

Evolution in Overcoming Barriers in Management of Diabetes: Hypoglycemia

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Abstract

The main objective of management of diabetes focuses on eliminating symptoms of hyperglycemia, preventing hyperglycemic and other metabolic complications, delaying onset of chronic deleterious microvascular disorders and reducing macrovascular risk. However, iatrogenic hypoglycemia remains a major limiting factor in attaining and maintaining desirable glycemic targets. Hypoglycemia is defined as plasma glucose concentration < 70 mg/dl exposing the individual to potential harm. Hypoglycemia is classified into level 1 being asymptomatic or symptomatic documented by blood sugar 54 - 69 mg/dl; level 2 with blood sugar < 54 mg/dl irrespective of symptoms and level 3 or “severe” requiring secondary assistance for resuscitation. Initial symptoms of hypoglycemia are attributed to catecholamine release whereas more serious manifestations are caused by neuroglycopenia. Moreover, nocturnal hypoglycemia and hypoglycemia unawareness present serious consequences including death. The most important goal is to identify patients at a high risk of hypoglycemia, patient education to be on alert for circumstances provoking hypoglycemia and modify treatment regimen based upon individual characteristics. Strategies to manage hypoglycemia are divided into 3 broad categories: 1) Prevention of hypoglycemia, 2) Use of novel technology such as self-blood glucose monitoring systems, insulin pumps, insulin auto injectors as well as newer therapeutic agents including regimens with low/no occurrence of hypoglycemia, and 3) Education of patients and caregivers in treatment of hypoglycemia e.g. use of oral glucose as well as use of glucagon kits.

Keywords

Diabetes, Hypoglycemia, Recognition, Prevention, Treatment

1. Introduction

The role of achieving desirable glycemic control in improving quality of life by eliminating symptoms of hyperglycemia as well as preventing acute metabolic and/or delaying micro and macro vascular complications in people with diabetes is well established [1]-[7]. However, iatrogenic hypoglycemia remains a major limiting factor in attaining and maintaining near normal glycemic indices [1]. Hypoglycemia is defined as abnormally low plasma or blood glucose concentration less than 70 mg/dl with a potential of exposing the individual to harm. Classification of iatrogenic hypoglycemia in subjects with diabetes has evolved over the last several years (Table 1).

Table 1. Changing guidelines for classification of hypoglycemia [8].

Classification of hypoglycemia		
American Diabetes Association Workgroup on Hypoglycemia - 2005 report		
Category	Criteria	
Severe	Symptoms requiring active assistance of another person to treat. Is independent of blood glucose	
Documented symptomatic	Symptoms with a measured low plasma glucose, self-treated	
Asymptomatic	No typical symptoms but, a measured low plasma glucose	
Probable symptomatic	Symptoms typical of hypoglycemia, not accompanied by a plasma glucose determination	
Pseudo/Relative	Typical symptoms of hypoglycemia with a measured PG concentration > 70 mg/dl	
Canadian Diabetes Association 2013: Hypoglycemia Clinical Practice Guidelines		
Category	Criteria	
Severe	Individual requires assistance of another person. Unconsciousness may occur. PG < 50 mg/dl	
Moderate	Autonomic and neuroglycopenic symptoms are present. The individual is able to self-treat	
Mild	Autonomic symptoms are present. The individual is able to self-treat	
American Diabetes Association Standards of Medical Care in Diabetes 2017		
Level	Glycaemic Criteria	Description
Glucose alert value (Level 1)	≤70 mg/dL	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy
Clinically significant hypoglycemia (Level 2)	<54 mg/dL	Sufficiently low to indicate serious, clinically important hypoglycemia
Severe hypoglycemia (Level 3)	No specific glucose threshold	Hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery

2. Clinical Manifestations of Iatrogenic Hypoglycemia

2.1. Type 1 Diabetes

Hypoglycemia is an inevitable event in patients with type 1 diabetes. Patients with type 1 diabetes have an especially high rate of occurrence of hypoglycemia with almost 3% - 4% of deaths being attributed to this dangerous side effect [5]-[15].

