

# 2001 Canadian Diabetes Association Clinical Practice Guidelines for the Prevention and Management of Hypoglycemia in Diabetes

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## ABSTRACT

### OBJECTIVE

To revise and expand the 1998 Clinical Practice Guidelines for the Management of Diabetes in Canada recommendations related to hypoglycemia and to identify and assess the evidence supporting the recommendations.

### OPTIONS

All aspects of drug-induced hypoglycemia, long-term complications of diabetes and treatment of hypoglycemia were reviewed.

### OUTCOMES

Evidence-based recommendations for the prevention and management of hypoglycemia in diabetes were reclassified as unchanged or modified from the 1998 guidelines or stated as new on the basis of a comprehensive review process.

### EVIDENCE

All recommendations were developed following the same methodology as the 1998 guidelines, which used a justifiable and reproducible process involving an explicit method for the citation and evaluation of supporting evidence.

### VALUES

All recommendations were subject to an external review and feedback process from the diabetes healthcare community as

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## RÉSUMÉ

### OBJECTIF

Passer en revue les Lignes directrices de pratique clinique 1998 pour le traitement du diabète au Canada afin d'élargir la portée des recommandations relatives à l'hypoglycémie, et définir et évaluer les observations qui appuient les recommandations.

### OPTIONS

Tous les aspects de l'hypoglycémie provoquée par les médicaments, les complications à long terme du diabète et le traitement de l'hypoglycémie ont été étudiés.

### RÉSULTATS

Les recommandations factuelles pour la prévention et le traitement de l'hypoglycémie liée au diabète ont été reclassées : certaines sont inchangées ou ont été modifiées par rapport aux lignes directrices de 1998 et d'autres ont été ajoutées par suite d'un examen approfondi.

### OBSERVATIONS

Toutes les recommandations ont été élaborées selon la même méthode que les recommandations qui figurent dans le document de 1998, c'est-à-dire selon un processus justifiable et reproductible comportant une méthode explicite de citation et d'évaluation des preuves à l'appui.

### VALEURS

Toutes les recommandations ont été soumises à un examen externe et ont été commentées par des pourvoyeurs de soins diabétologiques de même que d'autres experts et des spécialistes de la méthodologie de toutes les régions du Canada.

### AVANTAGES, DÉSAVANTAGES ET COÛTS

Selon d'importants essais cliniques, un équilibre métabolique plus rigoureux réduirait l'incidence des complications chez la

well as other experts and methodologists from across Canada.

### BENEFITS, HARM, COSTS

Significant clinical trials support the perspective that tighter metabolic control in most people with diabetes reduces the incidence of complications and hence their associated social, emotional and economic burdens. Drug-induced hypoglycemia is a major obstacle in achieving glycemic targets to prevent the development and progression of complications. A more comprehensive approach to the evidence-based prevention and management of hypoglycemia in diabetes will be instrumental in enhancing compliance with intensified regimens and reducing the burdens associated with complications.

### RECOMMENDATIONS

All recommendations of the 1998 guidelines pertaining to hypoglycemia have been reviewed and new recommendations added.

### VALIDATION

All recommendations with a grading above D were reviewed by 3 methodologists who were not involved in the initial assessment of evidence and grading of the recommendations.

plupart des personnes atteintes de diabète et, partant, le fardeau social, émotionnel et économique associé à ces complications. L'hypoglycémie provoquée par les médicaments est un obstacle majeur à l'atteinte des objectifs glycémiques qui visent à prévenir l'apparition et la progression des complications. Pour améliorer la fidélité aux traitements plus intensifs et alléger le fardeau associé aux complications, il faudra aborder de façon plus globale la prévention et le traitement factuels de l'hypoglycémie liée au diabète.

### RECOMMANDATIONS

Toutes les recommandations relatives à l'hypoglycémie qui figurent dans les lignes directrices de 1998 ont été passées en revue et de nouvelles recommandations ont été ajoutées.

### VALIDATION

Toutes les recommandations au-dessus de la catégorie D ont été évaluées par trois spécialistes de la méthodologie qui n'avaient pas participé à l'évaluation initiale des observations ni au classement des recommandations.

## INTRODUCTION

Drug-induced hypoglycemia (secondary to insulin injections or insulin secretagogues) is a major obstacle in achieving glycemic targets to prevent the development and progression of the chronic complications of diabetes, particularly type 1 diabetes. The clinical importance of hypoglycemia is related primarily to severe hypoglycemia, during which the cognitive function of a person is affected to the point that external help is required for reversal of the condition. The immediate danger of this mental alteration often requires the glycemic goals to be increased. The clinical importance of hypoglycemia is also related to its negative social and emotional impact and the potential reluctance to intensify therapy. In the evidence-based 1998 Clinical Practice Guidelines for the Management of Diabetes in Canada, 7 of the 93 recommendations were related to hypoglycemia (1,2). However, at the time of their publication, it was felt that hypoglycemia had still not been covered in sufficient detail, and that it should be the subject of a revision/expansion of the guidelines.

## METHODS

In November 1998, an expert committee was struck to develop evidence-based recommendations for the prevention and management of hypoglycemia in diabetes in Canada. The principles used for assigning levels of evidence to the relevant citations and making and grading recommendations were the same as those used in the 1998 clinical practice guidelines (1,2). In October 1999, the guidelines were presented in draft format at the Canadian Diabetes Association Annual Meeting in Ottawa, Ontario, and feedback from the Canadian diabetes healthcare

community was obtained. The guidelines were also subsequently distributed to several experts in the field for feedback, and all recommendations with a grading above D were reviewed by 3 methodologists not directly involved in the initial assessment of evidence and the grading of the recommendations.

