

Risk Factors of Hypoglycemia in Diabetics

1. Zahra Nazish 2. Muhammad Inayatullah 3. Faizan Mustafa

1. Asstt. Prof. of Medicine, 2. Prof. of Medicine, 3. Post Graduate Registrar, Medical Unit-III,
Nishtar Medical College and Hospital Multan

ABSTRACT

Objective: To find the frequency of risk factors of hypoglycemia in diabetics in our setup.

Study Design: Prospective observational study

Place and Duration of Study: This study was conducted at Emergency and Medical Wards Nishtar Hospital Multan from January 2010 to December 2013.

Patients and Methods: One hundred and eighteen patients presented with hypoglycemia to Nishtar Hospital Multan. One hundred and eighteen diabetic patients above the age of 16 years admitted with hypoglycemia were included in the study. Written informed consent was taken from the patients or the attendants in case of patients with altered state of consciousness. Approval was taken from hospital ethical committee.

Results: Mean age of patients was 60.46 ± 14.20 . Forty two patients (35.6%) were males and 76 (64.4%) were females. Mean duration of diabetes was 6.4 ± 6.04 years. Mean blood glucose level at the time of presentation was 36.25 ± 12.49 mg/dl. Thirty four (28.8%) patients had only neuroglycopenic symptoms without autonomic symptoms while 4 (3.4%) had autonomic symptoms alone. Eighty (67.8%) presented with both adrenergic and neuroglycopenic symptoms. Regarding risk factors, 77 (65.25%) had renal failure, 66 (55.93%) had missed meal, 37 (31.35%) had vomiting, 23 (19.49%) had recent increased dose of hypoglycemic agents, 19 (16.10%) had delayed meal, 16 (13.55%) had diarrhea, 14 (11.86%) had liver dysfunction and 2 (1.69%) had excessive physical activity.

Conclusion: Hypoglycemia is common in old patients with long history of diabetes. Patients usually present late when they develop neuroglycopenic symptoms. Renal failure and missed meal are most common risk factors followed by vomiting and increased dosage of hypoglycemic agents. Patients need education about early symptoms of hypoglycemia, common risk factors and remedial steps to avoid this serious complication.

Key Words: Diabetes mellitus, Hypoglycemia, Risk Factors.

INTRODUCTION

Diabetes mellitus is very common and hypoglycemia is its serious complication as a result of strict glycemic control. It can lead to neuronal damage and even sudden death. There are number of risk factors which can be identified to avoid this dreadful complication.

Diabetes mellitus is very common all over the world as well as in Pakistan. It has affected 240 million people worldwide and the number could increase up to 380 million by 2025.¹ According to a survey done by Shera AS et al, the prevalence of Diabetes in Pakistan in the urban versus the rural areas was 6.0% in men and 3.5% in women against 6.9% in men and 2.5% in women respectively.²

Diabetes causes microvascular complications which can be prevented by strict glycemic control. Hypoglycemia is a well-recognized complication of treatment of diabetes mellitus and also a barrier in its management.³ Attempts made at intensive glycemic control is associated with increase in the risk of hypoglycemia. It is defined as reduction in blood glucose to a level that induces symptoms and signs. Glucose level at which an individual becomes symptomatic is highly variable, threshold generally is less than 70 mg/dl.⁴ The clinical syndrome is documented by Whipple's triad: symptoms consistent

with hypoglycemia, a low plasma glucose concentration, and relief of those symptoms when plasma glucose is raised.⁵

Patients present with autonomic symptoms like palpitations, tremors, sweating and neuroglycopenic symptoms like confusion, fits and loss of consciousness. Normally autonomic symptoms precede neuroglycopenic symptoms and allow early warning and self-treatment. Failure to recognize autonomic symptoms of hypoglycemia is called hypoglycemia unawareness. It occurs due to impairment of counter regulatory system.⁶ It is seen in patients with frequent hypoglycemic episodes. It can lead to severe hypoglycemia which is defined as hypoglycemia requiring medical treatment.

