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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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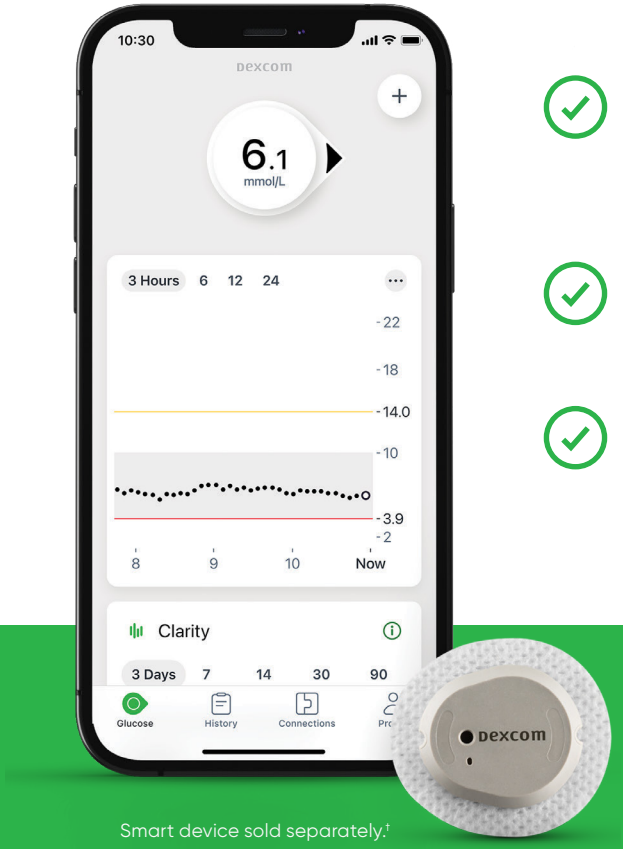

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Obstructive Sleep Apnea and Type 2 Diabetes

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Introduction

Obstructive sleep apnea (OSA) and type 2 diabetes (T2D) are commonly encountered diseases in clinical practice, and there appears to be a bidirectional relationship between these 2 diseases. The presence of OSA can increase the risk of developing T2D, increase the risk of micro- and macro-vascular complications, and increase the risk of mortality. Several management strategies are available that can positively impact the outcomes of patients living with co-existing T2D and OSA. Given this bidirectional relationship, the negative consequences of untreated OSA on outcomes in T2D, along with the currently available management strategies, screening for OSA in patients with T2D should be considered.

Obstructive Sleep Apnea

OSA is the repetitive collapse or near collapse of the upper airway during sleep, which leads to periodic events of apnea (complete cessation of breathing) and hypopnea (a substantial reduction in ventilation).[1] Repeated arousals are required to re-open the airway which leads to disrupted sleep.[2] The severity of OSA is directly correlated to the frequency of apnea and/or hypopnea events which are measured in number of events per hour using the Apnea-Hypopnea Index (AHI).

Patients with OSA often complain of excessive daytime sleepiness and disrupted sleep, and their bed partner can witness snoring or apnea events. Patients with T2D and OSA complain more frequently of nocturia, morning headaches, restless sleep, and leg movements when compared to patients without diabetes.[2] However, symptoms are not always present which is why clinicians must have a high degree of suspicion for this disease.

Risk factors for OSA include male sex, older age, the presence of obesity, micrognathia, and a higher neck circumference.[1-3]

Relationship Between Obstructive Sleep Apnea and Type 2 Diabetes

Nocturnal hypoxia as well as frequent arousals with interrupted sleep leads to fluctuations in blood pressure and increased sympathetic nervous activity, while nocturnal hypoxemia can lead to oxidative stress and β-cell dysfunction.[2,3] These negative physiologic consequences from OSA can lead to impaired glucose tolerance and increased insulin resistance. Furthermore, obesity is a risk factor for both OSA and T2D, and there is a direct correlation with weight and OSA severity.[3]

Prevalence studies of OSA have demonstrated that patients with moderate to severe OSA are more likely to have T2D.[4,5] In fact, up to two-thirds of patients with OSA may have glucose intolerance or diabetes, and a high number of these patients may remain undiagnosed.[5]

