Chapter

Symptoms of Hypoglycaemia

Panagiota Loumpardia and Mohammed S.B. Huda

Abstract

Hypoglycaemia is common in clinical practice for people with diabetes. However, the symptoms can vary between individuals and at different stages of their condition. Moreover, several factors influence symptoms experienced by people with diabetes, and many are amenable to intervention. Symptoms are commonly neuroglycopenic or neurogenic in aetiology, and these lead to different clusters of symptoms. Certain patient groups such as the elderly and pregnant women are particularly susceptible to hypoglycaemia. In this chapter, we describe the physiology and pathophysiology behind the symptoms of hypoglycaemia, with reference to current knowledge from neuroimaging studies, and outline potential interventions to modify or restore hypoglycaemia symptoms.

Keywords: hypoglycaemia, symptoms, treatment, hypoglycaemic unawareness

1. Introduction

Hypoglycaemia is common in clinical practice with up to 45% of people with type 1 diabetes mellitus (T1DM) experiencing mild to moderate hypoglycaemia and 6% experiencing severe hypoglycaemia [1]. The average individual with type 1 diabetes experiences two symptomatic hypoglycaemic episodes a week, and the prevalence of severe hypoglycaemia can be up to 30–40% [2].

The signs and symptoms of hypoglycaemia however can be variable and can change over time. In this chapter, we discuss the presentations of hypoglycaemia and the underlying pathophysiology.

2. Definition of hypoglycaemia

This has been a controversial area for many years, and only recently, a consensus has been developed. Normal blood glucose levels can range between 3.5 mmol/l (63 mg/dl) and 7.0 mmol/l (126 mg/dl), but individuals can develop lower values physiologically during fasting or starvation. Blood glucose levels less than 3.0 mmol/l (54 mg/dl) are associated with poorer clinical outcomes.

The International Study Group suggests that a level of <3.0 mmol/l (54 mg/dl) be defined as denoting serious clinically important hypoglycaemia, whether that level is associated with symptoms or not, and that incidences of hypoglycaemia within that range be reported during clinical trials and in clinical practice [3].

The statement outlines proposed glucose levels to define severe hypoglycaemia as:

- Level 1: a glucose alert value of 3.9 mmol/l (70 mg/dl) or less. This need not be reported routinely in clinical studies, although this would depend upon the purpose of the study.

- Level 2: a glucose level of <3.0 mmol/l (<54 mg/dl) is sufficiently low to indicate serious, clinically important hypoglycaemia.

- Level 3: severe hypoglycaemia, as defined by the American Diabetes Association, denotes severe cognitive impairment requiring external assistance for recovery.

2.1 Symptoms

The most frequently reported symptoms during hypoglycaemia in diabetes are sweating, trembling, inability to concentrate, weakness, hunger and blurred vision [4].

Generally, symptoms are divided into two groups:

a. Neuroglycopenic symptoms caused by brain glucose deprivation:

   - Cognitive impairment (altered perception, poor concentration, slow/hesitant speech, slow decision-making).

   - Behavioural changes (irritation, frustration, refusal to help).

   - Psychomotor abnormalities (incoordination, unsteadiness, weakness).

   - Seizure/coma.

   - Permanent neurological damage if prolonged severe hypoglycaemia.

b. Neurogenic symptoms caused by the sympathoadrenal response:

   - Adrenergic (palpitations, tremulousness, anxiety, arousal, skin pallor/flushing or blotchy rashes, tingling around the mouth/lips).

   - Cholinergic (sweating, hunger, paresthesia) [5].

To try and understand why the above symptoms are present, or not present, we describe physiological and pathophysiological response to hypoglycaemia in people with diabetes.

Glucose is the fuel for the most of the body functions including cerebral function. The brain is not able to synthesize glucose and therefore is critically dependent on a continuous glucose supply from the circulation (20% of circulated glucose).

Glucose is transported into the brain across the blood–brain barrier by the glucose transporter protein GLUT-1, and antecedent hypoglycaemia causes upregulation of this transporter [6]. If however the glucose level falls quickly to critically low levels, then despite the upregulation of the transporter, the supply is not adequate, and it may lead to impairment of brain function.

2.2 Physiological response to hypoglycaemia

Normal body physiology (without diabetes) has a sequence of responses to handle hypoglycaemia.