Asymptomatic hypoglycemia is a frequent side effect especially in type 1 diabetes with almost up to 10% of patients unknowingly suffering through it with a fall in plasma glucose reaching as low as <50 mg/dl (2.8 mM/l) [5] [10] [11] [15]. Continuous Glucose Monitoring System (CGMS) documented an average of two episodes of symptomatic hypoglycemia per week and 1 - 2 episodes of severe and temporarily disabling, hypoglycemia approximately once a year requiring hospitalization in subjects with both types receiving multiple daily doses of insulin [2] [12] [13]. Thus, hypoglycemia has become a “matter of fact” of life especially in type 1 diabetes with occurrence of thousands of episodes throughout their lifetime.

2.2. Type 2 Diabetes

Fortunately, the incidence of hypoglycemia is significantly lower during the initial stage of the disease in patients with type 2 diabetes when compared with subjects with type 1 diabetes. However, with the progression of the disease with gradual descent towards being insulin deficient, hypoglycemic events become more frequent due to exogenous insulin administration required for treatment owing to chronic escalating insulin deficiency [16]-[22]. Fortunately though, even with vigorous insulin therapy, the rates of severe hypoglycemia in type 2 diabetes are approximately about 10% of those in type 1 diabetes and range from nearly 62 - 170 episodes per 100 patient years [1] [2] [5] [11] [12] [13] [15] [20] [21] [23].

2.3. Manifestations of Hypoglycemia

Symptoms of Hypoglycemia are divided into 2 groups:

1) Induced by catecholamine or cholinergine release: jitters, shakiness, drenching sweats, palpitations, hunger, paresthesias, systolic hypertension etc. 2) Neuroglycopenic symptoms due to neuronal glucose deprivation activating autonomic nervous system responses and limiting neuronal metabolism [5] [22] [23] [24] [25]. They include sensations of warmth, weakness, fatigue, difficulty in concentration, confusion, behavioral changes, irritability and emotional instability. However, the most serious neuroglycopenic include confusion, convulsion, coma and occasionally death. Symptoms in group 1 often precede the more serious manifestations in group 2. Catecholamine mediated symptoms are thought to be related to the rapidity of fall in blood sugar and usually manifest with blood sugar falling below 70 mg/dl whereas neuroglycopenic manifestations often occur with blood sugar levels < 54 mg/dl.

Nocturnal hypoglycemia is suspected with presence of nightmares and/ or night sweats followed by headache, fatigue, confusion on awakening associated with rebound hyperglycemia (Somogyi effect). Determination of blood sugar level with self-blood glucose monitoring equipment is recommended to document the presence of hypoglycemia with onset of aforementioned symptoms followed by oral or parenteral administration of glucose for resuscitation.

Prior to advent of point of care blood glucose testing devices, hypoglycemia was suspected in all subjects with diabetes on onset of typical manifestations especially a change in mental status or loss of consciousness. Glucose was administered without confirmation of low blood sugar often with remission of symptoms. Moreover, deleterious outcomes were rarely noted on administration of glucose in subjects with diabetes with obtundation secondary to other causes. In contrast, occasionally, neuroglycopenic symptoms were attributed to neurological disorders, e.g. seizure, stroke etc. thus delaying the diagnosis and treatment with detrimental outcomes.

3. Diagnostic Criteria for Hypoglycemia

Whipple's triad is diagnostic and includes symptoms compatible with hypoglycemia confirmed by documentation of low plasma or blood glucose concentration and resolution of symptoms after ingestion or intravenous administration of glucose resulting in raised or normal blood sugar concentration. The triad holds well since the availability of point of contact glucose testing. Subjects with diabetes of moderate duration readily recognize onset of hypoglycemia even though the symptoms and signs of hypoglycemia are nonspecific. Hence it's crucial for the newly diagnosed diabetic patients to keep a regular record and monitoring of their low glucose levels coinciding with the onset of symptoms [5]. Since glucose levels less than 70 mg/dl can hamper defenses against subsequent hypoglycemia, we recommend provision of self-blood glucose testing kits to all subjects with diabetes irrespective of type as well as prescribed drugs.

