Original Article

Frequency and Predisposing Factors for Drug-Induced Hypoglycemia in Patients with Type-2 Diabetes Mellitus

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Abstract

Objective: Hypoglycemia is the most common complication of the treatment for diabetes mellitus. Various factors predispose an individual for drug-induced hypoglycemia. The aim of this study was to explore the relative frequency and likely predisposing factors for drug-induced hypoglycemia among type-2 diabetic patients in the United Arab Emirates (UAE). **Methods:** In this cross-sectional survey-based study which was conducted from February to April 2018 in two local community pharmacies in the UAE, diabetic patients underwent a structured interview on their diabetes mellitus status and management and specific open-ended questions related to hypoglycemic symptoms that they might have experienced and the occurrence of symptoms. Collected data were used to estimate the relative frequency of drug-induced hypoglycemia and to identify the probable predisposing factors and their contribution in causing hypoglycemia using relative risk, Chi-square test, and Fisher's exact test. **Findings:** The relative frequency of drug-induced hypoglycemia in our study was 46.25%. Patients' age of ≥65 years, duration of diabetes mellitus for more than 1 year, patients with more than one comorbid condition, and patients using more than one antidiabetic medication were predisposing for developing drug-induced hypoglycemia. **Conclusion:** The relative frequency of drug-induced hypoglycemia in a nontrial environment which lacks the special cares routinely provided in drug development clinical trials is high. We suggest that more attention should be paid to identify, prevent, and manage drug-induced hypoglycemia in type-2 diabetic patients who have more than 1 year of diabetes, more than one comorbidity, using more than one antidiabetic medication, and elderly.

Keywords: *Drug-induced hypoglycemia, predisposing factors, relative frequency, type-2 diabetes mellitus*

Received: November 2018.
Accepted: January 2019.

Introduction

Hypoglycemia is the most common complication in the treatment of diabetes mellitus that presents a barrier for effective blood glucose control.[1,2] Drug-induced hypoglycemic events are more frequent in diabetic patients using insulin preparations and insulin secretagogues compared to other class of antidiabetic medications.[3-5] Hypoglycemia may be acute that cannot be managed easily by patients themselves or by caretakers at home, and in some cases, it may be remarkably severe requiring hospitalization.[6] Hypoglycemia not only disturbs one's daily activities of the patients but also increases the risk of physical injuries and cardiovascular and cerebrovascular complications.[3] Many clinical trials have reported the local and global epidemiology of hypoglycemia. However, data on the frequency of drug-induced hypoglycemia in a nontrial environment (which lacks the special cares routinely provided in drug development clinical trials) are limited.

Access this article online

Quick Response Code:

Website: www.jrpp.net

DOI: 10.4103/jrpp.JRPP_18_58

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How to cite this article: Shariff A, Sridhar SB, Bittar HR, Hamad A, Ahmed R, Kadour G. Frequency and predisposing factors for drug-induced hypoglycemia in patients with type-2 diabetes mellitus. J Res Pharm Pract 2019;8:64-8.

This study was designed to investigate the relative frequency of self-reported drug-induced hypoglycemia and the probable predisposing factors associated with hypoglycemic events among type-2 diabetes mellitus patients in a local setting in the United Arab Emirates (UAE).

Methods

This cross-sectional survey-based study was conducted in two local community pharmacies in the UAE throughout 3 months between February and April 2018. The ethical clearance for this research approved by the institutional and regional research and ethics committees. Diabetic patients visiting community pharmacies for refilling their antidiabetic medications were requested to participate in the study. The inclusion criteria for enrolling patients in this study were type-2 diabetic patients of either gender, who were more than 18 years of age and taking at least one antidiabetic medication.

Following enrolment, all the patients underwent structured interview during which sociodemographic data (age, gender, nationality, education, and occupation) and data pertaining to diabetes mellitus such as duration of diabetes mellitus and information regarding antidiabetic medications (generic name/s, dose, frequency, route of administration and the length of treatment) used by them were collected and documented. Further, details related to hypoglycemia and its symptoms that they might have experienced in the past 2 weeks and frequency of symptoms and its management were also collected by asking specific open-ended questions and were documented.