All recommendations of the 1998 guidelines pertaining to hypoglycemia have been reviewed. The recommendations made in the present document are numbered in accordance with the numbering system in the main body of the 1998 guidelines, to lend consistency to the documents. In addition, each recommendation is described as being "Unchanged" (existed as such in the 1998 guidelines), "Modified" (was modified from the 1998 guidelines), or "New" (did not exist in the 1998 guidelines). The 1998 guidelines can be found at: [http://www.diabetes.ca/prof/cpg\\_98.html](http://www.diabetes.ca/prof/cpg_98.html).

## DEFINITION OF HYPOGLYCEMIA

The precise definition of hypoglycemia remains the subject of debate. Traditionally, clinical hypoglycemia is defined as a state in which there is: 1) autonomic or neuroglycopenic symptoms (Table 1), 2) a low plasma glucose level, and 3) relief with administration of carbohydrate (3).

As plasma glucose levels decrease in people without diabetes, various physiological consequences occur. At levels of 4.2 mmol/L, endogenous insulin secretion is suppressed. At approximate levels of 3.7 mmol/L, increased glucagon, epinephrine, cortisol and growth hormone secretion occur. When levels of 3.1 mmol/L are reached, autonomic symptoms appear. Cognitive dysfunction occurs at levels of approximately 2.5 mmol/L. These

**TABLE 1. Symptoms of hypoglycemia<sup>3</sup>**

<b>Neurogenic (Autonomic)*</b>	<b>Neuroglycopenic*</b>
Trembling (32–78%)	Difficulty concentrating (31–75%)
Palpitations (8–62%)	Confusion (13–53%)
Sweating (47–84%)	Weakness (28–71%)
Anxiety (10–44%)	Drowsiness (16–33%)
Hunger (39–49%)	Vision changes (24–60%)
Nausea (5–20%)	Difficulty speaking (7–41%)
Tingling (10–39%)	Headache (24–36%)
	Dizziness (11–41%)
	Tiredness (38–46%)

\*Percent frequency of symptoms

levels vary greatly between individuals and, as discussed later, can be affected by the antecedent glucose control in any individual. The definition of hypoglycemia has thus varied between studies from 2.5 to 4.0 mmol/L. As discussed below, the current guidelines propose a level of 4.0 mmol/L for clinical use in patients treated with insulin or an insulin secretagogue.

In people with diabetes, the severity of hypoglycemia is defined based on the clinical manifestations of the episodes. With a mild episode of hypoglycemia, autonomic mediated symptoms are present and the patient is able to self-treat. With a moderate episode, autonomic and neuroglycopenic mediated symptoms occur and the patient is able to self-treat. With severe hypoglycemia, the patient requires the assistance of another person, unconsciousness may occur and the plasma glucose is typically less than 2.8 mmol/L. Hypoglycemia unawareness occurs when the threshold for autonomic warning symptoms to appear becomes lower than the threshold for the neuroglycopenic symptoms, so that the first signs of hypoglycemia will often be confusion or loss of consciousness. Asymptomatic hypoglycemia is the presence of a biochemically low glucose level without any symptoms.

## **HYPOGLYCEMIA AND ORAL ANTIHYPERGLYCEMIC AGENTS**

Drug-induced hypoglycemia is the most common cause of hypoglycemia. It is estimated that hypoglycemia of any severity occurs annually in 5 to 20% of patients taking antihyperglycemic agents (4). Although these hypoglycemic episodes are rarely fatal, they can be associated with serious clinical sequelae. Therefore, it is important to prevent, recognize and treat hypoglycemic episodes secondary to the use of antihyperglycemic agents. Table 2 lists risk factors and drugs that can potentiate the effects of antihyperglycemic agents.

The incidence of hypoglycemia with use of antihyperglycemic agents is likely underestimated due to altered patient awareness of symptoms and underreporting of episodes. Few large and randomized clinical trials have compared the rates of hypoglycemia between antihyperglycemic agents. In addition, the frequency of

hypoglycemias is not mentioned in several publications.

Sulfonylureas and meglitinides (such as repaglinide) can cause hypoglycemia when used in monotherapy, as both classes of agents are insulin secretagogues. The frequency of hypoglycemic episodes with sulfonylureas tends to decrease after a few years of treatment (5).

The United Kingdom Prospective Diabetes Study (UKPDS) has demonstrated an increase in the incidence of hypoglycemia (and severe episodes) during intensive diabetes treatment with sulfonylureas. Over the first 10 years, the mean proportion of patients per year with 1 or more major hypoglycemic episodes while taking their assigned treatment was 0.4% for chlorpropamide, 0.6% for glibenclamide and 0.1% for diet. The corresponding rates for any hypoglycemic episodes were 11.0%, 17.7%, and 1.2%. No statistical analysis comparing rates with different agents was provided (6). Severe and prolonged hypoglycemia can occur with long-lasting sulfonylureas (i.e. chlorpropamide) in association with certain co-existent conditions (7) and in view of this, long-lasting sulfonylureas should probably be avoided in these situations (Table 2). Gliclazide is associated with fewer incidents of hypoglycemia than glyburide in the elderly (8). Repaglinide seems to be associated with less hypoglycemia, when compared to glyburide, if a meal is missed or delayed (9). Outside this particular context, sulfonylureas and repaglinide appear to be comparable in terms of hypoglycemic episodes (10,11).