4. Consequences of Hypoglycemia (Table 2)

Hypoglycemia potentially may result in serious outcomes especially in the elderly as well as all subjects following frequent recurrences.

Table 2. Adverse consequences of hypoglycemia.

Brain death
Ventricular arrhythmia
Non-fatal cardiac events like MI
Motor vehicle and other accidents
Autonomic failure leading to unrecognized hypoglycemia
Stroke
Suboptimal glycemic control
Employment limitations

5. Pathogenesis of Hypoglycemia in Diabetes

In normal subjects, initial defense against falling plasma glucose concentrations include the decline in insulin secretion, which decreases utilization of glucose by insulin sensitive tissues such as adipose tissue or skeletal muscle while also promoting hepatic and renal glucose production [1] [5]. Decline in plasma glucose stimulates glucagon secretion which plays a critical role in glucose counter-regulation by facilitating hepatic glycogenolysis and gluconeogenesis. In addition, catecholamines, cortisol and growth hormone are released promptly in response to falling glucose levels and prevent hypoglycemia by enhancing glucose production promptly (within minutes) [1] [5] [15].

A surplus of therapeutic insulin (absolute or relative) especially in association with inadequate food intake and/or exercise is established to lower plasma glucose concentrations into hypoglycemic range in subjects with both type 1 and type 2 diabetes. Hypoglycemia also occurs frequently in subjects with diabetes in presence of renal disease because of exaggerated peaks and longer duration of action due to decline in clearance of exogenous insulin. Rarely, generation of insulin antibodies may contribute to recurrent hypoglycemic events; “Autoimmune hypoglycemia” in subjects receiving insulin for several years [26]. Alternatively, impaired regulation in secretion of all three counter regulatory hormones, exacerbates and perpetuates occurrence of hypoglycemia in subjects with both type 1 and type 2 diabetes [1] [5] [15] [27]-[33].

Aberration of glucagon secretion by pancreatic alpha cells is more pronounced in comparison to other counter regulatory hormones. Glucagon response to declining glucose levels is inhibited, a signaling defect in diabetes of both types though with greater impairment in type 1 diabetes [34] [35] [36] [37] [38]. Fortunately, Glucagon secretory response to stimuli other than hypoglycemia such as amino acid infusion or ingestion of high protein diet is largely, though not entirely preserved [37] [38].

Preserved physiologic regulation of compensatory glucose secretion early in the course of type 2 diabetes is apparently responsible for relatively low frequency of hypoglycemia [1] [5] [39] [40] [41]. However, hypoglycemic events occur more frequently with worsening insulin deficiency secondary to progressive beta cell failure in type 2 diabetes [1] [5] [18] [39] [40]. Recurrent hypoglycemic episodes, eventually impair the hormonal and symptomatic responses to subsequent hypoglycemia and hence raise the threshold for low plasma glucose levels leading to hypoglycemia unawareness [30]. Alternatively, onset of autonomic failure (**Figure 1**) induced attenuation of sympathetic neural and hormonal as well as adrenomedullary responses to hypoglycemia in long standing diabetes leads to hypoglycemia unawareness with progression to potentially life threatening neuroglycopenic manifestations [1] [15] [39]-[45].

