An eBook on Diabetes

Chapter 4

Overview of Hypoglycemia

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1. Introduction

Hypoglycemia, or low blood sugar, is a condition characterized by a decrease in blood glucose concentration below physiological levels that expose the person to potential harm. Many people with diabetes are at risk of hypoglycemia. There are also conditions other than diabetes where hypoglycemia can occur, however they are rare. Hypoglycemia in people with diabetes is not a disease on its own, it is rather a complication that may be caused by the treatment of diabetes. The consequences of hypoglycemia may be significant and are twofold: 1. immediate – symptoms of low blood sugar impacting quality of life, potentially leading to a loss of consciousness and even death, and 2. indirect –preventing the satisfactory control of diabetes and contributing to the development of long-term complications associated with diabetes.

2. Background

Hypoglycemia results from the absolute or relative excess of endogenous or exogenous insulin and is a common complication related to the treatment of diabetes, particularly with insulin, glinide or sulfonylurea. Hypoglycemia occurs when the production of glucose by the body, or the ingestion of carbohydrates, can no longer match the glucose-lowering effect of insulin. Conditions associated with either a lower supply of carbohydrate, such as a delayed or smaller than expected meal, or with an increased demand for glucose, such as exercise, can trigger a low blood glucose episode in people taking insulin or other potent glucose-lowering medications. Glinide and sulfonylurea medications, referred to as secretagogues, are agents

enhancing pancreatic beta cells to release insulin. Exogenous insulins mimic the action of physiological insulin, enabling the absorption of blood glucose by bodily tissues, however the time-action profile of modern insulin preparations has been modified when compared to the native human insulin thus modulating the rate of absorption from the subcutaneous tissue and impacting the risk of hypoglycemia. One of the reasons which leads insulin-dependent people with diabetes to be susceptible to hypoglycemia is the very narrow therapeutic window of insulin, that is the range that exists between a dose that produces the desired, i.e. anti hyperglycemic effect and a dose that produces unwanted and possibly dangerous side effects, i.e. hypoglycemia. Secretagogues, drugs that enhance the release of endogenous insulin by the beta cells of the pancreas, are also associated with a relatively high risk of hypoglycemia. Other agents used in diabetes are unlikely to lead to hypoglycemia on their own but may contribute to low blood glucose episodes if taken in combination with insulin or secretagogue or in the case of a concurrent illness or prolonged fast. Hypoglycemia is clinically manifested when the blood glucose level falls below the lower limit of the physiological range. This level is approximately 70 mg/dL (3.9 mmol/L) and may vary to a certain extent between patients, as well as in an individual patient over time.

The two main hormones regulating the blood sugar metabolism are insulin and glucagon. Insulin is released by pancreatic beta cells whereas glucagon by pancreatic alpha cells. Insulin is an anabolic hormone that lowers the blood glucose level. It facilitates glucose uptake, increases synthesis and storage of glycogen (glucose store), increases lipids synthesis and decreases proteolysis, lipolysis and gluconeogenesis (synthesis of glucose). Glucagon in turn is a catabolic hormone, with actions the opposite of insulin: it elevates blood glucose through gluconeogenesis and glycogenolysis (the breakdown of glycogen). It also decreases the synthesis of fatty acids and decreases lipolysis. The release of insulin is triggered by a low blood sugar level whereas high blood sugar is a signal to release glucagon. In healthy people the interplay of these two hormones secures constant euglycemia, or blood glucose levels oscillating within a physiological range of 70 -140mg/dL (3.9-7.8 mmol/L) throughout the day. A state of euglycemia is maintained thanks to the rapid breakdown of glycogen into glucose and the release of glucose into the blood and vice versa, by the prompt absorption of the “excess” blood sugar by tissues such as muscles and its transformation into glycogen. Consequently, the level of glucose, which is the principal source of energy for cells, remains adequate after both, a copious dinner rich in fast-digesting carbohydrates as well as after an overnight fast. In people with diabetes, glucagon responses to treatment-induced hypoglycemia are lost during the first years after diagnosis (1). Alternative mechanisms aiming to restore the physiological blood glucose level, such as the release of the hormone epinephrine, then become more important. Although people with diabetes who are treated with agents such as insulin or secretagogues are particularly prone to hypoglycemia, it should be also noted that healthy individuals, if dosed with a high amount of insulin, would develop signs and symptoms of low blood glucose. This

