Impaired awareness of hypoglycaemia

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Abstract

Impaired awareness of hypoglycaemia (IAH), defined either clinically as the loss of subjective awareness of hypoglycaemia before the onset of cognitive impairment or biochemically as the loss of symptom perception until plasma glucose has fallen below 3 mmol/L (54 mg/dl), is the major modifiable risk factor for severe hypoglycaemia in T1DM and possibly in insulin-treated T2DM. This paper tells the story of IAH, its pathogenesis and its implications and the treatment strategies used to address it.

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Key words: hypoglycaemia, hypoglycaemia awareness, severe hypoglycaemia

Introduction

Impaired awareness of hypoglycaemia (IAH) may be defined as the diminished ability to perceive the onset of hypoglycaemia before the onset of cognitive dysfunction sufficient to alter behaviour and/or to prevent the coordination and execution of self-treatment. Normal counter-regulation to a falling blood glucose concentration is impaired in insulin-deficient diabetes: insulin action is maintained by exogenous injection or by drug-induced endogenous insulin secretion, and glucagon responses to hypoglycaemia are impaired.[1] Detectable defects in cognition start at a plasma glucose of 3 mmol/L (54 mg/dl),[2] a slightly lower concentration than that required to stimulate the counter-regulatory stress response and the symptoms of hypoglycaemia. In IAH, the glucose concentration required to drive the latter is reduced to well below 3 mmol/l,[2] explaining how the protection from severe hypoglycaemia (episodes which need to be treated by others because of cognitive dysfunction in the person experiencing the hypoglycaemia) that is afforded by timely self-treatment is lost. IAH is associated with a 6-fold increase in risk of severe hypoglycaemia in adults with T1DM,[3] and 17-fold increase in risk in people with T2DM who require insulin.[4] IAH affects 20 – 40% adults with T1DM,[3,5] even in the age of continuous glucose monitoring.[6] Although sometimes referred to as "hypoglycaemia associated autonomic failure" it is not associated with diabetic peripheral or autonomic neuropathy.[7]

The state of IAH in people with diabetes who are at risk for hypoglycaemia (those on insulin and insulin secretagogues) is diagnosed through the patient history, inspection of home monitoring records with the patient and sometimes in discussion with family members. The UK's National Institute of Health and Care Excellence (NICE) was one of the first bodies to mandate assessment of awareness status in people with diabetes at risk for hypoglycaemia at least annually in their guidelines, recommending use of the Gold score (Figure 1a).[8,9] The question used by the UK's DAFNE patient education system, asking people whether they usually experience symptoms of hypoglycaemia below, at or above 3 mmol/L (Figure 1b) is another quick method of assessment.[7] It is less subjective than the Gold score and less well established in the literature, although the association with risk for severe hypoglycaemia is at least as strong.[5] The more complex but very well validated Clarke score measures hypoglycaemia experience as well as awareness status,[10,11] and other scoring systems are used in research.[12,13,14]

IAH and its attendant increase in risk for severe hypoglycaemia has been demonstrated to be stressful for partners and family members.[14,15] More recently, IAH has been shown to be associated with higher scores for anxiety and depression,[16] illustrating the mental health burden of the condition on the people with diabetes and IAH themselves.

Who is at risk for problematic hypoglycaemia?

We have known for a long time that risk for severe hypoglycaemia is skewed. In one clinic-based study, 60% of adults with TiDM did not report any episodes of hypoglycaemia over a year.[17] In fact, 10% of the population reported nearly 70% of all severe hypoglycaemia. Increasing diabetes duration, and perhaps associated increasing age, and complexity of co-morbidities were unmodifiable risk factors – IAH was the one major modifiable risk factor left. The link between IAH and severe hypoglycaemia persists even with the use of continuous glucose monitoring (CGM).[6]

The management of IAH

There is an evidence-based pathway for the management of problematic hypoglycaemia (IAH plus more than one severe hypoglycaemia episode in a year) in T1DM.[18] Structured education in flexible insulin dose adjustment is probably the most powerful way to reduce severe hypoglycaemia and improve awareness status,[19,20] with benefit demonstrated in largely unselected populations. CGM and intermittent retrospectively monitored CGM (Flash) with alarms are of proven benefit, the former in people with IAH and/or a history of severe hypoglycaemia,[21] the latter

