

Hypoglycemia in type 2 diabetes

It is common, so what strategies can minimize the risk?

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Hypoglycemia is common in people with type 2 diabetes mellitus (T2DM) taking insulin, especially in the elderly population and in those with chronic kidney disease (CKD). This article delves into the evidence and clinical pearls that might help identify patients experiencing hypoglycemia and suggests some key strategies for drug-therapy modification to reduce this risk.

Case description

Judith is a 72-year-old woman whom you are seeing for the first time while working as a locum physician in a family medicine clinic. She reports having had T2DM for 20 years. She is concerned because most days she needs to eat a snack midafternoon and again a couple of hours after supper to prevent symptoms of hypoglycemia and her blood glucose levels decreasing below 4.5 mmol/L. This started a few months ago, and she is not happy with the associated weight gain. She also wakes during the night with sweats (“Just like when I went through menopause”) and feeling hungry. She usually goes back to sleep after having a glass of milk and crackers. She has no other new health concerns. Her recent blood glucose test results include the following: before breakfast or fasting, 5.4 to 9.8 mmol/L; before lunch, 5.3 to 8.4 mmol/L; before supper, 4.2 to 8.6 mmol/L; and at bedtime, 8.0 to 10.2 mmol/L. On further inquiry, Judith informs you that she received formal diabetes education 10 years ago when she started basal insulin; she has not seen an educator since then and was not aware that she could adjust her insulin doses. Her current diabetes medications (unchanged for the past couple of years) include 850 mg of metformin, twice daily; 26 units of insulin neutral protamine Hagedorn (NPH), twice daily in the morning and at bedtime; and 10 units of insulin lispro, 3 times daily before each meal.

Her other medical conditions include hypertension for more than 20 years; dyslipidemia; mild obesity (body mass index of 32.9 kg/m², weight of 80 kg, height of 156 cm); osteoarthritis of the hips, knees, and lumbar spine; chronic low back pain; diabetic nephropathy; stable nonproliferative diabetic retinopathy; and mild sensory diabetic peripheral neuropathy. She quit smoking 15 years ago. Judith lives on her own in an apartment; she performs all her activities of daily living, but physical activity is limited by her arthritis and chronic back pain. She uses a 4-wheeled walker when outside her apartment. She no longer drives. Her Clinical Frailty score is 5 (functionally dependent).¹

Other medications for Judith include 50 mg of chlorthalidone daily, 100 mg of losartan daily, 10 mg of amlodipine daily, 10 mg of rosuvastatin daily, acetaminophen as needed for back pain, 2000 IU of vitamin D daily, a daily multivitamin, 500 mg of glucose sulfate 3 times daily, and 500 mg of calcium carbonate daily.

Recent laboratory test results include normal findings for complete blood count, with a hemoglobin level of 110 g/L; normal electrolyte levels; a serum creatinine level of 149 µmol/L, with an estimated glomerular filtration rate (eGFR) of 30 mL/min; a urine albumin to creatinine ratio of 209.46 µg/mmol; a glycated hemoglobin A_{1c} (HbA_{1c}) level of 7.8%; a lipid profile including total cholesterol of 2.94 mmol/L, a triglyceride level of 1.09 mmol/L, a high-density lipoprotein level of 0.95 mmol/L, a low-density lipoprotein level of 1.49 mmol/L, and a non-high-density lipoprotein level of 1.99 mmol/L; and a thyroid-stimulating hormone level of 2.87 mIU/L. Reviewing the provincial laboratory result database you note that HbA_{1c} results have been in the 7.8% to 8.5% range in the past 2 years, and eGFR has declined from 45 mL/min 12 months ago to 30 to 34 mL/min on 3 tests in the past 6 months. Her creatinine clearance is 38 mL/min.

Why is Judith experiencing hypoglycemia, and how would you address her concerns?

Bringing evidence to practice

Hypoglycemia in people with T2DM. Historically, academic literature has focused on hypoglycemia in insulin-deficient type 1 diabetes.²⁻⁴ However, hypoglycemia is common in T2DM; it occurred in at least 63% of Canadian adults with T2DM using insulin in retrospective and prospective 6-month cohort studies.^{5,6} Hypoglycemia limits the ability to achieve optimal glycemic control in many patients requiring insulin therapy, and severe hypoglycemia is associated with increased morbidity and mortality particularly in the elderly.^{7,8} While some weight gain is expected with insulin therapy owing to the anabolic effects of insulin, excessive or rapid weight gain is often the result of an individual consuming extra carbohydrates to treat or prevent low glucose values (“feeding the insulin”) or overeating in response to the severe hunger associated with hypoglycemic episodes.⁷⁻¹⁰

Addressing key factors. Numerous factors are associated with an increased risk of hypoglycemia in adults using

insulin to treat T2DM (**Box 1**).^{4,11} While some of these are nonmodifiable risk factors, health care providers can play an important role in mitigating the risk of hypoglycemia by being aware of these factors, adjusting and individualizing glucose-lowering therapies, and ensuring access to diabetes self-management education (**Box 1**).^{4,11}

