Cognitive impairment and depression in patients with diabetic retinopathy

Marwa Ahmed[a], Mohamed El-Sayed[b], Mohamad Gad[c], Mohamad Al-Adlany[a]

Departments of [a]Internal Medicine, [b]Psychiatry, [c]Ophthalmology, Mansoura Faculty of Medicine, Mansoura University, Mansoura, Egypt

Correspondence to Mohamed El -Sayed, MBBCH, MSc, MD, Associate Professor of Psychiatry, Department of Psychiatry, Mansoura Faculty of Medicine, Mansoura University, Mansoura, Egypt.
e-mail: mohmits@yahoo.com

Received: 10 April 2019
Revised: 1 May 2019
Accepted: 7 May 2019
Published: 22 January 2020

Egyptian Journal of Psychiatry 2020, 41:1–6

Background
Several reports have shown that cognitive impairment risk is increased in diabetes mellitus by about 40%. Abnormalities in the retinal vascular cytoarchitecture resulting from diabetes might be responsible for cognitive impairment as the blood-brain and blood-retinal barriers are similar Such potential relationship between abnormalities in the retinal vascular structure and cognitive impairment is highly valuable in predicting the risk for cognitive impairment in diabetes.
Aim of the work
This study aims to examine the association between diabetic retinopathy and cognitive impairment in diabetic patients both type 1 and type 2.
Patients and methods
A total of 200 patients with diabetes were selected (120 diabetic patients with retinopathy, 46 diabetic nonretinopathy patients, and 34 newly diagnosed diabetic patients). All patients were assessed using retinal photography, Hamilton depression rating scale, mini-mental state examination, and trail making test.
Results
Cognitive impairment was significantly higher in individuals with diabetic retinopathy when compared with individuals without retinopathy and newly diagnosed diabetes mellitus. Patients with diabetic retinopathy were significantly more severely depressed relative to other groups of patients.
Conclusion
Our results revealed that diabetic retinopathy was associated with cognitive impairment. However, the degree of retinopathy did not appear to have significant correlation with the degree of cognitive impairment.

Keywords:
cognitive impairment, depression, diabetes, diabetic retinopathy

Egypt J Psychiatr 41:1–6
© 2020 Egyptian Journal of Psychiatry
1110-1105

Introduction

Diabetes mellitus is a main health problem all over the world. In 2010, it has been estimated that more than 200 million people suffer from it. The worldwide population is expected to increase by 62%, and the prevalence of diabetes mellitus is expected to increase by over 120% (Romero-Aroca *et al.*, 2012).

In Egypt, it has been detected that prevalence of diabetes mellitus in the urban population is higher in comparison to the rural population, regardless of higher (20%) or lower socioeconomic standard (13.5%) (Sherif and Sumpio, 2015).

One of the studies conducted in Egypt demonstrated that over a period of eighteen years, prevalence and incidence of diabetes mellitus type 1 had increased among children younger than 18 years living in the Nile Delta region. Higher occurrence of type 1 diabetes mellitus was observed in rural areas and female predominance was established. Seasonality in type 1 diabetes mellitus diagnosis was reported with a peak occurrence in winter (El-Ziny *et al.*, 2014).

There is a complex relationship between diabetes mellitus and psychiatric disorders (Alagiakrishnan and Sclater, 2012). It has been found that patients suffering from depression comorbid with type 2 diabetes mellitus often have poorer glycemic control in comparison to the non-depressed patients, which may progress to further health complications and increase in mortality rates. So, it is vital to note that one of the important risk factors for poorer quality of life is depression (Carper *et al.*, 2014).

The available evidence points to the way that risk of cognitive dysfunction is raised in diabetes, by about 40%. The association is more prominent in relation to more specific diseases of cognition with 2 folds increase risk for Alzheimer's disease and 3 folds increase risk for vascular dementia (Serlin *et al.*, 2011).

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

 DOI: 10.4103/ejpsy.ejpsy_13_19

There are embryological, anatomical and physiological properties shared by both the brain and the retina. Therefore, similar features were found between the blood brain barrier (BBB) and the blood retinal barrier (BRB) (Steuer *et al.*, 2005), and clinical evidence reveals correlated breakdown of the BRB and BBB under some clinical conditions (Ozkan *et al.*, 2014; Greiner *et al.*, 2015).

