Original Research

Therapy and characteristics of hypoglycemia in admitted diabetic patients

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Abstract

Hypoglycemia is a common complication of intensive diabetes mellitus therapy. This study was aimed to review the profile of admitted Libyan cases of non-pregnant adults and adolescents. A retrospective study for patients admitted to Tripoli Diabetes Hospital, Tripoli, Libya. Data were collected from medical files of diabetic patients with hypoglycemia from January 2017 to July 2018. Thus, during this period, a total of 29 cases with hypoglycemia were admitted to the hospital. Their age was ranged from 18 to 86 years in which 76.0% were female, 25.0% were non-smokers, 59.0% were married and 55.0% were non-employers. Patients with diabetes mellitus (86%) showed hypoglycemia attack per month of 3.90 ± 2.25. From the 25 cases with diabetes mellitus, 7.0% were newly diagnosed (> one year), 45.0% their duration of diabetes mellitus were more than 9 years and 35.0% were less than nine years. Their Hemoglobin A1C was on target (6.5–7.0%) in 21.0% of the cases, in which 17.0% were on below target range (< 6.5%) and 38.0% with poor control (> 7.0%). 14.0% were on glibenclamide, 3.0% on glimepiride and 69.0% on insulin. Patients on insulin therapy twice daily in 28.0%, triple in 17.0% and basal bolus regime in 24.0%. Hypoglycemia unawareness was presented in 17.0%, hypoglycemia was major in 45.0% of the cases, and in 38.0% were in daytime. Insulin induced hypoglycemia were in 66.0%, and suicidal attempt were in 10.0%. Exercise induced hypoglycemia 10.0% and 3.0% of cases with malignancy induced hypoglycemia. Co-exist systemic illness was mainly absent in 69.0% but cardiovascular diseases in 14.0% and renal diseases in 7.0%. Majority of cases were discharged in good condition (86.0%) and 14.0% discharged against medical advice. Hypoglycemia mostly occurs in patients with diabetes mellitus treated with insulin and in most the cases were reversible and saved with good management. Thus, patient education is a fundamental issue in prevention and reducing complications of hypoglycemia in patients with diabetes mellitus.

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Introduction

Iatrogenic hypoglycemia is the limiting factor in the glycemic management of diabetes mellitus (DM). It causes recurrent symptomatic and sometimes, at least temporarily, disabling episodes in most people with DM Type-1 as well as in many people with advanced DM Type-2, however, it is sometimes fatal [1]. Hypoglycemia is verified by Whipple's triad, as low plasma glucose level calculated with an accurate technique and disappear of the symptoms following the plasma glucose level is elevated.

In non-diabetes known as spontaneous hypoglycemia [2]. Hypoglycemia considerably influences on person's quality of life, their work, social communications and transporting [3]. The classification of hypoglycemia in

diabetes includes: severe hypoglycemia, documented symptomatic hypoglycemia, asymptomatic hypoglycemia, probable symptomatic hypoglycemia and relative hypoglycemia. People with DM greatly feared from hypoglycemia that has main barrier to achieve target control of blood sugar [2]. Common causes and risk factors such as medical issues like rapid improvement in and/or strict glycemic control, previous severe hypoglycemia, impaired awareness of hypoglycemia, long-duration Type-I diabetes, duration of insulin therapy in DM Type-II [3]. In addition, lipo-hypertrophy at injection sites causing variable insulin absorption, severe hepatic dysfunction, impaired renal function, inadequate treatment of previous hypoglycemia, terminal illness, bariatric surgery involving bowel resection and unrecognized other endocrine disorders, e.g. Addison's disease, as well as reduced carbohydrate intake for example: gastroparesis due to autonomic neuropathy causing variable carbohydrate absorption, malabsorption, e.g. coeliac disease, eating disorders. With life-style issues such as exercise, irregular lifestyle, increasing age, alcohol, early pregnancy and breast-feeding, no or inadequate glucose monitoring and factitious (deliberately induced) [3]. In hypoglycemia, physiological warning signs, sequences of responses comprising reduction in insulin secretion as glucose levels decreases within the physiological range, increases in glucagon and epinephrine secretions as glucose levels decline below the physiological range and more powerful sympatho-adrenal response with symptoms at plasma glucose levels of 50 - 55 mg per dl (2.8 - 3.0 mmol/l) [4]. Neurogenic (autonomic) symptoms (catecholamine mediated or adrenergic: tremors, palpitations and anxiety/arousal and acetylcholine mediated or cholinergic: sweating, hunger and paresthesia) are due to mainly sympathetic neural activation [5]. Neuroglycopenic symptoms (cognitive impairments, behavioral changes and psychomotor abnormalities and at lower glucose levels seizure and coma). The glycemic thresholds for these responses are dynamic [4]. They shift to higher plasma glucose level in people with poorly controlled DM Type-I and to lower plasma glucose levels in those with well controlled DM Type-I [6]. Characteristically, hypoglycemia induced functional brain failure is improved following the plasma glucose levels is elevated [4]. Rarely, hypoglycemia leads to sudden, possible cardiac arrhythmic, death or, if it is prolonged and severe, brain death [7]. A previous study revealed hypoglycemia causes 2 - 4% of deaths of people with diabetes and recent report shows that 6.0 - 10.0% of deaths of people with DM Type-I are due to hypoglycemia [4, 8].

