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 significantly lower cognitive scores, 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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<th>Population</th>
<th>Mean age</th>
<th>Follow-up year</th>
<th>Definition of dementia</th>
<th>Dementia RR (95% CI)</th>
<th>All</th>
<th>Alzheimer’s disease</th>
<th>Vascular dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ott et al. [66]*</td>
<td>Netherlands</td>
<td>6370 elderly persons from the community-based Rotterdam Study</td>
<td>68.9</td>
<td>2.1</td>
<td>DSM-III (dementia); NINCDS–ADRDA (AD); NINDS-AIREN (VaD)</td>
<td>1.9 (1.3–2.8)</td>
<td>1.9 (1.2–3.1)</td>
<td>2.0 (0.7–5.6)</td>
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<tr>
<td>Luchsinger et al. [67]*</td>
<td>USA</td>
<td>1262 healthy Medicare beneficiaries residing in northern Manhattan</td>
<td>75.6</td>
<td>4.3</td>
<td>DSM-IV (dementia); NINCDS–ADRDA (AD); Clinical judgment for stroke associated dementia (VaD)</td>
<td>1.3 (0.84–1.88)</td>
<td>3.4 (1.20–6.91)</td>
<td></td>
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</tr>
<tr>
<td>Peila et al. [68]*</td>
<td>USA Japanese-American</td>
<td>2574 Japanese-American elderly men from the fourth exam cohort (1991–1993) of the Honolulu-Asia aging study</td>
<td>77</td>
<td>3</td>
<td>DSM-III-R (dementia); NINCDS–ADRDA (AD); CADDTC (VaD)</td>
<td>1.5 (1.01–2.2)</td>
<td>1.8 (1.1–2.9)</td>
<td>2.3 (1.1–5.0)</td>
<td></td>
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<tr>
<td>Hassing et al. [69]*</td>
<td>Sweden</td>
<td>702 elderly individuals from the population-based Origins of Variance in the Old-Old study (OCTO-Twin Study)</td>
<td>83</td>
<td>6-8</td>
<td>DSM-III-R (dementia); NINCDS–ADRDA (AD); NINDS-AIREN (VaD)</td>
<td>–</td>
<td>0.85 (0.36–2.02)</td>
<td>3.63 (1.35–9.76)</td>
<td></td>
</tr>
<tr>
<td>MacKnight et al. [70]*</td>
<td>Canada</td>
<td>5574 elderly participants from the Canadian study of health and aging</td>
<td>84</td>
<td>5</td>
<td>DSM-III-R (dementia); NINCDS–ADRDA (AD); ICD-10 (VaD)</td>
<td>1.26 (0.90–1.76)</td>
<td>1.30 (0.83–2.03)</td>
<td>2.03 (1.15–3.57)</td>
<td></td>
</tr>
<tr>
<td>Xu et al. [71]*</td>
<td>Sweden</td>
<td>1501 community elderly dwellers from the Kungsholmen project</td>
<td>83</td>
<td>4.7</td>
<td>DSM-III-R (dementia); NINCDS–ADRDA (AD); NINDS-AIREN (VaD)</td>
<td>1.5 (1.0–2.1)</td>
<td>1.3 (0.9–2.1)</td>
<td>2.6 (1.2–6.1)</td>
<td></td>
</tr>
<tr>
<td>Akomolafe et al. [72]*</td>
<td>USA</td>
<td>2210 community-dwelling dementia-free elders from Framingham study original cohort</td>
<td>83</td>
<td></td>
<td>DSM-IV (dementia); NINCDS–ADRDA (AD); CADDTC (VaD)</td>
<td>1.20 (0.74–1.96)</td>
<td>1.15 (0.65–2.05)</td>
<td>0.81 (0.18–3.70)</td>
<td></td>
</tr>
<tr>
<td>Hayden et al. [73]*</td>
<td>USA</td>
<td>3264 aged 65 or older adults from the community-based cohort of Cache County Study of Memory Health and Aging (CCSMHA)</td>
<td>70</td>
<td>12.7</td>
<td>DSM-III-R (dementia); NINCDS–ADRDA (AD); NINDS-AIREN (VaD)</td>
<td>1.56 (0.90–2.56)</td>
<td>1.33 (0.66–2.46)</td>
<td>2.23 (0.88–5.17)</td>
<td></td>
</tr>
<tr>
<td>Irie et al. [74]*</td>
<td>USA</td>
<td>2547 dementia-free participants in the CHS (Cardiovascular Health Study) cognition study cohort</td>
<td>74.7</td>
<td></td>
<td>Screened positive for dementia—extensive neuropsychological and neurological examinations NINCDS–ADRDA (AD); NINDS-AIREN (VaD)</td>
<td>1.44 (1.03–2.01)</td>
<td>1.62 (0.98–2.67)</td>
<td>0.80 (0.30–2.09)</td>
<td></td>
</tr>
</tbody>
</table>