Renal insufficiency. The kidneys are involved in the degradation and excretion of insulin. As glomerular filtration rate declines below 45 mL/min, there is reduced clearance of both endogenous and exogenous insulin and an increased risk of hypoglycemia.^{9,12} Clinically this becomes more important as eGFR approaches 30 mL/min, necessitating a reduction in the total daily dose of exogenous insulin and an adjustment of dose or injection times of individual insulins, or both, to minimize insulin stacking.¹⁰

Physiologic insulin replacement. Insulin secretion by a normal pancreas has 2 components: basal (continuous secretion of small amounts of insulin not related to food) and bolus (spike in insulin secretion to deal with rises in blood glucose from food). When insulin-replacement therapy is used by an individual who is insulin deficient, guidelines suggest that the treatment regimen should mimic physiologic insulin action, with a basal insulin component of approximately 40% to 50% of the total daily insulin (TDI) and a prandial insulin component of 50% to 60% of the TDI divided and administered before meals.¹³⁻¹⁵ A high basal insulin dose might increase the tendency for hypoglycemia, particularly in individuals with CKD, although clinical trial data are limited.^{15,16}

Recognition, risk reduction, and management of hypoglycemia. All individuals taking insulin should be educated about the risk, prevention, recognition, and treatment of hypoglycemia.^{11,12,17} In addition, health care providers should consider asking about symptoms of hypoglycemia at diabetes-related visits, particularly if an individual has any of the factors listed in **Box 1**.^{4,11} This can be done in many ways. One approach involves asking screening questions about hypoglycemia and adding up risk factors for hypoglycemia (the RxFiles Perspectives on Hypoglycemia Risk Assess & Address Chart is available from **CFPlus***).

Some strategies to minimize the risk of hypoglycemia will be covered in our case discussion; others include relaxing HbA_{1c} targets, assessing insulin injection technique, and minimizing the use of oral medications associated with hypoglycemia (eg, sulfonylureas). See **CFPlus*** for more information.

*The RxFiles Perspectives on Hypoglycemia Risk Assess & Address Chart is available at www.cfp.ca. Go to the full text of the article online and click on the **CFPlus** tab.

Back to Judith

You review with Judith her recent laboratory test results, explaining that while her overall glycemic control (HbA_{1c} of 7.8%) is appropriate for her age and comorbidities (Clinical Frailty score of 5), the frequent episodes of mild hypoglycemia are causing her to gain weight and wake up at night. This needs to be addressed urgently to prevent an episode of severe hypoglycemia that could result in a fall, confusion, seizure, cardiac ischemia, or arrhythmia. You also explain the nature of her progressive CKD and why this necessitates adjustment of her diabetes medications to minimize hypoglycemia and the adverse events from the accumulation of metformin.

Modification of her insulin regimen is required to achieve a reduction in TDI dose in view of her renal insufficiency and to adjust the proportion of basal and prandial insulins to mimic physiologic insulin action. There are several ways to do this. Often a stepwise approach is best so that there are not too many changes at once. Judith's basal insulin is currently 63% of the TDI dose (52 units of insulin NPH), while her prandial insulin is 37% of the TDI dose (30 units insulin lispro). An initial step would be reducing the dose of basal insulin by at least 20% to eliminate nocturnal hypoglycemia and reduce the need to eat in between meals. While you would like to also switch her insulin NPH to a long-acting insulin analogue, Judith informs you that she has 6 cartridges of insulin

Box 1. Factors associated with higher risk of hypoglycemia in nonpregnant adults with T2DM treated with insulin

The following factors are associated with a higher risk of hypoglycemia:

- Previous episode of severe hypoglycemia
- Being elderly or frail
- Cognitive impairment
- Renal insufficiency
- Low HbA_{1c} (<6.5%)
- Long duration of diabetes (insulin deficient)
- Autonomic neuropathy
- Food insecurity or an erratic eating pattern
- Low health literacy or minimal diabetes education and self-management skills
- Insulin regimen does not mimic physiologic insulin action (basal insulin component too high)
- Prandial (meal-time) insulin with doses not adjusted for physical activity, reduced carbohydrate intake, or skipping meals
- Weight loss with no adjustment to glucose-lowering medications
- Withdrawal of medications that raise blood glucose, such as corticosteroids

HbA_{1c}—hemoglobin A_{1c}, T2DM—type 2 diabetes mellitus. Data from Amiel et al⁴ and Yale et al.¹¹

NPH at home and she cannot afford to waste these. Therefore, your initial recommendation is to reduce her insulin NPH to 20 units twice daily and continue with the same dose of insulin lispro. You suggest that she continue monitoring her blood glucose at home and schedule a follow-up appointment in 1 week.

You provide Judith with a handout on the recognition and treatment of hypoglycemia and suggest a prescription for glucagon for treatment of severe hypoglycemia. She informs you that she cannot afford nasal glucagon, and she does not feel that she would be able to manage a glucagon injection. You refer Judith to the local diabetes nurse educator, requesting a review of insulin injection technique and insulin adjustment for meals and activity.

