COMMENTARY

Pathophysiology of cognitive dysfunction in older people with type 2 diabetes: vascular changes or neurodegeneration?

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Abstract

Recent studies have revealed that type 2 diabetes mellitus (T2DM) is a risk factor for cognitive dysfunction or dementia, especially those related to Alzheimer's disease (AD). Basic research suggests that insulin accelerates Alzheimer-related pathology through its effects on the amyloid beta (Aβ). Several pathological studies with autopsy samples have demonstrated, however, that dementia subjects with diabetes have less AD-related neuropathology than subjects without diabetes. We and others have reported that small vessel diseases affect cognitive function in older diabetics. Asymptomatic ischemic lesions in T2DM subjects may lower the threshold for the development of dementia and this may explain the inconsistency between the basic research and clinicopathological studies. Longitudinal follow-up of T2DM subjects without overt dementia using both amyloid imaging and magnetic resonance imaging may elucidate these issues. Following up until the development of overt dementia would make it possible to compare both amyloid load and ischemic lesions before and after the development of dementia. Moreover, amyloid imaging in non-demented older people with or without insulin resistance would verify the role of insulin in the processing and deposition of Aβ. Vascular risk factors may represent a therapeutic target, while neurodegenerative pathologies have not yet been amenable to treatment. It remains to be investigated whether medical interventions on vascular risk factors have protective effects against the development and progress of dementia.

Keywords: *Alzheimer's disease, ischemic lesions, dementia, insulin, Aβ*

The prevalence of type 2 diabetes mellitus (T2DM) increases with age, and dementia also increases its incidence in later life. Therefore, the coincidence of T2DM and dementia increases with ageing. Moreover, recent studies have indicated that older people with T2DM have a higher risk of cognitive dysfunction or dementia [1]. There is ample evidence that T2DM is related not only to vascular dementia but also to clinical diagnosis of Alzheimer's disease (AD)-type dementia [2]. The precise mechanisms underlying T2DM-related cognitive dysfunction or development of dementia, especially AD-type dementia, remain to be elucidated, although several hypothetical mechanisms have been proposed. High glucose concentration, a major pathological characteristic of diabetes, may have toxic effects on neurons in the brain through osmotic insults and oxidative stress, and the maintenance of chronic high glucose also leads to the enhanced formation of advanced glycation endoproducts, which have potentially toxic effects on neurons.

Diabetes is associated with an increased release of inflammatory cytokines, and the excess inflammation may be neurotoxic.

T2DM, especially in conjunction with obesity, is characterised by insulin resistance and/or hyperinsulinaemia. Insulin resistance is defined as an inadequate response by insulin target tissues, such as skeletal muscle, liver and adipose tissue, to the physiological effects of circulating insulin, and often is accompanied by raised insulin levels. Basic research suggests that insulin accelerates AD-related pathology through its effects on the amyloid beta (Aβ) metabolism and tau phosphorylation [2]. Insulin reportedly raises Aβ concentrations in plasma in AD subjects, and these effects may contribute to the risk of AD in T2DM. The desensitization of insulin receptors, insulin resistance, reduces the synthesis of several proteins, including insulin-degrading enzyme (IDE). IDE degrades Aβ as well as insulin, and reduced amounts of IDE may result in greater

amyloid deposition. Less insulin signalling may also induce increased activity of glycogen synthase kinase-3β, which leads to the enhanced phosphorylation of tau protein and the formation of neurofibrillary tangles (NFTs). Several pathological studies with autopsy samples have demonstrated, however, that dementia subjects with diabetes have less AD-related neuropathology than subjects without diabetes. One study demonstrated that diabetics show significantly less AD-associated neuropathology [3], while another failed to show any relationship between diabetes and AD-associated neuropathology [4]. Why does this disparity exist between clinicopathological data and the implications of basic research?