The first response is to decrease insulin production from the β-cells and increase the glucose counter-regulatory (plasma glucose raising) hormones: glucagon and adrenaline. Glucagon and adrenaline are the principle hormones

to protect against acute hypoglycaemia by stimulating gluconeogenesis. Other hormones, cortisol and growth hormone play a less important role during hypoglycaemia. However deficiencies of these hormones can lead directly or exacerbate hypoglycaemia (i.e. Addison's disease, hypopituitarism). As plasma glucose concentration progressively falls, the increasing sympathoadrenal (sympathetic and adrenomedullary) response leads to neurogenic symptoms. These symptoms cause awareness of hypoglycaemia that prompts behavioural defense of ingestion of carbohydrates (hunger) [7, 8].

2.3 Pathophysiological response to hypoglycaemia

However, in people with type 1 or type 2 diabetes mellitus (T2DM), the above defense mechanisms may be compromised due to:

Relative or absolute therapeutic hyperinsulinemia may lead to hypoglycaemia without intervention. The physiological defense mechanism of downregulation of insulin secretion may be impaired due to β-cell failure.

β-cell failure is also associated with the loss of an appropriate increase in circulating glucagon [7–9]. In addition, the increase in circulating adrenalin is attenuated [7, 10]. Absent insulin/glucagon responses and attenuated epinephrine responses contribute to the clinical syndrome of defective glucose counter-regulation [7, 8, 10]. As a consequence of losing the physiological control of glucose homeostasis, the body will develop neuroglycopenic and neurogenic symptoms as already listed above. The glucose level at which cognitive function declines is subject to substantial variation (from levels between 3 and 4 mmol/l (54–72 mg/dl), whereas others continue to seemingly function with levels below 2.5 mmol/l (45 mg/dl). Almost all domains of cognitive function are potentially at risk during acute hypoglycaemia, with complex tasks being affected earlier than simple tasks [11].

2.4 Hypoglycaemic unawareness

The attenuated sympathoadrenal response is responsible for the reduced neurogenic symptom responses, well known contributing to the syndrome of hypoglycaemic unawareness [7, 8]. The patient has less time or no time between the onset of symptoms and the development of severe neuroglycopenia (impaired awareness/unawareness). Hypoglycaemic unawareness prevents patients from taking corrective action by eating which can potentially lead to seizure/coma and permanent neurological damage, if prolonged and severe. Thus, for many T1DM patients, the immediate fear of hypoglycaemia exceeds the fear of long-term diabetes complications [12, 13]. **Figure 1** is a diagrammatic summary of the physiological response to hypoglycaemia as well as the alterations in diabetes and hypoglycaemic unawareness.

In addition, certain drugs and alcohol may impair a patient's perception of these symptoms. Beta-blockers may diminish the effect of adrenaline, potentially leading to reduced adrenergic warning symptoms (i.e. tremor, palpitations). Beta-blockers are not contraindicated in diabetes, but they should be considered when dealing with recurrent hypoglycaemia or hypoglycaemic unawareness. Other factors that can modify physical symptoms of hypoglycaemia are listed in **Table 1**. Nocturnal hypoglycaemia that can affect a significant percentage of patients and can be unrecognized is a contributing factor to hypoglycaemic unawareness.

The syndrome of defective glucose counter-regulation and hypoglycaemic unawareness usually develops early in T1DM and later in T2DM, due to differing rates of progressive beta-cell failure and also due to insulin or sulphonylurea medications often being started later.

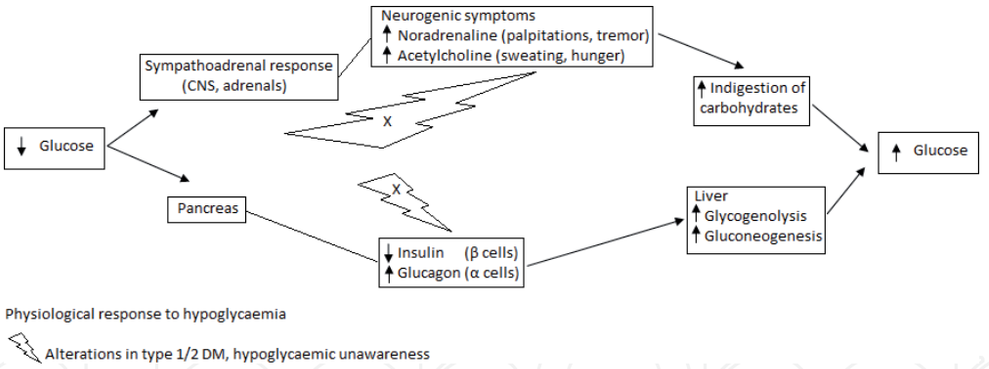

Figure 1.
A schematic diagram describing the physiological response to hypoglycaemia.