Prevention plans should be done to predict the risk for cognitive impairment. Screening for diabetic retinopathy would be an effective way to predict the risk for cognitive impairment (Patton *et al.*, 2005).

Aim of the study

This study aims to examine the association between diabetic retinopathy and cognitive impairment in diabetic patients, both type 1 and type 2.

Patients and methods

Selection of the patients

This cross-sectional study was carried out in inpatient and outpatient clinics of specialized medical hospital and ophthalmic center, Mansoura University, during the period from May 2015 to May 2016.

Ethical consideration

The study proposal was approved by IRB, Faculty of Medicine, Mansoura University. All participants gave an informed consent to participate in the study. Informed consent was taken from each patient, the consent contained appropriate details about nature of the study, method, aim of the work, and its futuristic importance. Confidentiality of data was assured.

Patients

The study was conducted on 200 diabetic patients.

The patients were divided into three groups: (a) 120 diabetic patients with retinopathy, (b) 46 diabetic nonretinopathy patients, and (c) 34 newly diagnosed diabetic patients.

Inclusion criteria

(a) Type 1 and type 2 DM and (b) age 15–50 years old were the inclusion criteria.

Exclusion criteria

(a) History of cerebrovascular stroke, (b) history of malignancy elsewhere in the body, (c) history of previous primary psychiatric disorders, and (d) presence of chronic medical diseases or medication that interfere with cognitive function were the exclusion criteria.

Assessment

(1) Initial assessment included the following: detailed history taking with stress on age; education; duration of diabetes; treatment modality whether insulin or oral drugs or both; controlled or not; presence of other diabetic complications, especially diabetic nephropathy; smoking history; and history of any other eye diseases, such as cataract, glaucoma, or errors of refraction that may affect cognitive function of the patients.
(2) Retinal photography and grading was done by an ophthalmologist using high-resolution digital retinal camera.
(3) Assessment of depression and cognitive functions:
    (a) Hamilton depression rating scale (Bagby*et al.*, 2004): scoring was as follows: scores of 0–7 are considered normal, scores of 8–13 are considered mild, from 14 to 18, are considered moderate, from 19 to 22 are considered severe, and more than or equal to 23 are considered very severe. Questions 18–20 may be recorded to give further information about the depression (such as whether diurnal variation or paranoid symptoms are present), but are not part of the scale (Williams, 1988).
    (b) Mini-mental state examination: it is a brief 30-point neuropsychometric test, for cognitive functions; a score higher than 26 (maximum score=30) indicates no cognitive impairment (Folstein*et al.*, 1975).
    (c) Trail making test (part a and part b).

Trail making test has an important spatial component that is connected to the right hemisphere and also evaluates visual-motor ability and perceptive quickness. In addition to the spatial component, test execution needs logical and sequential thought, which is why it is more connected to the left hemisphere. It also measures working memory, inhibition capacity, mental flexibility, alternating attention, and anticipation capacity (Coullaut-Valera *et al.*, 2011).The test requires the participant to connect a sequence of 25 consecutive targets on a sheet. There are two parts to the test: in part a, the targets are all numbers (1, 2, 3, etc.) and the participant needs to connect them in a sequential order, and in part b, the participant alternates between numbers and letters (1, A, 2, B, etc.) (Berberian *et al.*, 2019).

Scoring results for both trail making tests (trail making test A and B) are reported as the number of seconds

