Neurocognitive Changes and Their Neural Correlates in Patients with Type 2 Diabetes Mellitus

Junghyun H Lee[1,2,]*, Yera Choi[2,3,]*, Chansoo Jun[1,2], Young Sun Hong[2,4], Han Byul Cho[2,3], Jieun E Kim[2,5], In Kyoon Lyoo[1,2]

[1]College of Pharmacy and Graduate School of Pharmaceutical Sciences, Ewha Womans University; [2]Ewha Brain Institute, Ewha Womans University; [3]Interdisciplinary Program in Neuroscience, Seoul National University College of Natural Sciences; [4]Department of Internal Medicine, Ewha Womans University School of Medicine; [5]Department of Brain and Cognitive Sciences, Ewha Womans University Graduate School, Seoul, Korea

As the prevalence and life expectancy of type 2 diabetes mellitus (T2DM) continue to increase, the importance of effective detection and intervention for the complications of T2DM, especially neurocognitive complications including cognitive dysfunction and dementia, is receiving greater attention. T2DM is thought to influence cognitive function through an as yet unclear mechanism that involves multiple factors such as hyperglycemia, hypoglycemia, and vascular disease. Recent developments in neuroimaging methods have led to the identification of potential neural correlates of T2DM-related neurocognitive changes, which extend from structural to functional and metabolite alterations in the brain. The evidence indicates various changes in the T2DM brain, including global and regional atrophy, white matter hyperintensity, altered functional connectivity, and changes in neurometabolite levels. Continued neuroimaging research is expected to further elucidate the underpinnings of cognitive decline in T2DM and allow better diagnosis and treatment of the condition.

Keywords: Diabetes mellitus, type 2; Cognition disorders; Dementia; Hyperglycemia; Hypoglycemia; Magnetic resonance imaging; Magnetic resonance spectroscopy

INTRODUCTION

Diabetes mellitus (DM) has risen as an important global health concern with a continued worldwide increase in its prevalence [1]. Type 2 diabetes mellitus (T2DM) in particular is expected to become more common and widespread in many countries, with the proliferation of obesity and the aging of the population [2]. Meanwhile, achieving a normal life expectancy for T2DM patients has become more attainable through effective modulation of the life-threatening cardiovascular and renal complications associated with the disease [1,3]. Accordingly, an improved understanding of debilitating diabetic complications is now of even greater importance for the long-term management of T2DM. In particular, T2DM-induced neurocognitive changes including cognitive decline and dementia may significantly affect the quality of life of patients and their caregivers and pose challenges to clinicians and researchers. In the present review, we will discuss the characteristic cognitive impairment observed in T2DM and present a summary of the outcomes from recent neuroimaging studies focusing on

---

Corresponding author: In Kyoon Lyoo
College of Pharmacy and Graduate School of Pharmaceutical Sciences, Ewha Brain Institute, Ewha Womans University, Suite #202, Appenzeller Building, 52 Ewhayeodae-gil, Seodaemun-gu, Seoul 120-750, Korea
Tel: +82-2-3277-3039, **Fax:** +82-2-3277-3044, **E-mail:** inkylyoo@ewha.ac.kr
*These authors contributed equally to this work.

T2DM-related brain deficits in humans.

FEATURES OF NEUROCOGNITIVE CHANGES IN T2DM

DM in general is known to increase the risk of cognitive dysfunction and dementia [4-6]. A recent systematic review of longitudinal population-based studies revealed that the incidence rates of dementia were higher in diabetic populations than in nondiabetic populations [6]. A number of DM-related factors such as macrovascular and microvascular diseases, glucose toxicity, and hyperinsulinemia have been suggested to be involved in the emergence of cognitive impairment in DM [6], but the complexity of multifactorial influences makes it difficult to precisely delineate the exact determinants of the phenomenon.

The incidence rate of dementia in T2DM is suggested to be 1.5 to 2.5 times higher than that in the general population [2]. A meta-analysis based on nine population-based longitudinal studies in T2DM revealed a meaningful association between T2DM and progressive cognitive decline, including development of dementia [7]. Interestingly, the same cognitive domains that are impaired in T2DM are also observed to be affected in prediabetic stages [8], despite a smaller effect size [9]. These prediabetic cognitive deficits raise the possibility that glucose intolerance, which starts to arise in prediabetic or early diabetic stages, may play a role in the decline of cognitive function.

FACTORS INFLUENCING NEUROCOGNITIVE IMPAIRMENT IN T2DM

Complex factors including comorbid vascular diseases and the level of glycemic control are believed to influence the manifestation of cognitive impairment related to T2DM [2,10]. Here, we will briefly review some of the potential risk factors that have been repeatedly identified in the existing literature: hyperglycemia, hypoglycemia, and vascular diseases [2].

Hyperglycemia
Acute hyperglycemia induced by a glucose clamp technique in T2DM was reported to impede cognitive function in T2DM [11]. Also, in older women, an increased level of glycated hemoglobin (HbA1c), an indicator of average blood glucose levels over the past few months, was associated with the risk of developing cognitive impairment in later years [12]. These outcomes support the hypothesis that the hyperglycemic state is a major player in DM-related cognitive decline.

