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Lower cognitive performance among long-term type 1 diabetes survivors
A case–control study

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ABSTRACT

Objective: Patients with type 1 diabetes (T1D) have an increased risk of cognitive dysfunction. The cognitive decrement is believed to depend on macro- and microvascular complications and long disease duration. Some patients do not develop these complications, but still report cognitive symptoms. We examined if long-standing T1D without complications is associated with lower cognitive performance.
Methods: A group of patients (n = 43) with long-standing T1D (>30 years) without micro- or macro vascular complications was compared with a non-diabetic control group (n = 86) on six cognitive tests which probed episodic memory, semantic memory, episodic short-term memory, visual attention and psychomotor speed. Each patient was matched with two controls regarding age, gender and education. A linear mixed effect model was used to analyze the data.
Results: The mean age was 57 years and mean duration was 41 years. Patients with diabetes had lower diastolic blood pressure but BMI, waist circumference, systolic blood pressure and smoking did not differ between groups. Patients had lower results than non-diabetic controls in episodic short-term memory ($p < 0.001$) and also lower values on a test that mirrors visual attention and psychomotor speed ($p = 0.019$).
Conclusions: Long-standing T1D was associated with lower cognitive performance, regardless of other diabetes-related complications.

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1. Introduction

The lifespan of people with type 1 diabetes (T1D) has increased but still these patients are at a great risk for complications and premature mortality, primarily from cardiovascular disease.[1] Prolonged exposure to high blood glucose levels can lead to vascular end-organ damage.[2] However, a subgroup of patients with T1D appears to be "protected", and survives well into old age.[3–5]

In an Editorial in *Diabetologia* Edvin Gale identified three subgroups of type 1 diabetes survivors; those who had complications but survived, those with a slow disease progress who eventually developed complications, and those who never developed any complications.[5] Long-term T1D survivors (*e.g.* those with long-term diabetes without complications) are characterized by good glucose control, long-lived parents, normal blood pressure, low insulin requirements, high HDL-cholesterol level and regular exercise. In 2010, 18% of patients with T1D in the Swedish National Diabetes Register had disease duration of more than 30 years and no clinically significant complications registered.[6]

Type 1 diabetes is associated with structural abnormalities in the brain,[7,8] changes in functional brain networks,[9] and cognitive dysfunction.[10–13] In addition, depressive symptoms and fatigue is common,[11,13–15] and also mild to moderate slowing of mental speed and diminished mental flexibility.[10,11] According to a recent meta-analysis,[12] patients perform lower than controls on verbal and performance intelligence quotient, aspects of executive function, spatial memory, and motor speed. The decrement was found to be more pronounced in adults than children, indicating it may be associated with long-duration and complications rather than diabetes itself.

However, previous studies[7,9,10,12] addressing the effect of T1D on cognitive performance either included patients with shorter disease duration or did not exclude patients with diabetes-related

Conflicts of Interest: None declared.

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complications. To our knowledge, there are no studies of cognitive function among patients with long-term T1D without complications. Clinical experience is that many survivors complain about cognitive symptoms, and early retirement is common. Accordingly, the aim of the present study was to examine cognitive function among patients with long-termT1D without other clinically known diabetes-related complications.

1.1. Method

Participants were patients from the diabetes clinics in Sunderby Hospital in Luleå and the University Hospital of Umeå with more than 30 years of T1D and without diabetes-related complications. According to Gale[5] we defined them as "escapers", *i.e.* no cardiovascular, retinal, renal or neuropathic complications. Exclusion criteria were: cardio- and cerebrovascular events, proliferative retinopathy or laser treatment, persistent micro- or macro albuminuria, diabetic nephropathy and amputation. Out of 342 patients in Luleå and 680 patients in Umeå, 402 had a duration of more than 30 y; 357 patients with complications and 45 patients fulfilled the criteria for being without complications and accepted participation. Cognitive tests were administered by a trained nurse and each session took about 60 min to complete. There were two dropouts who found the tests exhausting and chose not to complete the session. Fig. 1 illustrates the sampling method.

