Review Article

Hypoglycemia: The neglected complication

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ABSTRACT

Hypoglycemia is an important complication of glucose-lowering therapy in patients with diabetes mellitus. Attempts made at intensive glycemic control invariably increases the risk of hypoglycemia. A six-fold increase in deaths due to diabetes has been attributed to patients experiencing severe hypoglycemia in comparison to those not experiencing severe hypoglycemia Repeated episodes of hypoglycemia can lead to impairment of the counter-regulatory system with the potential for development of hypoglycemia unawareness. The short- and long-term complications of diabetes related hypoglycemia include precipitation of acute cerebrovascular disease, myocardial infarction, neurocognitive dysfunction, retinal cell death and loss of vision in addition to health-related quality of life issues pertaining to sleep, driving, employment, recreational activities involving exercise and travel. There is an urgent need to examine the clinical spectrum and burden of hypoglycemia so that adequate control measures can be implemented against this neglected life-threatening complication. Early recognition of hypoglycemia risk factors, self-monitoring of blood glucose, selection of appropriate treatment regimens with minimal or no risk of hypoglycemia and appropriate educational programs for healthcare professionals and patients with diabetes are the major ways forward to maintain good glycemic control, minimize the risk of hypoglycemia and thereby prevent long-term complications.

Key words: Diabetes mellitus, glucagon, hypoglycemia, hypoglycemia unawareness, insulin, management, physiologic impact, quality of life

Introduction

Following the publication of the results of the Diabetes Control and Complications Trial (DCCT) in patients with type 1 diabetes mellitus (T1DM) and the United Kingdom Prospective Diabetes Study (UKPDS) in type 2 diabetic patients (T2DM), strict glycemic control has been heavily emphasized in the management of diabetes.[1,2] These findings redirected patient care strategies, with several guidelines setting target glycated hemoglobin (HbA1c) values at ≤7%.[3] However, three subsequent large randomized controlled trials (RCTs) looking at intensive glycemic control have either shown no benefit (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation, ADVANCE[4] and Veterans Affairs Diabetes Trial, VADT)[5] or an increase in all-cause mortality (Action to Control Cardiovascular Risk in Diabetes, ACCORD].[6] These trials have appropriately demonstrated that attempts made to achieve aggressive HbA1c goals (<6.5%) are associated with a three-fold increase in the risk of hypoglycemia, counterbalancing the benefits conferred by intensive glucose control.[7] Similar results were observed in Stockholm Diabetes Intervention study (SDIS) which showed a 2.5 times greater incidence of hypoglycemia in intensively treated patients with T1DM.[8] Likewise for patients with T2DM, the proportion of patients with one or more hypoglycemia episodes in a year was significantly higher in intensive treatment group compared to conventional group as observed in the UKPDS study.[2] Hypoglycemia, an often under-appreciated problem, is the most common and

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.117219

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serious side effect of glucose-lowering therapies. Repeated episodes of hypoglycemia can adversely affect defense mechanisms against falling blood glucose, resulting in significant morbidity and mortality which is reportedly associated with a six-fold increase in death.[9,10]

Evidence from several observational studies such as such as the UK Hypoglycemia Study,[11] a retrospective questionnaire based study from Denmark[12] and the Diabetes Audit and Research in Tayside, Scotland (DARTS) study[13] indicates that risk of hypoglycemia is particularly high among patients treated with insulin. Evidence from several studies suggests that severe hypoglycemia occurs in 35-42% of T1 DM patients and the rate of severe hypoglycemia is between 90-130 episodes/100 patient years.[14-17] The UK Hypoglycemia Study found that patients with longer duration of diabetes (>15 years) experienced higher rates of severe hypoglycemia than those with smaller duration (>5 years) (46% vs. 22%). The study also reported increased rates of hypoglycemia in those with longer duration of insulin treatment.[11] A retrospective questionnaire based study from Denmark in insulin treated type 2 diabetes patients reported at least one episode of severe hypoglycemia in 16.5% of patients with an incidence of 44 episodes/100 patient years.[12] Similarly, data from the DARTS study indicated that the severe hypoglycemia was 7.1% in patients with T1DM and 7.3% in patients with T2DM treated with insulin, compared with 0.8% in patients with T2DM treated with an oral sulfonylurea.[13] Moreover, hypoglycemic events, especially severe episodes, lead to a substantial increase in the direct and indirect costs of medical care.[13,18-21] People with T2DM lose on average three productive days, with a mean length of hospital stay between 6.6 and 9.5 days, following a severe hypoglycemic attack.[20,21] Given the compelling evidence of the potential harms associated with hypoglycemia, multiple strategies to minimize hypoglycemia should be adopted. The purpose of this review is to discuss the importance of hypoglycemia in the management of patients with DM, with an aim to improve understanding of the risk factors, impact and consequences of hypoglycemia. While recent progress related to prevention of hypoglycemia including patient education strategies and the use of newer therapeutic agents with a lower risk for hypoglycemia aim at achieving and maintaining optimal glycaemic control, hypoglycemia still remains a major challenge which needs to be addressed for better management and treatment of patients with diabetes.

Hypoglycemia: Causes, Symptoms and Risk Factors

Both the American Diabetes Association (ADA) and the European Medicines Agency have defined hypoglycemia as "any abnormally low plasma glucose concentration that exposes the subject to potential harm" with a proposed threshold plasma glucose value <70 mg/dL (<3.9 mmol/L).[22,23] Classification of hypoglycemia based on clinical manifestation and ability to self-treat has been shown in Figure 1. Iatrogenic hypoglycemia associated with diabetes medications are among the most common causes of hypoglycemia in patients with diabetes.[24,25] Although the frequency of hypoglycemic events in patients treated with OADs or incretin-based therapies may be lower than patients treated with insulin, evidence suggest higher incidence of hypoglycemia in patients treated with OAD[25] or incretin based therapies especially when glucagon like peptide-1 receptor agonists are combined with sulphonylureas.[26] So, it could be inferred that majority of hypoglycemic episodes experienced by patients with diabetes are related to medication. Hypoglycemia may also result from certain seldom causes such as pancreatic or non-islet cell tumors, autoimmune conditions, organ failure, endocrine disease, inborn errors of metabolism, dietary toxins, alcohol consumption, stress, infections and miscellaneous conditions (such as sepsis, starvation, severe excessive