For the purpose of categorizing the study population into hypoglycemia group, drug-induced hypoglycemia was defined as the presence of at least one typical symptom of hypoglycemia (hunger, tremor, generalized weakness, frank confusion, difficulty thinking blurred vision, behavioral changes, palpitations, lightheadedness/dizziness, sweating, loss of consciousness, headache, and seizure) and/or measured plasma blood glucose level >70 mg/dL at the time of the hypoglycemic event.[6]

Patients in the hypoglycemia group were further categorized into subgroups according to American Diabetes Association Workgroup definitions on different subtypes of hypoglycemia.[6,7]

Collected data were summated and entered into Microsoft excel sheet to ease the data analysis. The relative frequency of drug-induced hypoglycemia in the study population was calculated by dividing the number of patients with drug-induced hypoglycemia (numerator) by the total number of study participants (denominator).

The predisposing factors for the development of drug-induced hypoglycemia were identified by calculating relative risk (RR). The variables tested as predisposing factors were age, gender, number of comorbid conditions, duration of diabetes mellitus, and number of antidiabetic medications consumed by the study participants. RR more than one indicates increased risk of hypoglycemia in the presence of any of the variables tested. Chi-square and Fisher's exact tests of $P < 0.05$ were considered as statistically significant.

Results

A total of 160 patients satisfying inclusion criteria were enrolled in the study. The majority (150 [93.75%]) of the patients were adults between the ages of 21 and 64 years; ten (6.3%) patients were above the age of 65 years. Male population was higher (83 [51.8%]) compared to female population (77 [48.2%]). The majority (119 [74.4%]) of the patients were Arabs whereas 41 (25.6%) patients were non-Arabs.

Among 160 study participants, 74 patients met the criteria to be categorized under drug-induced hypoglycemia group. The relative frequency of drug-induced hypoglycemia in our study was 46.25% (74/160 × 100). A majority (45/74 [60.8%]) of the patients had "documented symptomatic hypoglycemia," followed by 10 patients being "probable symptomatic hypoglycemia" and eight patients being "severe hypoglycemia." There were two patients who had experienced typical hypoglycemic symptoms; however, when their blood glucose level was measured, it was above 70 mg/dl, and hence, they were categorized under "relative hypoglycemia" group, and another nine patients had "asymptomatic hypoglycemia."

The mean self-monitored blood glucose (SMBG) among patients in the drug-induced hypoglycemia group was 62.75 ± 5.8 mg/dL. In majority (38/74 [51.3%]) of the patients, the SMBG was between 61 and 70 mg/dL. Twenty-two patients had SMBG between 51 and 60 mg/dL, two patients had SMBG between 71 and 75 mg/dL, and two patients had SMBG between 41 and 50 mg/dL. In another ten patients, SMBG reading was either not available or not done during the hypoglycemic event.

The majority (43/74 [58%]) of the participants in the hypoglycemia group reported experiencing two symptoms of hypoglycemia, followed by 13 patients who experienced three symptoms. The details of some hypoglycemic symptoms experienced by the participants in drug-induced hypoglycemia group (74/160) are

presented in Table 1. Generalized weakness (32/74) followed by hunger (30/74) was the most common hypoglycemic symptom observed in our study. Tremors (21/74) and blurred vision (21/74) were the third most common hypoglycemic symptoms reported, and three patients had fainting/loss of consciousness. The frequency of drug-induced hypoglycemic symptoms reported by the participants in drug-induced hypoglycemia group (74/160) is presented in Table 2.

Among 74 participants with drug-induced hypoglycemia, a majority (31/74 [41.9%]) were taking two antidiabetic medications, followed by 23 (31%) patients taking three antidiabetic medications. There were 14 (18.9%) patients taking one antidiabetic medication, and six (8.1%) patients were taking four antidiabetic medications.

A majority (36 [48.6%]) of the patients managed drug-induced hypoglycemic event on their own by consuming nutrition rich in sugar such as dates, honey, chocolate, sugar candy, and fruit juices. All the eight patients with severe hypoglycemia were admitted to the hospital, seven of them received intravenous glucose, and one patient received intravenous glucose and glucagon. The maximum duration of hospital stay was 48 h.

