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OTHER FORMS OF DIABETES AND ITS COMPLICATIONS (JJ NOLAN AND H THABIT, SECTION EDITORS)

Cognitive Frailty in Older People with Type 2 Diabetes Mellitus: the Central Role of Hypoglycaemia and the Need for Prevention

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Abstract

Purpose of Review To highlight the central role of hypoglycaemia in the causation of cognitive frailty and explore ways of recognition and prevention of hypoglycaemia.

Recent Findings Cognitive frailty is an emerging new concept defined as the concomitant presence of physical frailty and cognitive impairment. In older people with diabetes, cognitive frailty is associated with an increased risk of mortality greater than from either physical frailty or cognitive impairment alone. Hypoglycaemia is directly associated with increased risk of cognitive impairment and physical frailty which are the two components of cognitive frailty. The incidence of hypoglycaemia in older people with diabetes is rising and hypoglycaemia-related hospitalisation has overtaken that of hyperglycaemia.

Summary Recognition of hypoglycaemic episodes in old age remains challenging which leads to misdiagnoses and under-reporting. Therefore, hypoglycaemia prevention strategies are needed. Research is still required to investigate whether prevention of hypoglycaemia would lead to a reduction in the incidence of cognitive frailty.

Keywords Cognition · Frailty · Hypoglycaemia · Older people · Diabetes mellitus

Introduction

The global prevalence of diabetes is increasing. Worldwide, there are 451 (8.4%) million cases aged between 18 and 99 years as estimated by the International Diabetes Federation in 2017. This figure is expected to increase to 693 (9.9%) million by 2045 [1]. The prevalence of diabetes increases with age. In high-income countries, the prevalence peaked (22%) at the age of 75 to 79 years old and almost half of the cases (44%) were above the age of 65 years [1]. In old age, diabetes is associated with high comorbidity burden and increased prevalence of geriatric syndromes including

Key Points • Cognitive frailty is a new concept that describes the co-existence of physical frailty and cognitive impairment.
• Cognitive frailty is associated with adverse outcomes in older people with diabetes.
• Hypoglycaemia may play a central role in the development of cognitive frailty in older people with diabetes.
• Hypoglycaemia incidence is increasing and its recognition remains challenging to health care professionals.
• Prevention strategies for hypoglycaemia are needed.

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cognitive dysfunction and frailty. Risk factors that lead to cognitive dysfunction and frailty in patients with diabetes may include shared factors that predispose to diabetes such as obesity and insulin resistance, diabetes-related factors such as chronic low-grade inflammation and hyperglycaemia and diabetes-associated factors such as cardiovascular complications [2, 3]. The simultaneous presence of both physical frailty and cognitive impairment synergistically increases the risk of mortality and has been termed "cognitive frailty" [4]. The concept of cognitive frailty was first suggested by Panza et al. in 2006 to describe risk factors for cognitive decline and the progression of mild cognitive impairment to dementia [5]. Recently, cognitive frailty has been defined by the International Association of Gerontology and Geriatrics (IAGG) consensus group as the co-existence of physical frailty and mild cognitive impairment in an attempt to capture a complex patient phenotype to enable early intervention and prevention of disability [6••]. Hypoglycaemia plays a role in the pathogenesis of cognitive dysfunction that leads to dementia and in the pathogenesis of physical dysfunction that leads to frailty. Therefore, hypoglycaemia increases the risk of cognitive frailty that leads to adverse outcomes. This manuscript reviews the association of hypoglycaemia, a potentially preventable risk factor, with cognitive frailty and explores ways of hypoglycaemia prevention.

Methods

We undertook a detailed literature enquiry with full assessment of relevant articles by searching the following databases: Google Schoolar, Medline, CINHL Complete and Embase. We used Medical Subject Heading (MeSH) terms: type 2 diabetes mellitus, cognitive dysfunction, cognitive impairment, dementia, older people, physical dysfunction, falls, frailty, disability and hypoglycaemia individually and in combination. Articles were reviewed for relevance by abstract. A manual search of citations in retrieved articles was performed in addition to the electronic literature search. We limited our selection to English language literature and to articles that investigated the relationship between hypoglycaemia and either physical or cognitive dysfunction or both and reported a clear outcome. For data extractions, all articles derived from the search enquiry were independently examined by the two authors (AHA and AJS) and data was extracted in a standardised format which included study design, population studied, intervention and main findings.

