Impaired awareness of hypoglycaemia: a review

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Abstract

Impaired awareness of hypoglycaemia (IAH) is an acquired complication of insulin therapy, which affects people with type 1 and insulin-treated type 2 diabetes mellitus, whereby the ability to perceive the onset of hypoglycaemia becomes diminished or absent. Deficiencies of the counter-regulatory hormonal responses to hypoglycaemia usually co-exist. The development of IAH and counter-regulatory failure greatly increases the risk of severe hypoglycaemia. Scoring systems have been developed that can be used in the clinical setting and assist with identification of this group of individuals at risk of severe hypoglycaemia. The mainstay of treatment of IAH is the scrupulous avoidance of hypoglycaemia.

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1. Definitions of hypoglycaemia

Hypoglycaemia is a major barrier to the implementation of intensive glycaemic control to treat diabetes. In the Diabetes Control and Complications Trial (DCCT) severe events were three-fold greater in the group with strict glycaemic control compared to those with conventional treatment [1]. In clinical practice, hypoglycaemia is defined by the ability of an individual to self-treat. Self-treated events are classified as “mild”, while “severe” hypoglycaemia is any episode that requires external assistance for recovery, and is not confined to coma alone. The arbitrary biochemical value of blood glucose that can be used to define hypoglycaemia is the subject of topical debate [2,3]. The American Diabetes Association (ADA) have selected a blood glucose of 3.9 mmol/L (70 mg/dl) or below as representing hypoglycaemia [4], but many clinicians consider that the use of this relatively high level as the cut-off will capture many episodes that are not clinically meaningful [5].

2. Frequency of hypoglycaemia

People with type 1 diabetes mellitus (T1DM) experience an average of one to two episodes of mild hypoglycaemia per week; one third experience an episode of severe hypoglycaemia annually [6]. Retrospective recall of severe hypoglycaemia is robust for up to one year in people with both types of diabetes [7,8], but recall of mild hypoglycaemia is limited
to one week [9]. Relatives report significantly more annual episodes of severe hypoglycaemia than people with T1DM do themselves [10]. The distribution of severe hypoglycaemia is skewed within a population so that most events are recorded by only a few individuals; identification of those at higher risk would have valuable clinical utility [7]. The frequency of sulfonylurea-induced hypoglycaemia is underestimated in people with type 2 diabetes mellitus (T2DM), and is common with long-acting preparations (e.g. glibenclamide). In a prospective study in the UK the prevalence of severe hypoglycaemic events associated with sulfonylurea therapy was 7%, comparable to the frequency observed in people with T2DM on insulin for less than 2 years [11].

3. Symptomatology of hypoglycaemia

The application of statistical methodology has enabled classification of the symptoms of hypoglycaemia in patients with T1DM: those generated by the activation of the sympathoadrenal system are termed autonomic and those occurring as a consequence of cerebral glucose deprivation are termed neuroglycopenic. Young adults also express a non-specific or malaise group of symptoms. These three groups of symptoms can be measured using the Edinburgh Hypoglycaemia Symptom Scale [12]. Although it has been claimed that awareness of hypoglycaemia is largely the result of autonomic, rather than neuroglycopenic symptoms [13], studies identifying the cardinal symptoms that alert people with T1DM to the onset of hypoglycaemia have shown that autonomic and neuroglycopenic symptoms are represented equally [14,15].

In older people with T2DM, neurological symptoms such as ataxia and visual disturbance are prominent, which may result in misdiagnosis [16]. Elderly people with T2DM report lower symptom scores but counter-regulatory responses to hypoglycaemia are relatively intact; the lower magnitude of the symptom response may therefore result from decreased sensitivity of end-organs in response to catecholamines [17,18]. In elderly people, symptoms of hypoglycaemia commence at a lower blood glucose threshold and cognitive dysfunction occurs at a higher threshold in comparison with those observed in young adults [19]. This compresses the interval between the onset of symptomatic hypoglycaemia and the development of cognitive dysfunction, so that both develop almost simultaneously and the protective effect of the symptomatic warning is lost [19]. Symptom scores correlate positively with estimates of diabetes severity in which their ability to identify the onset of hypoglycaemia becomes progressively impaired. “Impaired awareness of hypoglycaemia” (IAH) is a preferable nomenclature to the widely used “hypoglycaemia unawareness”, which suggests total loss of the symptomatic warning response that is seldom observed in clinical practice. IAH is an acquired complication of insulin treatment per se, in which the perception of the onset of hypoglycaemia becomes diminished or absent.

