

Original article / research

## **Clinical profile of hypoglycemia in diabetic patients : A prospective study in a tertiary care hospital**

Pankaj Seth\*\*, Amit Bery\*, Arun Kumar Gupta\*\*\*\*

\*\*Assistant Professor, Department of Emergency Medicine, Dayanand Medical and Hospital, Ludhiana, India.

\* Professor, Department of Medicine, Dayanand Medical and Hospital, Ludhiana, India.

\*\*\*\*Assistant Professor, Department of Emergency Medicine, Dayanand Medical and Hospital, Ludhiana, India.

Correspondence Address: Dr. Amit Bery, Professor, Department of Medicine, Dayanand Medical and Hospital, Ludhiana, India

E-mail: amitbery@yahoo.co.in.

## **Abstract**

**Background:** The term hypoglycemia refers to a clinical condition resulting from an abnormally low plasma glucose level ( $\leq 40$  mg/dl). Clinically, it is characterized by varying degree of neurological dysfunction and is responsive to the administration of glucose. Hypoglycemia is commonly caused by drugs used to treat diabetes mellitus.

**Objective:** To study the clinical profile, precipitating factors and outcome in the patients of hypoglycemia.

**Material and Methods:** This hospital based 2 years prospective study was conducted in the Department of Medicine, Kasturba Medical College and hospital, Manipal, Karnataka. Clinical profile of 100 diabetic patients on OHA's or Insulin treatment with the diagnosis of hypoglycemia ( $<40$ mg/dl without symptoms and  $<50$ mg/dl with symptoms) were analysed.

## **Results:**

Out of 100 patients, 30 (30%) patients were of type 1 diabetes mellitus and 70 (70%) patients of type 2 diabetes mellitus. The male:female ratio was 1:1.7. The most common precipitating factor was found to be delaying or skipping meals (80%), followed by decreased carbohydrate intake (70%), increase in insulin or OHAs dosage (54%), decrease in insulin requirement (10%). The most common autonomic symptom was sweating (90%) followed by palpitation (80%). Neuroglycopenic symptoms were observed at much lower blood glucose level. Majority of hypoglycemic patients (68%) had blood glucose in the range 31-40 mg/dl. 64 patients (64%) were on only insulin

therapy and 16 (16%) patients were on OHAs. 20 (20%) patients were on combination (insulin+OHAs) therapy. Maximum incidence of hypoglycemia was reported among patients who were on combination of short acting plus intermediate acting (i.e Premix – 30/70) Insulin. However, within the set of patients developing hypoglycaemia due to OHA's, the frequency was much higher (62.5%) with a combination therapy of OHA's as compared to monotherapy (37.5%). Present study did not show any mortality due to hypoglycemia.

### **Conclusion:**

Hypoglycemia is the most common acute metabolic complication of diabetes mellitus on treatment. Elderly diabetics, patients with chronic kidney disease and patients on long acting insulin/sulfonylureas (used either alone or in combination) are more prone to develop hypoglycemia. Diabetic patients should be familiar with hypoglycemia symptom profile so that they can perceive the early onset of hypoglycemia and an appropriate action can be taken immediately.

**Key words:** Hypoglycemia, Blood sugar, OHAs (oral hypoglycemic agents)

## INTRODUCTION

Hypoglycemia is the most common endocrine emergency faced by physicians. It is defined arbitrarily as a blood glucose of less than 50mg/dl with neuroglycopenic symptoms or less than 40 mg/dl in the absence of symptoms.<sup>[1]</sup> As a physician, hypoglycemia is more concerning than hyperglycemia because a patient can die from hypoglycemia. Hypoglycemia had been implicated as a cause of death in “dea-in-bed” syndrome in diabetic patients. Hypoglycemia impedes safe achievement of optimal glycemia. Severe hypoglycemia – that require the assistance of another person – is a clinical red flag.<sup>[1]</sup>

Hypoglycemia remains the most common and serious iatrogenic cause of morbidity in diabetic patients.<sup>[2]</sup> Large trials such as Veterans affairs diabetes trial and Action to control cardiovascular risk in diabetes trial have shown that there was a higher mortality in the group that had been treated intensively to achieve glycemic control.<sup>[3],[4]</sup> Hence, the American Diabetes Association (ADA) guidelines emphasized on individualizing targets and reducing risk of hypoglycemia in patients with long duration of diabetes and co-morbidities.<sup>[5]</sup> Targeted HbA1c levels in patients with Type 1 Diabetes and Type 2 Diabetes should be tailored to the individual, balancing the micro vascular complication with risk of hypoglycemia.<sup>[6-9]</sup> The American Diabetes Association’s most recent guidelines still recommended HbA1C goal for most adults to be less than 7 %, but also recognizes that less stringent goals (such as <8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced complications and comorbid conditions.<sup>[10]</sup> Main objective of this study is to know the clinical facts of hypoglycaemia, precipitating factors, symptomatology, early recognition and correction,

Prevention of recurrent episodes of hypoglycemia will reduce morbidity and mortality of diabetic patients.

