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Original Research Article

A case-control study on factors associated with hypoglycemia unawareness among the ambulatory type 2 diabetes mellitus patients in Bali, Indonesia

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Abstract

Purpose: *To determine the factors related to hypoglycemia unawareness (HU) in patients with type 2 diabetes mellitus (T2DM) in Bali-Indonesia.*
Methods: *A case-control study was conducted across three hospitals to investigate the incidence of HU as a primary outcome. Medical record data were collected to obtain information for further analysis. The primary data were analyzed using chi-square analysis, and variables with p-value ≤ 0.10 were further evaluated using multivariate logistic regression, with odds ratio (OR) parameters at 95 % confidence interval (CI). A two-tailed statistical analysis was then conducted, and p < 0.05 was considered statistically significant.*
Results: *Results of the multivariate analysis showed that five variables were significantly associated with HU incidents. These included insulin users (OR: 6.15 (CI 95: 1.65 - 22.86)), chronic kidney diseases (CKD) (OR: 6.56 (CI 95: 1.41 - 30.39)), diabetic neuropathy (OR: 24.61 (CI 95: 5.17 - 117.11)), hypertension (OR: 3.76 (CI 95: 1.01 - 13.96)), and dyslipidemia (OR: 6.44 (CI 95: 1.62 - 25.71)).*
Conclusion: *Variables in this study are in line with the characteristics of the ambulatory T2DM population in Bali-Indonesia. These factors are used as evidence by health workers in managing and mitigating the risk of HU, thereby reducing the associated health burden.*

Keywords: *Ambulatory, Bali, Hypoglycemia unawareness, Type 2 diabetes mellitus*

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INTRODUCTION

Hypoglycemia is an acute and unavoidable condition often experienced by patients with type 1 and 2 diabetes mellitus (DM) as a consequence of treatment [1,2]. It is defined by blood glucose levels of ≤ 70 mg/dL and characterized by autonomic or neuroglycopenic symptoms. Autonomic symptoms, which manifest when blood glucose levels are < 60 mg/dL, activate the autonomic nervous system, causing sudden hunger, trembling, sweating, restlessness, increased heart rate, nausea, and vomiting. At < 50 mg/dL, neuroglycopenic symptoms such as weakness, dizziness, headache, blurred vision, and decreased consciousness are experienced [1–4]. Therefore, immediate intervention is fundamental to prevent the progression of hypoglycemia, which may lead to death.

Hypoglycemia unawareness (HU) is defined as the inability to recognize a significant decline in blood glucose below normal levels. This condition has been identified to be the most life-threatening complication, as majority of patients do not show clear neuroglycopenic signs or autonomic symptoms [5,6]. Repeated hypoglycemic episodes contribute to suppression of the counter-regulatory hormonal and sympathetic responses. This leads to impaired awareness and consequently increases the risk of severe hypoglycemia [3]. Hypoglycemia unawareness (HU) has been reported to be associated with poor adherence to antidiabetic medication, uncontrolled blood glucose, repeated hypoglycemia events, chronic diabetes complications, anxiety, depression, long DM duration, and poor quality of life (QOL) [4,5,7].

A cohort study in Indonesia reported that 99.4 % of patients with type 2 diabetes mellitus (T2DM) experienced at least a hypoglycemic event in four weeks with a hypoglycemia incidence rate of 25.7 events per patient-year [2]. Prevalence of patients with HU tends to be lower compared to those who are aware, reaching approximately 9-25 %. It occurs in approximately 40 % of T1DM cases, with less frequency in T2DM but requires attention for safety purposes [5,8,9]. In Indonesia, numerous HU are undetected in the community and unrecorded in the health system, similar to an iceberg phenomenon.

Screening for HU in diabetes patients is essential to reduce the risk of hypoglycemia. Promotional efforts such as educating patients on treatment, risk factors, and prevention measures are vital to reducing the mortality rate and increasing QOL [10–12]. In Indonesia, data on risk factors associated with HU remains limited. Therefore, this study aimed to investigate factors related to HU in T2DM patients, particularly in Bali-Indonesia. The results are expected to be used as a piece of evidence that could help reduce the associated burden.

METHODS

Study design

The study used a case-control study design where T2DM patients with HU were included in the study group. Control group comprised patients without HU.