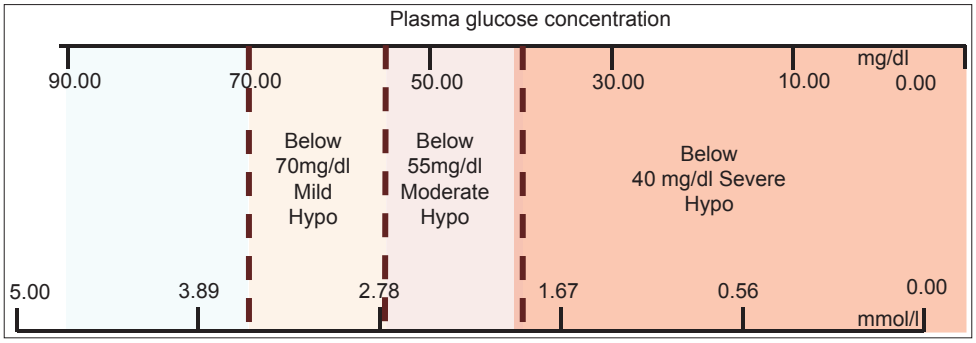

Figure 1: Classification of hypoglycemia Mild hypoglycemia is associated with the presence of autonomic symptoms and individuals are able to self-treat; Moderate hypoglycemia is associated with autonomic* and neuroglycopenic# symptoms and the individual is also able to self-treat; Severe hypoglycemia, the individual requires the assistance of another person and unconsciousness may occur; *Autonomic symptoms are those manifested as a cause of activation of the sympathetic nervous system and include trembling, palpitations, sweating, anxiety, hunger, nausea and tingling. #Neuroglycopenic symptoms are those manifested in response to decreased levels of glucose to the brain and include difficulty concentrating, confusion, weakness, drowsiness, vision changes, difficulty speaking, headache, dizziness and tiredness

exercise).[27] In a survey of diabetes patients (16-94 years of age) in Germany, UK and Spain showed that severe hypoglycemic events represent a substantial burden on national healthcare systems. Overall, insufficient food consumption was the most common cause identified for severe hypoglycemia (43% in T1DM and 47% in T2DM). Other causes included physical exercise (24% and 23%), insulin dose miscalculation (24% and 16%), stressful situations (12% and 17%), oscillating blood glucose levels (9% and 8%) and impaired hypoglycemia awareness (8% and 5%) in T1DM and T2DM, respectively.[28] [Table 1] summarizes the causes of hypoglycemia in people with diabetes.[25] Nocturnal hypoglycemia (an episode of abnormally low blood glucose (typically ≤63 mg/dL [approx. 3.5 mmol/L]) occurring at night time during sleep)[29] is an important condition observed in approximately 50% of children with T1DM especially those aged below 7 years.[30,31] It is often asymptomatic and undetected; occurring in more than half of blood glucose profiles performed overnight and may be prolonged.[31,32] Sudden nocturnal deaths also known as "dead in bed" syndrome has been attributed to nocturnal hypoglycemia, which account for 5%-6% of all deaths among young people with type 1 diabetes.[33,34] Contributory factors leading to nocturnal hypoglycemia may include increased physical activity in the last 24 h, imbalance between the antidiabetic regimen, longer time intervals between meals or impaired counter-regulatory mechanisms.[35,36] In addition, failure to detect warning symptoms of hypoglycemia due to reduced autonomic response during sleep may also aggravate the development of hypoglycemia.[37] Symptoms of hypoglycemia are categorized as neuroglycopenic or neurogenic (autonomic) which are further typified as adrenergic or cholinergic.[38] [Table 2] lists the symptoms and signs of hypoglycemia in people with diabetes.The most important risk factor for the occurrence of hypoglycemia is the aggressiveness of therapy applied to achieve glycemic control. An increased incidence of severe hypoglycemia with intensive glucose control therapy has been clearly demonstrated in several RCTs including DCCT, UKPDS, Treat-to-target trial (4-T), ADVANCE, ACCORD and VADT.[39] In addition to glucose-lowering medications, factors such as antecedent hypoglycemia,[26] alcohol, increased glucose utilization (e.g., exercise), decreased glucose production (e.g., liver disease), female sex, sleep,[40] duration of diabetes, age and progressive insulin deficiency were also found to be associated with an increased risk of hypoglycemia in patients with T2DM, which appears to be amplified in those who have received insulin for more than 10 years.[41] Multiple risk factors are associated with precipitation of hypoglycemia in the general population. The problem is of major concern when it comes to elderly patients with diabetes. The common risk factors for hypoglycemia in elderly patients has been summarized in Table 3.[42] Symptoms of hypoglycemia may become progressively less intense over time or even diminish altogether, resulting in hypoglycaemia unawareness of hypoglycemia in a significant proportion of patients with diabetes,[43] which is another important risk factor for severe hypoglycemia. Hypoglycaemia unawareness is associated with a 6-fold and 9-fold increased risk of severe hypoglycemia in patients with T1DM and T2DM, respectively.[44,45] [Table 4]

Table 1: Causes of hypoglycemia[25]

Cause	Examples
Incorrect insulin administration	Insulin taken in excess or at the wrong time relative to food intake and/or physical activity; incorrect type of insulin taken
Insufficient exogenous carbohydrate	Delayed or missed meals or overnight fast
Decreased endogenous glucose production	Excess alcohol consumption
Increased utilization of carbohydrate/depletion of hepatic glycogen stores	Exercise or weight loss
Increased insulin sensitivity	During the night, exercise, weight loss
Delayed gastric emptying	Condition such as gastroparesis
Decreased insulin clearance	Condition such as progressive renal failure

Table 2: Signs and symptoms of hypoglycemia

Early adrenergic symptoms	Neuroglycopenic signs
Pallor	Confusion
Diaphoresis	Slurred speech
Shakiness	Irrational or uncontrolled behavior
Hunger	Disorientation
Anxiety	Loss of consciousness
Irritability	Seizures
Headache	Pupillary sluggishness
Dizziness	Decreased response to noxious stimuli

Table 3: Risk factors for hypoglycemia in the elderly patients[42]

Life style related
Dietary error
Excessive physical activity
Alcohol intake
Drug related
Wrong dosage
Wrong time of administration
Wrong technique of administration
Medical disease related
Renal dysfunction
Hepatic dysfunction
Gastro intestinal dysfunction/malabsorption
Endocrine related
Hypo-pituitarism
Hypo-thyroidism
Hypo-adrenalism
Nervous system related
Cognitive impairment
Autonomic neuropathy
Gastrointestinal neuropathy

Table 4: Risk factors for hypoglycemia

Common risk factors of hypoglycemia
Strict glycemic control
Mismatch of insulin timing, amount, or type of carbohydrate intake
History of severe hypoglycemia
Sleep/general anesthesia or sedation that place patient in an altered consciousness
Duration of diabetes and age
Reduction of oral intake/New non per oral status
Impaired awareness of hypoglycemia
Angiotensin-converting enzyme genotype/C-peptide negativity
Critical illness (hepatic, cardiac, and renal failure; sepsis, and severe trauma)
Unexpected travel after injection of rapid-or fast-acting insulin
Less common risk factors of hypoglycemia
Endocrine deficiencies (cortisol, growth hormone, or both), non-β-cell tumor
Sudden reduction of corticosteroid dose
Pathological condition such as emesis/vomiting
Reduced rate of intravenous dextrose administration
Unexpected interruption of enteral feedings or parenteral nutrition
Drug dispensing error

summarizes the risk factors for hypoglycemia in general population with diabetes.

