Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13 (2019) 1759–1764

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Original Article

Assessment of comorbid mild cognitive impairment and depression in patients with type 2 diabetes mellitus

Talaat A. Abd Elaaty [a], Azza A. Ismail [a,*], Hesham A. Sheshtawy [b], Eman A. Sultan [c], Mohamed G. Ebrahim [a]

[a] Internal Medicine Department (Unit of Diabetes and Metabolism), Faculty of Medicine, Alexandria University, Alexandria, Egypt
[b] Neuro-psychiatry Department, Faculty of Medicine, Alexandria University, Alexandria, Egypt
[c] Public Health, Preventive and Social Medicine Department, Faculty of Medicine, Alexandria University, Alexandria, Egypt

ARTICLE INFO

Article history:
Received 4 February 2019
Accepted 5 March 2019

ABSTRACT

Context: Depression, mild cognitive impairment, and dementia are highly prevalent chronic conditions associated with social, medical, and economic burdens. Although there are several epidemiological studies that have reported the prevalence of mild cognitive impairment or depressive syndrome in elderly diabetic population little is known about the comorbidity of these conditions. We aimed to study the prevalence of comorbid mild cognitive impairment (MCI) and depression in patients with Type 2 diabetes mellitus and its relation to glycemic control.
Materials and methods: the present work was carried on 400 patients with T2DM. History taking, physical examination, laboratory investigations (with special emphasis on glycemic profile and lipid profile parameters) were done for every patient. Assessment of anxiety and depression using the HADS score and assessment of mild cognitive impairment using MoCA score were done.
Results: 76% of studied patients had depression of varying degrees while 56.8% of studied patients had MCI. Decreased level of HDL-cholesterol and increased HADS anxiety score were significant predictors of depression. On the other hand, increased level of total cholesterol, decreased level of HDL-cholesterol, increased HADS depression score and decreased MoCA score were significant predictors of anxiety. HDL-cholesterol HADS anxiety score, FBG, and duration of DM were the significant predictors of MCI.
Conclusion: Increased level of total cholesterol, decreased level of HDL-cholesterol, increased HADS depression score and decreased MoCA score were significant predictors of anxiety. HDL-cholesterol, HADS anxiety score, FBG, and duration of DM were the significant predictors of MCI.

1. Introduction

Globally, an estimated 422 million adults have DM according to the latest 2016 data from the World Health Organization (WHO) [1]. DM prevalence of 8.3% is increasing rapidly and previous 2013 estimates from the International Diabetes Federation (IDF) is that 381 million people having DM and the number is projected to almost double by 2030 [2]. There were over 7.8 million cases of DM in Egypt in 2015.

The WHO estimates that DM resulted in 1.5 million deaths in 2012 making it the 8th leading cause of death. However another 2.2 million deaths worldwide were attributable to high blood glucose and the increased risks of cardiovascular disease and other associated complications (e.g. renal failure) which often lead to premature death and are often listed as the underlying cause in death certificates rather than DM [1].

Mild cognitive impairment (MCI) is a clinical label which includes elderly subjects with memory impairment and with no significant daily functional disability. MCI is an important target for future Alzheimer's dementia (AD) prevention studies [3]. Because the majority of MCI individuals show progressive memory decline due to the presence of AD pathology in its earliest stages, this may be the optimum stage at which to intervene with preventive therapies [4]. Clinical studies reported a conversion rate from MCI to AD of 10–15%/year [5].

MCI has been associated with decreases in psychomotor speed [6], frontal lobe/executive function [7], verbal memory [8],

* Corresponding author.Unit of Diabetes & Metabolism, Department of Internal Medicine, Faculty of Medicine, Alexandria University, Egypt.
E-mail address: dr_azzak@yahoo.com (A.A. Ismail).

https://doi.org/10.1016/j.dsx.2019.03.012
1871-4021/

processing speed [8], complex motor functioning [9], working memory [10], immediate recall, delayed recall [11], verbal fluency [9], visual retention [12], and attention [13].

The incidence of both T2DM and dementia increase in later life, which increases the prevalence of the comorbidity of these pathologies. Moreover, recent studies have indicated that older people with T2DM have a higher risk of cognitive dysfunction or dementia [14]. Ample evidence has indicated that T2DM is related not only to vascular dementia (VD) but also to the clinical diagnosis of Alzheimer's disease (AD)-type dementia [15].