Table 1 Demographic variables among the three groups

	Diabetic retinopathy/ diabetic nonretinopathy	*P*1	Diabetic retinopathy/ newly diagnosed DM	*P*2	Diabetic nonretinopathy/ newly diagnosed DM	*P*3
Age (mean ±SD) (years)	31.4±9.4/32.9±10.2	0.860 (NS)	31.4±9.4/30.4±10.1	0.005 (S)	32.9±10.2/30.4±10.1	<0.001 (HS)
Sex [*n* (%)]						
Male	40 (33.3)/16 (34.8)	0.860 (NS)	40 (33.3)/11 (32.4)	0.915 (NS)	16 (34.8)/11 (32.4)	0.820 (NS)
Female	80 (66.7)/30 (65.2)	0.860 (NS)	80 (66.7)/23 (67.6)	0.915 (NS)	30 (65.2)/23 (67.6) (32.4)	0.820 (NS)
Residence [*n* (%)]						
Urban	52 (43.3)/33 (71.7)	0.001 (HS)	52 (43.3)/21 (61.7)	0.057 (S)	13 (28.3)/21 (61.7)	0.346 (NS)
Rural	68 (56.7)/13 (28.3)	0.001 (HS)	68 (56.7)/13 (28.3)?	0.057 (S)	33 (71.7)/13 (28.3)	0.346 (NS)
Occupation [*n* (%)]						
Yes	46 (38.3)/18 (39.1)	0.925 (NS)	46 (38.3)/27 (79.4)	<0.001 (HS)	18 (39.1)/27 (79.4)	<0.001 (HS)
No	74 (61.7)/28 (60.9)		74 (61.7)/7 (20.6)		28 (60.9)/7 (20.6)	

DM, diabetes mellitus; HS, highly significant; NS, nonsignificant; S, significant. *P*1 means the significance between diabetic retinopathy and diabetic nonretinopathy group. *P*2 means the significance between diabetic retinopathy and newly diagnosed DM group. *P*3 means the significance between diabetic nonretinopathy group and newly diagnosed DM group.

required for completion of the task; therefore, higher scores reveal greater impairment.

Statistical analysis

All statistical analyses were done using SPSS, version 20 for Windows (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). A two-tailed *P* value less than 0.05 was considered. Continuous data were expressed as mean ±SD and median interquartile range for parametric and nonparametric data, respectively. Comparative analysis of continuous parametric data between all study groups was done using one-way analysis of variance followed by planned contrast for comparison between individual groups. Comparative analysis of individuals with diabetic retinopathy and those without retinopathy regarding duration of DM was done using Mann–Whitney test. A comparative analysis of depression score between different studied groups was done using Kruskal–Wallis tests, followed by Mann–Whitney tests for comparison between individual groups.

Results

Table 1 shows there was no significant difference between individuals with diabetic retinopathy and those without retinopathy regarding age and sex. Meanwhile, the newly diagnosed were significantly younger than the other two groups. Prevalence of individuals from urban areas was found to be significantly higher in diabetic retinopathy group when compared with diabetic nonretinopathy group ($P<0.05$).

There were significantly more working individuals among the newly diagnosed group than each of the other groups ($P>0.05$).

Table 2 Comparison between different groups regarding duration of diabetes

	Diabetic retinopathy	Diabetic nonretinopathy	*P*
Duration of diabetes	12 (8–15.75)	6 (3–10)	<0.001 (HS)

HS, highly significant.

In Table 2, there was significantly shorter duration in nonretinopathy group ($P<0.001$).

Table 3 shows that depression was more in DM patients with diabetic retinopathy when compared with other groups ($P<0.001$).

Patients with diabetic retinopathy were significantly more severely depressed relative to other groups of patients ($P<0.05$).

Table 4 shows that cognitive impairment was significantly higher in individuals with diabetic retinopathy when compared with individuals without retinopathy and newly diagnosed DM ($P<0.05$).

In Table 5, depression severity was significantly negatively correlated with mini-mental state examination ($P<0.05$), whereas there was no significant correlation with trail making test ($P>0.05$).

Table 6 shows that there was no significant correlation between severity of retinopathy and cognitive impairment ($P>0.05$).

Discussion

In the current study, no significant difference was found between individuals with diabetic retinopathy

