

Major cardiovascular and neurological events among diabetic patients with severe hypoglycaemia at a tertiary care hospital in Bangladesh

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ABSTRACT

Background: Cardiovascular disease (CVD) is a major cause of death and disability among people with diabetes mellitus (DM). Hypoglycemia is a potential risk factor to augment life threatening CVD. This study intended to find out impact of severe hypoglycemia in adverse cardiovascular and neurological events among patients with DM.

Methods: This cross-sectional study was conducted among diabetic patients with severe hypoglycemia (plasma glucose <70 mg/dl or 3.9 mmol/l) admitted in BIRDEM General Hospital from March 2014 to April 2015. Patients were categorized into two groups depending on blood glucose values (group A <2.8 and group B e"2.8) for analytical purpose. Major cardiac events including acute myocardial infarction (MI), non ST elevated MI or arrhythmia were observed along with neurological outcome including acute stroke, hypoglycemic encephalopathy and convulsion by both relevant clinical examinations and investigations as appropriate. Data were collected at discharge or death if any.

Results: Among the 311 patients, 62% were in the age group of 51 to 60 years with mean age 49.02 years. Mean duration of DM was 8.5 (±5.4) years and in 85.5% cases HbA1c was e"7%. Majority was on insulin (79.41%); predominantly on premixed (33.5%) and self mixed (35.7%) regime. Meal related factors ($p < 0.001$) e.g., delayed or missed meal, insulin related factors ($p < 0.001$) e.g., miscalculation, overdosing were significant predisposing factors for developing hypoglycemia. Multivariate analysis revealed frequency of hypoglycemia was more in diabetic nephropathy ($p < 0.01$), chronic liver disease ($p = 0.01$), gastroparesis ($p = 0.01$), cognitive impairment ($p < 0.001$), established CVD ($p = 0.02$) and adrenal insufficiency ($p < 0.01$). Nocturnal hypoglycemia (33.80%) and hypoglycemic unawareness (44.23%) was also observed among the participants. Cardiovascular events were found in 98 (31.55%) individuals which included any form of arrhythmia ($p = 0.02$), non ST elevated MI ($p = 0.08$) and ST elevated MI ($p < 0.008$). Among the neurological events ($n = 67$, 21.54%), hypoglycemic encephalopathy ($p < 0.02$) and acute stroke ($p = 0.01$) were significant. Seizure happened in 15 individuals ($p = 0.53$). Nine patients died (death rate 2.89%). Predominant cause of death was acute MI (6, 66%) and hypoglycemic encephalopathy (3, 33.33%).

Conclusion: The major finding of this study suggest that severe hypoglycemia is strongly associated with fatal cardiovascular and neurological events including MI, acute stroke and hypoglycemic encephalopathy in diabetic patients predominantly treated with insulin. Mortality was found in 2.89% participants. Co morbidities including renal disease, liver disease, gastroparesis, cognitive impairment increased the vulnerability of developing severe hypoglycemia. In most of the cases, lifestyle factors are the precipitating causes of hypoglycemia, which are readily recognizable and easily modifiable. Therefore, appropriate diabetic education and periodic reevaluation of patient's knowledge, attitude and practice towards hypoglycemia is of utmost importance to prevent this common but life-threatening complication.

Key words: severe hypoglycemia, cardiovascular events, neurological events.

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INTRODUCTION

Severe hypoglycaemia is one of the major concerns in diabetes treatment. The potential life threatening effects of hypoglycaemia in cardiovascular system is well documented.^{1,2} Although the intensive treatment strategy in minimizing complications has been advocated by landmark studies previously^{3,4} but the disconcerting outcome and the potential dangers of hypoglycaemia have been highlighted in recent trials and epidemiological cohort which implicated in excess mortality.^{2,5,6} Hence, individualized targets of glycemic status has been emphasized by American Diabetes Association (ADA) particularly in patients with long duration of diabetes mellitus and co-morbidities to reduce the risk of hypoglycemia⁷

