

CLINICAL PRACTICE UPDATE IN
ENDOCRINOLOGY & DIABETES**LMC**

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**HYPOGLYCEMIA IN DIABETES:
A DISCUSSION OF THE HIGHS AND
LOWS IN CANADA****ONTARIO**

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Hypoglycemia is an undesired consequence associated with the use of sulfonylureas and insulin in the management of people with diabetes. Ultimately, our primary goal of preventing diabetes-related complications which entails achieving target glycemic levels and minimizing hypoglycemia. In reality, this challenge of finding the correct balance is an art as much as it is a science. This review will discuss hypoglycemia, focussing on severe hypoglycemia, and its associated morbidity on Canadians living with diabetes. Furthermore, it will address current strategies to treat severe hypoglycemia.

DEFINITION

Minor hypoglycemia is defined by the presence of autonomic symptoms and moderate hypoglycemia is based on the presence of autonomic and neuroglycopenic symptoms. In severe hypoglycemia, the individual is not capable of identifying or treating the episode themselves, and third-party assistance is required. The glucose values by which mild, moderate and severe hypoglycemia are classified vary, but generally severe hypoglycemia does not occur unless the glucose is < 2.8 mmol/L.

FREQUENCY OF HYPOGLYCEMIA: THE INTERNATIONAL HAT STUDY

The Hypoglycemia Assessment Tool (HAT) trial was a non-interventional, multicentre, 6-month retrospective/4-week prospective investigation of hypoglycemic events conducted during 2012–2013 at 2004 sites in 24 countries across six regions. Consecutive adult participants were enrolled during routine clinical consultation if they had Type 1 (T1D) or Type 2 diabetes (T2D) and were treated with insulin for >12 months. Hypoglycemia data was based on self-assessment questionnaires and patient diaries amongst 27,585 people with diabetes. The primary endpoint was the proportion of patients experiencing > 1 hypoglycemic event during the 4-week prospective observational period. They found that 83.0% of patients with T1D and 46.5% of patients with T2D self-reported hypoglycaemia. Rates of any, nocturnal and severe hypoglycaemia were 73.3, 11.3 and 4.9 events/patient year for T1D and 19.3, 3.7 and 2.5 events/patient year for T2D, respectively.

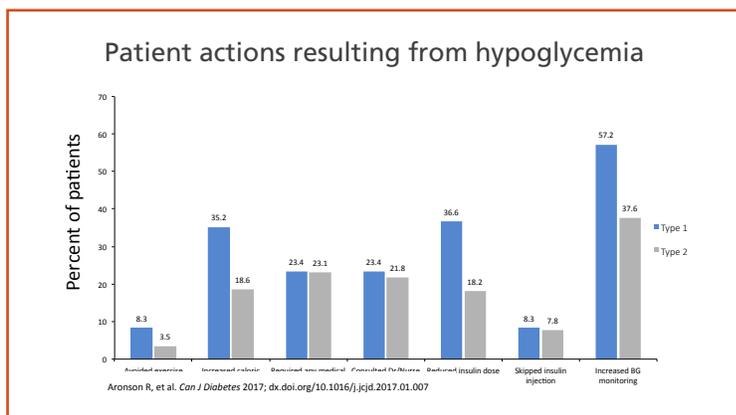
"...hypoglycemia is common in people with diabetes treated with insulin, and severe hypoglycemia can occur in both people with T1D and T2D."

The results of the HAT trial revealed that hypoglycemia is common in people with diabetes treated with insulin, and severe hypoglycemia can occur in both people with T1D and T2D.

FREQUENCY OF HYPOGLYCEMIA: CANADIAN DATA

An analysis of the subset of Canadian patients from the HAT study included 183 people with T1D and 315 people with T2D. Hypoglycemia was reported in 95.2% of people with T1D and 64.2% with T2D. Prospective rates of any, nocturnal and severe hypoglycemia were 69.3, 14.2, and 1.8 events per patient-year.

The In-Hypo DM study is a real world study of 552 people with T1D and T2D taking insulin and/or sulfonylureas in Canada who completed a questionnaire evaluating symptomatic hypoglycemia. The annualized severe hypoglycemia rate was 2.4 events per person-year with T1D (n=94) and 2.5 in people with T2D (n=456).