Determining the extent of the effect of hyperglycemia on cognitive decline in T2DM is complicated since many other factors associated with the diabetic condition also appear to be involved. For instance, according to a recent study with an elderly cohort, the effect of elevated fasting plasma glucose (FPG) levels on cognitive decline was not greater than that of hypertriglyceridemia or low high density lipoprotein levels [13]. Another study reported that the degree of hyperglycemia measured by the HbA1c level exhibited less predictive power as compared to the diabetic status itself [14]. It should be noted that using HbA1c or FPG as a marker for hyperglycemia in T2DM may have inherent limitations, as these measures do not fully reflect the short-term temporal variations in the hyperglycemic condition. Indeed, an investigation of the relationship between the T2DM-related cognitive decline and daily fluctuations in glucose levels found an independent correlation between glycemic instability and cognitive decline [15], indicating the potential importance of day-to-day glycemic control in DM-related cognitive impairment.

Hypoglycemia
Acute hypoglycemia, which may occur as a side effect of insulin administration, is known to disrupt brain functional efficiency [16]. In particular, an episode of severe hypoglycemia is known to be associated with neuronal damage in the brain areas crucial for learning and memory, including the hippocampus and cerebral cortices [17]. Hypoglycemia is thus likely to be influential in DM-related cognitive decline and related brain deficits. The excitotoxic effect of increased neuroactive amino acids has been suggested as a potential mechanism of neuronal damage induced by hypoglycemia [18]. The activation of neuronal nicotinamide adenine dinucleotide phosphate oxidase during glucose reperfusion, rather than hypoglycemia itself, has also been proposed as the direct cause of the neuronal damage [19].

Although hypoglycemia is more frequently observed in patients with T1DM, it is also common in patients with T2DM who are treated with insulin or orally-administered glucose-lowering drugs [20]. Thus far, investigations into the potential causal relationship between hypoglycemia and cognitive impairment in T2DM have resulted in mixed findings. In a study with an elderly population with T2DM, severe hypoglycemia was found to increase the risk of dementia [21]. Yet, there is evidence that cognitive dysfunction may actually be a cause of hypoglycemia rather than the result of it, as cognitive dysfunc-

tion may hinder adequate glycemic modulation through regular drug administration [22-24].

Vascular diseases

T2DM shows high comorbidity with many macrovascular and microvascular diseases [25]. A substantial amount of research suggests that vascular complications are a risk factor for cognitive decline in patients with DM [26,27]. DM has been suggested as an important risk factor in the pathogenesis of vascular dementia [28]. In patients with DM, brain alterations including white mater hyperintensity (WMH) and subcortical atrophy may arise as a result of the degeneration of cerebral small vessels [29]. These alterations are associated with the emergence of cognitive dysfunction [29]. Identification of a shared mechanism linking DM, cerebrovascular diseases, and cognitive decline would be an important research goal for the early detection of and intervention in DM-related neurocognitive impairment.

NEURAL CORRELATES OF NEUROCOGNITIVE IMPAIRMENT IN T2DM: EVIDENCE FROM NEUROIMAGING STUDIES

Both acute and chronic brain alterations in DM are presumed to be associated with the generation of cognitive impairment in DM [30]. Even though the exact pathophysiology linking DM and cognitive dysfunction remains unclear, recent brain imaging studies aided by state-of-the-art neuroscientific techniques have begun to shed light on related issues. In the following section, we will review the neuroimaging findings on the structural, functional, and metabolic changes that occur in the T2DM brain, to provide a more integrative understanding of the neurocognitive complications in T2DM.

Brain structural changes

DM is known to induce not only macroscopic but also microscopic changes in the brain. Several neuroimaging studies indicate that the brain structural alterations frequently observed in T2DM include global and regional atrophy in cortical and subcortical regions [31,32] and WMH [33].

Global brain atrophy and ventricular enlargements

Reductions in the total brain volume or cortical/subcortical brain volume in T2DM have been indicated by several neuroimaging studies [34]. Modest cerebral atrophy in the T2DM population has been consistently observed [32,35]. Further-

more, a significant association has been found between cerebral atrophy in DM and cognitive impairment, even after the effect of comorbid vascular diseases was adjusted [33]. Ventricular enlargement, an important index of cerebral atrophy and potential surrogate marker for dementia [36], has also been implicated in T2DM-related brain changes. A study with a middle-age population revealed a significant association between DM and greater ventricular size [37]. Furthermore, according to recent case-controlled studies, patients with T2DM showed greater increments in lateral ventricular volumes as well as shape alterations compared to control subjects [38,39]. With regard to the longitudinal trajectory of the changes, the rate of increase in lateral ventricular volumes in elderly patients with DM was faster than the rate of aging-related changes [40,41].

A number of factors have been suggested to be associated with brain atrophy in T2DM. Factors including retinopathy, extent of brain infarction, HbA1c level, and disease duration were associated with cortical atrophy [27,33]. In addition, several cross-sectional studies have demonstrated that indices such as comorbid hypertension, level of glycemic control, and history of hypoglycemic events are factors that may potentially affect the progression of cerebral atrophy in DM [35,40,42-45]. Results from animal models bring up the possibility that factors like glucose toxicity, hyperinsulinemia, and vascular damage have accelerating effects on the brain atrophy process [46,47]. Meanwhile, the use of cholesterol-lowering statin drugs is associated with less brain atrophy [27,44]. In sum, these findings propose the involvement of multiple factors in the development of DM-related brain structural alterations, although the inconsistency in research outcomes has not yet been entirely resolved.

Notably, along with the T2DM population, the prediabetic population also tends to exhibit cognitive dysfunction [48] and reduction in total brain volume [49]. As conditions like hyperinsulinemia and impaired glucose tolerance start to emerge during the prediabetic stage, cognitive dysfunction as well as brain alterations may occur even in the early stages of T2DM.