There is also an approximately 30% higher risk for developing incident T2D in patients with OSA when compared to those without OSA. Furthermore, the severity of OSA, indicated by a higher AHI score, and a longer time spent with oxygen saturations less than 90% increase the risk of incident T2D.[6]

Patients with co-existing T2D and OSA, have a higher risk of micro- and macro-vascular complications including: ischemic heart disease, atrial fibrillation, stroke/transient ischemic attack, peripheral vascular disease, peripheral neuropathy, chronic kidney disease, and albuminuria.[7] There is also an increased risk of mortality when both OSA and T2D are present.[7,8]

Screening and Testing for Obstructive Sleep Apnea:

Healthcare providers should have a high clinical suspicion for OSA. Given the high prevalence of OSA, and that it poses increased risks of morbidity and mortality, patients with T2D should be screened for the presence of OSA. As screening tools for OSA, sleep questionnaires perform similarly for patients with T2D as for patients without diabetes, with the Snoring, Tiredness, Observed apnea, high blood Pressure, Body mass index, Age, Neck circumference, and Gender (STOP-BANG) and Berlin questionnaires being the most sensitive.[2]

The STOP-BANG questionnaire is an acronym that assigns one point for the presence of each of the following: Snoring, daytime Tiredness, Observed apneas, high blood Pressure, a Body mass index (BMI) greater than 35 kg/m^2, Age greater than 50 years, Neck circumference greater than 40 cm, and male Gender. A score of 3 or greater has high sensitivity for OSA.[2] This questionnaire can be performed in a few minutes since it involves binary responses and only requires a few physical examination manoeuvres or measurements. The STOP-BANG questionnaire is also highly sensitive and performs similarly in patients with or without diabetes, making it a good choice for a screening tool for OSA in this population.

The Berlin questionnaire is also highly sensitive for OSA and performs similarly in patients with or without diabetes.[2] This questionnaire consists of 10 questions in 3 categories that evaluate: the severity of snoring (Questions 1–5), daytime sleepiness (Questions 6–9), and the presence of hypertension or obesity (Question 10). The categories for snoring or daytime sleepiness are considered positive if there are symptoms present at least 3–4 nights per week, whereas the third category is considered positive if the patient has a measured blood pressure greater than 140/90 mmHg, is currently taking anti-hypertensive medications, or has a BMI that is greater than 30 kg/m^2. Having at least 2 out of 3 categories positive on the Berlin questionnaire is highly sensitive for OSA.[2]

Patients identified as potentially having OSA, either based on clinical suspicion or screening questionnaires, should undergo diagnostic testing with an overnight sleep study.

Management Strategies

The management of patients with co-existing OSA and T2D can include non-pharmacological management, positive airway pressure therapy, as well as other devices aimed at reducing apnea/hypopnea events and improving sleep quality, pharmacologic management of diabetes, and surgical management options.

Non-Pharmacological Management

From the non-pharmacological perspective, a behavioural weight loss program in patients with obesity, OSA ,and T2D have been shown to be effective in reducing their AHI scores, reducing the severity of OSA, and have led to a 3-fold increase in the chances of OSA remission.[9] This program consisted of prescriptions for portion-controlled diets with recommended daily caloric intake as well as an activity prescription of 175 minutes per week. The changes noted in sleep apnea severity were independent of changes in hemoglobin A1c (HbA1c).

Additionally, patients should be counselled on the avoidance of sedating agents including alcohol and sedating medications.

