Review Article

Hypoglycemia in type 2 diabetes: Standpoint of an experts' committee (India hypoglycemia study group)

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ABSTRACT

The epidemic of type 2 diabetes and the recognition that achieving specific glycemic goals can substantially reduce morbidity have made the effective treatment of hyperglycemia a top priority. Despite compelling evidence that tight glycemic control is crucial for delaying disease progression, increased risk of hypoglycemia associated with such control underscore the complexity of diabetes management. In most cases, hypoglycemia results from an excess of insulin, either absolute or relative to the available glucose substrate and the factors perhaps exacerbating the risk are pharmacokinetic imperfections, behavioral, co-morbidities etc. Additionally, many patients remain undiagnosed, and many diagnosed patients are not treated appropriately. In this article, the challenges of hypoglycemia, confronting health care providers and their patients with diabetes, are discussed for making treatment decisions that will help minimize risk of hypoglycemia and eventually overcome formidable barriers to optimal diabetes management. Strategies to treat and minimize the frequency and severity of hypoglycemia without compromising on glycemic goals are also presented.

Key words: Experts' opinion, hypoglycemia, recommendations, type 2 diabetes

Introduction

Review of Evidences

Contemporary sedentary lifestyle and behavioral trends coupled with increased life expectancy profoundly have influenced the rise in type 2 diabetes and its complications in last four decades. Both micro-vascular and macro-vascular complications contribute to death and disability in type 2 diabetes and both are associated with elevated blood glucose levels. Thus, glycemic control remains a crucial first step for reducing the risk of these complications.

There is a plethora of evidence to suggest that intensive therapy with the goal of achieving euglycemia should be implemented as early as possible in patients with either type 1 or type 2 diabetes. Additionally, it is generally agreed that the Glycosylated hemoglobin (HbA1c) goal should be <7%. The Diabetes Control and Complications

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Trial (DCCT) and the Stockholm Diabetes Intervention Study (SDIS) showed that intensive therapy significantly reduced the incidence and progression of micro-vascular complications in patients with type 1 diabetes.[1,2] The United Kingdom Prospective Diabetes Study (UKPDS) and the Kumamoto study determined that stricter glycemic control could be useful in delaying the onset and progression of diabetic micro-vascular and possibly the macro-vascular complications as well in patients with type 2 diabetes.[3,4]

While the need for intensive management is clear and while so many therapeutic advances have been made, are we actually reaching these target HbA1c levels in clinical practice? The answer is a clear no as evidenced by numerous epidemiological studies showing that majority of patients in real life clinical setting, at any given point of time, are not on glycemic target. Risk of hypoglycemia is a reason often cited for not achieving the glycemic goals. This argument can actually be backed with evidences from the same studies that demonstrated reduced risk of complication with intensive glycemic control. The DCCT reported a three-fold increase in severe hypoglycemia with intensive versus conventional therapy during the trial.[5] In fact, a continuous curvilinear relation between glycemic control and incidence of hypoglycemia has been observed in DCCT [Figure 1].[1] The SDIS showed a 2.5 times greater incidence of severe hypoglycemia among intensively treated patients.[2] Similarly, for patients with type 2 diabetes, it was observed in the UKPDS study that the proportion of patients with one or more major, or any, hypoglycemic episode in a year was significantly higher in the intensive group than in the conventional group [Figure 2]. By intention-to-treat analyses, major hypoglycemic episodes occurred with Chlorpropamide (1.0%), Glibenclamide (1.4%), Insulin (1.8%), and diet (0.7%) and any hypoglycemic episodes in 16, 21, 28 and 10%, respectively.[3] A continuous curvilinear relation between glycemic control and incidence of hypoglycemia, similar to that observed in DCCT, has also been observed in a meta-analysis of 11 sponsored randomized trials comparing Insulin Glargine and Insulin Neutral Protamine Hagedorn (NPH) in patients with type 1 or type 2 diabetes.[6]

The risk of hypoglycemia increases with absolute or relative insulin excess (caused by exogenous insulin or agents that increase insulin secretion) or compromised glucose regulation.[7] In the earlier stages of type-2 diabetes when glucose counter-regulatory responses are still functional, hypoglycemia is less common than in patients with type 1 diabetes. However, since progressive β-cell failure is a key patho-physiological feature of type 2 diabetes, the characteristics of disease and frequency of hypoglycemic episodes eventually approach that of type 1 diabetes.[8]