Table 3 Comparison between different groups regarding severity of depression

Depression [*n* (%)]	Diabetic retinopathy/ diabetic nonretinopathy	*P*1	Diabetic retinopathy/ newly diagnosed DM	*P*2	Diabetic nonretinopathy/ newly diagnosed DM	*P*3	χ^2
Depression total score	21 (16–23)/ 10 (7–17)	<0.001 (HS)	21 (16–23)/ 10 (7–18)	<0.001 (HS)	10 (7–17)/10 (7–18)	0.522 (NS)	43.6
Normal mood	12 (10)/14 (30.4)	<0.001	12 (10)/12 (35.3)	0.021	14 (30.4)/12 (35.3)	0.195	72.5
Mild depression	6 (5)/20 (43.5)	0.005	6 (5)/9 (26.5)	0.002	20 (43.5)/9 (26.5)	0.213	75.3
Moderate	20 (16.7)/6 (13)	0.021	20 (16.7)/6 (17.6)	0.031	6 (13)/6 (17.6)	0.445	50.2
Severe	36 (30)/0 (0)	0.003	36 (30)/3 (8.8)	<0.001	0 (0)/3 (8.8)	0.235	13.8
Very severe	46 (38.3)/6 (13)	0.032	46 (38.3)/4 (11.8)	<0.001	6 (13)/4 (11.8)	0.195	23.5

DM, diabetes mellitus; HS, highly significant; NS, nonsignificant.

Table 4 Cognitive impairment among the three groups

	Diabetic retinopathy/ diabetic nonretinopathy	*P*1	Diabetic retinopathy/ newly diagnosed DM	*P*2	Diabetic nonretinopathy/newly diagnosed DM	*P*3	χ^2
MMSE [*n* (%)]							
Normal	102 (85)/46 (100)	0.010 (S)	102 (85)/34 (100)	0.029 (S)	46 (100)/34 (100)	–	13.2
Impaired	18 (15)/0 (0)	–	18 (15)/0 (0)	–	0 (0)/0 (0)	–	
Trail making test [*n* (%)]							
Average	42 (35)/30 (65.2)	<0.001 (HS)	42 (35)/26 (76.5)	<0.001 (HS)	30 (65.2)/26 (76.5)	<0.001 (HS)	24.5
Deficient	78 (65)/16 (34.8)	<0.001 (HS)	78 (65)/26(76.5)	<0.001 (HS)	16 (34.8)/26 (76.5)	<0.001 (HS)	24.5

DM, diabetes mellitus; HS, highly significant; MMSE, mini-mental state examination.

Table 5 Correlation between severity of depression and cognitive impairment

Outcome	Depression	*P*
MMSE	–0.444	<0.001 (HS)
Trail making test	0.125	0.078 (NS)

HS, highly significant; MMSE, mini-mental state examination; NS, nonsignificant.

Table 6 Correlation between severity of retinopathy and cognitive impairment

Outcome	Retinopathy	*P*
Mini-mental state examination	0.049	0.582 (NS)
Trail making test	0.003	0.974 (NS)

NS, nonsignificant.

and those without retinopathy as regard age and gender. However, prevalence of individuals from urban areas was found to be significantly higher in diabetic retinopathy group when compared to diabetic non-retinopathy group. Such differences between the rural and urban groups might be due to life style disparities. Although diet was found similar in both groups, there are still major variances in physical exercise. Aerobic activity is associated with improvement in endothelial function in type 1 diabetes mellitus patients through glucose-independent mechanisms (Alemu *et al.*, 2015).

The rural group of type 1 diabetes mellitus in the sample of this study, was formed mainly of subsistence farmers. They had an extremely demanding life style in contrast to the urban group. Karoline de Morais (2015) found that physical activity, when continued by farmers, is related to reduction in endothelial dysfunction, the early step in start of retinopathy. Also, it may also be a contributing factor for the lower levels of hypertension in the rural group (Karoline de Morais *et al.*, 2015).

The finding in this study regarding, the absence of current occupation in diabetic patients with retinopathy and depression in contrast to other two groups, was similar to the results of Egede (2004). This may be explained by that the occurrence of retinopathy in diabetic patients would have a great effect on vision, and subsequently, poorer quality of life. It was suggested that the co-occurrence of diabetes and depression has a synergistic consequence on disability resulting in decline in productivity and quality of life (Grandy *et al.*, 2008).

Two important findings were found in this study. First, depression was more common in diabetic patients with retinopathy when compared to other groups. Second, diabetic retinopathy patients had more severe depression. These two finding are in accord with a meta-analytic report reporting a consistent, statistically significant relationship between depression and diabetic retinopathy (Fiore *et al.*, 2015). Diagnosis of diabetes can be a shock, resulting in emotions and feelings guilt, anger or denial. Although anxiety and even sadness are considered as a normal part of adjusting or coping to changes in the patient

lifestyle, these feelings by some people did not disappear and could progress to persistent depression and/or anxiety disorder (Clarke and Currie, 2009).