Positive Pressure Therapy

Continuous Positive Airway Pressure (CPAP) therapy splints the airways open to prevent airway collapse, thereby improving AHI scores and improving sleep quality. Of note, the largest randomized controlled trial (RCT) to date that assessed CPAP for the prevention of cardiovascular events in those with OSA did not demonstrate a significant reduction in major cardiovascular morbidity or mortality.[10] Furthermore, the rate of newly diagnosed diabetes did not significantly differ between the CPAP and usual care group in this study. However, the negative result was likely due to the low nightly hours of CPAP usage in the trial. The mean CPAP usage was 3.3 hours per night, and only 42% of the patients in the CPAP arm had an adherence of greater than 4 hours per night. To further support this theory, a recent meta-analysis demonstrated a reduction in major adverse cardiac or cerebrovascular events by 31% in patients with a CPAP adherence of at least 4 hours per night.[11]

CPAP has been studied in patients with co-existing OSA and T2D, and has been shown to significantly reduce HbA1c levels with a direct correlation between hours of nightly CPAP usage and degree of reduction in HbA1c levels.[12] Furthermore, CPAP therapy adherence has been shown to significantly reduce healthcare resource utilization with a reduction in emergency department visits and hospitalizations.[13] Given the dose dependent effect of CPAP therapy and the importance of adherence, a combination of therapy initiation as well as a follow-up assessment of both treatment response and barriers to adherence should be considered. Adherence and tolerability may remain a barrier for certain patients.

Other Sleep Devices and Surgical Management of OSA

Other management strategies for reducing the AHI score in those with sleep apnea include mandibular advancement devices (MAD), upper airway surgery (UAS), and positional therapy.

As their name suggests, MADs advance the mandible forward to increase airway space and prevent airway collapse. A small pilot study that examined the use of MADs in patients with OSA and T2D demonstrated a significant reduction in sleepiness and the AHI score. There was a significant decrease in HbA1c levels in patients with mild to moderate, but not severe, OSA following treatment with MADs.[14] It is worth noting that although the use of MADs significantly decreased the AHI score in the severe OSA group, their AHI score remained moderately elevated following treatment, which may explain why there was no significant difference in HbA1c levels in the treatment group.

UAS serves to surgically increase the diameter of the upper airway to prevent airway collapse. A retrospective cohort study demonstrated that patients with OSA who underwent UAS had a significantly reduced risk of developing either an impaired fasting glucose level, impaired glucose tolerance test, or other abnormal glucose finding when compared to patients who were treated with CPAP alone.[15]

In select patients in which the majority of their apnea and hypopnea events occur in the supine position, positional therapy with devices to promote side sleeping and prevent sleeping in the supine position can be considered on a case-by-case basis.

While the results from these small pilot and retrospective studies demonstrated benefit, more evidence is needed regarding these therapies in patients with co-existing OSA and T2D.

Pharmacologic Management of Type 2 Diabetes

On the pharmacological side, there is evidence to support both the use of the glucagon-like peptide 1 (GLP-1) receptor agonist liraglutide as well as the sodium glucose co-transporter-2 (SGLT-2) inhibitors empagliflozin and ertugliflozin to treat or prevent OSA. In a small RCT, liraglutide was found to improve the following: BMI, AHI scores, systolic blood pressure, and oxygen saturations.[16] With regards to SGLT2-inhibitors, post-hoc analyses of the cardiovascular outcome trials demonstrated a relative reduction of the development of incident OSA by 47%.[17] These results should be confirmed with larger and prospectively analyzed RCTs. However, the above results are promising, and the cardiovascular benefit demonstrated by SGLT-2 inhibitors[18] makes this class of medications a potentially beneficial option for a comorbid population at high risk for cardiovascular complications.

- A recent trial, SURMOUNT-OSA, demonstrated superiority of tirzepatide in reducing AHI events compared to placebo in patient groups receiving PAP and not receiving PAP at baseline. Although patients with diabetes were excluded from this trial, tirzepatide is currently approved for diabetes management in Canada, and could potentially impact AHI in patients with diabetes and OSA.[19]

Bariatric Surgery

Finally, bariatric surgery has demonstrated positive outcomes for patients with both OSA and T2D. In a small group of patients who underwent Roux-en-Y Gastric bypass surgery, their post-operative AHI scores, BMI, and fasting glucose were all improved when compared to their pre-operative values.[20]

The evidence from some of the above studies suggest that weight loss, whether achieved through behavioural, pharmacologic, or surgical interventions, can improve both OSA and T2D.[9,16,20] This is in line with a previous longitudinal study demonstrating that a 10% weight loss can significantly reduce OSA severity.[21]