will happen when the physiological balance between anabolic and katabolic hormones gets disrupted by an excess of insulin, i.e. the glucagon synthesis rate is insufficient to match the glucose-lowering effects of insulin. People with diabetes, notably with T1DM, have impaired counter-regulatory responses to low blood glucose, rendering them even more susceptible to hypoglycemia, including severe hypoglycemia [2].

3. Signs and Symptoms of Hypoglycemia

The symptoms of hypoglycemia result from the reaction of the body to an insufficient concentration of glucose and from an attempt to increase the blood sugar level through alternative mechanisms. This process can be illustrated by the pain caused by a mild injury or burn – it's unpleasant but not harmful per se –an individual is alerted of an impending danger. Therefore, such symptoms, as long as properly interpreted, can serve as a warning of the development of acute hypoglycemia. However, if not treated in a timely and adequate way, the incident may pose a danger to such a person.

The symptoms and signs of hypoglycemia can be classified as adrenergic and neuroglycopenic. The initial symptoms result from the activation of the autonomic system and the secretion of counter regulatory hormones as a measure to preserve the supply of glucose to the brain [3]. Frequently encountered adrenergic symptoms include sweating, tremors or palpitations. Neurologic disfunction resulting from insufficient glucose level is referred to as neuroglycopenia and can be manifested by confusion, difficulty concentrating, or blurred vision. **Table 1** lists common sign and symptoms [4] of low blood glucose.

Table 1: Hypoglycemia signs and symptoms

Autonomic (adrenergic) signs and symptoms	Neuroglycopenic signs and symptoms	Non-specific symptoms
Shakiness	Poor concentration	Hunger
Sweatiness	Blurred or double vision	Headache
Trembling	Disturbed color vision	Nausea
Palpitations	Difficulty hearing	Tiredness
Pallor	Slurred speech	
	Poor judgment and confusion	
	Problems with short-term memory	
	Dizziness and unsteady gait	
	Loss of consciousness	
	Seizure	

In children, particularly in nursery school age children, hypoglycemia is often manifested by behavioral changes such as irritability, agitation, quietness, stubbornness, and tantrums and may be the result of a combination of neuroglycopenic and adrenergic responses [4]. This poses a challenge to parents, caregivers and teachers – a low blood glucose event in the absence of typical symptoms may be unnoticed or be misinterpreted, delaying the initiation of treatment. Consequently, the incidents may progress to a more severe form of hypoglycemia which may require medical intervention.

In older people adrenergic responses are less prominent, while neuroglycopenic symptoms predominate. Hypoglycemia in the elderly, who are often affected by numerous co-existing conditions, may be confused with a stroke, transient ischemic attack and early dementia [3]. This may also prevent the timely ingestion of carbohydrates and increase the risk of progression to severe hypoglycemia, where patients are no longer capable of self-treatment.

4. Classification

The classification of hypoglycemia into subcategories [5,6] helps evaluate the risk of hypoglycemia associated with various types of insulins and other drugs or interventions used in diabetes. It also helps interpret the results of clinical trials in diabetes. Regulatory authorities use the classification of hypoglycemia in order to assess the safety of new antidiabetic therapies or interventions in a standardized manner. A common understanding and application of hypoglycemia classification by health care professionals, trialists, regulators, health authorities and healthcare insurers helps to compare the head-to-head hypoglycemia risk of emerging therapies in diabetes with standard of care medications and interventions. This helps ensure that antidiabetic drugs introduced into the market have a satisfactory benefit – risk ratio on the one hand and give evidence to inform adjustments of diabetes management guidelines on the other. These definitions however do not play such an important role in the everyday care of an individual patient, although understanding the risks associated with different categories of hypoglycemia may help adjust treatment, which is particularly important for the prevention of severe hypoglycemia episodes.

