Original Article

Causes of Hypoglycemia in Diabetes Mellitus Patients

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ABSTRACT

OBJECTIVE: To determine the causes of hypoglycemia in diabetics presenting at Liaquat University Hospital Hyderabad/Jamshoro.

STUDY DESIGN: Descriptive observational study.

PLACE AND DURATION: Medical and Cardiology units of Liaquat University of Hospital Hyderabad /Jamshoro, from June 2007 to May 2008.

PATIENTS AND METHODS: One-hundred and one hypoglycemic cases were analyzed. A detailed enquiry about the presenting symptoms and mode of therapy was made. A thorough physical examination to look for diabetic complications and any concurrent illness was performed. Blood glucose was measured with the help of a Glucometer and response to glucose administration was also noted. Data were computed using SPSS software version 14. P-value up to 0.05 was considered significant.

RESULTS: Type-2 diabetics presented more commonly with hypoglycemia in adult diabetic population 81/101 (80.1%). Mean age for type-1 diabetics was 27.7 years and for type-2 diabetics 53.6 years. Male to female ratio was 3.3:1. Type-1 diabetic patients were either brittle diabetics with frequent dosage manipulations or those who had developed chronic complications. Majority of type-2 diabetics 74/81 (91.4%) were more than 40 years of age. Diabetic nephropathy, change in dose of hypoglycemic agents, missed meals, and use of concomitant medications were important associations with hypoglycemia in type 2 diabetic patients. All type-1 diabetics recovered completely after glucose administration. Amongst type 2 diabetics, 5 (6.41%) developed permanent disability and 6 (7.69%) patients died.

CONCLUSION: The adult males having type 2 diabetes suffer more from this complication. Recognition of different causes of hypoglycemia in diabetes patients and prompt treatment of hypoglycemia is important to prevent complications. The reasons of developing hypoglycemia most of the times were on patient's hand.

KEY WORDS: Hypoglycemia, Diabetes mellitus, Hemoglobin A1c, Plasma glucose level.

INTRODUCTION

Diabetes Mellitus is a diverse disorder; its main presentation is chronic hyperglycemia, caused by either insulin deficiency or resistance to the effects of insulin in peripheral tissues or a combination of both. Diabetes mellitus (DM) is a worldwide problem[1] and it is estimated that the number of diabetic patients will grow from 135 million to 380 million by the year 2025.[2] National diabetes survey conducted in Pakistan also showed an overall burden of disease to be around 22-25%[2]. Unfortunately the major increase would occur in the developing countries and in Pakistan the number of diabetics in the 2025 is estimated to be doubled[3]. It may affect cardiovascular system, renal system, nervous systems, eyes and the skin[1]. Diabetes care is complex and requires many issues to be addressed, beyond the glycaemic control[4]. Diabetes mellitus is a common secondary cause of hyperlipidaemia, particularly if glycaemic control is poor[5,6]. One local study has shown that one out of every three patients with Acute Myocardial Infarction was found to be diabetic, emphasizing its deleterious effects on the body[7]. It is associated with increased mortality and high risk of developing vascular, renal, retinal and neuropathic complications leading to premature disability and death.

Tight control of diabetes may lead to hypoglycemia. It is one of the serious complications associated with diabetes mellitus. Severe iatrogenic hypoglycemia in OHA-treated patients has a worse presentation, but is not associated with a higher long-term mortality than in insulin-treated patients[8]. The oral hypoglycemic agents can cause hypoglycemia when taken in overdose. The glucose level at which an individual becomes symptomatic is highly variable.[4] Patient may experience the symptoms of hypoglycemia when plasma glucose concentration is <54-mg/dl. Signs and symptoms of hypoglycemia can vary from person to person. The early symptoms are mild and occur due to stimulation of the sympathetic nervous system, when blood sugar falls below 70-mg/dl.[4] Hypoglycemia is a true emergency that needs to be promptly

managed as the antidote is readily available, and the consequences of delay in management can be devastating. Regardless of the cause, suspected hypoglycemia in any person must be diagnosed and treated immediately.[6,8]

It is important that patients with diabetes mellitus learn to recognize the symptoms of hypoglycemia so that they can take appropriate remedial measures. As these symptoms are usually missed, both by doctor and patient, hence the fatal consequences become inevitable. Our aim of the study is to determine the causes of hypoglycemia in diabetics and focus over this critical issue in our setup to recognize this acute fatal complication and so that it may help to plan preventive strategies in future.

