Hypoglycemia: Its effect on patients with diabetes

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Abstract

Hypogylcaemia is the presence of abnormally low blood sugar and can have multiple causes including iatrogenic side effects of diabetic medications. Hypoglycaemia increases morbidity and mortality in diabetic patients. It can also adversely affect the productivity and quality of life of patients.

We document the several consequences of hypoglycaemia including increased susceptibility to cardiac and neurological events.

We recommend tailored and structured patient education to ensure adequate knowledge about the causes and management of hypoglycaemia.

We envisage that over time increasing use of continuous glucose monitoring and automatic hypoglycaemic alerts will reduce the morbidity and mortality burden of hypoglycaemia.

Key words: hypoglycaemia, iatrogenic side effects, diabetes

Terms:
DM: Diabetes Mellitus,
DCCT: (Diabetes Control and Complications Trial),
IQ: Intelligence Quotient,
HbA1c: Hemoglobin A1c,
MRI: Magnetic Resonance Imaging,
GLP 1: Glucagon- like peptide – 1 receptor agonist,
SGLT-2: Sodium – glucose co transporter -2,
DPP-4 Dipeptidyl peptidase 4,
CGM: continuous glucose monitoring.

Introduction

Hypoglycemia is a common complication experienced by diabetic patients. It is the iatrogenic side effect of diabetic treatments, which results in increased morbidity and mortality. A working group of the American Diabetes Association and the Endocrine Society[1] defined iatrogenic hypoglycemia as "all episodes of an abnormally low plasma glucose concentration that exposes the individual to potential harm"[1]. It is not possible to assign a single threshold value to hypoglycemia episodes as it shifts to lower plasma glucose concentrations with recurrent hypoglycemic events and higher plasma glucose levels with poorly controlled diabetes.

Hypoglycemia has grave implications in terms of healthcare costs, adverse effects on productivity and the quality of life of patients [2,3,4,5,6]. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) strongly advise that in type 2 diabetic patients who are at high risk of hypoglycemia with advanced complications and have comorbid conditions, initiation of treatments which can cause hypoglycemia should be delayed unless essentially required [7]. Healthcare professionals need to realize the importance of hypoglycemia and their role in the delivery of patient-centered care to their patients. Hypoglycemia and its detrimental affects otherwise can result in severe morbidity and mortality [8].

Pathophysiology

In diabetics, severe hypoglycemia is due to defective glucose counter-regulation and hypoglycemia unawareness. Recurrent iatrogenic hypoglycemia, shifts glycemic threshold to lower plasma glucose concentration resulting in defective glucose counter-regulation[9].

Figure 1 and Figure 2 highlight that hypoglycemia unawareness is caused by the attenuated sympathoadrenal responses to hypoglycemia in both type 1 and type 2 diabetes.

Hypoglycemia can cause adrenergic symptoms and neuroglycopenic signs which can produce physical and psychological effects such as sweating, palpitations, shaking, hunger, confusion, drowsiness, odd behaviour, speech difficulty, loss of coordination, and headaches[10].

Hypoglycemia can produce clinical effects, which can have serious short term and long term consequences.