Three main variables are accounted for in the determination of a hypoglycemia category: the blood glucose level, the presence of symptoms and the ability to self-treat

- Asymptomatic hypoglycemia.

Asymptomatic hypoglycemia is an event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤70 mg/dL (≤3.9 mmol/L). The episode is detected through a routine blood glucose measurement. Except for the test result, neither the person with diabetes is aware that he or she has had a low blood glucose

episode, nor people who were witnessing the measurements.

- Pseudo-hypoglycemia.

Pseudo-hypoglycemia is an event during which the person with diabetes reports any of the typical symptoms of hypoglycemia with a measured plasma glucose concentration >70 mg/dL (3.9 mmol/L) but approaching that level.

The utility of these two categories is questionable and they are not analyzed systematically. Frequent asymptomatic hypoglycemia episodes, especially at lower blood glucose levels, should raise concerns about hypoglycemia unawareness.

- Severe hypoglycemia.

Severe hypoglycemia is an event requiring the assistance of another person to actively administer carbohydrates, glucagon, or to take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

- Documented symptomatic hypoglycemia.

Documented symptomatic hypoglycemia is an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration ≤70 mg/dL (≤3.9 mmol/L).

- Probable symptomatic hypoglycemia.

Probable symptomatic hypoglycemia is an event during which symptoms typical of hypoglycemia are not accompanied by aplasma glucose determination but that was presumably caused by a plasma glucose concentration ≤70 mg/dL (≤3.9 mmol/L).

The blood glucose level threshold for symptoms can vary between individuals as well as within the same individual on different occasions [8]. For the evaluation of hypoglycemia risk using documented hypoglycemia categories (i.e. those with plasma glucose measurement below 70 mg/dL (3.9 mmol/L)), additionally more stringent blood glucose thresholds of 54 mg/dL (3.0 mmol/L) or 50 mg/dL (2.8 mg/dL) are often employed. Analyses using these lower thresholds can help bring more clinically relevant conclusions about the risk and impact of hypoglycemia.

Another classification, intended for use in regulatory clinical trials, is centered around a blood glucose level that signifies the risk of immediate and long-term danger to the individual [7]. Here less attention is paid to the symptoms of hypoglycemia. This approach, with one

variable less, i.e. the presence of symptoms, can simplify comparisons between treatments in terms of the risk of hypoglycemia.

- Level 1 hypoglycemia [7]

A glucose alert value of 70 mg/dL (3.9 mmol/L) or less. This need not be reported routinely in clinical studies, although this would depend on the purpose of the study.

Plasma glucose below this level serves as an alert to assist patients, their families, and their caregivers that there may be a need to adjust insulin dosing or provide raid acting carbohydrate [8].

- Level 2 hypoglycemia

A glucose level of <3.0 mmol/L (<54 mg/dL) is sufficiently low to indicate serious, clinically important hypoglycemia.

Glucose concentrations below 54 mg/dL (3.0 mmol/L) do not occur under physiological conditions in nondiabetic individuals and the avoidance of these levels in people with diabetes is important to reduce the risk of immediate and long-term consequence of hypoglycemia.

- Level 3 hypoglycemia

Severe hypoglycemia (common category for both classifications), as defined by the ADA (5, 6), denotes severe cognitive impairment requiring external assistance for recovery.

The definition of severe hypoglycemia implies that the person with diabetes is unable to self-treat. This should be distinguished from incidents where assistance was offered out of kindness, but the patient could have taken the countermeasure him or herself. The latter situation should not be considered a ‘severe hypoglycemia’ event.

An inability to self-treat is usually caused by neuroglycopenic symptoms, alone or on top of adrenergic symptoms. A confused patient may still be able to take carbohydrate orally, while more severe cases require parenteral therapy with glucagon or intravenous glucose. In many cases severe hypoglycemia is reversed promptly without sequalae, although some cases, particularly when the initiation of treatment was delayed, will progress to more severe forms which can be immediately life-threatening. Consequently,the avoidance of hypoglycemia, and in particular,of severe hypoglycemia, should always be among the objectives of the management of diabetes.