The American Diabetes Association (ADA) Workgroup suggested that people with DM Type-I become worried about risk of hypoglycemia at a self-monitored plasma glucose level of ≤ 70 mg per dl (3.9 mmol/l) [9]. The source for that cut-off value is that, within the error of these amounts, 70 mg per dl approximates the lower limit of the post-absorptive plasma glucose concentration range and the glycemic threshold for activation of glucose counter-regulatory systems and is the highest low level reported to reduce counter - regulatory responses to subsequent hypoglycemia in non-diabetic individuals [9]. In people with known DM Type-I, the first and second physiological defenses counter to hypoglycemia-insulin reduction and glucagon elevation - are missing and the third physiological defense-epinephrine release is frequently insufficient [4]. The clinical syndrome of defective glucose counter-regulation-occurs in excessive insulin dose and low plasma glucose and loss of insulin and glucagon secretory responses, the attenuated epinephrine [4] that is related to a 25-fold or more elevated risk of severe iatrogenic hypoglycemia. The attenuated sympatho-adrenal response resulted in the clinical syndrome of hypoglycemia unawareness and, thus, absent of the behavioral defense, sugar intake [4]. Hypoglycemia unawareness is related with six-fold elevated risk of iatrogenic hypoglycemia [10]. The theory of hypoglycemia-associated autonomic failure (HAAF) in diabetes hypothesizes that new antecedent hypoglycemia or preceding exercise or sleep leads to defective glucose counter-regulation and hypoglycemia unawareness and, hence, a vicious cycle of recurrent hypoglycemia. Possibly, the most believable evidence of the clinical significance of HAAF is the result - originally in three independent laboratories [11] that as little as 2-3 weeks of careful prevention of hypoglycemia inverts hypoglycemia unawareness and improves the deficient epinephrine component of defective glucose counter-regulation, in most affected patients. Therefore, the aim of the current study is to review the profile of the admitted patients (non - pregnant adults and adolescents) in presented with low plasma glucose levels regarding frequency of hypoglycemia as cause of admission, character of hypoglycemia and etiology in addition to fasting in Ramadan.

Materials and methods

A retrospective study for inpatient with hypoglycemia at Teaching Hospital in Tripoli- Libya from 1st January,

2017 till 31st July, 2018 was conducted. Demography data of the patients were collected from medical files including age, gender, marital states, occupation, presence of DM, duration of DM, level of hemoglobin A1C (HbA1c) as an indicator of diabetes control, mode of treatment including type of oral hypoglycemic drugs and insulin. Insulin regime include frequency of doses as once, twice, multi-daily dose. Twenty-nine admitted Libyan cases of non-pregnant adults and adolescents presenting with hypoglycemia at the Hospital were included according to the inclusion criteria. According to local scientific committee guidelines at the hospital, no ethical approval is needed from patients, since all data were taken from previous registered files.

Hypoglycemia episodes' character include presence of hypo-glycemic un-awareness, time at hypo-glycaemia: day, night, fasting or post-food (exercise), also severity as minor or recurrent or major episodes, as well as number of previous hypo-cases per month included in this study. Causes of hypoglycemia in patients with DM as: commonly used anti-hyperglycemic agents like oral hypoglycemic drugs induced metformin, glibenclamide, glimepiride, gliclazide and Dipeptidyl-peptidase 4 (DPP4) inhibitor, sitagliptin. Insulin induced, fasting (Ramadan), over exercise, malignancy, suicidal attempt in patient known DM or in non - DM and presence of systemic diseases that may increase the risk of hypoglycemia as renal impairment, hepatic failure, cerebral-vascular accident (stroke), connective tissue disease. Fate (out-come) that cases either discharge in good general condition, transfer to other center, discharged agonist medical advice or death.