In the UKPDS, over 10 years of follow-up among patients taking therapy as allocated, the proportion of patients per year who had 1 or more major hypoglycemic attacks was 0.7% for diet alone and 0.0% for the metformin group. For any hypoglycemic episode, the corresponding proportions were 0.9% and 4.2%. No statistical analysis was provided (12). In 2 randomized, double-blind studies symptomatic hypoglycemia occurred in monotherapy in 2.0% or less of patients (13).

The frequency of hypoglycemia with thiazolidinediones is not significantly different from placebo. No cases of severe hypoglycemia have been reported with monotherapy with these agents (14-16).

**TABLE 2. Factors predisposing an individual to antihyperglycemic drug-induced hypoglycemia**

<b>Age</b>
• Elderly in the presence of co-existing comorbid conditions
<b>Impaired kidney or liver function</b>
<b>Adrenal insufficiency</b>
<b>Gastrointestinal disease</b>
<b>Lack of education on hypoglycemia</b>
<b>Lifestyle</b>
• Alcohol consumption in the absence of sufficient energy/carbohydrate intake
• Exercise
• Missed or delayed meals
<b>Medications</b>
• Salicylates (> 4 g per day)
• Sulfonamide antibiotics
• Tricyclic antidepressants
• Phenylbutazone
• Warfarin
• Fibrates
• Monoamine oxidase inhibitors
• Pentamidine
• Acetaminophen
• ACE inhibitors
• Beta blockers

Alpha-glucosidase inhibitors do not cause hypoglycemia (17). However, if a patient has a hypoglycemic reaction (because of concomitant therapy with insulin, for example), alpha-glucosidase inhibition may prevent sucrose or starch from being absorbed in a timely fashion for the treatment of hypoglycemia. Patients taking alpha-glucosidase inhibitors must therefore use glucose (dextrose tablets) or, if unavailable, milk or honey to treat hypoglycemia.

Combination therapy with oral antihyperglycemic agents of any class can also be associated with a several-fold increased likelihood of hypoglycemia (13) and in view of this patients should be advised, and receive appropriate education on hypoglycemia, before initiating combination therapy.

### Recommendations:

### Oral Antihyperglycemic Agents

**32 (Modified):** The initial oral agent used can be (in alphabetical order) an alpha-glucosidase inhibitor, a biguanide, an insulin secretagogue (sulfonyleurea or repaglinide), or a thiazolidinedione; the choice depends on the individual, taking into

consideration the following factors:

- Metformin should be considered as initial therapy for obese patients with type 2 diabetes. [Grade B, Level 2 (5)]
- To avoid unnecessary hypoglycemia, metformin, alpha-glucosidase inhibitors and/or thiazolidinediones should be considered before using the insulin secretagogues (sulfonyleureas and meglitinides) in patients at high risk of hypoglycemia. [Grade D, consensus]
- Metformin is associated with less weight gain and less hypoglycemia than sulfonyleureas [Grade B, Level 1(5,13)], but gastrointestinal side effects may be a limiting factor.
- Metformin is contraindicated in the presence of significant renal, cardiac or hepatic insufficiency, as it may cause lactic acidosis. [Grade D, consensus]
- An alpha-glucosidase inhibitor may be added to diet, metformin or sulfonyleurea therapy to improve glycemic control [Grade A, Level 1 (17)], but gastrointestinal side effects may be a limiting factor.

**33 (Unchanged):** If target glucose levels are not attainable with a single agent, an agent or agents from other classes may be added, until the maximum dose of an agent of each class is reached. [Grade A, Level 1 (17) for the addition of acarbose to other oral agents; Grade A, Level 1 (13) for the addition of metformin to sulfonyleurea; Grade D, Level 4 (18,19) for the addition of sulfonyleurea to other agents]

### Diabetes in the Elderly

**48 (Modified):** In elderly people, sulfonyleureas should be used with caution because the risk of hypoglycemia increases exponentially with age [Grade D, Level 5 (20)]. In general, initial doses should be half those of younger people, and doses should be increased more slowly. [Grade D, consensus] Gliclazide may be preferred over glyburide if a sulfonyleurea is to be used, as it is associated with a reduced frequency of hypoglycemic events compared with glyburide. [Grade A, Level 1 (8)]

## HYPOGLYCEMIA AND INSULIN THERAPY

### i) Intensive vs. conventional insulin therapy

Intensive insulin therapy is a mode of treatment for the person with diabetes that has the goal of achieving euglycemia or near-normal glycemia, using all available resources to accomplish this goal. The 1998 guidelines recommended that most people with diabetes should aim for optimal glucose levels to prevent or delay microvascular complications, and that to achieve target glucose levels, multiple daily injections or the use of continuous subcutaneous insulin infusion as part of an intensive diabetes management regimen are usually required for patients with type 1 diabetes.

Hypoglycemia is the most common adverse effect of intensive insulin therapy in type 1 diabetes. Although the increase in severe hypoglycemia with the intensification of therapy is not a

universal finding (21,22), in some studies the proportion of patients experiencing severe hypoglycemic episodes has increased during intensive therapy. During a 6.5-year follow-up in the Diabetes Control and Complications Trial (DCCT), 35% of patients in the conventional treatment group and 65% in the intensive group had at least 1 episode of severe hypoglycemia (23). The cumulative rates (episodes per 100 patient-years of follow-up) were 18.7 for the conventional approach and 61.2 for the intensive group, for a relative risk of 3.28 (95% CI 2.65–4.05,  $p < 0.001$ ) (23). Adolescents were found to be at even greater absolute risk (conventional: 27.8; intensive: 85.7 episodes per 100 patient-years) (24), but the relative risk was of the same order 2.96 (95% CI 1.90–4.62,  $p < 0.001$ ). The event rate per 100 patient-years for severe hypoglycemia defined as coma or seizure was 5.4 in the conventional treatment group and 16.3 in the intensive treatment group, for a relative risk of 3.02 (95% CI 2.36–3.86,  $p < 0.001$ ) (23).