Cognitive Dysfunction-Dementia

In the USA, dementia may affect up to 16% of older people with diabetes aged ≥ 65 years and about 24% of those aged ≥ 75 years [7]. In France, the estimated prevalence of cognitive impairment among older people (aged 75–79 years) with diabetes is around 29% [8]. In an audit of 11 nursing homes in the UK, 56% of older people with diabetes were found to have some form of dementia [9]. Diabetes and dementia may have a common pathogenic link [10]. This link may be through increased brain insulin resistance that leads to impaired insulin signalling, accelerated neuronal dysfunction and cognitive decline [11]. Therefore, the presence of diabetes increases the risk of cognitive dysfunction from mild cognitive impairment (MCI) to dementia. The proportion of patients who convert from MCI to dementia is 1.5–3 times higher for persons with diabetes compared to those without [12]. In a meta-analysis, diabetes was associated with an increased risk of MCI (relative risk 1.21, 95% confidence interval (CI) 1.02 to 1.45), Alzheimer disease (1.46, 1.20 to 1.77), vascular dementia (2.48, 2.08 to 2.96) and any dementia (1.51, 1.31 to 1.1.74) [13].

Physical Dysfunction-Frailty

Diabetes is associated with an increased risk of physical dysfunction and frailty. In a systematic review of 26 studies, diabetes increased the risk of mobility disability (odds ratio (OR) 1.71, 95% CI 1.53 to 1.91), instrumental activities of daily living (IADL) disability (1.65, 1.55 to 1.74) and ADL disability (1.82, 1.63 to 2.04) [14]. The traditional micro- and macrovascular diabetes-related complications in addition to the associated comorbidities may explain this association. For example, the loss of limbs or visual impairment may lead to limitation in performing ADL such as mobility and cognitive decline may limit performance in the IADL such as financial management [15]. However, diabetes-related complications and coexisting comorbidities do not seem to fully explain the progression of physical dysfunction into disability and unmeasured factors such as frailty may play a role [16]. Diabetes is associated with an accelerated ageing process that promotes frailty. This is likely due to increased risk of accelerated loss of leg muscle strength and muscle quality leading to sarcopenia, which is linked to frailty [17]. Diabetes-associated comorbidities such as hypertension and chronic kidney disease in addition to, oxidative stress, inflammation and insulin resistance may have a deleterious effect on skeletal muscle leading to sarcopenia and frailty [18, 19].

Cognitive Frailty

Frailty is a condition characterised by a reduction in physiological reserve and increased vulnerability to physical or

psychological stressors [20]. It is likely to result from a multisystem physiological dysregulation in cardiovascular, neuroendocrine, metabolic, immune and nervous systems [21]. Frailty has been previously explained by the physical phenotype concept, which represents a decline in functional reserve as described by Fried et al. and alternatively by the cumulative deficit model created by Rockwood et al., which states that progressive accumulation of health deficits at multiple system levels leads to increased vulnerability [22, 23]. Although frailty is a well-recognised clinical syndrome, measuring it in the clinical setting is still controversial [24]. A model of frailty that could be precisely measured at early stages is a clinical necessity for early intervention and prevention of progression [25]. The IAGG consensus group proposed the hypothesis of a possible new condition of cognitive frailty defined as the coexistence of physical frailty and mild cognitive impairment [6••]. The aim was to help early diagnosis, early intervention and to stimulate research in this area. This proposal however was purely conceptual and was not based on epidemiologic evidence. Frailty is a multidimensional syndrome that may affect both mental and physical function [26]. Therefore, cognitive frailty could be viewed as a separate entity as defined by the IAGG consensus group or frailty itself could be seen as a syndrome with a spectrum that includes both physical and cognitive dysfunction [27]. It has also been shown that the presence of both physical frailty and cognitive impairment to have a synergistic effect on adverse outcomes. In a prospective study of a total of 2696 individuals aged ≥ 55 years, the rates of mortality in persons with diabetes increased 2-fold in individuals with cognitive impairment alone, 4-fold in persons with physical frailty alone and 13-fold in those with both cognitive impairment and physically frailty [4].

The Central Role of Hypoglycaemia

Hypoglycaemia is common in older people with diabetes and has a multifactorial causality such as increasing age, multiple comorbidities and polypharmacy [28]. An incidence of 14.1% was reported in a German prospective data base study, which included 3347 patients of median age of 66.1 years [29]. In the same study, higher rates were observed in older (≥ 70 years old) than younger (< 60 years) patients (12.8% vs. 9.0%, $p < 0.01$) at a comparable glycaemic control (OR 1.68, 95% CI 1.16 to 2.45) [30]. In care homes, an incidence as high as 41.9% was reported over 1 year period due to an older and more comorbid population [31]. Hypoglycaemia plays a central role in the pathogenesis of cognitive frailty, as it is a risk factor for both its components: cognitive impairment and physical frailty.