Hypoglycemia: Physiological Impact on Body

Autonomic activation following an episode of hypoglycemia may be associated with a range of symptoms progressing from sweating and palpitations to cognitive dysfunction and seizures. Hypoglycemia can lead to coma and even death, depending on its severity or duration. Hypoglycemia could potentially cause sudden cardiac death by inducing either ischemic or depolarization/repolarization changes. Impaired cognitive function can have potentially deleterious and cumulative long-term effects on intellectual function, particularly in young children.

Hypoglycemia and the brain

Glucose is the metabolic fuel for the brain. Acute interruption of glucose supply may result in functional brain failure and eventually lead to coma and death. There is a possible association between repeated episodes of severe hypoglycemia and long term cognitive dysfunction. Åsvold *et al.,* reported that the overall cognitive scores were lower in children with diabetes who had experienced severe hypoglycemic episodes than those without history of severe hypoglycemia.[46] Earlier studies also showed that severe hypoglycemia may aggravate the severity of the neurocognitive dysfunction in patients with diabetes.[47] Severe hypoglycemic episodes in older patients with diabetes have been shown to be associated with an increased risk of dementia,[48] functional brain failure[49] and cerebellar ataxia.[50] In human autopsy studies, of patients dying after an episode of severe hypoglycemia, as well as in animal models, the superficial layers of the cerebral cortex, hippocampus and caudate nucleus, were reported to be affected.[51] More recently, Bree *et al.,* reported that severe hypoglycemia causes damage in the cortex and the hippocampus regions and the extent of damage was closely correlated to the presence of seizure-like activity.[52]

Hypoglycemia and the heart

Patients with T2DM are associated with increased risk of cardiovascular disease.[53-55] A number of trials, in particular the ACCORD trial investigated the effects of intensive blood glucose control on macrovascular outcomes in patients with T2DM, has demonstrated increased mortality rates in patients who experienced episodes of hypoglycemia.[6] This trial have also demonstrated that achieving HbA1c <6.5% is associated with a three-fold increased risk of hypoglycemia.[6] Hypoglycemia has profound effects on CV function. Acute hypoglycemia provokes sympatho-adrenal activation and release of epinephrine which in turn stimulates hemodynamic changes by increasing cardiac rate and peripheral systolic blood pressure, reducing central blood pressure and peripheral arterial resistance and by increasing myocardial contractility, stroke volume and cardiac output.[56] Consequently, there is a significant increase in cardiac workload during hypoglycemia, which might prove dangerous in many older people with T2DM suffering from coronary artery disease. It may also interfere with coronary arterial perfusion and promote myocardial ischemia.[57] Coronary arterial perfusion, which occurs mainly during diastole, is enhanced by normal elasticity of the arterial wall which synchronizes the return of the reflected pressure wave from the high-pressure arterioles, generated during each myocardial contraction to the heart with coronary arterial perfusion. In non-diabetic people, acute hypoglycemia is associated with a decline in arterial wall stiffness but in people with diabetes of long duration, arterial wall stiffness as such is greater and arteries are less elastic in response to hypoglycemia, manifesting in a lesser fall in central arterial pressure. The decreased elasticity of arterial walls also accelerates the return of the reflected wave causing its earlier arrival during late systole.[58,59] Hypoglycemia is associated with a pro-arrhythmic state attributable to the increased catecholamine release in both T1DM and T2DM patients.[60] Prolongation of corrected QT interval (QTc), in particular, may lead to a high risk of tachycardia, fibrillation and sudden cardiac death.[61,62] Sudden death during sleep has been described in patients with T1DM, possibly due to a significant cardiac arrhythmia induced by nocturnal hypoglycemia.[63] Hypoglycemia may also potentiate cardiac repolarizing abnormalities as a result of hypokalemia due to hyperinsulinemia

and increased secretion of catecholamines.[62] Effects of antecedent hypoglycemia on cardiac autonomic regulation may contribute to the occurrence of adverse cardiac events.[64] Hypoglycemia has also been associated with abnormalities in high- and low-frequency heart rate variability.[65] It is difficult to demonstrate a direct relationship between hypoglycemia and fatal CV event as blood glucose and cardiac monitoring are rarely performed simultaneously. However, there have been case reports associating myocardial infractions with hypoglycemia.[66] In case of reduced plasma glucose, electrocardiogram changes, including ectopic activity, flattening of T-wave, ST depression, ventricular tachycardia, and atrial fibrillation, have been reported.[67] However, larger clinical trials are necessary to specifically look at the association between hypoglycemia and CV events and to determine the mechanisms further.

Hypoglycemia and counter regulatory responses

Several counter regulatory responses are induced by hypoglycemia including a decrease in pancreatic beta-cell insulin secretion, an increase in pancreatic alpha-cell glucagon secretion, an increased sympatho-adrenal response with acute plasma increase in adrenaline and norepinephrine, as well increased secretion of ACTH/glucocorticoids.[68] Hypoglycemia is associated with increased values of inflammatory markers including C-reactive protein, interleukin (IL)-6, IL-8, tumor necrosis factor -α and endothelin-1[69] that may result in endothelial injury and abnormalities in coagulation resulting in increased risk for CV events. Furthermore, inflammatory cytokines like IL-1 have also been shown to increase the severity of hypoglycemia, thus perpetuating a positive feedback cycle [Figure 1].[70] Further effects of hypoglycemia are induction of abnormalities in platelet function and activation of the fibrinolytic system.[71]

Hypoglycemia and the eye

Hypoglycemia is can cause visual disorder in individuals with diabetes and has been linked with diplopia, dimness/blurred vision and loss of contrast sensitivity. Animal studies and *in-vitro* studies, have reported that a decrease in glucose concentrations was associated with reductions in retinal sensitivity,[72] reduced viability of all retinal cell types,[73] retinal cell death,[74] loss of vision, reduction of retinal responses, increased retinal degeneration[75] and cone cell death.[76] More recently, Khan *et al.,* demonstrated that acute effects of hypoglycemia in human eye led to significant reduction of central retinal function and contrast sensitivity.[77]

Figure 2 summarizes the physiological impact of hypoglycemia on different systems and their counter-regulatory responses.