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in a less selected population.[22] Replacing intermittent injections of insulin with continuous subcutaneous insulin infusion (pump) therapy also has older evidence to show benefit in reducing severe hypoglycaemia,[23] and the automated regulation of insulin delivery by pumps responding to data from linked CGM systems, including hybrid closed-loop systems, shows evidence of benefit.[24] Useful effects have been observed in populations at risk,[25,26] although protection from severe hypoglycaemia has not been seen in all studies,[27] and some have not focused on high-risk populations.[28] Ultimately, replacing the lost beta cells by islet or whole organ pancreas transplantation provides near-complete protection from severe hypoglycaemia as long as there is residual endogenous insulin secretion.[29,30]

Despite the success of these strategies, and the increasing sophistication of technological approaches to insulin replacement, there is still a need for new approaches. Anecdotal evidence of severe hypoglycaemia in people with diabetes who are on the most advanced technology persists,[31,32] and all the studies that show reduced severe hypoglycaemia in populations at high risk by education or technology show residual severe hypoglycaemia episodes.[5,20,21,24,25] In populations with IAH, technology has often failed to restore awareness.[21,23] There is of course also the issue of access to technology: it is likely to be a long time before everyone at risk for insulin-induced hypoglycaemia is able to have a closed-loop system they can manage themselves. But there are also issues around human engagement with technology, especially while it remains less than perfect. In one study where CGM was added to pump therapy in a population with high rate of IAH, nearly 20% of participants stopped using the technology for reasons such as alarm fatigue, local and technical problems or just not wearing it enough to gain benefit.[33]

The pathophysiology of IAH

IAH is associated with a defective counter-regulatory response: the triggering of hormonal and symptom responses happens at a lower plasma glucose level while the glucose threshold for cognitive dysfunction remains more or less fixed.[27] The defective counter-regulation is inducible by recurrent exposure to plasma glucose concentrations below 3 mmol/L.[34] The causality of antecedent hypoglycaemia has been established by its reversal – defective symptomatic responses to hypoglycaemia in experimental studies can be restored, sometimes with restoration of adrenaline responses, by avoidance of exposure to plasma glucose of less than 3 mmol/L.[35,36]

We have learned through neuroimaging studies that the central response to induced hypoglycaemia in IAH includes changes in activation of brain regions involved in stress responses and symptom perception but also of regions involved in emotional salience, aversion and memory, arousal and decision-making which are different from the responses seen in people without diabetes and those with diabetes but with preserved hypoglycaemia awareness.[37,38] Education plus technology can reduce Gold score and severe hypoglycaemia experience and can normalise responses in the brain's anterior cingulate cortex but not in frontal cortical regions such as the orbitofrontal cortex and dorsolateral pre-frontal cortex.[39] It is possible that some people have a predisposition to develop IAH as a response to hypoglycaemia: early data suggest increased prevalence of alexithymia and extremes of perfectionism in people with IAH.[40] These are personality traits which are thought to be established in early life and they would, at least in theory, predate the diagnosis of diabetes and problematic hypoglycaemia. Clinic-based studies have shown that about one third of people with T1DM at high risk for severe hypoglycaemia (25% of the whole clinic) expressed low concern about it;[41] in a qualitative study, 13 of 17 people with entrenched problematic hypoglycaemia did not describe a high level of worry about it.[42] They described thoughts about their hypoglycaemia that are perceived as barriers to hypoglycaemia avoidance – most notably, prioritisation of hyperglycaemia avoidance, normalising their asymptomatic hypoglycaemia and minimising concerns about hypoglycaemia.[42] De Zoysa created a 19-item questionnaire to help identify some of these thinking patterns, the Attitudes to Awareness (A2A) questionnaire, for use in people with problematic hypoglycaemia.[43] Such patterns have now been described also by people with problematic hypoglycaemia using CGM.[44]