Hypoglycaemia and Cognitive Impairment

Hypoglycaemia is a risk factor for cognitive dysfunction from mild cognitive impairment to dementia. Continuous glucose supply to the brain is essential for cognitive functioning as it is the main source of energy and cannot be synthesised or stored in the brain. Transient hypoglycaemia may lead to reversible impairment of cognitive function but persistent or severe hypoglycaemia may result in permanent neuronal damage [32]. Hypoglycaemia increases the risk of dementia by 2-fold [33]. The risk of dementia increases with increasing frequency of hypoglycaemic episodes. In a large US longitudinal cohort study of 16,667 patients, mean age 65 years, with type 2 diabetes followed up for 27 years, the risk of dementia increased by 26% for one episode of hypoglycaemia, 80% for two episodes and 94% for three or more episodes [34]. The dose-response relationship between the frequency of severe hypoglycaemia and incidence of dementia has also been shown in other studies [35, 36, 37•]. In the Edinburgh Type 2 Diabetes Study, a history of severe hypoglycaemia was associated with poorer initial cognitive ability and a more rapid rate of cognitive decline after 4 years of follow-up [38]. The relationship between hypoglycaemia and dementia has also been shown in older people newly diagnosed with diabetes mellitus [39]. Three studies have shown a relationship between hypoglycaemia and increased risk of neurocognitive dysfunction and mild cognitive impairment [40–42]. Recently, hypoglycaemia has been shown to be associated with cognitive decline, low brain volume and dementia [43]. In care home residents, hypoglycaemia was associated with cognitive decline [44]. Low blood glucose (< 4.7 mmol/L) also increased the risk of MCI in older people without history of diabetes (RR 1.57, 95% CI 1.14 to 2.32) suggesting a deleterious effect of low glucose on normal brains [45]. Although the cross-sectional phase of the Fremantle Diabetes Study, which included 302 participants with diabetes, mean age (SD) 75.7 (4.6) years has shown a relationship between hypoglycaemia and dementia, the prospective association between historical hypoglycaemia and cognitive decline in a subsample of the participants without dementia was not found. However, the prospective phase of this study was limited by the small number of participants ($n = 205$) and short duration of follow-up (18 months) which may have limited the power to detect any association between incident hypoglycaemia and cognitive dysfunction [46, 47]. Also, the cognitive decline in participants of the ACCORD-MIND and ADVANCE studies was similar in the intensive therapy arm, with more frequent hypoglycaemic episodes, compared to the usual care arm with less episodes suggesting that hypoglycaemia may not be related to cognitive function. However, these studies were not designed to investigate the relationship between hypoglycaemia and cognitive decline as a primary end point. It is also plausible that better glycaemic control in the

intervention arm may have improved cognitive function diluting any deleterious effect of hypoglycaemia on brain function [48, 49]. Studies showing an association between hypoglycaemia and cognitive decline in older people with diabetes are summarised in Table 1.

Hypoglycaemia and Physical Frailty

Physical frailty is a syndrome resulting from progressive accumulation of deficits in individuals' physical health over time, which affects their strength, balance, mobility and ability to perform activities of daily living and to live independently. Diabetes, diabetes-related complications and diabetes-associated comorbidities are associated with physical dysfunction and frailty [18, 19]. Hypoglycaemia may also lead to significant morbidity, frailty and disability. Several studies have demonstrated that hypoglycaemia or tight glycaemic control directly increases the risk of frailty, disability or functional decline. In an Italian study, the occurrence of hypoglycaemia was independently associated with worse Multidimensional Prognostic Index grade, a validated predictive tool for mortality related to the presence of impairments in different biological, clinical, functional, psychological and social domains, which suggests underlying frailty [50]. In a US prospective study, both low and high mean blood glucose levels increased the risk of frailty confirming a U-shaped relationship. The risk was in proportion to the blood glucose level. In other words, the risk was higher the lower or the higher blood glucose. The lowest risk of frailty was at a mean blood glucose level of 9.4 mmol/L (HbA1c 7.6%) [51•]. In a Japanese cross-sectional-prospective study, low HbA1c predicted frailty in a linear rather than a U-shaped relationship. After 6 months, the HbA1c values declined and the clinical frailty scale worsened significantly suggesting that HbA1c might be a reciprocal indicator of aggravation of frailty [52]. In another Japanese prospective study, low HbA1c was associated with an increased risk of disability as measured by the first support/need care certification. The increased incident of disability rate in this study was most likely due to the higher incidence of dementia in the lower HbA1c group, which supports our suggestion that hypoglycaemia is linked to both physical frailty and dementia and hence cognitive frailty [53]. In a cross-sectional French study, hypoglycaemia was associated with low body weight and increased prevalence of high comorbidity burden indicating frailty in a large cohort of very old (> 80 years) patients with diabetes hospitalised in geriatric care units [54]. In another cross-sectional Italian study in 150 nursing homes, low HbA1c tertile, mean (SD) 5.9% (0.4), was associated with losses in activities of daily living. Losses in ADL were negatively associated with HbA1c level and positively associated with the number of hypoglycaemic episodes [55]. Other studies have demonstrated that hypoglycaemia increases the risk of hip fracture in proportion to the frequency of hypoglycaemic episodes and risk of falls indirectly leading to frailty, which increased the incidence of hospitalisation and nursing home placements [56, 57]. Studies showing association between hypoglycaemia and physical dysfunction or frailty in older people with diabetes are summarised in Table 2.