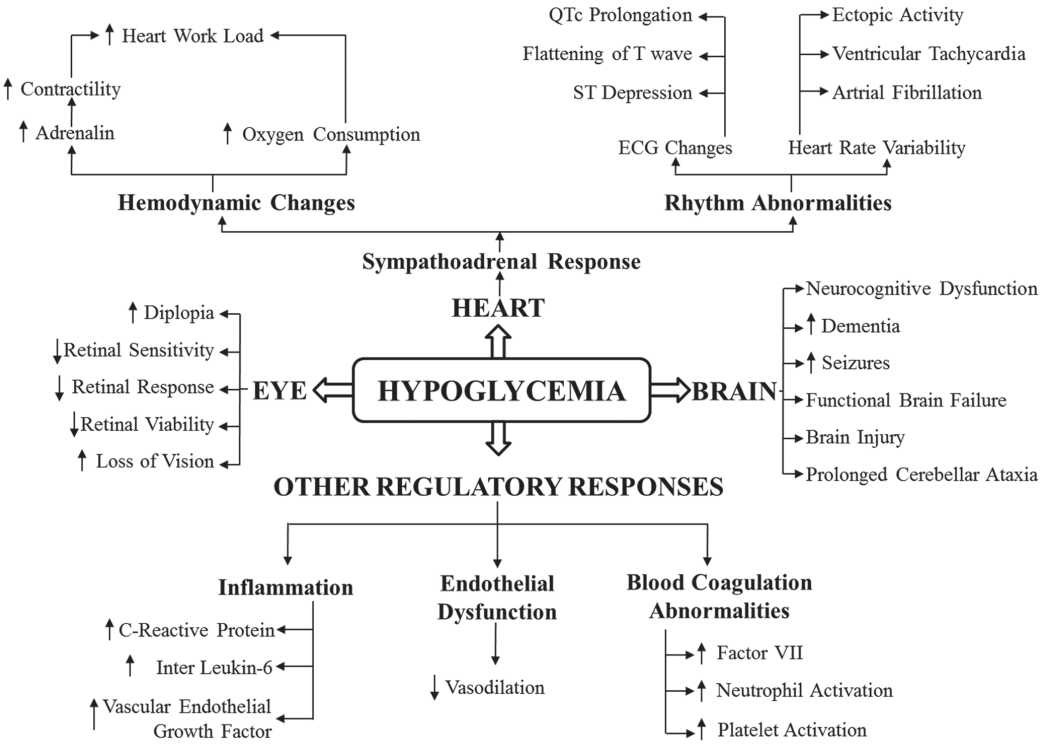

Figure 2: Physiological impact of hypoglycemia on different systems and their counter-regulatory responses. ECG: Electro cardiogram; ↑ denotes increased response; ↓ denotes decreased response

Hypoglycemia: Impact on Quality of Life

Hypoglycemia results in diminished psychological well-being and QoL. Recurrent hypoglycemic episodes generate feelings of powerlessness, anxiety, and depression amongst patients and their families.[78] Acute hypoglycemia can result in mood swings including irritability, stubbornness and feelings of depression.[79] A multicenter, cross-sectional, observational study in European patients with T2DM has evaluated the association between patient-reported hypoglycemic symptoms with ratings of HRQoL on a graduated EuroQol-5D visual analogue scale (EQ-5D VAS; 0-100 mm-scale) and patient-reported adverse events.[80] This study, reported that patients with symptoms of hypoglycemia had significantly lower EQ-5D VAS scores than patients without such symptoms (68.7 [16.9] *vs.* 73.5 [16.1] respectively), indicating a 4.8 (16.3) diminution of hypoglycemia on patients-reported QoL at $P < 0.0001$.[80] Compared with patients without hypoglycemic symptoms, patients with hypoglycemic symptoms had >3.5-fold increased risk of shakiness (95% CI 3.55, 2.9-4.4), almost 3-fold increased risk of sweating (95% CI 2.83, 2.3-3.5) and 2-fold increased risks of excessive fatigue, drowsiness, inability to concentrate, dizziness, hunger, asthenia and headache.[80] Using Insulin Treatment Satisfaction Questionnaire in an insulin-treated population, Brod and colleagues found no significant relationship between the type of minor hypoglycemic events (defined as symptomatic or asymptomatic) and overall treatment satisfaction. Diurnal hypoglycemic events however, did have a significant negative impact on overall treatment satisfaction. These events are more easily identified and bothersome to daily functioning compared with nocturnal events.[81] In patients experiencing hypoglycemic symptoms significantly lower HRQoL was reported on parameters including increased limitation on mobility (b = 0.66, OR = 1.93, $P < 0.0001$), usual activities (b = 0.58, OR = 1.78, $P < 0.0001$), increased pain/discomfort (b = 0.69, OR = 2.00, $P < 0.0001$) and anxiety/depression (b = 0.84, OR = 2.31, $P < 0.0001$).[82] Another study which evaluated the severity (defined as mild, moderate, severe and very severe) and frequency of hypoglycemia on QoL using the EQ-5D Questionnaire US-weighted summary score (utility) and worry subscale of the Hypoglycemia Fear Survey (HFS) reported a significant decrease in mean utility score (0.78 vs. 0.86, $P < 0.0001$) and increase in mean HFS score (17.5 vs. 7.2, $P < 0.0001$) compared with patients not reporting hypoglycemia.[83] The differences in mean scores between those with and without hypoglycemia increased with the level of severity for utility (0.03, 0.09, 0.18, 0.23) and HFS (6.1, 13.9, 20.1, 25.6), respectively, indicating an association between hypoglycemia with lower HRQoL.[83]

