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MINI REVIEW

Association between diabetes mellitus and post-stroke cognitive impairment

Kang-Po Lee[1,2], Jung-Sheng Chen[3], Chih-Yuan Wang[4]*

[1]College of Medicine, I-Shou University, Kaohsiung, Taiwan, [2]Stroke Center and Department of Neurology, E-Da Hospital, Kaohsiung, Taiwan, [3]Department of Medical Research, E-Da Hospital, Kaohsiung, Taiwan, and [4]Division of Endocrinology and Metabolism, Department of Internal Medicine, College of Medicine, National Taiwan University Hospital, National Taiwan University, Taipei, Taiwan

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***Correspondence**
Chih-Yuan Wang
Tel.: +886-2-23123456 ext 65371
Fax: +886-2-23934176
E-mail address:
cyw1965@gmail.com;
cyw1965@ntu.edu.tw

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ABSTRACT

Stroke survivors suffer from various physical, emotional, and cognitive impairments. These changes are dynamic and depend on multiple factors, including underlying diseases, baseline brain function and pathology, the site of the stroke and the post-stroke inflammation, neurogenesis as well as the subsequent remodeling of the neuro-network. First we review the structural and pathological changes of the brain in stroke survivors with diabetes mellitus, which may lead to post-stroke cognitive dysfunction. Second, we provide evidence of hyperglycemia, diabetes mellitus, hypoglycemia, and their relationship with post-stroke cognitive impairment (PSCI) and post-stroke dementia (PSD). In addition to conventional biomarkers, such as HbA1c, we also provide other novel tools to predict PSCI/PSD, such as glycemic variability, receptor for advanced glycation end products, and gut microbiota. Finally, we attempt to provide some modifying methods for glycemic control, focusing on the prevention of PSCI/PSD.

INTRODUCTION

Burden of stroke and post-stroke cognitive impairment (PSCI)

Globally, over 12.2 million people have experienced cerebrovascular events, doubling over the past 30 years.[1] Its prevalence has been increasing worldwide from 2010 to 2020. Stroke is the second leading cause of mortality, with 6.5 million people dying from stroke. Among patients having had a stroke, 62–87% have had an ischemic stroke, and the others have had a hemorrhagic stroke. Beside mortality, strokes cause morbidity and severe impairment in disability-adjusted life years. As for morbidity, not only acute insults leading to focal deficits matter, but also the later cognitive impairment and behavioral-emotional dysfunction may sometimes be more disturbing and costly. Patients having had a stroke may experience emotional liability, depression, insomnia, and even PSCI.[2] The prevalence of PSCI or dementia may be as high as 80% among stroke victims and may be associated with worse disability, morbidity, dependency, and high economic burden.[3] Previous studies and reviews have shown that old age,[4] lower education level,[5] atrial fibrillation,[6] hypertension, and increased blood pressure liability[7] are common risk factors for post-stroke cognitive decline. However, its relation to diabetes mellitus (DM) has been less studied, and conflicting data exist.

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DIABETES MELLITUS AND PSCI/POST-STROKE DEMENTIA (PSD)

Mechanism linking diabetes mellitus and PSCI/dementia

A previous review demonstrated that PSCI depends on multiple factors, including the location of the stroke, duration of the initial inflammatory response, late aberrant neurogenesis, and baseline brain pathologies.[7] The activation of microglia seems to play an important role in the inflammatory response.[8] Chronic hyperglycemia leads to pro-inflammatory microglial proliferation via the endothelin-1 system.[9] In contrast, an animal model has demonstrated that knocking down microglial activation ameliorates the inflammatory response after stroke and significantly prevents PSCI in such animals.[10] IL-17 T cells also play a role in diabetes-induced PSCI in female subjects.[11] In addition to the inflammatory response, the hyperglycemic state leads to tau hyper-phosphorylation in the hippocampus, exacerbating cognitive deficits after stroke.[12]

Prediabetes and impaired glucose level

Prediabetes remains controversial. One study suggested that patients with prediabetes have impaired cognitive function as early as 1 month post-stroke.[13] Another study suggested that impaired glucose levels are associated with acute impairment in executive function, especially in those with cortical infarction, but the effects attenuate with time until the 1 year follow-up.[14]