Circular and Reciprocal Interrelations

The relationship between physical frailty and cognitive impairment appears to be bidirectional: frailty increases the risk of cognitive impairment and cognitive impairment increases the risk of frailty. The mechanism explaining this link is unclear but could be due to shared pathological factors such as chronic inflammation, oxidative stress and impaired repair or related to hormonal, nutritional, cardiovascular or mental health factors [58]. The bidirectional relation between physical frailty and cognitive impairment increases the risk of cognitive frailty, which is the co-existence of both conditions. A bidirectional relationship also exists between cognitive impairment and hypoglycaemia. Hypoglycaemia increases the risk of cognitive impairment and cognitive impairment may lead to difficulty with self-care tasks and medication errors that lead to increased risk of hypoglycaemia [59]. The relationship between frailty and hypoglycaemia is also bidirectional: hypoglycaemia increases risk of frailty and frailty increases the risk of hypoglycaemia because frailty is a wasting disease associated with malnutrition, anorexia and weight loss [60]. Lower body mass index (BMI) of 20.1 kg/m^2, which may suggest underlying frailty, compared to a higher BMI of 27 kg/m^2 increased the severity of hypoglycaemia in older people with diabetes admitted to hospital with hypoglycaemia [61]. The emergence of frailty with reduced physiologic reserve and significant weight loss in older people with diabetes may lead to normalisation of blood glucose level and a state of burnt out diabetes that increases the risk of hypoglycaemia [62]. As a consequence, hypoglycaemia appears to play a central role in a circular relationship between frailty and cognitive function setting a viscous circle (Fig. 1). In addition to the cognitive and physical effects, hypoglycaemia is also associated with negative emotional effects such as an increased risk of depressive symptoms, low psychological wellbeing, fear, distress and poor quality of life that may lead to impairment in preforming activities of daily living, vulnerability, social isolation and further deterioration of cognitive frailty [63, 64]. Cognitive frailty may represent a precursor of neurodegenerative processes with a potential for reversibility [6••]. Therefore, prevention of hypoglycaemia may help reduce further irreversible deterioration.

Table 1 Studies exploring effect of hypoglycaemia on risk of cognitive dysfunction or dementia in older patients with type 2 diabetes mellitus