Driving and hypoglycemia

Driving is a common activity that is vulnerable to the effects of hypoglycemia. As evident from a simulator performance study, during episodes of hypoglycemia in patients with T1DM result in impaired task performance like driving across the midline and speeding.[84] A retrospective study by Cox *et al.,* suggested that drivers with T1DM are at an increased risk for driving mishaps than drivers with T2DM. Various factors that contribute to a higher probability of hypoglycemia-related driving mishaps include increased episodes of hypoglycemic blankness, less frequent self-monitoring blood glucose (SMBG), subcutaneous administration of insulin, greater carbohydrate utilization[85] besides mood changes, irritability and anger which impairs rapid decision making, sustained attention, analysis of complex visual stimuli and hand-eye coordination.[86] Acute hypoglycemia causes a progressive, reversible deterioration in cognitive function,[86-88] and patients may experience feelings of depression and anxiety which may affect their driving performance.[89] As a precautionary measure, SMBG should be performed when long journeys are planned.[90] In the United Kingdom, in accordance with current recommendations for assessing medical fitness to drive, the insulin-treated drivers in group 1 entitlement (car/motorcycle) and group 2 entitlements (lorry/bus) must be able to satisfy certain criteria. Insulin-treated drivers applying for group 1 license must have awareness of hypoglycemia; must not have had more than one episode of hypoglycemia requiring the assistance of another person in the preceding a year; must regularly monitor blood glucose levels which has been defined by the Secretary of State's Honorary Medical Advisory Panel on driving and diabetes as no more than 30 min before the start of the first journey and every 2 h while driving; must not be regarded as a likely source of danger to the public while driving; and must satisfy the visual standards for acuity and visual field.[91] Insulin-treated drivers must have full awareness of hypoglycemia; must demonstrate an understanding of the risks of hypoglycemia and must regularly monitor their blood glucose at least twice daily and at times relevant to driving, (not more than 2 h before the start of the first journey and every 2 h while driving), using a glucose meter with a memory function to measure and record blood glucose levels. At the annual examination by an independent consultant diabetologist, 3 m of blood glucose readings must be available.[91]

Sleep and hypoglycemia

Hypoglycemia occurring during sleep is a major area of concern, where episodes may be asymptomatic as a result of

impaired counter regulatory-hormonal response,[92] coupled with lower intensity of hypoglycemic symptom scores.[93] Sleep weakens neuroendocrine defense mechanisms against hypoglycemia and can cause fatal cardiac arrhythmia.[94] Episodes of nocturnal hypoglycemia represent a substantial proportion of hypoglycemic events that can occur any time of the night and often goes undetected.[95] A study using continuous glucose monitoring (CGM) identified unrecognized hypoglycemia in 60% of the patients, with 73.7% of those episodes occurring during night.[96] Although nocturnal hypoglycemia is asymptomatic, some patients experience sleep disturbances, morning headache, chronic fatigue, or mood changes. Convulsions or enuresis is particularly seen in children during nocturnal hypoglycemia.[97]

Employment and hypoglycemia

Hypoglycemia at work place can be awkward, embarrassing and frightening. Moreover; it is unacceptable in certain types of employment. In a prospective, survey for a year of 243 diabetic patients treated with insulin, it was found that 30% episodes of mild, and 11% episodes of severe hypoglycemia occurred at work.[98] The data clearly indicates that hypoglycemia can be dangerous to individuals working at heights or underwater, on railway tracks, on oil rigs, in coal mines, handling hot metals or heavy machines. A positive correlation has been observed between reduced productivity and increased health care costs associated with hypoglycemia among patients with T1DM or T2DM. In order to mitigate and manage the risk of hypoglycemia at workplace, planned action like counseling and expert medical advice should be included. SMBG, healthy food option at canteens, flexible meal times, arrangement to carry and consume emergency sugar, storage/disposal for medicines such as insulin and needles, and periodic time off for medical appointments should be supported for affected workers.[99] A multi-country study of 1404 respondents, which identified the impact on productivity of non-severe hypoglycemic events (NSHEs) occurring during working hours has shown that, 18.3% respondents either left work early or missed a full day with an average of 9.9h lost from working hours, 23.8% reported missing a meeting or work appointment, or not finishing a work task on time.[100] Impact of NSHEs outside of working hours also had an impact on respondents' work productivity resulting in absentism. Respondents who experienced a nocturnal NSHE, 22.7% reported arriving late for work or miss a full day of work. Nocturnal NSHEs also resulted in a missed meeting or work appointment or not finishing work on time among 31.8% of the respondents.[100] Results from a four-country survey has demonstrated that non-severe nocturnal hypoglycemic events (NSNHEs) were associated with a high proportion of respondents contacting a healthcare professional (18.6% T1DM, 27.8% T2DM), could not return to sleep at night (13.3% T1DM, 13.4% T2DM) and felt tired on the day following the event (71.2% for both). Among those working for pay, 18.4% T1DM and 28.1% T2DM respondents reported being absent from work due to the NSNHE, and 8.7% T1DM, 14.4% T2DM respondents also reported missing a meeting or work appointment or not finishing a task on time.[101]

Exercise, recreational activities and hypoglycemia

A number of factors have been identified that influence the risk of exercise-related hypoglycemia.[102] These include the nature, duration and intensity of exercise and its timing in relation to meals, site of insulin injection, the insulin regimen being used, and the ability to detect or react to a fall in blood glucose. Hypoglycemia during exercise may also result from impaired release of counter-regulatory hormones caused by a previous episode of hypoglycemia. Consequently, patients with T1DM who experience hypoglycemia on days preceding the final competitive event are at an increased risk on the day of the actual event due to an autonomic counter-regulatory failure during exercise.[103] Hypoglycemic episodes are common during endurance exercises such as marathon running and are multifactorial in etiology.[104,105] The frequency of hypoglycemia is higher in children during summer months, when physical activity is increased.[106] Evidence also suggests that intense and prolonged physical exercise following a recent episode of severe hypoglycemia can damage skeletal muscle and liver and can cause severe neuroglycopenic symptoms.[104]

Travel and hypoglycemia

Rapid travel across time zones can disrupt normal glycemic control and increase the risk of hypoglycemia because of irregular meal times and unpalatable meals, which may contain insufficient amount of carbohydrate.[107] The usual insulin regimen may be impossible to follow and problems of jet lag and fatigue may affect appetite and the timing of meals, as observed in travel sickness. Almost all individuals who travel long distances are subjected to physiological symptoms such as include insomnia, daytime somnolence, fatigue, stress, anorexia, nocturia, gastrointestinal discomforts, muscle aches and headaches[108] and psychological disturbances such as depressed mood, irritability, apathy, malaise, difficulty in concentrating, and decrements in both mental and physical performance[109] that may profoundly impair the decision making power of an individual.

Hypoglycemia: A Barrier in Diabetes Management

Hypoglycemia has long been recognized as an important limiting factor in the glycemic management of patients with

diabetes. It is a significant barrier in terms of adherence to medication and achieving normoglycemia with intensive therapy.[69] As was evident from the UKPDS[2] and US Veterans Affairs study,[110] intensive therapy is associated with an increased risk of severe hypoglycemia. Fear of hypoglycemia, an additional psychological burden that patients with T2DM experience can limit the aggressiveness of drug therapy resulting from reduced patients' willingness to take medication as directed.[111] A study that used the Hypoglycemic Fear Survey, which combined a worry and behavioral scale, found that patients with T2DM reported an increased fear of hypoglycemia over fear of long-term complications. Hypoglycemia was associated with significantly poor QoL and reduced treatment satisfaction.[25] Patients with diabetes who become hypoglycemic are also more susceptible to developing defective counter-regulation, leading to hypoglycemia unawareness which is a life-threatening situation and must be aggressively addressed.

