Hypoglycaemia Unawareness

JP Vignesh, V Mohan

Abstract

Hypoglycaemia is the most frequent and serious complication of insulin therapy and is three times more common in those who are intensively treated. Impaired awareness of hypoglycaemia is a major limitation to achieving tight diabetes. Asymptomatic biochemical hypoglycaemia occurs more frequently during routine blood glucose monitoring and this should alert the clinician that the individual is developing hypoglycaemic unawareness. Though the etiology of hypoglycaemic unawareness is multifactorial, possible mechanisms include chronic exposure to low blood glucose, antecedent hypoglycaemia, recurrent severe hypoglycaemia and the failure of counter-regulatory hormones.

Diabetic patients with history of impaired awareness of hypoglycaemia perform poorly on cognitive function testing and this may be restored by relaxation of glycaemic control. The question of whether human insulin produces hypoglycaemia awareness has been hotly debated but this does not appear to be a major problem considering the number of patients on human insulin. The decision to use one or other of the insulins therefore rests entirely with the physician.

Low blood glucose awareness training programmes can help to identify and prevent hypoglycaemia unawareness. Impaired awareness of hypoglycaemia can probably be reversed by scrupulous avoidance of hypoglycaemia. ©

Introduction

Hypoglycemia is the most common and most serious complication of insulin therapy. It is the major obstacle to improved glycaemic control through intensified insulin therapy. It should be remembered that for many patients (and their families), it is the most terrifying and disabling aspect of the diabetic control. The Diabetes Control and Complications Trial (DCCT),[1] the United Kingdom Prospective Diabetes Study (UKPDS)[2] and the other studies of intensive therapy,[3] showed that the frequency of hypoglycemia was higher in those who achieved tight diabetes control. Development of symptoms in response to a low blood glucose level provides a fundamental defence for the brain, by alerting the affected individual to the imminent development of neuroglycopenia, which provokes an appropriate response - ingesting some form of carbohydrate to reverse the decline in blood glucose. Failure of these warning symptoms to occur or delay in their occurrence until the blood glucose has fallen to a level which causes disabling neuroglycopenia, can have serious consequences. The crucial factor that makes hypoglycemia so important in the management of diabetes is the dependence of neural tissue on a continuous supply of glucose, interruption of which for more than a few minutes leads to central nervous system dysfunction, impaired cognition and eventually coma.

MV Diabetes Specialities Centre and Madras Diabetes Research Foundation, Gopalapuram, Chennai, India.
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Epidemiology

As the evidence emerged that tight metabolic control reduced the risk of microvascular complications, early attempts to maintain near normal glucose levels led to frequent and severe hypoglycemic episodes. The risk is three times greater in the group undertaking intensive therapy, in which the glucose targets were close to normal.[1] It is apparent that impaired awareness of hypoglycaemia is a major risk factor for severe hypoglycaemia. In the DCCT, 36% of all episodes of severe hypoglycaemia occurred with no warning symptoms in patients who were awake.[4] Impaired awareness of hypoglycaemia is common in people treated with insulin. While the chronic form of this acquired condition mainly affects those with type 1 diabetes, the risk also increases in people with progressive beta cell failure (insulin treated type-2 diabetes). In the UKPDS, the proportion of major hypoglycaemic events per year for first 10 years was 0.4% for chlorpropamide, 0.6% for glibenclamide and 2.3% for insulin.[2] The rates of hypoglycaemia rose as the duration and number of people treated with insulin therapy increased, with almost 50% of patients experiencing hypoglycaemia without warning symptoms after 25 years or more of treatment.[5]