One of the earliest findings from a large epidemiological study showing that T2DM patients had an increased risk for developing dementia came from the Rotterdam Study. Another study demonstrated a 65% increase of the risk for developing AD in T2DM subjects [16].

The National Institutes of Health (NIH) Diabetes Mellitus Interagency Coordinating Committee, in its 2010 strategic planning report, identifies cognition among the strategic priorities for diabetes research over the next decade. The report recommends inclusion of validated cognitive instruments in epidemiologic studies to further elucidate mechanisms of CNS complications in diabetes [17].

The cause of cognitive impairment and depression in type 2 diabetes is unknown, but it is most likely multifactorial. Chronic hyperglycemia, cerebral microvascular disease, severe hypoglycemia, and an increased prevalence of macrovascular disease could play significant role in pathophysiology of brain disturbances. Diabetes is associated with an increased release of inflammatory cytokines, and the excess inflammation may be neurotoxic [18].

Depressive disorders are a significant public health issue. They are prevalent, disabling, often chronic illnesses which cause a high economic burden for society related to both direct and indirect costs. Depressive disorders also influence significantly the outcome of comorbid medical illnesses such as cardiac diseases and cancer. Depression can be defined as a state of low mood and aversion to activity that can affect a person's thoughts, behavior, feelings and sense of well-being [19].

An association between depression and diabetes was recognised as early as the 17th century, when British physician Thomas Willis noted that diabetes frequently appeared in individuals who had experienced previous life stresses or sadness [20].

There is growing evidence regarding the bidirectional adverse interaction between diabetes and depression. A study found that depressive symptoms at baseline were associated with an increased incidence of diabetes. Also it is a predictive factor for the number and severity of diabetic complications [21].

Depressive symptoms are associated with decreased glycemic control and increased diabetic complications; conversely, poor metabolic control and functional impairment due to increasing complications may cause or worsen depression and lessen response to antidepressant treatment [22].

The reason for this timely relationship between depression and diabetes manifestation is unclear. It could be that people with elevated depressive symptoms are less attentive toward a healthy lifestyle, therefore increasing their risk for type 2 diabetes.

Alternative explanations for this finding refer to chronic dysregulations of the hypothalamic–pituitary–adrenal (HPA) axis such as high cortisol levels and reduced insulin sensitivity or an activation of the immune system leading to or fostering chronic inflammatory processes [23].

A third explanation stems from study results indicating that blood glucose is itself a potent regulator for mood states. In particular, hypoglycemia or severe hyperglycemia is able to induce negative emotional states in patients with diabetes [24].

The presence of depression in a patient with diabetes has been suggested as one of the possible causes of an inadequate metabolic control, especially for those patients who cannot achieve an adequate glycemic control despite intensive medical recommendations [25].

The present piece of work aimed to study the prevalence of comorbid Mild cognitive impairment (MCI) and depression in patients with Type 2 diabetes mellitus and its relation to glycemic control.

2. Materials and methods

The present work was carried on 400 patients with T2DM. History taking, physical examination, laboratory investigations (with special emphasis on glycemic profile and lipid profile parameters) were done for every patient. 198 patients were males and 202 patients were females. The age of the study group ranged from 30 to 70 years with a mean age of 50.01 ± 11.71 years. The duration of DM among studied cases ranged from 1 to 45 years with a mean duration of 18.14 ± 12.65 years.

Assessment of anxiety and depression using the HADS score and assessment of mild cognitive impairment using MoCA score were done.

3. Results

3.1. Age, sex, duration of diabetes

The ages of the studied cases ranged from 30 to 70 years with a mean age of 50.01 ± 11.71 years. Nearly a half (49.5%) of studied cases were males and the rest (50.5%) were females.

The duration of DM among studied cases ranged from one to 45 years with a mean duration of 18.14 ± 12.65 years. The majority (70%) of studied cases had DM for 10 years or more (see Table 1).

3.2. Glycemic profile

Table 3 revealed that the mean fasting blood glucose (FBG) among studied patients was 154.2 ± 35.23 mg/dl. About a third (32.2%) of the patients were controlled (FBG ≤ 130 mg/dl) while the other two thirds (67.8%) were uncontrolled. The mean HBA1c of studied patients was 7.76 ± 1.68%. Less than half (40.8%) of the patients were controlled (HBA1c < 7) while 59.2% were uncontrolled (see Table 2).