Conclusions

OSA is commonly associated with T2D and is highly prevalent in-patient populations with T2D. Screening tools for OSA perform similarly in patient populations with or without T2D and should therefore be used to screen for this disease. Management of co-existing T2D and OSA requires a multi-modal approach to improve glycaemic control, AHI scores, and BMI, with the aim of reducing cardiovascular morbidity and mortality. This multi-modal approach can include non-pharmacologic, positive pressure, sleep device, pharmacologic and surgical therapies.

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A Practical Approach to the Incidental Adrenal Mass

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Dr. Neal E. Rowe is an assistant professor of surgery at the University of Ottawa and attending urologist at the Ottawa Hospital. He is extensively involved in urology training at both the medical school and residency program levels. His clinical and research interests include surgical adrenal disease, localized and advanced kidney cancer, and management of benign prostate enlargement.

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Introduction

With modern use of abdominal imaging, incidental detection of adrenal masses is increasingly common. These lesions are estimated to be present in 4% of all patients and in up to 10% of the elderly population.[1,2] Fortunately, most adrenal masses are benign non-functioning adenomas.[3] However, some of these lesions are hyperfunctioning or harbour malignancy. A familiarity with the evaluation and management of incidental adrenal masses is of interest to endocrinologists as well as surgeons and primary care providers who order abdominal imaging tests.

In 2023 a multidisciplinary working group of Canadian radiologists, endocrinologists, and radiologists published an updated guideline on the diagnosis, management, and follow-up of the incidentally discovered adrenal mass.[4] This publication has helped clarify the necessary imaging and biochemical testing required prior to creating a management plan for a patient with an incidental adrenal lesion.

When faced with an adrenal mass, the clinician must answer 3 essential questions: **1)** Is the mass benign or malignant? **2)** Is the mass hormonally functional or non-functional? **3)** How should the mass be managed?

Imaging Evaluation: Is the mass benign or malignant?

The first step in the evaluation of an adrenal mass is to establish if it is benign or malignant. Non-contrast CT of the abdomen is the most validated test for this purpose due to the well-established characteristics of benign lesions. A low-density lesion (<10 Hounsfield units [HU]) that is homogenous and well circumscribed can be confidently diagnosed as a benign adenoma. A retrospective cohort study that included 2219 adrenal incidentalomas determined the risk of finding adrenocortical carcinoma was 0% if the HU value was <10, 0.5% if the HU value was 10–20, and 6.3% if the HU value was >20.1 Similarly, masses with large areas of macroscopic adipose tissue can be diagnosed as a benign myelolipoma on CT.

Not all masses will have benign features on non-contrast CT and indeed many adrenal masses will be classified as indeterminate. Up to 30% of adrenal adenomas will have densities of >10 HU and exhibit characteristics that overlap with those of pheochromocytoma and malignant lesions.[5-7] If an adrenal mass is classified as indeterminate then further evaluation with contrast enhanced washout CT or chemical shift MRI is needed. Few studies have directly compared the two modalities, thus it is difficult

to recommend one modality over the other. However, there are limitations to both CT and MRI which are outlined in **Table 1**.

Endocrine Evaluation: Is the mass hormonally functional or non-functional?

Screening for adrenal hyperfunction is an important step in the evaluation of an incidental adrenal mass. Both benign and malignant entities can lead to elevated and autonomous production of adrenal hormones (cortical and medullary). Specific elements of the history and physical examination in addition to the radiological findings will dictate which adrenal hormones should be evaluated. Many patients will not require all of the various screening tests.

Many incidental adrenal masses can be confidently described as benign adenomas on initial imaging. In the absence of hypertension or hypokalemia, screening for primary aldosteronism can be omitted for such cases.[8-10] Similarly, observational studies support not screening for pheochromocytoma if the HU is <10 on a non-contrast CT scan.[11-13] A summary the patients who should be screened, and the recommended screening tests is included in **Table 2**.