In view of Judith's advanced CKD, her metformin dose should be reduced to 500 mg twice daily. You provide a new prescription, noting the reason for the dose reduction and her current eGFR (30 to 34 mL/min) so that her pharmacist has this information.¹⁸ In addition, you arrange a nephrology consultation and provide Judith with a patient handout on sick-day management so that she is aware of the importance of holding metformin, chlorthalidone, and losartan if she develops any acute illness or dehydration.¹⁹

The following week Judith reports that she has had no further nocturnal symptoms, but she still requires a snack in the late afternoon to prevent her blood glucose levels dropping below 4.5 mmol/L.

Therefore, you reduce her morning dose of insulin NPH by a further 20%, to 16 units. Telephone follow-up a week later confirms that this dose reduction has resulted in no further symptoms of hypoglycemia. A follow-up visit is scheduled to consider changing her basal insulin.

Would switching Judith's basal insulin reduce her hypoglycemia risk?

Bringing evidence to practice

Another strategy to minimize the risk of hypoglycemia is the selection of basal insulin. Basal insulins differ in their pharmacokinetic or action profiles. Insulin NPH action peaks between 4 and 10 hours, which might lead to hypoglycemia in some patients, commonly in the early hours of the morning or in the afternoon or early evening, as in Judith's case, where prandial insulin is administered with all meals in addition to twice-daily insulin NPH.⁹ Long-acting insulin analogues, with the exception of insulin detemir, are considered to be nonpeaking.²⁰

Insulin glargine and insulin detemir reduce overall and nocturnal hypoglycemia compared with insulin NPH; however, severe hypoglycemia risk has been shown not to be different.²¹⁻²³ Newer insulin analogues, such as insulin glargine (300 units/mL) and insulin degludec appear to provide a small additional benefit over insulin glargine for nocturnal and overall hypoglycemia.²⁴⁻²⁶ Severe hypoglycemia is not consistently lowered.²⁵ **Table 1** provides head-to-head,

overall hypoglycemia rates among basal insulins.^{21,24,25} These trials were open-label (ie, unblinded), which might affect assessment of hypoglycemia, as this outcome can be subjective and was not always confirmed by blood glucose testing. Furthermore, most trials had aggressive glycemic targets (eg, fasting blood glucose of 4 to 5 mmol/L), and patients were typically younger than 65 years of age, which limits generalizability, especially to older adults like Judith. Based on the evidence and clinical experience, it is reasonable to switch from insulin NPH to long-acting insulin analogues in adults who experience hypoglycemia or who have risk factors for severe hypoglycemia (eg, elderly, frail, renal insufficiency), while balancing potential disadvantages such as higher costs. Switching insulin involves temporarily increased blood glucose monitoring and patient education. Often decreasing the insulin dose by 20% is required, as it is safer to underestimate and titrate.²⁷

Back to Judith

While Judith is no longer experiencing symptoms of hypoglycemia, she does have multiple risk factors placing her at high risk of severe hypoglycemia in the future. Switching from insulin NPH to a long-acting insulin analogue will be more expensive for her but has the advantage of only 1 injection per day and might result in a small reduction in her risk of hypoglycemia.²⁸ Based on this discussion, Judith decides to switch to a long-acting analogue and the following is implemented²⁸:

- Insulin NPH is discontinued (16 units in the morning and 20 units at bedtime) and switched to insulin glargine (29 units once daily; this equates to a 20% dose reduction of the 36 units of NPH per day).²⁷
- Basaglar, a biosimilar insulin glargine product, is selected because it is available in a KwikPen, which Judith uses for her rapid-acting insulin, and it is the least expensive long-acting analogue.
- You ask Judith to do more intensive blood glucose monitoring once again and maintain close follow-up with the diabetes educator so that she can guide ongoing insulin adjustment if needed.

Table 1. Head-to-head overall hypoglycemia rates among basal insulins

COMPARATOR	OVERALL HYPOGLYCEMIA RESULTS
CADTH meta-analysis ²¹	<ul style="list-style-type: none"> • NPH: 55.9% • Glargine: 47.2% • NNT = 12 over 6-12 mo
EDITION meta-analysis ²⁴	<ul style="list-style-type: none"> • 100 units/mL glargine: 72.8% • 300 units/mL glargine: 66.5% • NNT = 16 over 6 mo
SWITCH 2 trial ²⁵	<ul style="list-style-type: none"> • 100 units/mL glargine: 31.6% • Degludec: 22% • NNT = 11 over 7 mo
CADTH—Canadian Agency for Drugs and Technologies in Health, NNT—number needed to treat, NPH—neutral protamine Hagedorn.	

Conclusion

Any episode of hypoglycemia, irrespective of severity, should be addressed with a thoughtful approach that includes identification of causative or contributing factors, adjustment of glucose-lowering therapies, information for the patient and caregivers or family members on recognition and treatment of future episodes of hypoglycemia, and referral for additional diabetes education. ✨

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