## **MATERIAL AND METHODS**

The study was conducted on patients admitted in Department of Medicine Kasturba Medical College and hospital, Manipal, Karnataka during a span of 2 years (2016-2107). A total of 100 diabetic Patients (diabetes diagnosed as per American diabetes Association criteria) with Hypoglycemia (as per inclusion criteria) were selected for the study. The detailed history, clinical examinations and relevant laboratory investigations done for all the patients were evaluated and analyzed in detail. (Using Accu-Chek Nano Glucose meter, Roche Diagnostics, USA, Beckman Coulter Auto analyzer, USA and COBAS 6000, Auto Analyzer, Roche Diagnostics, USA). Study was conducted after institutional ethical committee approval. The statistical analysis was done using SPSS program.

## **INCLUSION CRITERIA**

Plasma glucose  $\leq 40$  mg/dl

## **RESULTS**

Out of 100 patients of diabetes (under treatment) included in study, 30 (30%) patients were suffering from type 1 diabetes mellitus and 70 (70%) patients from type 2 diabetes mellitus. The male:female ratio was 1:1.7. The maximum number of patients (44%) were in age group of 41 to 60 years. Majority of hypoglycemic patients (n=68,

68%) had blood glucose in the range 31-40 mg/dl and 26 (26%) had blood glucose between 21-30 mg/dl. Only 6 (6%) patients had blood glucose <20 mg/dl.

The most common symptom was sweating (90%) followed by palpitation (80%), incoordination (80%) and altered sensorium (64%). 6% of patients had tremors. Hunger and speech difficulty were reported in 50% of patients. Visual disturbance and headache were present in 40% of patients. 10% of patients had nausea. Two patients of hypoglycemia presented with hemiplegia but it recovered completely on treatment. (Figure 2)

The most common precipitating factor was found to be delaying or skipping meals (80%), followed by decreased carbohydrate intake (70%). In 54% patients, precipitating factor for hypoglycemia was increase in insulin or dose of oral hypoglycemic agent. In 10% of patients, hypoglycemia was due to decrease in insulin requirement due to clearance of infection, reduced renal clearance of Insulin (progression to chronic kidney disease). Most of the patients had more than one precipitating factor. (Figure 1)

Out of 100 patients, 64 (64%) were on only insulin therapy (short acting–regular insulin, mixture of short acting+intermediate acting insulin (30/70) and combination) and 16 (16%) patients were on oral hypoglycemic agents (Sulfonylureas, biguanides, thiazolidinediones). 20 (20%) patients were on combination (insulin+OHA) therapy. Out of 64 patients who were on insulin therapy alone, 36 (56.25%) were on mixture of short acting+intermediate acting insulin (i.e Premix Insulin 30/70) and 18 (28.12%) patients were on short acting (regular insulin).

Out of 16 patients who were on oral hypoglycemic agents alone, 6 (37.5%) patients were on Sulfonylureas (Glibenclamide) and other 10 (62.5%) patients were on various combination of oral hypoglycemic agents. None of the patients was on biguanide monotherapy. All hypoglycemia patients recovered fully following treatment without any neurological sequelae.

## **DISCUSSION**

Iatrogenic hypoglycemia is the limiting factor in the glycemic management of diabetes mellitus.<sup>[5]</sup> It causes recurrent symptomatic and sometimes (at least temporarily) disabling episodes in most patients with type 1 diabetes as well as in those with advanced type 2 diabetes, and is sometimes fatal.<sup>[11]</sup> Drug induced hypoglycemia occurs more frequently in older patients with underlying hepatic or renal dysfunction.<sup>[12]</sup> Present study showed that 70% hypoglycemic patients had Type 2 diabetes as compared to 30% patients with type 1 diabetes. In conformity with our observations, Heller<sup>[13]</sup> has reported that risks of hypoglycemia are less in type 2 diabetes mellitus patients, but are higher during insulin treatment. Hepburn et al.<sup>[14]</sup> in their study found that when matched for duration of insulin therapy (mean duration 12 years) and HbA<sub>1C</sub>, the frequency of severe hypoglycemia is similar in type 1 and type 2 diabetes mellitus patients. Higher incidence of hypoglycemia in type 2 diabetic patients in the present study may be due to the fact that some of these patients were admitted for surgical intervention and were temporarily put on insulin therapy as a part of pre-operative management of diabetes. The mean age of patients in this study was 57.68 years.