Patient and physician perceptions towards hypoglycemia

Patient perception of hypoglycemia can differ from clinical definitions. A patient who experiences an episode of hypoglycemia for the first time will often refer to that event as being "severe" because of the fear that they might become powerless to prevent their own morbidity without outside assistance.[112] This may result in lower treatment satisfaction and non-adherence to treatment that can contribute to adverse clinical outcomes.[113] Barriers to insulin therapy may also include the health care providers who may have a general reluctance to initiate insulin because of the potential risk for hypoglycemia.[114] Elucidation of these obstacles and the reasons behind them can expose needs in diabetes management and assist in meeting them, as the Diabetes Attitudes, Wishes and Needs (DAWN) study has shown.[115] The DAWN study involving >5,000 people with diabetes and almost 4,000 diabetes care providers, showed that diabetes care focusing solely on medical targets was not enough as more than half of people with diabetes do not enjoy good health and QoL (DAWN study).[116] The study highlighted the need for a new approach including psychosocial and behavioral aspects, which looks beyond the glycemic control for effective diabetes management.[116] On the other hand the results of Global Attitudes of Patients and Physicians (GAPP) study examining the factors associated with insulin injection omission/non-adherence in 1530 insulin treated adults reported one or more days of insulin omission/non-adherence in one-third of the patients. The study suggests that several modifiable risk factors including practical barriers, injection difficulties, lifestyle burden and regimen inflexibility have been associated with insulin injection omission/non-adherence in patients with diabetes.[117] The initial findings of the recent DAWN2™ study focusing on the experiences of family members of people with diabetes and the lack of support available to them as caregivers indicate that the families of people with diabetes carry a major burden of the diabetes pandemic.[118]

Hypoglycemia unawareness

Repeated hypoglycemia blunts symptomatic and hormonal responses to subsequent episodes leading to hypoglycemia unawareness, which is an acquired syndrome associated with insulin treatment.[40] It occurs when the ability to perceive the onset of hypoglycemia is either diminished or completely lost at the physiological plasma glucose concentration at which warning symptoms normally occur. For the purpose of developing a clinical scoring system, awareness of hypoglycemia has been arbitrarily classified into 3 broad categories.[119]

1. Normal awareness where the individual is always aware of the onset of hypoglycemia
2. Partial awareness where the symptom profile changes with a reduction either in the intensity or in the number of symptoms and in addition, the individual may be aware of some episodes of hypoglycemia but not of others
3. No awareness where the individual is no longer aware of any episode of hypoglycemia.

Hypoglycemia unawareness which is associated with a 3-6 times higher risk of severe hypoglycemia is prevalent in 25% to30% of adults with T1DM and increases with duration of insulin therapy.[45,120] Less than 10% of adults with T2DM treated with insulin have evidence of hypoglycemia unawareness, but in those with this syndrome, the risk of severe hypoglycemia increases 6-7 fold even during standard therapy and usually in such patients intensified insulin therapy is not advisable.[40] In addition, nocturnal hypoglycemia diminishes the degree of cognitive dysfunction during subsequent hypoglycemia which explains why people with T1DM develop hypoglycemia unawareness.[121]

Agents with a higher risk of causing hypoglycemia

Insulin

Despite high risk of hypoglycemia, several international guidelines on diabetes emphasize intensive insulin treatment designed to reduce the risk of long-term diabetic complications. Higher incidence of hypoglycemia, particularly among patients treated with insulin over extended periods of time, reinforce the idea that disease progression and increased insulin use subsequently increases the risk of hypoglycemia with clinical consequences ranging from mild discomfort to coma and even death.[122,123] The UK Hypoglycemia Study Group found that the incidence of severe hypoglycemia in patients with T1DM treated with insulin for >15 years was three times higher than in

those treated for <5 years. In patients with T2DM, the prevalence of severe hypoglycemia increased from 7% to 25% when comparing patients treated with insulin for <2 years with those treated for >5 years, respectively.[11] Initiation of insulin therapy is thus often delayed owing to substantial fear of hypoglycemia among patients with diabetes.[122]

Sulphonylureas

Sulphonylureas, commonly used as second-line therapy in patients with T2DM, promote insulin release independent of prevailing glucose value and as a result, hypoglycemia is an expected side effect. A meta-analysis of 21 studies comparing glyburide with other anti-diabetic medications, including insulin, revealed a 83% higher risk of hypoglycemia with glyburide compared with other sulfonylureas while the risk of hypoglycemia was 52% higher when compared with those taking other insulin secretagogues.[124] A multi-center RCT, comparing the efficacy and hypoglycemia rates of modified-release gliclazide and glimepiride used over a 6-m period, found that the use of glimepiride was associated with a higher incidence of hypoglycemia (8.9%) than gliclazide (3.7%).[125]

In a study, by van Staa and associates, evaluating the risk of hypoglycemia in patients with T2DM receiving chlorpropamide, tolbutamide, glyburide, glipizide, or gliclazide revealed that the risk of hypoglycemia was higher in patients on glyburide therapy than in those who used other sulfonylureas.[126] Similarly, a study comparing the rates of hypoglycemia with second-generation sulfonylureas revealed that hypoglycemia occurred twice as frequently in patients receiving glyburide than those receiving glipizide.[127]

Meglitinides

They trigger insulin secretion with a faster onset and shorter duration of action anticipating a lower risk of hypoglycemia. However, studies have shown that the risk of hypoglycemia with repaglinide was similar to second-generation sulfonylureas.[128] A recent meta-analysis examining clinical trials with nateglinide added to metformin showed a greater risk of hypoglycemia with nateglinide than with sulfonylureas (RR = 7.4 vs. 4.57, respectively).[9,129]

Management of Hypoglycemia

The most important goal is to identify the patients at a high risk of hypoglycemia and modify their treatment regimen based upon individual patient characteristics. Strategies to manage hypoglycemia can be divided into 3 broad categories:

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

Prevention of hypoglycemia

To prevent or reduce the risk of hypoglycemia, it is important that the patient understands and agrees to adhere to all aspects of the treatment plan in terms of both medication and lifestyle modification. Educating the patient and his/her family members, along with self-monitoring of blood glucose (SMBG) are of paramount importance to prevent hypoglycemic episodes.