In the Stockholm Diabetes Intervention Study, the corresponding figures were 73 and 86% during a 10-year follow-up period (25). In a 1997 meta-analysis of 14 trials, the median incidence of severe hypoglycemia was 4.6 and 7.9 episodes per 100 patient-years in the conventionally and intensively treated patients, respectively (26). The odds ratio for severe hypoglycemia was 2.99 (95% CI 2.45–3.64) during intensive therapy as compared with conventional therapy (26). In keeping with the DCCT, the risk of severe hypoglycemia was determined by the degree of normalization of glycemia achieved (26,27).

The 1997 meta-analysis indicated that the type of regimen used (multiple daily injections or continuous subcutaneous insulin infusion [CSII]) does not influence the risk of severe hypoglycemia independently of blood glucose control (26). Kerum et al reported a 1-year, randomized, crossover study of 35 patients comparing the frequency of hypoglycemia with multiple daily injections versus CSII (28). Despite significantly lower HbA<sub>1c</sub> levels in the CSII group during both crossover periods, there was no significant difference in the frequency of mild or severe hypoglycemia between the two groups.

There were substantial variations in the risk of severe hypoglycemia among the 29 centres participating in the DCCT (27). One possible reason for these differences is that insulin therapy and patient education were not standardized (27). In addition, the difference between those on conventional and those on intensive therapy tended to decrease with time, suggesting that there might be an effect of training with more intensive treatment (29). Over 2.5 years, the incidence of severe hypoglycemia in the intensive treatment group decreased from 120 per 100 patient years to around 48 per 100 patient years, while the incidence in the conventionally treated groups remained constant at about 24 per 100 patient years. The intensive treatment group at all clinics had significantly lower HbA<sub>1c</sub> levels than the conventionally treated group, but the relative risk of severe hypoglycemia varied from 11 down to 1, with no increased risk at all in 5 clinics (30). Furthermore, those clinics with the lowest HbA<sub>1c</sub> had no higher incidence of severe hypoglycemia than those clinics with the high-

est HbA<sub>1c</sub> (30). Other studies have suggested that with adequate self-management education, appropriate blood glucose targets, self-monitoring of blood glucose and professional support, intensive therapy may result in less hypoglycemia than reported in the DCCT (22,31–35).

In the UKPDS, the proportion of patients with type 2 diabetes experiencing a severe hypoglycemic episode in a year was significantly higher in the intensive group than in the conventional group ( $p < 0.0001$ ) (6), particularly for patients on insulin therapy. Although the risk of hypoglycemia was less than that seen in the DCCT, each year about 3% had a severe episode and 40% had a hypoglycemic episode.

## ii) Rapid-acting insulin analogues vs. human regular insulin

Studies have found no differences in the onset, magnitude and temporal pattern of the physiological, symptomatic and counter-regulatory hormonal responses to acute hypoglycemia induced by regular human insulin compared with the rapid-acting insulin analogues—lispro insulin (36–39) and insulin aspart (40,41).

Brunelle reported a large meta-analysis of the incidence of hypoglycemia for 2327 patients on lispro insulin compared with 2339 patients on human regular insulin (42). Seventy-two patients (3.1%) had a total of 102 severe hypoglycemic episodes during lispro insulin therapy, compared with 102 patients (4.4%) with a total of 131 episodes during regular human insulin therapy. The relative risk of hypoglycemia with lispro compared to regular insulin was 0.703 (95% CI 0.518–0.956;  $p = 0.024$ ) (42).

However, these results were obtained in a meta-analysis of different studies with variable insulin regimens. In addition, in these studies, HbA<sub>1c</sub> levels did not decrease with lispro insulin compared with human regular insulin, despite lower 2-hour postmeal blood glucoses with the lispro insulin. It is possible that the protective effect of lispro insulin on the risk for severe hypoglycemia was due to greater increases in blood glucose before meals and in the early part of the night (43). One study has demonstrated a significant reduction in severe hypoglycemic episodes in 90 subjects with type 1 diabetes treated with insulin aspart compared to human regular insulin (44), although findings were similar to the lispro studies with higher nocturnal blood glucose readings despite lower postprandial ones.

In the largest crossover study comparing lispro to human regular insulin as the pre-meal insulin, Anderson et al studied 1008 patients with type 1 diabetes over six months (45). The total number of hypoglycemic episodes occurring in patients on lispro insulin was 12% lower than with human regular insulin therapy ( $p < 0.001$ ). The largest relative improvement in hypoglycemia occurred overnight ( $p < 0.001$ ). This finding of reduced nocturnal hypoglycemia has been demonstrated in other studies with lispro insulin (46,47) and insulin aspart (48).

Several studies have examined the effect of lispro insulin on the risk for hypoglycemia in intensive treatment of type 1 diabetes (47,49–53). With both CSII (49,50) and multiple daily

injections (51-53), it is possible to decrease HbA<sub>1c</sub> by 0.3 to 0.4% with lispro insulin compared with human regular insulin, with no increase in the risk for mild and/or severe hypoglycemia. These observations suggest that for an identical HbA<sub>1c</sub> level, lispro insulin decreases the risk for hypoglycemia compared with human regular insulin.

