Aging In The Face of Diabetes: Severe Hypoglycemia in Older Adults

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About the Author

Dr. Alexandria Ratzki-Leewing is an Adjunct Professor in the Department of Epidemiology and Biostatistics and Research Scientist in the Department of Family Medicine at Schulich School of Medicine & Dentistry at Western University (Ontario, Canada). She is also Director of Western University's Diabetes Alliance Hypoglycemia Research Program. Over the last decade, Dr. Ratzki-Leewing has led multiple national and international studies on the real-world epidemiology of iatrogenic hypoglycemia, spanning over 10 countries. She is a Principal Investigator of the InHypo-DM study, and of the iNPHORM study, the largest US-based prospective investigation of Level 3 hypoglycemia risk. Dr. Ratzki-Leewing has presented and published widely with citations in the Diabetes Canada Clinical Practice Guidelines and the American Diabetes Association Standards of Care. In 2023, Dr. Ratzki-Leewing was awarded a Rising Star by the International Diabetes Center for her contributions to the field of hypoglycemia epidemiology.

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Introduction

Global rates of type 1 and type 2 diabetes (T1D, T2D) continue to climb, despite medical advancements. Older adults constitute one of the fastest growing segments of the diabetes population, backed by the world's unprecedented aging population, decreased diabetes mortality rates, and the obesity epidemic.[1] In Canada, individuals aged ≥65 years account for more than a quarter of all prevalent diabetes cases, far exceeding the other age groups.[2]

Older adults with diabetes face the highest risks of microvascular and macrovascular complications, which, compared to younger age cohorts, can contribute to significant functional loss, frailty, and premature mortality.[3] A considerable amount of research links intensive glucose-lowering with insulin or secretagogues to reduced cardiovascular disease.[4] However, the consequent risk of severe hypoglycemia and related sequelae can be particularly catastrophic for older adults, exacerbated by coexisting health conditions and age-related social needs.

Approximately 40% of Canadians with T2D aged ≥65 years currently use secretagogues, while 27% use insulin[5]—alongside all those with T1D. Longitudinal evidence suggests that since the year 2000, hospital admission rates for hypoglycemia have consistently surpassed those for hyperglycemia,

Classification	Glucose Criteria	Description	Treatment Modality
Level 3 "Severe hypoglycemia"	No threshold specified.	A medical emergency. Altered mental and/or physical functioning. High clinical relevance.	Not able to self-treat. External assistance is often required for recovery.

Table 1. Guideline classification of severe hypoglycemia; *courtesy of Alexandria Ratzki-Leewing, PhD, MSc.*

especially among individuals aged 75 years and above.[6] Economic modelling estimates that the Canadian healthcare system spends $125,932 CAD per year on iatrogenic hypoglycemia,[7] with the bulk of these costs likely allocated to people ≥65 years.[8]

Diabetes in older adults is a pressing public health issue in Canada, marked by clinical diversity and widespread use of medications that are prone to cause hypoglycemia. This review outlines recent epidemiologic findings on severe hypoglycemia among community-dwelling older adults with T1D or T2D treated with insulin or secretagogues. Understanding the complex factors contributing to severe hypoglycemia in this population is crucial for developing tailored prevention strategies that are both effective and safe.

Defining and Measuring Severe Hypoglycemia

Regardless of age, Diabetes Canada[9] and the American Diabetes Association[10] classify severe hypoglycemia as a 'Level 3' low blood glucose event causing altered mental or physical status such that professional or non-professional aid is required for recovery (**Table 1**). Common antecedents include incorrect treatment dosing, product mix-ups, and missed meals.[11]

Importantly, unlike non-severe hypoglycemia, there is no specified blood glucose value that delineates severe events, primarily because the threshold for symptom onset varies across individuals. Thus, while continuous glucose monitoring has proven effective at measuring non-severe hypoglycemia, it cannot precisely gauge the occurrence of severe hypoglycemia (an event qualitatively defined as requiring external aid). Instead, severe events are best captured via health records and, even more so, by self-report.

