ORIGINAL ARTICLE

Observational Study

Predictors of hypoglycemia in insulin-treated patients with type 2 diabetes mellitus in Basrah

Dhuha Tarik Nassar, Omran S Habib, Abbas Ali Mansour

Dhuha Tarik Nassar, Basrah Health Directorate, Basrah 61013, Iraq

Omran S Habib, Department of Epidemiology, Basrah College of Medicine, Basrah 61013, Iraq

Abbas Ali Mansour, Al-Faiha Specialized Diabetes, Endocrine and Metabolism Center (FDEMC), Chair Diabetes, Endocrine and Metabolism Division, Department of Medicine, Basrah College of Medicine, Basrah 61013, Iraq

Author contributions: All authors contributed equally to the manuscript.

Institutional review board statement: Ethical committee of Basrah College of Medicine approved the study.

Informed consent statement: Informed verbal consent was taken from all patients.

Conflict-of-interest statement: None.

Data sharing statement: None.

Manuscript source: Invited manuscript

Correspondence to: Abbas Ali Mansour, Professor of Medicine, Consultant Endocrinologist, Al-Faiha Specialized Diabetes, Endocrine and Metabolism Center (FDEMC), Chair Diabetes, Endocrine and Metabolism Division, Department of Medicine, Basrah College of Medicine, Hattin Post Office, P.O Box: 142, Basrah 61013, Iraq. aambaam@gmail.com
Telephone: +964-780-1403706

Abstract

AIM
To measure the incidence and determinants (predictors) of hypoglycemia among patients with type 2 diabetes mellitus (T2DM) who were on insulin treatment for at least one year.

METHODS
The present study is an out-patients based inquiry about the risk and predictors of hypoglycemia among patients with T2DM seeking care at the Al-Faiha Specialized Diabetes, Endocrine, and Metabolism Center, in Basrah over a period of 7 mo (from 15th of April, 2013 to 15th of October, 2013). The data used in the study were based on all detailed interview and selected laboratory investigations. A total of 336 patients could be included in the study.

RESULTS
The incidence of overall hypoglycemia among the studied patients was 75.3% within the last 3 mo preceding the interview. The incidence of hypoglycemia subtypes were 10.2% for severe hypoglycemia requiring medical assistance in the hospital, 44.36% for severe hypoglycemia treated at home by family; this includes both confirmed severe hypoglycemia with an incidence rate of 14.6% and unconfirmed severe hypoglycemia for which incidence rate was 29.76%. Regarding mild self-treated hypoglycemia, the incidence of confirmed mild hypoglycemia was 21.42%, for unconfirmed mild

hypoglycemia the incidence rate was 50.0% and for total mild hypoglycemia, the incidence rate was 71.42%. The most important predictors of hypoglycemia were a peripheral residence, increasing knowledge of hypoglycemia symptoms, in availability and increasing frequency of self-monitoring blood glucose, the presence of peripheral neuropathy, higher diastolic blood pressure, and lower Hemoglobin A1c.

CONCLUSION

Hypoglycemia is very common among insulin-treated patients with T2DM in Basrah. It was possible to identify some important predictors of hypoglycemia.

Key words: Diabetes mellitus; Insulin; Hypoglycemia; Out-patient; Type 2

Core tip: Outpatients study aimed to assess the frequency of hypoglycemia and their predictors among patients with type 2 diabetes mellitus on insulin for at least one year. The majority of patients (75.3%) had hypoglycemia in the preceding 3 mo. We identify some important predictors of hypoglycemia.

INTRODUCTION

Hypoglycemia is very frequent and serious complication of insulin therapy, especially in those with intensive treatment and unawareness of hypoglycemia is a very dangerous situation that complicated the problem more[1].

Severe hypoglycemia is defined to be an episode of hypoglycemia in which a patient requires help from another people. Thus, patients who are more compliant or precise in using their medication to lower their glucose levels are at greatest risk of hypoglycemia and its sequels[2,3].

Confirmed symptomatic hypoglycemia is an event during which classic symptoms of hypoglycemia was confirmed simultaneously by measured plasma glucose concentration < 70 mg/dL (3.9 mmol/L)[3]. Asymptomatic hypoglycemia is an attack not accompanied by classic symptoms of hypoglycemia but with a measured plasma glucose concentration < 70 mg/dL (3.9 mmol/L). Furthermore, probable symptomatic hypoglycemia is defined as symptoms of hypoglycemia that not proven by measuring simultaneous plasma glucose and assumed to be due to a plasma glucose concentration < 70 mg/dL (3.9 mmol/L).

It's well known that people with diabetes most of the times treat symptoms of hypoglycemia with the diet without measuring their plasma glucose at the same time. That why these episodes can be considered as probable hypoglycemia. These unconfirmed hypoglycemic episodes reported by the patients may affect the results of studies intended to evaluate the drugs that affect plasma glucose, but they should be declared by any mean as self-reported hypoglycemic episodes that are not confirmed.

