CME

Selected topics of hypoglycemia care

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ABSTRACT

OBJECTIVE To review 4 topics in hypoglycemia (HoG) care: diagnosis, circumstances predisposing to HoG, risk of adverse effects, and prevention.

QUALITY OF EVIDENCE MEDLINE was searched using the words hypoglycemia and diabetes mellitus. Other relevant sources were hand searched. Evidence was mostly level III and IV from consensus, from observation, and from the author's clinical experience.

MAIN MESSAGES Hypoglycemia can be diagnosed using clinical criteria or using a glucometer; it cannot be diagnosed after death. Capillary blood glucose testing for HoG is required only for patients taking insulin and insulin secretagogues. With intensified treatment of diabetes, a greater incidence of HoG is inevitable. Chronic morbidity and mortality resulting from HoG are believed to be rare. There are no reliable data on HoG-related mortality for idiopathic or accidental sudden death. Interventions by friends, family, colleagues, and teachers can prevent HoG.

CONCLUSION Clinical diagnosis of HoG deserves greater emphasis; when patients are unaware of having HoG, physicians must rely on blood glucose testing. Patients not taking insulin or insulin secretagogues need neither fear nor test for HoG. The risk of HoG should not preclude efforts to achieve best possible control of blood sugar. Patients with unstable cardiac arrhythmias, drivers of motor vehicles, and those in high-risk industrial occupations require special vigilance for HoG.

RÉSUMÉ

OBJECTIF Faire le point sur 4 aspects de l'hypoglycémie (HoG): diagnostic, prévention, circonstances favorisantes et effets indésirables potentiels.

QUALITÉ DES PREUVES Une recherche a été effectuée dans MEDLINE à l'aide des mots *hypoglycemia* et *diabetes mellitus*. D'autres données pertinentes ont également été tirées de la littérature. Les preuves étaient surtout de niveau III et IV et provenaient de consensus, d'observation et de l'expérience clinique de l'auteur.

PRINCIPAL MESSAGE L'hypoglycémie peut être diagnostiquée à partir de l'expérience clinique ou au moyen du glucomètre; le diagnostic est impossible après la mort. Le dosage du glucose dans le sang capillaire n'est requis que pour les patients qui reçoivent de l'insuline ou des sécrétagogues de l'insuline. Un traitement plus agressif du diabète entraîne inévitablement une plus grande incidence d'HoG. On croit que l'HoG est rarement responsable de décès ou de morbidité chronique. Il n'existe aucune donnée fiable permettant d'attribuer des morts subites accidentelles ou idiopathiques à l'HoG. Amis, parents, collègues et professeurs peuvent aider à prévenir l'HoG.

CONCLUSION Il faut porter plus d'attention au diagnostic clinique de l'HoG; quand le patient ignore qu'il fait de l'HoG, le médecin doit se fier au dosage de la glycémie. Les patients qui ne prennent ni insuline ni sécrétagogues de l'insuline n'ont pas à craindre l'HoG ni à subir de test pour cette condition. Le risque d'HoG ne devrait pas entraver les efforts visant à optimiser le contrôle de la glycémie. Pour ceux qui souffrent d'arythmie cardiaque instable, qui conduisent des véhicules automobiles ou qui occupent des emplois industriels à haut risque, une surveillance particulière de l'HoG s'impose.

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The introduction of insulin into diabetes care in 1921 had 3 consequences: diabetics survived much longer; longer survival led to diabetes-specific retinopathy, nephropathy, and neuropathy and to a greater risk of macrovascular disease; and some clinical observers soon realized that these "late complications" were directly related to the quality of blood glucose control but that hypoglycemia (HoG) set a limit to the pursuit of euglycemia. The response of physicians at the time was to realize that understanding and dealing with HoG was a prerequisite for intensive treatment of diabetes and that HoG in informed patients could be managed.[1-3]

The Diabetes Control and Complications Trial[4] and the United Kingdom Prospective Diabetes Study[5] confirmed the importance of tight glycemic control. But as intensive treatment became more widely accepted and type 2 diabetes in affluent societies assumed epidemic proportions, HoG emerged as a renewed concern.[6-10] Several comprehensive reviews of HoG encountered in care of patients with diabetes have recently been published.[11-14]

The care of an estimated 1.5 million diabetic patients in Canada rests to a large extent with family physicians.[15,16] This paper addresses 4 arbitrarily selected but common concerns in HoG care: diagnosis of HoG, circumstances predisposing to HoG, risks of adverse effects of HoG, and prevention of HoG. It addresses relevant clinical problems surrounding HoG care that tend to be neglected. The information is directed not only at physicians and educators but also at patients, as many patients are motivated and quite capable of learning how to deal with HoG. Some of the tables in this paper could serve as patient handouts.