6. Risk Factors for Hypoglycemia Excess of Insulin

Absolute or relative excess in circulating insulin due to endogenous production

Hypoglycemia-Associated Autonomic Failure

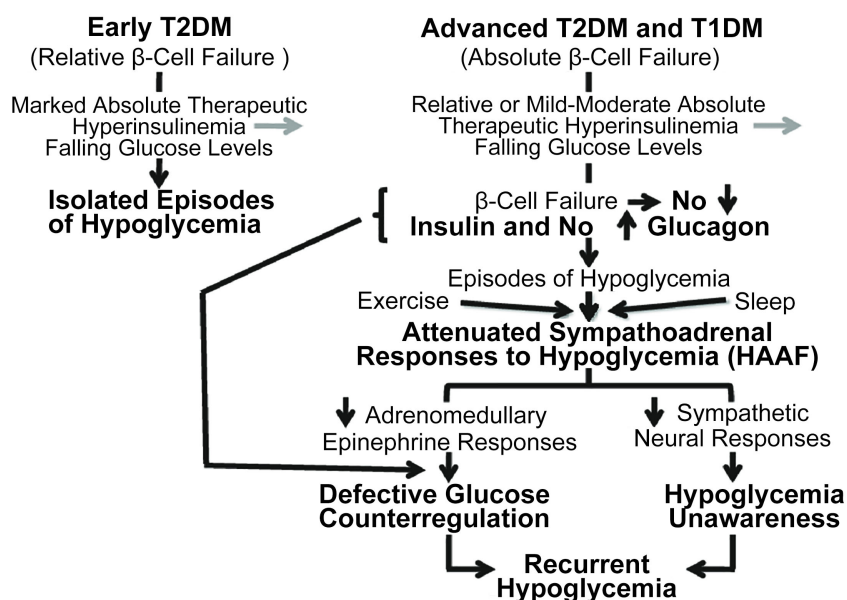


Figure 1. Diagrammatic depiction of hypoglycemia-associated autonomic failure in diabetes [70].

or via exogenous administration has proven to be a major risk factor for hypoglycemia [1] [5] [39] [40] [41]. However enhanced insulin sensitivity induced by drugs and/or exercise as well as increased physical activity also play a critical role in onset of hypoglycemia [3] [4] [44] [45] [46].

The most common cause of hypoglycemia in subjects with diabetes is the absolute or relatively increased circulating insulin concentrations following administration of insulin [47]-[56]. Amongst insulins, rapid acting variety is the most frequent culprits. However, newer analogs have been safer as compared to older prandial insulins [47] [48] [49] [50]. Alternatively, hypoglycemic events ensue during the night or early morning following administration of basal insulins especially at bedtime [51]-[56]. Hypoglycemia also occurs on administration of any insulin being ill timed, or of the wrong type, or if the dose is apparently excessive [47]-[56]. Enhanced insulin secretion following administration of insulin secretagogues contributes to occurrence of hypoglycemia in subjects with type 2 diabetes [3] [4] [45] [46] [47] [57] [58]. Finally, hypoglycemia may occur with overt aggressive glycemic control ($HbA1c < 6.5$), acute alcohol ingestion, adjuvant therapy with drugs for associated disorders, weight loss, progressive renal failure etc [47] [59] [60] [61] [62] [63]. Thus, the risk factors for hypoglycemia include erratic eating patterns, inappropriate administration of insulin or oral drugs, untimely exercise schedules, overtly aggressive control and most importantly, however unawareness.

Hypoglycemia unawareness is due to absence of manifestations mediated by catecholamine release. Thus, further decline in circulating glucose level ensues leading to life threatening neuroglycopenic manifestations including confusion,

convulsion and coma. Hypoglycemia unawareness is attributed to autonomic dysfunction, adrenal medullary failure, long duration of diabetes as well as drugs including ACE inhibitors as well as alpha and beta adrenergic blockers [64]-[73].

7. Treatment of Hypoglycemia

The foremost and vital aspect in treatment of hypoglycemia is to recognize the high risk patients and then titrate their treatment regimen accordingly. The approach to successfully manage hypoglycemia in subjects with diabetes is diversified into the following tenets:

- Prevention of hypoglycemia
- Use of available therapeutic agents/treatment regimens with low/no occurrence of hypoglycemia
- Treatment of hypoglycemia

Prevention and treatment of hypoglycemia have evolved with improvement in recognition following advent of point of care glucose testing tools, safer insulin formulations as well as oral drugs, individualized desirable glycemic targets based on patient characteristics and availability of diabetes education [45]-[62] [74]-[81]. Until the availability of self-monitoring of blood glucose (SMBG), diagnosis of hypoglycemia was based on symptoms alone. Similarly, the treatment consisted of either oral administration of granulated sugar or sweet liquids if the patient was awake enough to swallow. In presence of a change in mental status, the patient had to be rushed to the hospital for administration of glucose intravenously until glucagon kits were formulated and became available [82]-[87].