The heterogeneity of hypoglycemia may also contribute to the difficulties of determining the role of hypoglycemia in cognition decline and dementia [31]. The incidence of moderate and mild hypoglycemia is underestimated because the laboratory evidence to confirm these events is usually lacking. Although reports of severe hypoglycemia might be much more reliable, they account for only a small percentage of total hypoglycemia episodes [19]. Severe hypoglycemia may be associated with an increased risk of dementia and cognitive dysfunction [3,19,22,25,26]. However, the mechanisms by which mild to moderate hypoglycemia affect cognitive decline and dementia remain unclear [19,35]. Recurrent chronic hypoglycemia may increase the tolerability of immediate cognitive impairment, but its effect on long-term prognosis remains contentious [1,36,37].

2.1. Clinical evidence of hypoglycemia and cognitive decline

In a hospital-based retrospective study of 4,635 surgical patients in intensive care units (ICU) who were maintained under tight glycemic control via insulin infusion, investigators found that hypoglycemia episodes during their ICU stays were associated with aggravated critical illness-induced neurocognitive dysfunction 1 year later [38]. A cross-sectional population-based study of elderly T2DM patients also found that self-reported history of severe hypoglycemia was associated with poor late-life cognitive ability and that cognitive decline was independent of prior or premorbid cognitive ability [3,25].

2.2. Clinical evidence of hypoglycemia and dementia

Several cross-sectional and longitudinal cohort studies showed that hypoglycemic episodes were associated with an increased risk of dementia (Table 2). A study of older patients with diabetes reported that severe hypoglycemia increased the risks for both cognitive impairment and dementia, which presented as an inability to self-manage medications [39]. A longitudinal cohort study reported a 2.39% increase in the risk for dementia per year of follow-up in patients with a history of hypoglycemia, compared with patients without hypoglycemia; these findings were independent of glycemic control as assessed on the basis of HbA1c level and diabetes comorbidities [26]. Another prospective population-based study reported that patients with diabetes who experienced a hypoglycemic event had a 2.1-fold increased risk of dementia compared with those without a hypoglycemic event during the 12-year follow-up period [40]. By analyzing a dataset from the National Health Insurance Research Database in Taiwan, which enrolled 15,404 patients with diabetes, our group found that patients who had a prior in-hospital diagnosis of hypoglycemia were almost three times more likely to develop dementia, and multiple hypoglycemic episodes presented a graded risk increase in dementia during the 7-year follow-up period [22].

3. Possible pathophysiological links between hypoglycemia and dementia

3.1. Post-hypoglycemic encephalopathy

During hypoglycemia, glucose sensors are dominant in several brain area regions where the blood brain barrier (BBB) is leaky or absent, which allows glucose-sensing neurons to directly monitor glucose levels in the blood, in addition to detecting glucose levels in the brain and cerebrospinal fluid [1]. Glucose-sensing neurons may translate the rate or quantity of glucose oxidation into a neural signal that alters neuronal firing rates. The signaling mechanisms used by these neurons seem parallel to those used by pancreatic β- and α-cells [1,41]. Glucose-sensing neurons may be glucose-excited (GE) or glucose-inhibited (GI), and the counterbalance between GI and GE neuronal activities is responsible for regulating and maintaining blood glucose levels within the physiological range and ensuring an adequate supply of glucose to the brain. Recurrent exposure to hypoglycemia may disturb this relationship and balance [1,41].

Astrocytes may also play a role in glucose regulation when the brain is under hypoglycemic conditions [42]. Astrocytes and neurons are coupled, while glucose sensing can be modulated by other substances (fatty acids, insulin, leptins, and some neuropeptides) [1]. The astrocyte-neuron lactate shuttle hypothesis postulates that during neuronal activity, astrocytes respond to glutamatergic activation by increasing glucose utilization, enhancing glycolysis and lactate release; astrocytes may also rely on their glycogen reserves, and glycogenolysis is shown to be essential in rat hippocampal learning [43]. Animal studies found that severe hypoglycemia leads to necrosis of neurons not only in the hippocampus but also in the cortical regions [29,31].