5. Hypoglycemia unawareness

People with diabetes who face recurrent episodes of hypoglycemia as well as those who

maintain tight glycemic control are at risk of developing condition known as hypoglycemia unawareness (or impaired awareness of hypoglycemia - IAH), i.e. a state of absent or reduced ability to recognize the onset of a low blood glucose episode. The threshold of detection of symptoms decreases as a result of an impaired counter-regulatory hormone response. When it becomes sufficiently low, the affected person may not feel adrenergic symptoms before the neuroglycopenic symptoms, such as confusion, come on and consequently not get alerted to the need for a countermeasure to reverse the episode. Prevention and, if applicable, treatment of this syndrome is very important. Unrecognized and untreated hypoglycemia can result in a seizure or unconsciousness: hypoglycemia unawareness is a risk factor for severe hypoglycemia; the risk increases 6-fold if a person has IAH [9]. This vicious circle is sometimes referred to as 'hypoglycemia begets hypoglycemia', i.e. with an increasing rate of hypoglycemia episodes, even mild ones, the awareness becomes impaired which increases the risk of further low blood glucose episodes at higher levels. Most severe hypoglycemia episodes occur at night as the adrenergic response to low blood glucose is further reduced by sleep [10]. Furthermore, the counter-regulatory response can be impaired in the case of post-exercise hypoglycemia. An acceptable awareness of hypoglycemia can be restored after a few weeks of strict avoidance of hypoglycemia. This may be supported by structured education and/or by the use of continuous glucose monitoring systems (CGM) fitted with an alarm function alerting users to impending low blood glucose levels, or sensor-augmented pump therapy with the ability to suspend insulin infusion in the case where low blood glucose has been detected.

6. Consequences of hypoglycemia

One of the key objectives of diabetes management is to reduce exposure to high blood glucose as a measure to prevent or delay the complications of hyperglycemia. These efforts are likely to be hindered by occurrences of hypoglycemia, and in turn, more stringent, i.e. lower glycemic goals pose a greater risk of low blood glucose episodes. Indeed, one large study (ACCORD) [11] revealed that a greater rate of hypoglycemia, including severe hypoglycemia, occurred among people assigned to intensive therapy, i.e. a group targeting a very tight control of blood sugar levels as compared to those who followed the standard therapy. Taken together, the occurrence and/or the fear of hypoglycemia may adversely affect glycemic control among people with diabetes, mainly those treated with insulin or secretagogue. In people with type 2 diabetes who are naïve to insulin, the fear of hypoglycemia may delay the decision to initiate insulin treatment, resulting not only in persistent high blood glucose levels, but also contributing to or accelerating long-term micro- and macro-vascular complications.

The immediate consequences of hypoglycemia reflect the nature of its symptoms and are perceived as daily inconveniences. Mild episodes can be quickly self-treated. Incidents of hypoglycemia with neuroglycopenia while driving can result in motor vehicle accidents; similarly, activities relying on balance, coordination, vision and alertness may result in injuries,

if a person is inflicted by neuroglycopenia [12]. Severe hypoglycemia associated with a coma or seizure may be fatal in the absence of timely treatment delivered by a third party. The long-term consequences of recurrent hypoglycemia include the fear of hypoglycemia, which may result in a deterioration of the control of diabetes. The long-term impact on the heart and the vascular system is unknown, although there are reports suggesting a link between symptomatic hypoglycemia and an increased risk of cardiovascular incidents [14]. The rate of macro-vascular incidents in people with type 2 diabetes was correlated with the history of severe hypoglycemia [15]. These included coronary heart incidents with myocardial infarction and cerebrovascular incidents with strokes. People may put on weigh if excessive eating becomes a strategy to avoid hypoglycemia. Children with early onset type 1 diabetes who were exposed to severe hypoglycemia before the age of five may have impaired cognitive performance as the brain and neurons of young children are particularly susceptible to neuroglycopenia [12].