Quality of evidence

MEDLINE was searched using the key words hypoglycemia and diabetes mellitus for articles on HoG. Information in this paper is based on the articles found and also on the author's clinical experience. The term "hypoglycemia" is restricted to mean low blood glucose as an adverse event during treatment of diabetes with insulin or insulin secretagogues (I/IS). "Hypoglycemia unawareness" means a patient's clinical unawareness of HoG due to advanced late complications. A comprehensive review of HoG in diabetes can be found in the Canadian Diabetes Association's 2003 clinical practice guidelines.[17]

Diagnosis of hypoglycemia

There are 2 ways to diagnose HoG. One is by measuring capillary blood glucose (CBG). Capillary whole-blood glucose concentration as measured by current glucometers is adjusted to a level identical to venous serum glucose. The digital result seems accurate, but is not quite as accurate as it might seem[18] because there is no "accurate" numerical definition of HoG.[19,20] Also, CBG meters are at best accurate only to within ±15%,[21] and might be broken or used incorrectly by patients. In addition, emerging HoG can impair testing skills. Current clinical practice guidelines by consensus define HoG as CBG <4.0 mM/L. But some diabetics experience symptoms at higher CBG values, while nondiabetics might have values that are lower than 4.0 mM/L. Hypoglycemia is more than just low CBG levels; it is usually associated with typical clinical symptoms and signs.[22]

Another way to diagnose HoG is to use modified Whipple's criteria. In 1935, Whipple and Franz[23] suggested criteria for the diagnosis of HoG: clinical symptoms, low blood glucose levels, and relief through nourishment. These criteria still apply in a wider sense to patients treated with I/IS. Patients ought to be thoroughly familiar with the 3-step modification of these criteria (**Table 1**[23]): awareness of risky situations,

Table 1. Three-step method for clinical diagnosis of hypoglycemia

1. ARE YOU AT RISK OF HYPOGLYCEMIA?
• Did you delay or miss a meal or snack?
• Have you been more physically active than usual?
• Has the dose of any medication been raised or a new one added?
• Did you drink alcohol?
2. DO YOU EXPERIENCE "YOUR" SYMPTOMS MOST COMMONLY BY FEELING ANY OF THE FOLLOWING?
• Sweaty
• Shaky
• Hungry
• Weak or moody or confused
3. AS SOON AS YOU REALIZE THE RISK AND SENSE "YOUR" SYMPTOMS
• Take immediate nourishment that contains sugar. Do not delay by trying to call for help or by testing. Trust your senses. You cannot do any harm, even if you are wrong, but you might become unable to act if you delay. The quickest and most practical treatment is 3 dextrose tablets (5 g each, available in drugstores without prescription). Take 3 more in 15 minutes if necessary. Combination therapy with acarbose requires that you take dextrose (glucose, a monosaccharide) rather than table sugar (sucrose, a disaccharide) because acarbose inhibits the conversion of sucrose to glucose.
• You should feel better, usually within minutes. That confirms your diagnosis.
• Add 1 starch (eg, 6 soda crackers) for every half hour left until your next meal.
• Do not overtreat. Too much sugar could raise blood sugar excessively and leave you in doubt over what to do at the next regular test time.

Adapted from Whipple and Frantz.[23]

Levels of evidence

Level I: At least one properly conducted randomized controlled trial, systematic review, or meta-analysis
Level II: Other comparison trials, non-randomized, cohort, case-control, or epidemiologic studies, and preferably more than one study
Level III: Expert opinion or consensus statements

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knowledge of "personal" symptoms, and obtaining relief by ingesting sugar.

Self-monitoring of CBG is not a substitute for lack of knowledge of the modified criteria when dealing with HoG. Both have their place for diagnosing HoG in patients treated with I/IS. Among patients who have HoG unawareness or who are in high-risk occupations, CBG testing is, of course, mandatory. Incidentally, CBG testing is currently the most accepted way for all diabetics to monitor *hyper*glycemia.