Finlay, we have to define relative hypoglycemia. These symptoms of hypoglycemia reported by patients with diabetes but associated with simultaneously measured plasma glucose concentration > 70 mg/dL (3.9 mmol/L).

This last group of hypoglycemic episodes is seen more in those with long-standing diabetes with poor control. They per say may not be harmful, and they are no suitable outcome measures in clinical studies needed to evaluate drug therapy in diabetes, but again have to be reported though the symptoms happen with plasma glucose levels > 70 mg/dL (3.9 mmol/L).

In this study, we assess the frequency of hypoglycemia among insulin-treated patients with type 2 diabetes mellitus (T2DM) who were on insulin for at least one year.

MATERIALS AND METHODS

Study design

The study is a cross-sectional study investigating retrospectively the experience of hypoglycemia among patients with type T2DM receiving insulin for at least one year preceding the time of study who attended Al-Faiha Specialized Diabetes, Endocrine, and Metabolism Center (FDEMC). The study extended in the data collection phase over five month period from 15th of April to 15th of October 2013.

Sampling methods and sample size

A total of 336 patients were enrolled in the study. Data were collected through direct interview with the patients after ensuring their verbal agreement to take part in the study. On average 5-6 patients could be fully interviewed each working day.

Inclusion criteria

All patients with T2DM (no age limit) including men and non-pregnant women receiving insulin for at least one year proceeding the time of study who attended FDEMC. Informed verbal consent was taken from all patients, and the ethical committee of Basrah College of Medicine approved the study.

Questionnaire and data collection

A special questionnaire form was prepared for the purpose of data collection for this study. It covered the following

aspects. Personal characteristics including information on name, age, sex, job, address, level of education, marital status. Medical characteristics including family history of diabetes mellitus, duration of diabetes, duration of insulin use, type of insulin use, frequency of insulin used per day, dose of insulin per time of administration per day, total dose of insulin per day (for the preceding 3 mo), whether the patient is on oral hypoglycemic drug, its type dose, and frequency. Other questions include who inject insulin to the patient, state of patient's vision, patient's mobility, the source of medication, knowledge of the patient about symptoms of hypoglycemia.

Information on hypoglycemic attacks, including whether the patient had hypoglycemic attacks during the preceding three before the interview, type of hypoglycemic attack and timing during the day, events precipitating hypoglycemia, whether self-monitoring blood glucose (SMBG) device was available and the frequency of its use, did hypoglycemic attack was confirmed by SMBG or by venous blood and what was the blood glucose level, awareness of the patient for hypoglycemia.

History of other co-morbidities such as hypertension (HTN), ischemic heart disease (IHD), cerebrovascular accidents (CVA), amputation, chronic kidney disease (CKD), diabetic foot, and peripheral neuropathy (PNP).

The use of insulin by another family member at home or outside the home and whether the patient takes other concomitant medications with the insulin. Measurement of height and weight to obtain a body mass index (BMI) (done by a nurse on the day of the visit). Investigations were done in the laboratory of FDEMC on the day of the visit, and these include measurement of glycated hemoglobin (HbA1C), serum creatinine, and urine for albumin.

Definition of variables

Details related to hypoglycemia: Respondent's knowledge of hypoglycemia symptoms was grouped into yes or no. An incident of hypoglycemia, the respondent was asked if he or she developed, at least, one episode of hypoglycemia during the last 3 mo; this includes asking about the symptoms of hypoglycemia, and the answer was grouped into yes or no.

Type of hypoglycemia: By adopting the ADA definition of hypoglycemia[3,4], it was classified into: (1) severe need third party help in the hospital by a doctor; severe need second party help at home by family. Severe hypoglycemia also subdivided into confirmed severe hypoglycemia, and unconfirmed severe hypoglycemia; and (2) mild self-treated hypoglycemia was also subdivided into confirmed mild hypoglycemia and unconfirmed mild hypoglycemia. Confirmation of hypoglycemia (what was blood glucose level at the time of the attack?) was grouped into: By SMBG, by venous blood or not (hypoglycemia not confirmed). Awareness of hypoglycemia was grouped into yes or no[1].

Statistical analysis
Data were coded according to the variable definition and entered into a computer program: Statistical Package for Social Science (SPSS - version 20). Data were analyzed and presented in suitable tables. Three layers of tables are presented: Descriptive tables describing patients socio-demographic and medical characteristics, Cross-tabulations of the history of hypoglycemia with probable risk factors. χ^2 or Fisher's Exact test was used to find out the statistical association, *P* value < 0.05 was considered significant. Logistic regression analysis was done to identify significant predictors of hypoglycemia.

RESULTS
Socio-demographic characteristics of the studied patients included age range was 29-88 years with mean age of 54.47 years; 38.1% were in the age group 50-59 year; 28.0% were in the age group 60-69 year. Regarding gender, female cases showed predominance forming 61.9% compared to males who accounted for 38.1% of cases. More than one-quarter of patients (29.8%) had completed primary schooling. The majority were married accounting for 80.1%. Regarding residence, most of the respondents lived in Basrah city (67.3%).

