



ORIGINAL RESEARCH PAPER

General Medicine

APPROACH TO CLINICAL PROFILE OF PATIENTS PRESENTING WITH HYPOGLYCAEMIA SYMPTOMS AND AWARENESS

KEY WORDS: Hypoglycemia, Diabetes mellitus, symptoms, Insulin treatment.

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ABSTRACT

Hypoglycemia is a common, potentially avoidable consequence of diabetes treatment and is a major barrier to initiating or intensifying antihyperglycemic therapy in efforts to achieve better glycemic control. Therapy regimen and a history of hypoglycemia are the most important predictors of future events. Other risk factors include renal insufficiency, older age, and history of hypoglycemia-associated autonomic failure. Reported rates of hypoglycemia vary considerably among studies because of differences in study design, definitions used, and population included, among other factors. The detailed history and investigations were recorded. The data thus obtained was analyzed. One hundred patients of hypoglycaemia were included in the study. Most of the patients (68%) belonged to rural background. Type 2 Diabetes was present in 92% of patients. Overall a total of 36% patients were receiving insulin. Glimpiride was the most commonly used sulfonylurea. Mean random blood sugar on admission was 37.12mg/dl. Altered consciousness was the most common presentation in our study (90%). Most of the patients improved with treatment (98%). Elderly diabetics are more prone to the development of hypoglycaemia, especially those on insulin and sulfonylureas. Although the trained clinician can recognize the autonomic and neuroglycopenic symptoms of hypoglycemia even in a patient not on insulin, it remains challenging to decipher the etiology of a spontaneous hypoglycemic event. A logical and stepwise approach to the spontaneous hypoglycemic event allows for a conclusive diagnosis.

INTRODUCTION:

The clinical management of type 2 diabetes emphasizes the importance of glycemic control to reduce the risk of diabetes [1] related complications. In daily clinical practice, hypoglycemia is most commonly iatrogenic, caused by insulin or insulin secretagogue used to treat diabetes mellitus [1]. The diagnosis and treatment of a hypoglycemic event in a patient using medication to lower plasma glucose level are therefore straightforward. But spontaneous hypoglycemia in a non-diabetic patient confronts the clinician with a diagnostic enigma. Hypoglycemia is confirmed when Whipple's triad is present [2,3]: (1) symptoms or signs consistent with hypoglycemia, (2) a plasma glucose level less than 55 mg/dl, measured with a precise method such as a venous blood sample, and (3) resolution of symptoms after raising plasma glucose level [4]

Prolonged hypoglycemia can cause brain death and hypoglycemia has shown to increase all-cause mortality in cardiac patients [9,10]. Mortality is especially higher for the spontaneous hypoglycemia in non-diabetics [11]. Probably because the underlying cause heralds a more ominous prognosis and because these hypoglycemic events are a marker for vulnerability. Recurrence of hypoglycemia is a great source of morbidity and generates a great burden to the patient.

Hypoglycemia is a true medical emergency which requires prompt recognition and treatment to prevent organ and brain damage. The spectrum of symptoms depends on duration and severity of hypoglycemia and varied from autonomic activation to behavioral changes to altered cognitive function to seizures or coma. The short and long term complications include neurologic damage, trauma, cardiovascular events and death [10]. Severe untreated hypoglycemia can cause a significant economic and personal burden, therefore identification and prevention of hypoglycemia can reduce diabetes burden by prevention of hypoglycemia complications. Our institute is a tertiary care hospital catering to a large population, a majority from rural areas with limited access to healthcare facilities. Moreover, owing to poor economic condition, most of these patients are taking sulphonylureas which are less costly and even available in the

government supplies. We planned this study to find out the clinical profile and risk factors associated with hypoglycaemia in our population so that we can adopt certain measures to prevent this potentially fatal complication of diabetes mellitus.

MATERIAL AND METHODS:

This study was carried out in the Department of General Medicine, Arupadai veedu Medical College and Hospital, Puducherry. The data of the patients information was available from hospital records and patients were admitted with hypoglycaemia as per the inclusion criteria. Patients with blood glucose less than 70 mg/dl with or without symptoms of hypoglycaemia were included in the study and those patients with blood glucose more than 70 mg/dl even with symptoms of hypoglycaemia were excluded from the study. The detailed history including demographic profile, drug intake both prescription and otherwise and presenting symptoms with duration were recorded in the predesigned performa. Details of investigations, management and outcome were also recorded. The data thus obtained was analyzed to see different demographic profiles, duration and type of diabetes, presenting symptoms, findings of investigations and outcome.

RESULTS:

200 patients of hypoglycaemia were found to be eligible for inclusion in the study. Out of them, 120 (60%) patients were males and 80 (40%) were females. Age of the patients ranged from 25-76 years. 40 patients were more than 70 years of age. Most of the patients (70 %) belonged to rural background. Type 2 Diabetes was present in 94% of patients, 4% patients had Type 1 Diabetes and 2% patients had gestational diabetes. Mean duration of Diabetes was 10.4 years.

