

RESEARCH ARTICLE

Hypoglycaemia cases in diabetic patients with insulin and oral hypoglycemic agents: A retrospective research in a secondary health facility

Trung Quang Vo

Abstract

Objective: In Vietnam, prevalence of diabetes in adults is estimated at 5.5% and the total cases of diabetes in adults was over 3,5 million in 2017. Hypoglycaemia is one of the most-observed adverse reaction associated with the consumption of insulin and oral hypoglycaemia agents. The objective is to report the hypoglycaemia cases in type 2 diabetes mellitus (T2DM) patients with medication therapies attending a secondary health facility.

Methods: We conducted this retrospective research on 1,006 T2DM patients at Lam Dong General Hospital, Lam Dong province in three years between 2016 and 2018 using ICD-10 code of E11. A total of 523 eligible T2DM patients were enumerated to select hypoglycaemia cases while treated with insulin therapy or oral intake of hypoglycaemia agents. Information were extracted from hospital electronic databases, sensitive information was coded.

Results: Among 523 eligible T2DM patients, 92.4% (n=483) patients experienced at least one symptom of hypoglycaemia. The mean age of the selected patients was 51.2±5.2. Females were dominated by males in terms of number. Frequency of hypoglycaemia symptoms was 0-1 time per week for most of patients. The main hypoglycaemia symptoms that most of patients with T2DM suffered were sweating and drowsiness (83% and 70% respectively). Seizures, headache and loss of consciousness accounted for lowest percentages.

Conclusion: The frequency of hypoglycaemia in T2DM patients in Lam Dong General Hospital was very high. Physician consideration and patient education are necessary in hypoglycaemia management.

Keywords: Hypoglycaemia, Diabetes, Insulin, Vietnam. (JPMA 69: S-75 (Suppl. 2); 2019)

Introduction

Diabetes mellitus (DM) becomes a worldwide consideration, especially in developed countries. Type-2 diabetes mellitus (T2DM) has been encountered in younger age, which associated with fatty diet and lack of exercises. International Diabetes Federation (IDF) assessed the prevalence of DM diabetes mellitus (DM) among 425 million individuals all over the world. In Vietnam, prevalence of diabetes in adults is estimated at 5.5% and the total cases of diabetes in adults was over 3,5 million in 2017.¹ T2DM is increasing in terms of its prevalence at a rapid pace due to older age, decreased physical activity and increase in obesity.²

From the release of the first hypoglycaemia agents, medication therapies in T2DM treatment have developed significantly. Oral hypoglycaemia agents and insulin have performed their efficacy in plasma glucose concertation stabilization. Besides being effective, these drugs cause a range of adverse reactions, including hypoglycaemia. Hypoglycaemia is a diabetic complication which results in the shape of neuroglycopenic symptoms or at times death if not managed appropriately. T2DM has also an association with

macrovascular, microvascular and neuropathic disorders.³ The brain becomes neuroglycopenic during hypoglycaemia and it also promotes epinephrine secretion & norepinephrine including glucagon that has relevance to cardiovascular diseases (CVD) effects by rapid production response. There are no such signs of this situation and diabetes type has a positive role to play in the event of severe hypoglycaemia frequency.⁴ There are one and three events for the T1DM patients in a year; whereas, for T2DM 0.4 and 0.7. T2DM may also have a value of three as well. Previous research studies also report an event of 1.7 percent & 1.8 percent for episodes of hypoglycaemia.^{5,6}

Hypoglycaemia among T2DM patients may also contribute to the clinical outcomes compromised situation as a result of delayed or missed treatment of insulin.⁷⁻⁹ Another reason for events of hypoglycaemia is also known as overdose of medication such as insulin. Majority of the T2DM patients also follow lifestyle modification with oral intake of metformin in order to control the level of glycaemia as a first-line therapy. By contrast, as an eventual strategy good glycaemic control management among T2DM needs intensification of management. Old age, pregnancy and renal failure cases are at an increased risk of severe hypoglycaemia.^{10,11} The objective of this study was to report the hypoglycaemia cases in T2DM patients with medication therapies

.....
Department of Economic and Administrative Pharmacy, Pham Ngoc Thach University of Medicine, Ho Chi Minh City, Vietnam.
Correspondence: Email: trungvq@pnt.edu.vn

attending a secondary health facility.