Among the probable predisposing factors for the development of drug-induced hypoglycemia, significant association ($P < 0.05$) was observed between the occurrence of hypoglycemia and age (≥65 years), duration of diabetes mellitus (>1 year), number of c-morbidities (>1), and number of concomitant antidiabetic medications (>1). The details of assessed predisposing factors among the total study participants ($N = 160$) (where participants in drug-induced hypoglycemia and nonhypoglycemia groups were 74 and 86 respectively) are presented in Table 3.

Table 1: Number of hypoglycemic symptoms experienced by the participants in the drug-induced hypoglycemia group (*n*=74)

Number of hypoglycemic symptoms	Number of patients (%)
Two	43 (58)
Three	13 (17.5)
Four	4 (5.5)
More than four	5 (6.75)
Asymptomatic	9 (12.25)

Table 2: Frequency of hypoglycemic symptoms reported by the by the participants in the drug-induced hypoglycemia group (*n*=74)

Types of symptoms	Number of patients (%)
Generalized weakness	32 (43.25)
Hunger	30 (40.5)
Tremors	21 (28.4)
Blurred vision	21 (28.4)
Lightheadedness/dizziness	17 (23)
Sweating	14 (19)
Confusion/mental cloudiness	14 (19)
Headache	11 (14.9)
Sudden mood changes/irritability	5 (6.75)
Increased heartbeats	5 (6.75)
Fainting/loss of consciousness	3 (4)

Discussion

The relative frequency of drug-induced hypoglycemia in our study was higher compared to other reported studies.[8-11] Frequency of drug-induced hypoglycemia varies with study setting, study design, study population, sample size, type of antidiabetic medications used by the study participants, and most importantly the definition of hypoglycemia in a particular study.[5]

In our study, hypoglycemia was defined as the presence of at least one typical symptom of hypoglycemia with or without measured plasma blood glucose level <70 mg/dL at the time of the hypoglycemic event, which is similar to the definition of hypoglycemia adopted in a study conducted by Vikas *et al*. in a South Indian hospital.[8]

The study conducted by Turchin *et al*. in a teaching hospital reported a prevalence of drug-induced hypoglycemia as 7.7%, and in another study conducted by Wexler *et al*., it was 15%. This difference was mainly because Turchin *et al*. defined hypoglycemia as capillary blood glucose (CBG) level <50 mg/dl in their study in contrast to Wexler *et al*., who considered patients with CBG level <60 mg/dl as hypoglycemic.[10,11]

Insulin preparations and sulfonylureas (insulin secretagogues) are known to induce hypoglycemia more commonly (by their mechanism of action), resulting in high incidence of hypoglycemia reported for these class of antidiabetic medications compared to other classes.[12-15] Around one-third of the patients in the hypoglycemia group in our study were using insulin therapy (alone or with oral antidiabetic medication/s), and 17 patients (~23%) were using sulfonylureas (alone or with other oral antidiabetic medication/s). This could be another possible reason for the high frequency of drug-induced hypoglycemia in our study.

We assessed gender as one of the probable predisposing factors for drug-induced hypoglycemia. Although the frequency of drug-induced hypoglycemia is slightly high among the female population, there was no statistically significant difference observed concerning gender as a predisposing factor. Similar observations were documented in a study conducted by Leese *et al*. in the UK and in a review by Giorda *et al*.[16,17]

Table 3: Predisposing factors among study population (total study population (*n*=160); drug-induced hypoglycemia group (*n*=74) and nonhypoglycemia group (*n*=86)

Variable	Category	Drug-induced hypoglycemia		RR (95% CI)	*P*
		No (*n*=86)	Yes (*n*=74)		
Gender	Male	47	36	1 (reference)	0.448†
	Female	39	38	1.138 (0.815-1.589)	
Age group (years)	Adults (21-64)	85	65	1 (reference)	0.0061‡,*
	Elderly (≥65)	1	9	2.076 (1.576-2.737)	
Duration of diabetes mellitus	<6 months	32	4	1 (reference)	0.1594‡
	6 months to 1 year	35	12	2.297 (0.808-6.534)	
	1-5 years	16	29	5.800 (2.245-14.983)	<0.00001‡,*
	>5 years	3	29	8.156 (3.216-20.685)	<0.00001‡,*
Comorbid conditions	None	30	13	1 (reference)	0.410†
	One	51	31	1.250 (0.734-2.129)	
	Two	3	23	2.926 (1.820-4.704)	<0.00001‡,*
	Three	2	7	2.572 (1.450-4.562)	0.0192‡,*
Number of antidiabetic medications	One	83	14	1 (reference)	<0.00001‡,*
	>1	3	60	6.599 (4.052-10.746)	