PATIENTS AND METHODS

It was a descriptive observational study, conducted at Medical and Cardiology units of Liaquat University Hospital Hyderabad /Jamshoro, from June 2007 to May 2008. After assessing the previous history of the diabetic patients admitted with hypoglycemia, irrespective of the cause and consequences, we selected the size of 101 cases for the study. Every second diabetic patient admitted with hypoglycemia was designated as a study case. If the selected patient dropped due to fatal outcome, non-cooperation or any other reason, the next in queue was selected. Hypoglycemia episodes were grouped as severe, documented and asymptomatic according to following clinical criteria:

1. Severe Hypoglycemia: Hypoglycemia that was temporarily disabling and requiring the assistance of another person
2. Documented Hypoglycemia: Symptomatic hypoglycemia in which the patients were able to detect and self-treat.
3. Asymptomatic Hypoglycemia: Blood glucose level < 50mg/dl in the absence of symptoms.

Data were collected using a questionnaire comprising of socio-demographic features, medical history and past history. Different causes of hypoglycemia were determined by clinical features, physical examination and relevant laboratory investigations used for their final diagnosis. Both male and female known diabetics above the age of 15 years and patients having plasma glucose level below 50 mg/dL were included. Freshly diagnosed in ward with diabetes mellitus, on Corticosteroids or Immunosuppressant therapy, and those patients on parenteral dextrose therapy were excluded from the study.

Statistical Analysis

The filled questionnaires were coded and entered in statistical program SPSS version 14. Qualitative data (frequencies and percentages) were presented as n(%) and Pearson's chi-square was applied to compare the proportions among the variables. P-value ≤ 0.05 was considered as statistically significant for all comparisons.

RESULTS

Total 101 hypoglycemic cases were assessed. Eight patients had more than one documented episodes. Type-1 and type 2 diabetics were kept as separate groups (1 and 2 respectively). Type-2 diabetics formed the bulk being 81 (80.1%), 19 (18.9%) were type-1 diabetics and 1 (1%) patient had secondary diabetes (pituitary adenoma). Seventy-seven percent were males. Mean±SD age of type-2 diabetics was 53.6±10.5 years, whereas for type-1 diabetics it is 27.7±6.62 years. All type-1 diabetics were within 35 years of age. While 32 (39.5%) type-2 diabetics were 51-60 years old, 23 (28.3%) were 41-50 years, 19 (23.4%) were 61 or more and 7 (8.6%) were less than 40 years of age **(Table I)**. Group-1 included 19 patients, 14 males and 5 females. Twelve (63.1%) had diabetes for less than 10 years and 7 (36.8%) had diabetes for more than 10 years. All patients were receiving insulin, 16 (84.2%) were using regular insulin alone whereas remaining 3 (15.7%) were using it in combination with intermediate acting insulin, in twice or thrice daily doses. Majority, 17 (89.4%) injecting insulin themselves while remaining 2 (10.5%) were being injected by attendant or doctor. Injection technique was correct in 14 (73.6%). Abdomen, thigh, and upper arm were used as injection sites by 3 (15.7%), 16 (84.1%), and 1 (5.2%) patients respectively. Out of these 13 (68.4%) used multiple sites for injection. All the patients had history of previous episodes of hypoglycemia. Recovery from these episodes was complete. Group 2, which consisted of type-2 diabetic patients, included 81 (80.1%) patients, 63 (77.7%) males and 18 (22.2%) females. Their mean age was 53.66 ± 10.50 years, 1 (1.2%) was 21-30 years of age, 6 (7.4%) were 31-40, 23 (28.3%) were 41-50, 32 (39.5%) were 51-60 and only 19 (23.4%) were more than 61 years of age. Seven (8.6%) were receiving insulin, 71 (87.6%) on oral agents and 3 (3.7%) on diet control. Patient on diet included those without any pharmacological therapy as well as those patients, where insulin or demand for oral hypoglycemic drugs decreased following development of different complications. Those patients who were on diet control developed hypoglycemia secondary to over exertion and taking low calorie diet. Glycemic control was poor in 56 (69.1%) patients, adequate in 19 (23.4%) while in 6 (7.4%) patients; no record was available regarding previous control. Eleven (14.10%) patients also had past history of hypoglycemia but with prompt recovery. The HbA1c levels in 19 patients were 7.5%-8.0%; in 24 patients were 8.5%-9.5% and 38 patients' levels were 10%-11%.