Some medical aspects of the studied patients, where 40.2% have more than one 1st and 2nd degree relative with DM, regarding the frequency of insulin administration/day; 44.6% of patients received insulin three times daily, 42.9% received insulin twice daily.

On co-morbidities; 74.4% of them had HTN, 17.3%, and CVA reported IHD was reported by 6%. Amputation was evident in 3%, CKD in 26.8% and diabetic foot in 27.1%, and PNP in 90.2%.

Most of the patients (75.6%) injected themselves insulin and needed no external support, about vision; 81% of patients reported good vision, 87.8% were mobile alone without assistance. The majority of patients (66.1%) received insulin from more than one source. Regarding knowledge of hypoglycemia symptoms; 95.2% reported that they knew hypoglycemia symptoms.

Table 1 shows the incidence (%) of hypoglycemia (total and subtypes) in the last 3 mo as reported by the patients. The majority of patients (75.3%) had hypoglycemia in the preceding 3 mo. The incidence of hypoglycemia subtypes was 10.2% for severe hypoglycemia requiring medical assistance in the hospital, 44.36% for severe hypoglycemia treated at home by family; this includes both confirmed severe hypoglycemia with an incidence rate of 14.6% and unconfirmed severe hypoglycemia for which incidence rate was 29.76%.

Regarding mild self-treated hypoglycemia, the incidence of confirmed mild hypoglycemia was 21.42%, for unconfirmed mild hypoglycemia the incidence rate was 50.0% and for total mild hypoglycemia, the incidence rate was 71.42%.

More than half of the patients who had experienced hypoglycemia during the preceding 3 mo (57.6%) had

Table 1 Incidence, types, timing, and causes of hypoglycemia in 336 patients

Variable	*n* (%)
Hypoglycemia in the last 3 mo	253 (75.3)
Type of hypoglycemia	
Severe treated in hospital	34 (10.2)
Sever confirmed hypoglycemia treated at home by family (≤ 70 mg/dL)	49 (14.6)
Severe unconfirmed hypoglycemia treated at home by family or blood glucose > 70 mg/dL	100 (29.7)
Mild confirmed hypoglycemia (≤ 70 mg/dL)	72 (21.4)
Mild unconfirmed hypoglycemia or blood glucose > 70 mg/dL	168 (50.0)
Total severe hypoglycemia treated at home by family	149 (44.3)
Total mild hypoglycemia	240 (71.4)
Timing of hypoglycemia in the last 3 mo	
Nocturnal	22 (8.7)
Day time	83 (32.8)
Nocturnal and day time	148 (58.5)
Precipitating factors hypoglycemia	
Missed meal, delayed meal, eating a less amount of food	214 (84.6)
Performing an exercise	42 (16.6)
Doctor change the dose of insulin recently	12 (4.7)
Insulin dose adjusted by the patient, errors in the dose of insulin	7 (2.8)
No obvious cause	22 (8.7)
Awareness of hypoglycemia in the last 3 mo	
No	19 (7.5)

Table 2 Relation of hypoglycemia in the last 3 mo with age, gender, education, marital status and residence among 336 patients

	Hypoglycemia in the last 3 mo		Total (*n*)	*P* value
	Yes	No		
Age (yr)	*n* (%)	*n* (%)	27	0.944
29-39	22 (81.5)	5 (18.5)		
40-49	48 (73.8)	17 (26.2)	65	
50-59	97 (75.8)	31 (24.2)	128	
60-69	70 (74.5)	24 (25.5)	94	
≥ 70	16 (72.7)	6 (27.3)	22	
Gender				
Male	93 (72.7)	35 (27.3)	128	0.776
Female	160 (76.9)	48 (23.1)	208	
Education				
Illiterate	61 (76.2)	19 (23.8)	80	0.016
Just literate	37 (75.5)	12 (24.5)	49	
Primary school	83 (83.0)	17 (17.0)	100	
Intermediate school	44 (77.2)	13 (22.8)	57	
Secondary school	8 (50.0)	8 (50.0)	16	
College and more	20 (58.8)	14 (41.2)	34	
Marital status				
Single	5 (83.3)	1 (16.7)	6	0.604
Married	200 (74.3)	69 (25.7)	269	
Divorced	3 (60.0)	2 (40.0)	5	
Widowed	45 (80.4)	11 (19.6)	56	
Residence				
Basrah city	164 (72.6)	62 (27.4)	226	0.215
Northern Basrah	40 (72.4)	13 (27.65)	53	
Southern Basrah	5 (83.3)	1 (16.7)	6	
Eastern Basrah	12 (100.0)	0 (0.0)	12	
Western Basrah	32 (82.1)	7 (17.9)	39	

developed both nocturnal and daytime hypoglycemia.

The most common causes of hypoglycemia are factors related to a meal including missed meal, delayed meal or eating a less amount of food, and the majority of the patients are aware of hypoglycemia symptoms in the preceding 3 mo.