A valuable study by (Poongothai *et al.* 2011) found that prevalence of depression was higher in patients with retinopathy. Also, it was found that patients with depression are more susceptible to have an comorbid diabetes mellitus (Poongothai *et al.* 2017). Depression is associated with inflammatory and neuroendocrine responses which contribute to the progression of micro-vascular and macro-vascular complications in patients with type 2 diabetes (Poongothai *et al.* 2015). Depression was found to affect glycemic state in two ways; untreated depression could worsen control of glycemic state in diabetes, with increased possibility of complications and poor prognosis, while improvement in depression symptoms is linked to better control of glycemic state Poongothai *et al.* (2011). It was proposed that many patients with diabetes are not suffering from clinical depression but instead they showed high levels of diabetes distress resulting from the emotional and interpersonal stress of diabetes, physician communication and treatment plan Carper *et al.* (2014).

The present study found that there was highly significant difference between individuals with diabetic retinopathy group and individuals without retinopathy as regard duration of diabetes as it was significantly longer in the diabetic retinopathy group.

Duration of diabetes mellitus revealed positive correlation with clinical and subclinical cerebral vascular diseases and cerebral infarctions resulting in cognitive impairment. This finding is in agreement with other findings in which cerebral vascular diseases in middle-age predict cognitive decline in old age (Roberts *et al.*, 2008).

Ravona-Springer *et al.* (2014) showed that poor control of glycemic state foretold a decline in cognitive performance in old age. (Winkler *et al.*, 2014). Feinkohl and his Colleagues suggested that aggressive treatment by hypoglycemic drugs may induce permanent harm that predispose diabetic patients to cognitive impairment by the time these drugs were initiated (Feinkohl *et al.* 2015).

Overall, diabetic retinopathy can be viewed as a robust substitute marker for cognitive impairment in patients with diabetes, in which cerebral vascular disease may have a significant pathogenic role. This could be attributed to the fact that diabetes is associated with cerebrovascular dysfunction through ischemia of the micro-vascular system and endothelial dysfunction leading to a state of chronic cerebral hypo-perfusion and these changes may disturb regional cerebral blood flow leading to impairment in cerebral protein synthesis, a key factor for learning and memory (Hugenschmidt *et al.*, 2014).

Conclusions and recommendations

Our results revealed that diabetic retinopathy was associated with cognitive impairment. However, the degree of retinopathy did not appear to have significant correlation with the degree of cognitive impairment. Regarding depression, there was significant positive relationship between depression and duration of diabetes mellitus.

Thus, diabetic retinopathy was independently associated with cognitive impairment in diabetic patients. The cognitive impairment associated with diabetes may be vulnerable to preventive and therapeutic strategies through protecting the cerebral microvasculature and diminishing the harm and danger of the occurrence of mild vascular disease in old age diabetic patients.

Recommendations

Screening all diabetic patients for the presence of retinopathy regularly:

Screening and assessment of depression and cognitive function in patients with diabetic retinopathy.

Prospective studies for more follow up of patients.

Use of Neuropsychiatric battery for more detailed assessment of cognitive function.

Limitations of the study

Effect of treatment of diabetic retinopathy was not studied and its relationship to improvement of cognitive decline.

Compliance of the patients to treatment of diabetes and whether this may affect cognitive impairment or not was not studied.

Lack of follow up assessment for patients without significant retinopathy to show if there is a growing relationship between diabetic retinopathy progression and cognitive impairment. Visual acuity of patients was not assessed and its effect on cognitive function.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

Alagiakrishnan K, Sclater A (2012). Psychiatric disorders presenting in the elderly with type 2 diabetes mellitus. Am J Geriatr Psychiatry 20:645–652.

Alemu S, Abere D, Asamere T, Patterson CC, Parry EHO, Phillips DIW, Trimble ER (2015). Retinopathy in type 1 diabetes mellitus: major differences between rural and urban dwellers in Northwest Ethiopia. Diabetes Res Clin Pract 109:191–198.