Patients and Methods

A retrospective study was conducted using an electronic database at Lam Dong General Hospital, Lam Dong province during the three-year period between 2016 and 2018.

Lam Dong General Hospital is a secondary governmental hospital serving both the urban and rural population in the highland area of central southern Vietnam. The hospital has a capacity of 700 beds with 658 staffs, including 124 physicians, 267 nurses and 267 healthcare staffs (unpublished data).

Recorded information from 2016 to 2018 was extracted from the hospital electronic database using International Classification of Diseases Tenth Version (ICD-10).¹² A total of 1,006 patients with the ICD-10 code of E11 was enrolled. Outpatients; patients who do not comply with the treatment protocol and voluntarily discontinued treatment; those with unclear or missing medical record information; patients with hepatic failure, excessive alcoholism, renal failure or cardiac failure, were excluded. Of these, 523 patients' information was reviewed one by

one to include the patients who suffered from hypoglycaemia when treated with insulin or oral hypoglycaemic agents (OHA) or combined therapies. In the end, 483 patients who fulfilled the entire criteria were included in this study. Symtomatic hypoglycaemia is defined among patients with diabetes as the decrease of blood glucose level below 3.3 mmol/L (60 mg/dL).¹³

Statistical Analysis: All statistical analyses were performed using Microsoft Excel 2016. Descriptive statistics (frequency, percentage, mean and standard deviation) were used to summarize data on demographic characteristics; duration and frequency of hypoglycemic symptoms; and prevalence of hypoglycemic symptoms among T2DM patients.

This research protocol was approved by the Lam Dong General Hospital, Lam Dong province. Sensitivity information was coded to insure the anonymity. The whole data was used for research purposes only.

Results

After screening based on included and excluded criteria aforementioned, there were 483 patients chosen among