3.3. Prevalence of depression and anxiety

Fig. 1 show that more than three quarters (76%) of studied patients had depression of varying degrees according to HADS test scoring. These patients were classified according to severity into

Table 1
Distribution of the studied cases according to demographic data.

Demographic data	Studied cases (n = 400)	
	No.	%
Age (years)		
30-	97	24.3
40-	85	21.3
50-	114	28.5
60–70	104	26.0
Min. – Max.	30–70	
Mean ± SD.	50.01 ± 11.71	
Median (Q1-Q3)	51.0 (40.0–60.0)	
Sex		
Male	198	49.5
Female	202	50.5

Table 2
Distribution of the studied cases according to duration of diabetes.

Duration of diabetes (years)	Studied cases (n = 400)	
	No.	%
<10	120	30.0
≥10	280	70.0
Min. – Max.	1–45	
Mean ± SD.	18.14 ± 12.65	
Median (Q1-Q3)	14.0 (8.0–27.0)	

Table 3
Distribution of the studied cases according to glycemic profile.

Glycemic profile	Studied cases (n = 400)	
	No.	%
FBG (mg/dl)		
≤130 (Controlled)	129	32.2
>130 (Not controlled)	271	67.8
Min. – Max.	110–240	
Mean ± SD.	154.2 ± 35.23	
Median (Q1-Q3)	143.0 (125.0–175.0)	
HBA1c (%)		
<7 (Controlled)	163	40.8
≥7 (Not controlled)	237	59.2
Min. – Max.	6.2–13.0	
Mean ± SD.	7.76 ± 1.68	
Median (Q1-Q3)	7.15 (6.7–7.9)	

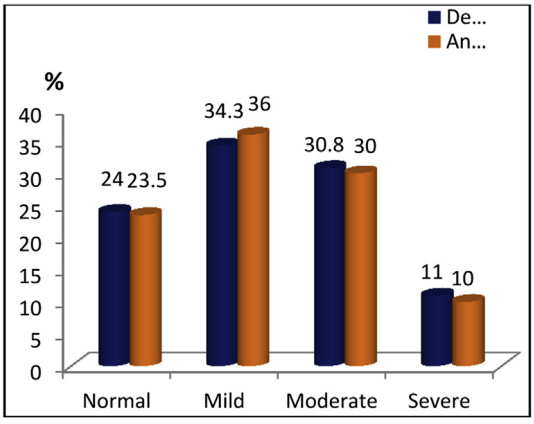

Fig. 1. Distribution of the studied cases according to HADS score.

patients with mild depression (34.3%), patients with moderate depression (30.8%) and those with severe depression (11%).

Similarly, more than three quarters (76.5%) of studied patients had anxiety of varying degrees according to HADS test scoring. These patients were classified according to severity into patients with mild anxiety (36%), patients with moderate anxiety (30%) and those with severe anxiety (10%).

3.4. Prevalence of mild cognitive impairment

Fig. 2 demonstrate that more than half (56.8%) of studied patients had mild cognitive impairment (MCI) according to Montreal Cognitive Assessment (MoCA) Test Score.

3.5. Relation between HADS and MoCA scores

Table 4 reveals a strong positive significant correlation was found between HADS depression score with HADS anxiety score ($r = 0.921$, $p < 0.001$). Moreover, a strong negative significant correlation was found between HADS depression score with MoCA score ($r = -0.772$, $p < 0.001$) and between HADS anxiety score with MoCA score ($r = -0.847$, $p < 0.001$).

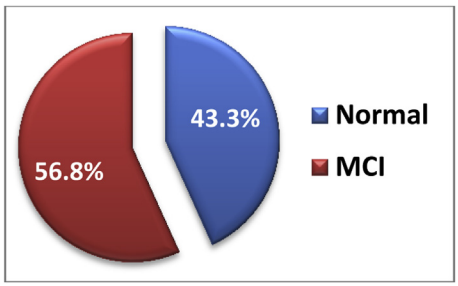

Fig. 2. Distribution of the studied cases according to MoCA test Score.

Table 4
Correlation between HADS scores and MoCA score for total sample.

Studied variables	HADS score (n = 400)			
	Depression		Anxiety	
	r	P	r	P
Depression score			0.921*	<0.001*
Anxiety score	0.921*	<0.001*		
MoCA score	−0.772*	<0.001*	−0.847*	<0.001*

r: Spearman's coefficient.
*: Statistically significant at $p \leq 0.05$.