Definition of hypoglycemic unawareness

No satisfactory definition of hypoglycaemic unawareness has been suggested to date. A simple definition for hypoglycaemia unawareness would be reduced ability or failure to recognise hypoglycemia at the physiological plasma glucose concentration at which warning symptoms normally occur. Asymptomatic biochemical hypoglycaemia occurs more frequently during routine blood glucose monitoring in diabetic patients who report impaired awareness of hypoglycemia, and such a record may alert the clinician to the possibility that an individual is developing this problem. Patients unaware of hypoglycemia either do not realise that the plasma glucose is decreasing and causing neuroglycopenia, or ultimately feel the symptoms, but at much lower plasma glucose levels (high thresholds). In older text books, hypoglycemia is usually defined as plasma glucose concentration below 50 mg/dl (2.7 mmol/l).[6,7] However, normally the release of counter-regulatory hormones in response to hypoglycemia is already evident for modest decrements in plasma glucose i.e. at a plasma glucose concentration of 65 mg/dl (3.5 mmol/l). Thus a modern physiological definition of hypoglycemia is any decrease in plasma glucose concentration below 65 mg/dl (3.5 mmol/l). This concept is important not only in physiology, but also to define the safe glycaemic targets for intensive therapy of Type 1 diabetes.[8,9]

Classification

Hepburn *et al*,[10] subdivided hypoglycemia awareness into the following categories.

a. **Normal awareness**: The individual is always aware of the onset of hypoglycemia.

b. **Partial awareness**: The symptom profile has changed 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.

c. **Absent awareness**: The individual is no longer aware of any episode of hypoglycemia.

In assessing the present state of hypoglycaemia awareness, it is desirable that the patient should have experienced one or more episode of hypoglycaemia within a defined time interval. Because hypoglycaemia awareness and its impairment lie on a continuum ranging from normality to complete inability to detect the onset of hypoglycaemia, a comparison can be made with earlier episodes of hypoglycaemia. Although, the subdivision into partial and absent awareness is artificial, it reflects the natural history of this clinical problem with a gradual progression of this disability, although total absence of clinical manifestation of hypoglycaemia (particularly the neuroglycopenic features) is extremely rare.[11] The impact of complete hypoglycemia unawareness on the affected individuals and their families is often devastating. The chances of suffering a severe attack increases 6-7 fold in those with unawareness, even during standard therapy[12] and such patients are usually excluded from attempting intensified insulin therapy .

Pathogenesis of hypoglycemia unawareness

The first response as the blood glucose concentration falls below normal is the acute release of counter-regulatory hormones (glucagon and epinephrine) which occurs at a plasma glucose level of 65-68 mg/dl.[13] If the blood glucose continues to fall, autonomic symptoms begin to appear around 58 mg/dl.[14] Cognitive function as measured by reaction time and other psychomotor tasks, starts to deteriorate around 54 mg/dl.[15] The protective glucagon response to hypoglycaemia, which is normal at diagnosis, begins to fail within 1-2 years duration in Type 1 diabetic subjects and after five years, an impaired or absent response is almost universal. The cause however remains unclear.[16] It appears unrelated to autonomic neuropathy. The pancreatic alpha cells fail to recognize hypoglycemia as a stimulus for release of glucagon but it is secreted normally in response to alanine. Perhaps, the most convincing hypothesis is the disruption of paracrine insulin cross task within the islets. A reduced sympathoadrenal response is also common in established diabetes, although the degree of impairment is more variable and it occurs after a longer duration of diabetes.[17] Epinephrine response to other stimuli such as exercise appears to be normal which is therefore also a selective failure of hypoglycemia recognition. Paraplegic patients with high cervical transection of the cord lose epinephrine secretion and the autonomic response to hypoglycaemia and simply fall into deep sleep.[18]