Patient education

Achieving adequate glycemic control without causing troublesome hypoglycemia is the key to providing optimum care to individuals with diabetes.[130] Education should be provided at a level appropriate to the patient understanding.[131] It is important to educate patients with DM about early identification of hypoglycemic symptoms, its causes, the various preventive measures and the available treatment options. These programs should also educate patients about the importance of frequent SMBG, good record keeping and regular follow-up with their primary care physicians.[131] There is evidence that blood glucose awareness training and cognitive behavioral therapy can help improve diabetes management. Interventions targeting health beliefs and attitudes about hypoglycemia and diabetes self-management can be more effective than knowledge-centered patient education, which focus on "symptom perception" in reducing hypoglycemia unawareness.[132]

Blood glucose monitoring

Regular measurement of blood glucose is one of the most effective ways of demonstrating blood glucose trends and identifying asymptomatic hypoglycemia.[9] It remains a core component of effective diabetes self-management in insulin-treated patients. Glucose monitoring can be done either by periodic self-monitoring of capillary blood glucose or by continuous glucose monitoring (CGM). In order to uncover hypoglycemia unawareness or high-risk patterns, periodic 7-point profile testing should be performed.[122]

SMBG can help detect hypoglycemia that would enable the patient to minimize the risk through appropriate insulin dose adjustments.[133] Although it is more frequently advised in patients with T1DM, T2DM patients treated with insulin may also benefit from regular monitoring in the prevention and self-treatment of hypoglycemia.[9] The recent ADA 2013 Standards of Care recommends, SMBG testing at least 6-8 times daily for patients using multiple daily injections (MDI) of insulin or continuous sub-cutaneous insulin infusion (CSII).[3]

CGM provides the patient with not only a real-time notification of interstitial blood glucose values but also sounds auditory alerts for extreme changes in blood glucose values, particularly nocturnal hypoglycemia in patients with T1DM.[134,135] CGM, together with intensive insulin therapy, can lower HbA1c values inT1DM who are ≥25 years.[136]

Use of novel therapeutic agents/treatment regimens with low/no occurrence of hypoglycemia

Pharmacological agents used in the treatment of diabetes should address the need of maintaining optimal glycemic control while reducing the risk of hypoglycemia. Consistent with their mechanisms of action, glucose-lowering agents can be broadly categorized as those having either a low- or a high-risk of hypoglycemia. As discussed earlier, agents that comprise the high-risk category include insulin, sulfonylurea and meglitinides, all of which increase the insulin level in a glucose-independent manner. On the other hand glucose-lowering agents such as biguanides (e.g., metformin), dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor (GLP-1R) agonists, alpha-glucosidase inhibitors, bile acid sequestrants (e.g., colesevelam), thiazolidinediones and amylin analog (e.g., pramlintide) are considered low-risk for hypoglycemia as they work in a glucose-dependent manner.[131] Selecting the appropriate regimen for patients with diabetes based on hypoglycemia risk is necessary to maintain good glycemic control.

Insulin therapy

An ideal insulin therapy for patients with diabetes should include long-acting basal insulin, to mimic the 24-hour endogenous insulin secretion by the pancreas and a bolus or short-acting insulin to mimic normal physiological insulin response to ingestion of a meal.[122] Advances in molecular biology have led to the development of insulin analogues with pharmacokinetic and pharmacodynamic profiles more to close to endogenous insulin with better glycemic control and reduced risk of hypoglycemia compared to traditional human insulin regimens such as human neutral protamine Hagedorn (NPH) insulin.[137] Modern insulin analogues include long-acting basal insulin analogs (e.g., detemir, glargine), short/rapid-acting insulin analogs (e.g., aspart, glulisine, lispro), and premixed insulin analogues (e.g., biphasic insulin aspart and insulin lispro).[122]

Basal insulin

Currently available basal insulins include NPH or isophane insulin, insulin glargine and insulin detemir. NPH insulin is a crystalline suspension of insulin with protamine and zinc that releases insulin at slower rate, providing intermediate-acting insulin with slow onset of action and longer duration of action than regular insulin. However, due to variable absorptions and peaks, most patients on this regimen experience early morning hypoglycemia.[122] To address these limitations, long-acting basal insulins analogues, insulin glargine and detemir have been developed which serve to mimic the basal action of insulin over a 24-hour period. Following once daily administration, both insulin glargine and detemir demonstrate a flat insulin profile that more closely matches endogenous insulin secretion.[138] A major advantage of these long-acting insulins is that they exhibit a substantially lower risk of overall hypoglycemic events while achieving similar to better glycemic control compared to NPH insulin. Evidence from studies indicate that patients treated with insulin glargine experience a 46% reduction in severe and 59% reduction in nocturnal hypoglycemia, compared with those treated with NPH insulin,[139] while use of insulin detemir was associated with a significant reduction in the risk of nocturnal hypoglycemia compared with NPH insulin. Administration of detemir in evening was associated with 65% ($P = 0.031$) reduction in nocturnal hypoglycemia, which further reduced by 87% ($P < 0.001$) with morning detemir compared to evening NPH.[140] In insulin-naïve patients with type 2 diabetes, addition of insulin detemir to oral antidiabetic drugs (metformin, insulin secretagogues, and α-glucosidase inhibitors) was associated with 47% reduction of all hypoglycemic events and 55% reduction in nocturnal hypoglycemia when compared with NPH insulin.[141] Evidence suggests that addition of basal insulin to existing OAD therapy in patients with T2DM confer less risk of hypoglycemia, particularly nocturnal hypoglycemia.[142-145] However, patients on this regimen often require addition of rapid-acting prandial insulin (basal-bolus regimen) as they tend to fail to achieve optimal glycemic control overtime.

Rapid-acting insulin

Basal/bolus therapy attempts to mimic the physiologic insulin release and provides a delicate balance between tight glycemic control and avoidance of hypoglycemia by combining insulins with different kinetic properties (intermediate- or long-acting-basal, with short-or rapid-acting-bolus). Bolus requirement are met by insulin preparations such as insulin lispro, insulin aspart, and insulin glulisine, which have a rapid onset, and shorter duration of action, thus reducing postprandial blood glucose excursions and the risk of hypoglycemia in the periods between meals. Insulin glulisine provides improved glycemic control with comparable symptomatic hypoglycemia versus regular human insulin (RHI) in the outpatient setting and may be considered a better choice than RHI in non-critically ill hospitalized patients.[146] Evidence from a crossover trial, comparing human regular insulin with insulin aspart, showed a 72% reduction in nocturnal hypoglycemia

while using insulin aspart.[147] There is also evidence to support lower incidence of hypoglycemia with intensified basal-bolus regimen using glargine/glulisine compared to premix therapy in a population with long-standing insulin-treated diabetes.[148]