The surge of sympathetic activity during hypoglycemic episodes has been suggested to be the underlying mechanism leading to destabilization of atherosclerotic plaques⁸, increased arrhythmia attributable to increased corrected QT interval⁹ and induction of cardiac and cerebral ischemia. Recently, the ADVANCE study suggested that hypoglycemia is associated with increased risks of a range of adverse clinical outcomes and it is considered to be a marker for vulnerability to such events for type 2 diabetic patients.¹⁰ Whether hypoglycemia is a risk factor or a marker, it is important to evaluate the possible correlates to both hypoglycemia and serious clinical outcome, including cardiovascular and neurological events. We conducted this study to evaluate the influences of severe hypoglycemia in cardiovascular and neurological outcomes in diabetic individual.

METHODS

This cross-sectional study was conducted among the diabetic patients admitted in BIRDEM General Hospital with hypoglycemia (plasma glucose concentration of <70 mg/dl or 3.9 mmol/l) from March 2014 to April 2015. Hypoglycemia in pregnant women was not approached for the study. Sample size was calculated at 95% confidence interval with 5% precision which arrived 164 using prevalence 70%.¹¹ Patients were categorized into two groups according to blood glucose value (group A <2.8 and group B ≥2.8) for analytical purpose. Major cardiac events including acute myocardial infarction (MI), non ST elevated MI or any form of arrhythmia were observed along with neurological outcome

including acute stroke, hypoglycemic encephalopathy and convulsion by both relevant clinical examinations and investigations as appropriate. All information were rewarded at the time of discharge or death if any.

RESULTS

A total 311 patients were selected as study population including 59% male and 41% female with mean age of 49.02 years. Most were living in urban area (67.84%). Mean duration of DM was 8.5 (±5.4) years and 85.5% participants did not have good glycemic control (HbA1c ≥7%) (Table I).

Table I. Baseline characteristics of the study respondents) N = 311)

Baseline characteristics	Number (%)
Age (years)	
<50	141 (45.33)
≥50	170 (54.66)
Mean ±SD :	49.02 (±15.99)
Gender	
Male	184 (59)
Female	127 (41)
Distribution of area of residence	
Urban	211 (67.84)
Rural	100 (32.15)
Education	
<Higher secondary school certificate	231 (74.3)
> Higher secondary school certificate	80 (25.7)
Duration of DM	
<10 years	189 (60.77)
≥10 years	122 (39.22)
Mean ± SD:	8.5 (±5.4)
Glycemic status	
HbA1c <7%	45 (14.5)
HbA1c ≥7%	255 (85.5)
Mean ± SD:	8.9 (±4.9)

Table II shows co morbidities associated with hypoglycemia. Among them CKD (p<0.01), chronic liver disease(p=0.01), established CVD (p=0.02) and adrenal insufficiency (p<0.01) were significantly associated with hypoglycemia.

Table II. Co morbidities associated with hypoglycemia

Co-morbidities	Hypoglycemia Blood sugar level		Total	OR; 95% CI	p value
	<2.8mmol/l	≥2.8mmol/l			
CKD	159	55	214	0.44(0.23-0.86)	<0.01
*CVD risk factors	57	10	67	1.77(0.85-3.70)	0.12
**Established CVD	33	17	50	0.47(0.24-0.91)	0.02
Autonomic Neuropathy	51	08	59	1.99(0.89-4.42)	0.08
CLD	32	02	34	5.0(1.16-21.44)	0.01
Malignancy	41	09	50	1.33(0.61-2.89)	0.47
Adrenal insufficiency	36	41	77	0.11(0.06-0.20)	<0.01

Level of significance was assessed by Chi-Square test *CV risk factors : HTN, Proteinuria, LV systolic or diastolic dysfunction, ankle brachial pressure index 0.9, **Established CVD : prior MI , stroke, revascularization, documented symptomatic CHD,