Determinants of hypoglycemia during the preceding 3 mo
In Table 2, although a higher percentage of hypoglycemia was reported in the younger age group 29-39 year and among females; there is no significant association between age and gender with experience of hypoglycemia during the preceding 3 mo; *P* > 0.05. There is a highly significant association with the education of respondents; *P* = 0.016 with the highest percentage in those who had completed primary schooling. There is no significant association between marital status and residence with experience of hypoglycemia during the preceding 3 mo (*P* > 0.05).

Table 3 shows there is no significant association of DM family history, duration of DM and duration of insulin treatment with experience of hypoglycemia during last 3 mo; *P* > 0.05. No significant association between type of insulin and experience of hypoglycemia during the preceding 3 mo (*P* > 0.05); while there is a highly significant association between the frequency of insulin administration per day and total dose of insulin per day with hypoglycemia in the last 3 mo (*P* < 0.05).

In Table 4, there is no significant association between dose of regular, premix and Neutral Protamine Hagedorn (NPH) insulin and experience of hypoglycemia during last 3 mo (*P* > 0.05). There is no significant association

between family support, vision, mobility and source of medications with experience of hypoglycemia during the preceding 3 mo; *P* > 0.05. While there was a significant association between knowledge of hypoglycemia symptoms and experience of hypoglycemia (*P* < 0.05).

Table 5 shows there is no significant association regarding availability and frequency of SMBG with experience of hypoglycemia during last 3 mo (*P* > 0.05).

Also, there is no significant association between HTN, CVA, CKD, amputation and diabetic foot with experience of hypoglycemia during the preceding 3 mo (*P* > 0.05), but a significant association does exist between IHD and PNP with experience of hypoglycemia during the preceding 3 mo (*P* < 0.05).

There is no significant association between insulin use by other family members, concomitant use of other medication and type of medication with experience of hypoglycemia during the preceding 3 mo (*P* > 0.05).

Table 6 shows that there is no significant association between BMI; systolic blood pressure; diastolic blood pressure; HbA1c; serum creatinine; urine for albumin with experience of hypoglycemia during last 3 mo (*P* > 0.05).

Logistic regression analysis
To overcome some of the interaction and confounding effects of the various predictors used in this study; a logistic regression analysis was done. Experience of hypoglycemia in the last 3 mo was used as the dependent

Table 3 Relation of hypoglycemia in the last 3 mo with diabetes mellitus family history, duration of diabetes mellitus, duration of insulin treatment, type of insulin, frequency and total dose

	Hypoglycemia in the last 3 mo		Total (*n*)	*P* value
	Yes *n* (%)	No *n* (%)		
Family history of DM				
None	85 (78.7)	23 (21.3)	108	0.601
One	68 (73.1)	25 (26.9)	93	
More than one	100 (74.1)	35 (25.9)	135	
Duration of DM (yr)				
1-10	140 (75.7)	45 (24.3)	185	0.877
11-20	92 (76.0)	29 (24.0)	121	
21-30	18 (69.2)	8 (30.8)	26	
≥ 31	3 (75.0)	1 (25.0)	4	
Duration of insulin treatment (yr)				
1-10	238 (74.8)	80 (25.2)	318	0.578
> 10	15 (83.3)	3 (16.7)	18	
Type of insulin				
Premix	75 (72.1)	29 (27.9)	104	0.239
Regular	6 (75.0)	2 (25.0)	8	
NPH	24 (64.9)	13 (35.1)	37	
Combination of 2 or 3 insulin types	148 (79.1)	39 (20.9)	187	
Frequency of insulin administration/d				
Once	3 (30.0)	7 (70.0)	10	0.001
Twice	107 (74.3)	37 (25.7)	144	
Thrice	126 (84.0)	24 (16.0)	150	
≥ Four times	17 (53.1)	15 (46.9)	32	
Total dose of insulin (unit/d)				
< 20	3 (37.5)	5 (62.5)	8	0.007
21-40	46 (75.4)	15 (24.6)	61	
41-60	121 (79.1)	32 (20.9)	153	
61-80	59 (81.9)	13 (18.1)	72	
81-100	17 (56.7)	13 (43.3)	30	
> 100	7 (58.3)	5 (41.7)	12	

DM: Diabetes mellitus; NPH: Neutral protamine hagedorn.

outcome variable, only peripheral residence, knowledge of hypoglycemia symptoms, availability and increasing frequency of SMBG, presence of PNP, higher diastolic blood pressure, and lower HbA1c were significant and independent predictors. All other studied variables were not predictors (Table 7).

DISCUSSION

The results of this study showed that most of the studied patients had experienced at least one episode of hypoglycemia during the last 3 mo (75.3%). The reported risk of hypoglycemia in this study is higher than the 43.3% that was reported by Fritsche *et al*[5], 45% by Donnelly *et al*[6] and the 64% by Henderson *et al*[7].