Zinman et al reported on 178 patients with type 1 diabetes randomized to receive either NPH or ultralente insulin once daily at bedtime with lispro insulin before meals (54). There was no difference in the incidence of hypoglycemia with these two basal insulin regimens. No significant differences for the rates of hypoglycemia between lispro and human regular insulin have been shown when used in CSII (55-58).

Tuominen et al compared the rate of hypoglycemia in 10 patients with type 1 diabetes following 40 minutes of cycle ergometer exercise performed either shortly (40 minutes) or later (180 minutes) after a breakfast and snack and injection of either lispro or human regular insulin (59). In the lispro-treated patients, the exercise-induced fall in plasma glucose was 2.2-fold greater ( $p < 0.01$ ) during the early exercise, but 46% less ( $p < 0.05$ ) during late exercise as compared to human regular insulin.

Two studies (60,61) have reported a lower rate of hypoglycemia in patients with type 2 diabetes treated with lispro insulin compared with human regular insulin. Anderson et al studied 772 patients with type 2 diabetes over 6 months in a randomized, crossover design (60). During lispro insulin therapy, the rate of hypoglycemia overall was less ( $3.18 \pm 0.16$  vs.  $3.43 \pm 0.19$  episodes per 30 days per patient,  $p < 0.02$ ). Overnight hypoglycemia was significantly reduced by 36% in the lispro group ( $0.47 \pm 0.05$  vs.  $0.73 \pm 0.07$ ,  $p < 0.001$ ). While there was a reduction in the incidence of severe hypoglycemia in the lispro-treated group, the numbers were too small to confer statistical significance. Both groups experienced similar decreases in HbA<sub>1c</sub> levels and had identical levels at the study endpoint.

### iii) Animal vs. human insulin

The introduction of human insulin in the 1980s was accompanied by claims that in some patients the symptomatic awareness of hypoglycemia was altered on transfer to human insulin (62). A number of studies have suggested no significant clinical difference in the symptomatic response to (38,63) or in the frequency of hypoglycemia (64,65) between animal and human insulin.

### iv) Lifestyle factors and insulin-induced hypoglycemia

Studies have suggested that self-management behaviours, less food, more insulin and more activity are associated with 85% of hypoglycemic episodes (66,67). For patients managed with fixed-dose insulin regimens, care should be taken to develop an individualized meal and activity plan that the person can and will follow (68).

Preferably, patients should be taught how to make adjustments to insulin dosage, diet and physical activity in response to

blood glucose levels (29,66,67). Bedtime snacks may be needed to avoid nocturnal hypoglycemia. The addition of protein to carbohydrate at bedtime has not demonstrated a reduction in hypoglycemia (69). Prepared snack bars with cornstarch have demonstrated some effectiveness in reducing overnight hypoglycemia (70,71). High protein content (vs. high fat content) of an evening meal has also demonstrated some protection against nocturnal hypoglycemia (72).

Knowledge of the acute effects of exercise is mandatory for any person treated with insulin. Unless considerable hyperglycemia (i.e. more than 15 mmol/L) and ketosis is present, low- to moderate-intensity exercise lowers glucose levels both during and after the activity, increasing the risk of a hypoglycemic episode. These effects on glucose levels can be modified by altering diet, insulin and the type and timing of exercise. In contrast, high-intensity exercise raises glycemia during and immediately after the bout. Self-monitoring of glucose level before, during, and especially for many hours after exercise is important for establishing the patient's response to exercise and guiding the appropriate management of exercise. In patients with type 1 diabetes, the use of intensive diabetes management regimens with either multiple daily injections or CSII provides additional flexibility in appropriately modifying the insulin dose for exercise (73,74).

### v) Hypoglycemia unawareness and glucose counterregulation

Severe hypoglycemic reactions are the main barrier to achieving optimal glucose control in people with type 1 diabetes (75). The major risk factors for severe hypoglycemia include a prior episode of severe hypoglycemia (23,29,76,77), a current low HbA<sub>1c</sub> (less than 6%) (23,29,78), hypoglycemia unawareness (79), long duration of diabetes (78,80) and autonomic neuropathy (81). Severe hypoglycemic episodes occur mostly at night (29,82) or in the absence of hypoglycemia awareness that alerts patients to take actions to correct their glucose levels. Adolescents were found to be even at greater risk (85.7 episodes per 100 patient-years) (24).

Glucagon responses to hypoglycemia are lost within the first few years after diagnosis of type 1 diabetes (83), and patients become dependent on sympathoadrenal responses for appropriate glucose counterregulation and for hypoglycemia awareness. It is therefore not surprising that autonomic neuropathy (defined as defects in both heart rate and systolic blood pressure changes with standing) has been shown to be an independent risk factor for severe hypoglycemia in people with type 1 diabetes (84), and those with autonomic neuropathy have further reduced epinephrine and norepinephrine responses to hypoglycemia (81). However, autonomic neuropathy is not required for hypoglycemia unawareness to be present.

