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The Diabetic Brain and Dementia

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Abbreviations: AD: Alzheimer's Disease; DM: Diabetes Mellitus; DMT2: Type 2 Diabetes Mellitus; MCI: Mild Cognitive Impairment

Alzheimer's Disease (AD) and Diabetes Mellitus (DM) are the two most common and devastating health problems in the elderly. They share a number of common features among which are important impact on quality of life and substantial health care costs. Epidemiological and biological evidence support a pathophysiological link between Type 2 Diabetes Mellitus (DMT2) and cognitive impairment [1-3]. A causative association between DM and Alzheimer's disease has been suggested on the basis of clinical, epidemiological, genetic and experimental studies [2,4-9]. Persons with DM have a higher incidence of cognitive decline and an increased risk of developing AD and other types of dementia, and comorbidity increases the risk [10,11]. Insulin resistance predicts medial temporal hypermetabolism in Mild Cognitive Impairment (MCI) conversion to AD [12] and glucose uptake changes in AD in medial temporal regions predicting worse memory performance [13]. DM has been shown to influence the rate of functional decline among patients with mild AD dementia than in those without comorbid DM [14]. However, the precise mechanisms involved in the development of AD in diabetics are not yet fully understood, and several pathogenic pathways have been discussed [3,4,15-20].

Autopsy studies stated that diabetic patients show significantly less AD pathology (senile plaques, neurofibrillary tangles, cerebral amyloid angiopathy, etc.) but more cerebrovascular lesions including microvascular lesions and white matter changes than subjects without DM [5,21-27]. Vasculo-neural dysfunction has been suggested to represent a potential etiological linkage between DMT2 and AD [6,28], while others suggested that the association between DM and dementia is only partially mediated through cerebrovascular disease and that DM is associated independently with overal dementia among elderly, but not with AD or vascular dementia [29].

Positive DMT2 status appears to exacerbate AD pathology in the presence of ApoE ε4 [30]. Although insulin mitigates Aβ deposition and hyperphosphorylation of tau [17,31], DM in combination with ApoE ε4 may lead to excessive phosphorylation of tau [32], but only in subjects with late stage AD [21]. DM modifies metabolism of Aβ and tau causing Aβ/tau-dependent pathological changes, although there is evidence that suggests an interaction of Aβ/tau-dependent and -independent mechanisms [31]. Evidence supports insulin's role in cognition, synaptic remodelling and facilitation of memory [33]. On the other hand, insulin has been shown to modulate the level of Aβ, to protect neurons against detrimental effects of Aβ on synapses [33]. It further facilitates reduction of amyloid plaques, downregulation of Aβ-derived diffusible ligand-binding sites and also to promote tau hypophosphorylation, which stabilizes microtubules. These data and the observation that the combination of insulin and other antidiabetic medication is associated with lower neuritic plaque density [23,34] are providing a rationale for using insulin to treat AD high-risk patients [35-37].

Insulin resistance, hyperinsulinemia and hyperglycemia can affect the amyloid cascade by reducing Aβ clearance and promote the onset of AD [9,28,38]. Overlapping with AD pathology, they aggravate the progression of neurodegeneration due to oxidative stress, disordered control of protein translation, neurotoxicity by Advanced Glycation End-Products (AGE), mitochondrial dysfunction, neuroinflammation, and a variety of other mechanisms as common pathogenic backgroud culminating in synaptic dysfunction and memory loss [16,26,39-44]. Recent research data indicate that there is a widespread conformational change in the protein control and other molecular mechanisms involved in both AD and DMT2 that form β-sheet like motifs, interacting with other proteins and consequently catalyzing their translation into the toxic state may lead to neurodegeneration and also to cerebral hypoperfusion, which result in dysfunction and degeneration of neuroglial cells and myelin components [45,46]. *In vivo* seeding and cross-seeding of local amyloid may represent another molecular link between AD and DMT2 [47].