Table III shows factors responsible for hypoglycaemia. Meal related factors (p <0.001), insulin related factors (p<0.001), Ageing (>50) (p=0.04) ,gastroparesis (p=0.01) and cognitive impairment(p<0.001) contributed significantly in causing hypoglycaemia

Table III. Factors responsible for hypoglycemia

Factor responsible	Blood Glucose level		Total	OR; 95% CI	p value
	<2.8mmol/l	≥2.8mmol/l			
*Meal related factors	173	31	204	2.95(1.69-5.12)	<0.001
**Insulin related factor	66	05	71	4.69(1.81-12.19)	<0.001
Unaccustomed physical exertion	32	08	40	1.13(0.49-2.59)	0.76
Ageing (>50)	26	02	28	3.95(0.91-17.10)	0.04
Gastro paresis	32	02	34	5.0(1.16-21.44)	0.01
Infection	12	02	14	1.71(0.37-7.85)	0.48
Cognitive impairment	17	52	69	11.39(6.96-18.65)	<0.001

Level of significance was assessed by Chi-Square test *meal related factors: delayed meal, missed meal, inadequate meal,** insulin related factors : overdosing, miscalculation, insulin syringe mismatch, lipoatrophy of skin,

Table IV shows cardiac outcome among the study respondents. Acute ST elevated myocardial infarction was significantly associated with hypoglycaemia (p 0.003) along with arrhythmia (p 0.02). Pattern of arrhythmia was distributed as follows, atrial /ventricular ectopic (n=19,61%) , atrial fibrillation (n= 7,22.58%) supraventricular tachycardia (n=2,6.45%) and ventricular tachycardia (n=1 ,3.22%)

Table IV. Cardiac outcome in study respondents

Cardiac outcome	Blood Glucose level		Total	OR; 95% CI	p value
	<2.8mmol/l n=243	≥2.8mmol/l n=68			
*Arrhythmia	29	02	31	4.47(1.03-19.24)	0.02
Non ST elevated MI	36	16	52	0.56(0.29-1.09)	0.08
Acute ST elevated MI	07	08	15	0.22(0.07-0.63)	0.003

Level of significance was assessed by Chi-Square test. * any form of atrial and ventricular tachy/brady arrhythmia were included. Atrial /ventricular ectopic (n=19,61%) , Atrial fibrillation (n= 7,22.58%) Supraventricular tachycardia (n=2,6.45%) Ventricular tachycardia (n=1 ,3.22%)

Table V shows neurological outcome of hypoglycemia. Convulsion, acute stroke and hypoglycaemic encephalopathy were observed among the study group but hypoglycaemic encephalopathy was significantly

associated with severe hypoglycaemia (p 0.02). Mortality rate following severe hypoglycaemia was 2.89 % among the study respondents. Predominant cause of death was acute myocardial infarction 6 (66%) and hypoglycemic encephalopathy 3(33.33%).

Table V. Neurological outcome of study respondents

Neurological outcome	Blood Glucose level		Total	OR;95% CI	p value
	<2.8mmol/l _n =243	≥2.8mmol/l _n =68			
Convulsion	13	02	15	1.87(0.39-12.29)	0.53
Acute stroke	01	—	01	-	1.0
Hypoglycemicencephalopathy	46	05	51	2.85(1.03-8.55)	0.02