5. Impaired defences against hypoglycaemia in T1DM

In normal health, when blood glucose falls to a level which may compromise the integrity of cognitive function, glucose counter-regulation is initiated (Fig. 1). This is triggered when blood glucose declines below the lower end of the normal range and is preceded by suppression of endogenous insulin secretion. Glucagon and adrenaline (epinephrine) are the most important counter-regulatory hormones to acute hypoglycaemia. In people with T1DM the glucagon response to hypoglycaemia rapidly declines and is lost within five years of diagnosis [23]. The adrenomedullary secretion of adrenaline (epinephrine) becomes important when these early defensive mechanisms are compromised [24]. In people with T1DM who are C-peptide negative, loss of endogenous insulin-secretory capacity and the glucagon response to hypoglycaemia underlie the fourfold increase in risk of severe hypoglycaemia [25]. Hyperinsulinaemia secondary to exogenous insulin administration frequently occurs in insulin-treated diabetes and persists in the presence of low blood glucose because normal glucose homeostasis is disrupted in T1DM and advanced T2DM. With time, sympathoadrenal activation becomes

4. Impaired Awareness of Hypoglycaemia (IAH)

In 1922, very shortly after insulin was first used to treat diabetes, Elliot Joslin observed that hypoglycaemia could occur without warning symptoms [21]. More than one third of episodes of severe hypoglycaemia that occur during waking hours are not accompanied by warning symptoms [22], and many people with insulin-treated diabetes develop a syndrome with a spectrum of severity in which their ability to identify the onset of hypoglycaemia becomes progressively impaired. “Impaired awareness of hypoglycaemia” (IAH) is a preferable nomenclature to the widely used “hypoglycaemia unawareness”, which suggests total loss of the symptomatic warning response that is seldom observed in clinical practice. IAH is an acquired complication of insulin treatment per se, in which the perception of the onset of hypoglycaemia becomes diminished or absent.

Figure 1. Figure showing glycaemic thresholds for counter-regulatory hormone release and clinical features of hypoglycaemia [24,63,64]
critical for protection of the brain from hypoglycaemia. One consequence is the generation of autonomic symptoms, the intensity of which is heightened by the secretion and circulation of catecholamines. Unfortunately, insulin-induced hypoglycaemia attenuates adrenaline release and moves the glycaemic threshold for its secretion to a lower blood glucose level, which both increases the risk of hypoglycaemia and reduces the intensity of symptoms generated during hypoglycaemia [26]. Reduced cortisol secretion also appears to contribute to counter-regulatory failure [27].

Recurrent hypoglycaemia increasingly impairs the normal defences against hypoglycaemia and diminishes the ability to detect hypoglycaemia (i.e. hypoglycaemia begets hypoglycaemia). This phenomenon of progressive counter-regulatory failure and loss of awareness of symptoms of hypoglycaemia, which coexist in T1DM [28] has been attributed by Cryer to adverse effects of exposure to recurrent hypoglycaemia on central autonomic centres, which then fail to respond effectively to a fall in blood glucose. Cryer has called this syndrome “Hypoglycaemia Associated Autonomic Failure (HAAF)” [29]. HAAF is thought to result from a failure of centrally mediated counter-regulation [29]. However, counter-regulatory hormonal failure is not the direct cause of IAH as avoidance of hypoglycaemia results in improved perception of symptoms without restoration of the normal counter-regulatory response [30]. Nevertheless, the two are closely related and probably share a common pathogenesis as suggested in figure 2.