Although, any age group is prone to hypoglycemia on treatment, however elderly patients on long acting preparations are more susceptible to hypoglycemic episodes. This may be attributed to multi-factorial causes like reduced clearance of anti-diabetic drugs because of reduced eGFR (Diabetic nephropathy), bed ridden state reduced oral intake, co-morbidities, drug interactions, etc. Hypoglycemia recognition can sometimes be difficult in elderly due to predominance of neurological (dizziness, weakness and confusion) rather than autonomic symptoms (sweating tremors). Symptoms of hypoglycaemia tend to be less specific with increasing age. Independent risk factors for severe hypoglycemia include recent hospitalization, advanced age and polypharmacy. Delaying or skipping meals was observed as the most important precipitating factor for hypoglycemia (80% of patients). Decreased carbohydrate intake as a causative factor was found in 70% of patients. These patients were eating less as compared to their regular diet during sick days or had anorexia due to their primary illness. All the patients were on hospital supplied diabetic diet. Increase in insulin or OHA dosage to achieve good glycemic control was the precipitating cause for hypoglycemia in 54% of patients. Decrease in insulin requirement was found in 10% of patients. This decrease was due to clearance of the primary infection like treatment of diabetic foot or delayed insulin clearance due to progression to Chronic kidney disease.

Symptom profile provoked by hypoglycemia is idiosyncratic and varies in character, pattern and intensity between individuals.<sup>[14]</sup> Symptoms of hypoglycemia vary depending on the age of the individual but the symptoms appear to be similar whether induced by sulfonylureas, insulin analogues, animal or human insulin.<sup>[15]</sup> Although, no single symptom is present consistently during hypoglycemia in all patients with



diabetes, some symptoms are more common than other.<sup>[16]</sup> In the present study sweating was the most common autonomic symptom (90%) followed by palpitation and inco-ordination (80%), altered sensorium (64%), tremors (60%), hunger and speech difficulty (50%), visual disturbances and headache (40%). Consistent to our results, McAulay *et al*<sup>[17]</sup> have reported similar prevalence of symptoms in their study with sweating in 80% of patients, palpitation (55%), incoordination (75%), altered sensorium (40%). Hunger and slurred speech were present in 60% and 40% of patients respectively. Visual disturbance in 20% and headache in 30% of patients. There is no single symptom that is exclusive to hypoglycemia alone. However, hypoglycemia unawareness is a major clinical problem in the management of Diabetic patients on Insulin therapy. The risk of severe episode of hypoglycemia increases 6-7 folds in these patients.<sup>[18]</sup>

Moreover, in a study by Pennebaker *et al.*<sup>[19]</sup> has found that no single symptom correlate significantly with a specific blood glucose concentration in humans. Hence, 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.

Our study showed insulin therapy was the most common cause of hypoglycemia accounting for 64% of diabetic patients. Carroll *et al.*<sup>[2]</sup> also found that insulin treatment of diabetes is the most common cause of severe hypoglycemia in adults. United Kingdom Prospective Diabetes Study (UKPDS)<sup>[20]</sup> reported severe hypoglycaemia in 11.2% of patients treated with insulin. In the present study, the majority of hypoglycaemia cases were receiving combination of OHA's rather than monotherapy.

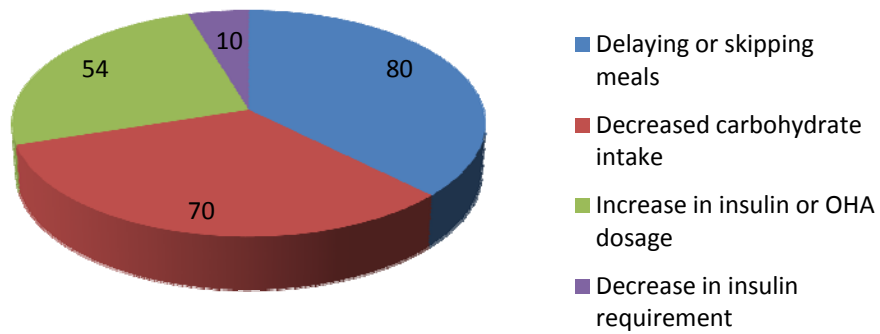
And the most common monotherapeutic offending agent was sulfonylurea. United Kingdom Prospective Diabetes Study (UKPDS) <sup>[20]</sup> has reported severe hypoglycemia due to sulfonylureas in 3.3% of patients and 2.4% of those treated with biguanides. Jennings *et al.* <sup>[22]</sup> have found, that hypoglycemia in patients receiving sulfonylurea treatment vary widely but were reported to be as high as 20% over a 6 month treatment period. Shorr *et al.* <sup>[23]</sup> described a crude rate of serious hypoglycemia (hospitalization, emergency department admission or death) of 1.23 per 100 person-years in users of sulfonylureas aged 65 years or older.

