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EDITORIAL

The bitter taste of hypoglycemia

Subhankar Chowdhury[1] · **Partha Pratim Chakraborty**[2]

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Hypoglycemia undoubtedly is the major obstacle to glycemic control in type 1, insulinopenic spectrum of type 2 and some other forms of diabetes, the "brittle diabetes" in particular. Strict glycemic control reduces the vascular complications of diabetes which comes at the cost of increased risk of hypoglycemia. The workgroup of the American Diabetes Association (ADA) and the Endocrine Society have defined hypoglycemia as all episodes of abnormally low plasma glucose concentration that expose the individual to potential harm [1], and the cutoff level of plasma glucose has arbitrarily been defined as 70 mg/dl. This value approximates the lower limit of plasma glucose concentration in the normal post-absorptive state. In healthy individuals, this particular level of plasma glucose is the threshold for activation of counter-regulatory mechanisms, and it is also low enough to potentially reduce the physiological defenses against subsequent hypoglycemia. More importantly perhaps, this value is higher than the plasma glucose levels required to produce symptoms of neuroglycopenia (<50/mg/dl), which allows a window of opportunity to accommodate the imperfect precision of the available glucometers at low values. The ADA workgroup has classified hypoglycemia in persons with diabetes in the following five types: severe, documented symptomatic, asymptomatic, probable symptomatic, and relative.

✉ Subhankar Chowdhury
subhankar.chowdhury@gmail.com

Partha Pratim Chakraborty
docparthapc@yahoo.co.in

[1] Department of Endocrinology & Metabolism, Institute of Post-Graduate Medical Education & Research/ SSKM Hospital, Room No: 9; Ronald Ross Building (4th floor), 244, A.J.C Bose road, Kolkata 700020, West Bengal, India

[2] Department of Medicine, Midnapore Medical College & Hospital, Hospital Road, Midnapore 721101, West Bengal, India

Hypoglycemia is a fact of life for many patients living with type 1 diabetes and it has been seen that on an average, they suffer from two episodes of symptomatic hypoglycemia per week and one episode of severe hypoglycemia per year. The event rates for severe hypoglycemia were 62 per 100 patient-years in the Diabetes Control and Complication Trial (DCCT) and 110 (treatment duration <5 years) and 320 (treatment duration >15 years) in these patient subset of the UK Hypoglycaemia Study Group [2, 3]. In comparison, hypoglycemia is definitely less frequent in type 2 diabetes. However, as the patients approach towards the insulin-deficient end of the spectrum of the disease, the incidence progressively increases. For example, in the UK Hypoglycemia Study, the incidence of severe hypoglycemia in insulin treated type 2 diabetics was 10 and 70 episodes per 100 patient-years if the treatment duration was less than 2 years or more than 5 years, respectively.

Hypoglycemia in diabetes is typically the outcome of relative or absolute iatrogenic hyperinsulinemia and compromised physiologic and behavioral defenses against declining plasma glucose concentrations. The well-known risk factors of hypoglycemia are wrong type or excessive or ill-timed dosing of insulin or insulin secretagogue, reduced insulin clearance (in renal failure), increased insulin sensitivity (low counter-regulatory hormones, following weight loss or exercise), decreased endogenous glucose production (liver failure), decreased exogenous glucose delivery (missed meal or fasting) and increased glucose utilization (during and shortly after exercise). Degree and duration of β-cell secretory defect, a history of severe hypoglycemia or hypoglycemia unawareness, recent antecedent hypoglycemia, prior exercise or sleep, and aggressive therapy are the indicators of compromised defenses against hypoglycemia. Other potential risk factors are some of the long-term complications of diabetes like gastroparesis, poor vision, and manual dexterity and

macroalbuminuria (even in absence of significantly decreased renal function). Though patients with diabetes and hypertension have a higher risk of micro and macro vascular complications and mortality relative to diabetes without hypertension, the effect of hypertension on the incidence of hypoglycemia is largely unknown. In a cross-sectional study involving more than 55,000 patients with type 2 diabetes, Tran et al. documented significantly higher prevalence of hypoglycemia in the presence of hypertension. Though the study has not looked into the class of antihypertensive medications, which are known to increase insulin sensitivity (ACE inhibitors, angiotensin receptor blockers) or hypoglycemia unawareness (β-blockers) and the underlying pathogenetic basis of such association, it calls for further research to confirm this particular association and identify the mechanisms involved. Co-prescription of many medications like ACE inhibitors, β-blockers, salicylates, and different antibiotics (fluoroquinolones, cotrimoxazole) have also been shown to increase the frequency of hypoglycemia. Fluoroquinolones, one of the commonly prescribed antibiotics worldwide, are known to cause hyperinsulinemic hypoglycemia by blocking ATP-sensitive potassium channels in the pancreatic β cells. Although incidences of hypoglycemia induced by fluoroquinolones (Gatifloxacin, Levofloxacin) have mostly been reported in adults with diabetes concomitantly taking insulin or insulin secretagogues, the adverse effect has also been reported in normoglycemic older individuals with renal impairment. In this issue, an interesting case of Lomefloxacin-induced hyperinsulinemic hypoglycemia has been reported in an 88-year-old male with prediabetes and stage 3 chronic kidney disease.