Study setting

The study was conducted in March 2024 at three hospitals in Bali Province, including Denpasar City, Badung Regency, and Buleleng Regency. Medical record data between January 2023 to July 2024 were collected.

Sample size

The sample size estimation used a 1:2 ratio, with 90 % statistical power at 5 % level of significance. Total minimum sample size required was 30 in study group and 60 in control group. Results were presented based on the guidelines of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) for case-control study design [13].

Case and control definition

Patients with and without HU during the observation period were included in the study and control group respectively.

Ethical consideration

The study was part of a larger project with a data collection process conducted accordingly. Approval was granted by the Ethics Commission of the Faculty of Medicine, Udayana University, Bali (approval no. 1165/UN.14.2.2.VII.14/LT/2024). Additionally, ethical clearance was obtained from the multicenter hospitals, including Denpasar City Hospital, Badung Regency Hospital, and Buleleng Regency Hospital, with approval number 052/EA/KEPK.RSBM.DISKES/2024, B/475/UN14.6/PT.01.04/2024, and 019/EC/KEPK-RSB/V/2023 respectively. Informed consent was obtained from participants using an approved and locally translated digital consent form. Patients were informed about the details of the study, including the general overview, purpose, risks, and benefits. Confidentiality was maintained throughout the study and conducted in accordance with the Declaration of Helsinki [14].

Inclusion criteria

Ambulatory T2DM patients who were recorded as having routine check-ups for at least the last three months, history of antidiabetic drugs intake, and medical record consisting of at least age, gender, body mass index (BMI), duration of DM, blood sugar profile for the last three months, list of drugs taken home, and complications.

Exclusion criteria

Unwillingness to provide access to personal data, incomplete, scattered, or inaccessible data, and patients who were recorded as dead during the observation period.

Data collection

Medical record data were extracted from three centers by six observers. Following the study criteria, the data were reviewed by the team to prevent loss and ensure accuracy and precision. The review step was conducted because the centers had not fully implemented electronic medical records. Furthermore, it addressed errors arising from practitioner handwriting, which could lead to misinterpretation of patients' therapy.

Variables

Primary variables were divided into dependent and independent. Dependent variable was the incidence of HU in ambulatory T2DM patients based on medical records. Meanwhile, independent variables were gender, age, BMI, DM duration, blood glucose profile, diabetes medications (oral or parenteral), and T2DM patient comorbidities. A multivariate analysis was conducted to determine the significant factor that affected HU and to investigate the interactions among the independent variables.

Potential bias

The study had some potential biases, such as not being able to obtain ideal patient characteristics between study and control groups. This could be attributed to design limitations that depended on availability and quality of the medical record data. Variables that affected HU events in ambulatory T2DM patients that were difficult to observe retrospectively include medication adherence, nutritional intake, beliefs, and support system at home.

Statistical analysis

Data was analyzed using the Statistical Packages for Social Sciences (SPSS 21.0 IBM, Armonk, NY, USA). Categorical data were presented in frequency and percentages (%). Analytical method was used to assess predictors of HU in T2DM patients in study and control groups. Furthermore, the primary data were analyzed using Chi-square analysis with odds ratio (OR) at 95 % confidence interval (CI). Variables with p-value ≤ 0.10 were further evaluated using multivariate logistic regression. Final statistical analysis was two-tailed with $p < 0.05$ considered statistically significant.

RESULTS

A total of 328 of 985 patients' data successfully passed the screening stage. However, only 132 met the inclusion criteria (Figure 1). Majority were males (55.3 %), obese (52 %) had survived DM for > 5 years, with 74 % having poor glucose control. Furthermore, metformin (54.55 %) and cardiovascular diseases (CVD) (62.88 %) were the most commonly used antidiabetic drugs and complications encountered respectively (Table 1).