It used to be thought that peripheral autonomic neuropathy was responsible for these attenuated responses and was the mechanism underlying IAH. Several studies have shown that autonomic dysfunction is not the primary cause, although its presence may contribute to a reduced magnitude of symptom intensity [31]. The most powerful argument against the involvement of autonomic neuropathy in the development of IAH is that this acquired syndrome is a dynamic process that can be worsened by exposure to recurrent hypoglycaemia and improved by scrupulous avoidance of hypoglycaemia, in contrast to autonomic neuropathy which, once established, is a permanent complication that progresses in severity [32].

In people with IAH, adaptation of the brain occurs, shifting the glycaemic thresholds for the generation of symptoms, counter-regulatory hormonal secretion, and the onset of cognitive impairment to lower blood glucose levels, so that more profound hypoglycaemia is required to provoke these responses [31]. Various mechanisms have been shown to cause this effect, including exposure to antecedent hypoglycaemia, recurrent hypoglycaemia and strict glycaemic control. As a consequence of the increasingly diminished (and eventually non-existent) interval between the onset of warning symptoms of hypoglycaemia and the development of significant neuroglycopenia, people with IAH have a much greater risk of developing severe hypoglycaemia [33]. By contrast, people with poor glycaemic control re-set their glycaemic thresholds upwards, i.e. they mount a counter-regulatory response and experience symptoms of hypoglycaemia at higher blood glucose levels than those with good control, often within a hyperglycaemic range [34]. Thus symptomatic responses are initiated at elevated blood glucose levels, which is termed “relative hypoglycaemia” [4]. Interestingly, the

![Figure 2. Pathophysiology of impaired awareness of hypoglycaemia and hypoglycaemia associated automatic failure (adapted from [31])](image-url)
glycaemic thresholds of people with T2DM who have good glycaemic control but are not treated with insulin are set at levels above those of non-diabetic individuals and people with T1DM [35,36]. This may have a protective effect against the development of severe hypoglycaemia.

6. Glucose sensing

The ventromedial thalamus (VMH) is a key glucose-sensing region involved in the detection of hypoglycaemia [37]. The counter-regulatory response is ameliorated to a large extent by maintaining cerebral euglycaemia in the presence of systemic hypoglycaemia [38]. Local perfusion of the VMH with glucose to maintain localised euglycaemia markedly suppressed the counter-regulatory response despite the presence of systemic hypoglycaemia [39]. Glucose sensing also occurs outside of the brain and sensors are located in the portal vein, intestine, carotid body and in glucokinase-sensing pancreatic beta cells [40]. In animal studies, portal vein glucose sensing is necessary for the attenuation of counter-regulatory responses following antecedent hypoglycaemia [41]. However, it appears to be less important in humans in whom hormonal and symptomatic responses are unaffected by prevention of portal hypoglycaemia [42] and peripheral glucose sensors do not appear to be important in stimulating the counter-regulatory response to acute hypoglycaemia. It is not yet known if glucose sensors in the brain are irreversibly damaged in people who have developed severe forms of IAH.

7. Variable susceptibility to hypoglycaemia in people with T2DM

People with T2DM comprise a heterogeneous population with abnormalities ranging from pronounced insulin resistance to advanced insulin deficiency, and with variable residual endogenous insulin-secretory capacity. In contrast with early T1DM, residual beta cell function is usual and glucagon secretion is preserved in people with T2DM on oral therapies, so limiting the development of severe hypoglycaemia [43,44]. Increased insulin resistance associated with central obesity may also limit the severity of any iatrogenic hypoglycaemia by blunting the glucose-lowering effect of exogenous insulin.

In T2DM progression to insulin dependence occurs at a variable rate. Once insulin deficiency has developed, the same downward shift occurs in the glycaemic threshold at which the counter-regulatory response is initiated and the glucagon response becomes attenuated [35]. These developments resemble the counter-regulatory abnormalities associated with T1DM and are associated with an increased risk of hypoglycaemia [11]. When intensive insulin therapy was used in a cohort of patients with insulin-treated T2DM to lower HbA1c from 10.2% to 6.7%, the counter-regulatory and symptomatic responses to subsequent hypoglycaemia were diminished, and were associated with a threefold higher rate of severe hypoglycaemia [45]. It is difficult to determine whether the diminished responses to hypoglycaemia were a direct result of improved glycaemic control or a consequence of the effects of recurrent exposure to antecedent hypoglycaemia.

