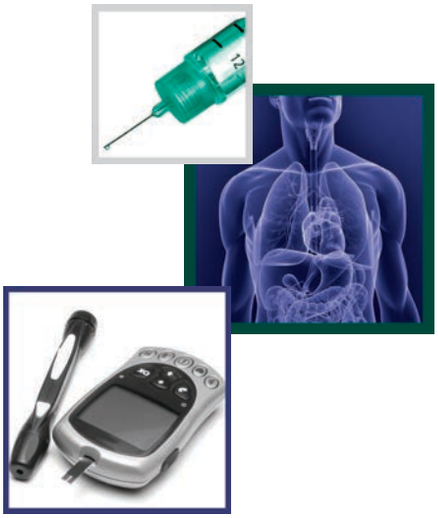
EDITORIAL

Is there anything positive about iatrogenic hypoglycemia in Type 1 diabetes?



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"Habituation to recurrent hypoglycemia, known to induce counter-regulatory impairments, thus appeared to provide some kind of (neuro)protection and a survival benefit."

Iatrogenic hypoglycemia is the most frequent acute complication of insulin therapy. Although the true incidence is difficult to ascertain, it is estimated that patients with Type 1 diabetes experience two to three hypoglycemic events per week and one severe event, requiring third-party assistance, once every 1–2 years [1]. There is substantial inter- and intra-individual variation in the incidence of hypoglycemic events, ranging from almost none to one or even multiple events per day. Hypoglycemia is considered to be the principal limiting factor to achieve optimal glycemic control in Type 1 diabetes because it is usually unavoidable in the pursuit of near-normal glucose levels [1]. Other factors impacting on the rate of hypoglycemia include (residual) β-cell function, the potency of glucose counter-regulatory function and hypoglycemic awareness. In addition, time of day (daytime versus nighttime), ambient temperature and other environmental factors (e.g., exercise or alcohol use) may play a role in the day-to-day variation.

Approximately 25–30% of patients with Type 1 diabetes have severely impaired hypoglycemic awareness, meaning that hypoglycemia does not or only minimally elicits classical warning symptoms, such as sweating, pounding heart or trembling. In these patients, counter-regulatory hormone responses to hypoglycemia are often similarly impaired, meaning that glucose levels may fall more or less unimpeded. Since antecedent hypoglycemia exerts an attenuating effect on the counter-regulatory and symptom responses to subsequent hypoglycemia [2], impairments in both counter-regulatory function and hypoglycemic awareness are thought to result from habituation to recurrent hypoglycemia. The clinical syndrome of severely impaired hypoglycemic awareness thus results from a vicious cycle of recurrent hypoglycemia and progressive counter-regulatory impairments. Patients with this syndrome are at a six- to ten-fold higher risk of severe hypoglycemia compared with those reporting normal hypoglycemic awareness [3].

Severe hypoglycemic events are feared by many patients, relatives and care providers, mainly because of the associated loss of self-control and its potential to cause direct or indirect harm. Extremely low blood glucose levels lasting for several hours may permanently damage the brain and occasionally be fatal. Although such events are extremely rare, a large survey of cause-specific mortality in the UK nevertheless attributed 4% of

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all deaths among Type 1 diabetic patients between the ages of 20 and 50 years directly to hypoglycemia [4]. This is probably an underestimation, since glucose levels are rarely measured at the time of death and hypoglycemia may not be coded under a single heading. Indeed, hypoglycemia could well have contributed to the almost a fifth of all deaths in this age group that resulted from accidents and violence, and that considerably exceeded the anticipated death toll in this category [4]. In addition, a proportion of unexplained nocturnal deaths of patients with Type 1 diabetes have been linked more directly to hypoglycemia. The dead-in-bed syndrome describes patients with Type 1 diabetes and a recent history of nocturnal hypoglycemia who are found dead after having gone to bed in apparently good health [5]. Since hypoglycemia may cause lengthening of the QT-interval, fatal ventricular arrhythmia is thought to underlie these deaths [6].