TABLE I:
AGE AND SEX DISTRIBUTION OF DIABETIC PATIENTS

	Type 1 DM (n=19)	Type 2 DM (n=81)	Secondary DM (n=01)	Total (n=101)
Age group				
15-20	3(15.8%)	0	1(100.0%)	4(4.0%)
21-30	9(47.4%)	1(1.2%)	0	10(9.9%)
31-40	7(36.8%)	6(7.4%)	0	1312.9%)
41-50	0	23(28.4%)	0	23(22.8%)
51-60	0	32(39.5%)	0	32(31.7%)
60 and above	0	19(23.5%)	0	19(18.8%)
Sex				
Male	14(73.7%)	63(77.7%)	- -	77(76.2%)
Female	05(26.3%)	18(22.2%)	01(100%)	24(23.8%)

TABLE II:
CAUSES OF HYPOGLYCEMIA IN DIABETICS

Variable	Type 1 DM	Type 2 DM	P value
Change in dose of medication	14(73.7%)	37(45.7%)	0.05
Missed meals	2(10.5%)	19(23.5%)	0.07
Excessive work/Exercise.	0	21(25.9%)	<0.001*
Poor control	0	56(69.1%)	<0.001*
Previous episodes of hypoglycemia	15(78.9%)	11(13.6%)	<0.001*
Nephropathy	14(73.7%)	58(71.6%)	0.81
Autonomic Neuropathy	4(21.1%)	32(39.5%)	0.13
Liver disease	0	31(38.3%)	0.002*
Concomitant medication	0	16(19.8%)	0.01
Others	0	1(1.2%)	<0.001*

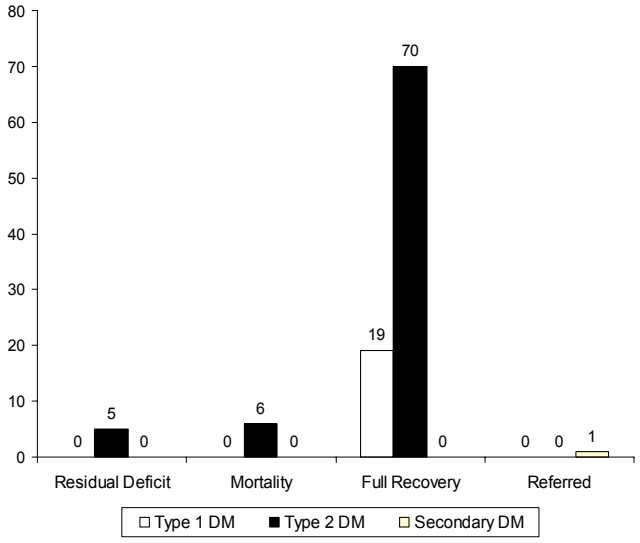
**P-value <0.01 is highly significant.* *P value ≤0.05 is significant.*

TABLE III:
CLINICAL FEATURES OF DIABETIC PATIENTS

Symptoms	Type 1 DM (n=19)	Type 2 DM (n=81)	P value
Palpitation	9(47.4%)	31(38.3%)	0.36
Pallor	10(52.6%)	3(3.7%)	<0.001*
Tremor	3(15.8%)	25(30.9%)	0.12
Sweating	11(57.9%)	34(42.0%)	0.24
Focal signs	0	5(6.2%)	<0.001*
Fits	1(5.3%)	6(7.4%)	0.003*
Coma I	0	4(4.9%)	<0.001*
Coma IV	2(10.5%)	9(11.1%)	0.02
Weakness	0	14(17.3%)	0.009
Chest pain	0	2(2.5%)	<0.001*

**P-value <0.01 is highly significant.*
P value ≤0.05 is significant.

FIGURE I:
OUTCOME AMONG STUDY SUBJECTS (n=101)



DISCUSSION

Diabetes mellitus is a major health problem and hypoglycemia is an important issue in its management. A comprehensive study of the problem should be based upon clinical assessment as well as biochemical and laboratory investigations, including correlation of blood glucose concentration with levels of insulin.