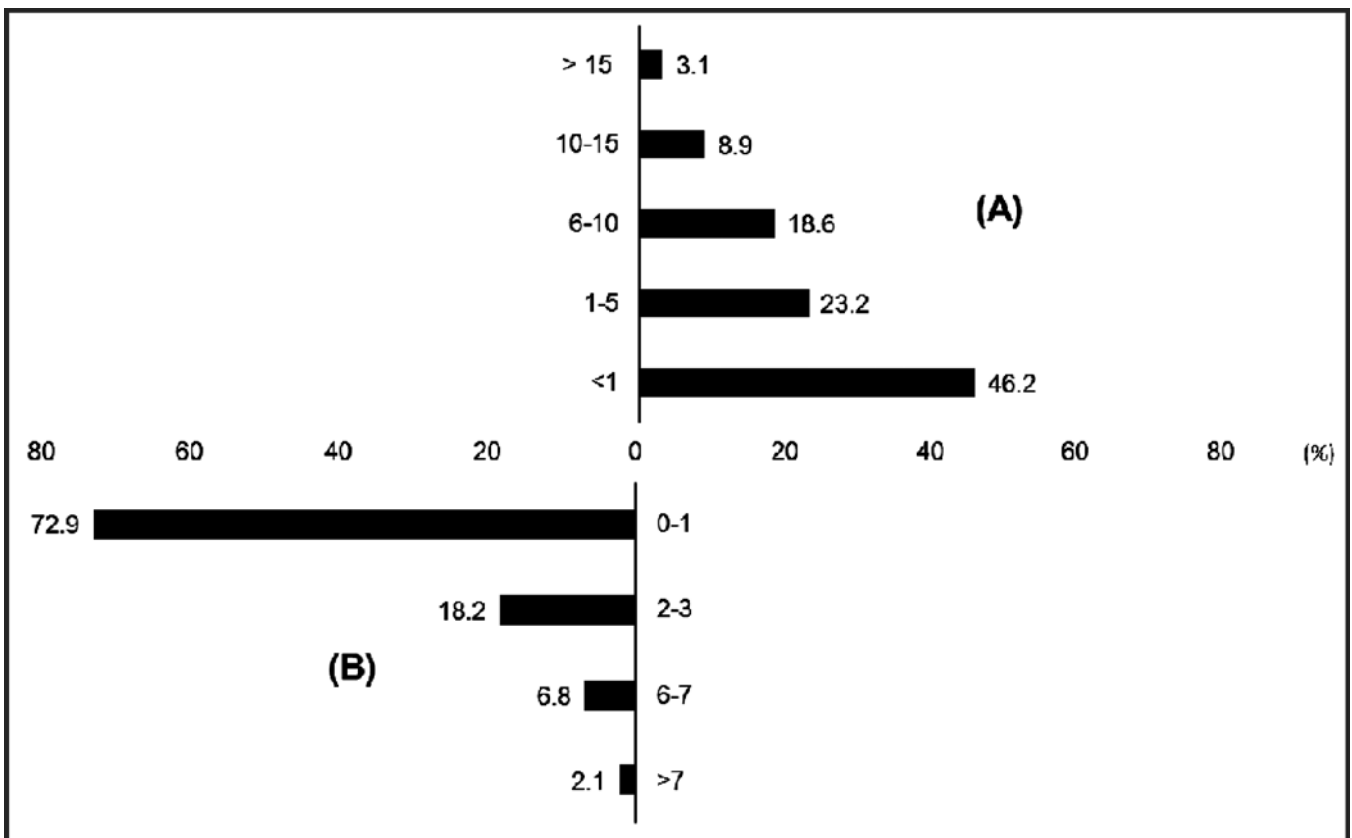


Figure-1: (A) Duration of hypoglycaemic symptoms (years)*. (B) Frequency of hypoglycaemic symptoms (times per week).

*Note: duration of hypoglycaemic symptoms is the time interval from the first to the latest point of time that patients suffered from any of hypoglycaemic symptoms; data presented as percentage.

Table-1: Demographic characteristics of 483 T2DM patients with hypoglycaemia [n, %].

Patients' characteristics	n	%	Patients' characteristics	n	%
Age (years)			Duration of T2DM (years)		
Mean (SD)		52.1(5.2)	Mean (SD)		9.3(2.7)
≤ 30	8	1.7	1-5	94	19.5
31 - <40	75	15.5	6-10	291	60.2
41 - <50	135	28.0	10-15	71	14.7
51 - <60	166	34.4	> 15	27	5.6
≥ 60	99	20.4	Cause of hypoglycaemia		
Gender			OHA's	156	32.3
Male	278	57.6	Insulin	87	18.0
Female	205	42.4	LOA	14	2.9
Marital status			Insulin + LOA	56	11.6
Married	398	82.4	OHA's + LOA	43	8.9
Unmarried	85	17.6	OHA's + Insulin	65	13.5
Family income ⁽¹⁾			Unkonwn	62	12.8
< 1	70	14.5	Complications		
1 - < 2	316	65.4	With complication(s)	102	21.1
≥ 2	97	20.1	Without complication	381	78.9
Adequate income or not			Smoking		
Yes	387	80.1	Yes	76	15.7
No	96	19.9	No	235	48.7
Educational status			Used to	56	11.6
Illiterate	17	3.5	Unkonwn	116	24.0
Primary	34	7.0	Alcohol consumption		
Secondary	68	14.1	Yes	109	22.6
Intermediate	98	20.3	No	288	59.6
Graduation	241	49.9	Used to	51	10.6
Post-Graduation	25	5.2	Unkonwn	35	7.2
BMI ⁽²⁾ (kg/m ²)			HbA1c		
<18.5	57	11.8	Mean (SD)		7.3(1.6)
18.5 - <23.0	245	50.7	Awareness of hypoglycaemia		
≥ 23.0	181	37.5	Yes	337	69.8
No	146	30.2			

Notes:⁽¹⁾: GDP per capita per month; 195.26 USD; ⁽²⁾: BMI = Weight (kg)÷{Height x Height (m²)}

Abbreviations: BMI, Body Mass Index; T2DM, Type 2 Diabetes Mellitus; SD, Standard Deviation; OHA's, Oral Hypoglycemic Agents; LOA, Loss Of Appetite.