3.6. Multiple linear regression analysis of factors affecting depression and anxiety HADS scores

Table 5 shows variables that were significantly associated with the high risk of depression and anxiety among studied diabetic patients as examined by multiple linear regression analysis.

Results of the linear regression analysis revealed that decreased level of HDL-cholesterol and increased HADS anxiety score were significant predictors of depression. On the other hand, increased level of total cholesterol, decreased level of HDL-cholesterol, increased HADS depression score and decreased MoCA score were significant predictors of anxiety.

Table 5
Multiple linear regression analysis of factors affecting Depression and Anxiety HADS scores among studied cases.

Studied variables	HADS score					
	Depression			Anxiety		
	B	t	p	B	t	p
Duration of DM	0.007	0.025	0.197	−0.003	0.005	0.461
HbA1c	−0.389	−0.900	0.369	−0.295	−0.824	0.410
Cholesterol	−0.013	−1.012	0.312	0.025	2.275	0.023*
HDL	−0.047	−2.724	0.007*	0.046	3.248	<0.001*
Depression score				0.706	32.086	<0.001*
Anxiety score	1.025	32.086	<0.001*			
MoCA score	0.001	0.008	0.994	−0.143	−8.541	<0.001*
F (P)	502.927* (<0.001*)			698.150* (<0.001*)		
R^2	0.885			0.914		

B: Regression coefficient.
t, p: calculated and p-value of *t*-test.
F (P): calculated and p-value of ANOVA test.
*: Statistically significant at $p \leq 0.05$.

3.7. Predictors of MCI; results of multivariate logistic regression analysis

Table 6 shows variables that were significantly associated with the high risk of MCI among studied diabetic patients as examined by multivariate logistic regression analysis. Results of the logistic regression analysis revealed that HDL-cholesterol HADS anxiety score, FBG, and duration of DM were the significant predictors of MCI. The patients with low HDL-cholesterol level were about three times more prone to MCI than those without (OR = 2.697). Moreover, patients having anxiety and those having uncontrolled FBG were about two times at higher risk of MCI (OR = 1.965 and 1.715 respectively). Also, patients with long duration of DM were slightly more prone to MCI (OR = 1.075).

4. Discussion

Type 2 diabetes mellitus and prediabetes have been associated with an increased risk of cognitive impairment, accelerated cognitive decline, and dementia among older adults.[76] Depression is commonly found as a co-morbid condition in chronic medical illnesses in general, and diabetes mellitus (DM) in particular. Depression in patients with DM represents a complex, co-morbid condition, which is the result of complicated interactions between bio-psycho-social and genetic factors. Depression originates as a direct consequence of neurochemical changes with DM, which harmfully affects health outcomes. The combination of diabetes and depression is associated with decrease in functional abilities and self-care.[6, 196–198]

The aim of the present work was to study the prevalence of comorbid Mild cognitive impairment (MCI) and depression in patients with Type 2 diabetes mellitus and its relation to glycemic control.

The present work was carried on 400 patients, 49.5% of them were males and 50.5% were females. The mean age of the studied subjects was 50.01 ± 11.71 years and the mean duration of diabetes was 18.14 ± 12.65 years. The majority (70%) of studied cases had DM for 10 years or more.

The mean FBG was >154.2 ± 35.23 mg/dl two thirds (67.8%) of the patients were uncontrolled (FBG > 130 mg/dl).

The mean HbA1c percentage was 7.759 ± 1.676%. There were 163 controlled patients (HBA1c < 7) and this represented 40.8% of the patients and 237 uncontrolled patients (HBA1c ≥ 7) which represented 59.2% of the patients.

More than three quarters (76.5%) of studied patients had anxiety of varying degrees according to HADS test scoring. Similarly, more than three quarters (76%) of studied patients had depression of varying degrees.

Mikaliūkštienė A. et al., found that the prevalence of anxiety in T2DM was 42.4% and the prevalence of mild to severe depression score was 28.5% [26]. Rajesh R. et al., found the that prevalence of anxiety was (21.0% vs. 7.3%, P = 0.001) as compared to healthy controls, while the prevalence of depression was (26.3% vs. 11.2%, P = 0.001) as compared to healthy controls [27].

Rustad et al., conducted a meta-analysis of 42 published studies that included 21,351 adults, and found that the prevalence of major depression in people with diabetes was 11%, and the prevalence of clinically relevant depression was 31% [28].