Severe hypoglycemia can cause neural damage, impaired cognitive function or even death.⁷ Severe hypoglycemia is also strongly associated with cardiovascular disease. Hypoglycemia can lead to a prothrombotic state which can predispose to cardiac ischemia. Alterations in ventricular repolarization can be the cause of sudden death.^{8,9}

Various risk factors have been identified like old age, long duration of diabetes mellitus, hypoglycemia unawareness, renal insufficiency, alcoholism, missed meal and poly pharmacy in different studies.^{11-15, 20-25}

MATERIALS AND METHODS

This study was carried out at emergency and medical wards of Nishtar Hospital Multan from January 2010 to December 2013. One hundred and eighteen diabetic patients above the age of 16 years admitted with hypoglycemia were included in the study.

Written informed consent was taken from the patients or the attendants in case of patients with altered state of consciousness. Approval was taken from hospital ethical committee.

Detailed history was taken regarding symptoms, duration of diabetes, family history of diabetes mellitus, medications with doses, meal timings or any excessive physical activity. Detailed examination was done including blood pressure and pulse at presentation and

after hypoglycemia was corrected. Blood samples for blood glucose, renal parameters and liver function tests were sent to central lab Nishtar Hospital. All details were filled in a Proforma.

RESULTS

The age of patients ranged from 20 to 96 years with a mean age of 60.46 ± 14.20 . Forty two patients (35.6%) were males and 76 (64.4%) were females. Duration of DM ranged from one day to 35 years with a mean duration of 6.4 ± 6.04 years. Family history of diabetes mellitus was present in 29 (24.57%) patients. (Table I) Blood glucose levels at the time of presentation ranged from 10 to 60mg/dl with a mean of 36.25 ± 12.49 mg/dl.

Table No.I:-Demography

	Oral Drugs (N=78)	Insulin (N=25)	Oral Drugs + Insulin (N=15)	Total(N=118)
Age (Mean)	62.51 ± 12.39	55.40 ± 18.76	58.20 ± 12.75	60.46 ± 14.20
<50	07(8.97%)	08 (32%)	03 (20%)	18 (15.3%)
≥50	71(91.03%)	17 (68%)	12 (80%)	100 (84.7%)
Sex				
Male	23 (29.48%)	10 (40%)	09 (60%)	42 (35.6%)
Female	55 (70.51%)	15 (60%)	06 (40%)	76 (64.4%)
Duration of DM (Mean)	5.77 ± 5.40	8.35 ± 7.61	6.75 ± 6.00	6.4 ± 6.04
<5yrs	42(53.84%)	12 (48%)	08 (53.33%)	62 (52.5%)
≥5yrs	36(46.15%)	13 (52%)	07 (46.66%)	56 (47.5 %)
Family history	20(25.64%)	08 (32%)	01 (6.66%)	29 (24.57%)

DM=Diabetes Mellitus

Values are presented as mean \pm standard deviation or number(% of total number)

Table No.2: Clinical presentation of patients of hypoglycemia

		Oral Drugs (N=78)	Insulin (N=25)	Oral Drugs + Insulin (N=15)	Total (N=118)
Neuroglycopenic symptoms	Unconsciousness	68 (87.17%)	15 (60%)	09 (60%)	92 (77.96%)
	Confusion	42 (53.84%)	12 (48%)	07 (46.66%)	61 (51.69%)
	Seizures	06 (7.69%)	09 (36%)	05 (33.33%)	20 (16.94%)
Adrenergic symptoms	Sweating	41 (52.56%)	18 (72%)	10 (66.66%)	69 (58.47%)
	Tremor	22 (28.20%)	09 (36%)	02 (13.33%)	33 (27.96%)
	Palpitations	17 (21.79%)	06 (24%)	02 (13.33%)	25 (21.18%)
	Paresthesia	03 (3.84%)	01 (4%)	0 (0%)	04 (3.38%)
	Hunger	02 (2.56%)	01 (4%)	01 (6.66%)	04 (3.38%)
Signs	Tachycardia	60 (76.92%)	16 ((64%)	13 (86.66%)	89 (75.42%)
	Pallor	56 (71.79%)	17 (68%)	09 (60%)	82 (69.49%)
	Sweating on exam	40 (51.28%)	18 (72%)	10 (66.66%)	68 (57.62%)

