Chapter 20

Diabetes Mellitus and Depression as Risk Factors for Dementia: SADEM Study

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Abstract

Aim: 3Evidence indicates that the comorbidity of dementia with diabetes and depression may affect most cognitive functions. Our chief interest was to examine the patterns of cognitive functioning in individuals diagnosed with dementia, diabetes, and depression as compared with dementia plus diabetes (DDM), or dementia plus depression (DD) and healthy controls.

Methods: We included 207 participants with dementia (age 60+), 83 with Alzheimer's disease (AD), 66 vascular dementia (VaD), and 58 mixed dementia (AD/VaD). The Mini-Mental State Examination (MMSE) was used for global neuropsychological assessment, and the Center for Epidemiologic Studies Depression Scale for symptoms of depression. Diabetes was confirmed by medical diagnosis. Results: Analysis showed differences in cognitive functioning among the groups with statistical significance. Notably, there was greater cognitive dysfunction in patients with diagnosis of dementia and depression than in controls, but the difference was reduced in patients with comorbid dementia diabetes. Subsequent comparisons indicated that vascular dementia with comorbid depression and diabetes presents significantly inferior cognitive performance than those with dementia alone or the control group.

Conclusions: These results suggest that dementia, when combined with depression or diabetes, adversely affects cognitive performance. These findings highlight the importance of identifying depression among diabetics and patients with dementia.

Keywords: dementia, depression, diabetes mellitus, cognitive function, Mexican population

1. Introduction

One of the most common neurological conditions that affect older adults is dementia[1]. In addition, public health reports in the United States show that one of the most frequent physical illnesses found in older adults is diabetes[2]. Dementia affects approximately 6–10% of people 65 years or older [1], and this prevalence rate increases with age. Neuropsychological impairment associated with dementia includes poor judgment, difficulty with calculation, and getting lost while driving [2]. Older patients with both dementia and depression typically show impairment in the domains of attention, memory, and psychomotor speed [3]. On the other hand, diabetes affects about 20% of people older than 65 years [4]. Patients treated for type II diabetes show cognitive deficits on brief cognitive screening [5], and subtle decrements in verbal memory and processing speed (mean difference in z scores -0.37 and -0.25 respectively) on in-depth cognitive testing. This suggests that diabetes is a significant risk factor for dementia [6]. Depression has been estimated to affect 1–5% of community-dwelling older adults [7]. Depression is common in dementia, with substantial variability in the reported base-rate ranging from 20 to 40% [4, 8, 9], and it is a probable risk factor for both vascular dementia (VaD) and Alzheimer's disease (AD) [10]. As for diabetes, the prevalence of depression is three times higher in these patients than in individuals free of diabetes (OR = 2.9, 95% CI 2.3–3.7) [10]. Diabetes and depression exhibit a closely linked bi-directional relationship: between 15 and 20% of people with diabetes will develop clinical depression, while depression is two to three times more common among people with diabetes compared to those without. Comorbid depression and diabetes have a 2.7-fold increased risk for dementia [11].

Taking these factors into account, our chief interest was to compare cognitive function in individuals diagnosed with dementia with comorbid diabetes and depressive symptoms, alone or combined, compared to those with dementia alone, and against healthy controls.

2. Methods

2.1. Subject

All subjects from that study come from the Study on Aging and Dementia in Mexico (SADEM). SADEM was a cross-sectional study conducted to determine the prevalence of MCI and dementia, between September 2009 and March 2010. Individuals age 60 years and older were invited into the study through a random sampling of the eligible population registered within 24 family medicine units from the Instituto Mexicano del Seguro Social (IMSS) encompassing all of Mexico City. All subjects were beneficiaries (users and non-users) of the IMSS. The inclusion criteria for SADEM were 1) community-dwelling individuals aged 60 years and older, living in Mexico City, 2) registered with IMSS; and 3) accepting to take part in the study through informed consent. We excluded individuals 1) resident in other states; 2) living in an institution; 3) altered mental status secondary to delirium; 4) died before study start; 5) currently taking antipsychotic medication (other psychotropic medications including antidepressants were allowed because of the potential negative impact of non-treatment on cogni-

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tion); and 6) those who refused to participate or who after two attempted visits could not be located. All participants were assessed at doctor's office by a geriatric specialized in geriatric cognitive disorders. The diagnosis of dementia was performed during the study SADEM and was based on the DSM-IV. All subjects were clinically assessed. Final diagnoses were assigned by a consensus expert panel made up of neuropsychologists, neurologists, and geriatricians [12]. All subjects participating in the study, or their caregivers, gave signed informed consent. The research protocol was reviewed and approved by The National Commission of Scientific Research as well as by the IMSS Ethics Commission (registration number 2010-785-005).

