

Only diabetic polyneuropathy and not cardiac autonomic dysfunction is associated with lower cognitive performance in type 2 diabetes from GRADE study

The study examined the question whether measures of cognition are related to the presence of diabetic peripheral neuropathy (DPN) and/or cardiovascular autonomic neuropathy (CAN) in middle-aged people with type 2 diabetes of <10 years of known duration. The study also aimed to determine candidate factors being common in both DPN/CAN and worse measures of cognition.

Methods. 4559 (90.3%) of the 5047 participants in GRADE study were included. DPN was assessed by the questionnaire and examination of the Michigan Neuropathy Screening Instrument (MNSI). CAN was assessed by two time-domain indices of heart rate variability (HRV) obtained from a standard 10-sec ECG recording: the SDNN (standard deviation of normally conducted R-R intervals) and the RMSSD (root mean square of successive differences between normal-to-normal R-R intervals). The cognitive tests assessed memory and frontal-executive abilities. Memory (verbal learning) was measured by immediate and delayed recall after distraction by using the Spanish English Verbal Learning Test (SEVLT). Executive function and processing speed were tested by the Digit Symbol Substitution Test (DSST). Ability to concentrate and organize data were established by animal and letter fluency tests.

Results. 27.5% and 9.8% of the study population had DPN and CAN at baseline, respectively. Participants with DPN had lower levels of measures of cognition than participants without DPN. On the contrary, participants with and without definite CAN had the same levels of cognitive function measures. In unadjusted regression models of DPN, all cognition scores were lower with higher DPN. After adjustment for covariates, the associations between DPN as a continuous variable and SEVLT-1-3 and DSST remained significant. As a dichotomous variable, only DSST remained lower with adjustment for covariates. Exploratory analysis revealed LDL-cholesterol, waist circumference and urine albumin-to-creatinine ratio (ACR) as candidate factors that could explain the relationships between DPN and cognitive performance.

Conclusions. DPN but not CAN was associated with lower performance in measures of cognition in middle-aged people with type 2 diabetes of <10 years of known duration.

Comments. This study brings hard data on the association of DPN but not CAN with lower performance in measures of cognition in middle-aged people with type 2 diabetes. This finding is very interesting as previous studies provided conflicting results on association between DPN and cognition and had mostly small sample sizes. GRADE has a large, well-characterized cohort, and employed widely used tests of DPN and CAN. Strength of the study is that associations were adjusted for depression as a confounder. Namely, depression is associated with painless DPN and more with painful DPN. However, the percentage of cognitive variation explained by DPN was small and cognitive deficits were slight. As stated by the authors, it may be a consequence of short diabetes duration, younger age (57 years) and relatively good glycaemic control of this cohort. With older age and longer diabetes duration, the association could be more prominent. Further limitation is that CAN was only assessed by time-domain measures of HRV and no data on B12 and TSH levels were available. Potential mediating role of sleep disturbance between neuropathy and cognitive deficit was not assessed either.

The study also determined candidate factors underlying the relationship between DPN and cognitive dysfunction. Proinflammatory state and metabolic changes accompanying obesity and endothelial dysfunction/microangiopathy are the suggested links between DPN, obesity, ACR and cognitive deficit in diabetes. However, no causal relationship between DPN and cognitive measures could be drawn because of the cross-sectional design of the study.

Anna Körei

Reference: Barzilay JI, Ghosh A, Busui RP, Ahmann A, Balasubramanyam A, Banerji MA, Cohen RM, Green J, Ismail-Beigi F, Martin CL, Seaquist E, Luchsinger JA; GRADE Research Group. The cross-sectional association of cognition with diabetic peripheral and autonomic neuropathy-The GRADE study. *J Diabetes Complications*. 2021 Dec;35(12):108047. doi: 10.1016/j.jdiacomp.2021.108047.

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