Beyond immediate and long-term health risks, severe hypoglycemia also impacts the quality of life of the person with diabetes and causes stress for their family. Nocturnal hypoglycemia impacts the quality of life to a greater extent than episodes during daytime [13]. People with diabetes who experience a certain number of severe hypoglycemia episodes over a period of time and/or those treated with insulin, may, depending on country specific regulations, lose their driving license. They can be disqualified from jobs where impaired level of awareness may pose a risk to themselves or to the public. Hypoglycemia, and specifically episodes of severe hypoglycemia may also influence other areas such as social life, travel plans sport activities, etc.

7. Prevention of hypoglycemia

Approaches to preventing hypoglycemia combine education with person specific considerations. This way more customized strategies can be worked out, addressing individual circumstances. Important elements to evaluate include the pattern of hypoglycemia episodes, such as the usual underlying reasons, the time of the day when most of the low blood glucose episodes occur and their intensity. Insights into the anti-diabetes treatment regime, particularly regarding insulin, eating habits, alcohol consumption and physical exercise are very important, too. Evaluation of other variables such as coexisting ailments, concomitant medications, ability of self-care or age will further inform the development of a comprehensive prevention plan adapted to individual needs.

Structured diabetes education is an important task intended to achieve and maintain a satisfactory control of diabetes while keeping the rate of low blood glucose episodes at an acceptable level. Education on hypoglycemia is usually provided as an element of the overall education on diabetes management, and attention should be paid to make the hypoglycemia portion prominent, particularly at the time when the insulin treatment is commenced. Many

reasons that put individuals with diabetes at risk of hypoglycemia are subject to modification. Well-designed training can give confidence and help avoid behaviors which can result in dangerously low blood glucose levels. Education should not be limited to a person with diabetes but also extended to their families and caregivers. Important elements to be covered by diabetes educators include the risk factors for hypoglycemia, encouragement to monitor blood glucose systematically and the benefits of doing so, as well as situations when such monitoring should be intensified. Next, an understanding of the warning signs of hypoglycemia is essential as this will help detect and treat an incident promptly as well as the need to always keep a source of glucose or glucagon available nearby. Further topics may include lifestyle considerations such as dietary habits, alcohol consumption, and advice about physical exercise. In people who use insulin-based therapy, particularly mealtime (short acting) insulin, the training should cover insulin dose adjustment principles. This is because most of the hypoglycemia is associated with mealtime insulin though basal insulin can induce hypoglycemia, too. Adaptation of mealtime insulin doses has to be coupled with the ability to estimate the carbohydrate content of food. And finally, hypoglycemia treatment principles should be discussed. Dedicated training should be offered to people who have developed unawareness of hypoglycemia so as to help them reverse this condition effectively. Diabetes educators need to be flexible and adapt the training content and pace to the level of comprehension of their trainees with diabetes.

A mindful selection of medications used to treat diabetes can help reduce the incidence of hypoglycemia. This mainly concerns agents that are potent in reducing blood glucose levels. For instance, newer formulations of basal insulin, with a more stable time-action profile, can help reduce the risk of nocturnal hypoglycemia. Since hypoglycemia is a recognized key limiting factor to achieving satisfactory glycemic goals, new technologies target solutions that can help reduceits rate among insulin treated people. Flash glucose monitoring systems enable blood glucose control without the need for finger pricks. Continuous glucose monitoring (CGM) systems can help detect instances of asymptomatic hypoglycemia, including nocturnal episodes. Coupled with an alarm function, which alerts users of the decreasing blood glucose level, they can be a powerful tool to help reduce the number of hypoglycemia incidents. A sensor-augmented pump, i.e. a combination of an insulin delivery system with blood glucose monitoring is another approach to help achieve satisfactory glycemic control through a significant reduction in the number of hypoglycemia incidents.

Severe and/or recurrent non-severe hypoglycemia should prompt an evaluation of the current treatment regimen and/or the glycemic targets by the health care provider, and relevant lifestyle and/or therapeutic adjustments should follow. People who are both able and motivated to monitor their blood glucose closely may have their glycemic goals set more tightly whereas people not able or not willing to do these checks frequently should avoid having too challenging go alsas this may put them at a significant risk of hypoglycemia.