With technological advances in SMBG, most episodes of symptomatic hypoglycemia are confirmed by point of care testing and therefore are effectively self-treated by ingestion of glucose in form of granules, tablets or gels. An initial glucose dose of 20 g is recommended [47] [61] [62]. Alternatively, 4 oz. of fruit juice or other sugar containing liquids may be administered. Glucose administration in any form should be repeated in 15 - 20 min if symptoms persist or the monitored blood sugar remains low. However, the glycemic response to oral glucose is typically short lived usually lasting up to 2 hours [47] [61] [62].

Continuous glucose monitoring systems especially with “alerts” indicating falling glucose trends help prevent occurrences of asymptomatic hypoglycemic events. Moreover, most recent insulin pumps are equipped with the ability to adjust the rate or total suspension of insulin administration on blood sugar falling below the set lowest target of blood glucose [74]-[81]. Thus, home blood glucose monitoring remains a core component of effective diabetes self-management with amelioration of both hyper and hypoglycemia. If a patient manifesting hypoglycemia is unable or unwilling (because of neuroglycopenia) to ingest carbohydrate, glucagon is administered by family members to treat hypoglycemia in type 1 diabetes [82]-[87]. However, in type 2 diabetes the use of glucagon may not be as effective as it stimulates insulin secretion concomitant with glycogenolysis. Glucagon was available only in injectable form until recently when other formulations including glucagon powder for nasal administration were approved by

Table 3. Guidelines for increasing food intake to allow for extra activity in diabetics on insulin therapy [91].

Activity increase/extra hour of activity (gm/carbohydrate)
Moderate activity (e.g., tennis, cycling, jogging, swimming) 10 - 15
Strenuous activity (e.g., shoveling snow, ice hockey, football) 30 - 50

regulatory agencies [82]-[87]. Intravenous glucose administration is more effective than glucagon in resuscitating patients with severe hypoglycemia. Nocturnal hypoglycemic events may be avoided by substituting pre-prandial administration of short-acting (regular) insulin by rapid acting insulin analogue (e.g., lispro or aspart) [47] [48] [49] [50]. Similarly, replacing long-acting insulin analogue (e.g., glargine or detemir) for intermediate-acting insulin.

(NPH) may also reduce the frequency of nocturnal hypoglycemia [51]-[56]. Episodes of nocturnal hypoglycemia may be almost totally ameliorated by administration of basal insulin glargine in the morning [55] [56]. Ingestion of a bedtime snack is another effective remedy [88].

Other approaches such as, night-time administration of terbutaline, caffeine, glucagon stimulating amino acid alanine and the slowly digested carbohydrate uncooked cornstarch have been reported though rarely recommended [89] [90]. Finally, exercise induced hypoglycemia can be prevented by appropriate strategies (Table 3).

In conclusion, hypoglycemia and subsequent fear of hypoglycemic episodes are pivotal parameters in diabetes management and can pose a substantial threat to optimal compliance to treatment. Severe hypoglycemia requiring the assistance of another person is a clinical emergency unless the onset is attributed to a remedial variable, such as a missed meal after insulin injection or a vigorous exercise without the appropriate regimen adjustment. A substantive alteration in the treatment regimen may be required to prevent recurrence. Lack of adjustment may result in an unacceptably high risk of recurrent severe hypoglycemia detrimental to life. However, attaining and maintaining desirable glycemic control while minimizing the risk of hypoglycemia has become feasible with advent of technological advances including continuous glucose monitor systems, insulin pumps, safer evolving formulations of insulin as well as newer oral agents and patient education.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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