The incidence of prior hypoglycemic episodes has been shown to be a crucial factor leading to hypoglycemia unawareness. Hypoglycemia has been reported to occur on average in people with type 1 diabetes at a frequency of approximately 2

episodes per week. In one study, increasing the frequency of hypoglycemia by 2 episodes per week (i.e. to 4 per week) resulted in a worsening in the defect of the hormonal responses to hypoglycemia (particularly epinephrine and pancreatic polypeptide) (34). This in turn can lead to a reduction in the self-detection of hypoglycemia and in defective glucose counterregulation. Defects in counterregulatory responses have also been shown in insulinoma patients (85). It has been suggested that an adaptation to recurrent hypoglycemia is a preservation of glucose uptake by the brain despite hypoglycemia, preserving cerebral metabolism but reducing the responses of counterregulatory hormones and awareness of hypoglycemia (86). The cortisol response to hypoglycemia has been suggested to be involved in the decreased counterregulatory responses to subsequent hypoglycemia by a central effect (87). Even the counterregulatory responses to exercise are blunted following an episode of hypoglycemia (88). Asymptomatic nocturnal hypoglycemia is common, and is often prolonged more than 4 hours (29,89-92). Hypoglycemia is more likely to cause seizures during the night than during the day (29). In the DCCT, 43% of episodes of severe hypoglycemia occurred between midnight and 8 am (29). Deep sleep has been shown to impair the counterregulatory hormone responses (particularly epinephrine,  $p=0.004$ ) to hypoglycemia in patients with diabetes and in normal subjects (93). To reduce the risk of asymptomatic nocturnal hypoglycemia, patients on intensive insulin therapy should periodically monitor overnight blood glucose levels at a time that corresponds with the peak action time of their overnight insulin.

The defects of hypoglycemia unawareness and defective glucose counterregulation are potentially reversible. In patients with insulinoma, reversal occurs after removal of the insulinoma (85). In successful recipients of pancreas transplantation, hypoglycemia-induced glucagon secretion and hepatic glucose production are normalized (94). Strict avoidance of hypoglycemia from 2 days to 3 months has been associated with an improvement in the recognition of severe hypoglycemia (95-97), in the counterregulatory hormone responses (98), or both (35,96,99-101). To explain the discrepancy between recognition and counterregulatory responses (decreased hormone responses, but normal awareness) it has been proposed that beta-adrenergic sensitivity might be increased in a compensatory way, and that loss of this increased beta-adrenergic sensitivity following repeated hypoglycemic episodes could lead to the reduced awareness (102). There are no data on the impact of these measures on the frequency of severe hypoglycemia, however. Nighttime CSII has recently shown improvement in hypoglycemia awareness and counterregulatory function (103).

Awareness programs such as Blood Glucose Awareness Training (BGAT) may have a positive effect on increasing accurate detection and treatment of hypoglycemia. The BGAT program involves instruction in interpretation of physical symptoms, performance cues, and moods and feelings as internal cues to blood glucose awareness; it also involves instruction on food, exercise, insulin dosage and action, time of day, and last

blood glucose reading as external cues to estimate blood glucose level. BGAT allowed reduced-awareness subjects (these individuals, while having less awareness, did have some hypoglycemic symptoms) to detect a greater percentage of blood glucose levels under 3.9 mmol/L (from 35 to 45%,  $p = 0.006$ ) (104-109).

Ingestion of caffeine has been shown to increase the sympathoadrenal and symptomatic responses during moderate hypoglycemia (110), but there are no data on the impact of caffeine consumption on the frequency of severe hypoglycemic episodes.

## Recommendations:

### Physical Training and Exercise

**28 (Unchanged):** In anyone treated with insulin, recommendations regarding alterations of diet, insulin regimen, injection sites and self-monitoring should be appropriate for the general level of physical activity or specific types of exercise undertaken. Oral agent doses may need to be decreased. [Grade D, consensus]

**28a (New):** Self-monitoring of glucose level before, during and especially for many hours after exercise, is important for establishing the patient's response to exercise and guiding the appropriate management of exercise. [Grade D, consensus]

**30 (Modified):** General advice regarding physical activity include:

- For those on insulin or insulin secretagogues, ingest rapidly absorbed carbohydrate if pre-exercise glucose level is under 5 mmol/L.
- For those on insulin injections, administer insulin into a site away from the most actively exercising extremities. [Grade D, consensus]

### Insulin Use in Type 1 Diabetes

**35a (New):** All patients currently on or starting intensive insulin programs should be counseled about the risk and prevention of hypoglycemia. They should be advised to perform frequent blood glucose monitoring and receive appropriate instruction on how to make adjustments in insulin dosage, diet and physical activity in response to blood glucose levels. The diabetes health care team should review the patient's experience with hypoglycemia at each visit. This should include an estimate of cause, frequency, symptoms, and recognition, severity and treatment. [Grade D, consensus]

**35b (New):** To reduce the risk of asymptomatic nocturnal hypoglycemia, patients should periodically monitor overnight blood glucose levels at a time that corresponds with the peak action time of their overnight insulin and consume a bedtime snack with at least 15 g carbohydrate and protein if the bedtime blood glucose level is under 7 mmol/L. [Grade D, consensus]

**36 (Modified):** Regular or a rapid-acting insulin analogue, or both, can be used before meals in intensified therapy (multiple daily injections and CSII). Lispro has been associated with lower post-prandial glucose levels and lower rates of hypoglycemia than regular insulin. [Grade A, Level 1 (111,112)] Aspart insulin has been associated with lower rates of hypoglycemia compared to human regular insulin. [Grade B, Level 2 (44)] Patients experiencing frequent hypoglycemic episodes on regular insulin should be tried on a fast-acting insulin analogue. [Grade D, consensus] Lispro is the preferred insulin for use in CSII. [Grade B, Level 2 (49)]