We reported higher prevalence of anxiety and depression compared to these studies but this can be explained by:

i. Different studies didn't agree on an approximate fixed prevalence rate of either anxiety or depression in T2DM
ii. In the present work we included patients with longer duration of T2DM compared to the previously mentioned studies.
iii. Different ethnic characteristics might have a role in the variability of reported prevalence rate of anxiety and depression in T2DM.

In the present work we demonstrated that more than half (56.8%) of studied patients had mild cognitive impairment (MCI) according to Montreal Cognitive Assessment (MoCA) Test Score.

Gao Y. et al., reported that the prevalence of MCI with T2DM prevalence was 13.5% which was more frequent than the prevalence of MCI for the general population [29], while Chukwuemeka O. et al., reported found that 40% of patients with T2DM had cognitive impairment [30].

We reported higher prevalence of MCI compared to these studies but this can be explained by the following:

i. Difference in the test used to assess the state in MCI, in the present work we used the MoCA test while Gao Y. et al., used the Petersen's diagnostic standard test for MCI [29], while Chukwuemeka O. et al., used the Mini mental state examination (MMSE) [30].
ii. Advanced age, low education attainment, unskilled occupation and presence of diabetic complications may play a role in the reported higher prevalence of MCI in the present work.

A strong positive significant correlation was found between HADS depression score with HADS anxiety score (r = 0.921, p < 0.001). Moreover, a strong negative significant correlation was found between HADS depression score with MoCA score (r = −0.772, p < 0.001) and between HADS anxiety score with MoCA score (r = −0.847, p < 0.001).

To our knowledge and after reviewing literature, the present work is the first study to speculate direct correlation between HADS and MoCA scores in patients with T2DM.

A positive significant correlation was found between HADS depression and anxiety scores with HbA1c% (r = 0.451 and 0.544) (p < 0.001).

These results match the results stated by Balhara et al., who found that the anxiety/depression scores were related to HbA1c levels (correlation-coefficient, 0.41; P = 0.03) [31]. In addition, Eren et al., reported that the number of depressive episodes correlated positively with HbA1c levels [32].

Another longitudinal study investigated the correlation between depression and A1C levels in T2DM patients with and without depression. The authors observed that type 2 diabetic patients with depression exhibited higher HbA1c levels compared to patients without depression in all time points evaluated [33].

Results of the linear regression analysis revealed that decreased level of HDL-cholesterol and increased HADS anxiety score were significant predictors of depression. On the other hand, increased

Table 6
Predictors of MCI; results of multivariate logistic regression analysis.

Studied variables	B	P	OR	95% C.I.
Duration of DM	0.073	0.001*	1.075	1.030–1.122
FBG	0.539	<0.001*	1.715	1.394–2.109
Cholesterol	0.023	0.296	0.977	0.936–1.02
HDL	−0.992	<0.001*	2.697	1.657–4.39
Depression score	0.132	0.400	1.141	0.839–1.55
Anxiety score	0.675	<0.001*	1.965	1.356–2.847
Model Chi-square (P)	368.895* (<0.001*)			
Constant (P)	7.245* (0.007*)			

B: Regression coefficient.
OR: Odds ratio.
C.I.: confidence interval.
*: Statistically significant at p ≤ 0.05.

level of total cholesterol, decreased level of HDL-cholesterol, increased HADS depression score and decreased MoCA score were significant predictors of anxiety.

These results are in concordance with what was reported by Chew et al., who stated that There were significant and distinctive associations of anxiety, depressive symptoms, health-related quality of life, and medication adherence with glycemic state, blood pressure and lipid profile biomarkers [34].

Results of the logistic regression analysis revealed that HDL-cholesterol, HADS anxiety score, FBG, and duration of DM were the significant predictors of MCI. The patients with low HDL-cholesterol level were about three times more prone to MCI than those without (OR = 2.697). Moreover, patients having anxiety and those having uncontrolled FBG were about two times at higher risk of MCI (OR = 1.965 and 1.715 respectively). Also, patients with long duration of DM were slightly more prone to MCI (OR = 1.075).

These results matched the results stated by Chen et al., who found that age, years of education, duration of diabetes, fasting blood glucose, glycated hemoglobin, hypertension and waist-to-hip ratio were correlated with total MoCA score in patients with type 2 diabetes mellitus [35].

