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Review

Association between hypoglycemia and dementia in patients with type 2 diabetes



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ABSTRACT

In addition to increased risks of macrovascular and microvascular complications, patients with type 2 diabetes mellitus (T2DM) usually also are at increased risk for cognitive impairment and dementia. Hypoglycemia, a common consequence of diabetes treatment, is considered an independent risk factor for dementia in patients with T2DM. Hypoglycemia and dementia are clinically underestimated and are related to poor outcomes; thus, they may compromise the life expectancy of patients with T2DM. Epidemiological evidence of hypoglycemia-associated cognitive decline and dementia is highly varied. Acute, severe hypoglycemic episodes induce chronic subclinical brain damage, cognitive decline, and subsequent dementia. However, the effects of recurrent moderate hypoglycemia on cognitive decline and dementia remain largely uninvestigated. Poor glycemic control (including fluctuation of hemoglobin A1C [HbA1c] and glucose values) and the viscous circle of bidirectional associations between dementia and hypoglycemia may be clinically relevant. The possible pathophysiological hypotheses include post-hypoglycemic neuronal damage, inflammatory processes, coagulation defects, endothelial abnormalities, and synaptic dysfunction of hippocampal neurons during hypoglycemia episodes. This article reviews previous findings, provides insight into the detection of groups at high risk of hypoglycemia-associated dementia, and proposes specific strategies to minimize the potential burdens associated with hypoglycemia-related neurocognitive disorders in patients with T2DM.

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1. Introduction

The pandemic of type 2 diabetes mellitus (T2DM) and the subsequent burden of disease-related morbidity and mortality have resulted in a global health issue [1,2]. In addition to affecting various peripheral organs, diabetes may also injure the central nervous system [1,3]. T2DM is a risk factor for dementia (Table 1) [3,4]. Results from the Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) trial reported that a 1% increase in hemoglobin A1C (HbA1C) values was associated with significantly lower scores in several cognitive tests [5]. Other studies have also shown that higher HbA1c levels were associated with lower cognitive score, more rapid cognitive decline, and greater rate of brain atrophy [3,5–9]. Although the causes of cognitive impairment in T2DM might be multifactorial, some investigators believe the relationship between poor glycemic control and impaired cognitive function is independent of other metabolic syndrome components [10–12].

Cognitive impairment and dementia may significantly contribute to the impairment of many functions, increased risks of fall and fractures [13], enhanced depressive symptoms [14], and altered quality of life [3,4], and may be an independent predictor of clinical outcomes of T2DM patients [3,4,15]. In a 2-year follow-up study, cognitive function at a low-normal level was associated with a 20% increase in mortality compared to higher normal levels among aged patients with diabetes [16].

To avoid these long-term complications, patients with diabetes were encouraged to achieve optimal glycemic control. However, hypoglycemia, a common consequence of diabetes treatment, is associated with severe morbidity and life-threatening conditions, and has become a major barrier to intensifying antidiabetic therapy [17–19]. Hypoglycemia is categorized as “mild” or “severe” according to the severity of the episode and can either be self-limiting or not. Plasma

concentrations less than 70 mg/dL are the standard cutoff values for classification of hypoglycemia in diabetes [20,21]. Several studies proposed that hypoglycemia increases the risks of cardiovascular events and cerebrovascular disease, as well as disease-related mortality [19,22–24]. Previous studies indicated that hypoglycemic episodes are associated with increased risks of dementia [3,19,22,25,26], and several studies reported the association between hypoglycemia and brain damage [19,27–30]. Both hypoglycemia and dementia are related to clinical outcomes, and have received increasing attention in the management of patients with T2DM.

2. Epidemiological association between hypoglycemia and cognitive decline and dementia

Studies on the relationship between hypoglycemia and dementia have been difficult, and the published results are inconsistent [31]. These discrepancies may reflect the different definitions of cognitive impairment, various age of the study subjects, missing information on the comorbidities and severity of diabetes, and the different durations and intensities of the hypoglycemic episodes [3,31]. Dementia is a syndrome caused by various diseases and injuries that affect the brain. It presents as memory loss and decline in mental ability that is severe enough to interfere with activities of daily living and is commonly accompanied by cognitive function impairment, while it does not affect consciousness [3,32,33]. Alzheimer's disease is the most common cause of dementia; however, vascular dementia, a mixed form of dementia, and other conditions (e.g., dementia with Lewy bodies and dementia in Parkinson's disease) also contribute to the progression of cognitive dysfunction [32,33]. Mild cognitive impairment, which represents the transitional phase from normal to subsequent dementia, has also been longitudinally correlated with diabetes and hypoglycemia [3,34].

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