Regarding clinical presentation, 92 (77.96%) patients were unconscious, 69 (58.47%) had sweating, 61 (51.69%) presented with confusion, 33(27.96%) had tremors, 25(21.18%) had palpitations, 20 (16.94%) had seizures, 4 (3.38%) had hunger and 4(3.38%) had paresthesia. On examination, 89 (75.42%) patients had

tachycardia, 82(69.49%) had pallor, clinical evidence of sweating was present in 68(57.62%). (Table 2)

Over all 114(96.6%) patients presented with neuroglycopenic symptoms and 84(71.2%) presented with adrenergic symptoms. Eighty patients (67.8%) presented with both adrenergic and neuroglycopenic symptoms. Thirty four (28.8%) patients had only

neuroglycopenic symptoms without adrenergic symptoms while 4(3.4%) had adrenergic symptoms alone without neuroglycopenic symptoms. (Table 3) Regarding risk factors evaluation, 77(65.25%) patients had renal failure, 66(55.93%) had missed meal, 37(31.35%) had vomiting, 23(19.49%) had increased dose of hypoglycemic agent, 19(16.10%) had delayed meal, 16(13.35%) had diarrhea, 14 (11.86%) had liver dysfunction and 2(1.69%) had excessive physical activity. (Table 4)

We divided the patients into three groups according to the treatment being taken: 78 (66.10%) patients were taking oral hypoglycemic drugs, 25 (21.18%) were on insulin and 15 (12.71%) patients were taking a combination of oral drug and insulin.

Demography, clinical presentation, comparison of neuroglycopenic and adrenergic symptoms and frequency of risk factors in these three groups is as shown in Table 1 to 4.

Table No.3: Comparison of Neuroglycopenic and Adrenergic symptoms

	Oral Drugs (N=78)	Insulin (N=25)	Oral Drugs + Insulin(N=15)	Total (N=118)
Neuroglycopenic symptoms	77(98.71%)	23(92%)	14(93.33%)	114 (96.6%)
Adrenergic symptoms	51(65.38%)	21(84%)	12(80%)	84 (71.2%)
Adrenergic + Neuroglycopenic symptoms	50(64.10%)	19(76%)	11((73.33%)	80 (67.8%)
Neuroglycopenic symptoms without Adrenergic symptoms	27(34.61%)	4(16%)	3(20%)	34(28.8%)
Adrenergic symptoms without Neuroglycopenic symptoms	01(1.28%)	2(8%)	1(6.66%)	4 (3.4%)
Without Adrenergic or Neuroglycopenic symptoms	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table No.4: Frequency of risk factors of hypoglycemia

Risk factors	Oral drugs (N=78)	Insulin(N=25)	Oral Drugs + Insulin (N=15)	Total (N=118)
Renal failure	53 (67.94%)	15 (60%)	09 (60%)	77 (65.25%)
Missed meal	46 (58.97%)	10 (40%)	10 (66.66%)	66 (55.93%)
Vomiting	24 (30.76%)	07 (28%)	06 (40%)	37 (31.35%)
Increased dose	09 (11.53%)	06 (24%)	08 (53.33%)	23 (19.49%)
Delayed meal	14 (17.94%)	03 (12%)	02(13.33%)	19 (16.10%)
Diarrhea	14 (17.94%)	02 (8%)	0 (0%)	16 (13.55%)
Hepatic dysfunction	07 (8.97%)	02 (8%)	05 (33.33%)	14 (11.86%)
Excessive physical activity	02 (2.56%)	0 (0%)	0 (0%)	02 (1.69%)

DISCUSSION

According to UK Prospective Diabetes Study and Diabetes Control and Complication Trial, strict blood glycemic control is necessary for management of diabetes to prevent its micro and macro vascular complications. However this can increase the risk of hypoglycemic events which is the most undesirable side effect of anti-diabetic drugs. This serious iatrogenic complication can be sometimes fatal.¹⁰

Identification of risk factors of hypoglycemia is necessary to predict and reduce its frequency. Many studies have been done to find these risk factors. Purpose of our study was to identify the common risk factors of hypoglycemia in diabetics in our setup so that we can educate our patients about their prevention.

