichotomized GDS) on cognition using 2-way ANCOVA.

Note:

* $P < 0.05$,

** 0.01,

*** $P < 0.001$

Abbreviations: Standard Error of Means(SEM), Geriatric Depression Scale (GDS).