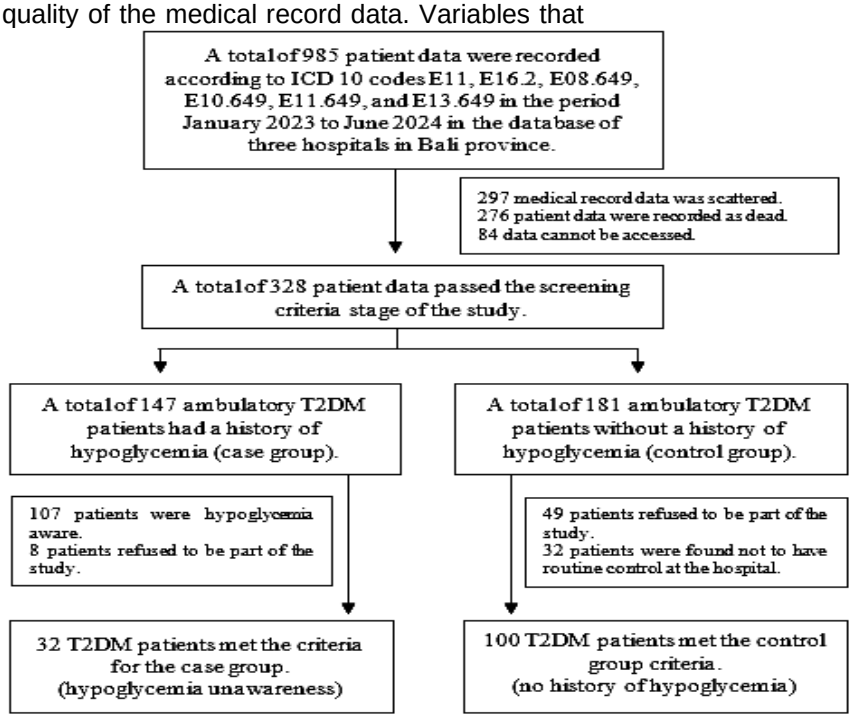

Figure 1: Flow diagram summarizing patient selection criteria for a case-control study

Table 1: T2DM Patients' characteristics (n =132)

Characteristics		Frequency (%)
Gender	Male (n %)	73(55.3)
	Female (n %)	59(44.7)
Ages (Years)	*Average ± SD*	*55.3±12.6*
	25-35	*7(5.3)*
	36-45	*16(12.1)*
	46-55	*46(34.9)*
	56-65	*34(25.8)*
	>65	*29(22.0)*
BMI	*Normal (19-25 kg/m^2); (n %)*	*63(47.7)*
	Overweight/Obese (>26 kg/m^2); (n %)	69(52.3)
T2DM Duration (Years)	<5	38(28.8)
	≥5	94(71.2)
Last Blood Glucose Profile	Uncontrolled (n %)	98(74.2)
	Controlled (n %)	34(25.8)
T2DM Medication	Insulin (n %)	59(44.7)
	SU (n %)	30(22.7)
	Metformin (n %)	72(54.6)
	DPP4-I (n %)	4(3.0)
	AGI (n %)	2(1.5)
	SGLT2-I (n %)	1(0.8)
Comorbidity and Complication	CKD (n %)	23(17.4)
	Neuropathy DM (n %)	56(42.4)
	Cardiovascular Diseases (n %)	83(62.9)
	Retinopathy DM (n %)	1(0.8)
	DMDF (n %)	25(18.9)
	Gastropathy DM (n %)	18(13.6)
	Hypertension (n %)	67(50.8)
	Dyslipidemia (n %)	24(18.2)

Note: n: number; SD: standard deviation; BMI: body mass index; T2DM: type 2 diabetes mellitus; uncontrolled blood glucose: HbA1C > 7 %, fasting > 126 mg, prandial & random > 200 mg/dL; controlled blood glucose: HbA1C < 7 %, fasting < 126 mg/dL, prandial & random < 200 mg/dL; SU: sulfonylurea; DPP4-I: dipeptidyl peptidase-4 Inhibitor; AGI: alpha-glucosidase inhibitor; SGLT2-I: sodium-glucose co-transporter 2 inhibitor; CKD: chronic kidney diseases; DM: diabetes mellitus; CVD: cardiovascular diseases; DMDF: diabetes mellitus diabetic foot

Bivariate analysis

A total of 19 variables were subjected to bivariate analysis (Table 2). Among this number, eight were found to significantly influence the incidence of HU, including insulin use, CKD, DM neuropathy, CVD, hypertension, dyslipidemia, and longer duration of DM (>5 years), with $p < 0.05$. Meanwhile, metformin was a significant variable but with a reverse OR value (OR 0.174). This suggested that the users were not at substantial risk of developing HU ($p < 0.05$).