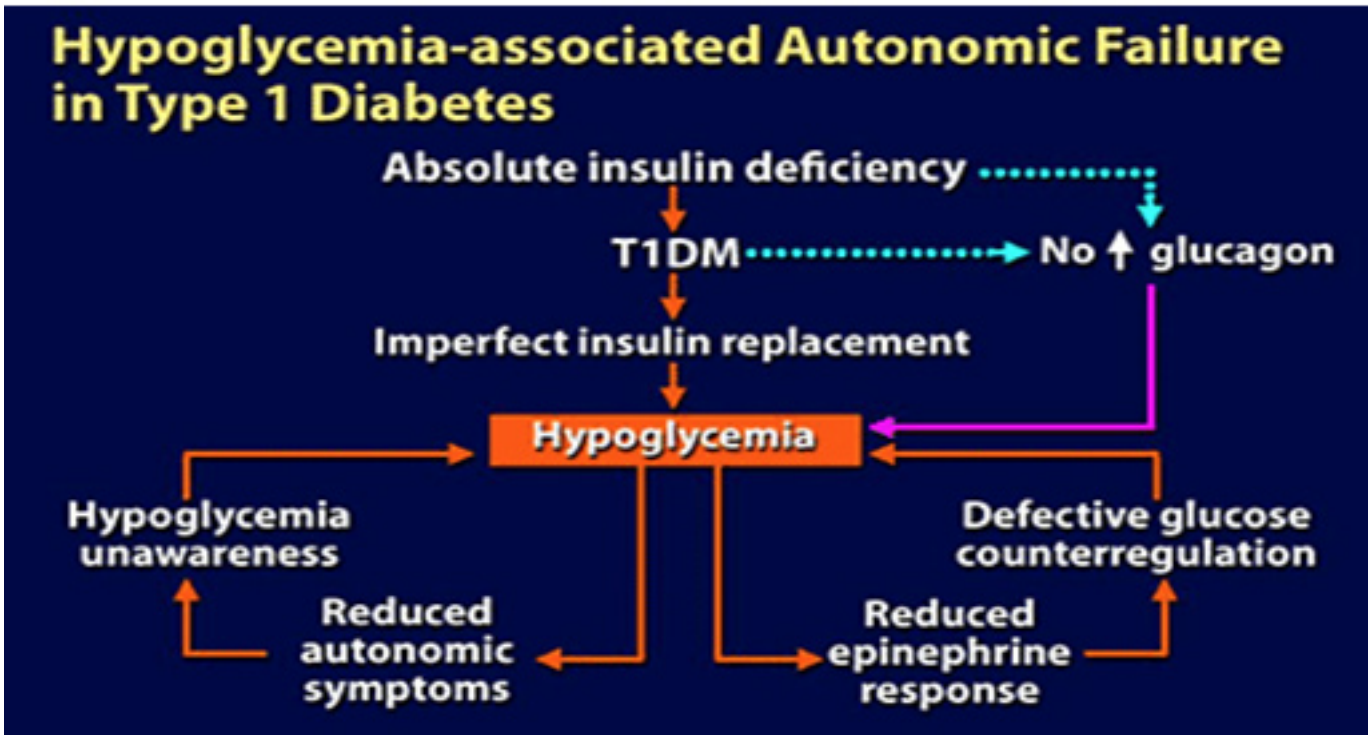

Figure 1: http://www.medscape.org/viewarticle/544445

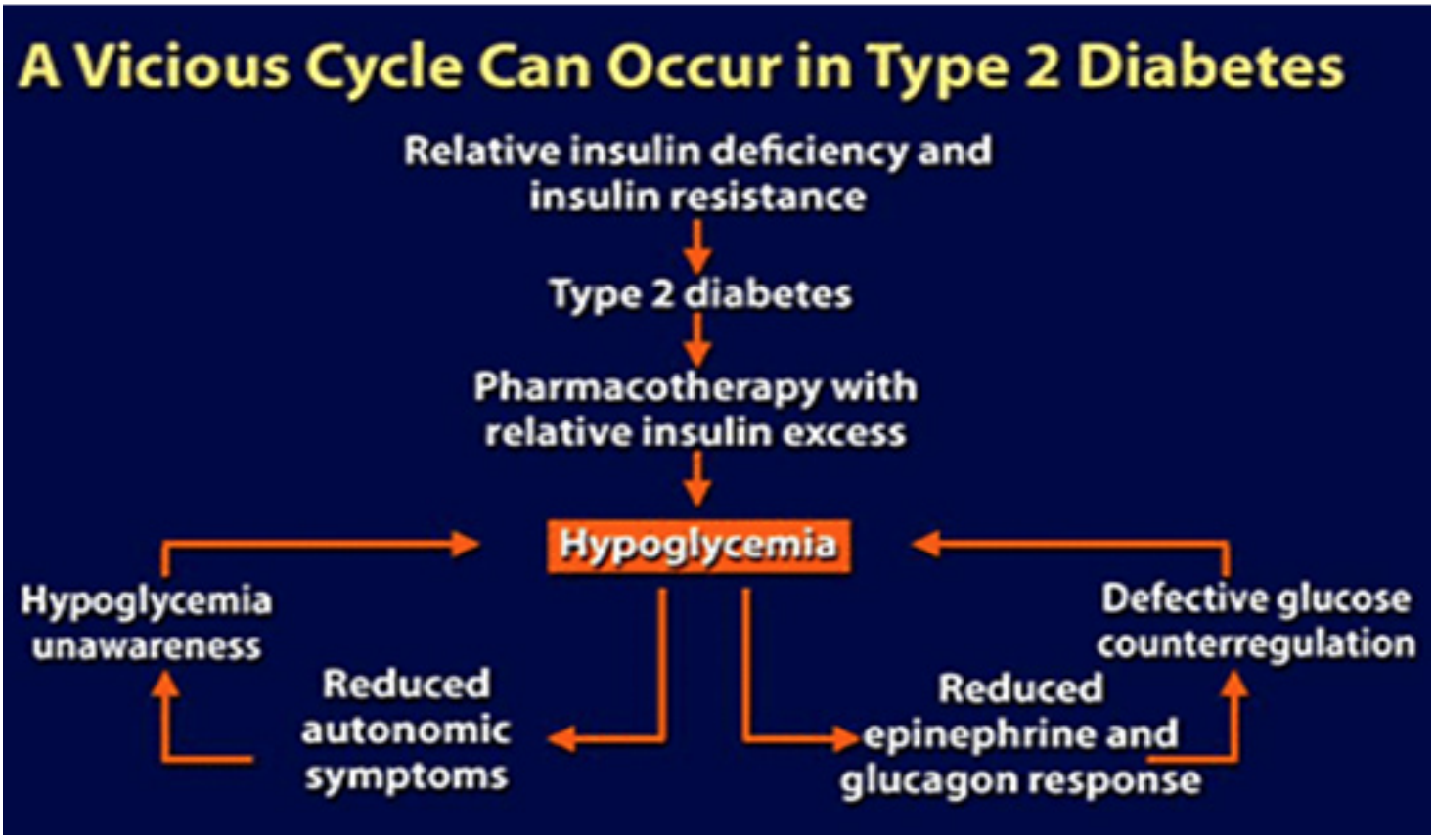

Figure 2: http://www.medscape.org/viewarticle/544445

Signs and symptoms of hypoglycemia:

Table 1. Signs and Symptoms of Hypoglycemia

Early Adrenergic Symptoms	Neuroglycopenic Signs
• Pallor	• Confusion
• Diaphoresis	• Slurred speech
• Tachycardia	• Irrational or uncontrolled behavior
• Shakiness	• Extreme fatigue
• Hunger	• Disorientation
• Anxiety	• Loss of consciousness
• Irritability	• Seizures
• Headache	• Pupillary sluggishness
• Dizziness	• Decreased response to noxious stimuli

Table 1: Tomky, D., M.S.N., R.N., C-A.N.P., C.D.E. 2005. Detection, Prevention, and Treatment of Hypoglycemia in the Hospital. Diabetes Spectrum. Jan, Vol 18, no. 1, pp. 39 - 44

Short-term effects of hypoglycemia:
Hypoglycemia causes some unpleasant effects. Mild hypoglycemic episodes are transient and quickly self-treated. However, mild to moderate neuroglycopenia can affect the performance of many activities at home or at work. It can result in serious harm such as hypoglycemia occurring when driving, which can cause fatal motor vehicle accidents[11]. Immediate hypoglycemia can precipitate problems with balance, coordination, vision, and level of consciousness. It can result in falls and serious injuries like fractures, head injury and joint dislocation whereas if hypoglycemia is severe and prolonged it can cause seizures, coma and in some cases strokes[12] .

Long-term effects of hypoglycemia:
Long-term sequelae of hypoglycemia beyond its short-term implications can result in acquired hypoglycemia syndromes. It can cause counter-regulatory hormonal deficiencies which normally corrects hypoglycemia and can also cause impaired awareness of hypoglycemia[13]. In some occupations hypoglycemia can result in individuals losing their jobs and people treated with insulin can be removed from working in dangerous areas, or their years-long professional roles may be lost if their work involves putting the public at risk. Insulin treatment and hypoglycemic episodes can incur restrictions on driving licensing in many countries[14]. It can affect other important spheres of life such as educational, social, sporting and travel activities [15].

Hypoglycemic episodes can produce fear amongst the patients. It can adversely affect their behaviour, quality of life and can affect adherence to their treatment thus resulting in suboptimal treatment for glycemic control[16].

The patients can then resort to under-dosing to avoid unpleasant effects of hypoglycemia. Hypoglycemia episodes can also encourage patients to eat more which is a defensive mechanism to prevent hypoglycemia. It can result in excessive weight gain. It can also have a profound negative effect on personal life. It can lead to difficult marital life and domestic disharmony[17].

Cardiovascular effects of hypoglycemia:
Hypoglycemia results in sympathetic system activation, which results in the release of large quantities of catecholamines. It is responsible for the hemodynamic effects of regional blood flow and marked influence on the cardiovascular system[18]. The increased cardiac workload puts profound cardiovascular (CV) stress especially in patients with pre–existing CV disease. It can at times result in Myocardial Ischemia (MI) or cardiac failure.