Although it is agreed that patients remember major events such as major hypoglycemia requiring second party help by medical personnel or by family easier than minor self-treated events; in the present study patients seemed to recall both minor and major hypoglycemic episodes including those hypoglycemic episodes which were treated in hospital or at home by family; this can be explained by the fact that hypoglycemic events including minor ones cause stress, anxiety and other sympathoadrenal symptoms that can be remembered even if it happened several mo ago especially if they are frequent[8,9].

Incidence rates of hypoglycemia subtypes (severe and mild) in the present study were generally higher than that reported in other studies. By Donnelly *et al*[6] the incidence of severe hypoglycemia requiring assistance was 3%, by Henderson *et al*[7] it was 15% and by United Kingdom Hypoglycemia Study Group it was 7% (incidence of mild hypoglycemia 51%)[10]. This excess in incidence may be due to poor adherence to the prescribed treatment regimens, fluctuation in the timing of meals and insulin doses, low education, presence of other diabetes complications especially diabetic nephropathy and autonomic neuropathy. Some patients who experienced minor hypoglycemia may receive unnecessary help from their relatives or unnecessary treatment in the emergency room; this could have lead to overestimation of severe hypoglycemia.

The incidence of severe hypoglycemia treated at home by the family and was confirmed by blood glucose measurement was lower than the incidence of severe unconfirmed hypoglycemia (14.6% *vs* 29.76%) and the same thing for mild self-treated hypoglycemia (incidence of confirmed hypoglycemia was 21.42% *vs* 50.0% for mild unconfirmed ones), this might be due to many patients choose to treat hypoglycemia without measuring blood glucose by SMBG or it is unavailable

	Hypoglycemia in the last 3 mo		Total (*n*)	*P* value
	Yes *n* (%)	No *n* (%)		
Regular dose (unit)				
1-10	7 (100.0)	0 (0.0)	7	0.347
11-20	84 (80.2)	21 (19.8)	105	
21-30	57 (77.0)	17 (23.0)	74	
> 30	5 (62.5)	3 (37.5)	8	
Total	153 (79.0)	41 (21.0)	194	
Premix dose (unit)				
1-10	2 (100.0)	0 (0.0)	2	0.45
11-20	78 (78.8)	21 (21.2)	99	
21-30	86 (77.3)	25 (22.7)	111	
> 30	10 (62.5)	6 (37.5)	16	
Total	176 (77.1)	52 (22.9)	228	
NPH dose (unit)				
1-10	4 (100.0)	0 (0.0)	4	0.528
11-20	37 (73.1)	14 (26.9)	51	
21-30	27 (66.7)	14 (33.3)	41	
> 30	6 (85.7)	1 (14.3)	7	
Total	74 (72.4)	29 (27.6)	103	
Family/social support				
Self	190 (74.8)	64 (25.2)	254	0.914
Others	51 (76.1)	16 (23.9)	67	
Self and others	12 (80.0)	3 (20.0)	15	
Vision				
Good	203 (74.6)	69 (25.4)	272	0.560
Poor	50 (78.1)	14 (21.9)	64	
Mobility				
Mobile alone	223 (75.6)	72 (24.4)	295	0.698
Mobile with assistance or use wheel chair	9 (81.8)	2 (18.2)	11	
Walk on stick	21 (70.0)	9 (30.0)	30	
Source of medications				
FDEMC[1]	63 (75.0)	21 (25.0)	84	0.507
Public clinic	7 (58.3)	5 (41.7)	12	
Private sector	13 (72.2)	5 (27.8)	18	
More than one source	170 (76.6)	52 (23.4)	222	
Knowledge of hypoglycemia symptoms				
Yes	246 (76.9)	74 (23.1)	320	0.003

Table 4 Relation of hypoglycemia during the last 3 mo with dose of insulin, family/social support, mobility, source of medications and knowledge of hypoglycemia symptoms

[1]Al-Faiha Specialized Diabetes, Endocrine and Metabolism Center. NPH: Neutral protamine hagedorn.

or not functioning; this is called (probable symptomatic hypoglycemia). Besides, patients with poor glycemic control and persistently high blood sugar levels could experience hypoglycemia at blood glucose level > 70 mg/dL (3.9 mmol/L), this is called (relative hypoglycemia)[5].

By the present study it was found that factors related to meal (missed meal, delayed meal and eating less amount of food in meals) were the most common precipitating factors of hypoglycemic events, this is agreed with what is known by most literatures[2,8,9,11].

Nocturnal hypoglycemia is a dangerous problem in patients with T2DM on insulin, if it is severe enough; it may lead to death or serious neurological impairment, it occurs in about two thirds of the studied patients. Eating less amount of food in dinner and use of bed time intermediate acting NPH human insulin may contribute to nocturnal hypoglycemia[2,8,12].

Hypoglycemia unawareness occurs in a minority of the studied patients who report episodes of severe hypoglycemia that necessitate medical management in hospitals. Long standing T2DM and recurrent hypo-glycemic episodes are possible risk factors[1]. These results agreed with those study of Akram *et al*[13].