8. Definition and prevalence of IAH

The lack of an acceptable clinical definition of IAH has hindered accurate ascertainment of the prevalence of IAH and research into this condition. “Awareness” of hypoglycaemia and its progressive impairment represent a continuum ranging from normal perception of the onset of hypoglycaemia to complete inability to detect its onset [31]. For the purposes of developing a clinical scoring system, awareness of hypoglycaemia was arbitrarily divided into normal, “partial” and “absent” awareness, where “partial” represented diminution of the ability to perceive the onset of hypoglycaemia, but without total absence of a symptomatic response [33,46]. Partial and absent awareness of hypoglycaemia combined was present in 25% of a group of 302 patients with T1DM [47], which was consistent with other surveys in which the syndrome was not precisely defined [48] and more recently the syndrome of IAH was identified in 19.5% of a randomly selected cohort of 518 people with T1DM attending a secondary care diabetes clinic [49]. IAH is less common in people with insulin-treated T2DM with an estimated incidence of 8–10% [50,51]. The extent to which IAH affects people treated with insulin secretagogues such as sulfonylurea therapy is not known. Although IAH affects a smaller proportion of people with insulin-treated T2DM, in view of the number of people being treated for this condition world-wide, this clinical problem will have a greater impact than is currently appreciated.

9. Risk factors for IAH

Factors that influence the normal awareness of hypoglycaemia are shown in table 1. Many episodes of severe hypoglycaemia are under-reported by people with IAH. Furthermore, if blood glucose monitoring is infrequent, many episodes of asymptomatic (or biochemical) hypoglycaemia are not detected. Major risk factors that are associated with the development of IAH in T1DM include increasing age and duration of diabetes and strict glycaemic control [7,52]. Behavioural factors are important with reduced adherence to suggested changes in insulin regimens being observed in people with IAH [53]. Despite reporting a greater fear of hypoglycaemia, people with IAH did not modify their behaviour to try and reduce the risk of hypoglycaemia [54]. Claims in the 1980s that human insulin can cause impaired awareness of hypoglycaemia in contrast to animal insulins [55] were not substantiated by extensive research, and a subsequent meta-analysis and Cochrane review have shown no difference in the frequencies of severe hypoglycaemia or in IAH between the use of human and animal insulins [56,57].
Table 1  
Factors influencing normal awareness of hypoglycaemia [31].

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<th>Internal</th>
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<td>Physiological</td>
<td>Drugs</td>
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<tr>
<td>Recent glycaemic control</td>
<td>Beta-blockers (non-selective)</td>
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<tr>
<td>Degree of neuroglycopenia</td>
<td>Hypnotics, tranquilisers</td>
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<td>Symptom intensity/sensitivity</td>
<td>Alcohol</td>
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<td>Psychological</td>
<td>Environmental</td>
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<td>Focused attention</td>
<td>Posture</td>
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<td>Congruence; denial</td>
<td>Distraction</td>
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<td>Competing explanations</td>
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<td>Education</td>
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<td>Symptom belief</td>
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Any medication which alters the response to sympathoadrenal stimulation and catecholamine release could potentially affect hypoglycaemia awareness; theoretically, beta blockers by suppressing adrenoceptor responses, should reduce counter-regulation and diminish the intensity of symptoms that are adrenergically-mediated. In effect, selective beta blockers do not appear to have any significant clinical effect. Glucose clamp experiments showed that the threshold for autonomic symptoms was shifted to a lower blood glucose level while neuroglycopenic symptoms and cognitive function were unaffected [58]. Usage of non-selective beta-blockers has been associated with an increased risk of severe hypoglycaemia [59]. During moderate hypoglycaemia, beta-blockers did not modify awareness or symptom intensity during hypoglycaemia [60]. Despite some case reports suggesting a reduction in symptom intensity during hypoglycaemia, a glucose clamp study in which non-depressed, non-diabetic subjects were given fluoxetine demonstrated that counter-regulatory hormone release was increased, but with no concurrent change in symptom scores [61].