Chronic hypoglycaemia in particular, appears to increase the expression of glucose transporters localized in the microvessels of the blood brain barrier (GLUT-1) as well as the neuron-specific glucose transporters (GLUT-3).[19] In diabetic patients with low values of glycosylated haemoglobin (HbA_1c) due to antecedent, frequent hypoglycemia, brain glucose uptake does not decrease during hypoglycaemia as it does in uncontrolled diabetic patients with elevated HbA_1c (less frequent hypoglycaemia) and in non-diabetic subjects.[20] Thus during subsequent hypoglycemia, the brain is less neuroglycopenic than normal and does not need to generate the counter-regulatory responses and the autonomic symptoms to defend and alert the subject about hypoglycaemia.This is the mechanism of cerebral adaptation causing impaired awareness of hypoglycaemia in chronic and antecedent (episodic) hypoglycaemia (Fig. 1). An additional mechanism of hypoglycaemia unawareness has been provided by Davis *et al*[21] who proposed that the responses of cortisol to antecedent hypoglycemia blunt the autonomic hormone response to subsequent hypoglycaemia and vice versa. Recently, McGregor *et al*[22] found reduced autonomic responses to hypoglycaemia after antecedent increase of cortisol levels by infusion of adrenocorticotropic (ACTH) hormone in healthy subjects. Interestingly, over the last decade, several studies have shown that alpha-adrenergic sensitivity is reduced in Type 1 diabetic patients and that antecedent hypoglycemia itself reduces alpha adrenergic sensitivity of subsequent hypoglycaemia, thus favouring the generation of hypoglycaemia unawareness.[23]

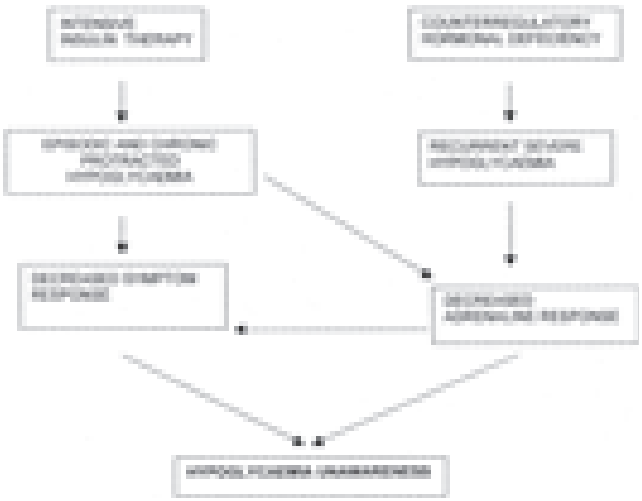

Fig. 1 : Schematic diagram on the development of hypoglycaemia unawareness

Moreover, there is some evidence that patients with established autonomic neuropathy may have an additional defect in epinephrine release during hypoglycaemia.[24] The term hypoglycaemia associated autonomic failure (HAAF) has been used to describe the specific defect of autonomic responses during hypoglycaemia and this term was introduced to distinguish this condition from classical autonomic neuropathy.[25] The possible mechanisms of impaired awareness of hypoglycaemia in certain clinical situations are discussed in Table 1.

Table 1 : Possible mechanism of hypoglycaemic unawareness in certain clinical situations.

Clinical situation	Possible mechanism
1. Increasing duration of diabetes	* Possibly repeated hypoglycemic damage to glucosensitive neurons.
2. Tight metabolic control	Antecedent hypoglycemia leading to: * up-regulation of neuronal glucose transport * Altered catecholamine sensitivity
3. Alcohol	* Suppression of autonomic peripheral responses (tremor) * Impaired cognition
4. Nocturnal	* Sleep and supine position preventing recognition of early symptoms (reducing sympatho-adrenal response).
5. Children	* Lack of abstract thought * Prominence of behavioural change
6. Elderly	* Prominence of impaired cognition * Possible reduced autonomic response * Reduced adrenergic sensitivity
7. Pregnancy	* Improved glycaemic control * Acquired defects in the physiological response to hypoglycaemia.

Does human insulin increase risk of hypoglycemic unawareness?