Hypoglycemia is frightening and inconvenient to patients and the fear of hypoglycemia prevents them from achieving optimal control. It also causes recurrent morbidity and at times mortality. Defective glucose counter-regulation, left-ward shift of the glycemic thresholds for sympathoadrenal outflow, and altered symptomatic and behavioral responses by recent antecedent hypoglycemia and the resultant hypoglycemia unawareness lead to a vicious cycle of recurrent hypoglycemia. Hypoglycemia-associated autonomic failure (HAAF) is a form of functional brain failure. Though distinct from classic diabetic autonomic neuropathy, the key feature of HAAF, an attenuated sympathoadrenal response to a given level of hypoglycemia, is more prominent in patients with diabetic autonomic neuropathy. The mechanism of the attenuated sympathoadrenal response is yet to be crystallized, and a number of hypotheses have been put forward like the cerebral-network hypothesis, the brain fuel-transport hypothesis, the brain-metabolism hypothesis, and the systemic-mediator hypothesis. In patients with one or more episodes of severe hypoglycemia, this functional disorder is usually reversible after a short-term (2–3 weeks) relaxation of glycemic targets.

There are evidences to show that a history of severe hypoglycemia in the elderly is associated with a greater risk of dementia. On the other hand, cognitive impairment is significantly associated with subsequent episodes of severe hypoglycemia in these patients. Contrary to previous belief, there is no association between frequency of severe hypoglycemia and cognitive decline in adolescents and younger adults with type 1 diabetes.

Prolonged and profound hypoglycemia can cause irreversible neurological damage as depicted in one of the accompanying case reports, and an estimated 2–4 % of people with type 1 diabetes die from hypoglycemia [4]. Though similar data are not available for patients with type 2 diabetes, severe hypoglycemia was associated with mortality in the ADVANCE and the ACCORD trial. The death rate in the ADVANCE in people with severe hypoglycemia was 19.5 %, in those without it was 9 %. And in ACCORD, it was 6.9 % in those with severe hypoglycemia and 4.1 % in those without. However, the relationships between hypoglycemia, achieved glycemia, treatment intensity, and death were not straightforward in the ACCORD trial. Hypoglycemia causes abnormal cardiac repolarization as evidenced by prolonged corrected QT interval and increased QT dispersion and a resultant fatal arrhythmia is perhaps the underlying cause of an unexpected death during the night, the so-called "dead in bed syndrome" described by Tattersall and Gill years ago. Interestingly, the relationship between severe hypoglycemia and adverse events in ADVANCE revealed that people who had severe hypoglycemia were found to have higher mortality even up to 48 months after the event. Majority of deaths in both ADVANCE and ACCORD occurred after a variable period from the hypoglycemic episodes, which raises the possibility of other underlying mechanisms in addition to acute arrhythmia. Acute hypoglycemia activates pro-inflammatory cytokines, increases platelet activation, decreases systemic fibrinolysis, promotes endothelial dysfunction, accelerates atherosclerosis, and may ultimately result in cardiovascular death.

Hypoglycemia while driving is regarded as a likely source of danger to the public. While the driver and licensing agency (DVLA) of the UK does not allow driving in individuals with more than one episode of severe hypoglycemia in the preceding 12 months, the awareness related to diabetes, therapy, self monitoring of blood glucose (SMBG), and related issues among drivers is poor in the eastern world as put forward by a small study from the United Arab Emirates in this issue of the journal.

Minimizing the risk of hypoglycemia requires acknowledging the problem, reevaluating the glycemic goal, applying the appropriate principles of aggressive glycemic therapy including SMBG, considering the risk factors for HAAF and patient education. At present, we have a wide range of antidiabetic medications in our therapeutic armamentarium in both oral and injectable forms which are anti-hyperglycemic rather

than hypoglycemic and these agents can help many patients reach and maintain their target safely without causing hypoglycemia. While targeting and maintenance of satisfactory glycemic control that can be achieved safely in a particular patient is of utmost importance, undue concerns about hypoglycemia should not be an excuse for poor glycemic control.

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