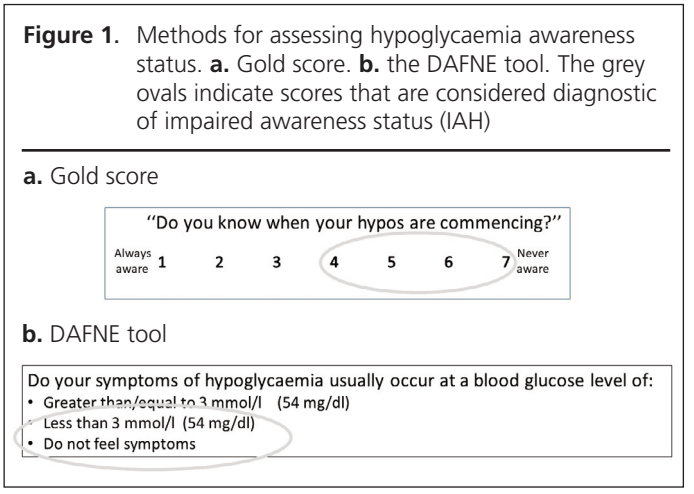

Figure 1. Methods for assessing hypoglycaemia awareness status. **a.** Gold score. **b.** the DAFNE tool. The grey ovals indicate scores that are considered diagnostic of impaired awareness status (IAH)

A novel approach – the HARPdoc programme

The described research suggested a need for a novel approach to hypoglycaemia avoidance and regain of awareness for a particular group of people with IAH that focuses on cognitions around hypoglycaemia. A team of diabetes physicians, educators and people with diabetes, led by the clinical psychologist, created a programme for small groups of individuals with otherwise treatment-resistant hypoglycaemia based on the evidence and using psychological theory, specifically motivational interviewing techniques and cognitive behavioural theory, to address cognitions around hypoglycaemia that act as barriers to hypoglycaemia avoidance and regain of awareness. We called the cognitions that were barriers to hypoglycaemia avoidance "thinking traps". An important principle underlying the programme is the "thinking trap" vicious cycle, in which IAH causes a person experiencing a low blood glucose to feel fine, endorsing and empowering the unhelpful thoughts, leading to delayed or absent action taken to treat the hypoglycaemia, and therefore prolonging and contribut-

Figure 2. The thinking traps vicious cycle, showing how impaired awareness of hypoglycaemia permits the entertainment of thoughts that tend to lead to undertreatment of hypoglycaemia, experience of which creates the counter-regulatory deficits that underpin impaired awareness

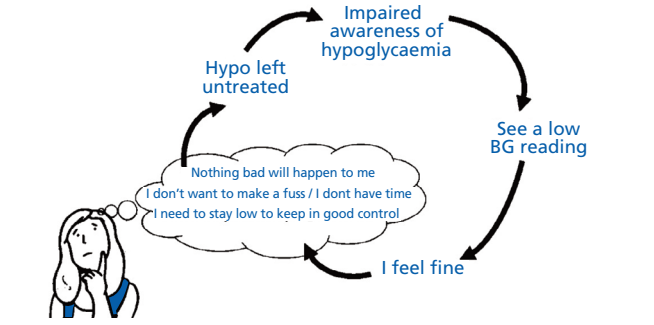

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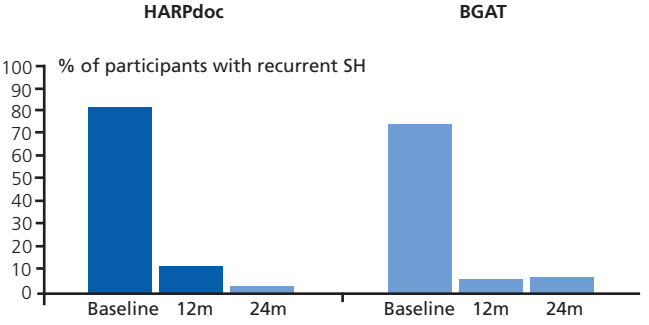
Figure 3. Percentage of people with recurrent severe hypoglycaemia (more than one episode per year) at baseline and 12- and 24-month follow-up in the HARPdoc RCT