Regional brain atrophy

Animal studies have presented the associations of the diabetic state with the neuronal changes in specific brain regions such as the hippocampus and prefrontal cortex, as well as with cognitive deficits [50,51]. By implementing a variety of neuroimaging analysis methods including voxel-based morphometry and cortical thickness analysis, recent human studies also have

yielded evidence of associations between DM and regional brain deficits [34]. The most consistently reported regional atrophy in the T2DM population is found in the medial temporal lobe, especially in the hippocampus [31,40,52]. For instance, cortical thickness and subcortical volumetric analysis of the T2DM group revealed prominent deficits in the hippocampus and middle temporal gyrus [40]. Another study demonstrated that T2DM was related to a higher risk of hippocampal atrophy [43]. Additionally, a volumetric reduction restricted to the hippocampus was observed along with a decline in memory function, starting from the early stages of T2DM [52]. Atrophic alterations in the medial temporal lobe, especially in the hippocampus, have also been reported as a robust neuroimaging finding in Alzheimer dementia (AD) [36] and thus suggest a possible mechanism connecting DM and dementia.

In addition to the brain volumetric reductions in the medial temporal lobe, deficits in the prefrontal regions have also been noted in a substantial body of research [53-56]. Specifically, patients with T2DM showed gray matter deficits in the prefrontal areas including the anterior cingulate and orbitofrontal regions, and the findings were robust even after adjusting for global brain atrophy [53,55]. The existing evidence suggests that prefrontal regions may act as neural correlates associated with depression and cognitive dysfunction [57,58]. Accordingly, prefrontal structural alterations in the diabetic brain may play a crucial role in central nervous complications, particularly in the depressive symptoms and cognitive impairment observed in T2DM.

White matter hyperintensity

WMH, a commonly observed phenomenon in the elderly brain, is known to increase with the normal aging process [59,60]. The findings on WMH in T2DM are rather inconsistent compared to those on cerebral atrophy [34]. Although some studies have identified DM as a risk factor accelerating the generation of WMH [61,62], in a longitudinal study no significant difference in the WMH progression rate was found between T2DM and control groups [40]. Furthermore, in a meta-analysis that inspected studies primarily conducted with a visual rating technique, no consistent association was found between T2DM and WMH [34]. While some researchers have presented additional negative findings [31,32,59], others have reported a significant association between WMH severity and DM [33,61]. In a study using volumetry analysis rather than visual rating, a prominent increase in the volume of white matter lesions was observed [38]. Some recent neuroimaging

studies present region-specific effects, since subcortical white matter lesions, but not periventricular white matter regions, show a significant association with T2DM [33,63]. In these studies, WMH severity was associated with the magnitude of the cognitive impairment, suggesting a role for WMH in the cognitive changes associated with T2DM [35,63]. The inconsistency in the research outcomes on WMH in T2DM may be explained by the different methodologies used for WMH rating and the large interindividual variability in WMH [34]. Accordingly, further large-scale longitudinal studies with appropriate quantitative methods to evaluate WMH are warranted.

Although WMH is considered to have complex interactions with vascular factors, the precise mechanisms involved are yet to be elucidated. A number of studies in T2DM proposed indices such as macrovascular factors, illness duration, HbA1c levels, hyperinsulinemia, and hypertension to be related to WMH in T2DM [6,27,63,64]. The presence of WMH in the deep white matter is correlated with neurodegenerative changes as well as with vascular abnormalities [65-67].

Brain functional changes

Changes in brain functional connectivity can be induced by structural changes, but they may also emerge before clinically observable changes in cognitive function occur, preceding apparent structural alterations [68,69]. There have been reports suggesting a resemblance between alterations of brain functional connectivity in T2DM and those in mild cognitive impairment in AD [70-72]. Furthermore, decreased glucose metabolism in the frontal, parieto-temporal, and cingulate regions, a characteristic feature in AD, is also observed in the prediabetic state [73]. In patients with T2DM, the functional connectivity between the hippocampus and other brain regions is reduced [72,74], and the decline in cognitive performance in T2DM is associated with a reduction in functional connectivity [72].

In a resting-state functional magnetic resonance imaging study, patients with DM and microvascular complications showed a decrease in brain functional connectivity, whereas those without such complications and healthy controls did not [75]. Diabetic retinopathy, an example of microvascular complications, has been identified as an independent risk factor for cognitive decline in DM [73]. Given these findings, microvascular complications may be potential players in the development of brain functional abnormalities and the associated cognitive decline observed in T2DM.

Metabolic brain changes: results from magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) enables noninvasive inspection of metabolites in the brain. MRS is also valuable for the detection of brain damage or abnormalities that would appear normal on other modalities [76], and thus may prove particularly useful in investigating the neurocognitive changes in DM.

Both human and animal MRS studies of DM suggest a decrease in the N-acetylaspartate (NAA)/creatine (Cr) ratio in a relatively consistent manner, while there are mixed results for the choline (Cho)/Cr ratio [77]. In a study using a rat model of DM, reductions in the NAA/Cr ratio and the NAA/Cho ratio were observed in diabetic rats, whereas the Cr/Cho rate was not significantly changed [78]. In a few human MRS studies, the NAA/Cr ratio was also found to be reduced in patients with DM [79-81]. A study reported that the Cho/Cr ratio was decreased in the frontal and parietal lobes of patients with T2DM [81], while another study observed an increase in the occipital lobe [82]. In the most recent MRS study on T2DM, a decrease in the NAA/Cr ratio and an increase in the Cho/Cr ratio in the lenticular nucleus were noted [77]. The literature suggests an association between NAA and neuronal damage, as well as one between Cho and glial proliferation [83]. These abnormalities in NAA and Cho levels in T2DM are in accordance with the hypothesis that DM may incur aberrant changes in the brain metabolites and associated neuronal damage.