Acute and severe hypoglycemia-associated sympathoadrenergic stimulation and cerebral neuroglycopenic symptoms were caused by counter-regulatory responses, and may drive physiological and behavioral changes [1]. Although these symptoms and signs could be transient and reversed by glucose infusion, evidence from studies has demonstrated hypoglycemia-induced permanent neuronal damage in regions of the hippocampus, especially in the dentate gyrus [27,38].

Previous studies indicate that recurrent moderate hypoglycemia can cause synaptic dysfunction even in the absence of neuronal death, particularly in hippocampal neurons [44]. Despite an animal model-based study that reported that recurrent moderate hypoglycemia appeared to protect against the consequences of severe hypoglycemia [29], other studies reported recurrent moderate hypoglycemia to be associated with a decline in intelligence quotient, persistent cognitive impairment, and other long-term effects in patients with diabetes [38,45].

3.2. Specific structural changes after hypoglycemic brain injury

Neuropathological changes found in patients with diabetes with fatal hypoglycemia provide evidence of the high
Table 2 – Hypoglycemic episodes increase the risk of cognitive decline and dementia among T2DM patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population (Nation)</th>
<th>Definition of cognitive dysfunction</th>
<th>Impact of hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duning et al. [38]</td>
<td>Germany</td>
<td>Neuro-psychological tests performed at least 1 year after ICU discharge</td>
<td>Hypoglycemia aggravates critical illness-induced neurocognitive dysfunction</td>
</tr>
<tr>
<td>N = 4635 patients in surgical intensive care unit, who were treated by tight glycemic control protocol</td>
<td>Hypoglycemia over a person’s lifetime and in the year prior to cognitive testing was assessed using a previously validated self-completion questionnaire</td>
<td>Hypoglycemia was associated with worse neurocognitive dysfunction test results</td>
<td></td>
</tr>
<tr>
<td>Aung et al. [25]</td>
<td>UK</td>
<td>Results of age-sensitive neuropsychological tests were combined to derive a late-life general cognitive ability “general factor” and vocabulary test scores</td>
<td>Self-reported history of severe hypoglycemia was associated with poorer late-life cognitive ability, and the cognitive ability decline was independent of prior/premorbid cognitive ability</td>
</tr>
<tr>
<td>N = 1066 60–75 years old</td>
<td>Hypoglycemia was associated with worse neurocognitive dysfunction test results.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bruce et al. [39]</td>
<td>Australia</td>
<td>Cognitive assessment: A two-step cognitive assessment</td>
<td>Severe hypoglycemia increase the risk of cognitive impairment (HR 3.00, 95% CI 1.06–8.48) inability to self-manage medications (HR 4.17, 95% CI 1.43–12.13)</td>
</tr>
<tr>
<td>N = 302 Age more than 70</td>
<td>Cognitive impairment assessment using the Mini-Mental State Examination (MMSE) Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE), and Question on subjective memory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whitmer et al. [26]</td>
<td>USA</td>
<td>Based on ICD-9-CM diagnosis codes. Dementia were identified from both inpatient and outpatient databases</td>
<td>A 2.39% increase in risk of dementia per year of follow-up for patients with history of hypoglycemia vs. patients without hypoglycemia</td>
</tr>
<tr>
<td>N = 166,677 Mean age: 65</td>
<td>Sex% male/female: 45.5/54.5 22-year follow-up for hypoglycemia episode</td>
<td>1 episode (HR, 1.26; 95% CI, 1.10–1.49)</td>
<td></td>
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<tr>
<td>2 episodes (HR, 1.80; 95% CI, 1.37–2.36) 3 or more episodes (HR, 1.94; 95% CI, 1.42–2.64) Fully adjusted HRs: 1 episode (HR, 1.42; 95% CI, 1.12–1.78) 2 or more episodes (HR, 2.36; 95% CI, 1.57–3.55)</td>
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<td></td>
</tr>
<tr>
<td>Yaffe et al. [40]</td>
<td>USA</td>
<td>Based on ICD-9-CM diagnosis codes or dementia medication. Dementia was identified by review of hospital records based on ICD-9-CM diagnosis codes as the primary or secondary diagnosis related to the hospitalization or by a prescribed dementia medication</td>
<td>A 2-fold increased risk of dementia compared with those who without hypoglycemic event 34.4% vs. 17.6% (multivariate-adjusted HR, 2.1; 95% CI, 1.0–4.4)</td>
</tr>
<tr>
<td>N = 783 Mean age: 74</td>
<td>Sex% male/female: 52.4/47.6 12-year follow-up period</td>
<td>1 episode (HR, 1.26; 95% CI, 1.10–1.49) 2 or more episodes (HR, 2.36; 95% CI, 1.57–3.55)</td>
<td></td>
</tr>
<tr>
<td>Lin and Sheu [22]</td>
<td>Taiwan</td>
<td>Based on ICD-9-CM diagnosis codes or dementia medication. Dementia were identified based on ICD-9-CM diagnostic codes from the outpatient or inpatient databases</td>
<td>A 3 times more likely to develop dementia (HR 2.76) in those who experienced hypoglycemic event</td>
</tr>
<tr>
<td>N = 15,404 Mean age: 64.2</td>
<td>Sex% male/female: 45.1/54.9 7-year follow-up period</td>
<td>Incidence rate of dementia Patients with hypoglycemia: 29.9 per 1000 person-years (95% CI 22.1–39.2)</td>
<td></td>
</tr>
<tr>
<td>Patients without hypoglycemia: 11.1 per 1000 person-years (95% CI 10.3–11.8)</td>
<td>Rate ratio (RR) values for dementia in subjects with hypoglycemia compared to those without hypoglycemia</td>
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HR: hazard ratio.