10. Clinical assessment of IAH

Glucose clamp studies have been used to determine awareness of hypoglycaemia [62] and to demonstrate the hierarchy of responses that occur as blood glucose declines. Autonomic symptoms occur before neuroglycopenic symptoms, with a difference of around 0.5 mmol/l between the thresholds at which they are generated [63,64]. However, this artificial and controlled experimental setting bears little relationship to everyday life with its myriad distractions, and this small threshold difference cannot be detected subjectively by affected individuals [14,15]. The most useful method of identifying impaired awareness of hypoglycaemia and its importance to the individual is to take a careful clinical history. People with T1DM who state that they have IAH are generally correct [46]. A structured questionnaire of hypoglycaemia experience has been developed to confirm the clinical history [46], while a simpler method employs a single question and asks the patient to score their awareness on a Likert scale (from 1 to 7), where a low score represents normal awareness and a high score designates loss of awareness [33]. To be utilised effectively the participant must have experienced hypoglycaemia on at least one occasion in the preceding year, and for reasons explained below, the answers must be based on experience of hypoglycaemia that occurs during waking hours. These two questionnaires display good concordance in the adult population [49]. A third method from Denmark, which has attempted to relate symptomatic awareness to subjective experience generally over-estimates the frequency of IAH, with almost two thirds of people with T1DM being described as having this problem, which is not consistent with clinical experience [49]. A revised, trichotomised version of this method that subdivided the patients into three groups: “aware”, “intermediate” and “impaired”, improved concordance with the two established methods [65], but the terminology used in the Danish method is open to misinterpretation. The semantics of IAH present difficulties and translation of the Clarke and Gold methods into languages other than English may introduce anomalies. The method of Clarke et al [46] has been validated by a Dutch study that also utilised prospective blood glucose monitoring and glucose clamps to assess hypoglycaemia awareness [66]. In both the Clarke and Gold methods a degree of uncertainty exists regarding assessment in the middle range, equivalent to a score of 3 in both scales. It is unclear if people with this score have definite IAH, or whether they may represent people with partial loss of awareness who have yet to progress to expression of the full-blown syndrome.

IAH is associated with a 2-4 fold higher frequency of asymptomatic biochemical hypoglycaemia (capillary blood glucose < 3.5 mmol/L) [33,52,67]. Continuous glucose monitoring (CGM) has demonstrated that much hypoglycaemia is undetected and has suggested that asymptomatic biochemical events are fourfold higher in people with IAH compared to those with normal awareness [68,69]. However, despite an increased risk of severe hypoglycaemia and evidence of more hypoglycaemia during prospective self-monitoring of capillary blood glucose, retrospective blood glucose analysis of CGM records for up to 72 hours of monitoring failed to identify those with IAH, who had a similar frequency, duration and severity of biochemical hypoglycaemia as those with normal awareness. At the time of this particular study the technology may not have been sufficiently sensitive to identify the presence of this syndrome [70], but increasingly sophisticated CGMS technology may improve detection by this approach.

11. Morbidity and mortality associated with IAH

People who have impaired awareness of hypoglycaemia have a much greater risk of severe hypoglycaemia, up to six fold, with its attendant morbidity [33,70]. Severe hypoglycaemia may result in many serious forms of morbidity including seizure, coma, fractures and joint dislocation and
cardiac arrhythmias, and is occasionally fatal. However, although these problems are more frequent in people with IAH, the frequencies of these morbidities associated with severe hypoglycaemia have not been formally estimated. The strict glycaemic control that is required during the management of gestational diabetes, when insulin is frequently necessary, is often associated with IAH of considerable severity, and an associated high risk of severe hypoglycaemia. Pregnant women with diabetes are subject to hypoglycaemia-induced morbidity, particularly in the first trimester [71].

12. Effect of alcohol, sleep and distraction on awareness of hypoglycaemia

Alcohol is an important risk factor for hypoglycaemia [72]. The clinical features of hypoglycaemia can be mistaken for those of alcohol intoxication which can delay correct treatment of the hypoglycaemic episode. Despite increased counter-regulatory responses in those who had consumed alcohol compared with those who had not, during experimental hypoglycaemia they were less likely to recognise that they were hypoglycaemic (2 out of 15 versus 11 out of 15) [73].