Glutamate is another key substance in the investigation of DM using MRS [84]. Glutamate is a highly important neurotransmitter involved in many crucial brain activities such as cognition [85,86] and can be particularly useful in the assessment of glucose metabolism within the cerebrum [87]. A number of MRS studies in T1DM illustrate associations between DM and glutamatergic alterations in the brain [56,88], yet the direction of change in glutamate levels appears to differ depending on the region of interest. While patients with T1DM show an elevated level of glutamate in the prefrontal region [56], the glutamate levels in T1DM have been reported to be lower in the occipital and parieto-occipital regions [88]. In depressed patients with T2DM, glutamine and glutamate concentrations were significantly reduced in the subcortical regions relative to healthy and diabetic control subjects [89]. A study based on a rat model found impaired glutamate-glutamine cycling in T2DM [90], while in a rat model of diabetic retinopathy, hyperglycemia was found to induce a dysfunction in glutamate transporters [91].

Since glutamate in the synaptic space would introduce a significant amount of noise to glutamatergic signal transduction, it is essential to uptake glutamate that has been released to the extracellular space [92,93]. Insulin not only enhances the glucose reuptake processes but also normalizes the altered glutamate uptaking properties in astrocytes [94]. Accordingly, the altered ability of glutamate reuptake in T2DM brain astrocytes indicates a potential impairment of brain signal transmission in DM [95]. As a considerable portion of the energy consumed in the brain is used in glutamatergic signaling [96], we propose that the diabetic brain, which shows lowered glucose metabolism, may also have difficulties in glutamate signaling. In any case, the investigation of DM-induced metabolite alterations in the human brain is still in its early stages, and further research should follow.

CONCLUSIONS

As T2DM has arisen as a global health problem affecting numerous individuals [1,3], the neurocognitive complications of T2DM including cognitive decline and dementia bring up important and challenging research questions in both clinical and research fields. Several conditions including hyperglycemia, hypoglycemia, and vascular diseases are suggested to be involved in the development of cognitive impairment in T2DM, although the precise mechanism is yet unclear due to the complexity of multifactorial influences. Recently, neuroimaging methods have been implemented in the investigation of the neural correlates underlying the association between T2DM and cognitive dysfunction. Studies have revealed changes in the T2DM brain at structural, functional, and metabolite levels and their potential role in cognitive changes. With further methodological developments, future neuroimaging studies in T2DM are expected to elucidate the underlying neural mechanisms of DM-related cognitive deficits.

CONFLICTS OF INTEREST

Dr. Lyoo has received research support from Lundbeck, Astra-Zeneca, GSK, and Boryung Pharmaceutical.

ACKNOWLEDGMENTS

REFERENCES

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047-53.

2. Strachan MW, Reynolds RM, Marioni RE, Price JF. Cognitive function, dementia and type 2 diabetes mellitus in the elderly. Nat Rev Endocrinol 2011;7:108-14.

3. Lutgers HL, Gerrits EG, Sluiter WJ, Ubink-Veltmaat LJ, Landman GW, Links TP, Gans RO, Smit AJ, Bilo HJ. Life expectancy in a large cohort of type 2 diabetes patients treated in primary care (ZODIAC-10). PLoS One 2009;4: e6817.

4. Gregg EW, Yaffe K, Cauley JA, Rolka DB, Blackwell TL, Narayan KM, Cummings SR. Is diabetes associated with cognitive impairment and cognitive decline among older women? Study of Osteoporotic Fractures Research Group. Arch Intern Med 2000;160:174-80.

5. Cukierman T, Gerstein HC, Williamson JD. Cognitive decline and dementia in diabetes: systematic overview of prospective observational studies. Diabetologia 2005;48: 2460-9.

6. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol 2006;5:64-74.

7. Allen KV, Frier BM, Strachan MW. The relationship between type 2 diabetes and cognitive dysfunction: longitudinal studies and their methodological limitations. Eur J Pharmacol 2004;490:169-75.

8. Messier C, Tsiakas M, Gagnon M, Desrochers A. Effect of age and glucoregulation on cognitive performance. J Clin Exp Neuropsychol 2010;32:809-21.

9. Reijmer YD, van den Berg E, Ruis C, Kappelle LJ, Biessels GJ. Cognitive dysfunction in patients with type 2 diabetes. Diabetes Metab Res Rev 2010;26:507-19.

10. Whitmer RA. Type 2 diabetes and risk of cognitive impairment and dementia. Curr Neurol Neurosci Rep 2007;7: 373-80.

11. Sommerfield AJ, Deary IJ, Frier BM. Acute hyperglycemia alters mood state and impairs cognitive performance in people with type 2 diabetes. Diabetes Care 2004;27: 2335-40.

12. Yaffe K, Blackwell T, Whitmer RA, Krueger K, Barrett Connor E. Glycosylated hemoglobin level and development of mild cognitive impairment or dementia in older women. J Nutr Health Aging 2006;10:293-5.

13. Raffaitin C, Feart C, Le Goff M, Amieva H, Helmer C, Akbaraly TN, Tzourio C, Gin H, Barberger-Gateau P. Metabolic syndrome and cognitive decline in French elders: the three-city study. Neurology 2011;76:518-25.

14. Christman AL, Matsushita K, Gottesman RF, Mosley T, Alonso A, Coresh J, Hill-Briggs F, Sharrett AR, Selvin E. Glycated haemoglobin and cognitive decline: the Atherosclerosis Risk in Communities (ARIC) study. Diabetologia 2011;54:1645-52.