1. Posture (the intensity of autonomic symptoms is greater in erect position compared to supine position)
2. Medications—toxins
   - Impairing ability to perceive and interpret symptoms (i.e. hypnotic medications, alcohol, beta-blockers)
   - Magnitude of symptomatic response (i.e. caffeine)

Table 1.
Factors that alter hypoglycaemic symptoms.

2.5 Hypoglycaemia-associated autonomic failure (HAAF)

HAAF is a dynamic functional disorder that includes several episodes of recent antecedent hypoglycaemia, combined with previous exercise or sleep, and causes defective glucose counter-regulation and hypoglycaemic unawareness. Late post-exercise hypoglycaemia occurs 6–15 h after strenuous exercise and is often nocturnal [14, 15]. Sleep-related HAAF is the result of further attenuation of the sympathoadrenal response to hypoglycaemia during sleep [16–18]. Subsequently, a vicious cycle of recurrent iatrogenic hypoglycaemia may occur. HAAF is distinct from the autonomic neuropathy. However, HAAF is more prominent in people with diabetic autonomic neuropathy [19, 20].

2.6 Symptoms in different groups

2.6.1 Children

Symptoms in children differ from those in adults. Children have a more vigorous catecholamine response to hypoglycaemia than adults. Behavioural changes such as irritability, stubbornness, quietness and tantrums may be the primary features of low blood glucose in children [21].

2.6.2 Elderly

This age group may have a more limited perception of autonomic symptoms of hypoglycaemia, which they report as lower intensity than young people. Therefore, older people are at greater risk of developing neuroglycopenia, as the warning symptoms do not always precede the development of cognitive dysfunction [22]. This may reduce the opportunity to take appropriate treatment before developing disabling confusion and neuroglycopenia. It is worth mentioning that the frequency of hypoglycaemia in this group is probably underestimated. This is partly because of inadequate

education in elderly or their relatives, and also frequently hypoglycaemic events are misinterpreted as TIAs, vertebrobasilar insufficiency and vasovagal attacks [23].

2.6.3 Pregnancy

It has been suggested that the intensity of the warning symptoms may be blunted during pregnancy [24, 25]. Of course this is very difficult to be study due to the ethical constraints surrounding the deliberate induction of experimental hypoglycaemia in early pregnancy. Considering that during pregnancy, women aim for stricter glycemic control, it is very difficult to distinguish whether the symptomatology is a true alteration in the symptomatic response or the result of tight glycemic control and increased antecedent hypoglycaemia.

2.7 Functional and metabolic studies during hypoglycaemia

Recurrent hypoglycaemia which impairs awareness and the subsequent brain adaption is of scientific interest but incompletely understood. Several studies have been performed in order to understand brain network function during declining glucose levels.

Studies have shown significant EEG changes in euglycemia and hypoglycaemia during day and night in children with T1DM (20). Various neuroimaging techniques have been employed to study brain glucose metabolism including positron emission tomography (PET), magnetic resonance spectroscopy (MRS), functional magnetic resonance imaging (fMRI) and arterial spin labelling (ASL) [26].

Studies that have employed the above techniques have shown that cerebral glucose metabolism appears to be largely maintained during moderate hypoglycaemia. However, recurrent hypoglycaemia may initiate cerebral adaptions at many different levels. There is interference with the accurate detection of hypoglycaemia, probably occurring at the level of the ventromedial hypothalamus. Brain areas that control appetite and induce fear and anxiety may not become activated during hypoglycaemia. The underlying mechanisms, as to whether altered glucose uptake or neuronal activation or both in the hypothalamic area is responsible, remain unclear. Interestingly, patients with T1DM (particularly with impaired awareness) seem to be better able in maintaining brain glucose metabolism during hypoglycaemia than healthy controls [26].

2.8 Reversing hypoglycaemic unawareness

Avoidance of hypoglycaemic events enables people with unawareness to regain their symptoms when the glucose level is low. Often, preventing hypoglycaemia for 2 weeks results in increased symptoms of a low blood glucose and a return to nearly normal symptoms after 3 months. There are different strategies that can be used in clinical practice to enable avoidance of hypoglycaemia. Some are listed below:

- *Set blood sugar targets higher*: this can lead to decreased frequency of hypoglycaemia.