Study	Patients	Aim to	Main findings
Yaffe K et al., prospective, USA, 2013 [33].	783 patients with DM, mean age 74 Y, F/U 12 Y.	Evaluate association of hypoglycaemia and dementia.	Patients with hypoglycaemia had 2-fold increased risk of developing dementia (HR 2.1, 95% CI 1.0 to 4.4).
Whitmer RA et al., longitudinal, USA, 2009 [34].	16,667 patients with DM, mean age 65 Y, F/U 27 Y.	Determine association of hypoglycaemia and dementia.	Graded increase in dementia risk with hypoglycaemia: 1 episode (HR 1.26, 95% CI 1.10 to 1.49), 2 episodes (1.80, 1.37 to 2.36) and ≥ 3 or episodes (1.94, 1.42 to 2.64).
Lin CH et al., prospective, Taiwan, 2013 [35].	15,404 patients with DM, mean age 64 Y, F/U 7 Y.	Investigate risk of dementia in patients with or without hypoglycaemia.	Incidence of dementia was higher in persons with (29.9/1000, 95% CI 22.1 to 39.2) compared to those without (11.1/1000, 10.3 to 11.8) hypoglycaemia (RR 1.6, 95% CI 1.19 to 2.14, $p = 0.002$), and relationship was linear (0.004).
Chin SO et al., prospective, Korea, 2016 [36].	1957 patients with DM, aged ≥ 60 Y, F/U 3.4 Y.	Investigate association of hypoglycaemia with dementia or cognitive dysfunction.	A. Hypoglycaemia was independently associated with dementia (HR 2.69, 95% CI 1.08 to 6.69, $p = 0.03$). B. There was a significant linear trend between dementia and number of hypoglycaemic events ($p = 0.03$).
Mehta HB et al., retrospective, UK, 2017 [37•].	53,055 patients > 65 Y old with DM.	Evaluate association of hypoglycaemia and dementia.	A. Hypoglycaemia increased risk of dementia (HR 1.27, 95% CI 1.06 to 1.51). B. Risk of dementia increased with increasing number of hypoglycaemic episodes: 1 episode (HR 1.26, 95% CI 1.03 to 1.54), 2 episodes (1.5, 1.09 to 2.08).
Feinkohl I et al., prospective, UK, 2014 [38].	831 patients with DM age 60–75 Y, F/U 4 Y.	Investigate association of hypoglycaemia and cognitive decline, a standardised general ability factor *g* was used.	A. Incident hypoglycaemia was associated with poorer cognitive ability at baseline (OR for lowest tertile of *g* 2.04 (95% CI 1.25 to 3.31, $p = 0.004$). B. Both history of hypoglycaemia and incident hypoglycaemia were associated with greater cognitive decline during follow-up (mean adjusted follow-up *g*s were − 0.23 vs. 0.03 ($p = 0.04$) and − 0.21 vs. 0.05 ($p = 0.03$) respectively.
Haroon NN et al., prospective, Canada, 2015 [39].	893,115 patients, median age 73 Y, F/U 5 Y.	Determine risk of dementia in patients with or without DM.	Hypoglycaemia predicted dementia ((HR 1.73, 95% CI 1.62 to 1.84).
Duning T et al., prospective, Germany, 2010 [40].	4635 patients in surgical ICU, treated with TGC.	Investigate whether hypoglycaemia causes neurocognitive dysfunction.	After at least 1 year following ICU discharge, hypoglycaemia aggravated neurocognitive visuospatial skill dysfunction, $p = 0.001$ compared to matched control.
Aung PP et al., cross-sectional, UK, 2012 [41].	1066 patients with DM, age 60–75 Y.	Determine association of hypoglycaemia and cognition measured by general factor *g*.	*g* was lower in persons reporting at least one episode of severe hypoglycaemia (− 0.34 vs 0.05, $p < 0.001$) compared to those who did not, independent of premorbid cognitive ability.
Gao Y et al., case control, China, 2015 [42].	246 pairs of diabetic MCI subjects and cognitively normal controls.	Identify diabetes-related factors associated with MCI.	Diabetic subjects with MCI had significantly more frequent episodes of hypoglycaemia compared to cognitively normal control ($p < 0.05$).
Lee AK et al., cross-sectional prospective, USA, 2018 [43].	2001 patients with DM, mean age 76 Y, F/U 15 Y.	Evaluate association of hypoglycaemia with cognitive decline, brain volume and dementia.	Severe hypoglycaemia was associated with: A. Dementia (OR 2.34, 95% CI 1.04 to 5.27). B. Small brain volume, (− 0.308 SD, − 0.612 to − 0.004). C. 15 years cognitive change (− 0.14 SD, − 0.34 to 0.06). D. Incident dementia (HR 2.54, 95% CI 1.78 to 3.63).
Alonso MAC et al., cross-sectional, Spain, 2017 [44].	654 care home residents, mean age 82.4 Y.	Establish relation of hypoglycaemia and cognitive impairment.	In residents with DM, low HbA1c (< 6.0%) was associated with higher cognitive impairment ($p = 0.04$).

DM diabetes mellitus, *Y* years, *F/U* follow-up, *HR* hazard ratio, *CI* confidence interval, *RR* relative risk, *OR* odds ratio, *ICU* intensive care unit, *TGC* tight glucose control, *MCI* mild cognitive impairment, *SD* standard deviation

Table 2 Studies exploring effect of hypoglycaemia on risk of physical dysfunction or frailty in older patients with type 2 diabetes mellitus