Management of Incidental Adrenal Masses: Surgery, monitor or ignore?

A management plan for an adrenal mass is predicated on both the functional status and the malignancy risk. There is an opportunity to intervene surgically when needed while also avoiding unnecessary testing and follow-up in low-risk patients.

Surgery

Surgery is the treatment of choice for many functional and malignant lesions, although there are some patients who will not benefit from surgical excision. While patients with unilateral cortisol hypersecretion and signs and symptoms of Cushing's syndrome should undergo extirpative surgery, it is less clear whether patients should undergo surgery if their condition is subclinical.[14] Mild autonomous cortisol secretion can be associated with conditions such as diabetes, hypertension, and dyslipidemia, however, very few of these patients progress to Cushing's syndrome.[15] Surgery may impact some of these comorbidities but the impact is not as profound as when patients have the full constellation of Cushing's symptoms. To this end, the role of surgery in mild autonomous cortisol secretion (MACS) is on a case-by-case basis.

Patients with primary aldosteronism and unilateral hypersecretion often benefit from adrenalectomy. Several studies have confirmed that this surgery can lead to a substantial improvement or resolution of hypertension and hypokalemia. Adrenal vein sampling should be performed in all patients considering surgery since CT or MRI imaging can be discordant with the actual site of hypersecretion in 37.8% of cases.[10] Many cases of primary aldosteronism will display bilateral hypersecretion even in the presence of a unilateral adenoma.

Surgery is the treatment of choice for adrenal pheochromocytoma. Pre-operative patient preparation with pharmacologic alpha blockade is critical to limit the impact of catecholamine surges at the time of excision.

Adrenocortical carcinoma (ACC) is an aggressive malignant tumour of the adrenal gland. When localized, surgical excision is the only opportunity for cure.[16] All patients with suspected ACC limited to the adrenal gland should be considered for surgical resection. While minimally invasive surgery is likely safe for small lesions, large or locally advanced tumours often require open surgical approaches and concurrent lymphadenectomy.

Monitor

Historically, the size of an incidental adrenal mass was one of the main indications for surgical excision.[3] Retrospective studies show that most surgically treated malignant tumours (ACC and pheochromocytoma) were larger than 4 cm at the time of treatment.[17] Nonetheless, when an adrenal mass has benign features on CT, the final pathology is concordant regardless of the size of the lesion.[11] With this in mind, the Canadian Urological Association now recommends that radiologically benign masses >4 cm should undergo repeat imaging in 6–12 months rather than surgical excision.[4] If a mass grows more than 5 mm per year the patient should be offered adrenalectomy. If a radiologically benign mass has minimal growth (<3 mm per year) then no further follow-up is required.

A greater challenge is to manage a non-functional but radiologically indeterminate mass. While many of such lesions will ultimately have benign pathology, this cannot be confirmed with conventional imaging tests. Such circumstances require shared decision making between patients and providers. Management options include repeat imaging in 3–6 months or proceeding with surgical resection.

	CT	MRI
Advantages	Adenoma has a rapid contrast washout Adrenocortical carcinoma has less contrast washout	Can detect adenomas with high sensitivity and specificity No radiation or iodinated contrast agents
Limitations	False positives: 1/3 of lipid-poor adenomas do not exhibit the typical contrast washout in the adenoma range False negatives: 1/3 of pheochromoctyomas and some malignant lesions will exhibit the typical contrast washout in the adenoma range	Decreased performance on lesions with an unenhanced HU of >30 Cost/availability

Table 1. Advantages and limitations of CT and MRI; *courtesy of Neal Rowe, MD*.