Level of significance was assessed by Chi-Square test

DISCUSSION

Hypoglycemia has been associated with major adverse cardiovascular outcomes in diabetic patients beyond hypoglycemic episodes themselves. Several epidemiological cohort and clinical trials has already reported hypoglycemia as a risk factor of cardiovascular outcome in recent years.^{2,13,14} Though post hoc analysis from this trails suggest that the excess mortality may not be the direct causality of severe hypoglycemia but surely a marker of vulnerability for adverse cardiovascular outcome. Our hospital based study was conducted among 311 diabetic patients who were having severe hypoglycemia to find out the correlates and impact of hypoglycemia in cardiovascular fatality. In demographic analysis age (>50 years) contributed to incidence of severe hypoglycemia. This might have been because of age related cognitive impairment, multiple co-morbidities and attenuated sympathoadrenal response to hypoglycemia. In this study more than eighty percent patients who experienced severe hypoglycemia had HbA1c >7%. Similar reports found in a study based on HbA1c and hypoglycemia¹⁵. Possible explanation might be lack of proper self-management education in this class of subjects. In Chicago, June 2013, ADA described association between HbA1c with self-reported hypoglycemia, though no causal pathways between this two were established. They concluded hypoglycemia was common irrespective of glycaemic status.¹²

We also evaluated the co-morbidities associated with hypoglycemia. Among them CKD, chronic liver disease, established CVD and adrenal insufficiency were significantly associated with hypoglycemia. Multiple factors were found responsible to contribute hypoglycemia in our study. Meal related factors including missed meal, delayed meal or small portion than regular intake contributed in most of the cases. Same finding in insulin related factors which also

included misunderstanding in dosing, technique or lack of sick day rule. These are the potentially reversible factors which reflect education is a prime part in diabetes management particularly patient on insulin. Third leading factor we found mental illness in any form like dementia, confusion, depression which made the scenario worse. Many previous studies focused on specific co-morbidities such as depression, dementia, CVD, stroke, cancer, history of falls, hypertension, liver cirrhosis or renal diseases. Some also suggest that hypoglycemia may be a marker for disease severity in routinely treated diabetic patients associated with multiple co-morbidities.^{16,17}

In this study, arrhythmia and acute MI were significantly associated with severe hypoglycemia which is consistent with the previous landmark studies.^{13,20} Severe hypoglycemia can induce pro-inflammatory, pro-thrombotic state and increased cardiac stress, along with potential reduction in coronary flow and predisposition to arrhythmias and fatal major cardiac events. This finding emphasize the need for individualized glycaemic target particularly in presence of multiple co-morbidities and elderly individual with pre-existing cardiac risk factors.

We also observed neurological events which was associated with severe hypoglycemia which ranges from transient stupor to seizure, coma even death. Several studies demonstrated the fact of neurological causality in response to hypoglycemia. As brain is in constant need of monosaccharide as a fuel, it is readily understandable the strong association of this fatality with hypoglycemia. More over the hierarchical hormonal stimulation in response to hypoglycemia is attenuated in diabetic individual in autonomic neuropathy and recurrent hypoglycemia thus lead to seizure, coma and even death without any warning symptoms. The death rate in our study was 2.89%. Similar finding echoed in

another study where they found headache, seizure, stroke-like episodes, cognitive dysfunction and coma as presenting feature. Among those death was 3.7%.¹² But in another study cumulative all cause mortality was fairly higher in long term follow up. In that study, the 3-year cumulative incidence of coronary heart disease was 10.8% and of mortality was 28.3% that indicates hypoglycemia not only a severe marker for acute complication but also a potent indicator of high mortality in long term. They also added hypoglycemia not only a marker of vulnerability or disease severity but also a causal factor related to this adversity.^{17,18} The finding from this study summon key monitoring in patients in severe hypoglycemia who has a potential risk of future serious adverse events including high mortality.

Conclusion

This study highlights strong association of severe hypoglycemia with both cardiovascular and neurological adverse outcome including acute MI, stroke and hypoglycemic encephalopathy. Death rate was 2.89% among the participants. This study concludes severe hypoglycemia is a potential risk factor along with causality for this adverse outcome. However, these temporal relationships necessitate the keen monitoring of glycemic status in diabetic patients which can eventually improve the overall outcome along with reduction of cardiovascular mortality with higher longevity.

Author's contribution: RSB, FA, MFA, MFP planned study RSB, FA, MFA, MFP drafted manuscript. All authors read and approved final manuscript.

Conflicts of interest: Nothing to declare.

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