Postmortem diagnosis of hypoglycemia

The sudden death of a diabetic patient treated with I/IS creates a unique diagnostic problem. Retrospective, postmortem diagnosis of HoG as a cause of, rather than incident to, idiopathic or accidental sudden death cannot at this time be proved by testing glucose levels in blood or spinal or vitreous fluid.[24] The morphologic changes in brain tissue caused by HoG, epilepsy, or ischemia are hard to distinguish from one another.[25,26]

Until reliable methods of diagnosing fatal HoG become available, the probability that death was caused by HoG rests on a high level of suspicion and on circumstantial evidence (**Table 2**). Primary care physicians, policemen, paramedics, and coroners should be alerted to this problem.

Who is at risk of experiencing hypoglycemia?

The medications listed in **Table 3** can cause HoG. Most patients well controlled on these drugs tend to have HoG occasionally. This is considered acceptable when patients are aiming for normal glycemic levels. If patients taking these medications deny ever having had HoG, physicians should suspect that control is suboptimal.

Some common conditions that make patients more sensitive to I/IS and predispose them to HoG are shown in **Table 4**. Some common conditions that cause insulin resistance and lower the risk of HoG are shown in **Table 5**.[26]

Treatments that do not lead to HoG are listed in **Table 6**. Patients receiving these treatments make up a large proportion of diabetics. It is important to reassure these patients that they are not at risk of HoG; need not test for it; need not fear it; and can be spared the expense, discomfort, and inconvenience of unnecessary testing. If patients begin taking I/IS, the doses of drugs listed in **Table 6** might have to be lowered to prevent HoG.

Table 2. Considerations for assessing risk of hypoglycemia or, if applicable, estimating the probability that hypoglycemia caused idiopathic or accidental sudden death

CONSIDERATION	LOWER RISK, LESS PROBABILITY	HIGHER RISK, GREATER PROBABILITY
Age	Older	Young
Duration of diabetes	Short	Long
Control as judged by the levels of CBG, hemoglobin AIc, and fructosamine	Suboptimal	Optimal
Adjusts to late meals and activity	Yes	No
History of frequent episodes of hypoglycemia	No	Yes
History of being unaware of hypoglycemia	No	Yes
Keeps a CBG diary	Yes	No
Keeps follow-up appointments	Yes	No
Frequency of CBG testing	Frequent	Rare or never

CBG—capillary blood glucose.

Table 3. Medications that can cause hypoglycemia

All insulins
All insulin secretagogues
• Glyburide or glybenclamide (eg, Diabeta, Euglucon)
• Gliclazide (eg, Diamicron)
• Repaglinide (GlucoNorm)
• Glimepiride (Amaryl)
• Nateglinide (Starlix)

Table 4. Common conditions that raise insulin sensitivity and risk of hypoglycemia

Leanness and youth
Physical activity
First trimester of pregnancy and the immediate postpartum period
Impaired liver function and alcoholism (depleted glycogen stores)
Impaired renal function (prolonged half-life of insulin)
Counter-regulatory hormone failure (adrenals, glucagon, growth hormone)
Autonomous neuropathy
Previous hypoglycemia
Being unaware of hypoglycemia
Total parenteral nutrition
Poor metabolic control due to lack of knowledge or motivation

Table 5. Common conditions associated with insulin resistance and lower risk of hypoglycemia

Obesity
Lack of physical activity
Excessive hormones (eg, corticosteroids)
Acute illness
Pregnancy (second and third trimester)
The dawn period (early morning hours)

Table 6. Treatments that do not cause hypoglycemia on their own

Diet and exercise alone
Metformin (eg, Glucophage)
Acarbose (Prandase)
Rosiglitazone (Avandia)
Pioglitazone (Actos)

Some do not agree with the notion that metformin does not in itself cause HoG. Most experts suggest that metformin monotherapy under *usual* circumstances does not cause clinically relevant HoG,[13,27-29] but might under *unusual* circumstances. Such circumstances include combination therapy with metformin and I/IS and the many causes of HoG unrelated to taking I/IS therapy.

How dangerous is hypoglycemia?

This question has been debated ever since insulin was added to diabetes care, especially among physicians whose painstaking clinical observations had convinced them that optimal glucose control was beneficial in preventing the acute and late complications of diabetes.[30] They understood the associated risk of HoG, but believed that risk was outweighed by benefit for informed patients. In this context, physicians should remember that the acute complications of diabetes (infections, impaired healing, weight loss, and ketoacidosis) greatly benefit from good control and that the difference between the control needed to prevent late, rather than acute, complications might be small.