Type-1 diabetics formed the smaller group (19 patients). All patients had a blood glucose level less than 50mg/dl. One (5.2%) had asymptomatic hypoglycemia, 4 (21.0%) had documented hypoglycemia, while severe hypoglycemia was observed in 14 (73.6%) patients. The data given in various international studies are for all diabetic patients and not just those with hypoglycemia and are, therefore, not comparable. All the patients had previous episode of hypoglycemia and had dosage manipulation, but 2 had history of missed meals. DCCT results also show missed meals and previous episodes as significant conventional risk factors[9]. Type-2 diabetics were mostly above the age of 40, except few who were below 40. In a study by Ben-Ami-H and colleagues comprising of 102 diabetic patients, old age has been correlated with the severity of hypoglycemia[10] but our data indicate that our population can develop severe hypoglycemia at a much earlier age.

Majority of the patients were receiving sulphonylureas with Metformin or Thiozolidinediones 71 (87.6%), followed by insulin 7 (8.6%). Three (3.7%) patients were not on any medication. Glibenclamide was the most commonly used hypoglycemic agent in 51 (62.9%) patients. This is in accordance with previous observations that Glibenclamide having a longer half-life and being a more potent hypoglycemic agent is frequently associated with hypoglycemia, but this can be a representation of prescribing patterns in a particular area as indicated in a study from Singapore[11].

Missed or delayed meal was responsible in 19 (23.4%) patients, 21 (25.9%) patients had history of over-exertion and 37 (45.6%) patients had recent change in dose, while 4 (4.9%) had no any apparent cause. Previous diabetic control was poor in majority of the patients i.e. 56 (69.1%), adequate in 19 (23.4%) patients and 6 (7.4%) patients had no record. Eleven (13.5%) patients had past history of hypoglycemia. This is in sharp contrast with type-1 diabetics, where 14 (73.6%) patients had dosage manipulation, 3 (15.7%) patients had history of over work and 2 (10.5%) patients had missed meals. All patients had past hypoglycemic episodes.

Severe hypoglycemia (SH) occurs as a consequence of a specific combination of numerous interacting biological and behavioral risk factors, such as inadequate counter regulation, intensive therapy, low HbA1c, reduced hypoglycemic awareness, inattention, and inappropriate self-treatment[12]. As a result, a prediction of SH based on just a few factors would be modestly accurate, as evidenced by studies that accounted for 7–18% of SH variance[13, 14].

Ter Braak et al[15] studied 82% of subjects were receiving intensive insulin treatment. The occurrence of severe hypoglycemia (SH) was 150 episodes/100 patient/years and affected 40.5% of the population. Hypoglycemic coma occurred in 19% of subjects (40 episodes/100 patient/years). Hayward et al[16] found in their study that 38% of patients treated with insulin reported hypoglycemic symptoms more than once a month.

Christopher D et al[17] studied 1055 patients. Prevalence of hypoglycemic symptoms was 12% for patients treated with diet alone, 16% for those using oral agents alone and 30% for those using any insulin ($P<0.01$). Severe hypoglycemia occurred only in 0.5% patients, all using insulin. Anna M. Sawka et al[18] revealed in the systemic review literature that low socioeconomic status was found to be associated with an increased incidence of severe hypoglycemia (both variably defined) in 8 of 9 studies examined.

It has been reported that 50% of episodes of hypoglycemia in hospitalized patients are due to chronic renal failure. They showed that hypoglycemia in 5% patients was related to renal failure. The duration of the hypoglycemia is variable. Dialysis also predisposes to hypoglycemia in uremia and patients may not be aware of it. Patients with initial plasma glucose of 5.5 mmol/l (100 mg/dl) or less who are hemodialyzed and who do not eat during dialysis may be particularly at risk, especially if they are on insulin or taking glucose-lowering medication[19].

CONCLUSION

In this study Type-2 diabetics present much more commonly than type-1 diabetics with hypoglycemia in adult population. Most of adult hypoglycemic type-1 individuals are either brittle diabetics or have devel-

oped complications. Recognition of different causes of hypoglycemia in diabetes patients and prompt treatment of hypoglycemia is important to prevent complications. Type-2 diabetics are prone to hypoglycemia in the setting of cardiac disease, liver disease, infections, drugs that potentiate the effect of anti-diabetic agents, diabetic nephropathy and less commonly autonomic neuropathy. The reasons of developing hypoglycemia, most of the time, were on patient's hand. Education of patients as well as doctors is mandatory in order to recognize different causes of hypoglycemia in diabetes patients and those individuals at risk, so as to prevent an episode of severe hypoglycemia that may prove fatal. When such an episode does occur, early recognition and treatment is required to prevent morbidity and mortality especially in those who present with atypical symptoms.

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