95% CI: 95% confidence interval.

UK: United Kingdom; USA: United States of America.
sensitivity of the cerebral area to hypoglycemia [31,46]. Computed tomography (CT) and magnetic resonance imaging (MRI) findings in vegetative patients after profound hypoglycemia associated with diabetes suggest that not all neurons and brain regions are equally sensitive to hypoglycemic injury; there appears to be a selective vulnerability, especially of neurons in the hippocampal area, temporal area, cerebral cortex, substantia nigra, and basal ganglia of the human brain [30,47]. Several studies have indicated that impairments of both the figure and spatial aspects of nonverbal memory are associated with temporal and hippocampal dysfunctions in patients with mild to moderate Alzheimer's disease [38,47].

3.3. Ischemic and cerebral vascular events caused by hypoglycemia

Animal studies show the extreme fragility of the hippocampus to hypoglycemia, with lesions similar to those induced by chronic ischemia or acute hypoxia [31,48]. Acute, severe hypoglycemia has been shown to induce transient ischemic and focal neurological deficit, and may result in neuronal cell death [22,27,38]. Inflammation, coagulation defects, and endothelial dysfunction during hypoglycemia may all contribute to cerebral ischemia and dementia [49]. Hypoglycemia reportedly activates the fibrinolytic system and induces platelet function abnormalities [22,49]. It may also stimulate the release of catecholamines, which lead to increased peripheral blood cell counts and adrenergic mechanisms that modulate these changes [22,50]. Levels of several inflammatory markers have been shown to increase during hypoglycemia, and increased inflammatory cytokines could result in endothelial injury and abnormal coagulation [49]. These inflammation processes, coagulations defects, and endothelial abnormalities during hypoglycemia may compromise vascular structures in the brain, which may lead to neuronal cell death and subsequent dementia [17,26].

4. Potential risk factors of hypoglycemia-associated dementia

The potential risk factors of hypoglycemia-associated dementia include ethnic/genetic and demographic factors [51], the duration and chronic vascular complications of diabetes [52], and the choice of antidiabetic drugs (especially in patients treated with insulin and/or sulfonylurea) [17,51–55]. Impaired liver and renal function may cause adverse medication reactions, including hypoglycemia. Alcohol is another potent hypoglycemic agent, as it reduces endogenous glucose production and glycogenolysis in the liver [17,51–55]. Poor glycemic control (including HbA1C levels and fluctuation of glucose values) has been associated with higher risks of hypoglycemia-related cognitive impairment [53–55].

Bidirectional associations between dementia and hypoglycemia are an important interaction issue [7,40]. Dementia might promote hypoglycemic incidents in patients with T2DM [31]. In the ADVANCE trial, severe cognitive dysfunction was associated with increased risk of severe hypoglycemia (hazard ratio, 2.10; 95% confidence interval [CI], 1.14–3.87) [15]. The post hoc analysis of the ACCORD trial concluded that poor cognitive function increases the risk of severe hypoglycemia in patients with T2DM [56]. Thus, the condition might fall into a vicious circle: while patients’ cognitive function declines, their ability to manage their diabetes and control their blood glucose levels also declines, potentially resulting in more frequent hypoglycemic episodes and progression of hypoglycemia-associated dementia [17].

