Pharmacology and Clinical Pharmacy Research
Volume 3 No 2 August 2018
ISSN:2527-7332 | e-ISSN: 2614-0020
doi: 10.15416/pcpr.v3i2.16453

Hypoglycemia Risk Factors among Hospitalized Type 2 Diabetes Mellitus Patients

Meilani Jayanti[1,2], Keri Lestari[2], Rizky Abdulah[2]

[1]Kandou General Hospital, Manado, North Sulawesi, Indonesia
[2]Department of Pharmacology and Clinical Pharmacy, Universitas Padjadjaran, Jatinangor, West Java, Indonesia

Abstract

Hypoglycemia is one of the most common complications of diabetes treatment. Recognition of hypoglycemia risk factors, blood glucose monitoring, selection of appropriate regimens and educational programs are important measures to prevent the risk of hypoglycemia. This study aimed to investigate hypoglycemia risk factors among hospitalized type 2 diabetes mellitus patients. This research employed retrospective method with case control design. We included 72 patients, which were categorized as case group or patients who experienced hypoglicemia (32%) and control group (68%). Several demographic and clinical characteristics were obtained from each patient. Multivariate logistic regression analysis showed that there were significant differences in several variables, including the reduction in food intake (OR 9.329 , 95% CI 1.69, 51.64) and HbA1c score (OR 0.503, 95% CI 0.321, 0.789) between case and control group. On the other hand, other variables such as polypharmacy, the use of certain antidiabetic drugs, the presence of comorbidities, age, and diabetes duration showed no significant association with hypoglycemic events. In conclusion, hypoglycemic risk factors among hospitalized type 2 diabetes mellitus patients were reduction in food intake and low HbA1c score.

Keywords: type 2 diabetes mellitus, hypoglycemia, food intake, HbA1c

Introduction

Hypoglycemic is an acute complication of diabetes mellitus (DM) and a major constraint in the management of DM. In addition, it can negatively influence the quality of life of DM patients.[1-3] Hypoglycemic event which is not immediately addressed can develop rapidly into serious events involving nerve damage, cognitive dysfunction, coma, seizures, even death.[4]

In observations made within 1 year, the mortality rate caused by hypoglycemic (22.6%) was higher than the mortality rate caused by hyperglycemic event (17.6%). Over a 12 year period, hospital admission rates for hyperglycemic decreased 38.6%, while hospital admissions for hypoglycemic increased 11.7%. Inpatient patients with hypoglycemic events have a higher comorbid

Corresponding author: Meilani Jayanti, Kandou General Hospital, Manado, North Sulawesi, Indonesia.
Email: meilani.jayanti@gmail.com
Received: 24 May 2018. **Revised:** 28 June 2018. **Published:** 1 August 2018.

ISSN:2527-7332 | e-ISSN: 2614-0020

burden than inpatients with hyperglycemic.[5]

Previous study showed that several risk factors of hypoglycemic events included elderly, increased physical activity, decreased carbohydrate intake, alcohol consumption, strict glycemic control, impaired renal or liver function, infection, presence of comorbidities, changes in pharmacological therapy regimens, and polypharmacy.[6-9]

Glycemic control should be done individually based on patient characteristics. Knowledge regarding hypoglycemia risk factors may be helpful in minimizing hypoglycemic risk, preventing long-term complications and improving patient quality of life.[6] Thus, this study aimed to investigate hypoglycemia risk factors among hospitalized type 2 DM patients.

Methods

Research subject and data retrieval

This research was conducted at Kandou General Hospital, Manado, with ethical clearance number: PP.22 / I / Diklit / 2016 and UPKT number 022 / EC-UPKT / I / 2016. This study used case-control design with retrospective approach. Inclusion criteria in this study were patients who were diagnosed with type 2 DM based on the International Classification of Diseases, which belongs to E11[9] (uncomplicated type 2 DM), treated in inpatients wards during January-December 2015, and received pharmacological therapy. The exclusion criteria in this study were patients with incomplete medical records data.

In this study, the case was a group of patients who experienced hypoglycemic episodes during treatment at the hospital. Meanwhile, the control is a type 2 DM patient who did not experience hypoglycemic episodes.

Measurement of variables.