Age-Related Hypoglycemia Pathophysiology and Consequences

For people with insulin- or secretagogue-treated diabetes, plasma insulin concentrations are largely unregulatable, with defective insulin autoregulation, iatrogenic hyperinsulinemia, and impaired physiological defences, which collectively increase the risk of hypoglycemia. In both T1D and advanced T2D, progressive insulin deficiency and reduced hormone responsiveness disrupt crosstalk between α- and β-cells, leading to dysregulation in glucagon secretion and action.

Age-related changes in pancreatic, renal, hepatic, neurologic, and cardiac physiologies further compromise adaptive responses to incipient lows in blood glucose levels. Notably, adrenergic responses to hypoglycemia diminish over time, causing the occurrence of autonomic symptoms at progressively lower blood glucose levels. Therefore, for the older adult, autonomic and neuroglycopenic symptoms are more likely to appear near-simultaneously, with little warning.[12] Symptoms also tend to become less diverse, specific, and intense with age, potentially delaying behavioural counteraction (e.g., carbohydrate intake).[13]

Because older adults are susceptible to neuroglycopenia or cognitive dysfunction from hypoglycemia, accidents resulting in personal injury are a common sequela in this population. Event-related falls with fractures are particularly concerning for older adults, as they both contribute to, and are perpetuated by, frailty.[14] Over time, repeated event exposure can lead to impaired awareness of hypoglycemia, microvascular complications, and progressive neurodegeneration, increasing the odds of dementia by 50%.[15] Severe hypoglycemia has also been linked to odds ratios of 1.81 and over 2 for cardiovascular events and mortality, respectively.[15] Whether this is a direct or correlative relationship remains indeterminate, despite suggestive evidence of causality.[16,17]

Other documented consequences of severe hypoglycemia include intensified fear of hypoglycemia,[18] increased diabetes-related distress,[18,19] low psychological well-being,[18] and

reduced health-related quality of life,[20] especially at the intersection of geriatric syndromes.[21]

The Frequency of Severe Hypoglycemia in Older Adults

Reported frequencies of diabetes-related severe hypoglycemia in older adults vary across the literature due largely to differences in event classification (e.g., requiring hospital aid versus any type of aid [such as from a family member or friend]) and data source (e.g., health record versus self-report).

Estimates Derived from Healthcare or Administrative Claims Records

Among older adults, rates of hospital-related hypoglycemia generally range from 0.00015 to 0.025 events per person-year.[22-25] In a Canadian study by Clemens *et al*., the percentage of T1D or T2D adults aged ≥66 years with a hypoglycemia-related hospital encounter decreased from 2002 to 2012; however, the absolute number of encounters appeared virtually unchanged.[26] By comparison, in a US claims study of adults aged ≥65 years, hypoglycemia admission rates rose by 11.7% from 1999 to 2011, exceeding hyperglycemia rates, which declined. Individuals 75 years or older reported approximately twice the number of hypoglycemia admissions as those aged between 65 to 74, with the highest rate reported by those over the age of 85 years.[6] A more recent claims analysis by McCoy *et al.* showed that, from 2011 to 2021, the overall adjusted rate of severe hypoglycemia decreased by 31% (p=0.02) in adults with T2D (hyperglycemia was less frequent), while remaining relatively stable (p=0.87) in T1D (hyperglycemia was more frequent).[27] This study was not exclusive to older adults, although nearly 50% of the sample was ≥65 years. Age-specific estimates were not reported.

Estimates Derived from Self-Report

Person-reported data can supply comprehensive insight into Level 3 hypoglycemia, enabling the capture of not only events treated within the healthcare system, but also those treated "at home" (e.g., by family or friends). In the recent Diabetes and Aging Study that included individuals aged 65 years and over, the incidence of self-reported Level 3 hypoglycemia was low at 3.7%; however, only between 26.5% and 36.5% of the participants were taking a hypoglycemia-inducing agent.[28] Conversely, in the US-wide iNPHORM panel survey of adults with T1D or T2D who were taking insulin and/or secretagogues, 20% of the participants aged ≥60 years reported at least one Level 3 hypoglycemia event over a follow-up period of ~10 months. The rate was 0.89 (95% confidence interval: 0.62–1.27) events per person-year.[29] Both incidence proportions and rates were higher in those with T1D than T2D. Overall, emergency care and hospitalization were required in 3.6% and 1.8% of all cases of T1D and T2D, respectively.