In this way for 3D study, we included all patients diagnosed with dementia vascular, Alzheimer disease, or both, diagnosed during the study SADEM, both sexes. Subjects were excluded if they had a) problems with vision, b) poor auditory capacity, c) history of alcohol abuse, d) Parkinsonism or meningioma, and e) incomplete assessment scales or neurological examination. Finally, 330 patients were included and stratified into following groups: a) patients with only dementia: Alzheimer (AD), vascular (VaD) and mixed (MD) (1D†), b) patients with only depression (1D†), c) patients with only diabetes mellitus (1D†), d) patients with AD and diabetes mellitus (2D†), e) patients with AD and depression (2D†), f) patients with VaD and diabetes mellitus (2D†), g) patients with VaD and depression (2D†), h) patients with MD and diabetes mellitus (2D†), i) patients with MD and depression (2D†), j) patients with AD and diabetes mellitus and depression (3D†), k) patients with VaD and diabetes mellitus and depression (3D†), and l) patients with MD and diabetes mellitus and depression (3D†).

2.2. Dementia evaluation

Dementia case newly recognized was conducted in two steps. First all participants of SADEM study were screened with the Mini-Mental State Examination (MMSE) [13]. All participants with a cutoff ≤24 adjustment for educational level in an aging Mexican population were underwent a battery of neuropsychological measures and a standardized neurological examination. We used the Clinical Dementia Rating or CDR to quantify the severity of symptoms of dementia [14]. Complete details of the evaluation and diagnostic procedures have been described earlier [12]. The final diagnosis of dementia was determined by consensus expert panel review including neuropsychologists, neurologists, and geriatric physicians. Each diagnosis was based on based on the Diagnostic and Statistical Manual of Mental Disorders criteria for dementia [15], (DMS-IV-R) criteria for dementia. Once dementia was diagnosed, subjects were further grouped according to whether they met the National Institute for Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [16], and/or the National Institute of Neurological Disorders and Stroke Association Internationale Pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria [17]. Diagnoses fell into three categories: a) probable Alzheimer's disease (AD), b) vascular dementia (VaD), and c) mixed type dementia (MD) and were ascertained using a two-step procedure: (1) diagnosis of dementia and (2) association of cognitive impairment to lesions of vascular of origin. The criteria for diagnosis of MD were that the course was suggestive of AD, and in addition, there were focal neurologic

symptoms suggestive of ischemia. The presence of vascular risk factors alone, in a patient with otherwise clinically typical AD, was not enough to support a diagnosis of MD. Hence, patients suspected of MD were subjected to all procedures for diagnosis.

2.3. Control subjects

The control group consisted of 134 subjects healthy from the SADEM study, which did not meet MCI or dementia criteria, they had a CDR score of zero, and a memory test performance <1.5 standard deviations from the mean for age. There were no significant differences between controls and cases for age or years of education ($p > 0.01$).

2.4. Cognitive measure

Cognitive testing was performed on all the patients in whom MMSE [14] and was used to evaluate global cognitive performance. For the purpose of the present study, the 11 MMSE subtests and the global MMSE score were considered independently: *spatial orientation* (state, county, town, place, and floor=5 points), *temporal orientation* (year, season, month, day, and date=5 points), *immediate memory* (immediately repeating three words=3 points), *attention/concentration* (If the participants had education as serially subtracting 7, beginning with 100, or, alternatively, spelling the word world backward for the participants without education=5 points), *delayed recall* (recalling the previously repeated three words=3 points), *language* (naming two items=2 points), *verbal repetition* (repeating a phrase=1 points), *reading a sentence* (reading aloud and understanding a sentence=1 points), *writing a sentence* (1 points), *verbal comprehension* (following a three-step command=3 points), and *constructional praxis* (copying a design=1 points). [The MMSE is thoroughly familiar to any readership in geriatrics or neurology. You would only need to specify the above if you were intending to present subscores. That might be a good idea if you do not have access to the neuropsychological scores].