A Korean study suggested hyperglycemia with and without diabetes mellitus is associated with PSCI less than 3 months follow-up.[15] The STROKOG Collaboration study, conducted 3–6 months after stroke, reported that patients with stroke who are prediabetic have normal cognitive function compared with other stroke victims.[16] Another study with a 12 year follow-up also suggested that prediabetes did not increase the risk of PSD.[17]

Type 2 diabetes mellitus

Patients with diabetes have a higher risk of in-hospital mortality or of being discharged to a nursing home. Despite functional deficits, patients with stroke comorbid with diabetes may have a higher risk of depression.[18] The association between diabetes mellitus and post-stroke cognitive function may be related to its duration and severity.[19]

Patients with diabetes mellitus have cognitive impairment at less than 1 week post-stroke.[20] Older studies have shown controversial data regarding cognitive function within 3 months. In the 1990s, studies suggested that diabetes mellitus was the only risk factor for PSD, not hypertension, hyperlipidemia, or coronary artery disease, increasing the odds ratio of dementia by 2.6 to 59.4 times in the 3 month follow-up.[21–23] However, another study conducted in 1998 with the same follow-up period suggested there was no such correlation between PSD and diabetes mellitus.[24] One study found that diabetes mellitus was associated with PSD at 3 months follow-up only in univariate regression analysis, but this correlation diminished after multivariate analysis.[19] For early post-stroke cognitive function, diabetes mellitus impaired the global cognition between 2 and 6 months and increased the risk of PSD[16,23,25–28]. The risk was consistent even after adjusting for stroke severity. At 6 months follow-up, diabetes mellitus patients had a higher risk of PSD with an odds ratio of 2.16, and the risk was more significant in men than in women.[29] However, an Egyptian study suggested no such correlation between diabetes mellitus and PSD.[30] For the subacute phase between 6 and 12 months, diabetes mellitus increased the odds ratio of PSCI by 5.8 times.[31]

After an acute decline, patients may experience varying recovery post stroke. One interesting study demonstrated that language improvement was noted particularly in patients with diabetes mellitus, as well as in patients with hypercholesterolemia and coronary artery disease.[32] For late PSCI, patients with stroke and type 2 diabetes mellitus have worse cognitive function after 2 years.[17,33,34] During the chronic phase, diabetes mellitus may even outweigh the effects of severe mesial temporal atrophy. One study showed that a history of diabetes mellitus instead of temporal atrophy is an independent predictor for PSD after 3 years.[35] Gender differences may exist in diabetes mellitus and long-term PSD, and there is a significant correlation in female but not in male patients for up to 5 years of follow-up.[18] If we observed even longer, long-term PSD is higher in DM patients after 12 years of follow-up period.[17]The relationships between prediabetes, type 2 diabetes mellitus, and PSCI/PSD are summarized in Table 1.

Biomarkers for PSCI/PSD

The HbA1c level is the most conventional marker for PSCI/PSD with higher levels indicating a high risk.[19] In addition to the long-term glucose level, the glucose variability is also significant. Elevated glucose variability as the mean absolute glucose (MAG) and an increased glucose gap are related to a higher risk of 3 month PSCI in patients with and without diabetes mellitus.[15,36] The most vulnerable regions are the frontal, memory, and executive domains. The increasing plasma level of receptor for advanced glycation end products (RAGE), especially the soluble and endogenous soluble RAGE in patients with stroke leads to vascular dementia.[37] However, in this study dementia is more likely to be pre-stroke comorbidity rather than PSD.

In addition to blood samples, the gut microbiota may also have a clinical significance. Dysbiosis can lead to both diabetes mellitus and cognitive impairments. In patients with PSCI and diabetes mellitus, there is an increased abundance of *Enterobacteriaceae*, *Proteobacteria* and a decreased abundance of *Firmicutes* in their gut microbiome.[38,39] A study proposed that the relative abundance level of *Enterobacteriaceae* may serve as a biomarker for PSCI in patients with diabetes mellitus.[39]