Hypertension was the most common co-morbid condition associated with diabetes in 60% patients followed by CAD (12%), Chronic kidney disease (10%), hypothyroidism (4%) and cerebrovascular disease, obesity and malignant disease in 4% each. 24% of the patients were receiving only insulin, 12 % patients were receiving insulin with oral drugs and 64% patients were receiving only oral drugs. Overall a total of 36% patients were receiving insulin. Among oral drugs, the most

common was metformin (64%) followed by sulphonylureas (60%). Glimperide was the most commonly used sulphonylurea whereas only 4 patients received gliclazide.

Other oral drugs used in decreasing order of frequency were DPP4 inhibitors (28%), glitazones (10%), SGLT2 inhibitors (4%). Altered consciousness ranging from mild confusion to comatose state was the most common presentation in our study (90%). 30% patients gave history of sweating as the initial symptom. Tremors and palpitations were present in 12% patients each. 8% patient had a generalised tonic clonic seizure at presentation and 2% patients had a focal neurological deficit

Table -1. Precipitating Causes Of Hypoglycaemia

Precipitating cause	Percentage of patients
Missed meal	152
Infection	32
Increased drug dose	16

Missed meal due to multiple reasons was the most common identified precipitating factor for hypoglycaemia in our patients 152 (76%). Infection was present at admission in 32 (16%) patients. Only 6 (6%) patients reported increased dose of oral drugs or insulin as the precipitating factor

Table -2. Duration Of Symptoms At Presentation.

Hospital presentation (hrs)	Number of patients (%)
Upto 1 hour	12
1-6 hrs	136
Upto 24 hours	44
More than 24 hours	8

8% patients reported a documented previous episode of hypoglycaemia. Mean glycosylated haemoglobin was 7.65% with minimum of 4.5% and maximum of 14.0%. 40 % patients had a good control of diabetes with glycosylated haemoglobin level less than 7%. Only 12 patients presented within 1 hour of symptom onset. Most 136 (68%) presented between 1-6 hours 8 patients presented after 24 hours.

DISCUSSION:

Hypoglycemia is a common, potentially avoidable consequence of diabetes treatment and a major barrier to better metabolic control in type 1 and type 2 diabetes. It is a significant concern of primary care practitioners and patients when it comes to initiating or intensifying antihyperglycemic therapy. Hypoglycemia can be defined in several ways: by plasma glucose values (biochemical definition), by symptoms (type and severity), and by time of day in which it occurs (daytime or nocturnal).[12-13] The literature is inconsistent in describing biochemical hypoglycemia.

The findings suggest that recent clinical guidance on the need for individualized goals for patients at high risk of hypoglycemia has yet to be incorporated into standard clinical practice. Better management of hypoglycemia needs to be advanced through the adoption of risk assessment and clinical decision support tools, patient education, and shared decision-making. Through effective cross-specialty and multi-stakeholder collaboration, we have an opportunity to increase awareness of hypoglycemia among providers and patients, and improve patient care. We believe this initiative will help us develop strategies to avoid hypoglycemic events while building support for the inclusion of hypoglycemia prevention in value-based diabetes care models.

The present study included patients from mainly rural with a mean age of 61.2 years and 40 patients were more than 70 years of age which makes them more susceptible to hypoglycaemia. The risk is further increased in this population with presence of multiple co-morbidities. Most of the patients had type 2 diabetes. We could not find any nondiabetic patient in our study. In contrast to our

findings,[12] Heller has reported that risks of hypoglycemia are less in type 2 diabetes mellitus patients, but are higher during [13] insulin treatment. Hepburn et al in their study found that when matched for duration of insulin therapy (mean duration 12 years) and HbA1C, the frequency of severe hypoglycaemia is similar in type 1 and type 2 diabetes mellitus patients.

Severe hypoglycemia has a considerable impact on wellbeing, productivity and quality of life in old people with diabetes [14]. Management goals for elderly patients should be an individualized process and must include a number of considerations. Numerous studies have demonstrated the benefits of avoiding intensive attenuation of HbA1C to prevent severe hypoglycemia. Patient training and treatment of the early symptoms of hypoglycemia may prevent the occurrence of further severe hypoglycemia and decrease the rate of hospitalization, mortality and cognitive impairment that directly affects the independence and functionality of older persons.

Patients on oral anti-diabetic drugs are also at risk for developing hypoglycemia. Agents such as metformine, dipeptidyl peptidase-4 inhibitors, and thiazolidines are preferable to sulphonylureas in minimizing hypoglycemic risks [15]. Because most of the patients were elderly, the presence of multiple co-morbidities was expected in these patients. The presence of CKD in 10% of patients made them prone to the development of hypoglycaemia. Because of the long duration of diabetes in most of the patients, a large number of them (36%) were using insulin. Common oral drugs incriminated for hypoglycaemia, sulphonylureas were used in a large number of patients, mainly glimepiride which has a long duration of action. Glimepiride when used with insulin, especially in elderly patients poses a high risk of [16] hypoglycaemia. Brijesh Mukherjee et al showed that insulin therapy was the most common cause of hypoglycemia accounting for 79% (either alone or in combination with OAD) 12 of diabetic patients.

