Hypoglycaemia, a global cause for concern

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Hypoglycaemia in diabetes is often considered to be relevant only to those with type 1 diabetes (T1D). Evidence has long been available that hypoglycaemia occurs in people with type 2 diabetes (T2D) using sulphonylureas. (Episodes will be more prolonged than with insulin alone.) However, the risk of hypoglycaemia in people with T2D has received little attention with the implication that it can be ignored.

In this short review, we argue that recent research shows that hypoglycaemia as a clinical problem is an important concern in T2D. In addition, since insulin treated T2D is more common that T1D, it presents an equal challenge, particularly since most individuals are cared for by the non-specialist, including general internist and primary care teams who may not fully understand the risks associated with hypoglycaemia.

Data emerging from recent clinical trials have generally given the impression that rates of severe hypoglycaemia in both types of diabetes are steadily falling and that, for T1D, they are now much lower than in the landmark Diabetes Control and Complications Trial, completed over 20 years ago. However, since clinical trials, by design mean that patients are treated strictly according to protocol (with considerable support from research and nursing staff) and that individuals with hypoglycaemia problems are specifically excluded, trials may underestimate the risk of hypoglycaemia compared to rates observed in routine clinical practice.

The Hypoglycaemia Assessment Tool (HAT) study (Figure 1) is a recently completed observational multi-centre epidemiological survey of over 27,000 people with T1D and T2D on insulin from 24 countries. The study aims were to measure the frequency, predictive factors and consequences of hypoglycaemia (both severe and symptomatic) in a variety of countries including developing countries, such as Argentina, Mexico and India. What was striking about the results was the frequency of hypoglycaemia compared to previous surveys.

Self-reported rates of severe hypoglycaemia (defined as needing the help of another person for recovery) were around 5 times higher than previous population based reports. Among insulin treated patients with T2D, the overall rate of severe hypoglycaemia was around 2.5 per person per year. Even allowing for limitations regarding the methodology of online reporting and the possibility that some individuals were self-selected, these are alarming results. Some of the highest rates were seen in developing countries.

Recent trials have suggested that the consequences of severe episodes may extend beyond those already well-recognised due to impaired cerebral function, which include impaired awareness, risk of accidents while driving and coma. The premature termination of the ACCORD trial was due to increased mortality in the intensive arm where there was a particularly aggressive approach to glucose control, associated with high rates of severe hypoglycaemia, startled the diabetes community. A number of subsequent studies have confirmed the association between severe hypoglycaemia and subsequent death downstream of the

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Although the data suggest hypoglycaemia was not the direct cause of the excess deaths in ACCORD, other research has identified plausible mechanisms whereby hypoglycaemia might lead to a cardiac death downstream.\(^6\)\(^-\)\(^8\)\(^-\)\(^10\) One study has reported prolonged asymptomatic hypoglycaemia at night associated with cardiac arrhythmias in patients with known cardiovascular disease.\(^11\)

Why is hypoglycaemia so common and what can be done to address the worrying situation described above? This question needs to be addressed with a global perspective, recognising that many countries lack the resources to use expensive technology such as insulin analogues, insulin pumps and continuous glucose monitoring. Even where available, most patients are not cared for by specialist teams with the expertise to use these devices.

### Addressing basic principles

Many underlying drivers of hypoglycaemia are well recognized. Furthermore, some of the most effective methods of prevention are relatively cheap and affordable even within healthcare systems short of resources.

From the point of view of the health care professional, the three underlying principles are:

1. Individualizing targets (with appropriate therapies) and adjusting these when individuals are particularly vulnerable to hypoglycaemia or its consequences.

2. Structured education/training for people with diabetes.

3. A health care team alert to potential problems with hypoglycaemia.

Recent publications, some described above, have established the case for individualizing therapy which has been endorsed by national and internationally approved guidance.\(^12\)

For those individuals recently diagnosed with T2D who require treatment with lifestyle advice and metformin, tight glucose targets are appropriate with HbA\(1c\) levels as low as possible with no risk of hypoglycaemia. When glucose levels rise, some agents such as incretin therapy or glucosidase inhibitors (when affordable) carry no risk of hypoglycaemia and can also be used knowing that they won’t increase the risk of hypoglycaemia. These should be the treatments of choice when the risk of hypoglycaemia is considered particularly high, e.g., people in high risk occupations or who report problematic hypoglycaemia.