Hormone Excess	Population	Tests	Interpretation	Ancillary Testing
Cortisol	All incidentalomas	1 mg Dexamethasone suppression test	≤50 nmol/L excludes cortisol hypersecretion 51–138 nmol/L possible autonomous cortisol secretion >138 nmol/L evidence of cortisol hypersecretion	ACTH testing (independency) 24-hour urinary-free cortisol, midnight salivary cortisol DHEAS
Aldosterone	Hypertension or hypokalemia	Aldosterone-to-renin ratio	20 ng/dL per ng/mL/hr, with a sensitivity and specificity of >90%	Saline suppression test Adrenal vein sampling for lateralization
Catecholamines	HU >10	24-hour urinary fractionated metanephrines Or Plasma free metanephrines	>2 times the upper limit of normal	N/A
Androgens	Virilization Suspected adrenocortical carcinoma	DHEAS, testosterone	Higher levels suggest a greater burden of disease	17β-estradiol, 17-OH progesterone, androstenedione, 17-OH pregnenolone, 11-deoxycorticosterone, progesterone, and estradiol

Table 2. Recommended screening tests for incidental adrenal masses; *courtesy of Neal Rowe, MD*.

Abbreviations: ACTH: adrenocorticotropic hormone, **DHEAS:** dehydroepiandrosterone sulfate, **HU:** Hounsfield unit

Ignore

Radiologic and hormonal evaluation of an incidental adrenal mass often confirms a small (<4 cm), benign (<10 HU) adenoma that is non-functioning. One study of over 2300 patients did not find any progression to malignancy if the initial workup identified an adrenal adenoma.[18] Similarly, in a large study of over 2000 such lesions, the risk of developing functionality was less than 2%.[19] Considering the very low rate of hormonal hypersecretion, it is reasonable to not subject such patients to routine hormonal screening. Overall, patients with small, benign, non-functional lesions do not require close follow-up and special testing. The main trigger for repeat evaluation would be symptoms or signs of hormone excess identified during routine medical history and physical examination.

Conclusions

Detection of an adrenal mass incidentally when imaging is performed for an unrelated indication is a common clinical circumstance. Fortunately, most incidental adrenal masses are non-functional and benign. However, a systematic evaluation of such lesions is paramount to rule out hormonal excess and to assess for malignant features. Patients with unilateral hormonal hypersecretion or suspected malignancy may benefit from timely surgical treatment.

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Finerenone in Diabetic Kidney Disease

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About the Author

Dr. Adam Cohn is a nephrologist in Ottawa. He completed medical school, residency and fellowship at the University of Ottawa. He is a staff physician at the Queensway-Carleton Hospital, and practices in private practice at JDC Medicine in Ottawa. His clinical focus is in diagnosis and management of non-dialysis CKD.

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Introduction

Diabetic kidney disease (DKD) affects 40% of individuals with diabetes mellitus (T2DM)[1] and is associated with an increased risk of cardiovascular events, hospitalization for heart failure, and premature death. Existing treatments focus on lifestyle measures, glycemic control, blood pressure and lipid management, inhibition of the renin-angiotensin-aldosterone system (RAAS), and the use of sodium glucose cotransporter 2 inhibitors (SGLT2-i).[2] However, substantial residual risk of progression to end-stage kidney disease (ESKD) or cardiovascular complications remain despite optimal therapy.[3] Finerenone, a non-steroidal mineralocorticoid antagonist (MRA), has been shown to reduce important outcomes when added to evidence-based therapies, and is approved by Health Canada as an adjunct to standard of care therapy in adults with chronic kidney disease (CKD) and T2DM to reduce the risk of ESKD and a sustained decrease in estimated glomerular filtration rate (eGFR), cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure.[4]

Mechanism of Action

Finerenone distinguishes itself from steroidal MRAs such as spironolactone and eplerenone through its "bulky" nonsteroidal structure, which confers high affinity and selectivity for the mineralocorticoid receptor.[5] By antagonizing aldosterone, finerenone mitigates its pro-inflammatory and pro-fibrotic effects on renal and cardiovascular tissues. In contrast to steroidal MRAs, the selective activity of finerenone causes fewer of the off-target, estrogen-related side effects such as gynecomastia.