Sleep is a physiological state where warning symptoms of hypoglycaemia are usually absent and presents a particular problem to people with T1DM as many severe episodes occur during sleep, which is mainly nocturnal [22]. Symptomatic responses to hypoglycaemia are diminished in the supine posture [58] and the plasma adrenaline response is also lower when lying down [74]. When hypoglycaemia occurs during sleep, counter-regulatory responses, particularly the release of catecholamines, are markedly attenuated in people with T1DM compared with responses when they are awake [75,76]. Adults with T1DM experienced less disruption to their quality of sleep during hypoglycaemia, spending 77% of the time asleep in comparison to 26% in non-diabetic participants [75]. During hypoglycaemia only 1 person out of 16 with T1DM awoke during hypoglycaemia in comparison to 10 out of 16 of those without diabetes [77]. Unrecognised nocturnal hypoglycaemia presents a possible explanation why people with T1DM develop IAH, by modifying glycaemic thresholds to subsequent hypoglycaemia [78].

Driving simulator studies have shown that people with T1DM whose symptomatic awareness is not impaired are often unaware of the onset of cognitive dysfunction while modest hypoglycaemia is being induced and fail to take corrective action [79]. Participants failed to recognise both deterioration in their driving performance and their current hypoglycaemic status, this may be partly attributable to distraction. People who are distracted by a stressful event report lower symptom intensity scores during acute hypoglycaemia despite greater counter-regulatory hormonal release [80].

13. Effect of IAH on cognitive function

People with IAH often state that they do not experience any cognitive impairment during hypoglycaemia and are capable of carrying out the usual activities of daily living even though they may be exposed to frequent asymptomatic hypoglycaemia. To some extent this is true, as cognitive function is less affected during moderate hypoglycaemia and recovery is quicker compared than in people with T1DM who have normal awareness [81]. The glycaemic threshold for cognitive dysfunction is re-set at a lower blood glucose level, in the same way as those for generation of symptoms and the stimulation of counter-regulatory hormonal secretion [62,82]. Other studies have indicated that cognitive dysfunction occurs at lower blood glucose levels in those with IAH compared to those with normal awareness or people without diabetes [62,83]. As already noted, nocturnal hypoglycaemia diminishes the degree of cognitive impairment during subsequent hypoglycaemia [78]. It is sometimes difficult to convince a few people with IAH both of the scale of the problem and the imperative to avoid hypoglycaemia wherever possible, especially when consultations with specialists tend to focus on the necessity of attaining good glycaemic control. However, most people with this syndrome are fully cognisant of the dangers that it imposes, and the threat to retaining their driving licence and some forms of employment.

Exposure of the brain to repeated episodes of hypoglycaemia over many years in people with T1DM had no apparent effect on long term cognitive function in the DCCT/EDIC study [84]. However, the long term effects of recurrent exposure to hypoglycaemia, both severe and mild, are more difficult to determine in patients who have established IAH. Animal studies have shown that antecedent moderate hypoglycaemia can protect the brain against subsequent severe hypoglycaemia with evidence of less neuronal damage [85]. While people with IAH develop a lesser degree of cognitive impairment during mild hypoglycaemia, with apparent resistance to the cerebral effects of moderate hypoglycaemia, because profound neuroglycopenia is a relatively common occurrence it seems likely that this will have significant adverse long term effects on cognitive function. People with IAH have been shown to perform less well on a limited number of cognitive function tests applied during both euglycaemia and hypoglycaemia [82]. More profound cognitive dysfunction during acute hypoglycaemia was observed in those with IAH compared to those with normal awareness [86]. However, few studies have examined the long-term effects on cognitive function in people who have developed impaired awareness of hypoglycaemia, which is associated with a very much high frequency of severe hypoglycaemia [33,52]. One such study has suggested that significant cognitive impairment occurs in affected patients [87].