Similarly, the results reported by Ashrafi F. et al., who found that Lower FBS level was significantly associated with better MoCA score.

These results match those reported by Ming et al. who demonstrated that type 2 diabetic patients with MCI had a longer duration of diabetes; higher low density lipoprotein cholesterol (LDL-C), triglycerides, total cholesterol, HbA1c, and BMI; and lower high-density lipoprotein cholesterol (HDL-C) ($P < 0.05$) [36].

5. Conclusion

Patients with T2DM have a high prevalence of mild cognitive impairment, anxiety and depression. A strong positive significant correlation was found between HADS depression score and HADS anxiety score and a strong negative significant correlation was found between HADS anxiety and depression scores with MoCA score.

In view of results and conclusion of the study, we recommend that maintaining tight glycemic control and within normal range lipid profile parameters is very important to avoid long term complications and to decrease the incidence of mild cognitive impairment, anxiety and depression in diabetic patients.

Conflicts of interest

None.

Acknowledgement and Funding

This research was funded by Internal Medicine Department (Diabetes Unit), Neuro-psychiatry Department and Department of Public Health, Preventive and Social Medicine, Faculty of Medicine, Alexandria University, Egypt.

References

[1] Roglic G. WHO Global report on diabetes: a summary. International Journal of Noncommunicable Diseases 2016;1(1):3.
[2] Rathmann W, Giani G. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27(10):2568–9. author reply 9.
[3] Petersen RC, Smith GE, Ivnik RJ, Tangalos EG, Schaid DJ, Thibodeau SN, et al. Apolipoprotein E status as a predictor of the development of Alzheimer's disease in memory-impaired individuals. Jama 1995;273(16):1274–8.
[4] Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53(4):695–9.
[5] Tierney MC, Szalai JP, Snow WG, Fisher RH, Nores A, Nadon G, et al. Prediction of probable Alzheimer's disease in memory-impaired patients: a prospective longitudinal study. Neurology 1996;46(3):661–5.
[6] Gregg EW, Yaffe K, Cauley JA, Rolka DB, Blackwell TL, Narayan KM, et al. Is diabetes associated with cognitive impairment and cognitive decline among older women? Study of Osteoporotic Fractures Research Group. Arch Intern Med 2000;160(2):174–80.
[7] Perlmuter LC, Hakami MK, Hodgson-Harrington C, Ginsberg J, Katz J, Singer DE, et al. Decreased cognitive function in aging non-insulin-dependent diabetic patients. Am J Med 1984;77(6):1043–8.
[8] Messier C. Impact of impaired glucose tolerance and type 2 diabetes on cognitive aging. Neurobiol Aging 2005;26(Suppl 1):26–30.
[9] Reaven GM, Thompson LW, Nahum D, Haskins E. Relationship between hyperglycemia and cognitive function in older NIDDM patients. Diabetes Care 1990;13(1):16–21.
[10] Munshi M, Grande L, Hayes M, Ayres D, Suhl E, Capelson R, et al. Cognitive dysfunction is associated with poor diabetes control in older adults. Diabetes Care 2006;29(8):1794–9.
[11] Grodstein F, Chen J, Wilson RS, Manson JE. Type 2 diabetes and cognitive function in community-dwelling elderly women. Diabetes Care 2001;24(6):1060–5.
[12] Mooradian AD, Perryman K, Fitten J, Kavonian GD, Morley JE. Cortical function in elderly non-insulin dependent diabetic patients. Behavioral and electrophysiologic studies. Arch Intern Med 1988;148(11):2369–72.
[13] Fontbonne A, Berr C, Ducimetiere P, Alperovitch A. Changes in cognitive abilities over a 4-year period are unfavorably affected in elderly diabetic subjects: results of the Epidemiology of Vascular Aging Study. Diabetes Care 2001;24(2):366–70.
[14] Stewart R, Liolitsa D. Type 2 diabetes mellitus, cognitive impairment and dementia. Diabet Med 1999;16(2):93–112.
[15] Li L, Holscher C. Common pathological processes in Alzheimer disease and type 2 diabetes: a review. Brain Res Rev 2007;56(2):384–402.
[16] Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: the Rotterdam Study. Neurology 1999;53(9):1937–42.