More recently, the most contentious issue is whether the species of insulin affects awareness of hypoglycaemia, specifically, whether human insulin affects the epinephrine response. Despite extensive research efforts, the question of whether human insulin affects the awareness of hypoglycaemia remains unproven. Berger *et al*[26] in a double blind, randomized cross-over trial of human and porcine insulins reported that the initial symptoms seemed more often to be 'adrenergic' with porcine and 'neuroglycopenic' with human insulin. However most of the studies which were performed in patients who specifically claimed to have developed impaired awareness of hypoglycaemia after being changed to human insulin showed no differences in the hormonal or symptomatic responses to hypoglycaemia.[27] The only exception is the study by Teuscher *et al*, [28] where they claim that patients experienced more frequent hypoglycaemia, altered warning symptoms and impaired awareness of hypoglycaemia with the use of human insulin. A number of attempts world over have been made to answer this question, including a recent Cochrane review which compared the effects of human insulin and animal insulins in diabetic patients from 1996 to May 2002.[29] It was concluded that both human and animal insulins are equally good and the decision to use one or other of the insulin rests entirely with the physician. In the authors' view also there does not appear to be any hypoglycaemia unawareness issue with human insulin given the fact that thousands of patients have been treated with human insulin. Therefore the decision of choosing a particular insulin ultimately falls upon the physician who should make the right choice depending on the diagnosis, expected clinical outcome and the affordability of the patient. While changing over from animal to human insulins, however it is prudent to start with a slightly lower insulin dose.

Complications of hypoglycaemic unawareness

Hypoglycaemia unawareness can cause a wide range of neurological symptoms and clinical signs which can be subtle or severe, reversible or permanent. Impaired awareness of hypoglycaemia is a major risk factor for severe hypoglycaemia.[4] Long term neurological manifestations of severe insulin induced hypoglycaemic unawareness are motor/sensory hemiparesis, choreo-athetosis, epilepsy, brain stem syndrome and psychological manifestations including cognitive impairment with behavioral abnormalities and automatism. Children with Type 1 diabetes who suffer repeated and severe hypoglycaemia when below five years of age have lower mental abilities later on in life and may have behaviour problems.[30] Severe hypoglycaemia has a detrimental effect on cognitive functions as well.[31,32] Limited evidence from prospective studies, namely the Diabetes Control and Complications Trial (DCCT) and the Stockholm Diabetes Intervention Study[33] indicate that cognitive function does not deteriorate in patients who suffer recurrent hypoglycaemia, at least in the time scale (less than 10 years) of these studies. However, it must be borne in the mind that participants in these studies were young, highly motivated, above average in intelligence, free of advanced complications, with no history of severe hypoglycaemia before entering the study and they also received a very high level of support from health professionals. The formal measurement of cognitive function during controlled hypoglycaemia (blood glucose around 45mg/dl) showed that patients with Type 1

diabetes who had impaired hypoglycaemia awareness exhibited more profound cognitive dysfunction during acute hypoglycaemic episodes than those with normal awareness and that this persisted for longer periods following recovery of blood glucose.[34] Intellectual activity is likely to be affected and cause sub-optimal performance during this recovery period. This has implications for skilled tasks such as driving or operating machinery and equipment. Symptomatic and neuroendocrine responses to hypoglycaemia in insulin treated diabetes are diminished in hypoglycaemia unawareness in association with strict glycaemic control (HbA1c in non-diabetic range), antecedent (episodic) hypoglycaemia and chronic (protracted) hypoglycaemia and this may be restored by relaxation of glycaemic control or scrupulous avoidance of hypoglycaemia. The changes in the EEG are not specific for hypoglycaemia, but resemble those seen in hypoxia and other metabolic encephalopathies.[35] Cerebral edema is a dreaded albeit rare complication of severe insulin induced impaired awareness hypoglycaemia and should be suspected if further deterioration or false localising signs ensue. This is often very resistant to treatment and is usually fatal. Urgent imaging of the brain is imperative to exclude other potentially remediable causes of neurological abnormalities or coma.