The independent variables measured in this study were several demographic and clinical characteristics which were predicted to be associated with hypoglicemic event, including age, sex, duration of DM (years), duration of treatment, body mass index (BMI), decreased food intake, laboratory results, comorbidities, certain antidiabetic medication, concomitant drugs, and polypharmacy. Laboratory results included hemoglobin, hematocrit, platelets, leukocytes, erythrocytes, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), serum creatinine, HbA1c, albumin, total protein, total cholesterol, triglycerides, uric acid, sodium and potassium. Concomitant drugs included benzodiazepines, allopurinol, salicylates, angiotensin-converting enzyme inhibitors (ACEI), rennin-angiotensin system blockers (RASBs), calcium channel blockers (CCB), beta-blockers, lipid lowering agents, diuretics. Polypharmacy is defined as the use of $\geq$ 5 drugs by a patient. Concomitant diseases included hypertension, coronary artery disease, congestive heart failure, dyslipidemia, infection, chronic kidney disease, cancer and cirrhosis. The dependent variable measured in this study was the development of hypoglycemic events with serum glucose levels measured <70 mg/dl or the presence of symptoms that met the Whipple's Triad (low glucose serum, hypoglycemic symptoms, and loss of symptoms after glucose administration) during treatment at the hospital.

Statistical analysis

Numerical data is presented as mean ± SD (standard deviation). It was then analyzed by t-test or Mann-Whitney test. Categorical data is displayed as percentage (%) of frequency. It was then analyzed by Chi-square test or Fisher's exact test. Bivariate analysis was performed to assess the association between

Table 1. Characteristics of participants

Characteristics	Hypoglycemia (n=23)	Non-hypoglycemia (n= 49)	P-value*
General characteristics			
Sex			
Male	8 (34.8)	15 (30.6)	0.723+
Female	15 (65.2)	34 (69.4)	
Age (years)	61.78 ± 12.19	58.77±10.92	0.297
DM duration	9.61 ± 9.19	6.73 ± 7.05	0.306**
Treatment duration	10.87 ± 5.55	9.06 ± 4.99	0.14
BMI (kg/m2)	21.65 ± 3.97	23.81 ± 3.65	0.015
Reduction of nutrition intake	19 (65.5)	10 (34.5)	< 0.001+
Laboratory result			
Haemoglobin (g/dl)	10.46 ± 2.70	12.01 ± 2.40	0.017
Hematocrite (%)	33.60 ± 6.84	34.36 ± 7.24	0.674
Thrombocyte (cell/µl)	277,913.04 ± 111.707	271,469.39 ± 105.539	0.989
Leukocyte (cell/µl)	11,965.74 ± 2972.32	9401.12 ± 3046,76	0.001
Erithrocyte (juta/µl)	3.86 ± 0.79	4.11 ± 0.93	0.262
HbA1c (mg/dl)	8 ± 1.5	11.38 ± 2.6	< 0.001
Ureum (mg/dl)	81.79 ± 69.75	38.17 ± 19.49	0.007
Serum creatinin (mg/dl)	2.93 ± 3.08	1.17 ± 0.62	0.014**
Uric acid (mg/dl)	6.88 ± 2.85	5.43 ± 1.63	0.018**
Albumin (g/dl)	3.10 ± 0.65	3.44 ± 0.63	0.037
Protein total (g/dl)	6,62 ± 0.46	6.68 ± 0.61	0.68
Natrium (mg/dl)	131.65 ± 7.85	131.96 ± 8.61	0.885
Kalium (mg/dl)	3.78 ± 1.03	3.80 ± 0.90	0.944
Cholesterol (mg/dl)	175.09 ± 42.49	174.47 ± 50.46	0.96
Trygliceride (mg/dl)	140.57 ± 66.16	150.29 ± 77.95	0.408**
SGOT (U/l)	28.26 ± 24.17	27.96 ± 24.33	0.479**
SGPT (U/l)	20.65 ± 14.30	26.90 ± 43.45	0.976**
Concomitant disease			
Hypertension	13 (56.5)	21 (42.9)	0.279+
Chronic renal impairment	13 (56.5)	10 (20.4)	0.002+
Coronary heart disease	3 (13.0)	3 (6.1)	0.376++
Congestive heart failure	3 (13.0)	4 (8.2)	0.673++
Dyslipidemia	5 (21.7)	5 (10.2)	0.273++
Infection	17 (73.9)	12 (24.5)	< 0.001+
Cancer	1 (4.3)	2 (4.1)	1.000++
Cirrhosis	0 (0)	1 (2)	1.000++
Medication			
Insulin	17 (73.9)	34 (69.4)	0.694+
Oral Antidiabetes			
Sulfonilurea	9 (39.1)	11 (22.4)	0.141+
Metformin	7 (30.4)	9 (18.4)	0.251+
Thiazolidindione	0 (0)	1 (2.0)	1.000++
Acarbose	0 (0)	1 (2.0)	1.000++
DPP IV-Inhibitor	0 (0)	1 (2.0)	1.000++
Benzodiazepine	3 (13.0)	1 (2.0)	0.093++
ACEI	4 (17.4)	6 (12.2)	0.716++
RASB	9 (39.1)	16 (32.7)	0.590+
CCB	7 (30.4)	14 (28.6)	0.871+
Beta-blockers	2 (8.7)	2 (4.1)	0.588++
Diuretic	3 (13.0)	5 (10.2)	0.704++
Lipid lowering agent	5 (21.7)	9 (18.4)	0.756++
Salicylates	2 (8.7)	5 (10.2)	1.000++
Allopurinol	1 (4.3)	4 (8.2)	1.000++
Polypharmacy	18 (78.3)	18 (36.7)	0.001