The longer-acting sulphonylureas such as glibenclamide and chlorpropamide are associated with more severe hypoglycemia than the shorter-acting drugs [17]. Occasional episodes of hypoglycemia with Metformin, as the most commonly used anti-diabetic drug, are reported when an imbalance between food intake and dose of Metformin is presented [18].

Though 64% of our patients were receiving metformin, and many patients were also receiving other drugs like DPP4 inhibitors, glitazones, SGLT2 inhibitors and acarbose but all these were in combination with either insulin or sulphonylureas. No patient was on glinides. Therefore risk of hypoglycaemia with drugs other than insulin and sulphonylureas cannot be ascertained. Most of our patients (90%) presented with altered consciousness of varying severity and classical symptoms like sweating, tremors and palpitations were present in lesser number of patients. Given the aspecificity of autonomic and neuroglycopenic symptoms and signs during hypoglycemia, one should use Whipple's triad to document hypoglycemia. Signs and symptoms consistent with hypoglycemia, during a state of low plasma glucose (b55 mg/dl), that resolves after plasma glucose is raised, indicating fulfillment of this triad. The spectrum of symptoms depends on duration and severity of hypoglycemia and varied from autonomic activation to behavioral changes to altered cognitive function to seizures or coma.

Unfortunately, the symptoms experienced are inconsistent between individuals, which complicates our efforts in identifying hypoglycemia and in counseling patients who experience these symptoms. Elderly patients also report different symptoms and have different responses to

hypoglycemia (eg, diminished autonomic symptoms and more prominent neuroglycopenic symptoms). Thus, hypoglycemia can be misdiagnosed as delirium or neurologic events. Cognitive impairments in the elderly may contribute to the increased risk of hypoglycemia, and hypoglycemia may further worsen or increase the risk of cognitive issues.

Sweating was the most common autonomic symptom followed by palpitation, in-coordination, altered sensorium, tremors and other symptoms. As most of our patients presented late to the hospital with an average duration of 7.2 hours and most of them being elderly, altered consciousness is the most common presentation. As glycaemia comes down, the activation of the autonomic nervous system leads to neurogenic symptoms (palpitations, sweating, hunger, anxiety, tremors, etc.), which allows the perception of hypoglycaemia (hypoglycaemia awareness). It is important that diabetic patient on treatment should be familiar with their own symptom profile, so that they can perceive the early onset of hypoglycemia and know what appropriate action has to be taken.

Missing of a meal due to multiple reasons was the commonest precipitating factor identified in our patients. Most of our patients were admitted with first episode of hypoglycaemia and only 8 patients reported previous documented admission with hypoglycaemia. Majority of the patients had good glycemic control (average HbA1c 7.7%) and most were on multiple drugs targeted to achieve strict glycemic control. The fact that most of our patients recovered with treatment underlies the importance of early recognition of hypoglycaemia symptoms and appropriate and timely treatment and preventive measures.

Lifestyle approaches are the mainstay of prevention of hypoglycemia. These include having a well-balanced diet, eating regular small meals, self-monitoring of blood glucose at appropriate frequency, carrying a source of rescue carbohydrate such as fruit or candy at all times, and avoiding defensive overeating to avert a hypoglycemic event. Compared with regular insulin, rapid-acting insulin analogs have a more rapid onset of action, higher peak action, and shorter duration of action, which more closely approximates endogenous mealtime insulin response, allowing more flexibility in the time of meals and exercise, and, consequently, a lower risk of severe hypoglycemic events. Hypoglycemia is more common in patients taking insulin and sulfonylureas especially glimeperide. Elderly patients are more prone to hypoglycaemia due to multiple co-morbidities and impaired metabolism of drugs. Education of the patient and caregivers about symptoms of hypoglycaemia and its management should be a part of every hospital visit in these patients.

CONCLUSION:

Elderly patients are more prone to hypoglycaemia due to multiple co-morbidities and impaired metabolism of drugs. Although the trained clinician can recognize the autonomic and neuroglycopenic symptoms of hypoglycemia even in a patient not on insulin, it remains challenging to decipher the etiology of a spontaneous hypoglycemic event. A logical and stepwise approach to the spontaneous hypoglycemic event allows for a conclusive diagnosis. Recognition of hypoglycemia risk factors, blood glucose monitoring, selection of appropriate regimens, education programs for healthcare professionals and patients with diabetes are the major issues to maintain good glycemic control, minimize the risk of hypoglycemia, and prevent long-term complications.

A better chance of achieving their glucose control goals while avoiding the morbidity and mortality associated with hypoglycemia. Accordingly, future diabetes guidelines will have to define a minimum HbA1c value, especially for

patients with longstanding diabetes. Selecting or modifying therapy to reduce hypoglycemia can take one of the variables of diabetes management and turn it into somewhat more of a constant, minimizing hypoglycemia risk.

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