Bagby RM, Ryder AG, Schuller DR, Marshall MB (2004). The Hamilton depression rating scale: has the gold standard become a lead weight? Am J Psychiatry 161:2163–2177.

Berberian AA, Ary G, Dias NM, Mecca TP, Comfort WE, Bressan RA, Lacerda AT (2019). Component mechanisms of executive function in schizophrenia and their contribution to functional outcomes. Rev Brasil Psiquiat (Sao Paulo, Brazil) 41:22–30.

Carper MM, Lara T, Gonzalez JS, Wexler DJ, Psaros C, Safren SA (2014). The differential associations of depression and diabetes distress with quality of life domains in type 2 diabetes. J Behav Med 37:501–510.

Clarke DM, Currie KC (2009). Depression, anxiety and their relationship with chronic diseases: a review of the epidemiology, risk and treatment evidence. Med J Aust 190(7 Suppl):S54–S60.

Coullaut-Valera R, Del Rio IA-D, de Arrue-Ruiloba R, Coullaut-Valera J, Bajo-Breton R (2011). Cognitive deterioration associated with the use of different psychoactive substances. Actas Esp Psiquiatr 39:168–173.

Ding J, Patton N, Deary IJ, Strachan MWJ, Fowkes FGR, Mitchell RJ, Price JF (2008). Retinal microvascular abnormalities and cognitive dysfunction: a systematic review. Br J Ophthalmol 92:1017–1025.

Egede LE (2004). Effects of depression on work loss and disability bed days in individuals with diabetes. Diabetes Care 27:1751–1753.

El-Ziny MAE-M, Salem NA-B, El-Hawary AK, Chalaby NM, Elsharkawy AA-E (2014). Epidemiology of childhood type 1 diabetes mellitus in Nile Delta, Northern Egypt – a retrospective study. J Clin Res Pediatr Endocrinol 6:9–15.

Feinkohl I, Price JF, Strachan MWJ, Frier BM (2015). The impact of diabetes on cognitive decline: potential vascular, metabolic, and psychosocial risk factors. Alzheimer's Res Ther 7:46.

Fiore V, Marci M, Poggi A, Giagulli VA, Licchelli B, Iacoviello M, *et al.* (2015). The association between diabetes and depression: a very disabling condition. Endocrine 48:14–24.

Folstein MF, Folstein SE, McHugh PR (1975). 'Mini-Mental State'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189–198.

Grandy S, Chapman RH, Fox KM (2008). Quality of life and depression of people living with type 2 diabetes mellitus and those at low and high risk for type 2 diabetes: findings from the study to help improve early evaluation and management of risk factors leading to diabetes (SHIELD). Int J Clin Pract 62:562–568.

Greiner J, Dorovini-Zis K, Taylor TE, Molyneux ME, Beare NAV, Kamiza S, White VA (2015). Correlation of hemorrhage, axonal damage, and blood-tissue barrier disruption in brain and retina of Malawian children with fatal cerebral malaria. Front Cell Infect Microbiol 5:18.

Hilal S, Ong Y-T, Cheung CY, Tan C, Venketasubramanian N, Niessen WJ, *et al.* (2014). Microvascular network alterations in retina of subjects with cerebral small vessel disease. Neurosci Lett 577:95–100.

Hugenschmidt CE, Lovato JF, Ambrosius WT, Bryan RN, Gerstein HC, Horowitz KR, *et al.* (2014). The cross-sectional and longitudinal associations of diabetic retinopathy with cognitive function and brain mri findings: the action to control cardiovascular risk in diabetes (ACCORD) trial. Diabetes Care 37:3244–3252.

IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.

Ikram MK, de Jong FJ, Vernooij MW, Hofman A, Niessen WJ, van der Lugt A, *et al.* (2013). Retinal vascular calibers associate differentially with cerebral gray matter and white matter atrophy. Alzheimer Dis Assoc Disord 27:351–355.

Karoline de Morais P, Sales MM, Alves de Almeida J, Motta-Santos D, Victor de Sousa C, Simoes HG (2015). Effects of aerobic exercise intensity on 24-h ambulatory blood pressure in individuals with type 2 diabetes and prehypertension. J Phys Ther Sci 27:51–56.