* t-test ; ** Mann-Whitney ; + chi-square; ++ Fisher's exact: (alternative of Chi-square with expected count < 5)

Table 2. Results of bivariate analysis

Independent Variable	Odds Ratio	(95% CI)	P value
BMI (kg/m^2)	0.839	0.714 – 0.984	0.031
Reduction on nutrition intake	18.525	5.137 – 66.805	< 0.001
Laboratory result			
Hemoglobin (g/dl)	0.782	0.633 – 0.965	0.022
Leukocyte (cell/µl)	1	1 – 1	0.003
HbA1c (mg/dl)	0.501	0.360 – 0.696	< 0.001
Ureum (mg/dl)	1.025	1.008 – 1.0042	0.003
Creatinine serum (mg/dl)	2.016	1.207 – 3.367	0.007
Uric acid (mg/dl)	1.427	1.062 – 1.917	0.018
Albumin (g/dl)	0.427	0.188 – 0.967	0.041
Concomitant disease			
Renal chronic disease			
No	Ref	-	
Yes	5.07	1.725 – 14.901	0.003
Infection			
No	Ref	-	
Yes	8.736	2.806 – 27.203	< 0.001
Polypharmacy			
No	Ref	-	
Yes	6.2	1.966 – 19.551	0.002

independent and dependent variables. Multivariate analysis using a logistic regression test was employed to determine risk factors associated with hypoglycemic events.

Results and Discussion

Table 1 shows the results of univariate analysis that describes the characteristics of data in each study group and initial bivariate analysis that illustrates the association between independent and dependent variables. From the total 72 patients who were included in this study, the mean age was 59.8 ± 11.3 years and more than half were female (68.1%). The hypoglycemic group had a significantly lower mean value of BMI (21.65) and showed a significantly higher percentage of food intake frequency (65.5%) (p <0.001) than the non-hypoglycemic group. Laboratory results such as hemoglobin, HbA1c, ureum and albumin showed significantly lower mean values in the hypoglycemic group. While leukocytes, serum creatinine and uric acid showed significantly higher mean values in the hypoglycemic group. Higher frequency differences were significantly indicated by chronic kidney disease (56.5%, p 0.002) and infection (73.9%, p <0.001). The percentage of polypharmacy (78.3%) showed significant value (p 0.001) higher in the hypoglycemic group.

Before performing multivariate analysis, the researchers conducted independent variable selection using bivariate analysis. Bivariate analysis can be seen in Table 2. There are 10 qualified variables included in multivariate modeling, *i.e.,* BMI, decreased food intake, hemoglobin, HbA1c, serum creatinine, uric acid, albumin, chronic kidney disease, infection and polypharmacy.

Table 3. Results of multivariate analysis

Variable	Odds Ratio	95% CI		P value
		Lower	Upper	
BMI	0.789	0.603	1.033	0.084
Nutrition intake	9.329	1.686	51.637	0.011*
HbA1c	0.503	0.321	0.789	0.003*
Creatinine srum	1.838	0.932	3.626	0.079
Constant	6477.760			0.032

* Variable that was statistically significant

Multivariate analysis of hypoglycemia risk factors can be seen in Table 3. Multivariate logistic regression analysis showed that there were significant differences in the reduction of food intake (OR 9.329 , 95% CI 1.69, 51.64) and HbA1c score (OR 0.503, 95% CI 0.321, 0.789) between case and control group.