Cardiac arrhythmias:
Hypoglycemia can have adverse effects on the cardiac cycle. It affects cardiac electrophysiology by affecting cardiac repolarization resulting in pro-arrhythmogenic changes[19]. It produces ST segment changes, T – wave morphological alteration and prolongation of the Q – T interval. Sympathetic system activation and release of catecholamines produce a fall in plasma Potassium (K) levels. Thus, hypoglycaemia can lead to arrhythmias[20]. Recently continuous glucose monitoring studies have established a link between hypoglycemia and abnormal cardiac rhythms. Ventricular arrhythmias were noted in patients with asymptomatic biochemical hypoglycemia (glucose levels < 3.1mmol/l) particularly during the night[21]. Hypoglycemic episodes at night tend to be longer, 170 minutes during the night versus 62 minutes during the day [22]. The change in the balance of sympathovagal cardiac response could be responsible for arrhythmias induced by hypoglycemia at night. Vagal activation following activation of counter-regulation hormones to counter hypoglycemia promotes ventricular ectopic beats, changes in heart rate and bradycardia which at times can progress to a fatal arrhythmia[22]. Nocturnal hypoglycemia and its effects on Type 1 Diabetics can be more fatal. Type 1 Diabetics could suffer life-threatening arrhythmia and can be found dead in bed which can be referred to as the 'Dead in bed syndrome'. A review of the glucose monitoring records of a 23 year old type 1 diabetic patient who was found dead in bed showed he had a hypoglycemic event. [23]. The 'dead in bed' syndrome is associated with type 1 diabetes, but patients who are treated with insulin for type 2 diabetes have also been found dead and were assumed to have had an acute coronary syndrome or stroke.

Pathophysiological response to hypoglycemia and cardiovascular risk:
Hypoglycemia can trigger pathophysiological responses, which can persist in the body for several days. These reactions can affect vascular and autonomic functions, which in turn increases cardiovascular risk. In type 2 diabetic patients fasting glycaemia <4.5 mmol/l is thought to be associated with enhanced thrombin formation and formation of denser fibrin clots, especially when strict glycemic control was achieved (HbA1c<6.0%)[24]. It was noted that repeated periods of asymptomatic low glycaemia in type 2 diabetes promotes a prothrombotic state, leading to increased mortality following hypoglycemia[24].

Adequate glycemic control can be cardio-protective whereas repeated or severe hypoglycemia can trigger in a diabetic individual, cardiovascular dysfunction or instability, resulting in an acute cardiac event. From the evidence presented above it would be sensible to deduce that nocturnal hypoglycemia, in particular for those diabetics treated with insulin, should be avoided. Intensive management, which results in strict glycemic control in those patients who have cardiovascular disease, can cause serious cardiovascular complications of hypoglycemia which can be fatal.

Neurological effects of hypoglycemia:
Cognitive impairment
Physiological and biochemical functions of the brain are entirely dependent on the continuous supply of glucose as their primary source of energy. Any threat to the supply of its energy source called neuroglycopenia, can show an immediate deficit in its working. Failure to take appropriate corrective measures or failure of counter-regularly mechanisms can result in severe irreversible brain

damage. Cognitive functions, particularly those which are attention demanding, involve rapid responses and engage complex thought processes to undertake multitasking, are severely affected [25]. In a study involving type 1 diabetes patients, it was noted that complete cognitive recovery time can exceed 60 minutes even after restoration of normoglycemia. This recovery time is also influenced by the former state of awareness of hypoglycemia[26]. The majority of immediate undesirable effects of hypoglycemia which result in serious impairment to carry out normal day to day activities are the result of impaired cognitive function. It results in erratic and irrational behavior, confusion, visual and balance problems, falls and accidents and severe neurological sequelae like seizures and coma. Hypoglycemic episodes which cause seizures can result in sudden death by inducing cardiac arrhythmias[27].

Hypoglycemia and Cerebral Ischemia:

It is established that during acute hypoglycemia, blood flow to certain parts of the brain is increased to enhance the supply of glucose to the most vulnerable areas of the brain[28]. It is an adaptive response of the brain to recurrent hypoglycemia, which can result in permanent changes in the regional blood flow in the brain. It may lead to the loss of auto-regulation of blood supply increasing the risk of localized cerebral ischemia occurring during hypoglycemic episodes. Transient ischemic attacks and hemiplegia are recognized morbidity of hypoglycemia mainly affecting the elderly population who have a coexisting cerebrovascular disease[29].