15. Rizzo MR, Marfella R, Barbieri M, Boccardi V, Vestini F, Lettieri B, Canonico S, Paolisso G. Relationships between daily acute glucose fluctuations and cognitive performance among aged type 2 diabetic patients. Diabetes Care 2010; 33:2169-74.

16. Gonder-Frederick LA, Zrebiec JF, Bauchowitz AU, Ritterband LM, Magee JC, Cox DJ, Clarke WL. Cognitive function is disrupted by both hypo- and hyperglycemia in school-aged children with type 1 diabetes: a field study. Diabetes Care 2009;32:1001-6.

17. Bree AJ, Puente EC, Daphna-Iken D, Fisher SJ. Diabetes increases brain damage caused by severe hypoglycemia. Am J Physiol Endocrinol Metab 2009;297:E194-201.

18. Auer RN, Siesjo BK. Hypoglycaemia: brain neurochemistry and neuropathology. Baillieres Clin Endocrinol Metab 1993;7:611-25.

19. Suh SW, Gum ET, Hamby AM, Chan PH, Swanson RA. Hypoglycemic neuronal death is triggered by glucose reperfusion and activation of neuronal NADPH oxidase. J Clin Invest 2007;117:910-8.

20. Zammitt NN, Frier BM. Hypoglycemia in type 2 diabetes: pathophysiology, frequency, and effects of different treatment modalities. Diabetes Care 2005;28:2948-61.

21. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP Jr, Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. JAMA 2009; 301:1565-72.

22. Punthakee Z, Miller ME, Launer LJ, Williamson JD, Lazar RM, Cukierman-Yaffee T, Seaquist ER, Ismail-Beigi F, Sullivan MD, Lovato LC, Bergenstal RM, Gerstein HC; ACCORD Group of Investigators; ACCORD-MIND Investigators. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes: post hoc epidemiologic analysis of the ACCORD trial. Diabetes Care 2012;35: 787-93.

23. de Galan BE, Zoungas S, Chalmers J, Anderson C, Dufouil C, Pillai A, Cooper M, Grobbee DE, Hackett M, Hamet P, Heller SR, Lisheng L, MacMahon S, Mancia G, Neal B,

Pan CY, Patel A, Poulter N, Travert F, Woodward M; ADVANCE Collaborative Group. Cognitive function and risks of cardiovascular disease and hypoglycaemia in patients with type 2 diabetes: the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial. Diabetologia 2009;52:2328-36.

24. Munshi M, Grande L, Hayes M, Ayres D, Suhl E, Capelson R, Lin S, Milberg W, Weinger K. Cognitive dysfunction is associated with poor diabetes control in older adults. Diabetes Care 2006;29:1794-9.

25. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405-12.

26. Ryan CM, Geckle MO, Orchard TJ. Cognitive efficiency declines over time in adults with type 1 diabetes: effects of micro- and macrovascular complications. Diabetologia 2003;46:940-8.

27. Manschot SM, Biessels GJ, de Valk H, Algra A, Rutten GE, van der Grond J, Kappelle LJ; Utrecht Diabetic Encephalopathy Study Group. Metabolic and vascular determinants of impaired cognitive performance and abnormalities on brain magnetic resonance imaging in patients with type 2 diabetes. Diabetologia 2007;50:2388-97.

28. Yoshitake T, Kiyohara Y, Kato I, Ohmura T, Iwamoto H, Nakayama K, Ohmori S, Nomiyama K, Kawano H, Ueda K, Sueishi K, Tsuneyoshi M, Fujishima M. Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: the Hisayama Study. Neurology 1995;45:1161-8.

29. Akisaki T, Sakurai T, Takata T, Umegaki H, Araki A, Mizuno S, Tanaka S, Ohashi Y, Iguchi A, Yokono K, Ito H. Cognitive dysfunction associates with white matter hyperintensities and subcortical atrophy on magnetic resonance imaging of the elderly diabetes mellitus Japanese elderly diabetes intervention trial (J-EDIT). Diabetes Metab Res Rev 2006;22:376-84.

30. Biessels GJ, van der Heide LP, Kamal A, Bleys RL, Gispen WH. Ageing and diabetes: implications for brain function. Eur J Pharmacol 2002;441:1-14.

31. den Heijer T, Vermeer SE, van Dijk EJ, Prins ND, Koudstaal PJ, Hofman A, Breteler MM. Type 2 diabetes and atrophy of medial temporal lobe structures on brain MRI. Diabetologia 2003;46:1604-10.

32. Schmidt R, Launer LJ, Nilsson LG, Pajak A, Sans S, Berger K, Breteler MM, de Ridder M, Dufouil C, Fuhrer R, Giampaoli S, Hofman A; CASCADE Consortium. Magnetic resonance imaging of the brain in diabetes: the Cardiovascular Determinants of Dementia (CASCADE) Study. Diabetes 2004;53:687-92.

33. Manschot SM, Brands AM, van der Grond J, Kessels RP, Algra A, Kappelle LJ, Biessels GJ; Utrecht Diabetic Encephalopathy Study Group. Brain magnetic resonance imaging correlates of impaired cognition in patients with type 2 diabetes. Diabetes 2006;55:1106-13.

34. van Harten B, de Leeuw FE, Weinstein HC, Scheltens P, Biessels GJ. Brain imaging in patients with diabetes: a systematic review. Diabetes Care 2006;29:2539-48.