Study	Patients	Aim to	Main findings
Pilotto A et al., cross-sectional, Italy, 2014 [50].	1342 patients with DM, mean (SD) age 73.3 (5.5) Y, 57 diabetes centres.	Identify characteristics associated with multidimensional impairment.	A. 161 patients (12.0%) reported at least one episode of hypoglycaemia in 3 months prior to enrolment. B. Hypoglycaemic episodes were associated with increased risk of moderate to severe multidimensional prognostic index grade, OR 1.83, 95% CI 1.17 to 2.86, $p = 0.008$.
Zaslavsky O et al., prospective, USA, 2016 [51•].	1848 patients ≥ 65 Y, F/U 4.8 Y.	Examine relation between blood glucose level and risk of frailty.	A. Risk of frailty increased as blood glucose level either decreased or increased: 1. 8.3 mmol/L (HbA1c 6.9%), HR 1.41, 95% CI 1.12 to 1.78. 2. 8.9 mmol/L (7.2%), 1.1, 1.0 to 1.20. 3. 9.4 mmol/L (7.6%), 1 (ref). 4. 10.0 mmol/L (7.9), 1.08, 1.0 to 1.17. 5. 10.6 (8.2), 1.3, 1.08 to 1.56.
Yanagita I et al., cross-sectional-prospective, Japan, 2018 [52].	132 hospitalised patients with DM, mean (SD) age 78.3 (8.0) Y.	Evaluate frailty risk factors including HbA1c using clinical frailty scale (CFS).	A. HbA1c was significantly lower, mean (SD) 7.13 (0.99) in the frail compared to non-frail, 7.27 (1.04) group, $p < 0.001$. B. Values of HbA1c inversely correlated with the values of CFS ($r = -0.31$, $p < 0.01$). C. In multiple regression analysis, HbA1c independently predicted frailty ($\beta = -0.367$, $p < 0.01$).
Morita T et al., prospective, Japan, 2017 [53].	184 patients with DM aged 65–94 Y, F/U 5 Y.	Investigate if low HbA1c is associated with risk of support/care need certification.	HbA1c < 6.0% was associated with increased risk of: A. Support/care need certification (HR 3.45, 95% CI 1.02 to 11.6, p=0.046) compared to HbA1c of 6.5 to < 7.0%. B. Support /care need certification because of dementia (12.5, 3.0 to 52.2, p=0.001) compared to HbA1c ≥ 6.0%.
De Decker L et al., cross-sectional, France, 2017 [54].	1552 patients with DM, mean (SD) age 86.4 (4.4) Y.	Determine association of hypoglycaemia and high burden of comorbidities.	Patients with hypoglycaemia had: A. Lower body weight ($p = 0.004$). B. More renal function impairment ($p < 0.001$). C. Greater level of dependency ($p < 0.001$). D. Higher prevalence of dementia ($p = 0.006$). E. Higher prevalence of cardiovascular disease ($p < 0.001$). F. Higher Charlson comorbidity index (4.7 vs 3.8, $p < 0.001$).
Abbatecola AM et al., cross-sectional, Italy, 2015 [55].	1845 patients with DM in 150 nursing homes, mean (SD) age 82 (8.0) Y.	Explore association of low HbA1c and losses in ADL.	A. Lower HbA1c tertile was associated with impairment in ADL ($\beta = -0.014$, $p = 0.002$). B. ADL impairments were independently negatively associated with HbA1c level ($r = -0.11$, $p < 0.001$) and positively associated with number of hypoglycaemic events ($r = 0.10$, $p < 0.001$).
Mattishent K et al., meta-analysis, UK, 2016 [56].	17 observational studies, 1.86 million older (> 60 Y) DM patients.	Assess serious adverse events associated with hypoglycaemia.	Hypoglycaemia was associated with macrovascular complications (OR 1.83, 95% CI 1.64 to 2.05), microvascular complications (1.77, 1.49 to 2.10), falls (1.89, 1.54 to 2.32), fractures (1.92, 1.56 to 2.38) and mortality (2.04, 1.68 to 2.47).
Hung YC et al., case control, Taiwan, 2017 [57].	2588 patients with DM, 5173 control, mean age 70 Y, F/U 3.9 Y.	Assess risk of severe hypoglycaemia-related hip fracture.	A. Severe hypoglycaemia increased risk of hip fracture (HR 1.71, 95% CI 1.35 to 2.16). B. Risk of hip fracture increased significantly with increased frequency of hypoglyaemic episodes from 1.4-fold for < 3 episodes to 57.5-fold for ≥ 6 episodes per year.

DM diabetes mellitus, *SD* standard deviation, *Y* years, *OR* odds ratio, *CI* confidence interval, *F/U* follow-up, *HR* hazard ratio, *ADL* activities of daily living

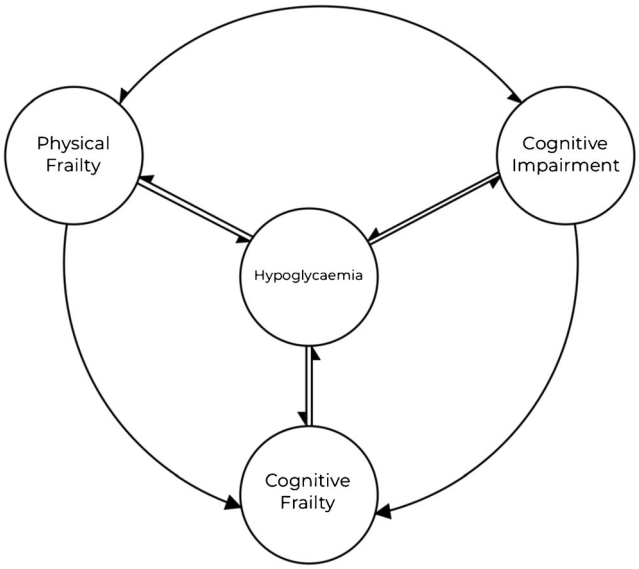

Fig. 1 Circular relation of hypoglycaemia, cognitive impairment and physical frailty leading to the development of cognitive frailty with hypoglycaemia playing a central role

Prevention

Hypoglycaemia is a potentially preventable risk factor for cognitive frailty and therefore, older people with diabetes should have individualised care plans that include hypoglycaemia education, setting safe glycaemic goals, regular medications review, and early recognition and management of hypoglycaemia.