Potential treatment or preventive methods

As both hyperglycemia and diabetes mellitus are associated with a higher risk of PSCI and dementia, better control of blood sugar is well understood as a method to prevent such complications. The choice between different oral hyperglycemic agents and insulin has been far less discussed. Current evidence regarding PSCI or dementia is scarce. However, we may look into previous studies comparing different oral hyperglycemic agents and the risk of dementia, mostly Alzheimer's disease. Previous studies have suggested metformin exposure is associated with less dementia.[40] However, another study suggested that the long-term use of metformin may increase the risk of Alzheimer's disease.[41] Thiazolidinedione may improve cognitive function in patients with mild cognitive impairment to moderate dementia, but not in those with APOE4.[42,43] A study showed less cognitive decline with dipeptidyl peptidase-4 (DPP-4) inhibitors compared with that of sulfonylureas in nursing home residents.[44] A meta-analysis showed a lower risk of dementia in comparison with other oral hyperglycemic agents (OHA) for DPP-4 inhibitor but not glucagon-like peptide 1 receptor agonists (GLP-1 RA).[45] Sodium-glucose cotransporter 2 (SGLT2) inhibitors have shown improved cognitive function with both short-term and long-term usage.[46,47] The benefits of SGLT2 are believed to be an inhibition of the pro-inflammatory pathway and a reduction in cerebrovascular disease risk.[48] There are limited data regarding cognitive function with meglitinides, α-glucosidase inhibitors.

Table 1 | The reviewed correlation between prediabetes, type 2 diabetes mellitus, and PSCI/PSD

References	(*N*) Population	Duration of evaluation	Result
Prediabetes			
Wang *et al.*[13]	(201) ischemia	1 month	OR 3.062 (1.130–8.299)
Kruyt *et al.*[14]	(113) ischemia	1 year	Acute phase: lower executive function 1-year follow up: no differences
Lo *et al.*[16]	(1601) ischemia	3–6 months	No significance
Shang *et al.*[17]	(2655) patients	12 years	HR 0.95 (0.42–2.12)
Type 2 diabetes mellitus			
Mizrahi *et al.*[20]	(707) ischemia	1 week	OR 1.46 (1.05–2.05)
Szatmári *et al.*[21]	(176) ischemia	3 months	Diabetes were noted more in patients with post-stroke cognitive loss (P = 0.043)
Censori *et al.*[22]	(146) ischemia	3 months	OR 59.4 (4.3–821.0)
Pohjasvaara *et al.*[24]	(337) ischemia	3 months	No significance
Klimkowicz-Mrowiec *et al.*[23]	(218) ischemia; (32) hemorrhage	3 months	OR 2.67 (1.06–6.57)
Jacquin *et al.*[27]	(204) ischemia; (16) hemorrhage	3 months	OR 3.57 (1.57–8.09)
Desmond *et al.*[28]	(453) ischemia	3 months	OR 1.80 (1.06–3.04)
Swardfager *et al.*[29]	(223) ischemia; (119) hemorrhage	3 months	OR 2.12 (1.20–3.74)
Lo *et al.*[25]	(3520) ischemia	2–6 months	SD −0.53 (−0.67, −0.40)
Lo *et al.*[16]	(1601) ischemia	3–6 months	SD −0.59 (−0.82 to −0.36)
Al Fawal *et al.*[30]	(380) stroke patients	6 months	No significance
Ding *et al.*[31]	(179) ischemia	6–12 months	OR 5.825 (2.068–16.412)
Hénon *et al.*[26]	(202) stroke patients	1 year	RR 4.12 (1.65–10.34)
Aam *et al.*[32]	(582) ischemia; (53) hemorrhage	3 months 1.5 years	language improvements were noted particularly in patients with diabetes mellitus
Ben Assayag *et al.*[34]	(575) ischemia or TIA patients	2 years	HR 1.96 (1.04–3.67)
Cordoliani-Mackowiak *et al*[35]	(132) ischemia; (20) hemorrhage	3 years	RR 3.53 (1.45–8.58)
Luchsinger *et al.*[34]	(1262) elderly patients	4.3 years	RR 3.4 (1.7–6.9)
Ouk *et al.*[19]	(23579) ischemia	5.6 years	HR 1.14 (1.10–1.26); especially female
Shang *et al.*[17]	(2655) patients	12 years	HR 3.32 (1.36–8.10)

HR, hazard ratio; OR, odds ratio; RR, relative risk.