Statistical presentation: Data were presented as frequency and percentage.

Results

As shown in **Table 1**, the total number of cases admitted to the hospital for 2017 were 408 patients and 20 patients (5.0%) were found to be hypoglycemic. In 2018, the total number of cases admitted were 697 patients and only 9 patients (1.2%) with hypoglycemia. Their age was ranged from 18 to 86 years with a mean value of 44.82 ± 2.2, in which 75.9% were female, 25.0% were non-smokers, 58.6% were married, 55.2% were non employers, 86.2% were patients with DM and number of hypoglycemia attack per month was found to be 3.9 ± 2.25. There were 25 cases with DM with two cases (6.9%) were newly diagnosed (< 1 year), 13 cases (44.8%) their duration of DM illness was less than nine years, and 10 cases (34.5%) were more than 10 years.

Table 1: Demographical distribution of the patient's characters at Tripoli Diabetes Hospital

Characters	Frequency (%)
Gender	
Female	22 (75.9%)
Male	07 (24.1%)
Age in years	
≤ 19 years	03 (10.3%)
20 - 49	13 (44.8%)
50 - 79	10 (34.5%)
≥ 80	03 (10.3%)
Mean age	44.82 ± 2.24
Marital states	
Married	17 (58.6%)
Single	11 (37.9%)
Divorced	01 (03.4%)
Occupation	
Employer	13 (44.8%)
Non-employer	16 (55.2%)
Presence of DM	
Yes	25 (86.2%)
No	04 (13.8%)
Smokers	
No	25 (86.2%)
Active	01 (03.4%)
Passive smokers	01 (03.4%)
Ex-smokers	02 (06.9%)
Systemic illnesses	
Other endocrine-hypothyroid	02 (06.9%)
Connective tissue diseases	01 (03.4%)
CVD diseases	04 (13.8%)
Renal diseases	02 (06.9%)
No other illness	20 (69.0%)
Causes	
Glibenclamide induced	05 (17.2%)
Glimepiride induced	01 (03.4%)
Insulin induced	19 (65.5%)
Exercise induced	03 (10.3%)
Malignancy	01 (03.4%)
Suicide (self-induced)	
Yes	03 (10.3%)
No	26 (89.7%)
Outcome	
Discharge	25 (86.2%)
Discharge with medical advise	04 (13.8%)

Tables 2 and 3 show that $HBA1_C$ was on target (6.5-7.0%) in 20.7% of the cases in which 17.2% were below the range (> 6.5%) and 37.9% with poor (> 7.0%). The treatment results reveal that 13.8%, were on glibenclamide, 3.4% were on glimepiride and 69.0% were on insulin therapy. Patients on insulin were given different regimes: twice daily (27.6%), triple daily (17.2%) and basal bolus regime (24.1%). Also, in **Table 3**, hypoglycemia unawareness was presented in 17.2%, where hypoglycemia was major (need assistant or loss of conscious) in 44.8% of cases and in 37.9% were in daytime.

Table 2: Distribution of the Libyan patients regarding investigations, treatment and hypo-characters

Investigations	Frequency (%)
$HBA1_C$	
<6.5	05 (17.2%)
6.5-7%	06 (20.7%)
>7%	11 (37.9%)
Non - DM	04 (13.8%)
Missed	03 (10.3%)
Treatments	
Glibenclamide	04 (13.8%)
Glimepiride	01 (03.4%)
Insulin	20 (69.0%)
Non-DM	04 (13.8%)
Insulin regime	
Twice daily	08 (27.6%)
Triple daily	05 (17.2%)
Basal bolus	07 (24.1%)
Hypo-unawareness	
Yes	05 (17.2%)
No	24 (82.8%)
Hypo-time	
Day	11 (37.9%)
Night	02 (06.9%)
Fasting	04 (13.8%)
Exercise	03 (10.3%)
All	09 (31.0%)
Hypo-severity	
Minor	08 (27.6%)
Recurrent	08 (27.6%)
Major	13 (44.8%)
Hypo-frequency	
< 3	07(27.1%)
3-5	16(55.1%)
>5	05(17.2%)