Ozkan ERG, Topcuoglu MA, Arsava EM. (2014). Blood-retina-barrier disruption accompanying blood-brain-barrier dysfunction in posterior reversible encephalopathy syndrome. J Neurol Sci 346:315–317.

Patton N, Aslam T, Macgillivray T, Pattie A, Deary IJ, Dhillon B (2005). Retinal vascular image analysis as a potential screening tool for cerebrovascular disease: a rationale based on homology between cerebral and retinal microvasculatures. J Anat 206:319–348.

Poongothai S, Anjana RM, Pradeepa R, Ganesan A, Unnikrishnan R, Rema M, Mohan V (2011). Association of depression with complications of type 2 diabetes – the Chennai Urban Rural Epidemiology Study (CURES- 102). J Assoc Phys India 59:644–648.

Poongothai S, Anjana RM, Radha S, Sundari BB, Rani CSS, Mohan V (2017). Epidemiology of depression and Its relationship to diabetes in India. J Assoc Phys India 65:60–66.

Poongothai S, Pradeepa R, Indulekha K, Surendar J, Mohan V (2015). Association of depression with common carotid artery intima media thickness and augmentation index in a large Urban South Indian population- the Chennai Urban rural epidemiology study (CURES - 138). Indian J Endocrinol Metabol 19:136–142.

Qiu C, Cotch MF, Sigurdsson S, Jonsson PV, Jonsdottir MK, Sveinbjrnsdottir S, *et al.* (2010). Cerebral microbleeds, retinopathy, and dementia: the AGES-Reykjavik Study. Neurology 75:2221–2228.

Ravona-Springer R, Heymann A, Schmeidler J, Moshier E, Godbold J, Sano M, *et al.* (2014). Trajectories in glycemic control over time are associated with cognitive performance in elderly subjects with type 2 diabetes. PloS One 9: e97384.

Rawlings AM, *et al.* (2014). Diabetes in midlife and cognitive change over 20 years: a cohort study. Ann Inter Med 161:785–793.

Roberts RO, Geda YE, Knopman DS, Christianson TJH, Pankratz VS, Boeve BF, *et al.* (2008). 'Association of duration and severity of diabetes mellitus with mild cognitive impairment. Arch Neurol 65:1066–1073.

Romero-Aroca P, Baget-Bernaldiz M, Reyes-Torres J, Fernandez-Ballart J, Plana-Gil N, Mendez-Marin I, Pareja-Rios A (2012). Relationship between diabetic retinopathy, microalbuminuria and overt nephropathy, and twenty-year incidence follow-up of a sample of type 1 diabetic patients. J Diabetes Complications 26:506–512.

Serlin Y, Levy J, Shalev H. (2011). Vascular pathology and blood-brain barrier disruption in cognitive and psychiatric complications of type 2 diabetes mellitus. Cardiovasc Psychiatry Neurol 2011:609202.

Sherif S, Sumpio BE. (2015). Economic development and diabetes prevalence in MENA countries: Egypt and Saudi Arabia comparison. World J Diabetes 6:304–311.

Steuer H, Jaworski A, Elger B, Kaussmann M, Keldenich J, Schneider H, *et al.* (2005). Functional characterization and comparison of the outer blood-retina barrier and the blood-brain barrier. Invest Ophthalmol & Vis Sci 46:1047–1053.

Thompson CS, Hakim AM. (2009). Living beyond our physiological means: small vessel disease of the brain is an expression of a systemic failure in arteriolar function: a unifying hypothesis. Stroke 40:e322–e330.

Williams JB (1988). A structured interview guide for the hamilton depression rating scale. Arch Gen Psychiatry 45:742–747.

Winkler A, Dlugaj M, Weimar C, Jockel K-H, Erbel R, Dragano N, Moebus S (2014). Association of diabetes mellitus and mild cognitive impairment in middle-aged men and women. J Alzheimer's Dis 42:1269–1277.

Zoungas S, *et al.* (2014). Impact of age, age at diagnosis and duration of diabetes on the risk of macrovascular and microvascular complications and death in type 2 diabetes. Diabetologia 57:2465–2474.