Journal of Diabetes and Its Complications 30 (2016) 1548–1554

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Hypoglycemia, frailty and dementia in older people with diabetes: Reciprocal relations and clinical implications

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ARTICLE INFO

Article history:
Received 8 June 2016
Received in revised form 22 July 2016
Accepted 23 July 2016
Available online 27 July 2016

Keywords:
Older people
Diabetes mellitus
Frailty
Dementia
Hypoglycemia

ABSTRACT

The relationships between hypoglycemia, frailty and dementia appear to be reciprocal and can lead to a vicious circle. Frailty appears to be a crucial factor increasing the risk for both hypoglycemia and dementia, initiating the reciprocal relationships. Weight loss is likely to be the underlying risk factor for frailty. Many frail older people with diabetes seem to have unnecessarily tight glycemic control, being treated with hypoglycemic medications that likely increase the risk of hypoglycemia. As patients get older with significant weight loss their glycemic targets should be reviewed, and reduction or even withdrawal of their hypoglycemic medications should be considered.

1. Introduction

Progressive decline in cognitive function leading to dementia is common in older people with diabetes. Dementia affects up to 16% of patients with diabetes aged ≥65 years and 24% of those aged ≥75 years (Feil et al., 2011; Thorpe et al., 2012). The relative risk (RR) of Alzheimer's disease is 1.56 {95% confidence interval (CI) 1.41 to 1.73), that of vascular dementia is 2.27 (1.94 to 2.66) and that of all types of dementia is 1.73 (1.65 to 1.82) compared to those without diabetes (Gudala, Bansal, Schifano, & Bhansali, 2013). Persistent hyperglycemia on one hand increases the risk of cerebrovascular disease by inducing inflammation, endothelial dysfunction, oxidative stress and insulin resistance leading to an increased incidence of vascular dementia (Middleton & Yaffe, 2009). Accelerated brain aging from altered amyloid metabolism, increased protein glycation and direct cerebral glucotoxicity may explain the increased risk of Alzheimer's dementia (Biessels, Staekenborg, Brunner, Brayne, & Scheltens, 2006). On the other hand, repeated episodes of severe hypoglycemia may be implicated in inducing cognitive impairment and dementia; however, this issue remains controversial. Frailty is an emerging complication of diabetes related to diabetes-associated decline in physical and cognitive function. It is associated with weight loss and malnutrition which may increase the likelihood of hypoglycemia (Hubbard, Lang, Llewellyn, & Rockwood, 2010). The rate of progression of frailty increases with aging likely due to diminishing physiologic reserve and is accelerated by the presence of brain pathologies such as Alzheimer's diseases (Buchman, Yu, Wilson, Schneider, & Bennett, 2013). Therefore, frailty appears to be associated with both hypoglycemia and dementia. In this review we have explored the relationships between hypoglycemia, frailty and dementia and its implications in clinical practice.

2. Methods

We have performed a search of Medline and Embase from 1996 to present using keywords relating to hypoglycemia, frailty, dementia, older people, diabetes mellitus and management. Only English language articles were selected. Articles were reviewed for relevance by abstract. A manual review of citations in retrieved articles was performed in addition to the electronic literature search. The final list of cited references was chosen on the basis relevance to the topic of review.

2.1. Hypoglycemia in old age

The real incidence of hypoglycemia in older people with diabetes may be under-estimated. Hypoglycemia incidence is likely to be higher in older age due to associated comorbidities and polypharmacy, and tends to be less recognized due to altered adaptive physiologic responses to low glucose levels as we get older. There is scarce literature on the incidence of hypoglycemia specific to older people due to the heterogeneity of this age group, particularly in those

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http://dx.doi.org/10.1016/j.jdiacomp.2016.07.027
1056-8727/

living in care homes. The incidence of serious hypoglycemia (defined as an episode leading to fatal outcome or hospital admission) was 1.23% for patients treated with sulfonylureas and 2.76% for those treated with insulin in a US retrospective population-based study of 19,932 Medicaid patients, aged ≥65 years (Shorr, Ray, Daugherty, & Griffin, 1997). The incidence of hypoglycemia of any severity was 14.1% over a 12 month period in a more recent prospective study of DiaRegis (multicenter registry of patients with diabetes) in Germany which included 3347 patients (median age 66.1 years) (Tschöpe, Bramlage, Binz, et al., 2012). Older age seems to be associated with increased incidence of hypoglycemia (12.8% for those ≥75 vs 9.0%, for those <60 years old, $p < 0.01$) in a prospective observational study of 3810 patients in primary care (Bramlage et al., 2012). In care homes the incidence of hypoglycemic episodes is higher occurring in 41.9% of patients in one study over a one year period (median 2, range 1–10 episodes per patient per year) due to older age and higher level of comorbidities in this population (Chen, Lin, Lai, & Hwang, 2008). The recognition of hypoglycemia may be difficult due to the predominance of neurological rather than autonomic symptoms resulting in misdiagnosis (Jaap, Jones, McCrimmon, Deary, & Frier, 1998). Another diagnostic challenge is the similarities in the clinical presentation of hypoglycemia with that of dementia where patients present with agitation, increased confusion or behavioral changes. Symptoms can also be generally nonspecific such as fatigue or weakness leading to under-recognition and under reporting by patients and physicians, subsequently leading to underestimated frequency (Bonds et al., 2012).