The clinical implications of hypoglycemia stems from the fact that it has been considered as the most important limiting factor in the glycemic management of patients with diabetes and a significant barrier in terms of adherence to medication and achievement of the life-long goal to attain euglycemia. It has further been suggested that the presence (or fear) of hypoglycemia can limit the aggressiveness of drug therapy to achieve reduction of micro-and macro-vascular complications, decrease adherence to diet and reduce patients' willingness to take medications as directed. Additionally, hypoglycemia causes recurrent morbidity in many patients with type 2 diabetes, worsens their quality of life and is sometimes fatal. It also impairs defenses against subsequent hypoglycemia because of autonomic failure (Hypoglycemia Associated Autonomic Failure) and has even been causally linked to neuro-cognitive deterioration and detrimental changes in cardiac electro-physiology. Attempts have been made to quantify the economic burden of hypoglycemia as well, though this varies from country to country as estimates will be affected by factors such as the prevalence of hypoglycemia; classifications of hypoglycemic events; patient characteristics; knowledge and attitudes to hypoglycemic events; and varying quality and implementation of care across different healthcare systems.[7,9]

Experts' Viewpoint

Although hypoglycemia is well recognized as a problem in management of type 1 diabetes, it has traditionally been considered to be a minor problem of the treatment modalities used for type 2 diabetes. The underestimation of importance of hypoglycemia in type 2 diabetes may be a misperception based on inadequate information. The occurrence of hypoglycemia in the treatment of type 2 diabetes is well recognized, but is more protean in nature, having different risk factors and clinical features according to the nature of the hypoglycemic therapy, the extent of the insulin secretory deficit and the duration of diabetes.

The paucity of data on epidemiology of hypoglycemia in type 2 diabetes from clinical studies is of serious concern, particularly with most of the data generated being antecedent to other primary scientific objective(s). Its estimates are largely based on data collected either in retrospective studies or in highly selected patients in the controlled research settings. Variations in study design, heterogeneity of study populations, different recall periods, changes in conventions of care over time and differing definitions of hypoglycemia have further confounded attempts to derive accurate overall figures for the frequency of hypoglycemia in type 2 diabetes. It is worth highlighting that from India, which has the second largest number of diabetes patients, there is negligible data on epidemiology of hypoglycemia.

In the setting of real life clinical practice, while the uncommon but severe form of hypoglycemia episodes are relatively easy to recognize in patients on oral anti-hyperglycemic agents, the milder episodes often escape notice of treating physicians. This is not only because of the non-specific nature of the symptoms, but may also be due to fact that patients are reluctant in reporting such episodes to their respective treating physicians. Thus, an opportunity to institute a corrective plan for smoother and long-term glycemic control is lost.

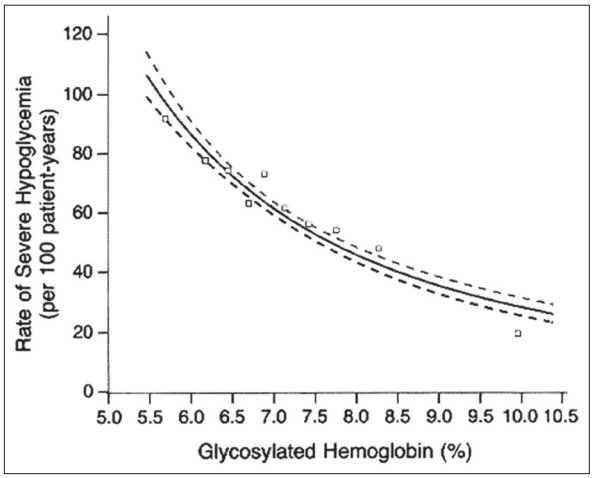

Figure 1: Rate of severe hypoglycemia in patients receiving intensive therapy, according to their mean glycosylated hemoglobin values during the trial.[1] Adapted with permission from the DCCT research group. New England Journal of Medicine 1993; 329: 977-86. All rights reserved

Balancing glycemic control by correcting hyperglycemia and preventing hypoglycemia is the key for providing optimum care of patients with diabetes. Clearly, it is preferable to prevent, rather than treat, hypoglycemia. With that principle as the nucleus and considering the grim situation as described in the previous sections, it is high time for all the stakeholders to join hands and work together in two directions; first, to generate quality data on this topic in form of well-designed, prospective, real-life large epidemiological studies so as to better understand its magnitude, associations, risk factors and implications; and second, to spread awareness and knowledge of about topic to both health care providers and patients using simple tools to discuss aspects like risk factors, preventive measures and identification of hypoglycemic episodes.