8. Treatment of hypoglycemia

Non-severe hypoglycemia is usually self-treated, with countermeasure consisting of fast-digesting carbohydrates, which could be a glucose tablet, sugary candy, or a drink such as fruit juice or non-diet soda. Such carbohydrates are promptly absorbed as glucose into the blood. People with diabetes, especially those treated with insulin should always have a countermeasure with them. Approximately 15 to 20 grams of carbohydrates should be taken when blood glucose of 70 mg/dL or less (3.9 mmol/dL) has been measured, regardless if accompanied by symptoms or not. Prompt treatment of hypoglycemia will prevent the episode from progressing to a more severe form. Blood glucose levels should be re-checked after approximately 15 minutes, and the treatment repeated if the level is still 70 mg/dL (3.9 mmol/dL) or less. These steps should be repeated until the blood glucose goes above this level. Snacks containing fat or protein, such as chocolate bars, are inappropriate for the initial treatment as they slow down the absorption of sugar and delay the restoration of a normal blood glucose level. Once the incident has been reversed, a meal or snack with slower-acting carbohydrates, e.g. a biscuit or some fruit, can be taken to prevent a reoccurrence.

More severe cases, when the ability to take counter measures orally is impaired will require treatment with a glucagon injection. Family members and caregivers should be educated how to administer glucagon. Intravenous glucose is usually given in a hospital setting.

9. Risk factors

The main risk factor for hypoglycemia is an absolute or relative excess of insulin [16]. An absolute excess of insulin could be the result of too high a dose of insulin, what may happen when the carbohydrate content of a meal was overestimated, or through accidental overdose, e.g. when an incorrect (too high) number of units were dialed on the insulin pen. Pen mix-up, i.e. an accidental injection using a mealtime insulin pen instead of the intended basal insulin dose can occur among people on mealtime and basal insulin treatment (basal-bolus regimen). A relative insulin excess happens with reduced food intake or missed meals, in situations where glucose utilization is increased such as during exercise, or when endogenous glucose production is decreased which can be seen after alcohol intake.

Physical exercise affects glucose response in many ways: through increased insulin absorption, increased sensitivity to insulin, and increased peripheral glucose utilization with a depletion of glucose stores. Exercise can also induce deficits in counter-regulatory hormones thus impairing the detection of symptoms. The risk of hypoglycemia is not only increased during and right after exercise, but also several hours later. Consequently, nocturnal hypoglycemia can occur for this reason. The risk is modulated by factors such as the duration, intensity, and type of exercise, and the time of day. Prevention combines frequent blood glucose monitoring, adjustment of basal and mealtime insulin doses and carbohydrate ingestion.

Alcohol reduces blood glucose levels by decreasing gluconeogenesis. Furthermore, the consumption of ethanol impairs hypoglycemia awareness and blunts the counter-regulatory response to hypoglycemia. Finally, symptoms of hypoglycemia can be masked by the neurological effects of alcohol.

Other risk factors include hypoglycemia unawareness and a history of recent severe hypoglycemia. Rates of hypoglycemia are greater in older people who have had diabetes for longer, particularly with those whose insulin therapy is lasting longer. Rates of severe hypoglycemia were shown to almost double in people aged > 60 years as compared to people < 60 years [17]. Very young children are also more predisposed to severe episodes. Coexisting conditions that put patients with diabetes at a greater risk of hypoglycemia include chronic kidney disease, coeliac disease, and hypothyroidism.

10. Conclusion

Hypoglycemia, particularly in people with diabetes who are dependent on insulin, is a major limiting factor in the attempts to achieve a satisfactory control of glycemia. It also poses immediate and long-term risks and impairs quality of life. Diabetes education and targeting individual risk factors are among the prevention strategies. Technological advances in the field of blood glucose monitoring and insulin delivery systems open the perspective for a further reduction in the rate of low blood glucose episodes, and consequently for a better control of diabetes which may delay or prevent diabetes complications.

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