35. Jongen C, Biessels GJ. Structural brain imaging in diabetes: a methodological perspective. Eur J Pharmacol 2008;585:208-18.

36. Frisoni GB, Fox NC, Jack CR, Scheltens P, Thompson PM. The clinical use of structural MRI in Alzheimer disease. Nat Rev Neurol 2010;6:67-77.

37. Knopman DS, Mosley TH, Catellier DJ, Sharrett AR; Atherosclerosis Risk in Communities (ARIC) Study. Cardiovascular risk factors and cerebral atrophy in a middle-aged cohort. Neurology 2005;65:876-81.

38. Jongen C, van der Grond J, Kappelle LJ, Biessels GJ, Viergever MA, Pluim JP; Utrecht Diabetic Encephalopathy Study Group. Automated measurement of brain and white matter lesion volume in type 2 diabetes mellitus. Diabetologia 2007;50:1509-16.

39. Lee JH, Yoon S, Renshaw PF, Kim TS, Jung JJ, Choi Y, Kim BN, Jacobson AM, Lyoo IK. Morphometric changes in lateral ventricles of patients with recent-onset type 2 diabetes mellitus. PLoS One 2013;8:e60515.

40. Brundel M, van den Heuvel M, de Bresser J, Kappelle LJ, Biessels GJ; Utrecht Diabetic Encephalopathy Study Group. Cerebral cortical thickness in patients with type 2 diabetes. J Neurol Sci 2010;299:126-30.

41. Carmichael OT, Kuller LH, Lopez OL, Thompson PM, Dutton RA, Lu A, Lee SE, Lee JY, Aizenstein HJ, Meltzer CC, Liu YX, Toga AW, Becker JT. Cerebral ventricular changes associated with transitions between normal cognitive function, mild cognitive impairment, and dementia. Alzheimer Dis Assoc Disord 2007;21:14-24.

42. Enzinger C, Fazekas F, Matthews PM, Ropele S, Schmidt H, Smith S, Schmidt R. Risk factors for progression of brain atrophy in aging: six-year follow-up of normal sub-

jects. Neurology 2005;64:1704-11.

43. Korf ESC, White LR, Scheltens P, Launer LJ. Brain aging in very old men with type 2 diabetes: the Honolulu-Asia Aging Study. Diabetes Care 2006;29:2268-74.

44. Musen G, Lyoo IK, Sparks CR, Weinger K, Hwang J, Ryan CM, Jimerson DC, Hennen J, Renshaw PF, Jacobson AM. Effects of type 1 diabetes on gray matter density as measured by voxel-based morphometry. Diabetes 2006;55:326-33.

45. Saczynski JS, Siggurdsson S, Jonsson PV, Eiriksdottir G, Olafsdottir E, Kjartansson O, Harris TB, van Buchem MA, Gudnason V, Launer LJ. Glycemic status and brain injury in older individuals: the age gene/environment susceptibility-Reykjavik study. Diabetes Care 2009;32:1608-13.

46. Toth C, Schmidt AM, Tuor UI, Francis G, Foniok T, Brussee V, Kaur J, Yan SF, Martinez JA, Barber PA, Buchan A, Zochodne DW. Diabetes, leukoencephalopathy and rage. Neurobiol Dis 2006;23:445-61.

47. Francis GJ, Martinez JA, Liu WQ, Xu K, Ayer A, Fine J, Tuor UI, Glazner G, Hanson LR, Frey WH 2nd, Toth C. Intranasal insulin prevents cognitive decline, cerebral atrophy and white matter changes in murine type I diabetic encephalopathy. Brain 2008;131(Pt 12):3311-34.

48. Yaffe K, Blackwell T, Kanaya AM, Davidowitz N, Barrett-Connor E, Krueger K. Diabetes, impaired fasting glucose, and development of cognitive impairment in older women. Neurology 2004;63:658-63.

49. Tan ZS, Beiser AS, Fox CS, Au R, Himali JJ, Debette S, Decarli C, Vasan RS, Wolf PA, Seshadri S. Association of metabolic dysregulation with volumetric brain magnetic resonance imaging and cognitive markers of subclinical brain aging in middle-aged adults: the Framingham Offspring Study. Diabetes Care 2011;34:1766-70.

50. Klein, JP, Waxman SG. The brain in diabetes: molecular changes in neurons and their implications for end-organ damage. Lancet Neurol 2003;2:548-54.

51. Enhamre E, Carlsson A, Gronbladh A, Watanabe H, Hallberg M, Nyberg F. The expression of growth hormone receptor gene transcript in the prefrontal cortex is affected in male mice with diabetes-induced learning impairments. Neurosci Lett 2012;523:82-6.

52. Gold SM, Dziobek I, Sweat V, Tirsi A, Rogers K, Bruehl H, Tsui W, Richardson S, Javier E, Convit A. Hippocampal damage and memory impairments as possible early brain complications of type 2 diabetes. Diabetologia 2007;50: 711-9.

53. Ajilore O, Narr K, Rosenthal J, Pham D, Hamilton L, Watari K, Elderkin-Thompson V, Darwin C, Toga A, Kumar A. Regional cortical gray matter thickness differences associated with type 2 diabetes and major depression. Psychiatry Res 2010;184:63-70.

54. Lyoo IK, Yoon S, Jacobson AM, Hwang J, Musen G, Kim JE, Simonson DC, Bae S, Bolo N, Kim DJ, Weinger K, Lee JH, Ryan CM, Renshaw PF. Prefrontal cortical deficits in type 1 diabetes mellitus: brain correlates of comorbid depression. Arch Gen Psychiatry 2012;69:1267-76.