In **Table 4**, induced hypoglycemia were in 4 cases with suicidal attempt (13.8%), all were female, 3 were non - diabetes (their age range is 19 - 29 years), one case was newly diagnosed diabetes with $HBA1_c$ on target, insulin use was in 75.0% of patients (3 cases out of 4) and only one case with glibenclamide induced hypoglycemia in non-diabetes young female. Glibenclamide induced hypoglycemia were in 17.2%, glimepiride induced hypoglycemia were in 3.4%, none with gliclazide, exercise induced hypoglycemia in 10.3% and with malignancy induced hypoglycemia in 3.4% of cases. Co-exist systemic illnesses were absent in 69.0%, cardiovascular diseases in 13.8%, renal diseases were present in 6.9%, connective tissue diseases were present in 3.4% of the cases and 6.9% of the cases were with other endocrine diseases such as hypo-thyroid. Cases were discharged in good condition (86.2%), 13.8 % were discharge against medical advice and no mortality were recorded (**Table 4**).

Table 3: Causes of hypoglycemia in diabetic and non-diabetic cases

	DM	Non-DM
Glibenclamide	4	1
Glimepiride	1	0
Insulin	17	2
Exercise	3	0
Malignancy	0	1
Total	**25**	**4**

Table 4: Characters of cases admitted to Tripoli Diabetes Hospital

Case	Gender	Age (years)	Marital state	Induced by	Diabetes mellitus	Fate
Cases admitted with self-induced hypoglycemia (suicidal attempt)						
1	Female	19	Married	Insulin	Non-DM	Discharge
2	Female	29	Single	Insulin	Non-DM	Discharge
3	Female	20	Married	Insulin	DM (newly on basal–bolus regime)	Discharge
4	Female	23	Married	glibenclamide	Non-DM	Discharge
Cases admitted with hypoglycemia in Ramadan month (from a total of 214 cases)						
1	Male	78	Married	Malignance	Non-DM	Discharge
2	Female	60	Married	Insulin twice H/O recurrent hypoglycemia	DM with > 10 years HBA_{1c} < 6.5	Discharge
3	Female	50	Divorced	Insulin mixtard three times	DM > 10 years, HBA1c > 7	Discharge
4	Female	35	Single	Glibenclamid	DM with 2-9, HBA1c > 7	Discharge
5	Female	82	Yes	Glibenclamid	DM < 6.5 Duration 2-9 years with hypothyroidism	Discharge
6	Male	65	Yes	Insulin mixtard twice	DM > 10 years, HBA1c on target, with heart disease.	

Discussion

Hypoglycemia is common complication of insulin therapy in DM. Thus, about 90% of all insulin-treated patients have suffered hypoglycemic events. Hypoglycemia rate differs between reports but generally, patients with DM Type-I have an average of two episodes of symptomatic hypoglycemia per week and one episode of severe hypoglycemia once a year [11-13]. An expected 2 - 4% of deaths were due to hypoglycemia [12]. The