Standard recommendations

Definition

Over decades, a variety of criteria have been used to define hypoglycemic events. An early, very practical, and widely accepted definition of hypoglycemia is the presence of classical Whipple's triad: Decreased plasma glucose concentration, symptoms compatible with hypoglycemia and rapid attenuation of those symptoms by correction of the low glucose. However, The American Diabetes Association (ADA) assembled a Workgroup on Hypoglycemia in June of 2004 to discuss and arrive at a consensus as to how hypoglycemia should be defined and

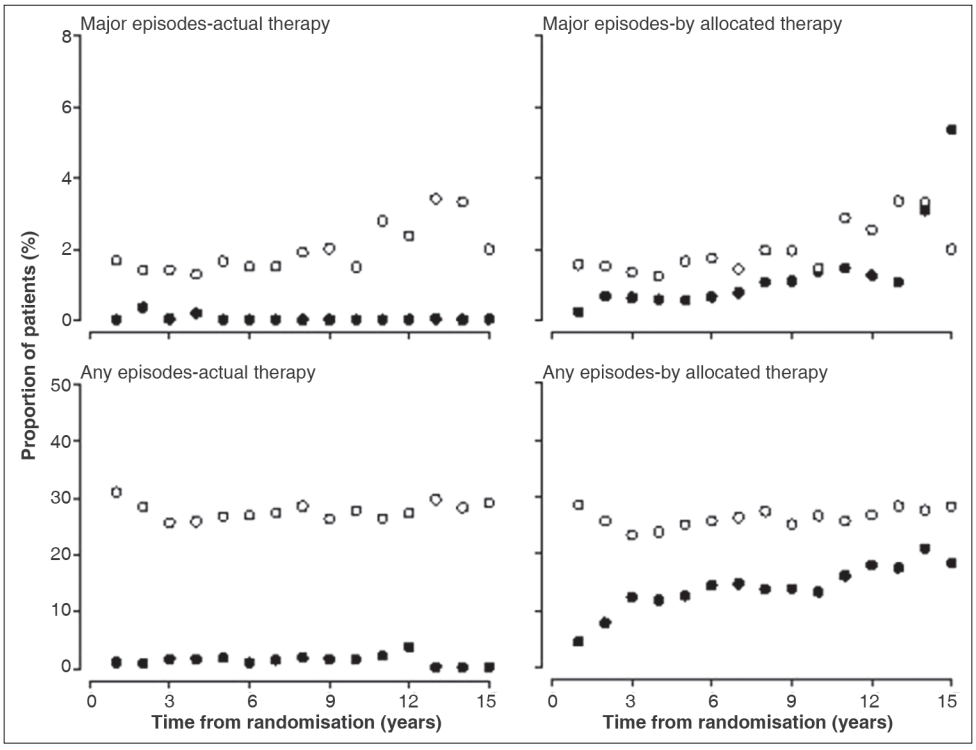

Figure 2: Major and any hypoglycemic episodes per year by intention-to-treat analysis and actual therapy for intensive and conventional treatment,[3] adapted with permission from UK Prospective diabetes study (UKPDS) group. UKPDS 33. The Lancet 1998; 352: 837-53. All rights reserved

reported in context of clinical studies in patients with diabetes.[10] This consensus also addresses the controversy related to method of glucose measurement and states that though laboratory-based plasma glucose measurement would be ideal, monitor-based estimates (or those with a validated glucose sensor) are the only practical method.[10] The following classification was proposed:

- Severe Hypoglycemia: An episode requiring the assistance of another person to raise the plasma glucose concentration resulting in resolution of symptoms, with or without a measured low plasma glucose concentration.
- Documented Symptomatic Hypoglycemia: Symptoms consistent with hypoglycemia with a measured plasma glucose concentration <70mg/dL (3.9mmol/L).
- Asymptomatic Hypoglycemia: A measured plasma glucose concentration <70mg/dL (3.9mmol/L) in the absence of symptoms.
- Probable Symptomatic Hypoglycemia: Typical symptoms of hypoglycemia without a measured plasma glucose concentration.
- Relative Hypoglycemia: Typical symptoms of hypoglycemia with a measured plasma glucose concentration >70mg/dL (3.9mmol/L) but approaching that level.(Such episodes occur in people with poorly controlled diabetes).