In conclusion, there is evidence for multiple mechanisms contributing to the pathological interaction between DMT2 and dementia, the relationship of which is regulated by several modifiers, e.g., genetic risk, ageing, ApoE status, cardiovascular and general status of an individual [48] including hypertension and obesity [49], thus forming a complex vicious circle that underlies the interaction between AD and DM [46]. Recent population-based studies concluded that management of modifiable risk factors for cognitive decline and dementia, such as cardiovascular risk factors (diabetes, obesity, smoking, and hypertension) may reduce the risk of cognitive decline [50,51]. Since a disturbance of insulin signal transduction may be of pathogenic relevance in AD and related dementias, antidiabetic drugs may have an important role in treating MCI and AD [52,53] and insulin therapy could be effective in slowing cognitive decline in patients with AD [54]. More information is needed about cerebral hypofunction and underlying pathologies in the context with DM, and better identification of the mechanisms whereby DM modifies the pathophysiological mechanisms leading to cognitive impairment through the modification of insulin signaling are required to develop potential preventive and therapeutic strategies.

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References

1. Barbagallo M, Dominguez LJ (2014) Type 2 diabetes mellitus and Alzheimer's disease. World J Diabetes 5: 889-893.
2. Huang CC, Chung CM, Leu HB, Lin LY, Chiu CC, et al. (2014) Diabetes mellitus and the risk of Alzheimer's disease: a nationwide population-based study. PLoS One 9: e87095.
3. Feinkohl I, Price JF, Strachan MW, Frier BM (2015) The impact of diabetes on cognitive decline: potential vascular, metabolic, and psychosocial risk factors. Alzheimers Res Ther 7: 46.
4. Hao K, Di Narzo AF, Ho L, Luo W, Li S, et al. (2015) Shared genetic etiology underlying Alzheimer's disease and type 2 diabetes. Mol Aspects Med.
5. Vagelatos NT, Eslick GD (2013) Type 2 diabetes as a risk factor for Alzheimer's disease: the confounders, interactions, and neuropathology associated with this relationship. Epidemiol Rev 35: 152-160.
6. Wang F, Guo X, Shen X, Kream RM, Mantione KJ, et al. (2014) Vascular dysfunction associated with type 2 diabetes and Alzheimer's disease: a potential etiological linkage. Med Sci Monit Basic Res 20: 118-129.
7. Bitel CL, Kasinathan C, Kaswala RH, Klein WL, Frederikse PH (2012) Amyloid-beta and tau pathology of Alzheimer's disease induced by diabetes in a rabbit animal model. J Alzheimers Dis 32: 291-305.
8. Carvalho C, Santos MS, Oliveira CR, Moreira PI (2015) Alzheimer's disease and type 2 diabetes-related alterations in brain mitochondria, autophagy and synaptic markers. Biochim Biophys Acta 1852: 1665-1675.
9. Ronnemaa E, Zethelius B, Sundelof J, Sundstrom J, Degerman-Gunnarsson M, et al. (2008) Impaired insulin secretion increases the risk of Alzheimer disease. Neurology 71: 1065-1071.
10. Haroon NN, Austin PC, Shah BR, Wu J, Gill SS, et al. (2015) Risk of Dementia in Seniors With Newly Diagnosed Diabetes: A Population-Based Study. Diabetes Care.
11. Kuo SC, Lai SW, Hung HC, Muo CH, Hung SC, et al. (2015) Association between comorbidities and dementia in diabetes mellitus patients: population-based retrospective cohort study. J Diabetes Complications.
12. Willette AA, Modanlo N, Kapogiannis D (2015) Insulin resistance predicts medial temporal hypermetabolism in mild cognitive impairment conversion to Alzheimer disease. Diabetes 64: 1933-1940.
13. Willette AA, Bendlin BB, Starks EJ, Birdsill AC, Johnson SC, et al. (2015) 2015b - Association of Insulin Resistance With Cerebral Glucose Uptake in Late Middle-Aged Adults at Risk for Alzheimer Disease. JAMA Neurol 72:1013-1020.
14. Ascher-Svanum H, Chen YF, Hake A, Kahle-Wrobleski K, Schuster D, et al. (2015) Cognitive and Functional Decline in Patients With Mild Alzheimer Dementia With or Without Comorbid Diabetes. Clin Ther 37: 1195-1205.
15. Chiu WC, Ho WC, Liao DL, Lin MH, Chiu CC, et al. (2015) Progress of diabetic severity and risk of dementia. J Clin Endocrinol Metab 100: 2899-2908.
16. Verdile G, Fuller SJ, Martins RN (2015) The role of type 2 diabetes in neurodegeneration. Neurobiol Dis.
17. Bedse G, Di Domenico F, Serviddio G, Cassano T (2015) Aberrant insulin signaling in Alzheimer's disease: current knowledge. Front Neurosci 9: 204.
18. 18. Holscher C (2011) Diabetes as a risk factor for Alzheimer's disease: insulin signalling impairment in the brain as an alternative model of Alzheimer's disease. Biochem Soc Trans 39: 891-897.
19. Strachan MW, Reynolds RM, Frier BM, Mitchell RJ, Price JF (2008) The relationship between type 2 diabetes and dementia. Br Med Bull 88: 131-146.