**36a (New):** Substituting a rapid-acting insulin analogue for human regular insulin at supertime may prevent the delayed nighttime effect of regular insulin and reduce the risk of nocturnal hypoglycemia (45-48). Administering basal insulin at bedtime rather than at supertime, or instituting CSII, may also reduce the risk of nocturnal hypoglycemia. [Grade D, consensus]

**36b (New):** Risk factors for severe hypoglycemia should be identified in people with type 1 diabetes so that appropriate strategies can be used to prevent hypoglycemia. (Grade A) Established risk factors include a) history of previous severe hypoglycemic event [Level 1 (23)], a greater reduction in HbA<sub>1c</sub> [Level 1 (26)] and recurrent previous hypoglycemic reactions [Level 1 (23)]. Pre-school age children unable to detect/treat mild hypoglycemia on their own should also be considered at high risk. [Grade D, consensus] The patients at high risk should be informed of their risk, counselled along with their significant others on avoidance and treatment (including glucagon), and if necessary have their insulin regimen adjusted appropriately to avoid these events. [Grade D, consensus]

**36c (New):** During insulin therapy of type 1 diabetes, the frequency of mild hypoglycemic episodes should be minimized, particularly in those at high risk, in an attempt to reduce the development of hypoglycemia unawareness. [Grade D, consensus (34)]

**36d (New):** In individuals with hypoglycemia unawareness, the following strategies should be implemented to reduce the risk of hypoglycemia, the risk of hypoglycemia unawareness, and to increase physiologic counter-regulatory responses to hypoglycemia: increased frequency of glucose monitoring, increase in the glucose targets, and multiple insulin injections with increased glucose targets [Grade D, level 4 (35,96,99-101)]

**36e (New):** Patients switching from animal to human insulin do not require counseling about any change in frequency or perception of hypoglycemia. [Grade A, Level 1 (63-65)]

**36f (New):** In hospitalized patients, efforts must be made to ensure that patients on insulin have ready access to an appropriate form of glucose at all times, particularly when NPO or during diagnostic procedures. [Grade D]

## LONG-TERM COMPLICATIONS OF SEVERE HYPOGLYCEMIA

The potential long-term complications of severe hypoglycemia are mild intellectual impairment and permanent neurologic sequelae such as hemiparesis and pontine dysfunction. The latter are rare and reported only in case studies.

In adults, retrospective studies suggested a link with frequent severe hypoglycemia (5 or more episodes) and a decrease in intellectual performance. These impairments were small but depending on the individuals' occupation, could interfere with their performance in daily life.

People with diabetes with a history of severe hypoglycemia, when compared to matched subjects with diabetes without severe hypoglycemia and patients without diabetes, were found to perform more poorly in a number of intellectual tests: immediate memory and finger tapping (113), word recall test and verbal fluency (114), performance IQ (115), Weschler Performance test and Trail Making Test (116). In some studies, a correlation was found between the frequency of severe hypoglycemic reactions and the performance IQ (115-118).

In contrast, the available prospective studies did not find an association between intensive diabetes management and cognitive function (119,120). Since intensive management is linked with more frequent severe hypoglycemia, it is extrapolated that, similarly, severe hypoglycemia is not linked with a decrease in cognitive function. However, the time interval studied was relatively short (5 years). Although the DCCT group did a sub-analysis comparing the cognitive function in the patients with repeated severe hypoglycemia (more than 5 episodes) to those without, the group with hypoglycemia was small (23 patients) and the power of this analysis was therefore insufficient.

In children, although researchers have used numerous tests and found different ones to be abnormal, a negative effect of diabetes on cognitive function was more consistently found. These abnormal findings are linked with age at diagnosis, duration of diabetes, frequency of severe hypoglycemia and intensive therapy. Diabetes and hypoglycemia alone did not significantly affect results of the IQ; but early onset of diabetes was significantly associated with a decreased score. The early onset subgroup was also more likely to have had frequent hypoglycemia and the effects of these two factors could not be dissociated (121). A significant decrease in some components of attention was described in subjects with diabetes, particularly in those diagnosed before 6 years of age. A history of severe hypoglycemia with seizures was linked with a lower verbal IQ and with select, focus and inhibition attentional components (122).

People with diabetes diagnosed before age 15 were shown to have worse memory than control subjects. Those with a history of severe hypoglycemia had additional specific deficits in the delayed recall of verbal information and vocabulary tests (123).

In a prospective study, no difference was found in the neuropsychological profile of children within 3 months of diagnosis of diabetes, compared to controls. Two years later, defects in speed of processing information, acquisition of new knowledge

and conceptual reasoning abilities were found in children with diabetes, particularly in younger children (124). Another prospective study of children from diagnosis of diabetes up to 7 years later revealed a decline in verbal IQ, particularly in those with a history of severe hypoglycemia (125).

In contrast to the adult studies comparing intensive management to conventional management, a decreased intellectual performance was associated with intensive management of diabetes in children. The delayed declarative memory was assessed specifically in a group of intensively treated subjects compared to conventionally treated subjects and nondiabetic subjects. As a group, the intensively-managed subjects performed less accurately and/or more slowly on the different memory tests. Both diabetic groups were slower on motor speed tasks. Because the group on intensive management had more hypoglycemic episodes, the authors concluded these changes were associated with the frequency of severe hypoglycemia, although no specific analysis was done to demonstrate this (126).

As in the adult literature, no study definitely answers the question of the long-term effects of hypoglycemia on cognitive function. However, the available information is more suggestive of increased risks of cognitive impairment with repeated hypoglycemia in childhood (125,127).

