

Neurodegeneration contributes more to cognitive impairment than microvascular injury in middle-aged patients with type 2 diabetes

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Xin Li PhD, Bing Zhang PhD

Department of Radiology, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University

We found that neurodegeneration contributes more to cognitive impairment than microvascular injury in middle-aged patients with type 2 diabetes. Both NAFLD and high BMI were independently associated with neurodegeneration. Neurodegeneration mediated association between metabolic dysregulation and cognitive impairment.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES																																			
Neurodegeneration and microvascular injury were associated with cognitive impairment in T2D. Obesity or NAFLD were also related to brain damage. We aimed to investigate the patterns of neurodegeneration and microvascular injury in middle-aged T2D patients with NAFLD or high BMI, and to analyze their relationships with metabolic parameters and cognitive function.	A total of 516 middle-aged subjects were enrolled, including 451 patients with T2D and 65 normal controls. The patients were further divided into four subgroups including the presence of NAFLD or high BMI. All participants underwent MRI, clinical assessments, and cognitive tests. Brain gray volume and cortical thickness represent neurodegeneration, and PSMD and WMH reflect microvascular injury. Partial correlation, canonical correlation, and mediation effect model analysis were employed to assess the relationship.	The T2D patients showed widespread brain atrophy. Both NAFLD and high BMI were independently associated with neurodegeneration, with no significant interaction effect. No significant differences were found in PSMD or WMH volume, and neither NAFLD nor high BMI had a significant impact on microvascular injury. Neurodegeneration mediated the association between metabolic dysregulation and cognitive impairment, while microvascular injury did not.	These findings provide a theoretical basis for early identification and risk stratification of diabetes-related cognitive impairment. A <table><tr><th>Parameters</th><th>Metabolism</th><th>MoCA</th><th>PCS</th><th>EXF</th><th>DEM</th><th>VSA</th></tr><tr><td>Total brain volume</td><td>*</td><td>***</td><td>***</td><td>***</td><td>**</td><td>***</td></tr><tr><td>Subcortical structures volume</td><td>***</td><td>***</td><td>***</td><td>**</td><td>***</td><td>***</td></tr><tr><td>Hippocampal subfield volume</td><td>**</td><td></td><td>***</td><td></td><td></td><td>***</td></tr><tr><td>Cortical thickness</td><td>***</td><td>**</td><td>***</td><td>**</td><td>**</td><td>*</td></tr></table> 0.15 r 0.4 Total brain volume Metabolism $\beta = 0.2135$ $P < 0.001^{***}$ Processing speed $\beta = -0.1345$ $P = 0.0078^{**}$ Direct effect: 1.4734 (-3.8791, 6.8259) Indirect effect: -1.5541 (-3.4584, -0.3706) Total brain volume Metabolism $\beta = 0.2348$ $P < 0.001^{***}$ Visuospatial ability $\beta = 0.2190$ $P < 0.001^{***}$ Direct effect: 0.5177 (-0.5909, 1.6262) Indirect effect: 0.5391 (0.2164, 1.1097) Hippocampal subfield volume Metabolism $\beta = 0.3172$ $P < 0.001^{***}$ Processing speed $\beta = 0.1967$ $P < 0.001^{***}$ Direct effect: 1.0971 (-5.5250, 7.7192) Indirect effect: 4.1068 (1.8314, 6.7362) Hippocampal subfield volume Metabolism $\beta = 0.2348$ $P < 0.001^{***}$ Visuospatial ability $\beta = 0.2190$ $P < 0.001^{***}$ Direct effect: -0.0870 (-1.4842, 1.3102) Indirect effect: -1.0444 (-1.6004, -0.5797)	Parameters	Metabolism	MoCA	PCS	EXF	DEM	VSA	Total brain volume	*	***	***	***	**	***	Subcortical structures volume	***	***	***	**	***	***	Hippocampal subfield volume	**		***			***	Cortical thickness	***	**	***	**	**	*	Lee EH, et al, Different associations between body mass index and Alzheimer's markers depending on metabolic health. <i>Alzheimers Res Ther</i> 2024, 16(1):194. Dove A, et al, Cardiometabolic multimorbidity accelerates cognitive decline and dementia progression. <i>Alzheimers Dement</i> 2023, 19(3):821-830.
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Xin Li lixin_med@smail.nju.edu.cn Nanjing Drum Tower Hospital ALZHEIMER'S ASSOCIATION AAIC>26																																							