In our study we found that hypoglycemia is more common in old age as mean age of patients was 60.46±14.20 years. Linn YY et al found mean age of 74.1± 9.8years.¹¹ Burderer et al observed that mean age of patients was 61.7 ± 13.0 years.¹² Shorr et al also

found that advanced age is a risk factor for hypoglycemia.¹³

In our study 64.4% patients were females. Allen et al observed that 60.5% patients were females.¹⁴ Heller et al found that 70% patients were males.¹⁵ So hypoglycemia can occur in both females and males. Although the prevalence of diabetes is higher in men than in women.^{2,16}

In our study mean duration of diabetes was 6.44 ± 6.04 years which is much shorter than that reported by Heller et al who observed that mean duration of diabetes was 29.8 years in type 2 diabetics.¹⁵ Allen et al also found that hypoglycemia is associated with longer duration of diabetes.¹⁴ So patients with long duration of diabetes should be well educated about risk factors of hypoglycemia and their prevention.

Out of 118 patients, 66.10% were taking oral drugs, 21.18% were on Insulin and 12.71% were taking both oral drugs and insulin. These results are comparable with a study done by Ha et al (65.9% were on oral drugs, 29% on insulin and 5% on both insulin and oral drugs).¹⁷ But we cannot conclude that hypoglycemia is

more common with oral drugs without knowing the percentage of diabetic patients taking oral drugs. Perhaps we have more type 2 diabetic patients taking oral drugs in our population. Although oral hypoglycemic drugs are known to cause severe hypoglycemia requiring hospital admission in patients with chronic kidney disease.¹⁸

Regarding clinical presentation we observed that 28.8% patients presented with neuroglycopenic symptoms alone without preceding adrenergic symptoms indicating hypoglycemia unawareness. Similar to our study Burge et al found hypoglycemia unawareness in 25% cases.¹⁹ In a study done by Leese et al, 36% patients presented with coma.²⁰ Feher et al observed fits and coma in 49% patients.²¹ While in some other studies frequencies observed were much less (5% and 8% by Muhlhauser et al²² and Henderson et al²³ respectively). Patients with impaired awareness of hypoglycemia could have a high risk of severe hypoglycemia.

This indicates that very few patients present early and our patients have very little education about these warning symptoms of hypoglycemia. They are brought to the hospital when they develop altered consciousness.

In our study only 3.4% patients presented with adrenergic symptoms alone. Over all 67.8% patients presented with both neuroglycopenic and adrenergic symptoms. Our study indicated that majority of our patients present late. Either our patients are not aware of early symptoms of hypoglycemia or even if they are aware, they don't react to manage them. Or perhaps patients with these early symptoms are treated by local doctors and don't present to tertiary care hospitals. All clinicians must educate their diabetic patients about these warning symptoms and advise them to take some sweet food which otherwise is restricted in their diets.²⁴

Regarding risk factors of hypoglycemia in our study the most common was renal impairment found in 65.25% patients. Similarly many other studies done by Lin YY et al, Krinsley et al and Koster et al also showed that renal insufficiency was a risk factor for hypoglycemia.^{11,25,26} This is due to longer half-life of medicines that need renal excretion. As well as decreased renal gluconeogenesis in patients who are also anorexic. All clinicians must monitor serum creatinine levels in diabetics. A serum creatinine level of more than 2mg/dl is a contraindication for most oral drugs; these should be replaced by safer drugs or insulin.²⁷ Targets of glycemic control should also be relaxed in renal dysfunction.

A common risk factor of hypoglycemia in diabetics is delayed or missed meal as observed in some other studies.^{11,28} In our study 55.93% gave history of missed meal while 16.10% delayed their meals. Burge et al found that 80% cases of hypoglycemia were due to missed meal.¹⁹ In our study 31.35% patients took their meals but they vomited either due to renal failure or due to gastropathy also common in diabetics. For prevention of hypoglycemia all patients must know the

importance of taking their meal within 30 minutes of injection of insulin or intake of oral anti-diabetics. Similarly, if patient has diarrhea and/or vomiting hypoglycemia can occur. In this situation blood glucose should be monitored and patient should immediately contact nearby hospital for parenteral nutrition.²⁴

Excessive dosage of anti-diabetics is also a cause of hypoglycemia. In our study 19.49% gave history of recent increase in their doses of anti-diabetic drugs either by their doctors or by themselves. Feher et al observed increased dose of insulin as a predisposing factor in 17% hypoglycemic patients.²¹ Ha et al observed change in the dose of current medication in 12.5% cases of hypoglycemia.¹⁷ Burge et al also observed that drug over dosage is a risk factor for hypoglycemia.¹⁹ Patients should never attempt to increase the doses of anti-diabetic drugs without advice of their physician.