Prevention and management

Prevention of hypoglycaemia unawareness is an important part of modern day intensive diabetes therapy. Subcutaneous insulin replacement is so imperfect that mild hypoglycemia in inevitably induced from time to time, which in turn induces unawareness of hypoglycaemia. In theory, if one were able to prevent hypoglycaemia from the clinical onset of diabetes, hypoglycaemia unawareness should never occur. In fact, meticulous prevention of hypoglycaemia in diabetic patients previously suffering from recurrent hypoglycemia, fully reverses the syndrome of hypoglycaemia unawareness and impaired release of adrenaline in short term diabetes.[36]

Altered physiological responses to hypoglycaemia suggests that these defects are functional rather than structural, that they might be reversible, at least in part, by strict avoidance of hypoglycemia. The central aim of a hypoglycemia - reversal programme is to prevent any period of hypoglycemia for atleast four weeks. A patient who lives in fear of hypoglycemia will never achieve adequate glycemic control. Appropriate education includes an emphasis on regular snacks at right times, warnings to take special care at periods of greater risk (before lunch and around tea), moderation in alcohol intake, driving and advise on the amount of carbohydrate needed to control symptoms. Patients should also be educated about the danger of delayed hypoglycemia after heavy alcohol intake or prolonged exercise. Education, reassurance and a determined attempt should be made to eradicate the problem. Blood glucose targets should be relaxed but not abandoned. These are the essential components of a hypoglycaemia reversal programme. Is there a safe range of HbA_1c? Pampanelli *et al* [8] studied physiological responses in patients with Type 1 diabetes undertaking intensive insulin therapy. The rates of severe hypoglycaemia were increased among those with HbA1c<6% and therefore it was suggested that using current therapy, an HbA_1c of between 6-7% represents the best compromise between the risk of severe hypoglycemia and that of developing microvascular complications. The place of rapid acting insulin analogues in preventing or reversing hypoglycaemia unawareness is yet to be determined. An alternative approach is to use continuous subcutaneous insulin infusion (CSII), especially at night, as this leads to reduced hypoglycemic episodes and improved counter-regulatory and symptomatic responses to hypoglycemia in patients with Type 1 diabetes.[37] Table 2 summarizes the treatment strategies for patients with impaired hypoglycemic awareness.

Table 2 : Treatment strategies for patients with impaired awareness of hypoglycemia

*	Frequent blood glucose monitoring (including nocturnal measurements).
*	Avoid blood glucose values <65mg/dl.
*	Avoid HbA1c in non-diabetic range (target range is relaxed but not abandoned).
*	Use predominantly, short-acting insulins (e.g. Basal-bolus regimen; insulin analogues, CSII).
*	Appropriate education on regular snacks between meals and at bed time, containing unrefined carbohydrate, and counseling regarding alcohol and exercise schedules.
*	Continuing repetitive and timely education, reassurance and a determined approach.
*	Patients should be educated about subtle neuroglycopenic symptoms.(Blood glucose awareness training programmes (BGAT) may help.

CONCLUSIONS

Taken together, these observations indicate that frequent hypoglycemia in Type 1 diabetes, caused either by inappropriate treatment and /or impaired counter-regulation, rapidly induces loss of symptoms and blunts the release of counter-regulatory hormones in response to hypoglycemia. Asymptomatic hypoglycaemia can be diagnosed by routine blood glucose monitoring and should alert the patient and clinician to the possibility of developing impaired awareness of hypoglycaemia. Enormous advances have been made in our knowledge of the physiology and patho-physiology of impaired awareness of hypoglycemia and these have to be put with practice. This review has tried to show, that much can be done to reduce the frequency and severity of hypoglycemia unawareness without compromising glycaemic control. Though the debate on the risk of a single severe episode of hypoglycaemia compared to the risk of recurrent minor episodes of hypoglycaemia continues, both should ideally be avoided, especially in children. The good news is that prevention of hypoglycemia largely, if not fully, reverses unawareness and improves counter-regulation to hypoglycemia.

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