Mortality. Four leading medical textbooks quote mortality rates due to HoG in insulin-treated diabetic patients of 2% to 4%.[31-34] These very high figures, however, are usually derived from high-risk populations and cannot be applied to I/IS–treated diabetic patients in general.[35-37] Later publications have supported the notion that intensive treatment, despite a greater incidence of HoG, is justified.[38-41]

Severe HoG caused by attempted suicide with an overdose of I/IS, even when combined with extreme conditions (eg, alcohol and exposure), is reported to have a surprisingly low mortality rate.[42] Death due to insulin shock treatment for psychosis, as practised between 1928 and 1935, albeit poorly documented, seemed not to be a concern,[43] and HoG-related death in insulinoma,[44] during pregnancy,[45,46] and during treatment with sulfonylurea,[47,48] has been reported only very rarely. In the author's experience, death due to severe HoG is very rare.

The fact that sudden death might be attributable to HoG must nevertheless be kept in mind. Drivers with HoG could be a grave threat to themselves as well as bystanders; they need elaborate training in HoG awareness and care. Physicians in Ontario are required by law to report motor vehicle accidents in which patients treated with I/IS have been involved.[49]

Morbidity. Numerous publications have dealt with neuropsychiatric problems attributed to HoG,[50] including impaired cognitive function and unmasking of an epileptic focus. Silent myocardial infarction,[51] angina,[52,53] and progression of retinopathy[54] have also been attributed to HoG.

A recent study of 58 children who had experienced severe HoG failed to identify impaired cognitive function 18 months later[55] (level III evidence). Nevertheless, the subject remains controversial, and every effort must be made to avoid HoG in children younger than 5 years.[56,57]

Treatment with I/IS usually leads to weight gain in patients with type 1[58] and type 2[59] diabetes for several reasons. Significant weight gain might be the first, most common, and yet least acknowledged adverse effect of HoG. Obesity is one of the major causes of type 2 diabetes; it adds insulin resistance to any already existing insulin deficiency. This should be viewed against the fact that a substantial number of people with type 2 diabetes can control their diabetes with weight loss alone. Weight should be closely monitored after starting treatment with I/IS.

Hypoglycemia occurs in a range of patients, from those who are stable and well controlled to those who are brittle and poorly controlled. The latter include those with autonomous neuropathy, those with HoG unawareness, and those with personality disorders. These patients will have to sacrifice some glucose control to avoid HoG. Blanket statements about risk of HoG tend to be misleading and should be avoided. It is safe to conclude, however, that occasional mild HoG in a controlled setting is an inevitable and acceptable part of optimal glucose control in patients taking I/IS. Risk of HoG can be estimated from the criteria listed in **Table 2**. In general, patients need not fear HoG if they know what it is, how to recognize it, how to manage it, and how to prevent it.

Preventing hypoglycemia

Prevention of HoG includes steps listed in **Table 7** for patients and in **Table 8**[60] for physicians. Extra nourishment must be taken before, during, and after activity as required (eg, 1 starch = 6 soda crackers or 3 dextrose tablets every 20 to 30 minutes). If the activity can be anticipated, insulin should be lowered in advance. Capillary blood glucose must be checked before and after exercise and at times in the early morning hours. Hypoglycemia can come on several hours after the extra activity ceases.

Meals and snacks must be eaten within 15 to 30 minutes of scheduled time. If a meal is expected to be late, patients should have 1 starch for every half-hour of

Table 7. Ways for patients to prevent hypoglycemia

Be familiar with hypoglycemia care
Wear a Medic-Alert bracelet or other identification bearing your name and telephone number
Explain to a family member or friend how to recognize and deal with hypoglycemia
Always have both a fast-acting carbohydrate (eg, dextrose tablets) and a slow-acting carbohydrate (eg, soda crackers) on hand
Have some nourishment (a meal or a snack) every 3 hours while awake, and keep mealtimes to within 15 to 30 minutes of scheduled times
For greater-than-usual physical activity, take extra food before starting and lower your dose of insulin or insulin secretagogues
Carry a glucagon kit. Using the kit you can raise your blood sugar long enough to take oral nourishment

Table 8. Ways for physicians to prevent hypoglycemia

Add metformin to stabilize blood sugar levels
Replace glyburide with gliclazide or glimepiride
Replace Toronto insulin with insulin lispro or aspart[60]
For hospitalized patients, always order glucose snacks at bedside
For hospitalized patients, leave orders for 1 mg of subcutaneous glucagon when needed
Test, and if necessary treat, capillary blood glucose levels before patients drive motor vehicles or start high-risk occupations
Lower treatment goals in selected patients (those with comorbid conditions, older age, inability to cope)

delay to bridge the gap and should deduct this from the following meal. Mealtimes are more flexible and snacks can be omitted with fast- and short-acting medications, such as insulin analogues (insulin lispro or aspart) or oral medications (repaglinide, nateglinide).

