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Can tight glycemic control in diabetes benefit cognition?

Raimund I. Herzog and Robert S. Sherwin

Yale School of Medicine, 300 Cedar Street, TAC S141, New Haven, CT 06519, USA

Abstract

Intensive glucose management, if begun early, diminishes the long-term complications of diabetes. Whether the cognitive domain also benefits from such therapy is not clear, and has remained subject to investigation. Do the new results from the ACCORD-MIND study settle the issue?

Insulin resistance and chronic hyperglycemia induce neurodegenerative and neurovascular processes that have been linked to early cognitive decline in patients with type 2 diabetes.¹ Early institution of intensive glucose control diminishes long-term microvascular and macrovascular complications of type 1 and type 2 diabetes.^{2,3} Intensive glucose management can, however, cause frequent bouts of severe hypoglycemia, such that any vascular benefit from this intervention could, theoretically, be offset by hypoglycemia-induced impairments, including cognitive decline.

Long-term (~18 years) follow-up of intensively treated, relatively young patients with type 1 diabetes found no adverse cognitive effects, and indicated that poor glycemic control might promote mild cognitive deterioration,⁴ but less is known about cognitive outcomes in patients with type 2 diabetes under intensive glucose management. Because this older patient population exhibits mild deficits in memory and information processing compared with age-matched nondiabetic controls, efforts to prevent cognitive decline are especially important.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial assessed whether aggressive glucose lowering to a target glycated hemoglobin (Hb_{A1c}) level of <6.0% of total hemoglobin versus standard therapy (Hb_{A1c} 7.0–7.9%) can improve cardiovascular outcomes in elderly patients with longstanding diabetes who are at high risk of cardiovascular complications.⁵ Within ACCORD, the Memory in Diabetes (MIND) study was a randomized, open-label substudy that aimed to determine whether restoration of normoglycemia in type 2 diabetes influences cognitive performance or age-related brain atrophy.⁶

Of the 2,977 patients enrolled in the MIND substudy, 1,378 participants completed the intensive intervention and 1,416 completed the standard intervention. Characteristics of the participants and changes in blood glucose levels were representative of those in the parent

Correspondence to: R. I. Herzog, raimund.herzog@yale.edu.

Competing interests

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ACCORD trial. The primary outcome, cognitive performance, was measured using a Digit Symbol Substitution Test (DSST) at baseline and at 20 and 40 months after enrollment. Total brain volume was measured using MRI-based morphometry in a smaller subset of patients before and 40 months after initiation of treatment.

An unexpected increase in cardiovascular events and mortality in the intensive-glucose-control arm of ACCORD after a mean follow-up period of 3.5 years led to discontinuation of the trial.⁵ Despite the early termination, most of the individuals enrolled in ACCORD-MIND had almost completed the predetermined goal of 40 months of follow-up, and the results of this substudy have recently been reported by Launer and colleagues.⁶ Although the study provided evidence of preserved brain volume following intensive glucose lowering, no statistically significant difference between the groups with regard to the primary end point, cognitive performance, was found. The authors concluded that intensive glucose lowering should not be undertaken to delay cognitive impairment in elderly patients with longstanding type 2 diabetes.

Do these findings mean that the question as to whether intensive management prevents cognitive deficits is, once and for all, off the table? Our response would be “not quite yet.” Several important factors could have influenced the negative study outcome, and careful inspection of the data reveals clues to suggest that follow-up questions should be addressed in subsequent studies.

Hypoglycemia in the intensive-treatment group probably had the most profound influence on the MIND results. Assuming that the frequency distribution of hypoglycemic events in the MIND cohort was similar to that seen in the ACCORD cohort (episodes requiring medical assistance in the intensive-treatment versus the standard-treatment arms were 4.28 versus 1.37 per 100 person-years), the exposure to hypoglycemia must have been considerable.⁷ Although patients with a prior history of severe hypoglycemia were explicitly excluded from the MIND study, the occurrence of hypoglycemia during the trial was not factored into Launer and colleagues’ mixed-model analysis.⁶

In addition to diabetes *per se*,¹ hypoglycemia in type 2 diabetes has recently been identified as an additional risk factor for development of dementia.⁸ From our own work we know that exposure to recurrent hypoglycemia, on the one hand, and exposure to prolonged hyperglycemia, on the other, leads to adaptations in brain metabolism, some of which are protective, whereas others are maladaptive.⁹ The aggressive glucose-lowering regimen in MIND might have led to acute brain injury from severe hypoglycemia in some patients that offset the benefits conferred by reduced exposure to hyperglycemia in other patients. The coexistence of preserved brain volume and higher prevalence of abnormal white matter lesions on MRI in the intensive-treatment arm than in the standard-treatment arm may attest to this fact. Furthermore, to achieve normoglycemia, patients in the intensive-treatment arm were generally given multiple oral agents, often in conjunction with insulin. The polypharmacy approach, rather than insulin alone, might thereby have had adverse effects in addition to hypoglycemia.

Another confounding factor, which was only revealed in a follow-up ACCORD-MIND analysis, was the association between microvascular renal complications and poor cognitive performance. As diabetic nephropathy was not included in the initial mixed-model adjustments of the MIND study, a separate analysis of results from this group of patients—who were at a high risk of cognitive decline¹⁰ and might benefit from the elimination of chronic hyperglycemia—could not be conducted.

The specific study population itself could also have obscured differences between intensive and conventional therapy groups. Given the age and health status of the patients involved, the damage to brain structures may have already occurred at the time the trial commenced, thereby making an effect of glucose-lowering treatment on cognitive capacity difficult to show. Consistent with this possibility, a subgroup analysis (albeit underpowered to show statistical significance) indicated a positive trend towards preserved cognitive function in intensively treated patients who were newly diagnosed or <60 years of age. Importance of intervention at a young age is also consistent with the failure to show benefit of aggressive treatment on cardiovascular outcomes in ACCORD. Finally, the study duration may simply have been too short to allow significant cognitive differences to develop between the study arms, a possibility that is supported by the detection of preserved brain volume in the intensive-treatment group.

Future studies should certainly include long-term follow-up of the cohort from the MIND study, which will allow us to determine whether aggressive normalization of plasma glucose for a relatively short time has an impact on long-term cognitive decline and is protective against dementia. In the meantime, we believe that patients with advanced complications, such as those in the ACCORD-MIND study, would benefit from less-complex drug regimens and a glycemic target that improves—but does not attempt to entirely normalize—plasma glucose levels. Intensive glucose management is considerably more likely to be effective earlier in the course of type 2 diabetes, at a time when glucose control is easier to achieve and vascular complications and cognitive changes are less advanced. These assumptions will need to be directly tested in future long-term prospective studies to improve the clinical management of cognitive decline in type 2 diabetes.

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