The Challenges of Under-Recognition

Because severe hypoglycemia in older adults can present with atypical neurological symptoms[30] (as opposed to autonomic symptoms), the true real-world frequency of events is prone to underestimation. Visual disturbances, slurred speech, incoordination, or impaired balance resulting from severe hypoglycemia may be misdiagnosed as stroke, vertigo, or visual impairment. Moreover, associated behavioural changes may be mistaken as symptoms of dementia.[31,32] Impaired awareness of hypoglycemia, memory impairment, and sub-optimal clinical inquiry pose further challenges to accurate event capture.

Age-Related Risk Factors of Severe Hypoglycemia

Given the high level of heterogeneity in the older population with diabetes, chronological age per se is often considered a poor discriminator of severe hypoglycemia risk. Rather, susceptibility to such events is more likely governed by a complex array of medical and non-medical factors that interrelate with those of the natural aging process.

Hypoglycemia-Prone Medications

Across the US population aged ≥65 years, insulin and secretagogues rank among the top four drugs linked to serious adverse events requiring hospitalization, with 95% of these cases attributed to hypoglycemia.[33] While insulin typically confers a higher risk of events than secretagogues, it is the concurrent use of both that is often most dangerous—particularly for older adults. In a large US T2D study comparing individuals aged ≥65 years to those <65 years, the odds ratios of hospitalization due to severe hypoglycemia were 4.7 for insulin plus secretagogue use, 4.2 for insulin (without secretagogue) use, and 3.9 for secretagogue use (without insulin).[34] According to the InHypo-DM survey, 20% of Canadians with T2D (mean age: 53.4 years) reported using insulin plus secretagogues.[35]

Glycemic Management

Older adults with diabetes rarely attain guideline-recommended A1C values. Data on US adults aged ≥65 years indicate that between 34% to 52% of those with T1D[36] and up to 50% of those with T2D who use insulin or secretagogues are treated to tight A1C targets, irrespective of clinical complexity.[37] In a real-world study by Lega *et al.*, 61% of Canadians with diabetes aged ≥75 years were treated to tight glycemic targets, of which 22%—including a third with at least one comorbidity—were potentially overtreated with insulin or secretagogues.[38] Among this subgroup, the probability of severe hypoglycemia resulting in hospitalizations was 6-times that reported by those treated to conservative glycemic control. Paradoxically, an increased risk of hypoglycemia is also observed in older adults with A1C levels above recommended targets, highlighting the adverse effects of not only potential overtreatment, but also undertreatment.[37]

A1C and Health Status

Recent evidence suggests that the health status of an older adult plays a critical role in determining whether, and the extent to which, that individual benefits from optimal glycemic management. In a US study by Lipska *et al*. involving insulin- or secretagogue-treated adults with T2D aged ≥65 years, those in good health (i.e., with 2 comorbidities and no impairments) who achieved the recommended A1C values experienced fewer complications, including severe hypoglycemia, compared to those in good health with A1C values below or above the recommended target ranges.[37] In contrast, for those in intermediate health (i.e., with multiple but not end-stage conditions), achieving the A1C target values improved complication rates, but only when compared to those in intermediate health with glycemic values above the target range. No association between A1C values and the status of complications was observed for those in poor health (i.e., with severe or end-stage conditions), despite having the worst outcomes. Other studies also report non-significant or tenuous associations between A1C values and hypoglycemia.

Impaired Awareness of Hypoglycemia

Research suggests that 10% of adults aged ~60 years or above with insulin-treated T2D[39] and 31% of those with T1D[40] have impaired awareness of hypoglycemia. Compared to those with intact awareness of hypoglycemia, individuals with T2D or T1D with impaired awareness face a 17-fold increase[41] and 6-fold[40] attendant likelihood of severe events, respectively. The high prevalence of impaired awareness in older adults is driven principally by the past occurrence of hypoglycemia, as well as age-related physiologic deficits in counterregulatory glucose responses.