20. De Felice FG, Lourenco MV, Ferreira ST (2014) How does brain insulin resistance develop in Alzheimer's disease? Alzheimers Dement 10: S26-32.
21. Alafuzoff I, Aho L, Helisalmi S, Mannermaa A, Soininen H (2009) Beta-amyloid deposition in brains of subjects with diabetes. Neuropathol Appl Neurobiol 35: 60-68.
22. Umegaki H (2010) Pathophysiology of cognitive dysfunction in older people with type 2 diabetes: vascular changes or neurodegeneration? Age Ageing 39: 8-10.
23. Beeri MS, Silverman JM, Davis KL, Marin D, Grossman HZ, et al. (2005) Type 2 diabetes is negatively associated with Alzheimer's disease neuropathology. J Gerontol A Biol Sci Med Sci 60: 471-475.
24. Nelson PT, Smith CD, Abner EA, Schmitt FA, Scheff SW, et al. (2009) Human cerebral neuropathology of Type 2 diabetes mellitus. Biochim Biophys Acta 1792: 454-469.
25. Ahtiluoto S, Polvikoski T, Peltonen M, Solomon A, Tuomilehto J, et al. (2010) Diabetes, Alzheimer disease, and vascular dementia: a population-based neuropathologic study. Neurology 75: 1195-1202.
26. Takeda S, Sato N, Rakugi H, Morishita R (2011) Molecular mechanisms linking diabetes mellitus and Alzheimer disease: beta-amyloid peptide, insulin signaling, and neuronal function. Mol Biosyst 7: 1822-1827.
27. Roriz-Filho JS, Sá-Roriz TM, Rosset I, Camozzato AL, Santos AC, et al. (2009) (Pre)diabetes, brain aging, and cognition. Biochim Biophys Acta 1792: 432-443.
28. Winkler EA, Nishida Y, Sagare AP, Rege SV, Bell RD, et al. (2015) GLUT1 reductions exacerbate Alzheimer's disease vasculo-neuronal dysfunction and degeneration. Nat Neurosci 18: 521-530.
29. Lu ZK, Li M, Yuan J, Wu J (2015) The role of cerebrovascular disease and the association between diabetes mellitus and dementia among aged medicare beneficiaries. Int J Geriatr Psychiatry.
30. Malek-Ahmadi M, Beach T, Obradov A, Sue L, Belden C, et al. (2013) Increased Alzheimer's disease neuropathology is associated with type 2 diabetes and ApoE epsilon.4 carrier status. Curr Alzheimer Res 10: 654-659.
31. Sato N, Morishita R (2014) Brain alterations and clinical symptoms of dementia in diabetes: abeta/tau-dependent and independent mechanisms. Front Endocrinol (Lausanne) 5: 143.
32. Matsuzaki T, Sasaki K, Tanizaki Y, Hata J, Fujimi K, et al. (2010) Insulin resistance is associated with the pathology of Alzheimer disease: the Hisayama study. Neurology 75: 764-770.
33. Bilotta F, Lauretta MP, Tewari A, Rosa G (2013) Insulin signaling in the central nervous system and Alzheimer's disease. J Alzheimers Dis Parkinsonism 3: e129.
34. Beeri MS, Schmeidler J, Silverman JM, Gandy S, Wysocki M, et al. (2008) Insulin in combination with other diabetes medication is associated with less Alzheimer neuropathology. Neurology 71: 750-757.
35. Rdzak GM, Abdelghany O (2014) Does insulin therapy for type 1 diabetes mellitus protect against Alzheimer's disease? Pharmacotherapy 34: 1317-1323.
36. Benedict C, Frey WH, 2nd, Schioth HB, Schultes B, Born J, et al. (2011) Intranasal insulin as a therapeutic option in the treatment of cognitive impairments. Exp Gerontol 46: 112-115.
37. Miller BW, Willett KC, Desilets AR (2011) Rosiglitazone and pioglitazone for the treatment of Alzheimer's disease. Ann Pharmacother 45: 1416-1424.
38. de Oliveira Lanna ME, Pimentel MLV, Novis SAP (2014) Diabetes effects in Alzheimer disease: the interactive role of insulin and Aß peptide. J Alzheimers Dis Parkinsonism 4: 151, doi: 110.4172/2161-0460.1000151.
39. Rosales-Corral S, Tan DX, Manchester L, Reiter RJ (2015) Diabetes and Alzheimer disease, two overlapping pathologies with the same background: oxidative stress. Oxid Med Cell Longev 2015: 985845.
40. Lourenco MV, Ferreira ST, De Felice FG (2015) Neuronal stress signaling and eIF2alpha phosphorylation as molecular links between Alzheimer's disease and diabetes. Prog Neurobiol 129: 37-57.
41. De Felice FG, Ferreira ST (2014) Inflammation, defective insulin signaling, and mitochondrial dysfunction as common molecular denominators connecting type 2 diabetes to Alzheimer disease. Diabetes 63: 2262-2272.
42. Butterfield DA, Di Domenico F, Barone E (2014) Elevated risk of type 2 diabetes for development of Alzheimer disease: a key role for oxidative stress in brain. Biochim Biophys Acta 1842: 1693-1706.
43. Adeghate E, Donath T, Adem A (2013) Alzheimer disease and diabetes mellitus: do they have anything in common? Curr Alzheimer Res 10: 609-617.
44. Spauwen PJ, van Eupen MG, Kohler S, Stehouwer CD, Verhey FR, et al. (2015) Associations of advanced glycation end-products with cognitive functions in individuals with and without type 2 diabetes: the maastricht study. J Clin Endocrinol Metab 100: 951-960.
45. Ashraf GM, Greig NH, Khan TA, Hassan I, Tabrez S, et al. (2014) Protein misfolding and aggregation in Alzheimer's disease and type 2 diabetes mellitus. CNS Neurol Disord Drug Targets 13: 1280-1293.