Phase 2 Clinical Trials

The ARTS trial, a multicentre, randomized, parallel-group, Phase II study with double-blind placebo and open-label spironolactone comparator arms, enrolled patients with HFrEF and CKD (eGFR 30-90 mL/min/1.73 m^2).[6] The safety and tolerability of various doses of finerenone in patients with HFrEF and mild CKD were confirmed. The mean increases in serum potassium concentration were significantly smaller in the finerenone group than in the spironolactone group. GFR decreased significantly more in the spironolactone group than in the finerenone group. Systolic blood pressure (SBP) decreased significantly in the spironolactone group,

whereas in the finerenone group it remained similar to placebo. In another multicentre, randomized, double-blind, placebo-controlled, parallel-group trial of patients with T2DM with albuminuria who were receiving a RAS blocker, finerenone reduced the ratio of urine albumin-creatinine-ratio (UACR) at 90 days in a dose-dependent manner by up to 48%.[7] There was no significant change in eGFR or significant difference in adverse events between the groups. Twelve of 821 participants (who were all receiving finerenone) experienced serum potassium readings of at least 5.6 mmol/L, leading to discontinuation of study treatment.

Phase 3 Clinical Trials

FIDELIO-DKD[8] and FIGARO-DKD[9] were two large double-blind, randomized, placebo-controlled trials with complementary designs, aimed at investigating kidney-related and cardiovascular endpoints, respectively, in adult patients with T2DM and CKD (eGFR 25-90 mL/min/1.73 m^2 and uACR >30 mg/g) treated with maximum tolerated dose or RAAS inhibition. In the FIDELIO-DKD trial, 5734 patients with T2DM and CKD (mean eGFR: 44.3 ± 12.6 mL/min/1.73 m^2; median UACR: 852 mg/g) were randomized to finerenone or placebo. Patients randomized to finerenone experienced an 18% reduction in the primary endpoint (composite of kidney failure, a sustained decrease of at least 40% in the eGFR from baseline over a period of at least 4 weeks, or death from renal causes). Cardiovascular outcomes also occurred less commonly in the finerenone group compared to placebo. In FIGARO-DKD, 7437 patients with T2DM and less advanced CKD (mean eGFR: 67.8 ± 21.7 mL/min/1.73 m^2; median UACR: 308 mg/g) were randomized to finerenone or placebo. Finerenone reduced composite cardiovascular outcomes by 13% compared to placebo. The composite kidney outcome was reduced by 23% in the finerenone group compared to placebo.

The incidence of adverse events was similar in both active and placebo arms of both studies. The incidence of hyperkalemia was higher in the finerenone arms of both studies (18.3% vs 9.0%, 10.8% vs 5.3% respectively). There were no deaths attributable to hyperkalemia. A total of 2.3% and 1.2% of FIDELIO-DKD and FIGARO-DKD finerenone-treated participants discontinued the drug permanently because of hyperkalemia, compared to 0.9% and 0.4% in the respective placebo arms.

In a pre-specified meta-analysis of these two trials, FIDELITY, the combined data from these two trials was analyzed.[10] In the combined analysis, finerenone reduced cardiovascular outcomes by 14%. There was a 22% relative risk reduction in the incidence of hospitalization for heart failure and a 23% reduction in the composite kidney outcome. This included a 30% reduction in decrease of eGFR by ≥57% and a 20% reduction in ESKD.

Based on these studies, regulators and professional societies have recommended finerenone be used in addition to standard of care for reducing kidney and cardiovascular complications of DKD.

- **Kidney Disease:**
  Improving Global Outcomes (KDIGO) 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease: *Recommendation 1.4.1:* We suggest a nonsteroidal mineralocorticoid receptor antagonist with proven kidney or cardiovascular benefit for patients with T2DM, an eGFR ‡25 mL/min per 1.73 m^2, normal serum potassium concentration, and albuminuria (>30 mg/g [>3 mg/mmol]]) despite maximum tolerated dose of RAS inhibitor (RASi) (2A).[11]

- **American Diabetes Association.**
  Chronic Kidney Disease and Risk Management:
  Standards of Care in Diabetes 2024:
  Recommendation 11.5d: As people with CKD and albuminuria are at increased risk for cardiovascular events and CKD progression, a nonsteroidal mineralocorticoid receptor antagonist that has been shown to be effective in clinical trials is recommended to reduce cardiovascular events and CKD progression (if eGFR is ≥ 25 mL/min/1.73 m^2). Potassium levels should be monitored. A.[12]