- *Education*: educating patients in insulin adjustment is important. For example, a UK-based structured education program, Dose Adjustment for Normal eating (DAFNE), restores awareness in 43% of people with impaired awareness of hypoglycaemia [27]. Similarly, the HypoCOMPaSS trial showed that education around the prompt treatment of hypoglycaemia was as important as technologies such as insulin pump therapy and glucose sensors [28].

- *Insulin pumps and continuous glucose sensors*: insulin pump therapy, particularly sensor-augmented insulin pumps, has a role in reducing severe hypoglycaemia and restoring unawareness [29].

- *Islet cell transplantation/pancreatic transplant*: studies suggest immediate improvement of hypoglycaemic awareness in cases of functioning islet transplantation [30]. Reversal of hypoglycaemia-associated autonomic failure is responsible for the long-term maintenance of hypoglycaemic awareness that returns after islet cell/pancreas transplantation [31].

3. Conclusions

Hypoglycaemia symptoms are variable and usually arise from impairment in counter-regulatory hormone or sympathoadrenal responses. Certain patient groups such as children, the elderly and pregnant women may be particularly vulnerable. A degree of hypoglycaemic unawareness is often a consequence of recurrent hypoglycaemia and can be challenging to manage. Various strategies including education, technology and islet/pancreas transplants may all be useful.

Conflicts of interest

None declared.

Author details

Panagiota Loumpardia and Mohammed S.B. Huda*
Department of Diabetes and Metabolism, St Bartholomew's and Royal London Hospitals, Barts Health NHS Trust, London, UK

*Address all correspondence to: bobby.huda1@nhs.net

References

[1] Edridge CL, Dunkley AJ, Bodicoat DH, Rose TC, Gray LJ, Davies MJ, et al. Prevalence and incidence of hypoglycaemia in 532,542 people with type 2 diabetes on oral therapies and insulin: A systematic review and meta-analysis of population based studies. PLoS One. 2015;**10**(6):e0126427

[2] Frier BM. The incidence and impact of hypoglycemia in type 1 and type 2 diabetes. International Diabetes Monitor. 2009;**21**:210-218

[3] International Hypoglycaemia Study Group. Glucose concentrations of less than 3.0 Mmol/L (54 Mg/DL) should be reported in clinical trials: A joint position statement of the American Diabetes Association and the European Association for the Study of diabetes. Diabetes Care. 2017;**40**(1):155-157

[4] Hepburn DA, Deary IJ, Frier BM. Classification of symptoms of hypoglycaemia in insulin-treated diabetic patients using factor analysis: Relationship to hypoglycaemia unawareness. Diabetic Medicine: A Journal of the British Diabetic Association. 1992;**9**(1):70-75

[5] Meyer C, Grossmann R, Mitrakou A, Mahler R, Veneman T, Gerich J, et al. Effects of autonomic neuropathy on counterregulation and awareness of hypoglycemia in type 1 diabetic patients. Diabetes Care. 1998;**21**(11):1960-1966

[6] Dienel GA. Fueling and imaging brain activation. ASN Neuro. 2012;**4**(5):e00093

[7] Cryer PE. The barrier of hypoglycemia in diabetes. Diabetes. 2008;**57**(12):3169-3176

[8] Cryer P. Hypoglycemia in Diabetes: Pathophysiology, Prevalence, and Prevention. American Diabetes Association; 2016. ISBN: 978-1-58040-649-9

[9] Cryer PE. Mechanisms of hypoglycemia-associated autonomic failure in diabetes. New England Journal of Medicine. 2013;**369**(4):362-372

[10] Dagogo-Jack SE, Craft S, Cryer PE. Hypoglycemia-associated autonomic failure in insulin-dependent diabetes mellitus. Recent antecedent hypoglycemia reduces autonomic responses to, symptoms of, and defense against subsequent hypoglycemia. Journal of Clinical Investigation. 1993;**91**(3):819-828

[11] Graveling AJ, Deary IJ, Frier BM. Acute hypoglycemia impairs executive cognitive function in adults with and without type 1 diabetes. Diabetes Care. 2013;**36**(10):3240-3246

[12] Cryer PE. Banting lecture. Hypoglycemia: The limiting factor in the management of IDDM. Diabetes. 1994;**43**(11):1378-1389

[13] Sherwin RS. Bringing light to the dark side of insulin. Diabetes. 2008;**57**(9):2259-2268

[14] MacDonald MJ. Postexercise late-onset hypoglycemia in insulin-dependent diabetic patients. Diabetes Care. 1987;**10**(5):584-588