All hypoglycemic patients recovered fully following treatment without any neurological sequelae and no mortality was seen in this study. Usually, death from cerebral edema caused by hypoglycemia is extremely rare. <sup>[16]</sup> However, hypoglycemia had been implicated in “dead-in-bed” syndrome and in chronic cognitive impairment. <sup>[24]</sup> Klatt *et al.* <sup>[25]</sup> found 0.2% of death due to hypoglycemic coma. Macleod *et al.* <sup>[26]</sup> found “dead-in-bed” syndrome may account for 6% of deaths in diabetic patients under the age of 40. Sartor <sup>[27]</sup> reported the greatest incidence of mortality in childhood onset insulin dependent diabetes between 15-19 years of age. In our study, 100% recovery rate may be attributed to the fact that all patients had hypoglycemia in the hospital, so early detection and effective treatment was given.

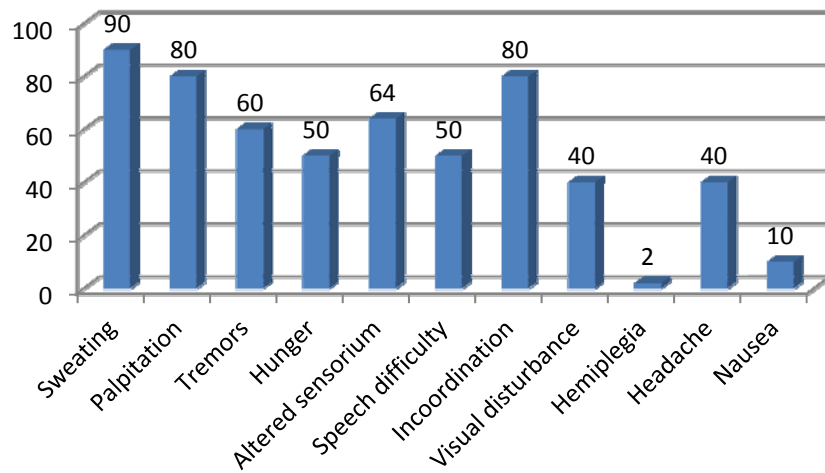
## **CONCLUSION**

Delaying or skipping meals was found to be the most common precipitating factor for hypoglycemia. Insulin treatment alone was the most common causative factor for hypoglycemia. Among sulfonylureas, glibenclamide was the most common offending

agent causing hypoglycemia in elderly. Elimination of hypoglycemia from the lives of people with diabetes will likely be accomplished by new treatment methods that provide plasma glucose-regulated insulin secretion with newer treatment modalities such as automated insulin pumps and artificial/ bionic pancreas.<sup>[21]</sup>



**Figure 1. Precipitating factors for hypoglycemia**



**Figure 2. Symptomatology in patients with hypoglycemia (%age)**

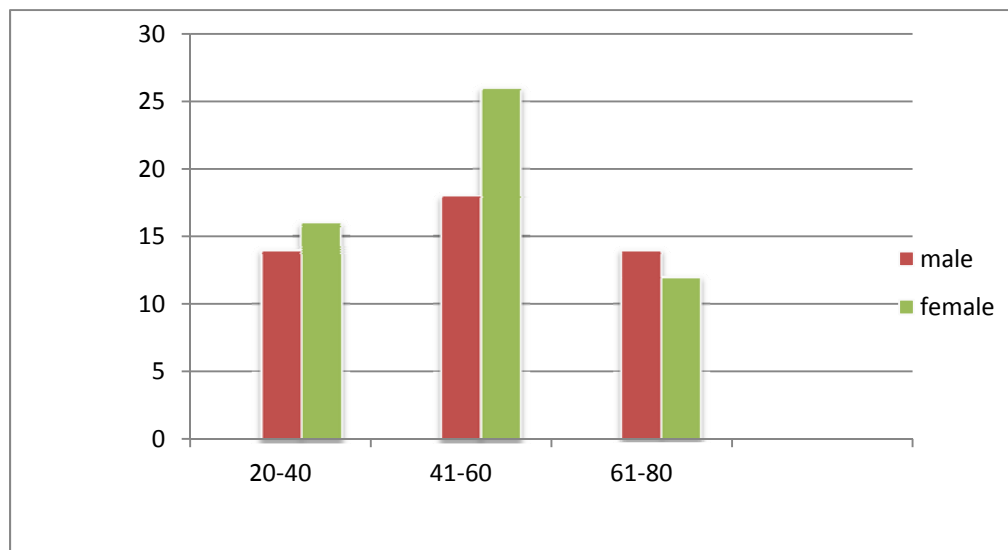


Figure 3. Age & Sex distribution in patients with Hypoglycemia

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