The control group, tested in 2008–2010, was randomly assigned from the Betula prospective cohort study, a longitudinal population-based study of memory and health in Umeå, Sweden.[16,17] In order to avoid test–retest effect we included only individuals who were tested for their first time as control group. Exclusion criteria for the control group were self-reported diabetes and major cognitive disorder, defined as a Mini Mental State Examination (MMSE) score below 24. Each patient were individually matched to two diabetes-free controls with the same gender, age (±3 years), and level of education. Educational level was dichotomized into two groups: low education ≤13 years and higher education >13 years.

1.2. Cognitive tests

The test battery consisted of six tests from the Betula study that probed episodic memory (free recall of sentences), semantic memory (fluency A, fluency B, fluency professions), episodic short-term memory (free recall of words), visual attention and psychomotor speed (letter-digit substitution). These measures are extensively described elsewhere[16,17] and the psychometric properties have been found acceptable.[18] In free recall of words, there was no delayed recall administered, which means that the test does not measure episodic long-term memory, but rather short-term memory and aspects of working memory. The task was to learn 12 words and immediately after presentation to recall as many as possible.

1.3. Ethics

The PROLONG study was approved by the medical ethics committee at the University of Lund in Sweden. The Betula study was approved by the regional board of the ethics committee in Umeå, Sweden.

1.4. Statistical analyses

Descriptive data are presented as mean values with standard deviations (SD), numbers (n) and proportions (%). Independent samples *t* tests and chi-square test was used to test for differences in means and proportions regarding clinical characteristics. Analysis of differences in cognitive performance between patients and controls was made with linear mixed effects models treating each case and the corresponding controls as a random component. Further, the covariance structure chosen was simply a scaled identity matrix. The checking of whether the assumptions underlying the analysis by linear mixed models were fulfilled was performed through common inspection of residuals. There were no signs of serious deviations suggesting that the models would fit the data poorly. IBM SPSS Statistics 24 was used.

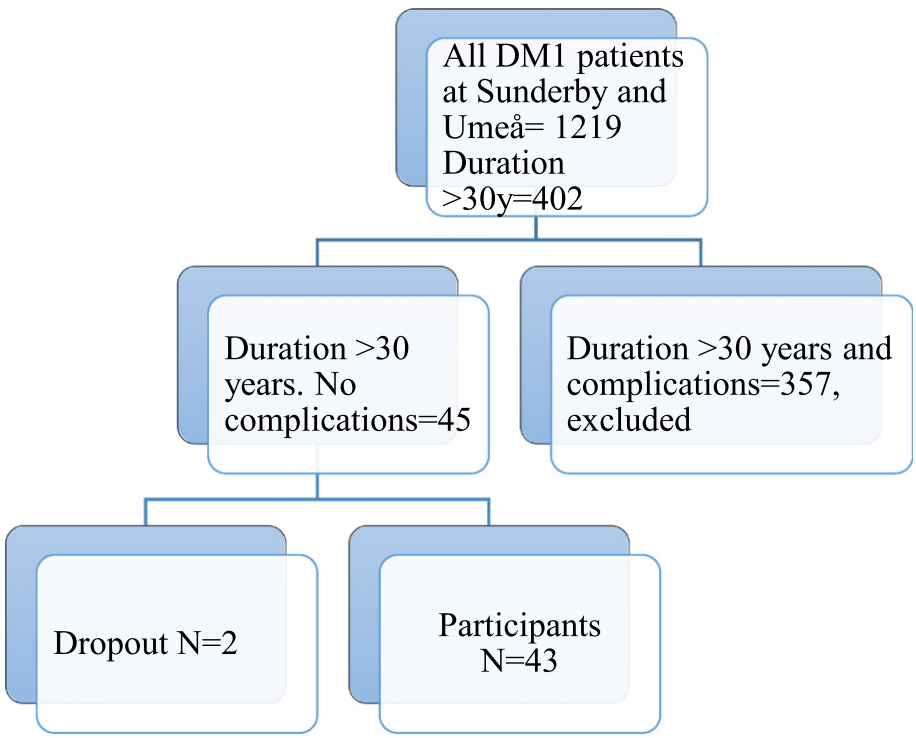

Fig. 1. Flow chart of patient recruitment and selection.

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