14. Neuroimaging studies

The effect of hypoglycaemia on the brain can be directly visualised with neuroimaging techniques such as positron
emission tomography (PET) and functional magnetic resonance imaging (fMRI). During euglycaemia, glucose is the obligate metabolic substrate required to maintain cerebral function, and this is unchanged during hypoglycaemia [88]. The likely contribution of other energy sources (e.g. lactate) remains small although there is some evidence that people with T1DM may be better able to utilise these alternative fuel sources [89,90].

PET can be used to examine whole brain and regional changes in glucose metabolism. While animal models have indicated that antecedent hypoglycaemia increases glucose transport from blood to brain, thus allowing the brain to extract glucose more efficiently, this has not been shown in humans using PET [91]. Global brain glucose content falls during acute hypoglycaemia with no difference apparent between those with normal and those with impaired awareness, again implying that global glucose extraction is not enhanced by antecedent hypoglycaemia [92].

Studies of regional brain activation have identified key areas involved in glucose homeostasis and thus give insight into the pathophysiology underlying hypoglycaemia awareness. Glucose uptake by the ventromedial hypothalamus, thought to be a key glucose sensor, is reduced in people with IAH [93]. Antecedent hypoglycaemia was induced in healthy adults to induce a state of counter-regulatory failure; subsequent hypoglycaemia resulted in an increase in activity of the dorsal midline thalamus, which is thought to have an inhibitory role in reducing counter-regulatory responses following antecedent hypoglycaemia [94]. In this study, antecedent hypoglycaemia was again used to show a relative reduction in glucose metabolism in cortical areas that are involved in symptom perception [91]. This reduction was also demonstrated in people with IAH [92]. Activation of the amygdala is thought to be an unpleasant subjective experience associated with fear and anxiety. During acute hypoglycaemia, [18F] – fluorodeoxyglucose PET scanning showed greater activation in the amygdala in people with normal hypoglycaemia awareness compared to those with IAH (Fig. 3) [95]. These regional changes in people with IAH can be considered to be an example of “stress sensitisation”, whereby repeated exposure to a specific stress results in a reduced response. In contrast, a relative increase in activation was observed in the lateral orbitofrontal cortex during hypoglycaemia in people with IAH; activation of these areas is thought to reduce appetite and limit an appreciation of danger associated with hypoglycaemia (Fig. 3) [95].

15. Management of IAH

The mainstay of treatment of IAH is the complete avoidance of hypoglycaemia, which is of course very difficult to achieve. Reducing the frequency of hypoglycaemia can be attempted by various measures as shown in table 2. Hypoglycaemia awareness can be restored by scrupulous avoidance of hypoglycaemia, although this may be at the cost of jeopardising glycaemic control [96,97]. Hypoglycaemia avoidance can lead to a significant improvement in hypoglycaemia symptom scores during exposure to subsequent hypoglycaemia [97]. Long term effectiveness of these hypoglycaemia avoidance programmes was demonstrated in a small cohort (n=4) three years after a period of hypoglycaemia avoidance for three months. During hypoglycaemia, the symptom scores remained higher than baseline but less than those achieved immediately after the period of hypoglycaemia avoidance [98]. Hypoglycaemia avoidance programmes are labour intensive for both patient and clinician as they tend to require frequent monitoring of blood glucose including measurements at night, with frequent insulin dose adjustments which may take months to implement [99]. Despite the improvement in symptom scores, deficient counter-regulatory hormonal responses to subsequent hypoglycaemia

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<tr>
<th>Table 2</th>
<th>Treatment strategies for people with IAH [31].</th>
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<tr>
<td>Frequent blood glucose monitoring (including nocturnal measurements)</td>
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<tr>
<td>Avoid blood glucose values &lt; 4.0mmol/L</td>
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<tr>
<td>Revise blood glucose targets upwards (e.g. prandial target 6.0-12.0 mmol/L &amp; bedtime &gt; 8.0 mmol/L)</td>
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<tr>
<td>Avoid HbA1c being within non-diabetic range</td>
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<tr>
<td>Use predominantly short-acting insulins (basal bolus regimen; CSII; insulin analogues)</td>
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<tr>
<td>Regular snacks between meals and at bedtime, containing unrefined carbohydrate</td>
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<tr>
<td>Appropriate additional carbohydrate consumption and/or insulin dose adjustment before exercise</td>
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<tr>
<td>Learn to identify subtle neuroglycopenic cues to low blood glucose</td>
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Figure 3. Cerebral correlates of unawareness [95].
A: Regions where aware subjects show relatively greater uptake with hypoglycaemia than unaware subjects, showing amygdala, cerebellum, and brainstem regions.
B: Regions where aware subjects show relatively lower uptake than unaware subjects with hypoglycaemia showing right lateral orbital-frontal cortex.