In this study, decreased food intake was the most dominant hypoglycemic risk factor. Research conducted in Atlanta found that the most hypoglycemic associated events were skipping meals or delaying meals.[10] A study conducted in Mexico in patients treated in the emergency room found that a history of fasting or skipping meals before admission increased the probability of occurrence hypoglycemic nearly 20 fold.[11] Previous studies also showed that restriction of carbohydrate intake was one of the drug-induced hypoglycemic risk factors. A decrease in carbohydrate intake can lead to lower stored energy reserves and allow for the development of severe hypoglycemic events.[12]

Decreased HbA1c levels were statistically associated with hypoglycemic event. This finding is similar with previous study showed that lower HbA1c level was associated with higher hypoglycemia prevalence.[10] This study found no association between the use of benzodiazepines, ACEI, RASB, CCB, beta-blockers, diuretics, and lipid lowering agents with hypoglycemic events during hospitalization. Although these drugs have been reported to increase the risk of hypoglycemic events,[9] it is likely that most hypoglycemic episodes are relatively mild or undocumented. In the final model of multivariate analysis, polypharmacy was not significant risk factor for hypoglycemic events during hospitalization. Polypharmacy defined in this study included the use of additional drugs that have not been proven to cause hypoglycemic event.

Most of the patients with type 2 DM included in the study received insulin therapy with a higher percentage of insulin use in the hypoglycemic group. However, the use of insulin showed no significant association with hypoglycemic events. It is possible that the use of insulin and oral antidiabetic drugs already meet the standard of therapy established by the hospital. Based on previous research in the same setting, the use of antidiabetic drugs in 2013 was rational with exact indication criteria of 86.96%, exact dosage of 97.32% and precise drugs and patients reached 100% in this hospital.[15]

Conclusions

In conclusion, hypoglycemia risk factors among hospitalized type 2 DM patients were reduction in food intake and low HbA1c score.

Acknowledgement
Not declared.

Funding
None.

Conflict of interest
None.

References

1. Tschöpe D, Bramlage P, Binz C, *et al*. Incidence and predictors of hypoglycaemia in type 2 diabetes: an analysis of the prospective DiaRegis registry. *Biomed Central Endocrine Disorders*. 2012;12:23.
2. Ahrén B. Avoiding hypoglycemia: a key to success for glucose lowering therapy in type 2 diabetes. *Vascular Health Risk Management.* 2013;9:155-163.
3. Sussman M, Sierra JA, Garg S. Economic impact of hypoglicemia among insulin treated-patients with diabetes. *Journal of Medical Economics*. 2016;19(11):1099-1106.
4. Rozance PJ, Hay WW. Describing hypoglycemia: definition or operational threshold? *Early Human Development.* 2010;86(5):275-280.
5. Lipska KJ, Ross JS, Wang Y, *et.al*. National trends in US hospital admissions for hyperglycemia and hypoglycemia among medicare beneficiaries. *Journal of American Medical Association Internal Medicine.* 2014;174(7):1116-1124.
6. Shafiee G, Tehrani MM, Pajouhi M, Larijani B. The importance of hypoglycemia in diabetic patients. *Journal of Diabetes and Metabolic Disorders.* 2011;11:17.
7. Barnett AH, Cradock S, Fisher. Key consideration around the risks and consequences of hypoglycemia in people with type 2 diabetes. *International Journal of Clinical Practice.* 2010;64(8): 1121-1129.
8. McCrimmon RJ, Sherwin RS. Hypoglycemia in type 1 diabetes. *Diabetes.* 2010;59(10):2333-2339.
9. Amiel SA, Dixon T, Mann R, *et al*. Hypoglycaemia in type 2 diabetes. *Diabetic Medicine.* 2008;25:245-254.
10. Gehlaut RR, Dogbey GY, Schwartz FL. Hypoglycemia in type 2 diabetes: more common than you think. *Journal of Diabetes Science and Technology.* 2015;9(5):999-1005.
11. Duran-Nah JJ, Morales AR, Smitheram J, Medina CC. Risk factors associated with symptomatic hypoglycemia in type 2 diabetes mellitus patients. *Revista de Investigación Clínica*. 2008;60(6):451-458.
12. Vue MH, Setter SM. Drug-induced glucose alteration: drug induced hypoglicemia. *Diabetes Spectrum.* 2011;24(3):171-177.
13. Sanchai T, Patumanond J. Severe hypoglicemia in type II diabetes at Nakornpiing general hospital: a study on clinical risk factors. *Journal of the Medical Association of Thailand.* 2011;94(12):1435-1440.
14. Lipska KJ, Warton EM, Huang ES, Moffet HH, Inzucchi SE, Krumholz HM, *et al*. The diabetes and aging study: HbA1c and risk of severe hypoglycemia in type 2 diabetes. *Diabetes Care.* 2013; 36:3535-3542.
15. Hangdiyanto A, Yamlean PVY, Supriati HS. Assessment of the rationality of the use of type 2 diabetes mellitus medication among hospitalized patients at Dr. Kandou general hospital, Manado. *Pharmacon.* 2014; 3(2):77-86.