In the Canadian sub-study of the HAT trial, we gained a better understanding of how hypoglycemia can lead to undesirable choices that may adversely affect the health of the person with diabetes. During the 4 week prospective component of this trial, hypoglycemia resulted in 5.2% of patients avoiding exercise, 7.9% skipping insulin doses, 24.6% increasing caloric intake, and 24.8% reducing their insulin dose (Figure 1).

Patient Characteristics	Environmental Factors
Previous severe hypoglycemia	Missing meals / smaller quantity
Chronic kidney disease	Exercise
Low economic status - food access	Alcohol
Low health literacy	Errors in insulin administration
A1c <6.0%	Type of insulin
Age (preschool, adolescence, elderly)	
Pregnancy	
Cognitive impairment	
Meds that mask symptoms of hypoglycemia (eg beta blockers)	
Hypoglycemia unawareness	
Long duration of insulin use	

The approximate cost of hypoglycemia in Canada is about \$2,900 per person based on a mean annual cost of hospitalizations, clinic visits, and work absenteeism. About half of the severe hypoglycemia episodes that occur in people with T2D in Canada require medical assistance. Hypoglycemia and severe hypoglycemia also significantly impact driving, but this topic is beyond the scope of this review.

These studies demonstrate that hypoglycemia is common, perhaps more common than we suspected in Canada, in people with diabetes, and that severe hypoglycemia does occur in both people with T1D and T2D.

PREDICTORS OF HYPOGLYCEMIA

There are certain factors that increase the likelihood of developing severe hypoglycemia. Some of these are based on patient characteristics and others on environmental factors.

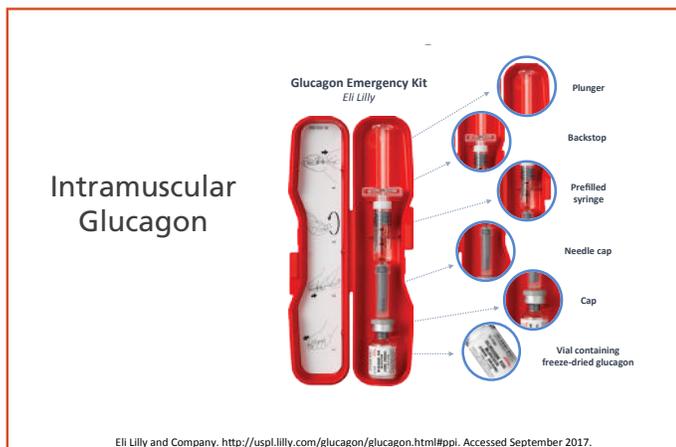
MORBIDITY OF HYPOGLYCEMIA

Hypoglycemia is a significant issue for people living with diabetes and this is especially true for any person that has experienced an episode of severe hypoglycemia. A Canadian study showed that about 64% of people with T1D (n=55) and 84% of people with T2D (n= 19) who had a prior episode of severe hypoglycemia developed a fear of future hypoglycemia.

It appears that hypoglycemia invokes a profound behavioural response, swinging the pendulum the other way, resulting in people avoiding subsequent hypoglycemia at all costs, consequential undesirable healthy choices, and hyperglycemia with associated complications. Severe hypoglycemia leads to important financial, psychological and physiological morbidity.

TREATMENT OF SEVERE HYPOGLYCEMIA

In a person that can swallow safely, it is recommended to ingest 20 g of simple carbohydrate for severe hypoglycemia. Close glucose monitoring is important as further treatment with more carbohydrates for refractory hypoglycemia may be necessary, plus a snack/meal following the event once euglycemia is restored to prevent rebound hypoglycemia. In people with a decreased level of consciousness, the administration of glucagon is recommended followed by carbohydrate ingestion once safe to swallow. This is usually accompanied by the assistance from emergency medical services. It is also important that all people who experience a severe hypoglycemia episode discuss this event with their medical team.



Eli Lilly and Company. <http://uspl.lilly.com/glucagon/glucagon.html#ppi>. Accessed September 2017.

GLUCAGON - INTRAMUSCULAR [Figure 2]

Even though severe hypoglycemia can occur in anyone with diabetes being treated with insulin and/or sulfonylureas, often health care professionals do not prescribe glucagon. This is especially true for people with T2D, even when managed with basal-bolus insulin regimens.

