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Managing hypoglycaemia

Ahmed Iqbal, BSc (Hons) MBBS (Hons) MRCP, Medical Research Council Clinical Research Training Fellow and Specialty Registrar in Diabetes and Endocrinology, Simon Heller, BA MB BChir DM FRCP, Professor of Clinical Diabetes & Honorary Consultant Physician *

Department of Human Metabolism and Oncology, University of Sheffield, School of Medicine and Biomedical Sciences, Beech Hill Road, Sheffield, S10 2RX, UK

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Intensive glycaemic control reduces the diabetic microvascular disease burden but iatrogenic hypoglycaemia is a major barrier preventing tight glycaemic control because of the limitations of subcutaneous insulin preparations and insulin secretagogues. Severe hypoglycaemia is uncommon early in the disease as robust physiological defences, particularly glucagon and adrenaline release, limit falls in blood glucose whilst associated autonomic symptoms drive patients to take action by ingesting oral carbohydrate. With increasing diabetes duration, glucagon release is progressively impaired and sympatho-adrenal responses are activated at lower glucose levels. Repeated hypoglycaemic episodes contribute to impaired defences, increasing the risk of severe hypoglycaemia in a vicious downward spiral. Managing hypoglycaemia requires a systematic clinical approach with structured insulin self-management training and support of experienced diabetes educators. Judicious use of technologies includes insulin analogues, insulin pump therapy, continuous glucose monitoring, and in a few cases islet cell transplantation. Some individuals require specialist psychological support.

* Corresponding author.
E-mail addresses: ahmed.iqbal@sheffield.ac.uk (A. Iqbal), s.heller@sheffield.ac.uk (S. Heller).

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Introduction

Since the earliest description by Banting, the clinical challenges of hypoglycaemia have been recognised as a major side effect of insulin treatment [1]. More precise analyses of the pathophysiology did not emerge until around 20 years later in R D Lawrence's account of symptoms of iatrogenic hypoglycaemia as "being akin to a dose of adrenaline" [2]. A more detailed understanding of why individuals with insulin treated diabetes are so vulnerable to hypoglycaemia had to await accurate measurements of both blood glucose and the relevant endocrine responses in the 1980s. These insights have been followed by the development of experimental human and animal models. Studies have continued to the present day, although to date there have been few specific treatments which can prevent hypoglycaemia. The key to managing and preventing hypoglycaemia requires a good understanding of both the pathophysiology and insulin therapeutics. In this review we will consider the epidemiology, pathophysiology and consequences of hypoglycaemia, but concentrate on its practical management.

Definition and epidemiology

The precise definition of hypoglycaemia continues to be debated. An American Diabetes Association (ADA) working party has attempted a comprehensive definition [3]. They have defined "severe hypoglycaemia" as an episode requiring the assistance of another person to administer treatment, "documented symptomatic hypoglycaemia" as the presence of common symptoms of hypoglycaemia with a measured plasma glucose <3.9 mmol/L, "probable symptomatic hypoglycaemia" as self-reported symptoms not verified by a glucose measurement and "relative hypoglycaemia" as the presence of symptoms with a plasma glucose >3.9 mmol/L.

It is clear that a single definition cannot encompass all types of hypoglycaemia. Indeed, even within these categories there continues to be no consensus. For example, the definition of severe hypoglycaemia does not apply to children who rely on their parents or other adults for recovery even from relatively mild episodes. Thus, paediatricians define severe hypoglycaemia as coma or needing parenteral treatment.

Furthermore, in clinical trials, organisations, both commercial and academic, frequently use different definitions. It is therefore often difficult to compare directly, epidemiological studies and clinical trial data. This also means that meta-analyses often exclude detailed discussion of even severe hypoglycaemia due to the observed 'heterogeneity' between studies.

It is important to note that data from clinical trials report rates of hypoglycaemia, including severe, which are many times lower than rates collected from observational data. In the Diabetes Control and Complications Trial (DCCT), which is considered to have resulted in an epidemic of severe hypoglycaemia in the intensive arm, reported rates expressed in episodes per patient year were considerably lower than rates from observational studies. More recent clinical trials have reported even lower rates of severe hypoglycaemia [4]. In contrast, data reported in observational studies have shown virtually no reduction in rates of severe hypoglycaemia over the last 20 years, despite the introduction of analogue insulins and continuous subcutaneous insulin infusion (CSII) (Table 1) [5–9]. These data

Table 1
Frequency of severe hypoglycaemia in diabetes, a summary of observational studies.

Study	Number of patients	Age (years) Median (range) or mean ± SD	Follow up (months)	Frequency of hypoglycaemia (episodes/per person/year)	Proportion affected (%)
MacLeod, 1993 [5] (Scotland)	600	41 (14–79)	12	1.6	29
Ter Braak 2000 [6] (Denmark)	195	41 ± 14	12	1.5	41
Pedersen-Bjergaard 2004 [7] (Denmark)	1076	40 (18–81)	12	1.3	37
UK Hypoglycaemia Study Group 2007 [8]	100 (46 < 5 years;	<5y 41 ± 13	9–12	1.1	22
(United Kingdom)	54 > 15 years)	>15y: 53 ± 10		3.2	46
Kristensen 2012 [9] (Denmark)	3861	48 ± 15	12	1.2	31