Factors increasing the risk of hypoglycemia in patients of type 2 diabetes[7]

Hypoglycemia is appropriately viewed as the result of the interplay of relative or absolute insulin excess and compromised glucose counter-regulation in insulin deficient type 1 diabetes and advanced type 2 diabetes. Several factors put individuals at risk for a hypoglycemic episode. These include:

I. Situations with Insulin excess alone (conventional risk factors)
   - Insulin (or insulin secretagogue or sensitizer) doses are excessive, ill-timed, or of the wrong type
   - Exogenous glucose delivery is decreased, such as after missed meals or snacks and during overnight fast
   - Endogenous glucose production is decreased, such as following alcohol ingestion
   - Glucose utilization is increased, such as during exercise.
   - Sensitivity to insulin is increased, such as late after exercise, in the middle of the night, and after weight loss, increased fitness, or improved glycemic control, or during treatment with an insulin sensitizer
   - Insulin clearance is decreased, such as with progressive renal failure

II. Situations with Insulin excess and compromised glucose counter-regulation
   - Endogenous Insulin deficiency (long standing type 2 diabetes)
   - History of severe hypoglycemia, hypoglycemia unawareness, or both
   - Aggressive glycemic therapy per se, as evidenced by lower HbA1c levels, lower glycemic goals, or both

III. Other uncommon risk factors:
   - General anesthesia or sedation that places patient in an altered consciousness
   - Critical illnesses (hepatic, cardiac, and renal failure; sepsis; and severe trauma)
   - Endocrine deficiencies (cortisol, growth hormone, or both)
   - Sudden reduction of corticosteroid dose
   - Concomitant medications: Several agents can increase the potential of sulfonylureas to cause hypoglycemia by displacement from albumin-binding sites (high dose aspirin, sulfonamides, warfarin, fibrates), decrease hepatic metabolism (warfarin), decreased renal excretion (aspirin, allopurinol), stimulation of insulin secretion (non-steroidal anti-inflammatory drugs) or increase peripheral glucose uptake (angiotensin converting enzyme inhibitors, aspirin).[11]

Measures to minimize risk of hypoglycemia in patients of type 2 diabetes[7]

I. Addressing the issue of hypoglycemia during every patient visit, actively looking for it and educating the patient

II. Apply the principles of aggressive glycemic therapy
   - Patient education and empowerment
   - Frequent Self-Monitoring Blood Glucose (SMBG) - SMBG, a simple and effective tool that can help achieve the fine balance between good glycemic control and reduced risk of hypoglycemia, is grossly underutilized in India. The proportion of patients with diabetes in India who own a blood glucose testing meter has been reported to be 1.8% Bjork *et al.* and 0.2% by Mohan *et al.*[11,12] Even though cost is the most commonly cited factor limiting uptake of SMBG, spreading awareness amongst patients can substantially enhance uptake, particularly with lower cost devices now available.[12-14]
   - Appropriate and flexible insulin (and other drug) regimens
   - Individualized glycemic goals-ADA now suggests that less-stringent HbA1C goals (such as <8%) may be appropriate for patients with a history of severe

hypoglycemia, limited life expectancy, advanced micro-vascular or macro-vascular complications, extensive co-morbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain (level of evidence B).[15]

- To identify and track the episodes of hypoglycemia where Stanford hypoglycemia questionnaire might be a simple, user friendly and validated tool for in clinic assessment of hypoglycemia.
- Ongoing professional guidance and support

III. Consider both the conventional risk factors and those indicative of compromised glucose counter-regulation
- Drug selection and regimen
- Short-term scrupulous avoidance of hypoglycemia in patients with hypoglycemia-associated autonomic failure

Treatment of hypoglycemia in patients of type 2 diabetes[15]

- Glucose (15-20g) or any glucose containing carbohydrate is the preferred treatment for the conscious individual with hypoglycemia. This should be repeated after 15 minutes if there is continued hypoglycemia. Once glucose returns to normal, the individual should consume a meal or snack to prevent recurrence of hypoglycemia (level of evidence E). Unconscious patients need emergency medical care and intravenous administration 50-100ml of 25% dextrose.
- Glucagon should be prescribed for all individuals at significant risk of severe hypoglycemia, and caregivers or family members of these individuals instructed in its administration (level of evidence E). An initial intra-muscular or sub-cutaneous dose of 0.5mg can be repeated if there is no symptomatic improvement.

Concluding Remarks

ADA Workgroup on hypoglycemia suggested that a significant reduction in the frequency of documented hypoglycemia (plasma glucose ≥70 mg/dl, with or without symptoms, of ≥30% by a new drug, device, or management strategy would represent a clinically important improvement over existing therapeutic practices.[10] This proposed combination of structured research and increasing physicians' as well patients' awareness, could well be one such management strategy. The key lies in partnership between all the relevant stakeholders and an unconditional commitment against this barrier of hypoglycemia.

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