Recognition

Recognition of hypoglycaemia is less clear in older people with diabetes. With increasing age, the autonomic warning symptoms of hypoglycaemia become less intense, the unawareness of hypoglycaemia becomes more common, and the reaction time for correction becomes more restricted which may put older people with diabetes at an increased risk of severe hypoglycaemic episodes [65]. Another diagnostic challenge is the similarities in the clinical presentation of hypoglycaemia with that of dementia where patients present with agitation, increased confusion or behavioural changes. The non-specific nature of symptoms such as fatigue or weakness may lead to under-recognition and under-reporting by patients and physicians, subsequently leading to underestimated frequency [66]. In a primary care study, possible hypoglycaemia misdiagnosed as nausea, falls or unsteadiness was common in older people with diabetes who were on insulin therapy and had a previous history of hypoglycaemia [67]. Therefore, regular blood glucose monitoring is essential to exclude hypoglycaemia in older people with diabetes who are at risk and presenting with a non-specific symptom. Risk factors that increase the risk of hypoglycaemia in older people are summarised in Table 3 [28].

Glycaemic Control

Intensive glycaemic control with HbA1c < 53 mmol/mol (7.0%) increases the risk of severe hypoglycaemia by 1.5- to 3.0-fold. Clinical trial analysis suggests that a range of HbA1c from 58 mmol/mol (7.5%) to 75 mmol/mol (9.0%) for frail older people with diabetes is appropriate [68]. Main guidelines emphasise the concept of individualisations of goal setting and recommend HbA1c ranges based on patients' characteristics and health status from tight levels for independent patients to relaxed control for patients with reduced function (Table 4) [69–73]. However, the sole reliance on HbA1c may not prevent hypoglycaemia and may lead to overtreatment as HbA1c misses daily fluctuations in blood glucose levels. Continuous glucose monitoring in older patients (> 70 years) has shown increased prevalence of daily hypoglycaemic episodes in patients with relaxed HbA1c values of 64–75 mmol/mol (8.0–9.0%) [74]. Therefore, daily blood glucose monitoring in high-risk patients, such as those on insulin therapy, is as important as HbA1c levels. Another factor is the stability of glucose control. Instability of HbA1c or variability of blood glucose values is associated with worse cognitive performance, increased mortality and grey matter atrophy in older

Table 3 Risk factors for hypoglycaemia in older people with diabetes [28]

- Advanced age
- Multiple comorbidities
- Polypharmacy
- Insulin or sulfonylurea therapy
- Long duration of diabetes mellitus
- Hypo unawareness
- Cognitive dysfunction
- Depression
- Physical frailty
- Malnutrition
- Tight glycaemic control
- Renal/liver impairment
- History of hypoglycaemia
- Fasting for a procedure
- Sedative medications
- Decreased oral intake
- Sliding scale insulin
- Irregular eating pattern
- Social isolation
- Alcohol excess
- Acute illness
- Impaired self-care ability
- Recent hospitalisation

Table 4 Main guidelines recommendations for HbA1c targets and avoiding hypoglycaemia

Organisation	HbA1c targets	Avoiding hypoglycaemia
IDF, 2013 [69]	A. Independent, 53–59 mmol/mol (7–7.5%) B. Dependent, 53–64 mmol/mol (7.0–8.0%) C. Frail/dementia, < 69 mmol/mol (< 8.5%) D. End of life: symptomatic, HbA1c not recommended.	A. Assess risk and individualise plans. B. Avoid blood glucose level < 6.0 mmol/L. C. Consider HbA1c < 53 mmol/mol (7.0%) as a warning for overtreatment. D. Monitor blood glucose for patients on insulin or sulfonylurea. E. Medications review in patients who had a hypoglycaemic episode. F. Education for health care professionals and patients. G. Monitor self-administration ability for patients on insulin.
IAGG, 2012 [70]	A general target of 53–59 (7.0–7.5%) mmol/mol is recommended.	A. Risks of hypoglycaemia should be identified. B. Focused education for patients and carers. C. Hypoglycaemia leading to hospitalisation should trigger a specialist review. D. FBG < 6.0 mmol/L should be avoided (not below 6) and hypoglycaemic therapy should start only if FBG persistently > 7.0 mmol/L (not before 7).
IPS, 2018 [71]	A. Mild-moderate frailty, 53–64 mmol/mol (7.0–8.0%). B. Severe frailty, 59–69 mmol/mol (7.5–8.5%).	A. Regular assessment of hypoglycaemia risk. B. Educational programmes for patients and cares that suits their cognitive abilities. C. Individualised blood glucose range in care plans. D. Regular assessment of cognitive and physical functions especially in patients on insulin therapy. E. Blood glucose monitoring for patients on insulin therapy. F. Hypoglycaemic medications with less hypoglycaemic potential. G. Simplification of insulin regimen. H. Deintensification of medications in patients with tight control.
EDWPOP, 2011 [72]	A. Independent, 53–59 mmol/mol (7.0–7.5%) B. Dependent, 60–69 mmol/mol (7.6–8.5%)	A. Assess patients for risk of hypoglycaemia. B. Use agents with less hypoglycaemic potential in patients with moderate to high risk. C. Avoid polypharmacy and overtreatment in frail patients.
ADA, 2018 [73]	A. Healthy, < 58 mmol/mol (7.5%). B. Morbidity, < 64 mmol/mol (8.0%) C. Limited life expectancy, < 69 mmol/mol (8.5%).	A. Risk of hypoglycaemia should be assessed and managed by adjusting glycaemic targets and hypoglycaemic medications. B. Routinely screen patients for emerging cognitive dysfunction and discuss findings with patients and carers.