The long-term impact of severe hypoglycemia on cognitive function is very difficult to evaluate. This can only be done by a long-term prospective study. The numerous tests used by different researchers render comparisons between studies and reproducibility difficult. Further, evaluating the impact of hypoglycemia on cognitive function would require a baseline evaluation at diagnosis of diabetes, prospective follow-up to ascertain the exposure to severe hypoglycemia followed by re-evaluation of the cognitive function over years of follow-up. However, there would still remain a bias by the “natural” selection of the subjects: the subjects experiencing repeated severe hypoglycemia may have characteristics that predispose them to both severe hypoglycemia and deterioration of their cognitive function.

## Recommendations:

### Diabetes in Children and Adolescents

**41 (Modified):** The metabolic goals and therapeutic strategies for adolescents over 12 years of age are the same as those for adults [Grade A, Level 1 (24,128)]. The target HbA<sub>1c</sub> for prepubertal children is 120 to 140% of the upper limit of normal with targets for glucose and HbA<sub>1c</sub> graduated according to the child’s age. [Grade D, consensus] Extreme caution is required to avoid hypoglycemia in children age 5 years or less, because of the permanent cognitive deficit that may occur in this age group. [Grade D, Level 4 (122,129,130)]

### TREATMENT OF HYPOGLYCEMIA

The goals of hypoglycemia treatment are to detect and treat a

low blood glucose level promptly by using an intervention that provides the fastest rise in blood glucose to a safe level, thereby removing the risk of injury, and to relieve symptoms quickly while avoiding over-treatment (and resulting rebound hyperglycemia and weight gain).

Little evidence is available to support the widely recommended treatment for acute hypoglycemia as 10 g of a variety of carbohydrates. More recent evidence suggests that 15 g of glucose (monosaccharide) is required to produce a rise in blood glucose of approximately 2.1 mmol/L within 20 minutes, with adequate symptom relief for most people (131-135). This has not been well studied in patients with gastropathy. A 20 g oral glucose dose will produce a blood glucose increment of approximately 3.6 mmol/L at 45 minutes (132,133). Other choices such as milk and orange juice are slower to raise blood glucose levels and provide symptom relief (132,133). Glucose gel is quite slow (less than 1 mmol/L rise at 20 minutes) and must be swallowed to have a significant effect (131,136,137). There is no evidence to support the practice of administering glucose gel buccally since absorption through the mucosa is minimal, if any (137). Alpha-glucosidase inhibitors delay the digestion of sucrose and starch. Therefore, patients taking alpha-glucosidase inhibitors must use glucose (dextrose) tablets, or, if unavailable, milk or honey to treat hypoglycemia (138).

Glucagon 1 mg administered subcutaneously or intramuscularly produces a significant blood glucose rise (from 3.0 to 12 mmol/L) within 60 minutes (68).

Sulfonylurea-induced severe hypoglycemia can be long-lasting, requiring hospitalization and long-term glucose infusion (139). An IV bolus of 50% dextrose, followed by an infusion of 10% dextrose for several hours may be needed. Recurrent hypoglycemia may require a second bolus of 50% dextrose and treatment with either diazoxide (139) or octreotide, 50 µg subcutaneously (140). Glucagon is not recommended for hypoglycemia induced by sulfonylureas (68).

## Recommendations:

**94 (New):** Mild to moderate hypoglycemia should be treated by the oral ingestion of 15 g of carbohydrate, preferably as glucose or sucrose tablets or solution or hydrolyzed polysaccharide. These are preferable to orange juice and glucose gels [Grade B, level 2 (131)]. Patients should be encouraged to wait 15 minutes, retest blood glucose and retreat with another 15 g of glucose if the blood glucose remains < 4.0 mmol/L. In smaller children, 10 g of glucose may be used initially. [Grade D, consensus]

**95 (New):** Severe hypoglycemia in a conscious person should be treated by the oral ingestion of 20 g of carbohydrate, preferably as glucose tablets or equivalent. Patients should be encouraged to wait 15 minutes, retest blood glucose and retreat with another 15 g glucose if it remains < 4.0 mmol/L. [Grade D, consensus]

**96 (New):** Severe hypoglycemia in an unconscious person, in the home situation, should be treated with 1 mg glucagon subcutaneously or intramuscularly (68). In children 5 years of age or younger, a dose of 0.5 mg should be used (68,134). Caregivers or support person should call for Emergency Services and the episode should be discussed with the health-care team as soon as possible. Hospitalization is probably not required once consciousness and the ability to take oral food have been restored. In the home situation, support persons should be taught to administer glucagon by injection. [Grade D, consensus]

**97 (New):** For severe hypoglycemia with unconsciousness, IV glucose, 10 to 25 g (20 to 50 cc of D50W), given over 1 to 3 minutes, is the standard medical and paramedical treatment, despite the problems of IV access and possible phlebitis (68,132,134). [Grade D, consensus]

**98 (New):** In hospitalized patients, a PRN order for glucagon should be considered for any patient at risk for severe hypoglycemia (i.e. insulin requiring and hospitalized for concurrent illness) when IV access is not readily available. [Grade D, consensus]

**99 (New):** To prevent repeated hypoglycemia, the person should have in addition to the fast-acting treatment above, once the hypoglycemia has been reversed, their usual meal or snack. A snack (including 15 g of carbohydrate and a protein source) is recommended if a meal is more than 1 hour away and in the absence of complicating factors. [Grade D, consensus]

**100 (New):** All patients currently on or starting therapy with insulin or insulin secretagogues should be counseled about the recognition and prevention of drug-induced hypoglycemia. [Grade D, consensus]

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