[17] Committee DMIC. Advances and emerging opportunities in diabetes research: a stragegic planning report of the diabetes mellitus interagency coordinating committee. US Department of Health and Human Services, National Institutes of Health, Diabetes Mellitus Interagency Coordinating Committee; 2011.
[18] Kodl CT, Seaquist ER. Cognitive dysfunction and diabetes mellitus. Endocr Rev 2008;29(4):494–511.
[19] Cassano P, Fava M. Depression and public health: an overview. J Psychosom Res 2002;53(4):849–57.
[20] Moulton CD, Pickup JC, Ismail K. The link between depression and diabetes: the search for shared mechanisms. Lancet Diabetes Endocrinol 2015;3(6):461–71.
[21] Carnethon MR, Biggs ML, Barzilay JI, Smith NL, Vaccarino V, Bertoni AG, et al. Longitudinal association between depressive symptoms and incident type 2 diabetes mellitus in older adults: the cardiovascular health study. Arch Intern Med 2007;167(8):802–7.
[22] Katon W, von Korff M, Ciechanowski P, Russo J, Lin E, Simon G, et al. Behavioral and clinical factors associated with depression among individuals with diabetes. Diabetes Care 2004;27(4):914–20.
[23] Pickup JC. Inflammation and activated innate immunity in the pathogenesis of type 2 diabetes. Diabetes Care 2004;27(3):813–23.
[24] Hermanns N, Scheff C, Kulzer B, Weyers P, Pauli P, Kubiak T, et al. Association of glucose levels and glucose variability with mood in type 1 diabetic patients. Diabetologia 2007;50(5):930–3.
[25] Siddiqui S. Depression in type 2 diabetes mellitus–a brief review. Diabetes Metab Syndr 2014;8(1):62–5.
[26] Mikaliukstiene A, Zagminas K, Juozulynas A, Narkauskaite L, Salyga J, Jankauskiene K, et al. Prevalence and determinants of anxiety and depression symptoms in patients with type 2 diabetes in Lithuania. Med Sci Mon Int Med J Exp Clin Res 2014;20:182–90.
[27] Rajput R, Gehlawat P, Gehlan D, Gupta R, Rajput M. Prevalence and predictors of depression and anxiety in patients of diabetes mellitus in a tertiary care center. Indian J Endocrinol Metab 2016;20(6):746–51.
[28] Rustad JK, Musselman DL, Nemeroff CB. The relationship of depression and diabetes: pathophysiological and treatment implications. Psychoneuroendocrinology 2011;36(9):1276–86.
[29] Gao Y, Xiao Y, Miao R, Zhao J, Cui M, Huang G, et al. The prevalence of mild cognitive impairment with type 2 diabetes mellitus among elderly people in China: a cross-sectional study. Arch Gerontol Geriatr 2016;62:138–42.
[30] Eze CO, Ezeokpo BC, Kalu UA, Onwuekwe IO. The prevalence of cognitive impairment amongst type 2 diabetes mellitus patients at abakaliki south-east Nigeria. J Diabetes Metab Syndr Disord 2015;1(1).
[31] Balhara YPS, Sagar R. Correlates of anxiety and depression among patients with type 2 diabetes mellitus. Indian J Endocrinol Metab 2011;15(Suppl1):S50–4.
[32] Eren I, Erdi O, Ozcankaya R. [Relationship between blood glucose control and psychiatric disorders in type II diabetic patients]. Türk Psikiyatri Derg 2003;14(3):184–91.
[33] Richardson LK, Egede LE, Mueller M, Echols CL, Gebregziabher M. Longitudinal effects of depression on glycemic control in veterans with Type 2 diabetes.

Gen Hosp Psychiatry 2008;30(6):509–14.
[34] Chew BH, Sherina MS, Hassan NH. Association of diabetes-related distress, depression, medication adherence, and health-related quality of life with glycated hemoglobin, blood pressure, and lipids in adult patients with type 2 diabetes: a cross-sectional study. Therapeut Clin Risk Manag 2015;11:669–81.
[35] Chen S, Zuo X, Li Y, Jiang T, Zhang N, Dai F, et al. Ghrelin is a possible new predictor associated with executive function in patients with type 2 diabetes mellitus. J Diabetes Investig 2017;8(3):306–13.
[36] Niu M-j, Yin F-z, Liu L-x, Fang Y, Xuan X-m, Wu G-f. Non-high-density lipoprotein cholesterol and other risk factors of mild cognitive impairment among Chinese type 2 diabetic patients. J Diabet Complicat 2013;27(5):443–6.