Practical Aspects and Implementation

Finerenone has been studied as an add-on therapy on top of a maximally tolerated ACEi or ARB dose. For individuals with eGFR >60 mL/min/1.73 m^2 and a serum potassium ≤4.8 mmol/L, a 20 mg once daily dose is used. Serum potassium should be rechecked after 1 month, and periodically thereafter. For those with an eGFR >25 to <60 mL/min/1.73 m^2, and serum potassium ≤4.8 mmol/L, a 10 mg dose of finerenone is initiated. If the serum potassium remains below 4.8 mmol/L at one month, the dose is raised to the target 20 mg daily dose with a further recheck of potassium after one month and periodically thereafter. If potassium rises above 5.5 mmol/L in a 20 mg treated patient, the dose is usually reduced to 10 mg daily. If the serum potassium returns to acceptable levels the lower

eGFR (mL/min)	Starting Dose of Finerenone
>60 mL/min	20 mg
>25 to <60	10 mg
<25 mL/min	Not recommended

Table 1. Starting patients on finerenone; *courtesy of Adam Cohn, MD, FRCPC.*

Serum Potassium (mmol/L)	Current dose of finerenone of 10 mg	Current dose of finerenone of 20 mg
<4.8	Increase to 20 mg if eGFR has not decreased >30% vs. prior measurement	Maintain 20 mg
>4.8 to 5.5	Maintain 10 mg	Maintain 20 mg
>5.5	Withold. Restart at 10 mg if serum potassium <5.0 mmol/L.	Withhold. Restart at 10 mg if serum potassium <5.0 mmol/L

Table 2. Adjusting the dose of finerenone; *courtesy of Adam Cohn, MD, FRCPC.*

dose can be continued. It is advised that patients be counselled on sick day advice for finerenone and ACEi/ARB therapy. Serum potassium is rechecked at 4 months and periodically thereafter (**Tables 1 and 2**).

In both FIDELIO-DKD and FIGARO-DKD, patients were eligible to receive a SGLT2i at the discretion of the treating physician. For example, in the FIDELIO-DKD study, 259/5674 patients were taking an SGLT2i at study enrollment, and a further 328 patients initiated SGLT2i during the trial.[13] In those patients, the benefits of finerenone compared to placebo were similar with and without SGLT2i use. There were fewer hyperkalemia-related events with finerenone in the SGLT2i treated group (**Figure 1**).

Finerenone is well tolerated with few systemic side effects. There is a much lower incidence of gynecomastia compared to agents such as spironolactone or eplerenone.[14]

The starting dose is based on the patient's eGFR (**Table 1**).

Do not initiate if serum potassium is >5.0 mmol/L. If serum potassium >4.8 to 5 mmol/L, initiation may be considered with additional monitoring in the first 4 weeks based on patient characteristics and serum potassium levels.

Dose adjustments are based on the patient's serum potassium and eGFR. Check serum potassium 4 weeks after initiation, restart or dose adjustment, and periodically thereafter. For patients with renal impairment, measure eGFR 4 weeks after initiation to determine up titration (**Table 2.**).

Conclusion

Finerenone, a novel non-steroidal MRA, has been demonstrated to reduce albuminuria and preserve eGFR. In patients with T2DM and a wide range of eGFR and albuminuria levels, finerenone has reduced progression of CKD and the incidence of ESKD and has reduced the incidence of heart failure and cardiovascular outcomes in general. This medication is now recommended by numerous global guidelines to prevent progression of CKD and heart disease in this population, in addition to standard of care with a RAASi agent. It is safe and effective when used concurrently with a SGLT2i. Patients will require periodic monitoring of serum potassium levels, and dose adjustment will usually mitigate hyperkalemia. Finerenone is now part of the growing list of medications that have been shown to help patients living with T2DM and CKD prevent development of devastating complications such as progressive loss of kidney function, ESKD and heart failure.

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