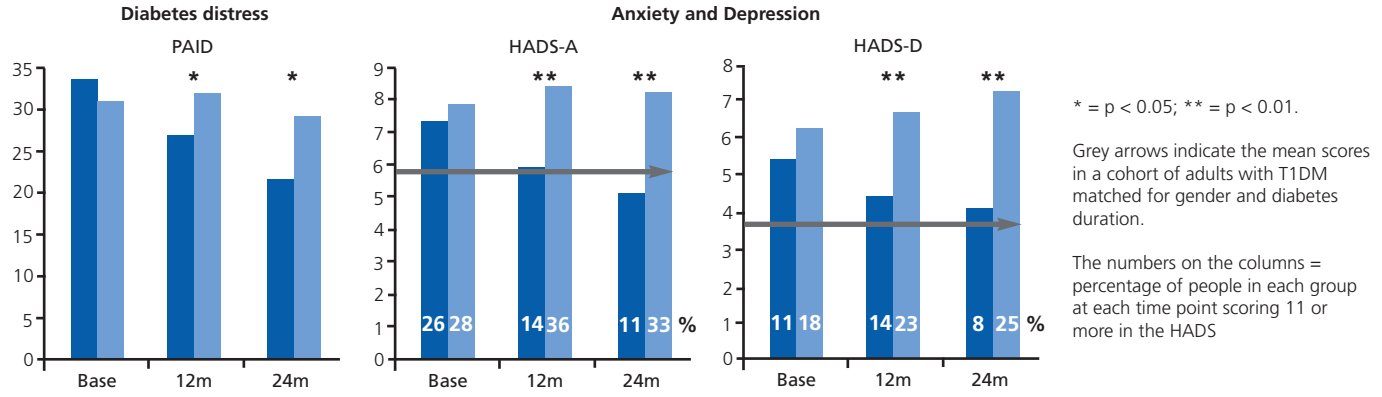
ing to the maintenance of the IAH (Figure 2).

The programme was tested in a pilot in the UK's DAFNE programme,[45] it not being suitable for people whose hypoglycaemia may be driven by lack of factual knowledge about insulin dose adjustment around lifestyle events to minimise hypoglycaemia risk. After adjusting for educator and participant feedback in the pilot, the programme was refined into the current HARPdoc programme. This is a curriculum-driven group intervention delivered over six weeks by two experienced diabetes educators who have been trained and supported to deliver it by the clinical psychologist. The programme uses motivational interviewing and cognitive behavioural theory, focusing tightly on addressing cognitions believed to act as barriers to hypoglycaemia avoidance. We tested it in a randomised controlled trial against Blood Glucose Awareness Training, BGAT,[46] an earlier psycho-educational programme, also manualised, designed to be delivered by one educator in eight 2-hour sessions which addresses knowledge and behaviours to predict and minimise both high and low extremes of glucose.[47] We chose this programme because of its proven ability to reduce severe hypoglycaemia and improve hypoglycaemia awareness.[48] NICE recommends it for people with problematic hypoglycaemia complicating their T1DM management but it has never been tested in people who have already completed a structured education programme such as DAFNE, which is in common usage in the UK. There was interest in its impact on hypoglycaemia that persisted or had recurred post-DAFNE. One of the psychologists from the team that had created BGAT joined our trial team, as BGAT was not currently in use in the form in which it had been trialled and it needed updating to reflect newer insulins and monitoring systems. We also needed to re-configure the programme to be delivered over the same time frame (four full-day face-to-face group sessions over six weeks, with one-to-one contact in weeks 4 and 5 optional for the BGAT participants).

The clinical trial data are still being analysed but the baseline data and the primary and main secondary outcomes are published.[49,50] As anticipated, the trial, which had three centres in the UK and one in the US, recruited people mostly of long diabetes duration (mean±SD 35.8±15.4 years) of whom more than half had had problematic hypoglycaemia for ten years or more despite having undertaken structured education in flexible insulin therapy and remaining under the care of specialist teams, with access to latest technology. We were recruiting between 2017 to 2019 and hybrid closed-loop systems were not available but pumps and real-time continuous glucose monitoring (CGM) were. It is relevant that while nearly 80% of individuals had been offered pumps and more than 60% CGM, fewer than half were using any form of technology at recruitment. Accepting that the better the technology the more acceptable it will be to people with T1DM, the present evidence suggests that people with entrenched IAH may struggle either to engage with it or to get the expected benefits when they do.