AD has been thought to be a neurodegenerative disorder, which can be sharply distinguished from vascular dementia. Recent studies, however, suggest that the distinction between AD and vascular dementia may not be tenable. There is now substantial and growing evidence that vascular disorders and/or impaired cerebral perfusion contribute to the development of sporadic AD. For example, cerebrovascular pathology including stroke seems to play an important role in the eventual development of the clinical symptoms of AD [5].

On cerebral magnetic resonance imaging (MRI), white matter hyperintensities and lacunae, both of which are frequently observed in the elderly, are generally viewed as evidence of small vessel disease in the brain (white matter lesions and lacunae). These lesions are frequently concomitant with Alzheimer-related neuropathology (senile plaques and NFTs) and contributes to cognitive impairment in AD subjects [6]. We previously reported that small vessel diseases affect cognitive function in older diabetics who have not developed either overt dementia or symptomatic stroke [7, 8]. The number of asymptomatic infarcts and the extent of white matter lesions in the brain detected with MRI were found to be associated with the scores of several cognitive functional tests, especially the digit symbol substitution test, a neurocognitive test that primarily reflects declines in perceptual speed. We also reported that an inflammatory cytokine, tumour necrosis factor-α, which is a risk factor for atherosclerosis, is related to cognitive dysfunction in older non-demented diabetics [9]. A recent study demonstrated that T2DM subjects with clinical diagnosis of dementia have less Alzheimer-related pathology but more ischaemic lesions [10]. This supports the hypothesis that small vessel disease lowers the threshold for the development of dementia. That is, if subjects have the same level of cognitive dysfunction, those with a combination of two types of pathologies have fewer pathological changes in each of their pathologies than those with a single pathology which is severe enough to cause the cognitive dysfunction. Therefore, these pathological reports do not necessarily refute the possibility that DM accelerates the development of Alzheimer-related neuropathology in the patients with clinical diagnosis of dementia. Arvanitakis *et al*. demonstrated in 2004 that T2DM increases the incidence of AD by clinical diagnosis [11], but T2DM ameliorated perceptual speed but not global cognition. A previous study [12] and our own studies [7, 8] showed that cerebral ischaemic lesions are preferentially associated with a lower measure of perceptual speed. These results also suggest that small vessel disease contributes to cognitive decline in these populations.

Hypertension is often accompanied by diabetes, and several longitudinal studies appear to support the notion that hypertension predisposes to cognitive decline and the development of dementia [13]. Vascular alterations induced by high blood pressure may contribute to cognitive dysfunction. Hypertension is also associated with cerebrovascular disease including lacunar brain infarcts and white matter lesions, which may contribute to cognitive impairment in diabetics.

Recently, amyloid imaging technology with positron emission tomography, which visualises Aβ depositions in the human brain, has been developed and is now widely available [14] although some limitations of resolution and specificity still exist. This technology can be used to investigate the relative contributions of ischaemic and neurodegenerative changes to the increasing development of dementia in T2DM subjects. Longitudinal follow-up of T2DM subjects without overt dementia using both amyloid imaging and MRI may help to elucidate these issues, especially with higher field MRI with some potential for the imaging small vessel diseases [15] as well as diffusion tensor imaging method [16]. Following up until the development of overt dementia would make it possible to compare both amyloid load and ischaemic lesions before and after the development of dementia. Moreover, amyloid imaging in non-demented older people with or without insulin resistance would verify the hypothesis that insulin plays a role in the processing and deposition of Aβ. These investigations are important considering the future availability of disease-modifying therapeutics such as Aβ vaccination and inhibitors for Aβ secretions.

At present, vascular risk factors may represent a therapeutic target, while neurodegenerative pathologies have not yet been amenable to treatment. Vascular risk factors including diabetes and hypertension are reportedly associated with the progression of lacunae and white matter lesions [17]; however, the beneficial effects on cognitive function of pharmaceutical interventions with antidiabetics and antihypertensives are less clear in terms of the inhibition of the progress of lacunae and white matter lesions. It remains to be investigated whether medical interventions on vascular risk factors have protective effects against the development and progress of dementia. If such protective effects do exist, the underlying mechanism of the therapeutic effects should be interesting, whether it relies on the inhibition of the development of vascular lesions or in that of the neurodegenerative process.