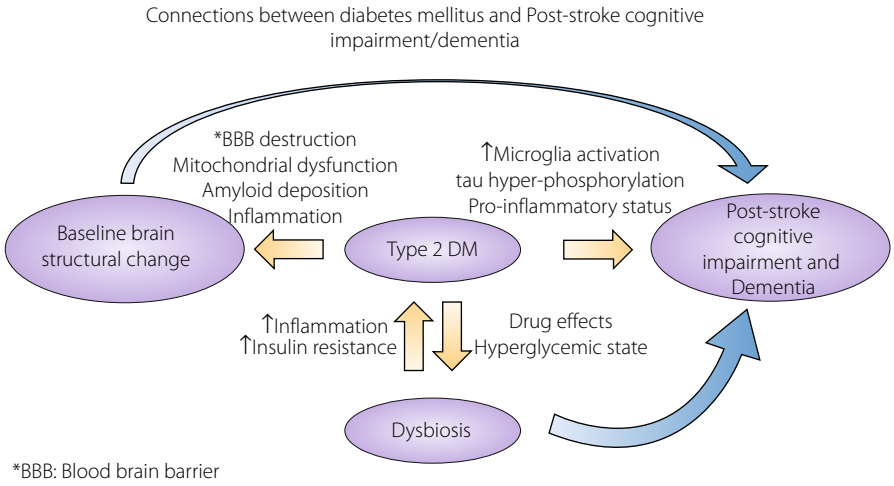

Figure 1 | Connections between diabetes mellitus and post-stroke cognitive impairment/dementia: Patients with type 2 diabetes mellitus had a high risk of PSCI/PSD because of baseline brain structural changes and exacerbation of the post-stroke inflammatory response. Moreover, dysbiosis may induce both type 2 diabetes mellitus and PSCI/PSD directly.

However, the use of insulin is different. Insulin use was shown to increase the risk of dementia in a meta-analysis analyzing 3,590 patients with diabetes mellitus, possibly owing to an increasing risk of hypoglycemia.[49] Nevertheless, treatment with intranasal insulin showed an improvement in cognitive function in both non-demented patients and in patients with Alzheimer's disease.[50]

CONCLUSION

PSD and PSCI impose heavy burdens on patients, families, and society. However, cognitive function after stroke is dynamic and dysfunction is often overlooked. Impaired fasting glucose, prediabetes, type 2 diabetes mellitus, hypoglycemia, and glycemic variability may lead to cognitive dysfunction after stroke by various mechanisms and pathways. There is emerging evidence regarding the association between different medications for diabetes mellitus and cognitive function. However, their relationship with the PSCI/PSD warrants further investigation. Further studies should first focus on medications that show potential for Alzheimer's disease and dementia to determine the most suitable diabetes mellitus medication for patients with diabetes mellitus experiencing stroke. Since dysbiosis has been recognized as a potential risk factor for PSCI, the reconstruction of gut microbiota may provide another treatment and a preventive method for PSCI/PSD in patients with stroke as well as diabetes mellitus. The relationship between diabetes mellitus, PSCI/PSD, and dysbiosis is summarized in Figure 1.

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DISCLOSURE

The authors declare no conflict of interest.
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REFERENCES

1. Feigin VL, Brainin M, Norrving B, *et al*. World stroke organization (WSO): Global stroke fact sheet 2022. *Int J Stroke* 2022; 17: 18–29.
2. Morris PL, Robinson RG, Raphael B. Emotional lability after stroke. *Aust N Z J Psychiatry* 1993; 27: 601–605.
3. Qu Y, Zhuo L, Li N, *et al*. Prevalence of post-stroke cognitive impairment in China: A community-based, cross-sectional study. *PLOS One* 2015; 10: e0122864.
4. Levine DA, Wadley VG, Langa KM, *et al*. Risk factors for poststroke cognitive decline: The REGARDS study (reasons for geographic and racial differences in stroke). *Stroke* 2018; 49: 987–994.
5. Pendlebury ST, Rothwell PM. Incidence and prevalence of dementia associated with transient ischaemic attack and stroke: analysis of the population-based Oxford vascular study. *Lancet Neurol* 2019; 18: 248–258.
6. Gorelick PB, Scuteri A, Black SE, *et al*. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. *Stroke* 2011; 42: 2672–2713.