Coexistence of chronic liver disease in a diabetic patient is also a risk factor for hypoglycemia.²⁹ In our study 11.86% patients had abnormal liver function tests. Burge et al also observed liver disease as a risk factor of hypoglycemia.¹⁹ Liver has important role in glucose homeostasis. Some anti-diabetic drugs are contraindicated or their doses need to be reduced in liver dysfunction. Targets of glycemic control should also be relaxed in hepatic dysfunction.³⁰

Unaccustomed physical activity is another risk factor which should be avoided or extra meal should be taken before such activity. Although in our study we found that only 1.69% patients gave history of unaccustomed exercise. Burge et al also observed that strenuous exercise can cause hypoglycemia.¹⁹ Feher et al observed exercise as a predisposing in 12% cases¹⁸ while Ha et al observed it in 9% cases.²¹ Lesser frequency of exercise as a risk factor in our study could be due to sedentary life style of our patients. Diabetic children, athletes and players should take extra meal before starting the play. Patients should carry a fast acting carbohydrate when they exercise.²⁴

CONCLUSION

Hypoglycemia is common in old patients with long history of diabetes. Patients usually present late when they develop neuroglycopenic symptoms. Renal failure and missed meal are important risk factors of hypoglycemia in our patients followed by vomiting, increased dosage of hypoglycemic agents, delayed meal, diarrhea, liver dysfunction and excessive physical activity. Patients need education about early symptoms of hypoglycemia as well as about common risk factors to avoid this serious complication. Important preventive measures include monitoring renal parameters and adjustment of treatment accordingly, emphasis in the instruction about regularity of meals, monitoring blood glucose levels in case of diarrhea, vomiting and liver dysfunction and avoiding unaccustomed exercise or taking an extra meal prior to it.