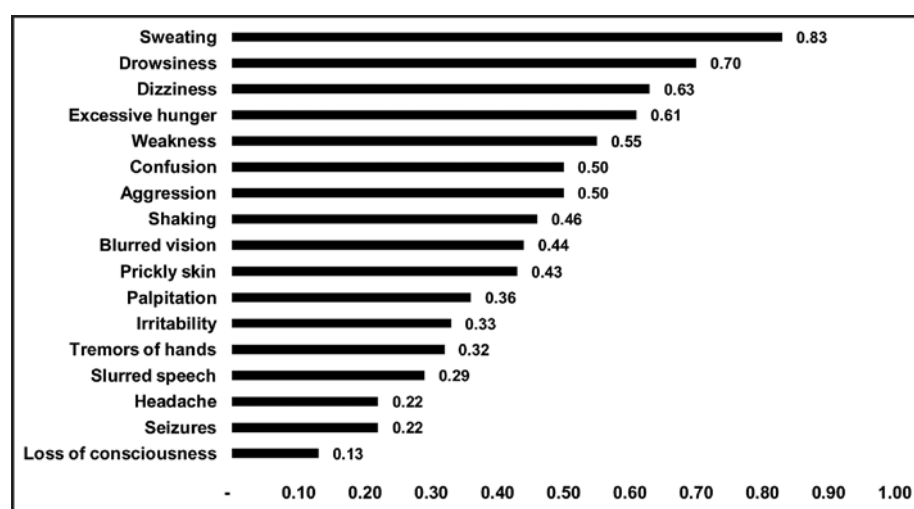


Figure-2: Prevalence of hypoglycaemic symptoms among patients with T2DM in Vietnam (2016-2018, n=483).

which most were between the age of 51 to 59 years (mean: 51.2±5.2) and the percentage of males was slightly higher (57.6% vs 42.4%). Nearly half of participants were in the normal range of BMI (Body Mass Index). Participants with no complications had a diabetes duration of 9.3 years with a HbA1c between 5.7 to 8.9. Hypoglycaemia, was related to OHA's (oral hypoglycemics agents) in one-third patients 156 (32.3%), followed by insulin 87 (18%) and the combination of insulin and OHA's 65 (13.5%). Approximately 337 (70%) patients affirmed that they could

recognized their hypoglycaemia symptoms. The demographic characteristics are expressed in Table-1.

Nearly half of patients 201 (46.2%) suffered symptoms of hypoglycaemia in less than one year, followed by 23.2% of patients with 1-5-year period. The figure for 10-15 year were 8.9% of total patients. Patients with above 15 years were lowest, just 3.1%. Frequency of hypoglycemic symptoms per week was 0-1 for most of patients. T2DM patients who suffered 2-3 time per week was 18.2% compared to 2.1% patients with more than 7 time. Data were presented in Figure-1. The main hypoglycemic symptoms that most of patients with T2DM suffered were sweating and drowsiness (83% and 70% respectively). Half of the patients got features such as dizziness, weakness, aggression, confusion and excessive hunger in their time-life. Seizures, headache and loss of consciousness accounted for lowest percentages among patients (each below than 25%). Prevalence of hypoglycaemic symptoms among T2DM patients in Vietnam was presented in Figure-2.

Discussion

This was a three-year retrospective study conducted with the objective of finding the characteristics of T2DM patients who suffered from hypoglycaemia during admission and hospitalization.

Among 523 eligible T2DM patients, 483 (92.4%) patients experienced at least one symptom of hypoglycaemia. This percentage was similar to the latest studies in Chennai (India)¹⁴ and Petaling Jaya (Malaysia),¹⁵ which were 96% and 82.7% respectively. These numbers were extremely higher than those reported by American Association of Clinical Endocrinologists. Thereby, 55% among 2,350 Americans with T2DM reported having experienced hypoglycaemia.

Background characteristics of patients in this study were similar to the two latest studies from India and Malaysia. The mean age of participants in Malaysian study was 62.5 ± 12.2 years,¹⁵ higher than in this study (52.1 ± 5.2). The Malaysian authors also found that age was significantly associated with severe hypoglycaemia ($p < 0.05$). Barnett AH (2010)¹⁶ and Umpierrez GE (2011)¹⁷ reported the same results in their studies. According to Alagiakrishnan K (2010), the aging process became less effective in hypoglycaemia prevention.¹⁸ Moreover, hypoglycaemia response in elderly people became weak and the symptoms usually were severe. Diminished autonomic symptoms such as fatigue and headache resulted in late diagnosis of hypoglycaemia.