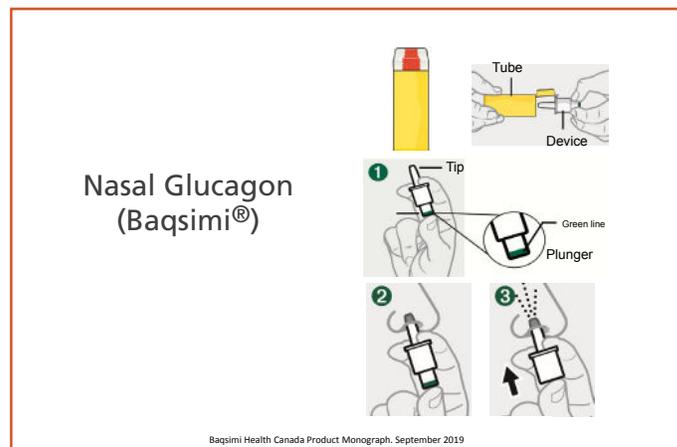
Intramuscular glucagon requires reconstitution, preparation of the correct dose (1 mg), and administration by a third party. Ideally, the person who is administering the intramuscular glucagon should be trained to ensure the delivery is done properly and quickly, although this is seldomly the case. The intramuscular glucagon powder, before reconstitution, has a shelf life of about 3 years.

GLUCAGON- INTRANASAL [Figure 3]

A novel preparation of glucagon has now become available in Canada. This preparation is 3 mg and is administered intranasally (Baqsimi®). It has a shelf life of about 18 months. A randomized, crossover noninferiority trial in people with T1D experiencing hypoglycemia comparing the two different glucagon preparations showed that intranasal glucagon was as successful as intramuscular glucagon in restoring a plasma glucose > 3.9 mmol/L or increasing glucose > 1.1 mmol/L from its lowest value within 30 minutes of administration. There were more headaches/ facial stuffiness (25% vs 9%) and nasal symptoms (18% vs 1%) with intranasal glucagon compared with intramuscular glucagon.

A simulation study comparing intramuscular and intranasal glucagon administration found that nasal glucagon resulted in a faster administration and fewer failures using intranasal glucagon amongst both trained and untrained caregivers/acquaintances. Even people already accustomed to administering insulin injections found it easier to deliver glucagon intranasally than intramuscularly.

“nasal glucagon resulted in a faster administration and fewer failures using intranasal glucagon amongst both trained and untrained caregivers/acquaintances.”



Baqsimi Health Canada Product Monograph. September 2019

CONCLUSIONS

Hypoglycemia is a major source of anxiety and fear in people living with diabetes. This fear is accentuated after episodes of severe hypoglycemia. The morbidity associated with severe hypoglycemia is profound and can significantly affect an individual's health through psychological, behavioural and physiological mechanisms. It is important to identify modifiable factors based on both individual and environmental factors leading to severe hypoglycemia. The primary goal is to prevent subsequent episodes. It is important for health care professionals to educate people with diabetes and their caregivers about hypoglycemia and severe hypoglycemia with an emphasis on recognition, prevention and treatment. For severe hypoglycemia, glucagon is an often essential and life-saving treatment. It is essential for health care professionals to ensure that prescriptions are given to appropriate patients. Nasal glucagon is a new, innovative and simpler way of administering glucagon that is proven to be as effective as intramuscular glucagon for treating severe hypoglycemia episodes.

References:

1. Diabetes Canada Clinical Practice Guidelines Expert Committee. Can J Diabetes. 2018
2. Khunti K et al. Regional variations in definitions and rates of hypoglycaemia: findings from the global HAT observational study of 27 585 people with Type 1 and insulin treated Type 2 diabetes mellitus. Diabet Med. 2018
3. Aronson R et al. The Canadian Hypoglycemia Assessment Tool Program: Insights In to Rates and Implications of Hypoglycemia From an Observational Study. Can J Diabetes. 2018
4. Ratzki-Leewing A et al. Real-world crude incidence of hypoglycemia in adults with diabetes: Results of the InHypo-DM Study, Canada. BMJ Open Diabetes Res Care. 2018
5. Leiter LA, et al. Assessment of the impact of fear of hypoglycemic episodes on glycemic and hypoglycemia management Can J Diabetes. 2005
6. O'Reilly et al. Direct Health-Care Costs and Productivity Costs Associated With Hypoglycemia in Adults With Type 1 and Type 2 Diabetes Mellitus That Participated in the Canadian Hypoglycemia Assessment Tool Program. Can J Diabetes. 2005
7. My Health Alberta website. Topic Overview page, Diabetes: How to give glucagon. Last updated July 25, 2018. Available at: <https://myhealth.alberta.ca>.
8. Rickels MR et al. Intranasal Glucagon for Treatment of Insulin-Induced Hypoglycemia in Adults With Type 1 Diabetes: A Randomized Crossover Noninferiority Study. Diabetes Care. 2016
9. Yale JF et al. Faster Use and Fewer Failures with Needle-Free Nasal Glucagon Versus Injectable Glucagon in Severe Hypoglycemia Rescue: A Simulation Study Diabetes Technol Ther. 2017