REFERENCES

1. Qidwai W, Ashfaq T. Imminent Epidemic of Diabetes Mellitus in Pakistan: Issues and challenges for Health care providers {editorial}. *JLUMHS* 2010;9(3):112-3.
2. Shera AS, Jawad F, Maqsood A. Prevalence of Diabetes in Pakistan. *Diabetes Res Clin Pract* 2007;76(2):219-22
3. Cryer PE. The Barrier of Hypoglycemia in Diabetes. *Diabetes* 2008;57(12):3169-76.
4. American Diabetes Association work group on Hypoglycemia. Defining and reporting Hypoglycemia in Diabetes. *Diabetes Care* 2005;28:1245-9.
5. Whipple AO. The surgical therapy of hyperinsulinism. *J Int Chir* 1938;3:237-76
6. Kalra S, Mukherjee JJ, Venkataraman S, Bantmal G, Shaikh S, Saboo B, et al. Hypoglycemia : The neglected complication. *Indian J Endocrinol Metab* 2013;17(5): 819-34.
7. Languren G, Montiel T, Julio-Amilpas A, Massieu L. Neuronal damage and cognitive impairment associated with hypoglycemia: An integrated view. *NeurochemInt* 2013;63(4):331-43.
8. Frier BM, Scherthaner G, Heller SR. Hypoglycemia and cardiovascular risks. *Diabetes Care* 2011;34(1):132-7.
9. Robinson RT, Harris ND, Ireland RH, Lee S, Newman C, Heller SR. Mechanisms of abnormal cardiac repolarization during insulin induced hypoglycemia. *Diabetes* 2003; 52(6): 1469-74.
10. Davis S, Alonso M. Hypoglycemia as a barrier to glycemic control. *J Diabetes Complications* 2004; 18(1):60-8.
11. Lin YY, Hsu CW, Sheu WH, Chu SJ, Wu CH, Tsai SH. Risk factors for recurrent hypoglycemia in hospitalized diabetic patients admitted for severe hypoglycemia. *YMJ* 2010; 51(3): 367-74.
12. Bruderer SG, Bodmer M, Jick SS, Bader G, Schlienger RG, Meier CR. Incidence of and risk factors for hypoglycemia in treated type 2 diabetes mellitus patients in the UK – a nested case-control analysis. *Diabetes Obes Metab* 2014;doi: 10.1111/dom.12282.
13. Shorr RI, Ray WA, Daugherty JR, Griffin MR. Incidence and risk factors for serious hypoglycemia in older persons insulin and sulfonylureas. *Arch Intern Med* 1997;157(15): 1681-86
14. Allen C, Le Caire T, Palta M, Daniel K, Meredith M, D'A Lessio DJ. Risk factors for frequent and severe hypoglycemia in type 1 Diabetes Mellitus. *Diabetes Care* 2001; 24(11): 1878-8.
15. Heller SR, Choudhary P, Davies C, Emery C, Campbell MJ, Freeman J, et al. Risk of hypoglycemia in type 1 and 2 diabetes: Effect of treatment modalities and their duration. *Diabetologia* 2007;50(6):1140-47.
16. American Diabetic Association: Statistics about Diabetes. Data from 2011 National Diabetes fact sheet (released Jan 26, 2011).
17. Ha WC, Oh SJ, Kim JH, Lee JM, Chang SA, Sohn TS, et al. Severe hypoglycemia is a serious complication and becoming an economic burden in diabetes. *Diabetes Metab J* 2012;36(4):280-4.
18. Chen SY, Lee YC, Alas V, Greene M, Brixner D. Outcomes associated with concordance of oral antidiabetic drug treatments to prescribing information in patients with type 2 diabetes mellitus and chronic kidney disease. *J Med Econ* 2013;16(5): 586-95.
19. Burge MR, Fiorentino KS, Fischette C, Qualls CR, Schade DS. A Prospective trial of risk factors for Sulfonylurea-Induced hypoglycemia in type 2 Diabetes Mellitus. *JAMA* 1998; 279(2): 137-43
20. Leese GP, Wang J, Broomhall J, Kelly P, Marsden A, Morrison W, et al. Frequency of severe hypoglycemia requiring emergency treatment in Type 1 and Type 2 Diabetes. *Diabetes Care* 2003; 26(4):1176-80.
21. Feher MD, Grout P, Kennedy A, Elkeles RS, Touquet R. Hypoglycemia in an inner city accident and emergency department: a 12 month survey. *Arch Emerg Med* 1989;6(3):183-8.
22. Mulhauser I, Overmann H, Bender R, Bott U, Berger M. Risk factors of severe hypoglycemia in adult patients with Type 1 Diabetes- A prospective population based study. *Diabetologia* 1998;41: 1274-82.
23. Henderson JN, Allen KV, Deary IJ, Frier BM. Hypoglycemia in Insulin treated type 2 Diabetes: frequency, symptoms and impaired awareness. *Diabet Med* 2003; 20(12):1016-21.
24. Nazish Z. Prevention and Management of Hypoglycemia in Diabetics {editorial}. *NMJ* 2010; 2(3): 67-8.
25. Krinsley JS, Grover A. Severe hypoglycemia in critically ill patients: risk factors and outcome. *Critical Care Med* 2007; 35(10): 2262-67.
26. Koster K, Dippel FW, Rathman W. Predictors of hypoglycemia in insulin treated type 2 diabetes patients in primary care: A retrospective data base analysis. *Prim Care Diabetes* 2013;9918(13):117-4.
27. Cavanaugh K L. Diabetes Management Issues for Patients with Chronic Kidney Disease. *Clin Diabetes* 2007;25:390-97.
28. Cryer PE, Davis SN, Shamon H. Hypoglycemia in Diabetes. *Diabetes Care* 2003; 26: 1902-12.
29. Gundling F, Seidl H, Strassen I, Haller B, Siegmund T, Umgelter A, et al. Clinical manifestations and treatment options in patients with cirrhosis and diabetes mellitus. *Digestion* 2013;87(2):75-84.
30. Khan R, Foster GR, Chowdhury TA. Managing diabetes in patients with chronic liver disease. *Postgrad Med* 2012;124(4):130-7.