2.5. Depression

In addition to neuropsychological tests, depression symptoms were evaluated using the Center for Epidemiologic Studies Depression Scale (CES-D), a validated 20-item scale consisting of four factors: depressive affect, somatic complaints, positive affect, and interpersonal relations. Scores on the CES-D ranged from 0 to 60, where 0–15 is indicative of absence of depression, and scores of 16–60 are indicative of depressive symptomatology [18]. The presence of depression was corroborated with the self-reported treatment with antidepressants, selective serotonin reuptake inhibitors (SSRI—i.e., paroxetine, sertraline, fluoxetine, venlafaxine, citalopram), or tricyclic antidepressants at any time during the four-month preceding the interview.

2.6. Diabetes assessment

Diagnosis of diabetes mellitus was based on the patients' self-report to the question, "Are you taking medication for diabetes?" These diabetes diagnoses were then confirmed by blood glucose measurements, a fasting plasma glucose concentration >7.0 mmol/l (whole blood

>6.1 mmol/l) and hemoglobin A1c (HbA1c) (<48 mmol/mol (6.5%), and treatment. All patients in this study were receiving treatment for diabetes, and 90% of patients were taking sulfonylureas for controlling diabetes with the remaining 10% on insulin therapy.

2.7. Statistical analyses

We examined effects of dementia by type, depression, and diabetes by themselves. All comparisons were performed with MANOVAs that are being conducted using a Bonferroni correction of m [19], with dementia (AD, VaD, mixed), depression (yes/no), and diabetes mellitus (yes/no) as between-subject factors. The same MANOVAs models were then used within each diagnostic group (AD, VaD, MD). Main effects and statistically significant difference between groups were assessed by F-test [20]. Additionally, a complementary analysis to better interpret the results was carried-out using the standardized mean effect sizes (Hedges' g). Hedges' g is calculated on the basis of the standardized mean difference effect size, which uses the pooled within-groups SD but corrects for bias from small sample sizes. These effect sizes indicate the mean difference between two variables expressed in standard deviation units. Hedges' g is a conservative estimate of effect size, which typically is interpreted by Cohen's d guidelines (small effect=0.20, medium effect=0.50, large effect=0.80) [21]. A positive effect size indicates that the MMSE score in the control group was superior to the diagnostic groups, whereas a negative effect size indicates that the diagnostic groups outperformed the control.

3. Results

Table 1 presents the descriptive statistics (mean ± SD) of diagnostic groups. First of all, the MANOVA models revealed that the interaction effects were not significant on sex, age, and education ($p < 0.005$). When considering the main effect of the 2D† in the MMSE score, the MANOVAs demonstrated significant effect on diabetes mellitus and depression, AD-depression, and AD-diabetes mellitus, similarly MD-diabetes mellitus, ($p < 0.005$). With the complete model, we can identify significant differences between the means of the diagnostic groups (F: 39.36, p: 0.000, R2: 0.614), indicating significant differences between the three dementias and cognitive performance.

For each diagnostic groups, we measure cognitive functioning (MMSE total scores) by calculating the difference of mean. We then convert the difference to a standardized effect size by dividing it by the pooled standard deviation for the diagnostic groups. These results are shown in **Table 2**. The margin of error (for a 95% confidence interval) for each estimate is shown. For example, the global cognitive functioning measured in effect size from group AD-depression is -3.02 standard deviation. Because the margin of error for this estimate is 0.28, the lower bound of its 95% confidence interval is -3.54, and the upper bound is -2.46. The cognitive performance in **Table 2** exhibits a strikingly consistent pattern for combination of all three types of dementia with diabetes. Global cognitive functioning is largest in the groups with AD and then decline steadily into the groups with VaD and MD.