55. Kumar A, Haroon E, Darwin C, Pham D, Ajilore O, Rodriguez G, Mintz J. Gray matter prefrontal changes in type 2 diabetes detected using MRI. J Magn Reson Imaging 2008;27:14-9.

56. Lyoo IK, Yoon SJ, Musen G, Simonson DC, Weinger K, Bolo N, Ryan CM, Kim JE, Renshaw PF, Jacobson AM. Altered prefrontal glutamate-glutamine-gamma-aminobutyric acid levels and relation to low cognitive performance and depressive symptoms in type 1 diabetes mellitus. Arch Gen Psychiatry 2009;66:878-87.

57. Koenigs M, Grafman J. The functional neuroanatomy of depression: distinct roles for ventromedial and dorsolateral prefrontal cortex. Behav Brain Res 2009;201:239-43.

58. Mollica RF, Lyoo IK, Chernoff MC, Bui HX, Lavelle J, Yoon SJ, Kim JE, Renshaw PF. Brain structural abnormalities and mental health sequelae in South Vietnamese ex-political detainees who survived traumatic head injury and torture. Arch Gen Psychiatry 2009;66:1221-32.

59. Schmidt R, Enzinger C, Ropele S, Schmidt H, Fazekas F; Austrian Stroke Prevention Study. Progression of cerebral white matter lesions: 6-year results of the Austrian Stroke Prevention Study. Lancet 2003;361:2046-8.

60. de Leeuw FE, de Groot JC, Achten E, Oudkerk M, Ramos LM, Heijboer R, Hofman A, Jolles J, van Gijn J, Breteler MM. Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam Scan Study. J Neurol Neurosurg Psychiatry 2001;70:9-14.

61. Taylor WD, MacFall JR, Provenzale JM, Payne ME, McQuoid DR, Steffens DC, Krishnan KR. Serial MR imaging of volumes of hyperintense white matter lesions in elderly patients: correlation with vascular risk factors. AJR Am J Roentgenol 2003;181:571-6.

62. Gouw AA, van der Flier WM, Fazekas F, van Straaten EC, Pantoni L, Poggesi A, Inzitari D, Erkinjuntti T, Wahlund LO, Waldemar G, Schmidt R, Scheltens P, Barkhof F; LADIS Study Group. Progression of white matter hyperintensities and incidence of new lacunes over a 3-year period:

the Leukoaraiosis and Disability study. Stroke 2008;39: 1414-20.

63. van Harten B, Oosterman JM, Potter van Loon BJ, Scheltens P, Weinstein HC. Brain lesions on MRI in elderly patients with type 2 diabetes mellitus. Eur Neurol 2007; 57:70-4.

64. Murray AD, Staff RT, Shenkin SD, Deary IJ, Starr JM, Whalley LJ. Brain white matter hyperintensities: relative importance of vascular risk factors in nondemented elderly people. Radiology 2005;237:251-7.

65. van Swieten JC, van den Hout JH, van Ketel BA, Hijdra A, Wokke JH, van Gijn J. Periventricular lesions in the white matter on magnetic resonance imaging in the elderly. A morphometric correlation with arteriolosclerosis and dilated perivascular spaces. Brain 1991;114(Pt 2):761-74.

66. Fazekas F, Kleinert R, Offenbacher H, Schmidt R, Kleinert G, Payer F, Radner H, Lechner H. Pathologic correlates of incidental MRI white matter signal hyperintensities. Neurology 1993;43:1683-9.

67. Pantoni L, Garcia JH. Pathogenesis of leukoaraiosis: a review. Stroke 1997;28:652-9.

68. Devous MD. Functional brain imaging in the dementias: role in early detection, differential diagnosis, and longitudinal studies. Eur J Nucl Med Mol Imaging 2002;29:1685-96.

69. Wolf H, Jelic V, Gertz HJ, Nordberg A, Julin P, Wahlund LO. A critical discussion of the role of neuroimaging in mild cognitive impairment. Acta Neurol Scand Suppl 2003; 179:52-76.

70. Allen G, Barnard H, McColl R, Hester AL, Fields JA, Weiner MF, Ringe WK, Lipton AM, Brooker M, McDonald E, Rubin CD, Cullum CM. Reduced hippocampal functional connectivity in Alzheimer disease. Arch Neurol 2007;64:1482-7.

71. Sorg C, Riedl V, Muhlau M, Calhoun VD, Eichele T, Laer L, Drzezga A, Forstl H, Kurz A, Zimmer C, Wohlschlager AM. Selective changes of resting-state networks in individuals at risk for Alzheimer's disease. Proc Natl Acad Sci U S A 2007;104:18760-5.

72. Zhou H, Lu W, Shi Y, Bai F, Chang J, Yuan Y, Teng G, Zhang Z. Impairments in cognition and resting-state connectivity of the hippocampus in elderly subjects with type 2 diabetes. Neurosci Lett 2010;473:5-10.

73. Baker LD, Cross DJ, Minoshima S, Belongia D, Watson GS, Craft S. Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabe-

tes. Arch Neurol 2011;68:51-7.

74. Musen G, Jacobson AM, Bolo NR, Simonson DC, Shenton ME, McCartney RL, Flores VL, Hoogenboom WS. Resting-state brain functional connectivity is altered in type 2 diabetes. Diabetes 2012;61:2375-9.

75. van Duinkerken E, Schoonheim MM, Sanz-Arigita EJ, RG IJ, Moll AC, Snoek FJ, Ryan CM, Klein M, Diamant M, Barkhof F. Resting-state brain networks in type 1 diabetic patients with and without microangiopathy and their relation to cognitive functions and disease variables. Diabetes 2012;61:1814-21.