7. Lee KP, Chang AYW, Sung PS. Association between blood pressure, blood pressure variability, and post-stroke cognitive impairment. *Biomedicine* 2021; 9.
8. Barić A, Dobrivojević Radmilović M. Microglia and bradykinin cross talk in poststroke cognitive impairment in diabetes. *Am J Physiol Cell Physiol* 2021; 320: C613–c618.
9. Chen C, Wu S, Hong Z, *et al*. Chronic hyperglycemia regulates microglia polarization through ERK5. *Aging (Albany NY)* 2019; 11: 697–706.
10. Jackson L, Dumanli S, Johnson MH, *et al*. Microglia knockdown reduces inflammation and preserves cognition in diabetic animals after experimental stroke. *J Neuroinflammation* 2020; 17: 137.
11. Jackson L, Li W, Abdul Y, *et al*. Diabetic stroke promotes a sexually dimorphic expansion of T cells. *Neuromolecular Med* 2019; 21: 445–453.
12. Zhang T, Pan BS, Sun GC, *et al*. Diabetes synergistically exacerbates poststroke dementia and tau abnormality in brain. *Neurochem Int* 2010; 56: 955–961.
13. Wang Q, Zhao K, Cai Y, *et al*. Prediabetes is associated with post-stroke cognitive impairment in ischaemic stroke patients. *Brain Res* 2018; 1687:137–143.
14. Kruyt ND, Nys GMS, van der Worp HB, *et al*. Hyperglycemia and cognitive outcome after ischemic stroke. *J Neurol Sci* 2008; 270: 141–147.
15. Lim JS, Kim C, Oh MS, *et al*. Effects of glycemic variability and hyperglycemia in acute ischemic stroke on post-stroke cognitive impairments. *J Diabetes Complications* 2018; 32: 682–687.
16. Lo JW, Crawford JD, Samaras K, *et al*. Association of Prediabetes and Type 2 diabetes with cognitive function after stroke: a STROKOG collaboration study. *Stroke* 2020; 51: 1640–1646.
17. Shang Y, Fratiglioni L, Marseglia A, *et al*. Association of diabetes with stroke and post-stroke dementia: a population-based cohort study. *Alzheimers Dement* 2020; 16: 1003–1012.
18. Ouk M, Wu CY, Colby-Milley J, *et al*. Depression and diabetes mellitus multimorbidity is associated with loss of Independence and dementia poststroke. *Stroke* 2020; 51: 3531–3540.
19. Ma ZY, Wu YY, Cui HYL, *et al*. Factors influencing post-stroke cognitive impairment in patients with type 2 diabetes mellitus. *Clin Interv Aging* 2022; 17: 653–664.
20. Mizrahi EH, Waitzman A, Blumstein T, *et al*. Diabetes mellitus predicts cognitive impairment in patients with ischemic stroke. *Am J Alzheimers Dis Other Demen* 2010; 25: 362–366.
21. Szatmári S, Fekete I, Csiba L, *et al*. Screening of vascular cognitive impairment on a Hungarian cohort. *Psychiatry Clin Neurosci* 1999; 53: 39–43.
22. Censori B, Manara O, Agostinis C, *et al*. Dementia after first stroke. *Stroke* 1996; 27: 1205–1210.
23. Klimkowicz-Mrowiec A, Dziedzic T, Słowik A, *et al*. Predictors of poststroke dementia: results of a hospital-based study in Poland. *Dement Geriatr Cogn Disord* 2006; 21: 328–334.
24. Pohjasvaara T, Erkinjuntti T, Ylikoski R, *et al*. Clinical determinants of poststroke dementia. *Stroke* 1998; 29: 75–81.
25. Lo JW, Crawford JD, Desmond DW, *et al*. Profile of and risk factors for poststroke cognitive impairment in diverse ethnoregional groups. *Neurology* 2019; 93: e2257–e2271.
26. Hénon H, Durieu I, Guerouaou D, *et al*. Poststroke dementia: incidence and relationship to prestroke cognitive decline. *Neurology* 2001; 57: 1216–1222.
27. Jacquin A, Binquet C, Rouaud O, *et al*. Post-stroke cognitive impairment: high prevalence and determining factors in a cohort of mild stroke. *J Alzheimers Dis* 2014; 40: 1029–1038.
28. Desmond DW, Moroney JT, Paik MC, *et al*. Frequency and clinical determinants of dementia after ischemic stroke. *Neurology* 2000; 54: 1124–1131.
29. Swardfager W, MacIntosh BJ. Depression, type 2 diabetes, and poststroke cognitive impairment. *Neurorehabil Neural Repair* 2017; 31: 48–55.
30. Al Fawal B, Ibrahim A, Abd Elhamed M. Post-stroke dementia: frequency, predictors, and health impact. *Egyptian J Neurol Psychiatr Neurosurg* 2021; 57: 15.
31. Ding MY, Xu Y, Wang YZ, *et al*. Predictors of cognitive impairment after stroke: a prospective stroke cohort study. *J Alzheimers Dis* 2019; 71: 1139–1151.
32. Aam S, Gynnild MN, Munthe-Kaas R, *et al*. The impact of vascular risk factors on post-stroke cognitive impairment: the nor-COAST study. *Front Neurol* 2021; 12.
33. Ben Assayag E, Eldor R, Korczyn AD, *et al*. Type 2 diabetes mellitus and impaired renal function are associated with brain alterations and poststroke cognitive decline. *Stroke* 2017; 48: 2368–2374.
34. Luchsinger JA, Tang MX, Stern Y, *et al*. Diabetes mellitus and risk of Alzheimer's disease and dementia with stroke in a multiethnic cohort. *Am J Epidemiol* 2001; 154: 635–641.
35. Cordoliani-Mackowiak MA, Hénon H, Pruvo JP, *et al*. Poststroke dementia: influence of hippocampal atrophy. *Arch Neurol* 2003; 60: 585–590.
36. Lee M, Lim JS, Kim Y, *et al*. Effects of glycemic gap on post-stroke cognitive impairment in acute ischemic stroke patients. *Brain Sci* 2021; 11.
37. Tang SC, Yang KC, Hu CJ, *et al*. Elevated plasma level of soluble form of RAGE in ischemic stroke patients with dementia. *Neuromolecular Med* 2017; 19: 579–583.
38. Koszewiczz M, Jaroch J, Brzecka A, *et al*. Dysbiosis is one of the risk factor for stroke and cognitive impairment and potential target for treatment. *Pharmacol Res* 2021; 164: 105277.
39. Ling Y, Gong T, Zhang J, *et al*. Gut microbiome signatures are biomarkers for cognitive impairment in patients with ischemic stroke. *Front Aging Neurosci* 2020; 12: 511562.