Premixed insulin

They contain a combination of a short-acting and intermediate-acting insulin in standard proportions supplementing both basal and bolus insulin within a single injection thus facilitating fewer daily injections.[122] However, they should be used with caution in patients with less structured lifestyles and eating habits.[133] The use of premixed insulin analogues have been reported to reduce the risk of hypoglycemic events compared with premixed human insulins.[149] A meta-analysis of 22 trials comparing the effect of premixed, basal or prandial insulin on glycemic control and adverse events in people with T2DM has shown a reduction in nocturnal episodes of hypoglycemia with premixed insulin analogues.[150] Another recent meta-analysis indicated that BIAsp 30 was associated with a significantly lower rate of nocturnal and major hypoglycemia compared to premixed human insulin in T2DM patients.[151]

Continuous sub-cutaneous insulin infusion

The ADA[3] and the National Institute for Health and Clinical Excellence (NICE, 2008)[152] recommend CSII for patients who fail to achieve euglycemia with multiple daily injections (MDI) of insulin due to hypoglycemia. A meta-analysis of 22 RCTs confirmed that both HbA1c level and the rate of severe hypoglycemia were significantly lower during CSII compared with MDI.[153] CSII is safer intensive insulin regimen than MDI because of the reduced risk of hypoglycemia, especially severe hypoglycemia. Recent non-randomized clinic trial reports have demonstrated that improved glycemic control can be achieved without an increased risk for severe hypoglycemia when patients are switched from MDI to CSII therapy.[149]

Incretin therapy

Incretin-based therapies are a recent addition in the therapeutic armamentarium of diabetes management. Incretins are gastrointestinal hormones that stimulate postprandial release of insulin from β-cells in glucose dependent manner ("incretin effect"). The incretin system can be pharmacologically influenced through GLP-1 analogues and DPP-4 inhibitors. GLP-1 analogues are injectable peptides that act as agonists of the GLP-1 receptor, which are more resistant to DPP-4 and so have longer action than human GLP-1. While DPP-4 inhibitors are oral agents that prolong the activity of endogenously released GLP-1 and GIP by inhibiting the DPP-4 enzyme. They have the advantage of an extremely low hypoglycemic risk because of their glucose-dependent action.[9] A recent meta-analysis, examining the efficacy of various OADs and GLP-1 analogues, exenatide and liraglutide, in lowering HbA1c, has shown lower rates of hypoglycemia associated with the incretin therapies when used in combination with metformin.[129] The "Liraglutide Effect and Action in Diabetes" (LEAD) series of clinical trials which examined liraglutide against various comparators, showed no increased risk of hypoglycemia in the study arm receiving liraglutide.[154,155] Similarly, several RCTs that have examined the use of exenatide in lieu of basal insulin have been associated with lower rates of nocturnal hypoglycemia.[156] The low risk of hypoglycemia when DPP-4 inhibitors are used in combination with metformin makes them an attractive choice as second-line therapy.[9] Overall, when used as monotherapy or in combination with other blood glucose-lowering agents, incretins would be most beneficial in patients with T2DM who have multiple comorbidities, elderly patients who live alone, or patients at high risk of falls, because these patients may be unable to respond appropriately to an episode of severe hypoglycemia or may be at increased risk of hypoglycemia unawareness.[122]

Glucagon

Glucagon is a counter-regulatory hormone to insulin, secreted by the pancreas to maintain glucose production in the liver.[157] It may be considered a first-line treatment for severe hypoglycemia in patients with diabetes treated on insulin.[25] The recombinant glucagon has a short half-life (~8-18 minutes) achieving maximum plasma concentration within minutes following sub-cutaneous or intramuscular injection, thus preventing delay in commencement of treatment and need for hospitalization during severe hypoglycemic episodes.[158,159] Evidence suggests that glucagon is safe, tolerable and efficacious in restoring the blood glucose to normal in a hypoglycemic event and can lead to a faster recovery than calling for paramedics and waiting for them to start an IV line to give dextrose.[160-162] Generally, parenteral glucagon is used in patients with T1DM for severe hypoglycemia, while intravenous glucose is commonly used in patients with T2DM. Glucagon may be considered for use in T2DM patients with advanced disease and receiving intensive insulin therapy[163] while it should be avoided in patients on sulfonylureas.[123] Side effects associated with glucagon treatment include nausea and vomiting, but are often rare and there have been no reports of adverse reactions indicative of glucagon toxicity.

Glucagon kits are now available which comprise a vial of glucagon powder, a syringe prefilled with solvent and supportive text and graphic instructions for reconstitution and use in an emergency situation.[25] Educating caregivers

of the patient about glucagon kits and its use to ensure accurate administration is highly recommended. They should also be advised on the importance of avoiding any delay in treating the patient experiencing hypoglycemia and measures to be taken to restore normal blood glucose levels should be considered.

Treatment of hypoglycemia

A conscious patient with hypoglycemia should be treated with oral administration of 15-20 grams of carbohydrate (4 teaspoons of sugar or glucose). This should be followed by a SMBG 15 minutes later and the treatment should be repeated if hypoglycemia is persisting. The patient should be advised to eat a regular meal or have a snack to prevent recurrence of hypoglycemia. If a patient is unconscious and unable to accept food orally, immediate administration of intravenous glucose is necessary; alternatively glucagon may be administered intramuscularly at home by a family member. Treatment should be modified in the event of hypoglycemia occurring repeatedly at a particular time of the day or in the event of hypoglycemia unawareness.

Conclusions

Hypoglycemia, an often neglected complication of diabetes therapy, has far-reaching clinical, economical, and social impacts. Mild hypoglycemia reduces QoL, while severe hypoglycemia is life-threatening and can precipitate major cardiovascular and cerebrovascular events. Careful attention should be paid while deciding upon a treatment regimen for the management of diabetes such that adequate glycemic control measures can be implemented against the life-threatening complication of hypoglycemia. To improve diabetes-related outcomes, including reducing the risk and consequences of hypoglycemia, effective patient education is essential. Physician-patient collaboration is vital to develop and modify a treatment plan that is acceptable to the patient. The use of newer antidiabetic medications with little or no risk of hypoglycemia will reduce the future risk of hypoglycemia. Empowering patients with the tools to monitor hypoglycemia, making them aware of the risks of hypoglycemia and the available preventive strategies, together with an individualized plan of treatment, can decrease the frequency and severity of hypoglycemia.

Acknowledgement

The authors thank Jeevan Scientific Technology Limited, Hyderabad, for providing writing assistance in the development of this manuscript.

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Cite this article as: Kalra S, Mukherjee JJ, Venkataraman S, Bantwal G, Shaikh S, Saboo B, *et al*. Hypoglycemia: The neglected complication. Indian J Endocr Metab 2013;17:819-34.

Source of Support: Writing Support by Novo Nordisk, **Conflict of Interest:** None declared.