5. Suggested management strategies

5.1. Comprehensive education and monitoring of blood glucose levels

The central nervous system of patients with T2DM may be at risk of acute damage due to hyperglycemia and hypoglycemia, and may also be exposed to various chronic complications of hyperglycemia and post-hypoglycemia brain injury [1]. Some principles may be helpful in preventing hypoglycemia, including self-management with self-monitoring of blood glucose (SMBG) levels [19]. Appropriate education with acceptable information on the symptoms/signs and the risks of hypoglycemia, and prevention and self-management of hypoglycemia are clearly required. SMBG provides direct information and evaluation of glucose levels, and can be a guide for hypoglycemia management and treatment [19,57].

5.2. Appropriate medication regimens

Anti-diabetic drugs also play an important role in the development of hypoglycemia. Certain drugs may provide better postprandial glycemic control and lower the risk of hypoglycemia, which may prevent cognitive decline in older patients with diabetes [7,58]. Metformin, a widely accepted first-line treatment for T2DM, could normalize the reduction of cell proliferation and neuroblast differentiation in rat hippocampal dentate gyrus, which may help reduce neuronal injury [59,60]. Novel classes of anti-diabetic drugs such as glucagon-like peptide 1 (GLP-1) mimetics may help regulate insulin secretion, overcome an increasingly recognized GLP-1-resistant state, and improve peripheral (and possibly brain) insulin signaling; thus, they may minimize neuronal cell loss and even possibly rescue cognitive decline in Alzheimer’s disease models [61]. Dipeptidyl peptidase-4 inhibitors, may also offer neuroprotective effects by increasing GLP-1 levels and decreasing amyloid beta 42, total tau, and phosphorylated tau levels, as well as neuroinflammation [62]. Dapagliflozin, acts as a potent dual inhibitor of sodium–glucose transporter-2, and may also inhibit acetylcholinesterase, which has long been regarded as a therapeutic target for Alzheimer’s disease [63].

5.3. Individualized glycemic targets

With rapidly increasing number of older patients with T2DM, the estimated number of patients with both hypoglycemia and dementia is also increasing [6,9,10,16,25,26,37,39,40]. Therefore, maintaining blood glucose level within an optimal range and avoiding hypoglycemia are emerging challenges. Appropriate management strategies, including education about SMBG, optimal medication regimens, and individual
glycemic targets are urgently required. Individualized therapeutic targets should be established and coordinated with patients, their family support system, and the diabetes care team [19,64]. The involvement of a diabetes care team not only provides professional knowledge but also allows for the monitoring of complications from diabetes, and for early detection and management of hypoglycemia [19,64]. For patients with T2DM who require insulin treatment, careful evaluation and appropriate education regarding hypoglycemia management should be implemented [17,53,55]. Specific insulin regimens (such as a rapid-acting prandial insulin and/or a long-acting insulin) with SMBG may help physicians and patients work together to achieve their individualized glycemic goal.

5.4. Early detection of dementia

Although early detection is important, implementation of dementia screening and diagnostic programs for patients with T2DM has several problems and barriers [7]. Neurocognitive tests such as the 7-min screen neurocognitive battery are considered screening tests for cognitive impairment and early detection of dementia, and may also be valid screening tools for mild cognitive decline [65]. Other cognitive tests used in clinical practice include the Mini-Mental Status Examination, Mini Cognitive Assessment Instrument, Cognitive Abilities Screening Instrument, Montreal Cognitive Assessment, and Clinical Dementia Rating [4,5,39]. Imaging examinations such as CT or MRI may be useful. However, cognitive tests are time consuming and imaging examinations are expensive [7]. Defining high-risk groups and preventing or slowing disease progression are important to reduce the burden associated with diabetes-related neurocognitive disorder [1].

6. Conclusions

The causes of dementia and cognitive impairment in patients with T2DM are multifactorial, making it difficult to differentiate causal effects and to identify the predominant culprits. Acute, severe hypoglycemic episodes may cause chronic subclinical brain damage and lead to dementia. Multiple hypoglycemic episodes present graded increase in risk. The cumulative effects of recurrent moderate hypoglycemia on dementia remain uncertain. Possible pathophysiological links between hypoglycemia and dementia have been proposed. Appropriate diabetes management strategies are needed to achieve ideal glucose targets and minimize the risks of hypoglycemia. Early detection of high-risk groups is necessary in order to reduce the burden associated with diabetes-related neurocognitive disorders.

Authors’ contributions

Yi-Jing Sheen: Drafting of the manuscript.
Wayne H.-H. Sheu: Drafting of the manuscript, critical revision for intellectual content, and final approval of the published version.

Conflicts of interest

None.

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