	MMSE				Ages			Education			Sex			
	n	**Mean**	**SD**	**P of corrected model ages**	**Mean**	**SD**	**P**	**Mean**	**SD**	**P**	**Male (%)**	**Female (%)**	**P**	**R2**
Control group (0D †)	134	30.2	3.3	**0.00**	71.8	7.6	0.009.1	5.5	**0.00**	46.5	53.5	**0.00**	0.37
Group diabetes mellitus (1D †)	28	29.2	5.1	**0.00**	71.6	7.0	0.037.0	6.2	**0.00**	52.5	47.5	**0.00**	0.67
Group depression (1D †)	84	30.2	3.2	**0.00**	69.4	6.7	0.008.9	5.9	**0.00**	56.5	43.5	**0.00**	0.33
Group diabetes mellitus and depression (2D †)	10	28.7	6.7	**0.01**	67.8	8.1	0.016.9	6.2	0.35	45.6	54.4	**0.02**	0.72
Group AD * (1D †)	37	18.7	7.4	**0.03**	76.3	8.7	0.036.4	5.1	0.11	66.3	33.7	0.10	0.24
Group AD-depression (2D †)	25	18.7	5.3	**0.03**	78.2	8.9	0.035.8	5.1	0.68	75.0	25.0	0.07	0.35
Group AD-diabetes mellitus (2D †)	13	21.4	4.5	0.52	74.5	10.0	0.424.1	3.7	0.76	23.8	76.2	**0.00**	0.21
Group AD-diabetes and depression (3D †)	8	21.8	4.2	0.95	74.3	7.4	0.907.0	6.6	0.71	75.0	25.0	0.86	0.08
Group with VaD * (1D †)	24	21.5	4.2	0.48	76.0	8.5	0.246.7	6.6	0.89	55.2	44.8	0.41	0.12
Group VaD-Depression (2D †)	19	19.7	6.2	0.53	80.0	8.3	0.185.6	4.2	0.86	57.1	42.9	0.10	0.53
Group VaD-diabetes mellitus (2D †)	10	20.8	6.5	0.37	78.3	6.6	0.235.9	5.0	0.33	45.8	54.2	0.10	0.39
Group VaD-diabetes and depression (3D †)	14	20.8	6.0	0.46	76.7	7.9	0.416.6	6.5	0.30	57.1	42.9	0.88	0.22
Group MD * (1D †)	12	17.4	5.8	0.51	76.7	8.9	0.225.8	6.8	0.64	41.4	58.6	0.76	0.24
Group MD-depression (2D †)	7	15.3	7.7	0.47	77.3	9.8	0.229.7	6.0	0.48	21.1	78.9	0.30	0.39
Group MD-diabetes mellitus (2D †)	27	18.0	4.9	0.67	77.8	9.2	0.456.6	5.4	0.30	26.3	73.7	**0.01**	0.07
Group MD-diabetes and depression (3D †)	12	17.9	6.4	0.38	78.9	7.8	0.877.5	4.9	0.26	16.7	83.3	0.13	0.31

MANOVA (complete model): sum of squares = 14913.79, gl: 18, F: 39.36, p: 0.000, R2: 0.614.

MMSE: mini-mental state examination; 0D: group without "D", 1D group with one D, 2D group with 2D, 3D group with 3D; C-E: mean of control group—mean of group (0D or 1D or 2D or 3D).

*Dementia: Alzheimer (AD), vascular (VaD), and mixed (MD).

†D is dementia or diabetes mellitus or depression.

Table 1. Demographic characteristic of diagnostic groups.