With the current increase in the older population, T2DM-associated cognitive dysfunction and dementia are an increasingly larger problem. A greater understanding of the relevant pathophysiology and the establishment of better therapeutic interventions are urgent issues.

Key points

- Ischaemic lesions including lacunae and white matter lesions affect cognitive function in diabetic older people.
- The relative pathological contribution in diabetes-related cognitive dysfunction of vascular changes and neurodegenerative processes merits further investigation.
- Further studies are warranted to determine whether medical interventions on vascular risk factors have protective effects against cognitive function in diabetics.

Conflict of interest

None to declare.

References

1. Stewart R, Liolitsa D. Type 2 diabetes mellitus, cognitive impairment and dementia. Diabet Med 1999; 16: 93–112.
2. Li L, Hölscher C. Common pathological processes in Alzheimer disease and type 2 diabetes: a review. Brain Res Rev 2007; 56: 384–402.
3. Beeri MS, Silverman JM, Davis KL et al. Type 2 diabetes is negatively associated with Alzheimer's disease neuropathology. J Gerontol A Biol Sci Med Sci 2005; 60: 471–5.
4. Arvanitakis Z, Schneider JA, Wilson RS et al. Diabetes is related to cerebral infarction but not to AD pathology in older persons. Neurology 2006; 67: 1960–5.
5. de la Torre JC. Is Alzheimer's disease a neurodegenerative or a vascular disorder? Data, dogma, and dialectics. Lancet Neurol 2004; 3: 184–90.
6. Riekse RG, Leverenz JB, McCormick W et al. Effect of vascular lesions on cognition in Alzheimer's disease: a community-based study. J Am Geriatr Soc 2004; 52: 1442–8.
7. Akisaki T, Sakurai T, Takata T et al. 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.
8. Umegaki H, Kawamura T, Mogi N, Umemura T, Kanai A, Sano T. Glucose control levels, ischaemic brain lesions, and hyperinsulinaemia were associated with cognitive dysfunction in diabetic elderly. Age Ageing 2008; 37: 458–61.
9. Suzuki M, Umegaki H, Ieda S, Mogi N, Iguchi A. Factors associated with cognitive impairment in elderly patients with diabetes mellitus. J Am Geriatr Soc 2006; 54: 558–9.
10. Sonnen JA, Larson EB, Brickell K et al. Different patterns of cerebral injury in dementia with or without diabetes. Arch Neurol 2009; 66: 315–22.
11. Arvanitakis Z, Wilson RS, Bienias JL, Evans DA, Bennett DA. Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function. Arch Neurol 2004; 61: 661–6.
12. Schneider JA, Wilson RS, Cochran EJ et al. Relation of cerebral infarctions to dementia and cognitive function in older persons. Neurology 2003; 60: 1082–8.
13. Peters R, Beckett N, Forette F et al. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. Lancet Neurol 2008; 7: 683–9.
14. Ikonomovic MD, Klunk WE, Abrahamson EE et al. Post-mortem correlates of in vivo PiB-PET amyloid imaging in a typical case of Alzheimer's disease. Brain 2008; 131: 1630–45.
15. Novak V, Abduljalil AM, Novak P, Robitaille PM. High-resolution ultrahigh-field MRI of stroke. Magn Reson Imaging 2005; 23: 539–48.
16. Kodl CT, Franc DT, Rao JP, Anderson FS et al. Diffusion tensor imaging identifies deficits in white matter microstructure in subjects with type 1 diabetes that correlate with reduced neurocognitive function. Diabetes 2008; 57: 3083–9.
17. Gouw AA, van der Flier WM, Fazekas F et al. 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.