Prevention of HoG-related motor vehicle accidents requires special vigilance. Patients might need to check CBG levels before getting behind the wheel, especially if they are at higher risk of HoG. Long-distance drivers must have nourishment every 2 to 3 hours. Blood glucose awareness training has improved driving records.[61] Similar considerations apply to people in other high-risk occupations.

Prevention of severe HoG with nearly uncontrollable frequency in lean type 1 diabetics of long duration who have HoG unawarenes is one of the most challenging problems in diabetes care. Intensive education, thorough coordination of detailed and timed meal plans, carbohydrate counting, timing of physical activity, appropriate selection of medication, continuous subcutaneous insulin infusion, and in general more attention to detail can provide (albeit often incomplete) help.

Conclusion

Caring for HoG in family practice can be difficult with respect to diagnosis, incidence, adverse events, and prevention.

EDITOR'S KEY POINTS

- Increased focus on tight control of blood sugar for diabetes has resulted in greater risk of episodes of hypoglycemia. Hypoglycemia is not diagnosed solely by measuring blood glucose; it is also diagnosed by recognizing specific symptoms in individual patients.
- Treatment with insulin and insulin-secreting medications (eg, glyburide) predispose patients to hypoglycemia; certain activities and conditions, such as heavy exercise, leanness, and impaired liver function (alcoholism), aggravate that tendency.
- Evidence for specific mortality and morbidity associated with hypoglycemia is weak, but there are significant secondary risks for those who must be constantly attentive at work, such as drivers, pilots, and those in industrial occupations.
- Educating patients about the risks of, and preventive measures for, hypoglycema is the best way to minimize its occurrence.

POINTS DE REPÈRE DU RÉDACTEUR

- L'accent mis sur le contrôle étroit de la glycémie des diabétiques a entraîné un risque accru d'épisodes d'hypoglycémie. Le diagnostic d'HoG ne repose pas uniquement sur la mesure de la glycémie; des symptômes spécifiques chez un patient peuvent aussi suggérer le diagnostic.
- L'insuline et les agents qui stimulent la sécrétion de l'insuline (par ex., le glyburide) prédisposent aussi à l'HoG et certaines conditions ou activités comme la maigreur, l'exercice intense ou une dysfonction hépatique (éthylisme) accentuent cette tendance.
- Il y a peu de preuves de décès ou de morbidité spécifiquement associée à l'HoG, mais ceux dont le métier requiert une attention constante, comme les conducteurs, pilotes ou travailleurs de l'industrie, présentent des risques secondaires importants.
- La meilleure façon de réduire l'incidence de l'HoG est d'instruire le patient des risques qu'il court et de la façon de prévenir l'HoG.

- Hypoglycemia caused by I/IS is a distinct clinical entity.
- Having patients test their CBG levels is not a substitute for understanding clinical HoG and dealing with it. Patients taking I/IS should be taught how to recognize and treat HoG.
- Patients not taking I/IS need not worry about HoG.
- Evidence for clinically significant, HoG-related, chronic morbidity is inconclusive but weak. Documentation of HoG-related mortality is incomplete, partly owing to the difficulty of diagnosing it after death. More clinical research on permanent morbidity and on mortality caused by HoG is needed. Occasional mild HoG is inevitable in any reasonably stable diabetic patient. In a controlled clinical setting, HoG does not preclude intensive efforts at best possible control.
- Choosing an appropriate I/IS from the many types available and careful timing of meals and activity can help patients deal with HoG. A limited life expectancy, due to advanced age or comorbid conditions, or a lack of motivation, could justify less than optimal control.

The problems surrounding HoG are not expected to

be overcome merely by more technology or by lowering standards of control. Clinical observation, educated judgment, more time and attention to patients, and better education of patients, teachers, and physicians are legitimate ways to improve HoG care.

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