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Type of dementia	Mean difference (C–E)	p-Value for mean difference (2-tailed T-test)	95% confidence interval for effect size		Effect size	Bias corrected (Hedges)	Standard error of effect size estimate	95% confidence interval for effect size	
			Lower	Upper				Lower	Upper
Control group (0D †)									
Group diabetes (1D †)	-1.04	0.303	-2.55	-9.89	-0.28	-0.28	0.21	-0.69	0.13
Group depression (1D †)	-0.05	0.944	-0.94	0.85	-0.01	-0.01	0.14	-0.29	0.26
Group diabetes and depression (2D †)	-1.54	0.332	-3.89	0.81	-0.42	-0.42	0.33	-1.07	0.22
Group AD * (1D †)	-11.55	**0.000**	-13.20	-9.89	-2.56	-2.55	0.23	-3.00	-2.09
Group AD-depression (2D †)	-11.56	**0.000**	-13.21	-9.91	-3.02	-3.00	0.28	-3.54	-2.46
Group AD-diabetes (2D †)	-8.81	**0.000**	-11.78	-6.84	-2.57	-2.55	0.33	-3.19	-1.91
Group AD-diabetes and depression (3D †)	-8.43	**0.000**	-10.86	-6.01	-2.50	-2.49	0.39	-3.26	-1.72
Group with VaD * (1D †)	-8.78	**0.000**	-10.29	-7.26	-2.54	-2.52	0.26	-3.04	-2.01
Group VaD-depression (2D †)	-10.52	**0.000**	-12.35	-8.69	-2.78	-2.77	0.29	-3.34	-2.20
Group VaD-diabetes (2D †)	-12.20	**0.000**	-11.78	-7.11	-2.62	-2.60	0.36	-3.31	-1.89
Group VaD-diabetes and depression (3D †)	-9.48	**0.000**	-11.50	-7.47	-2.61	-2.60	0.32	-3.22	-1.97
Group MD * (1D †)	-13.78	**0.000**	-15.95	-11.61	-3.78	-3.76	0.37	-4.49	-3.03
Group MD-depression (2D †)	-14.97	**0.000**	-17.74	-12.10	-4.14	-4.11	0.46	-5.21	-3.21
Group MD-diabetes (2D †)	-12.20	**0.000**	-13.71	-10.69	-3.36	-3.34	0.28	-3.89	-2.79
Group MD-diabetes and depression (3D †)	-12.32	**0.000**	-14.49	-10.15	-3.38	-3.36	0.36	-4.07	-2.66

MMSE: mini-mental state examination; 0D: group without "D", 1D group with one D, 2D group with 2D, 3D group with 3D; C-E: mean of control group—mean of group (0D or 1D or 2D or 3D).

*Dementia: Alzheimer (AD), vascular (VaD), and mixed (MD).

†D is dementia or diabetes mellitus or depression.

Table 2. Mean and effect sizes of the MMSE by type of dementia.

We illustrate such cognitive performance gaps in **Figure 1**, which shows differences in terms of effect sizes, that is, the difference in mean scores divided by the standard deviation of scores for all groups. When comparing among the dementia groups, we observed that patients with AD presented better cognitive performance than patients with the diagnosis of VaD and MD, while patients with MD-depression had worse cognitive performance than patients with any type of dementias and diabetes and depression. Which confirms the finding that the worst cognitive performance is evident in the groups od MD and depression (**Figure 1**).

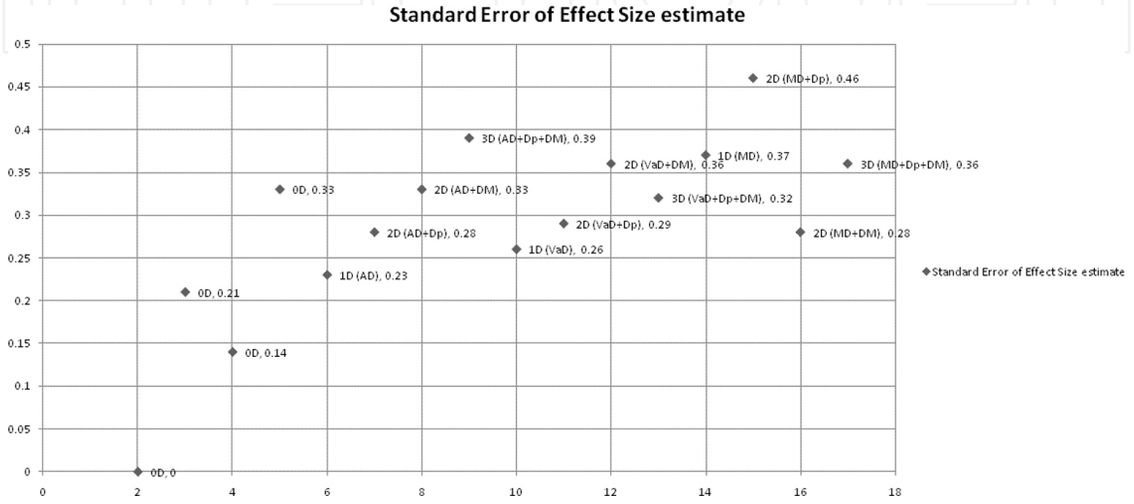

Figure 1. Hedges' g of the MMSE by type of dementia. Alzheimer (AD), vascular (VaD), and mixed (MD) and "#" is the number of "D" a group has (0 or 1 or 2 or 3), and the letter "D" is dementia or diabetes mellitus or depression.