No relation was found in the present study of hypoglycemia to age. The same findings were obtained by Davis *et al*[14], while contradictory results were reported in other studies that concluded aging as an important risk factor of hypoglycemia[15-18].

This may be due to that elderly people constitute a small proportion of the studied patients (only 6.5%).

Although in our study females predominates males; no association was found between gender and hypoglycemia, several recent studies support our findings[14,19,20].

There is a significant association between hypoglycemia and level of education at the level of univariate analysis (*P* < 0.05) but this association has disappeared at the level of logistic regression. Hypoglycemia is more prevalent among illiterate patients or those with lower than secondary school qualification. Low educational attainment may mean less understanding and carelessness regarding the dangerous complications of hypoglycemia and the importance of adherence to

Table 5 Relation of hypoglycemia during the last 3 mo with availability, frequency of self-monitoring of blood glucose, common co-morbidities, and concomitant medication use (other than OHD)

	Hypoglycemia in the last 3 mo		Total (*n*)	*P* value
	Yes *n* (%)	No *n* (%)		
Availability of SMBG				
Available and used	124 (75.2)	41 (24.8)	165	0.996
Not available	102 (75.6)	33 (24.4)	135	
Available and not used	27 (75.0)	9 (25.0)	36	
Frequency of SMBG use				
Once/mo	19 (79.2)	5 (20.8)	24	0.164
1-2 times/wk	48 (67.6)	23 (32.4)	71	
Once daily	23 (74.2)	8 (25.8)	31	
Twice daily	8 (88.9)	1 (11.1)	9	
Thrice daily	2 (50.0)	2 (50.0)	4	
According to patients condition	25 (89.3)	3 (10.7)	28	
Common co-morbidities				
HTN	106 (72.1)	41 (27.9)	147	0.232
IHD	50 (86.2)	8 (13.8)	58	0.034
CVA	15 (75.0)	5 (25.0)	20	0.975
Amputation	7 (70.0)	3 (30.0)	10	0.693
Diabetic foot	72 (79.1)	19 (20.9)	91	0.322
CKD	66 (73.3)	24 (26.7)	90	0.614
PNP	235 (77.6)	68 (22.4)	303	0.004
Insulin use by other family members				
At home	21 (80.8)	5 (19.2)	26	0.764
Outside home	42 (76.4)	13 (23.6)	55	
Non	190 (74.5)	65 (25.5)	255	
Concomitant medication use (other than OHD)				
Yes	215 (74.1)	75 (25.9)	290	0.216

SMBG: Self-monitoring of blood glucose; HTN: Hypertension; IHD: Ischemic heart diseases; CVA: Cerebrovascular accidents; CKD: Chronic kidney disease; PNP: Peripheral neuropathy.

the treatment plan and those patients may be unable to adjust insulin doses according to their daily activities or meals. These results did agree with results found by ACCORD[21].

There was no significant association between marital status and hypoglycemia in our study, a result that agrees with what was found by Bruce *et al*[22] but contradicts the results of Akram *et al*[13] in that being married is a risk factor for hypoglycemia.

Although there is no significant association between residence and hypoglycemia at univariate analysis; a strong negative association does exist at the level of multivariate analysis ($P < 0.05$) which implies that patient from periphery of Basrah (outside the major city of Basrah) experienced hypoglycemia more than patients from Basrah city, this could be explained partially by difficult access to these patients to FDEMC according to their appointments to adjust their insulin regimens and partly because patients living in rural areas may have relatively low education than those living in Basrah city which is found to be significantly associated with hypoglycemia in our study and others[21,23].

No relationship was found in our study between duration of DM and hypoglycemia, the same is found by some studies[14,19,22]. But not in ACCORD[21] which is a large randomized controlled trial that follow-up large number of patients for several years most of them were elderly and have longer duration of diabetes and Akram

et al[13] who found that the risk of hypoglycemia increased progressively when the duration of diabetes was more than 16 years and United Kingdom Hypoglycemia Study Group[10] who found that risk of hypoglycemia in insulin treated patients increased after 5 years of therapy. The present study is a cross sectional one that investigated retrospectively the experience of hypoglycemia among diabetic patients in the last 3 and 12 mo and more than half of them were diagnosed with diabetes for less than 10 years. Thus the duration of diabetes in the studied patients is relatively short and could not allow the effect of duration to be identified.

In addition, no significant association between types of insulins studied [regular human, premix human (70:30) and NPH] with hypoglycemia. The risk of hypoglycemia is seems to be similar with these types. Akram *et al*[13] and Miller *et al*[24] found that the relationship between type of insulin and risk of severe hypoglycemia is inconsistent.

There is a significant association between the frequency of insulin administration per a day with the experience of hypoglycemia in the preceding 3 mo, which is an established fact in insulin therapy[25].

There is a significant association between presence of IHD and hypoglycemia at the level of univariate analysis ($P < 0.05$) but this association has disappeared at the level of logistic regression. IHD as a part of macrovascular complications of DM is found to be a significant predictor of hypoglycemia[26].