The majority in the both Malaysian and Vietnamese

participants were neither smokers nor alcohol-drinkers. In 2013, Ahren B explored alcohol consumption as one of contributing risk factors for hypoglycaemia.¹⁹ The others identified risk factors were sulphonylurea therapy, missed meal, delayed exercise and medication irregularly.

Most of patients in Vanishree S's study had T2DM for a duration of equal or less than 10 years (61.2%). similar to those in this study (79.7%). However, a half of Indian patients had experienced hypoglycaemia for 1-5 years, while 46.2% Vietnamese patients had experienced hypoglycaemia for under one year. Vietnamese participants, however, suffered from hypoglycaemia more frequently (0-1 times per week, 73%) than those in India (rarely, 51%). The frequency of hypoglycaemia in T2DM depends on the degree and the type of diabetes management. Bahjri S (2013) reported that among those who received the standard diabetes management, the frequency of mild hypoglycaemia was 1.5 episodes per patient per year and the frequency of severe hypoglycaemia was 0.02 episodes per patient per year.²⁰

The prevalence of hypoglycaemia symptoms in the two studies were slightly different from each other. In India, weaknesses was the most-observed symptom (76.2%) whereas seizure was the least-observed (0.8%). These figures in this study were 55% and 22% respectively. Vietnamese patients experienced most from sweating (83%) and least-experienced from loss of consciousness (13%).

In this study, the main cause of hypoglycaemia was OHAs ($n=156$, 32.3%). This finding was different from the others. The Malaysian study found insulin intake on admission and during hospital stay to be the main cause ($n=404$, 71.4%). In addition, they proved that insulin consumption was associated with the severity of hypoglycaemia episodes ($p=0.0001$). The Indian study also found the significant difference on the percentage of hypoglycaemia episodes between the two groups of medication usage: only OHAs versus insulin with OHAs ($p=0.003$). Insulin was also considered to be associated with the frequency of hypoglycaemia in previous studies. It was indicated by Miller CD (2001) that the prevalence of hypoglycaemic symptoms was 12% in patients on a diet alone, 16% in patients using OHAs alone, and 30% among those using insulin. Severe hypoglycemic symptoms, moreover, were observed only among patients using insulin.²¹

This study has limitations that should be considered. Although severities (mild, moderate, severe) is one of the most important parameters in hypoglycaemia assessment, this study could not document it, due to the

shortage of information. The study subjects were diagnosed to have hypoglycaemia based on plasma glucose concentration, which was not always measured. In addition, hypoglycaemia occurrence was highly influenced by patients self-monitoring which was very frequent. The subjective symptoms of hypoglycaemia were also easily confused with the other conditions. These symptoms not only occurred in T2DM patients but also in normal individuals. The association between prevalence of hypoglycemia and the risk factors could not be explored.

Despite the limitations, this study was the first one to be conducted in Vietnam with the aim of reporting hypoglycaemia cases in T2DM patients. It highlights the percentage of hypoglycaemia in the sample, frequency and symptoms of hypoglycaemia.

Conclusion

This study found that the frequency of hypoglycaemia in T2DM patients in Lam Dong General Hospital was very high. Physicians should consider these findings in their prescription and patients care. It is also important to educate the patients on their self-monitoring, drug compliance and appropriate diet to prevent hypoglycaemia.

Acknowledgement: The author would like to acknowledge the volunteer participants for data collection. No funding was received for this analysis.

Disclaimer: None to declare.

Conflict of Interest: None to declare.

Funding Disclosure: None to declare.