4. Discussion

To our knowledge, this is the first study to attempt to examine the specific patterns of performance on measures of neuropsychological functioning among those with diagnosis of dementia with co-existing diabetes and depression. We found supporting evidence showing the variation in the neuropsychological functioning between individuals with 3Ds in contrast to dementia patients with either comorbid depression or diabetes. Overall, patients with dementia with coexisting diabetes and depression had greater cognitive impairment relative to dementia only, or healthy controls. There was a non-significant trend for cognitive scores of dementia and depression group to fall between the dementia with diabetes groups. These results illustrate the importance of controlling for depression and diabetes when diagnosing cognition. Some studies suggest that depression is a risk factor for dementia and depression treatment may be a causal factor for dementia [22]. Furthermore, depression may increase vulnerability to and/or exacerbate existing cognitive deficits [23]. Additionally, Ritchie et al. [24] examined the association between depression and diabetes and report that 36.8% of the patients with dementia have depression, while only 10.6% have diabetes. Similar reports [25] show that 23.7% of patients with dementia have dementia and depression. While the precise neurobiological mechanisms underlying depression and cognitive abnormalities in type 2

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diabetes are unknown, both cognitive impairment and diabetes have been observed among older adults with major depression. In our study, patients with dementia and diabetes had lower scores on cognitive performance relative to healthy controls, which is consistent with previously reports in other populations.

Overall, type 2 diabetes has been associated with mild cognitive deficits, most frequently in the domains of verbal memory, processing speed, and to a lesser degree, executive functioning (see review) [5]. Another study suggests that there is a protector effect of insulin on surface plasma insulin receptors, although it is possible that the improvement of cognitive function is due to better glucose control rather than a direct effect on the neurons [27]. However, methodological and study design differences, such as variations in sampling, assessment instruments, degree of diabetes severity, and the presence of comorbid illnesses, have resulted in inconclusive results. Consistent with the literature on diabetes research, research examining the relationship between depression and cognitive functioning is filled with mixed results, as mentioned above. There is evidence suggesting that the pattern of cognitive impairment varies by depression subgroup or severity (e.g., major versus minor depression) [30, 31]. In general, depression has been linked with a range of declines in cognitive domains, including memory, executive functioning, attention, and psychomotor speed [32].

The present study differs from others in that previous studies typically relied only on self-report for depression with varying measurement instruments. In our study, we also corroborated our depression status with the medical prescription of any antidepressant.

The present study had several limitations. First, the specific treatments of the patients with diabetes were not verified, so that it is impossible to draw conclusions about the influence of diabetes treatment on cognitive impairment in this sample. Time with any of the conditions was not available, so the effect of short versus long term cannot be confirmed. In addition, other comorbidities, especially those affecting vascular, neuronal, or metabolic status, were not taken into account. The nature of the design does not allow for explanation of the mechanisms of the relationships observed. Another important limitation of this study is that we included only the MMSE, which is not a diagnostic instrument, to assess the cognitive function. We understand this test is widely used for its ability to follow cognitive changes over time [33]. Despite these limitations, with our large sample size, rigorous study design, and broad socioeconomic, and educational characteristics of our participants, we believe that it is possible to make valid inferences to the elderly population residing in Mexico City.

The patients with triple diagnoses of dementia, depression, and diabetes demonstrated greater cognitive dysfunction relative to those with double or single diagnosis of dementia. Additional research is needed to unravel this relationship, as to whether the cognitive impairment accrued in patients with DDD. These findings highlight the importance of identifying depression among diabetics and patients with dementia. Since depression is readily treatable, remission should lead to improved cognitive function and quality of life. The role of neuropsychology is expanding due to the increasing demand for differential diagnosis and to draw conclusions about patients' abilities to function independently. Further research is necessary to define and recognize patients with dementia with comorbid conditions.

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