46. Sato N, Takeda S, Uchio-Yamada K, Ueda H, Fujisawa T, et al. (2011) Role of insulin signaling in the interaction between Alzheimer disease and diabetes mellitus: a missing link to therapeutic potential. Curr Aging Sci 4: 118-127.

47. Oskarsson ME, Paulsson JF, Schultz SW, Ingelsson M, Westermark P, et al. (2015) In vivo seeding and cross-seeding of localized amyloidosis: a molecular link between type 2 diabetes and Alzheimer disease. Am J Pathol 185: 834-846.

48. Jayaraman A, Pike CJ (2014) Alzheimer's disease and type 2 diabetes: multiple mechanisms contribute to interactions. Curr Diab Rep 14: 476.

49. Ostergaard SD, Mukherjee S, Sharp SJ, Proitsi P, Lotta LA, et al. (2015) Associations between Potentially Modifiable Risk Factors and Alzheimer Disease: A Mendelian Randomization Study. PLoS Med 12: e1001841; discussion e1001841.

50. Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, et al. (2015) Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. Alzheimers Dement 11: 718-726.

51. Li JQ, Tan L, Wang HF, Tan MS, Xu W, et al. (2015) Risk factors for predicting progression from mild cognitive impairment to Alzheimer's disease: a systematic review and meta-analysis of cohort studies. J Neurol Neurosurg Psychiatry.

52. Alagiakrishnan K, Sankaralingam S, Ghosh M, Mereu L, Senior P (2013) Antidiabetic drugs and their potential role in treating mild cognitive impairment and Alzheimer's disease. Discov Med 16: 277-286.

53. Walker JM, Harrison FE (2015) Shared neuropathological characteristics of obesity, type 2 diabetes and Alzheimer's disease: impacts on cognitive decline. Nutrients 7: 7332-7357.

54. Plastino M, Fava A, Pirritano D, Cotronei P, Sacco N, et al. (2010) Effects of insulinic therapy on cognitive impairment in patients with Alzheimer disease and diabetes mellitus type-2. J Neurol Sci 288: 112-116.