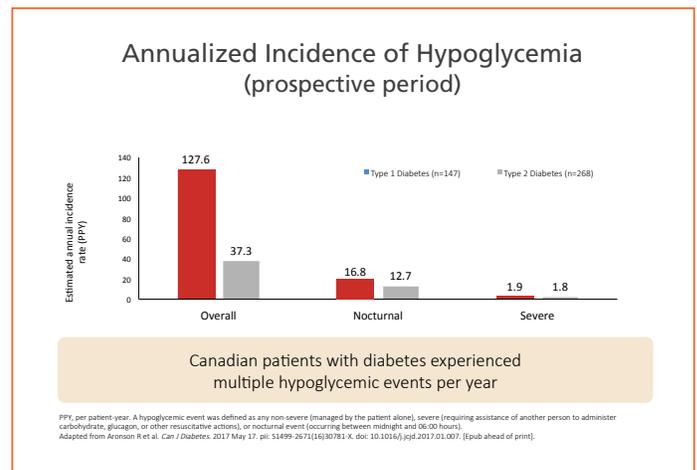
AUTHORS' PERSPECTIVES: HYPOGLYCEMIA TODAY



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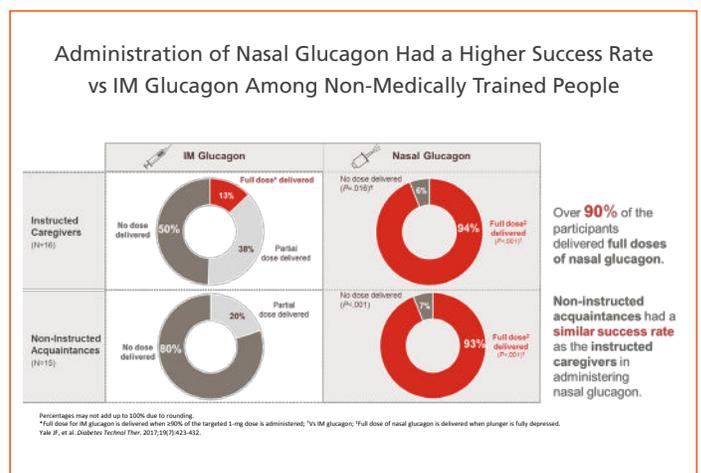
The Canadian Hypoglycemia Assessment Tool (HAT) trial discovered that among insulin-users, when they're allowed to report anonymously, hypoglycemia is much more frequent than we'd previously understood from clinical trials: over 120 events per patient-year for those with T1D and nearly 40 events per patient-year for those with T2D. We also identified that fear of hypoglycemia is very high with 20% of the participants reporting a their fear at a "terrified" level, especially if they'd already experienced a severe hypoglycemia event.

The HAT study also provided unique new insights into how people respond to hypoglycemia – of any type. Nearly a quarter of participants required medical assistance and/or consulted their healthcare provider and the same proportion went on to either increase their caloric intake and/or avoid physical exercise and nearly 80% skipped a subsequent insulin injection or reduced their insulin dose for some period of time. Most prominently, healthcare cost burden perspective, nearly half of participants increased their blood glucose monitoring after hypoglycemia by up to 5 additional tests per day.



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A Simulation Study

We assessed whether caregivers of people with diabetes trained in the use of injectable glucagon and nasal glucagon (in random order), or untrained acquaintances, were able to administer these drugs when exposed to a simulation with a manikin. We were surprised to view the difficulties in giving injectable glucagon experienced by caregivers trained 2 weeks prior. The difficulties went from injecting the diluant liquid alone, breaking the needle in the process, not diluting completely the glucagon powder before recovering the glucagon, and even injecting insulin rather than glucagon. Nasal glucagon was much easier to administer, even by untrained people (Figure 4). The only error with nasal glucagon was not pushing the plunger fully to initiate the puff.



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