Hypoglycemia and neurological development:

MRI studies on youth with type 1 diabetes have found some effects of antecedent hypoglycemia on brain structure[30]. This finding is consistent with the idea that the developing brain may be more vulnerable to hypoglycemia insults. Any detrimental effect on the cognitive function and development depends on the age of the individual exposed at the time of the recurrent hypoglycemic insults. In a 16-year follow-up study, it was suggested that children who had type 1 Diabetes Mellitus and who were < 5 years and had experienced severe hypoglycemia episodes were found to have reduced cognition compared to children with Type 1 DM who had no early exposure to hypoglycemia[31]. Similarly, in another study, it was noted 106 children with type 1 diabetes (aged 6 – 17 years) and control children who had no diabetes, had no difference in cognitive function at baseline; after 12 years of follow-up children with type 1 diabetes had lower verbal and full-scale IQs than in the control group. It was noted that the lower verbal IQ was associated with frequency of hypoglycemia exposure[32]. It is also a fact that the brain appears to be resistant to the effects of recurrent hypoglycemia in the middle years of life, as established by the DCCT (Diabetes Control and Complications Trial), 20 year follow- up study. No difference in cognitive abilities between the intensive and standard treatment arms was found. The subjects in the intensive treatment arm did suffer from a higher frequency of hypoglycemic episodes but had no notable impact on their cognition[33]. However, the elderly may be more vulnerable to the effects of hypoglycemia. Hypoglycemic insults in patients with type 2 diabetes mellitus may have a detrimental effect on their cognition and can put them at risk of developing dementia. The relationship between hypoglycemia and cognitive decline is possibly bidirectional[34,35].

Measures to prevent hypoglycemia and its adverse effects on patients:

Patient education

There is clear evidence that educating patients about diabetes, its management and preventing its complications improves patient outcomes.[36] The educational programme enables patients, and their carers to recognize symptoms of hypoglycemia and provides them with the guidelines to treat it appropriately with oral carbohydrates or glucagon. It is also imperative that patients have a clear understanding of how their medications work so they can minimise the risk of hypoglycemic episodes. There is clear evidence that structured educational programs delivered in routine clinical settings reduced severe hypoglycemic rates, improved hypoglycemic awareness and reduced psychological distress[37].

Dietary intervention

Diabetic patients need to recognize foods containing carbohydrates and their effect on blood glucose. It should be a part of the patient education programme, which improves patient knowledge about various diets and their glycemic index. Patients who are on a long acting and fixed insulin must be encouraged to follow a predictable meal plan whereas patients on more flexible insulin regimens must be aware that prandial insulin injections need to be used at meal times. Patients on insulin or hypoglycemia-inducing medication should be encouraged to carry carbohydrates at all times to treat hypoglycemia.

Exercise management

Glucose utilization increases with physical activity. Prolonged strenuous exercise, recently increased exercise intensity and inadequate energy supply during exertional activity increases risk of hypoglycemia[38]. It is important that patients are advised to monitor their blood glucose levels before and after exercise. They must ensure that they consume enough calories beforehand to prevent hypoglycemia during exertional activities or exercise sessions. They must carry readily absorbable carbohydrates to correct hypoglycemia when embarking on any exertional activity, which is out of their norm. Similarly, on days when they plan to undertake a strenuous activity, they must readjust their insulin dose, especially those patients who had previous episodes of exercise-induced hypoglycemia.

Medication review:

Hypoglycemic episodes which are not related to factors like missed meals, exercise induced and alcohol intake may be due to excessive diabetic medication doses. It is important that patients who are on insulin or hypoglycemia-inducing medication should have regular monitoring and review of medication. Any vulnerable periods highlighted from their blood glucose monitoring should warrant prompt

medication dose adjustment to prevent hypoglycemic episodes. These adjustments may include changing types of insulin or reducing the dose of the medication. Recent advances in continuous subcutaneous insulin infusion offer great flexibility in dosing and preventing iatrogenic hypoglycemia. Recent advances in pancreatic islet cells transplantation, in future, can result in improvement in glycemic control and prevention of iatrogenic hypoglycemia[39].