[15] Tansey MJ, Tsalikian E, Beck RW, Mauras N, Buckingham BA, Weinzimer SA, et al. The effects of aerobic exercise on glucose and counterregulatory hormone concentrations in children with type 1 diabetes. Diabetes Care. 2006;**29**(1):20-25

[16] Banarer S, Cryer PE. Sleep-related hypoglycemia-associated autonomic failure in type 1 diabetes:

Reduced awakening from sleep during hypoglycemia. Diabetes. 2003;**52**(5):1195-1203

[17] Jones TW, Porter P, Sherwin RS, Davis EA, O'Leary P, Frazer F, et al. Decreased epinephrine responses to hypoglycemia during sleep. The New England Journal of Medicine. 1998;**338**(23):1657-1662

[18] Schultes B, Jauch-Chara K, Gais S, Hallschmid M, Reiprich E, Kern W, et al. Defective awakening response to nocturnal hypoglycemia in patients with type 1 diabetes mellitus. PLoS Medicine. 2007;**4**(2):e69

[19] Bottini P, Boschetti E, Pampanelli S, Ciofetta M, Del Sindaco P, Scionti L, et al. Contribution of autonomic neuropathy to reduced plasma adrenaline responses to hypoglycemia in IDDM: Evidence for a nonselective defect. Diabetes. 1997;**46**(5):814-823

[20] Hansen GL, Foli-Andersen P, Fredheim S, Juhl C, Remvig LF, Rose MH, et al. Hypoglycemia-associated EEG changes in prepubertal children with type 1 diabetes. Journal of Diabetes Science and Technology. 1 Nov 2016;**10**(6):1222-1229. [Accessed: April 22, 2019]

[21] McCrimmon RJ, Gold AE, Deary IJ, Kelnar CJ, Frier BM. Symptoms of hypoglycemia in children with IDDM. Diabetes Care. 1995;**18**(6):858-861

[22] Matyka K, Evans M, Lomas J, Cranston I, Macdonald I, Amiel SA. Altered hierarchy of protective responses against severe hypoglycemia in normal aging in healthy men. Diabetes Care. 1997;**20**(2):135-141

[23] McAulay V, Deary IJ, Frier BM. Symptoms of hypoglycaemia in people with diabetes. Diabetic Medicine: A Journal of the British Diabetic Association. 2001;**18**(9):690-705

[24] Rayburn W, Piehl E, Jacober S, Schork A, Ploughman L. Severe hypoglycemia during pregnancy: Its frequency and predisposing factors in diabetic women. International Journal of Gynaecology and Obstetrics: The Official Organ of the International Federation of Gynaecology and Obstetrics. 1986;**24**(4):263-268

[25] Kimmerle R, Heinemann L, Delecki A, Berger M. Severe hypoglycemia incidence and predisposing factors in 85 pregnancies of type I diabetic women. Diabetes Care. 1992;**15**(8):1034-1037

[26] Rooijackers HMM, Wiegers EC, Tack CJ, van der Graaf M, de Galan BE. Brain glucose metabolism during hypoglycemia in type 1 diabetes: Insights from functional and metabolic neuroimaging studies. Cellular and Molecular Life Sciences: CMLS. 2016;**73**(4):705-722

[27] Nicole de Z, Rogers H, Stadler M, Gianfrancesco C, Beveridge S, Britneff E, et al. A psychoeducational program to restore hypoglycemia awareness: The DAFNE-HART pilot study. Diabetes Care. 2014;**37**(3):863-866

[28] Little SA, Speight J, Leelarathna L, Walkinshaw E, Tan HK, Bowes A, et al. Sustained reduction in severe hypoglycemia in adults with type 1 diabetes complicated by impaired awareness of hypoglycemia: Two-year follow-up in the HypoCOMPaSS randomized clinical trial. Diabetes Care. 2018;**41**(8):1600-1607

[29] Bosi E, Choudhary P, de Valk HW, Lablanche S, Castañeda J, de Portu S, et al. Efficacy and safety of suspend-before-low insulin pump technology in hypoglycaemia-prone adults with type 1 diabetes (SMILE): An open-label randomised controlled trial. The Lancet. Diabetes and Endocrinology. 2019;**7**(6):462-472

[30] Maffi P, Secchi A. Clinical results of islet transplantation. Pharmacological Research. 2015;**98**:86-91

[31] Kamel JT, Goodman DJ, Howe K, Cook MJ, Ward GM, Roberts LJ. Assessment of the relationship between hypoglycaemia awareness and autonomic function following islet cell/pancreas transplantation. Diabetes/Metabolism Research and Reviews. 2015;**31**(6):646-650