2.2. Hypoglycemia and cognitive function

Glucose is the main source of energy for the neurons and cannot be synthesized or stored in the brain tissue. Therefore, continuous glucose supply to the brain is essential for accurate cognitive functioning. Transient hypoglycemia may lead to reversible impairment of cognitive function. However, persistent or severe hypoglycemia may result in permanent neuronal damage (Bree, Puente, Daphna-Iken, & Fisher, 2009). The brain is vulnerable to hypoglycemia particularly in old age. With increasing age subclinical hypoglycemia or episodes with fewer symptoms may further reduce awareness of the onset of a severe episode because the glycemic threshold has been lowered. In other words, an episode of hypoglycemia can induce further hypoglycemia, setting a vicious circle and inducing what is called post-hypoglycemic encephalopathy (Cryer, 2005). Hypoglycemia increases platelet aggregation and fibrinogen formation and could lead to microvascular events accelerating cerebrovascular compromise and contributing to brain atrophy and cognitive impairment (Wright & Frier, 2008). Severe hypoglycemia may also affect the blood–brain barrier integrity and can damage receptors in the brain areas critical for learning and memory (Suh, Hamby, & Swanson, 2007). In the aging vulnerable brain, hypoglycemia may aggravate the underlying pathological conditions or trigger new degenerative changes depending on overall brain health, leading to further cognitive impairment.

2.3. Hypoglycemia and dementia—a bidirectional relationship

A bi-directional relationship exists between dementia and hypoglycemia in older people with diabetes. Patients with cognitive dysfunction may have difficulty with tasks such as identification and treatment of low glucose levels and self-administration of medication, setting a vicious circle of more frequent hypoglycemic episodes and worsening cognitive decline (Mattishent & Loke, 2016).

2.3.1. Hypoglycemia causes dementia

In a large longitudinal cohort study of 16,667 patients, mean age 65 years, with type 2 diabetes followed up for 27 years in the US, Whitmer et al. found that severe hypoglycemic episodes defined as episodes leading to hospitalization were associated with an increased risk of dementia. There was a dose–response relationship between the frequency of severe hypoglycemia and the incidence of dementia. Patients with single or multiple episodes had a graded increase in the risk: 26% for one episode, 80% for two episodes and 94% for three or more episodes. The attributable risk of dementia between individuals with and without a history of hypoglycemia was 2.39% per year, 95% CI 1.72% to 3.01%. These findings were independent of glycemic control, type of diabetes treatment and comorbidities (Whitmer, Karter, Yaffe, Quesenberry, & Selby, 2009). In another prospective population-based study to evaluate the association between hypoglycemia and dementia in a cohort of 783 older biracial adults with diabetes, mean age 74.0 (2.8) years, Yaffe et al. found that participants who experienced a hypoglycemic event had a 2-fold increased risk for developing dementia compared with those who have not (34.4% vs 17.6%, $p < 0.001$). Multivariate-adjusted hazard ratio (HR) was 2.1 and 95% CI was 1.0 to 4.4 after 12 years of follow-up (Yaffe et al., 2013). The association remained significant after adjustment for age, sex, educational level, ethnicity, and comorbidities. The dose–response relationship between the frequency of severe hypoglycemic episodes and the incidence of dementia has also been shown in a large Taiwanese national population database study of 15,404 patients with type 2 diabetes and no history of dementia. The incidence rate of dementia was about 3% in those with history of hypoglycemia compared to 1% in those without after 7 years of follow-up. The increased number of hypoglycemic episodes enhanced the risk of developing dementia ($p < 0.001$) (Lin & Sheu, 2013). In the Edinburgh Type 2 Diabetes Study of 831 patients with type 2 diabetes, aged 60–75 years, there was a correlation between cognitive function and self-reported history of severe hypoglycemia. A history of severe hypoglycemia was associated with poorer initial cognitive ability and a more rapid rate of cognitive decline after 4 years of follow-up (Feinkohl et al., 2014). The relationship between hypoglycemia and dementia has also been shown in older people newly diagnosed with diabetes mellitus (Haroon et al., 2015). (Table 1) 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 hypoglycemia and dementia, the prospective association between historical hypoglycemia 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 hypoglycemia and cognitive dysfunction (Bruce et al., 2009). This negative association between hypoglycemia and dementia has also been shown in the ACCORD-MIND and ADVANCE trials in which patients in the intensive therapy arm, with more frequent hypoglycemic episodes, had a similar decline in cognitive function compared to those in the usual care arm with less hypoglycemia. However, these studies were not designed to directly investigate the relationship between hypoglycemia and cognitive decline as a primary end point. It is also plausible that better glycemic control in the intervention arm may have improved cognitive function diluting any deleterious effect of hypoglycemia on cognition (de Galan et al., 2009; Launer et al., 2011).

2.3.2. Dementia causes hypoglycemia

In a cross sectional Italian study of 2258 patients with diabetes residents in care homes (1138 with dementia, 1120 with no dementia), severe hypoglycemia was more prevalent in patients with dementia (18%) compared to patients without dementia (8%) (Abbatecola et al., 2015). In the multicenter German/Austrian diabetes patient registry study, patients with combined diabetes and dementia had higher rates of severe hypoglycemia (14.8% vs 10.4%, $p < 0.001$) compared to those with diabetes alone for the same