Table 6 Relation of hypoglycemia during the last 3 mo with body mass index, systolic blood pressure; diastolic blood pressure; hemoglobin A1c; serum creatinine; urine for albumin

Variables	Hypoglycemia in the last 3 mo		Total (*n*)	*P* value
	Yes *n* (%)	No *n* (%)		
BMI (kg/m^2)				
Thin or normal (< 25.00)	46 (83.6)	9 (16.4)	55	0.123
Overweight (25.0-29.9)	95 (77.2)	28 (22.8)	123	
Obese (30.00-39.99)	93 (68.9)	42 (31.1)	135	
Morbid obesity (⩾ 40)	18 (81.8)	4 (18.2)	22	
Total	252 (75.2)	83 (24.8)	335[1]	
Systolic blood pressure (mmHg)				
Normal (< 130)	91 (79.8)	23 (20.2)	114	0.157
Prehypertension (130-139)	62 (79.5)	16 (20.5)	78	
Stage 1 hypertension (140-159)	76 (71.0)	31 (29.0)	107	
Stage 2 hypertension (⩾ 160)	24 (64.9)	13 (35.1)	37	
Total	25 (375.3)	83 (24.7)	336	
Diastolic blood pressure (mmHg)				
Normal (< 80)	63 (78.8)	17 (21.2)	80	0.792
Pre-hypertension (80-89)	148 (74.4)	51 (25.6)	199	
Stage 1 hypertension (90-99)	38 (74.5)	13 (25.5)	51	
Stage 2 hypertension (⩾ 100)	4 (66.7)	2 (33.3)	6	
Total	253 (75.3)	83 (24.7)	336	
HbA1c (%)				
< 7.0	10 (83.3)	2 (16.7)	12	0.117
7.0-10.0	136 (79.1)	36 (20.9)	172	
10.1-13.0	85 (73.3)	31 (26.7)	116	
> 13.0	22 (61.1)	14 (38.9)	36	
Total	253 (75.3)	83 (24.7)	336	
Serum creatinine (mg/dL)				
< 0.7	66 (72.5)	25 (27.5)	91	0.632
0.7-1.4	167 (75.9)	53 (24.1)	220	
> 1.4	3 (100.0)	0 (0.0)	3	
Total	236 (75.2)	78 (24.8)	314[2]	
Urine for albumin (positive)	65 (75.6)	21 (24.4)	86	0.947
Total	235 (75.3)	77 (24.7)	312[3]	

[1]BMI had not been measured for one patient due to bilateral lower limb amputation; [2,3]Unequal numbers because some of the patients did not complete their investigations. BMI: Body mass index; HbA1c: Hemoglobin A1c.

Furthermore a significant association between the presence of PNP and risk of hypoglycemia (*P* < 0.05) both at the level of univariate and logistic regression analyses was found. PNP may reflect advanced diabetes and its associated microvascular complications, *e.g.*, autonomic neuropathy. This result agrees with what was found by Miller *et al*[27].

No relation was found between family/social support, vision and mobility with risk of hypoglycemia. These factors were not applied as risk factors in the previously mentioned large randomized controlled trials UKPDS[28], ACCORD[21], VADT[29], United Kingdom Hypoglycemia Study Group[10]. We explored their effect as indicators of severity of diabetes and thus we assumed a patient who needed support and restricted vision and mobility was likely to develop hypoglycemia.

At the level of univariate analysis there is a significant relationship between knowledge of hypoglycemia symptoms and hypoglycemia (*P* < 0.05), while at the level of logistic regression also there is a strong positive association with knowledge of hypoglycemia symptoms (*P* < 0.05), *i.e.*, the more knowledge of hypoglycemic symptoms the more hypoglycemia was reported. Although most patients who experience hypoglycemia have prior knowledge of hypoglycemia symptoms; this knowledge did not protect them from hypoglycemia and this may be due to low education, poor understanding of the importance of adjusting insulin dose and time of injection according to daily activities or the amount and time of meals. Also it may indicate that health education is inadequate, medical practitioners should spent more effort to teach their patients about signs, symptoms, and proper treatment of hypoglycemia, as well has how to prevent it[30].

There is no significant relationship between availability and frequency of SMBG with risk of hypoglycemia; while at the level of logistic regression analysis we found that the availability of SMBG *per se* decreases the risk of hypoglycemia (*P* < 0.05) and frequent use of SMBG associated with more hypoglycemia. Frequent use of SMBG does not protect patients from hypoglycemia nor predict it but probably remind the patient with signals of hypoglycemia, or this may be due to bad storage conditions of the device and strips, high temperature and humidity, absence of hand washing prior to testing. Anyhow, our result agrees with a number of other studies[31-33].