40. Teng Z, Feng J, Qi Q, *et al*. *Long-term use of metformin is associated with reduced risk of cognitive impairment with alleviation of cerebral small vessel disease burden in patients with type 2 diabetes*. Frontiers in aging. *Neuroscience* 2021; 13: 773797
41. Imfeld P, Bodmer M, Jick SS, *et al*. Metformin, other antidiabetic drugs, and risk of Alzheimer's disease: a population-based case–control study. *J Am Geriatr Soc* 2012; 60: 916–921.
42. Watson GS, Cholerton BA, Reger MA, *et al*. Preserved cognition in patients with early Alzheimer disease and amnestic mild cognitive impairment during treatment with rosiglitazone: a preliminary study. *Am J Geriatr Psychiatry* 2005; 13: 950–958.
43. Risner ME, Saunders AM, Altman JFB, *et al*. Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease. *Pharmacogenomics J* 2006; 6: 246–254.
44. Zullo AR, Duprey MS, Smith RJ, *et al*. Effects of dipeptidyl peptidase-4 inhibitors and sulphonylureas on cognitive and physical function in nursing home residents. *Diabetes Obes Metab* 2022; 24: 247–256.
45. Jin Y, Zhao H, Hou Y, *et al*. The effects of dipeptidyl peptidase-4 inhibitors and glucagon-like peptide 1 receptor agonists on cognitive functions in adults with type 2 diabetes mellitus: a systematic review and meta-analysis. *Acta Diabetol* 2020; 57: 1129–1144.
46. Mone P, Lombardi A, Gambardella J, *et al*. Empagliflozin improves cognitive impairment in frail older adults with type 2 diabetes and heart failure with preserved ejection fraction. *Diabetes Care* 2022; 45: 1247–1251.
47. Low S, Goh KS, Ng TP, *et al*. Association between use of sodium-glucose co-Transporter-2 (SGLT2) inhibito rs and cognitive function in a longitudinal study of patients with type 2 diabetes. *J Alzheimers Dis* 2022; 87: 635–642.
48. Noel JA, Hougen I, Sood MM. The intersection of SGLT2 inhibitors, cognitive impairment, and CKD. *Front Neurol* 2022; 13: 823569.
49. Weinstein G, Davis-Plourde KL, Conner S, *et al*. Association of metformin, sulfonylurea and insulin use with brain structure and function and risk of dementia and Alzheimer's disease: Pooled analysis from 5 cohorts. *PLoS One* 2019; 14: e0212293.
50. Benedict C, Hallschmid M, Hatke A, *et al*. Intranasal insulin improves memory in humans. *Psychoneuroendocrinology* 2004; 29: 1326–1334.