However, if the affordable choice of treatment requires the use of insulin secretagogues such as sulphonylureas, additional actions by the healthcare professional (HCP) are needed. Firstly, only sulphonylureas with a shorter duration of action should be prescribed. Additional safety measures include: checking renal function; starting medication at a low dose; warning patients about the symptoms of hypoglycaemia; and urging them to report episodes to their professional carers. If possible, individuals taking sulphonylureas should learn to test their blood glucose with clear instructions to eat regularly, test their blood glucose if they have symptoms and take...
action if their blood glucose falls below 70 mg/dl (4mmol/L).

For those patients who require insulin to achieve targets, the above instructions also apply. It is important to note that basal insulin replacement alone carries a lower risk of hypoglycaemia than regimens including fast acting insulins, although patients with greater insulin deficiency will need both to achieve glycaemic control. For people with established, long duration diabetes and those affected with complications (some such as renal impairment or known CVD are particularly important), then more realistic and safe glucose targets should be agreed. Some now propose HbA1c levels at or just below 8% (63.9 mmol/mol) as appropriate.13

There is now substantial evidence (mostly obtained in studies involving adults with T1D) that structured training and education programmes not only improve HbA1c levels but substantially reduce rates of severe hypoglycaemia (and diabetic ketoacidosis) in insulin users (Figure 2).14-16 It seems self evident that patients should receive systematic training to use a life-saving medication like insulin (with potentially dangerous side-effects if used inexpertly) safely, but even in countries with well developed healthcare systems, the proportion of individuals who receive such training is alarmingly small.

Important principles for the HCP to convey include detailed instruction about the duration and variability of different insulins, appropriate use of glucose monitoring and corrective insulin doses and understanding the effects of food, particularly carbohydrates, on blood glucose. From the point of view of the individual living with either T1D or T2D (and their immediate family), a good layman’s understanding of hypoglycaemia is essential. In particular, a knowledge of the range of hypoglycaemic symptoms, how to treat without overcorrection and an appreciation that repeated episodes can diminish the warning symptoms that predict a severe attack (also called hypoglycaemic unawareness).

It is also critical for the HCP to communicate the importance of the alert level of 70mg/dL (4mmol/L) as a signal to which respond to immediately to prevent hypoglycaemia sufficient to impair cognitive function < 55mg/dL (3 mmol/L), and also to consider the need to adjust future insulin dose.17 Indeed, HCPs should make sure they assess hypoglycaemia awareness in everyone at risk (if symptoms are not felt before the blood glucose has fallen below 3 mmol/L, the patient is at higher risk for severe hypoglycaemia). HCPs should also be aware that hypoglycaemia can present as dementia in the older patient, and be accepted as such by family members. The importance of identifying nocturnal episodes (usually asymptomatic) should be recognised and can be detected, in the absence of continuous glucose monitoring (CGM), by testing occasional overnight blood glucose. Addressing these basic principles is within the capability of all professionals who care for people with diabetes and should be part of a standard care pathway.

Technological innovations such as CGM and insulin pump therapy are helpful but will remain prohibitively expensive.

Figure 2: Effect of structured training course on severe hypoglycaemia in type 1 diabetes

Data on iPhone with the help of an app - a luxury not everyone can afford

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and unavailable for many years for the vast majority of people with insulin-treated diabetes. In the meantime, we have a duty to ensure that many more individuals receive basic and effective treatment which allows them to minimise the risk of hypoglycaemia and achieve glucose targets safely. The most important message is to make sure that our HCPs are actively and adequately assessing and managing the risk of hypoglycaemia for each person living with diabetes.

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The International Hypoglycaemia Study Group (IHSG) is a learned panel of healthcare professionals who examine issues associated with the problem of hypoglycaemia in people with diabetes. The IHSG seeks to improve the scientific understanding of hypoglycaemia, as well as its importance as a barrier to optimal glycaemic control, by means of raising awareness.

References