The trial was designed as a superiority study, intended to show that HARPdoc was more effective than BGAT in reducing severe hypoglycaemia in this very high risk population (baseline rate of severe hypoglycaemia mean±SD 27.9±7.2) who had previously completed another structured education programme. Our primary outcome was the difference in rates of severe hypoglycaemia at either or both of the follow-up times of 12 and 24 months. The final trial result was negative, for BGAT reduced severe hypoglycaemia to a median of zero, making it difficult for HARPdoc to do better! The statistical analysis plan did not include a comparison of the changes in hypoglycaemia over time but Figure 3 shows that both programmes were very effective, with just a hint that the impact of HARPdoc continues to evolve over two years, which was in line with one of our hypotheses (that the impact of HARPdoc would be better sustained because of having addressed important cognitions that underpinned the IAH). There was no difference between the two programmes on Gold scores of hypoglycaemia awareness status, although we can note that HARPdoc increased the proportion of people scoring 3 or less (aware) from zero to 36.6% at 12 months and 43% at 24 months. There were, however, potentially clinically important secondary outcomes for the trial in which HARPdoc was superior to BGAT, and these included the mental health scores. Scores for diabetes distress, anxiety and depression were high at baseline compared with a comparator group matched for

Figure 4. Impact of HARPdoc (dark blue) and BGAT (light blue) on scores for diabetes distress (the Problem Areas in Diabetes questionnaire) on the left, Anxiety (Hospital Anxiety and Depression Scores – Anxiety) in the centre and depression (Hospital and Anxiety Depression Scores – Depression) on the right. HARPdoc is associated with lower scores compared to BGAT at 12- and 24-month follow-up.



diabetes duration and gender but without problematic hypoglycaemia.[49] The scores were significantly lower at both 12 and 24 months in the HARPdoc group (Figure 3).[50] Although still being analysed, preliminary analyses from the implementation science analysis of the trial suggest that both participants and educators rated HARPdoc higher than BGAT for acceptability, appropriateness and feasibility and that HARPdoc is the more cost-effective programme for reasons that are still being investigated.[51]

Conclusions

A cohort of people with T1DM and problematic hypoglycaemia persists despite deployment of best treatment. At present the estimate for prevalence of this cohort lies between 4 and 8% of the adult population with T1DM. They are a highly vulnerable group, with impaired mental health and quality of life. They express thoughts that drive behaviours that impair their ability to avoid hypoglycaemia. It is possible, and probably cost-effective, to address these thoughts with an intervention that can be offered after structured education, and ideally also continuous glucose monitoring, have failed to resolve their situation. While continuing improvements in technology may help, they are unlikely to resolve the problem for these people in the foreseeable future. In a very recent report from the US Type 1 Diabetes Exchange population, reported at the EASD of 2022, Professor Laffel described 16-19% of people using diabetes therapeutic technology who continue to report severe hypoglycaemic events, including those using hybrid closed loop.[52]

Conflict of interest SAA has served on advisory boards for NovoNordisk and Medtronic and spoken at educational events sponsored by Sanofi and NovoNordisk in the past three years. She is a co-investigator in the EU IMI HypoRESOLVE programme. The HARPdoc RCT was sponsored by the Juvenile Diabetes Research Foundation, with additional support from the NIHR S E London CLAHRC and from Dexcom. The views expressed here are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Key messages

- Impaired awareness of hypoglycaemia (IAH) in diabetes greatly increases risk of severe hypoglycaemia and may be associated with impaired mental health status
- Awareness status should be measured routinely in consultations with people at risk – those using exogenous insulin or insulin secretagogues
- Addressing thoughts about hypoglycaemia may be necessary for some with IAH to achieve better outcomes from the therapeutic pathway.

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