IDF International Diabetes Federation, *IAGG* International Association of Gerontology and Geriatrics, *FBG* fasting blood glucose, *IPS* international position statement, *EDWPOP* European Diabetes Working Party for Older People, *ADA* American Diabetes Association

people with diabetes suggesting that a stable glycaemic level in the middle range is associated with lower risks [75–77].

Hypoglycaemic Therapy

Glucose-lowering drugs with less hypoglycaemic risk potential is preferred in older people with diabetes to reduce the risk of hypoglycaemia and also some of these drugs may have a possible neuroprotective effects [78, 79]. Most of older people with diabetes and tight glycaemic control are treated with either sulfonylurea, insulin or both putting them at high risk of hypoglycaemia [80]. This therapy is more common in patients with comorbid diabetes and dementia who are at the highest risk of hypoglycaemia due to their comorbidities [81]. Reduction of insulin dosage and simplification of complex insulin regimen to a once daily long acting insulin analogue injection with or without the use of non-insulin agents may help reduce the risk of hypoglycaemia and improve the stress level without deterioration of glycaemic control [82]. People who have erratic eating patterns and unpredictable caloric intake could be managed with a regimen where short acting insulin analogues are administered only after meal consumption, thus reducing the risk of hypoglycaemia if a meal is missed or only partly consumed. A closed loop automated insulin delivery system linked with continuous glucose monitoring without meal-time boluses was recently proved to be safe and effective in hospitalised older patients with type 2 diabetes, although larger studies are still needed [83].

Care Plans

Care plans should be individualised with a dynamic goal setting that changes as patient functional level changes and always weighs the balance between the benefits of glycaemic control with the risks of hypoglycaemia. Development of shared care protocols between primary and secondary care, flexibility in services that are sensitive to the changing needs of patients and clinical contacts with patients that are long enough to allow individualisation of care plans are needed [84]. Educational programmes should be suitable for patients and carers 'cognitive abilities and focused on how to recognise and treat hypoglycaemia [85]. The atypical presentation

Table 5 Summary of guidelines recommendations-AVOID HYPOS [69–73]

- Assess risk of hypoglycaemia
- Vigilance monitoring of blood glucose in high risk patients
- Optimise therapy with less hypoglycaemic potential medications
- Individualised care plans
- Deintensify overtreatment
- Health care professionals, patients and carers education
- Yearly screening for cognitive dysfunction
- Physical ability to administer insulin monitoring
- Overall dynamic goal setting to match changes in patients' function
- Simplification of insulin regimen

of hypoglycaemia and its negative impact on older people with diabetes seems to be underestimated by health care professionals [86]. There should not be concerns among primary care professionals about any negative repercussions or litigations following deintensification of hypoglycaemic medications in patients at high risk of hypoglycaemia [87]. Hypoglycaemia prediction algorithms to identify patients at risk of hypoglycaemia and electronic medical record-based alerts to prompt physicians to review hypoglycaemic therapy in older people with diabetes are promising development strategies that may help reduce the incidence of hypoglycaemia [88, 89]. Main guidelines recommendations for reducing hypoglycaemia are detailed in Table 4 and summarised in Table 5.

Conclusion

Cognitive frailty is associated with significant adverse functional and mortality outcomes in older people with diabetes. Hypoglycaemia is likely to play a central role in the development of cognitive frailty and the relationship between physical frailty, cognitive impairment and hypoglycaemia is circular. Therefore, strategies to prevent hypoglycaemia in vulnerable older people with diabetes are required to reduce the decline in physical and cognitive function, slow the progression to disability and improve the outcomes.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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