

Dementia and Diabetes: Towards the Prevention of Dementia Through Glycemic Control

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Alzheimer's disease (AD) and Vascular Dementia (VD) are two major pathologies causing dementia. In the past, these two conditions were sharply distinguished. AD was considered neurodegenerative and VD atherosclerotic, caused by any of several atherosclerogenic diseases including Diabetes Mellitus (DM). Recent advances of this field, however, have revealed that these conditions are mutually associated and create a spectrum, from one end of pure neuro degeneration to the other end of pure ischemia; furthermore, vascular risk factors including DM increase the risk for both AD and VD [1].

The underlying mechanism of the association of DM and dementia, especially AD, is still ambiguous though several hypotheses have been raised. The toxic effects of high glucose on neurons, insulin resistance, impaired endothelial functions, etc. have been suggested [2].

Currently available treatments for dementia are limited to alleviating some disease symptoms, and are not able to reverse the pathological progress. Therefore, there is a worldwide demand for data that would aid in the prevention of dementia. Although it has been clarified that the comorbidity of DM increases the risk of dementia, it remains unclear how blood glucose control contributes to reducing the risk of dementia or retarding the progression of dementia.

Recently, a large cohort study, the ACCORD-MIND trial, reported that intensive glycemic control did not contribute to the maintenance or improvement of cognitive function compared to standard glycemic control. After 40 months' intervention, the median HbA1c in intensive and standard groups were clearly separated, at 6.6% vs. 7.5%. However, cognitive outcomes were not significantly different, although the total brain volume measured by MRI was greater in the intensive-treatment group [3]. These results were rather disappointing because the analysis of baseline data of this trial suggested that a lower glycohemoglobin level was associated with better cognition, which stimulated our expectation for the prevention of cognitive decline by glycemic control [4]. In the ACCORD study as high as 77% of participants in the intensive group used insulin and the glycemic decrement was rather rapid (1.4% decrement of HbA1c in first 4 months) [5]. More intensive glycemic treatment often induces hypoglycemia, especially in the elderly. ACCORD-MIND is a sub-study of the larger study, ACCORD. In the ACCORD study, participants in the intensive group reported a mean of 1.06 hypoglycemic episodes (self-monitored blood glucose <70 mg/dL or <3.9 mmol/L) in the 7 days preceding their regular 4-month visit, whereas participants in the standard group reported an average of 0.29 episodes. Unrecognized hypoglycemia was reported, on average, at 5.8% of the intensive group's 4-month visits and 2.6% of the standard group's visits [6]. The harm associated with severe hypoglycemia might counterbalance the potential benefit of glycemic control on the central nervous system. Indeed, Whitmer et al. reported that severe hypoglycemic episodes are risk factors for later incidence of dementia [7].

Recently, several studies have suggested that microvascular complications, as represented by diabetic nephropathy, are closely associated with cognitive decline [8,9]. Other studies including non-diabetic subjects have also suggested that microvascular disease of the kidney manifesting as albuminuria is associated with cognitive decline [10]. The effects of blood glucose control on microvascular

complications are well-established. These observations may suggest that good blood glucose control without inducing hypoglycemia could lead to the prevention of cognitive decline. Smaller studies with less intensive glycemia treatment suggested that glycemic control is beneficial [11,12].

The meta-analysis of randomized control trials to assess intensive glycemic control did not show its benefits on all-cause mortality [13]. On the other hand, an observation of large cohorts reported that the mortality curve was U-shaped and that the lowest mortality was at an HbA1c level of 7.5% [14]. The optimal intensity of glycemic treatment and the combination of therapeutics in the elderly who are at risk of cognitive decline remains to be elucidated.

With recent development of anti-diabetic therapeutics we now have several strong modalities of treatment in terms of glycemic control. Diabetic complications, which probably include cognitive impairment, disturb quality of life, especially in older diabetics. More research regarding glycemic control and its potential to reduce the incidence of dementia and slow the progression of cognitive impairment or dementia is warranted.

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