No significant association was found between CVA and amputation with risk of hypoglycemia, same findings

Table 7 Results of logistic regression showing significant predictors of hypoglycemia in the last 3 mo

	B	Sig.	Exp (B)
Significant predictors			
Residence	-0.247	0.030	0.782
Knowledge of hypoglycemia symptoms	1.133	0.044	3.104
Availability of SMBG	-0.599	0.030	0.550
Frequency of SMBG	-0.228	0.031	0.796
PNP	-1.391	0.002	0.249
Diastolic blood pressure	-0.046	0.013	0.955
Systolic blood pressure	0.020	0.053	1.020
HbA1c	0.153	0.021	1.165
Non-significant predictors			
Age	0.002	0.960	1.002
Gender	-0.425	0.200	0.654
Education	0.067	0.505	1.069
Duration of DM	-0.019	0.42	0.981
Frequency of insulin administration/d	-0.381	0.259	0.683
Dose of regular insulin	-0.021	0.215	0.979
Dose of premix insulin	-0.027	0.305	0.974
Dose of NPH	-0.022	0.429	0.979
A total dose of insulin	0.018	0.148	1.018
Mobility	0.117	0.440	1.124
HTN	0.594	0.117	1.811
IHD	-0.758	0.081	0.469
CKD	0.307	0.614	1.359
BMI	0.033	0.208	1.033

SMBG: Self-monitoring of blood glucose; HbA1c: Hemoglobin A1c; HTN: Hypertension; IHD: Ischemic heart diseases; CKD: Chronic kidney disease; PNP: Peripheral neuropathy; BMI: Body mass index; DM: Diabetes mellitus; NPH: Neutral protamine hagedorn.

obtained by other studies in that there is no significant association between macrovascular complications of diabetes including CVA and amputation with risk of hypoglycemia[13,19].

Also no significant association was found between diabetic foot and risk of hypoglycemia, this agree with what is found by other studies which suppose that no significant association between microvascular complications of diabetes and risk of hypoglycemia[14].

Although it is agreed that in advanced kidney diseases, insulin excretion from kidneys will decrease and thus the risk of hypoglycemia will increase[14,27]. No significant association was found between, CKD and risk of hypoglycemia, this looks similar to what is found by other studies[19,24]. There was no significant association between BMI and hypoglycemia, similar results were found by other studies[14,19,24].

No significant association was found between systolic and diastolic blood pressure and risk of hypoglycemia at level of univariate analysis but there is a significant positive association between diastolic blood pressure and risk of hypoglycemia at the level of logistic regression ($P < 0.05$), *i.e.,* as the diastolic blood pressure increase; the risk of hypoglycemia will increase too. Similar results were found by other studies[34]. This association may be related to antihypertensive drugs those patients use, namely the ACE inhibitors, which are suggested to be a risk factor for hypoglycemia[35].

Although no significant association was found bet-

ween HbA1c and hypoglycemia at the level of univariate analysis; there was a strong negative association, *i.e.,* the lower the HbA1c; the more the risk of hypoglycemia, this is consistent with what is found by several large studies[21,28]. In that intensive glycemic control and HbA1c goal < 7 is associated with increased risk of hypoglycemia (both major and minor).

Taking the results as a whole, particularly the logistic regression analysis, the only residence (rural), knowledge of hypoglycemia symptoms, availability and increasing frequency of SMBG, the presence of the PNP, high diastolic blood pressure and low HbA1c were significant and independent predictors of hypoglycemia. All other studied variables were not predictors.

Limitations of the study
Although every patient entering this center (FDEMC) on the day of the interview was checked to see if he or she met the inclusion criteria; selection bias cannot be excluded. Another limitation is that a small proportion of patients did not complete their investigations regarding fasting glucose (12.5%), random glucose (12.3%), serum creatinine (6.5%), urine for albumin (7.1%) measurement.

In conclusion, hypoglycemia is very common among insulin treated patients with T2DM Basrah. It was possible to identify a number of important predictors of hypoglycemia.

ACKNOWLEDGMENTS

COMMENTS

Background
Hypoglycemia is one the important barrier for initiating and continuing insulin therapy in type 2 diabetes (T2DM) for patients and doctors. Overcoming this barrier will be fundamental to start insulin at earlier stage.

Research frontiers
Basrah is one the largest city in Iraq. Data on the hypoglycemia frequency is lacking in Iraq and this city. This study will start to give baseline hypoglycemia frequency in insulin treated patients with T2DM.

Innovations and breakthroughs
This study showed that some form of hypoglycemia accord in more than three quarter of patients with T2DM treated with insulin. The important predictors of hypoglycemia were residence (rural), knowledge of hypoglycemia symptoms, availability and increasing frequency of self-monitoring blood glucose, the presence of the peripheral neuropathy, high diastolic blood pressure and low hemoglobin A1c (HbA1c).

Applications
This study provided for the first time data on the frequency of hypoglycemia for the first time in Basrah (Southern Iraq), which seems to be very common.

Terminology
Hypoglycemia is state of low blood glucose that ranges from mild that can be

self-treated to severe which the need help by the others including the hospital. It can be symptomatic or a symptomatic, documented by blood glucose estimation or not and nocturnal or daytime.

Peer-review

This paper is well written and the information that contains is a useful tool for physiology and the correlation between miRNAs and impaired fracture healing.

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