All hazards aside, it should be appreciated that the vast majority of patients with Type 1 diabetes recover from hypoglycemia (even severe hypoglycemia) uneventfully. Regarding long-term prognosis, it is undoubtedly better to aim for tight glycemic control, accepting that this will lead to (recurrent) hypoglycemia, than to scrupulously avoid any hypoglycemia by pursuing higher glucose targets. Indeed, the Diabetes Control and Complications Trial has clearly shown that strict glycemic control considerably reduces the risk of long-term micro- and macro-vascular complications, despite a threefold higher incidence of severe hypoglycemia [7,8]. On the population level, most cohort studies have failed to show a relationship between severe hypoglycemia and cognitive dysfunction, cardiovascular complications or mortality in people with Type 1 diabetes [9,10]. This contrasts with such associations in patients with Type 2 diabetes [11], which is remarkable since their risk of hypoglycemia, in general, and that of severe hypoglycemia, in particular, is manyfold lower compared with Type 1 diabetes.

"Hypoglycemic preconditioning should be considered when balancing risks and benefits of intensive insulin therapy for each individual patient."

How can we explain this apparent discrepancy between hypoglycemia's potential to cause serious harm and its usually benign behavior in the daily lives of most patients with Type 1 diabetes? Animal studies suggest a key role for habituation. Indeed, brain cells of streptozotocin-induced diabetic rats that were exposed and habituated to chronic hyperglycemia (plasma glucose: ~21 mmol/l) were more likely to die during severe, profound hypoglycemia (plasma glucose <0.85 mmol/l) than those of nondiabetic control animals [12]. This enhanced vulnerability of brain cells to severe hypoglycemia could be reversed when glucose levels had been normalized with insulin treatment [13]. Moreover, when the rats had been subjected to several antecedent episodes of moderate hypoglycemia, a subsequent profound hypoglycemic episode caused less brain cell damage and cognitive impairment compared with animals not subjected to antecedent hypoglycemia [14]. Animals 'pretreated' with hypoglycemia were also less likely to die from profound hypoglycemia, whereas chronically hyperglycemic animals were more likely to die [15]. Habituation to recurrent hypoglycemia, known to induce counter-regulatory impairments, thus appeared to provide some kind of (neuro) protection and a survival benefit.

Whether such potential beneficial effects of recurrent hypoglycemia can be extrapolated to humans is highly uncertain, but evidence for the opposite is similarly lacking. A *post hoc* analysis of the ACCORD study showed that survival in patients with Type 2 diabetes was inversely related to self-reported incidence of hypoglycemia and hypoglycemic awareness [16]. Using ^{13}C magnetic resonance spectroscopy, we recently reported a greater cerebral metabolic rate during moderate hypoglycemia in patients with Type 1 diabetes than in nondiabetic subjects. There was an inverse correlation between cerebral metabolic rate and HbA1c levels, suggesting a role for antecedent hypoglycemia [17]. Since blood-to-brain glucose transport was not altered [18], influx of nonglucose carbohydrates as alternative sources of energy appears plausible. Various observations suggest lactate as a likely candidate. Lactate production is stimulated during hypoglycemia, reduces cerebral glucose needs, provides neuroprotection and is even more energy efficient than glucose, as it requires fewer enzymatic steps to metabolize and yields more ATP. Brain lactate levels in the extracellular fluid during cognitive testing increase more in rats subjected to recurrent hypoglycemia than in rats not subjected to antecedent hypoglycemia [19]. The capacity to transport monocarboxylate acids, such as lactate, across the blood–brain barrier was greater in well-controlled Type 1 diabetic patients with a history of recurrent hypoglycemia than in nondiabetic controls [20]. Parenthetically, since cerebral substrate deficiency, rather than the actual glucose value *per se*, appears to be the driving force behind glucose counter-regulatory function, increased cerebral uptake of lactate could also underlie impairments in hypoglycemic awareness.

Ever since the introduction of insulin more than 90 years ago, hypoglycemia has remained a continuing threat for patients with Type 1 diabetes, despite major advances in the development of insulin preparations, administrative devices and monitoring equipment. It appears somewhat counterintuitive to even consider possible benefits of what is so clearly an unwanted adverse effect of insulin therapy that most patients and care providers would wish to avoid. However, it should be appreciated that the human body's strategy to cope with potentially damaging stressful conditions of any kind is aimed at adaptation, endurance and protection. In that respect, there is a remarkable analogy with the concept of ischemic preconditioning, where transient ischemic periods protect against harm from a prolonged period of ischemia [21]. Some, therefore, refer to the phenomenon of hypoglycemia-induced protection as hypoglycemic preconditioning [15]. Future studies are required to establish whether and to what extent hypoglycemic preconditioning can be demonstrated in humans, and how it affects long-term prognosis in patients with Type 1 diabetes. Hypoglycemic preconditioning should be considered when balancing risks and benefits of intensive insulin therapy for each individual patient.

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