†Chi-square test, ‡Fisher's exact test, **P*<0.05 is statistically significant. RR=Relative risk, CI=Confidence interval

Age was another predisposing factor that was tested in our study. We observed that type-2 diabetic patients in advanced age (>65 years) are more susceptible to drug-induced hypoglycemia. In general, age-related physiological changes in the liver and kidneys often decrease the clearance of any antidiabetic medications, leading to their enhanced biological half-life and increased likelihood of hypoglycemia. Aging also compromises the physiological defenses of glucose counter-regulation, thereby the frequency of hypoglycemic episodes increases in elderly diabetic patients. Furthermore, an increased number of comorbid conditions in elderly patients can lead to polypharmacy that further increases the chances of drug interactions resulting in increased susceptibility of hypoglycemia.[18,19] A study conducted by Kagansky *et al*. also documented similar observations concerning drug-induced hypoglycemia among elderly diabetic patients.[20]

There is a significant relationship between some comorbidities and drug-induced hypoglycemic events. Diabetic patients often on polypharmacy either due to co-existing clinical condition/s or most likely to manage diabetes-related complications.[21] In addition, diabetic patients tend to receive over-the-counter medications and follow alternative health approaches such as traditional medicines and naturopathy that are more likely to interact with their antidiabetic medications and predispose them for increased frequency of hypoglycemic episodes.[22] We Observed increased likelihood of drug-induced hypoglycemia in patients with two and three comorbid conditions compared to patients having one or no comorbid condition. Similar observations were also reported by the study conducted by Maynard *et al*. in which authors describe that the risk of drug-induced hypoglycemia increased with increased number of comorbid conditions.[23]

In our study, patients having diabetes mellitus since 1–5 years of duration and >5 years of duration were more susceptible for drug-induced hypoglycemia, compared to patients having diabetes mellitus since <1 year. These findings are similar to that of observed in the other two studies conducted by Lin *et al*. and Ben-Ami *et al*.[24,25] This is probably because diabetic patients will show progressively impaired glucagon response in a hypoglycemic state within first 5 years of diagnosis and within 10 years of diagnosis, most of the patients will have impaired epinephrine response leading to frequent episodes of hypoglycemia.[26,27]

We observed that the likelihood of drug-induced hypoglycemic events increases with use of more than one antidiabetic medication. Twenty-eight patients (37.8%) in the hypoglycemia group were identified to have potential drug–drug interactions between the antidiabetic medications that they were using. The probable mechanism of hypoglycemia in those patients might be due to altered glucose metabolism or a synergism that further linked to increased frequency.[27,28] These findings are very much similar to the observations of Ben-Ami *et al*.'s study.[25]

The strengths of our study are that we defined hypoglycemia broadly to match the real-world scenario that can give us the actual frequency of hypoglycemic events in a nontrial environment, which was not there in the majority of the other published studies. The important limitations were, this study was conducted in only two sites and for short duration with less number of population.

In conclusion, our study emphasizes the need for adequate knowledge on safe use of antidiabetic medications by the patients that can contribute to reducing the frequency of hypoglycemic events. Pharmacists are at a right position to support individualized patient care by adequately reviewing the medications and providing suitable counseling on safe use of antidiabetic medications that can add to early detection, prevention, and management of hypoglycemia in at-risk patients.

Authors' Contribution

All authors contributed to the concept of this research, study design, data gathering, analysis or interpretation, and revised the drafted manuscript and approved its final version. They also are accountable about the content of this manuscript and guarantee the integrity of research.

Acknowledgments

We would like to sincerely thank Dr. Gurumadhva Rao, President, RAK Medical and Health Sciences University, Dr. Padma GM Rao, Dean, RAK College of Pharmaceutical Sciences, RAK Medical and Health Sciences University, all the study participants, and owners of community pharmacies for their continuous support and encouragement for the research work.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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