Glucose monitoring:
It is important for patients who are at risk of hypoglycemia that they have vigorous glucose monitoring, as severe hypoglycemic episodes can lead to severe morbidity and can be fatal. Patients on insulin, sulfonylureas, or glinides must monitor their blood glucose whenever they experience symptoms of hypoglycemia. They must ingest carbohydrates to correct the hypoglycemia promptly and collect information that can be used by the clinician to adjust their medications to avoid future hypoglycemia. Patients having basal - bolus insulin therapy should monitor their blood glucose before each meal and calculate the dose of rapid-acting insulin accordingly. Such safe monitoring and dosing practices will likely reduce the risk of hypoglycemia.

Novel treatments:
Long-acting analogues of insulin have been developed which have shown some modest benefit in lowering the risk of nocturnal hypoglycemic events in insulin-treated patients[40]. Similarly, new classes of oral and injectable glucose-lowering drugs such as incretin mimetics (GLP – 1 receptor agonists and DPP-4 inhibitors) and the SGLT-2 inhibitors have demonstrated reduced frequency of severe hypoglycemia[41]. High risk of mortality and morbidity associated with hypoglycemia makes use of these medications a preference to sulphonylureas particularly in vulnerable groups such as the frail elderly. The current limitation of using these drugs is the cost implication, as these medications are more expensive than sulphonylureas and metformin. In future, therapies that would effectively manage diabetes without the risk of hypoglycemia will be preferred both by clinicians and patients.

Recent advances:
New tools and monitoring systems have been developed for real-time and continuous glucose monitoring. It provides helpful information to the patients resulting in measures to avoid hypoglycemia, e.g. suspending insulin delivery on a pump or taking a snack to improve calorie consumption. New continuous glucose monitors come with audible and vibratory alarms which can be particularly helpful in avoiding nocturnal hypoglycemia and improving hypoglycemic awareness. In a hyperinsulinemic hypoglycemic clamp study in type 1 diabetics with hypoglycemic unawareness, four weeks of real-time CGM use restored the epinephrine response and improved adrenergic symptoms[42]. Real-time continuous glucose monitoring (CGM) has demonstrated its benefits in preventing severe hypoglycemia in people with impaired hypoglycemic awareness[43]. Real-time CGM might ultimately be the way forward through which the risks of hypoglycemia can be substantially reduced.

The other way forward is addressing the method of insulin delivery. Continuous subcutaneous insulin delivery systems lessen the risk of severe hypoglycemia in children and adults with type 1 diabetes[44]. A meta-analysis concluded, the risk of hypoglycemia with type 1 diabetes was much lower while using continuous subcutaneous insulin infusion than using multiple daily injections with the greatest benefit to the patients with the most severe hypoglycemia while on multiple daily injections[45].

Recently, work has been underway on the artificial pancreas, which connects continuous glucose monitoring to an insulin pump through sophisticated predictive algorithms. When it comes to use, it will eliminate hypoglycemic episodes. Several internationally collaborative groups are working on this project. The first step in this direction is the development of low-glucose suspend pump. This device shuts off insulin delivery for up to 2 hours once the interstitial glucose concentration reaches a preset threshold; it will be a great asset in preventing mortality and morbidity from nocturnal hypoglycemia once it comes into full use[46]. A study using sensor- segmented insulin- pump therapy with the threshold – suspend feature, showed the reduction in nocturnal hypoglycemia, without any increase in glycated haemoglobin value[47].

Conclusion

Adequate education of patients and their relatives can help in reduction of the risk of severe hypoglycemic episodes. Patients may not understand straightforward and fundamental information about recognizing and management of hypoglycemia. Even if the information is provided, it can easily be neglected and at times, its grave consequences are ignored. Clinicians need to remain alert to the potential risks of hypoglycemia in individual patients and should robustly review patients who are on high-risk therapies.

Formal patient training programmes have clearly shown benefit in reducing the risk of hypoglycemic episodes. It has shown better management of severe, life-threatening hypoglycemic events by patients and their relatives. In our day to day practice, the resources and time required to provide such intensive training and standard educational measures about dietary modification, practical advice about physical exercise, emphasis on careful glucose monitoring and appropriate adjustment of medications are still far from the desired standards. More specific therapeutic strategies are required based on individual patient needs, especially for those patients who have developed impaired awareness of hypoglycemia. In these patients frequent or continuous blood glucose testing is essential and permanent sub-cutaneous insulin infusion can be of great value.

Hypoglycemia because of its effects on the cardiovascular system and the brain can lead to severe morbidity and mortality. Glycemic targets need to be adjusted on the individual patient basis. They need to be safe and have to be less strict in high-risk groups such as patients with coronary heart disease, very young children and the frail elderly.

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