frequency of hypoglycemia is usually under-assessed because of trouble in the recognition of hypoglycemia that would include constant blood glucose tests also, in some clinical trials hypoglycemia is not a primary outcome which makes it challenging to guess the rate of hypoglycemia. Although the incidence of severe hypoglycemia is low of the total hypoglycemic. Therefore, hypoglycemia in clinical trials may be lower than in clinical practice. The incidence of hypoglycemia is lower in people with DM Type-II than in DM Type-1 [12]. A British study revealed that in patients with DM Type-II, the risk of severe hypoglycemia is little in the first few years and rises to 25% in advanced DM Type-II. The prevalence of DM Type-II is 20-fold greater than DM Type-I and many patients with DM Type-II lastly necessitate insulin therapy, so the greatest events of hypoglycemia occur in patients with DM-II. The longer-acting sulphonylurea linked with more severe hypoglycemia than shorter-acting drugs [12]. Infrequent events of hypoglycemia with metformin are explained as discrepancy between food ingestion and the dose. In meta-analysis report of 46 studies assessments that prevalence of hypoglycemia is 45% for mild to moderate and 06% for severe in population-based studies of DM Type-II [13]. However, on average one patient with DM Type-II suffers 19 milds to moderate events and 0.8 severe episodes per year. Severe hypoglycemia prevalence was similar for those on treatment regimens with or without sulphonylurea. Graham and others [14] reported total 244 episodes of severe hypoglycemia were recorded in 160 patients, comprising 69 people with DM Type-I, 66 with DM Type-II treated with insulin and 23 with DM Type-II treated with sulfonylurea tablets. Incidence rates were 11.5 and 11.8 events per 100 patient-years for DM Type-I and DM Type-II patients treated with insulin, respectively. Samir et al. [15] reported retrospective chart review to study self-monitored blood glucose data for three months prior to a patient's HbA_{1c} test. The outcome was hypoglycemia occurred more frequently in DM Type-I than in DM Type-II but 19% of DM Type-II diabetic patients did experience at least one episode of severe hypoglycemia. For DM Type-I diabetes, hypoglycemia had a positive association with glycemic variability and duration of diabetes and a negative association with HbA_{1c} and lowest blood glucose. For DM Type-II, positive association was noted with glycemic variability and negative association with age and lowest blood sugar. Confirming that defining factors predisposing to hypoglycemia in DM Type-II is difficult. Lower HbA_{1c} is potential predictor of hypoglycemia in type I but not in DM Type-II. Longer duration of diabetes illness for DM Type-I and younger age for DM Type-II are associated with more hypoglycemia. During the fasting-month of Ramadan, hypoglycemia as cause of admission has not been increased in comparison with non-fasting months that may indicate our patients are well tolerated in Ramadan fasting-month, improvement of our services especially pre-Ramadan education and availability of the new generation sulphonylurea with very low risk of hypoglycemia. In 2017, only two cases admitted with low blood glucose that not due to fasting, that was going with Abdulwahab et al. [16]. In 2018, four cases, two were insulin induce with history of recurrent hypoglycemia, advice to be non-fasting, other two were glibenclamide induced in case with no regular diabetes care follow-up. A retrospective cohort study to evaluate the characteristics of patients with DM admitted during the fasting month of Ramadan compared with the non-fasting month [16]. There is no difference in reasons for admission due to metabolic complications, length of hospital stay, or in hospital mortality between patients with DM admitted during Ramadan and Dhu al-Qidah month. A prospective cohort study on the effect of various risk factors on hypoglycemia in DM patients who fast during Ramadan registered the rate of hypoglycemia to be 1.6 times higher during the fasting compared with non - fasting periods [17]. The difference was smaller than indicated [18]. Hence, they observed that good metabolic control (HBA_{1c} < 08%) and old age increased Relative Risk more than twice while taking breakfast prior to fasting (Sahur meal) reduces Relative Risk to less than half. The effect of fasting during Ramadan on rates of hypoglycemia in patients with DM is uncertainty. The study [18] showed that fasting during Ramadan increased the risk of severe hypoglycemia some 04.7-fold on patients with DM Type-II and 07.5-fold in patients with DM Type-II. Severe hypoglycemia was more frequent in patients in whom the dosage of oral hypoglycemic agents or insulin was changed and in those who reported a significant change in their life style [18]. Insulin has commonly been used in people admitted with self-induced hypoglycemia with suicidal attempt. Perhaps, the first reported case in 1934 by female with DM, 50 years old with use of high dose of insulin for a suicidal purpose actually being depressed due to financial problems. Then, there have been described cases of suicidal self-use of insulin [19]. Evidence about the consumption of oral anti-hyperglycemic drugs for suicidal has come mostly from case reports. Metformin was used in massive quantities with an intention to suicidal in few patients. Other drugs

that were used with suicidal purpose involve liraglutide, phenformin and sitagliptin [19].

Hazard of misuse of anti-hyperglycemic drugs for suicidal attempt is not limited to the patient but even expands to the closed relative who live near the patient [19]. There has currently been estimated the frequency, causes, outcomes and characters of hypo-glycaemia, in patients admitted with hypo-glycaemia in studied period (during fasting Ramadan month and non - fasting months). The frequency of hypoglycemia among admitted cases were about 10.0% per month. Most of these cases with diabetes treated with insulin, number of documented hypoglycemia per month per patient was 3.9 ± 2.25 and the majority of cases were on mixtard insulin twice daily. Hypoglycemia unawareness present in about 20% and the major hypoglycemia event were present in about 50%.

Conclusion

The major cause of hypo in patients with DM is insulin induced due to misuse of insulin by doctors or patients themselves that need to be revised, necessitate educational interventions and individualization of therapies to reduce risk of hypoglycemia and weight gain. During Ramadan fasting, hypoglycemia as cause of admission was not increased in comparison with non-fasting months which may indicate patients are well tolerated Ramadan fasting. Thus, improvement of the services especially pre-Ramadan education and availability of new generation sulphonylurea with low risk of hypoglycemia are well observed.

Ethical issues

Including plagiarism, Informed Consent, data fabrication or falsification and double publication or submission have completely been observed by authors.

Conflict of interest

The authors declare that they have no competing interests.

Author's contribution

Both authors equally contributed.

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