Coexisting Conditions and Geriatric Syndromes

Multimorbidity can profoundly influence the risk of severe hypoglycemia in older adults with T1D or T2D, especially those with longer diabetes durations. Cognitive dysfunction—possibly accelerated by repeated hypoglycemia—can impede optimal self-management behaviour and, in turn, amplify the risk of hypoglycemic events.[42] Older individuals with diabetes and dementia are particularly vulnerable to severe hypoglycemia, reporting 3-times the number of events as those with diabetes alone.[43] Moreover, renal insufficiency is linked to a greater than 2-fold risk of severe hypoglycemia.[44] Other conditions demonstrating predictive effects include depression[45]—often accompanied by psychomotor retardation—and difficulties performing activities of daily living.[44]

Additionally, the literature reports positive associations for co-occurring geriatric syndromes. In a study of adults aged ≥65 years with diabetes, frailty was found to significantly increase the risk of severe hypoglycemia, especially in those ≥80 years old, who take ≥5 medications and have been recently discharged from hospital.[46] Sarcopenia can also reduce functional capacity. Muscle mass loss compounded by age-related decline in proprioception and reduced mobility can predispose older adults to hypoglycemia-related falls.[15] Finally, retinopathy and conditions affecting fine motor skills (e.g., peripheral neuropathy) may lead to medication errors that cause hypoglycemia.

Polypharmacy

The use of multiple medications by older adults with diabetes, while highly prevalent, increases the risk for adverse drug events and interactions, particularly among individuals aged 80 years or those on 5 agents.[47] Notably, angiotensin-converting enzyme inhibitor or beta blocker use, especially with insulin, can abet iatrogenic severe hypoglycemia by blunting already compromised autonomic responses. The risks associated with polypharmacy are compounded by age-related physiological changes and prolonged diabetes duration, which alter the pharmacokinetics and pharmacodynamics of hypoglycemia-prone medications. Furthermore, progressive declines in lean body mass, hepatic blood flow, renal function, and tissue sensitivity

to insulin may prolong therapeutic half-lives of medications, increasing the subsequent probability of events.

Exercise and Diet

During physical activity, older adults with diabetes may struggle to regulate their blood glucose due to inefficient counter-regulatory responses and functional decline. These factors can hinder hypoglycemic event detection and complicate medication adjustment. With increasing age, sub-optimal glycemic control, neuropathy, and sweating increase the risk for heat-related illness during exercise in older adults,[48,49] especially among those with coexisting cardiovascular complications or pulmonary disease.[50] Chronic hyperglycemia can also provoke dehydration, potentially leading to unpredictable changes in blood glucose levels.

In addition to exercise, various dietary factors have been shown to contribute to the risk of hypoglycemia in older adults with diabetes. Age-related changes in appetite, taste perception, and chewing ability may lead to reduced food intake, potentially resulting in malnutrition, weight loss, and disruptions to optimal medication use.[51] Alterations in gastric emptying and gastrointestinal motility further affect the absorption of carbohydrates and, thus, increase the complexities of therapeutic management.

Social Determinants of Health

Further research is needed to assess the effect of age-related social needs on severe hypoglycemia in older populations with diabetes. Results from a US-based survey (mean age: 58 years) indicate inverse relationships between educational attainment, health literacy, and annual income, with risks for severe hypoglycemia.[52,53] Food insecurity has also been shown to double hypoglycemic event rates.[54] Other social factors that may predict the occurrence of severe hypoglycemia among older adults include area-level deprivation, inequitable care provision, social isolation, and certain cultural practices such as Ramadan.

Conclusion

Despite therapeutic and technologic advancements, the burden of iatrogenic severe hypoglycemia among older adults remains concerningly high and unabated, both in Canada and abroad. The consequences of these hypoglycemic events can be devastating, ranging from acute and long-term physical and psychosocial morbidity to premature mortality. The complexity of age-related factors contributing to severe hypoglycemia mirrors the dynamic heterogeneity of this population, which can range from robust to frail. Insights gleaned from this review can lead to improved risk-tailored diabetes management approaches that are effective and, most importantly, safe.

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