References

1. International Diabetes Federation (IDF). Diabetes in Vietnam. [Online] 2017 [Cited 2019 February 20]. Available from URL: <https://www.idf.org/our-network/regions-members/western-pacific/members/119-vietnam.html>
2. Mustafa SAEO. Study of Optic Nerve Diameter in Diabetic Patients Using Magnetic Resonance Imaging (MRI). Sudan University of Science and Technology 2018. [Uncited].
3. Peimani M, Monjazebi F, Ghodssi-Ghassemabadi R, Nasli-Esfahani E. A peer support intervention in improving glycemic control in patients with type 2 diabetes. *Patient Educ Couns* 2018;101:460-466.
4. Sharma B, Mittal A, Dabur R. Mechanistic approach of anti-diabetic compounds identified from natural sources. *Chem Biol* 2018;5:63-99.
5. Newton P, Asimakopoulou K, Scambler S. A Qualitative Exploration of Motivation to Self-Manage and Styles of Self-Management amongst People Living with Type 2 Diabetes. *J Diabetes Res* 2015;2015:638205.
6. Sheuly AH. Prevalence of diabetes among tuberculosis patients attending a tertiary care hospital. University of Dhaka 2018. [Uncited].
7. Echouffo-Tcheugui JB, Sheng S, DeVore AD, Matsouaka RA, Hernandez AF, Yancy CW, et al. Glycated hemoglobin and outcomes of heart failure (from get with the guidelines-heart failure). *Am J Cardiol* 2019;123:618-626.
8. Choi SH, Youn DK, Choi MG, Ryu OH. Characteristics of hypoglycemia patients visiting the emergency department of a university hospital. *J Korean Diabetes* 2016;17:202-11.
9. Ryan CM, Klein BEK, Lee KE, Cruickshanks KJ, Klein R. Associations between recent severe hypoglycemia, retinal vessel diameters, and cognition in adults with type 1 diabetes. *J Diabetes Complications* 2016;30:1513-1518.
10. Pedersen-Bjergaard U, Thorsteinsson B. Reporting severe hypoglycemia in type 1 diabetes: facts and pitfalls. *Curr Diab Rep* 2017;17:131.
11. Siddiqui MU, Ali I, Zakariya M, Asghar SP, Ahmed MR, Ibrahim GH. Frequency of hypomagnesemia in patients with uncontrolled type ii diabetes mellitus. *Pak Armed Forces Med J* 2016;66:845-50.
12. World Health Organization. International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10)-WHO Version. [Online] 2016 [Cited 2018 October 01]. Available from URL: <https://icd.who.int/browse10/2016/en#/I/X>
13. Katon WJ, Young BA, Russo J, Lin EH, Ciechanowski P, Ludman EJ, et al. Association of depression with increased risk of severe hypoglycemic episodes in patients with diabetes. *Ann Fam Med* 2013;11:245-50.
14. Shriram V, Mahadevan S, Anitharani M, Jagadeesh NS, Kurup SB, Vidya TA, et al. Reported hypoglycemia in Type 2 diabetes mellitus patients: Prevalence and practices-a hospital-based study. *Indian J Endocrinol Metab* 2017;21:148-153.
15. Huri HZ, Aziz MIA, Vethakkan SR, Widodo RT. Factors associated with hypoglycemia episodes in hospitalized type 2 diabetes mellitus patients in a tertiary health facility in Malaysia. *Trop J Pharm Res* 2016;15:1313-20.
16. Barnett AH, Craddock S, Fisher M, Hall G, Hughes E, Middleton A. Key considerations around the risks and consequences of hypoglycaemia in people with type 2 diabetes. *Int J Clin Pract* 2010;64:1121-9.
17. Umpierrez GE, Smiley D, Jacobs S, Peng L, Temponi A, Mulligan P, et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 surgery). *Diabetes Care* 2011;34:256-61.
18. Alagiakrishnan K, Mereu L. Approach to managing hypoglycemia in elderly patients with diabetes. *Postgrad Med* 2010;122:129-37.
19. Ahrén B. Avoiding hypoglycemia: a key to success for glucose-lowering therapy in type 2 diabetes. *Vasc Health Risk Manag* 2013;9:155-63.
20. Bahijri S, Borai A, Ajabnoor G, Abdul Khaliq A, AlQassas I, Al-Shehri D, et al. Relative metabolic stability, but disrupted circadian cortisol secretion during the fasting month of Ramadan. *PLoS One* 2013;8:e60917.
21. Miller CD, Phillips LS, Ziemer DC, Gallina DL, Cook CB, El-Kebbi IM. Hypoglycemia in patients with type 2 diabetes mellitus. *Arch Intern Med* 2001;161:1653-59.