76. Garnett MR, Blamire AM, Corkill RG, Cadoux-Hudson TA, Rajagopalan B, Styles P. Early proton magnetic resonance spectroscopy in normal-appearing brain correlates with outcome in patients following traumatic brain injury. Brain 2000;123(Pt 10):2046-54.

77. Lin Y, Zhou J, Sha L, Li Y, Qu X, Liu L, Chen H, An Z, Wang Y, Sun C. Metabolite differences in the lenticular nucleus in type 2 diabetes mellitus shown by proton MR spectroscopy. AJNR Am J Neuroradiol 2013;34:1692-6.

78. Biessels GJ, Braun KP, de Graaf RA, van Eijsden P, Gispen WH, Nicolay K. Cerebral metabolism in streptozotocin-diabetic rats: an in vivo magnetic resonance spectroscopy study. Diabetologia 2001;44:346-53.

79. Kario K, Ishikawa J, Hoshide S, Matsui Y, Morinari M, Eguchi K, Ishikawa S, Shimada K. Diabetic brain damage in hypertension: role of renin-angiotensin system. Hypertension 2005;45:887-93.

80. Kreis R, Ross BD. Cerebral metabolic disturbances in patients with subacute and chronic diabetes mellitus: detection with proton MR spectroscopy. Radiology 1992;184: 123-30.

81. Sahin I, Alkan A, Keskin L, Cikim A, Karakas HM, Firat AK, Sigirci A. Evaluation of in vivo cerebral metabolism on proton magnetic resonance spectroscopy in patients with impaired glucose tolerance and type 2 diabetes mellitus. J Diabetes Complications 2008;22:254-60.

82. Modi S, Bhattacharya M, Sekhri T, Rana P, Tripathi RP, Khushu S. Assessment of the metabolic profile in type 2 diabetes mellitus and hypothyroidism through proton MR spectroscopy. Magn Reson Imaging 2008;26:420-5.

83. Bitsch A, Bruhn H, Vougioukas V, Stringaris A, Lassmann H, Frahm J, Bruck W. Inflammatory CNS demyelination: histopathologic correlation with in vivo quantitative proton MR spectroscopy. AJNR Am J Neuroradiol 1999;20:1619-27.

84. Trudeau F, Gagnon S, Massicotte G. Hippocampal synap-

tic plasticity and glutamate receptor regulation: influences of diabetes mellitus. Eur J Pharmacol 2004;490:177-86.

85. Lisman JE, Fellous JM, Wang XJ. A role for NMDA-receptor channels in working memory. Nat Neurosc 1998;1: 273-5.

86. Schubert F, Gallinat J, Seifert F, Rinneberg H. Glutamate concentrations in human brain using single voxel proton magnetic resonance spectroscopy at 3 Tesla. Neuroimage 2004;21:1762-71.

87. Pfund Z, Chugani DC, Juhasz C, Muzik O, Chugani HT, Wilds IB, Seraji-Bozorgzad N, Moore GJ. Evidence for coupling between glucose metabolism and glutamate cycling using FDG PET and 1H magnetic resonance spectroscopy in patients with epilepsy. J Cereb Blood Flow Metab 2000;20:871-8.

88. Mangia S, Kumar AF, Moheet AA, Roberts RJ, Eberly LE, Seaquist ER, Tkac I. Neurochemical profile of patients with type 1 diabetes measured by (1)H-MRS at 4 T. J Cereb Blood Flow Metab 2013;33:754-9.

89. Ajilore O, Haroon E, Kumaran S, Darwin C, Binesh N, Mintz J, Miller J, Thomas MA, Kumar A. Measurement of brain metabolites in patients with type 2 diabetes and major depression using proton magnetic resonance spectroscopy. Neuropsychopharmacology 2007;32:1224-31.

90. Sickmann HM, Waagepetersen HS, Schousboe A, Benie AJ, Bouman SD. Obesity and type 2 diabetes in rats are associated with altered brain glycogen and amino-acid homeostasis. J Cereb Blood Flow Metab 2010;30:1527-37.

91. Li Q, Puro DG. Diabetes-induced dysfunction of the glutamate transporter in retinal Muller cells. Invest Ophthalmol Vis Sci 2002;43:3109-16.

92. Rothstein JD, Dykes-Hoberg M, Pardo CA, Bristol LA, Jin L, Kuncl RW, Kanai Y, Hediger MA, Wang Y, Schielke JP, Welty DF. Knockout of glutamate transporters reveals a major role for astroglial transport in excitotoxicity and clearance of glutamate. Neuron 1996;16:675-86.

93. Bergles DE, Jahr CE. Glial contribution to glutamate uptake at Schaffer collateral-commissural synapses in the hippocampus. J Neurosci 1998;18:7709-16.

94. Coleman ES, Dennis JC, Braden TD, Judd RL, Posner P. Insulin treatment prevents diabetes-induced alterations in astrocyte glutamate uptake and GFAP content in rats at 4 and 8 weeks of diabetes duration. Brain Res 2010;1306: 131-41.

95. Brands AM, Biessels GJ, de Haan EH, Kappelle LJ, Kessels RP. The effects of type 1 diabetes on cognitive performance: a meta-analysis. Diabetes Care 2005;28:726-35.

96. Howarth C, Gleeson P, Attwell D. Updated energy budgets for neural computation in the neocortex and cerebellum. J Cereb Blood Flow Metab 2012;32:1222-32.