are relatively unaffected [30,97]. This illustrates a divergence between continuing subnormal counter-regulatory response and an improvement in symptomatic responses, which suggests that other factors are probably important in promoting the symptomatic recovery.

Although it has been suggested that people with IAH may have reduced sensitivity to beta agonists, one study has shown that beta-adrenoceptor sensitivity is preserved [100]. Beta agonists (e.g. terbutaline) have been shown to significantly reduce nocturnal hypoglycaemia at the cost of inducing morning hyperglycaemia [101,102]. Beta agonists have therefore been suggested as possible therapeutic options. Caffeine has been shown to augment symptom intensity and improve counter-regulatory responses [103]. Functional MRI shows caffeine can restore regional brain activation normally lost during acute hypoglycaemia [104]. However, the daily doses required may not make this a practical proposition in treating people with IAH.

One potential advantage of long-acting insulin analogues is their association with a lower rate of nocturnal hypoglycaemia [105]. Hypoglycaemia induced by insulin detemir generated higher symptom scores when compared with human insulin although the difference in total symptom scores only just achieved significance (p=0.048) and the study was not blinded to insulin type [106]. Substitution of nocturnal continuous subcutaneous insulin infusion (CSII) for isophane (NPH) insulin at bedtime resulted in a lower frequency of hypoglycaemia. Warning symptoms and counter-regulatory responses were improved during subsequent acute hypoglycaemia [107]. CSII was used for 24 months in a cohort in which 95% had established IAH and had experienced two or more episodes of severe hypoglycaemia in the preceding two years. The participants reported fewer episodes of severe hypoglycaemia, an improved quality of life, unchanged glycaemic control and an improved symptomatic response to experimentally-induced hypoglycaemia [108]. Administration of bolus doses of glucagon at times of impending hypoglycaemia during CSII lowered the frequency of hypoglycaemia [109]. IAH can also be relieved by islet cell transplantation, with a decline in prevalence from 87% before transplantation to 13% post-transplantation together with an increase in the blood glucose threshold that was required to trigger symptoms of hypoglycaemia, from 2.3 mmol/L (41 mg/dL) to 3.2 mmol/L (58mg/dL) [110].

16. Conclusion

Impaired awareness of hypoglycaemia is an acquired syndrome associated with the use of insulin and exposure to hypoglycaemia that is common in people with T1DM and is observed less frequently in insulin-treated T2DM. It should be defined by the loss of ability to perceive the onset of hypoglycaemia, which is usually manifested by a reduced intensity and number of symptoms and a change in symptom profile. Asymptomatic biochemical hypoglycaemia occurs more frequently and people with established IAH have a much higher risk of developing severe hypoglycaemia. In those affected, cognitive dysfunction is less pronounced during acute hypoglycaemia and recovery is more rapid. However, the glycaemic thresholds for the generation of symptoms, counter-regulatory hormonal secretion and cognitive impairment are re-set at lower blood glucose levels as a result of cerebral adaptation, which allows little opportunity for correcting hypoglycaemia when blood glucose falls to dangerously low levels, and neuroglycopenia rapidly supervenes which prevents appropriate self-treatment. Exposure to antecedent hypoglycaemia, especially repeated episodes, is an important factor in the pathogenesis of IAH. Neuroimaging has allowed identification of key areas of the brain that are involved in maintaining glucose homeostasis and responding to hypoglycaemia. Two methods are currently available for the assessment of awareness of hypoglycaemia in adults, which can be used to identify people with impaired awareness. As antecedent hypoglycaemia appears to have an important role in the pathogenesis of IAH, scrupulous avoidance of hypoglycaemia appears to be crucial in maintaining defences against the development or progression of IAH.

17. Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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