Multivariate analysis

A total of eight variables were subjected to multivariate analysis. Based on the results of multivariate analysis in this study (Table 3), five variables were majorly associated with HU incidents which include insulin use (OR: 6.15 (CI 95: 1.65 - 22.86)), CKD (OR: 6.56 (CI 95: 1.41 - 30.39)), DM neuropathy (OR: 24.61 (CI 95: 5.17 - 117.11)), hypertension (OR: 3.76 (CI 95: 1.01 - 13.96)), and dyslipidemia (OR: 6.44 (CI 95: 1.62 - 25.71)).

DISCUSSION

Incidence of HU in T2DM and T1DM patients was 9-25 and ≥ 40 %, respectively. However, T2DM patients need to be aware of the potential for HU, as it may lead to life-threatening episodes, significant morbidity, and a lack of optimal glycemic control [5,11,15]. In this study, five risk factors were associated with the occurrence of HU in T2DM patients. Significantly, insulin users were discovered to be 6.2 times more at risk, with the most frequently reported cause being changes to the regimen.

These changes included unreported increases in insulin dosage, incorrect dosage, and the use of different types of insulin. Also, other causes of hypoglycemia, such as stringent glycemic control and attempts to control hemoglobin HbA1C levels, need further investigation [3,11,16]. In this study, CKD was discovered to be a factor associated with HU, with a risk 6.5 times greater compared to controls.

Table 2: Bivariate analysis in the first stages of determining contributing factors associated with hypoglycemia unawareness in ambulatory T2DM patients

Variable		**HU case (n=32)**	**Non-HU control (n=100)**	*P-value* **(χ^2)**	*OR* **(CI 95%)**
Gender	Male (n %)	18(56.3)	55(55.0)	0.901	1.05(0.47-2.35)
	Female (n %)	14(43.8)	45(45.0)		
Ages (years)	Elderly (≥ 65); (n %)	8(25.0)	24(24.0)	0.909	1.06(0.42-2.66)
	Adult (20< ages <65); (n %)	24(75.0)	76(76.0)		
Diabetes Medication (User)	Insulin (n %)	26(81.3)	33(33.0)	0.001*[a]	8.80(3.30-23.46)*
	SU (n %)	10(31.3)	20(20.0)	0.186	1.82(0.74-4.44)
	Metformin (n %)	12(37.5)	60(60.0)	0.026*[a]	0.40(0.18-0.91)*
	DPP4-I (n %)	0(0.0)	4(4.0)	0.248	1.34(1.21-1.48)
	AGI (n %)	1(3.1)	1(1.0)	0.392	3.19(0.19-52.57)
	SGLT2-I (n %)	0(0.0)	1(1.0)	0.570	1.32(1.20-1.46)
Comorbidity	CKD (n %)	13(40.6)	10(10.0)	0.001*[a]	6.16(2.35-16.11)*
	Neuropathy DM (n %)	25(78.1)	31(31.0)	0.001*[a]	7.95(3.12-20.33)*
	CVD (n %)	29(90.6)	54(54.0)	0.001*[a]	8.24(2.35-28.80)*
	Retinopathy (n %)	0(0.0)	1(1.0)	0.570	1.32(1.20-1.46)
	DMDF (n %)	7(21.9)	18(18.0)	0.626	1.28(0.48-3.40)
	Gastropathy (n %)	6(18.8)	12(12.0)	0.333	1.69(0.58-4.95)
	Hypertension (n %)	26(81.3)	41(41.0)	0.001*[a]	6.24(2.36-16.50)*
	Dyslipidemia (n %)	13(40.6)	11(11.0)	0.001*[a]	5.54(2.16-14.22)*
Blood Glucose (mg/dL)	Uncontrolled (n %)	24(75.0)	74(74.0)	0.910	1.05(0.42-2.64)
	Controlled (n %)	8(25.0)	26(26.0)		
DM Duration (years)	≥5 (n %)	31(96.9)	63(63.0)	0.001*[a]	18.21(2.39-138.94)*
	<5 (n %)	1(3.1)	37(37.0)		
BMI (kg/m^2)	Over/Under Weight (n %)	14(43.8)	55(55.0)	0.267	0.64(0.29-1.42)
	Normal Weight (n %)	18(56.3)	45(45.0)		

Note: n: number; SD: standard deviation; OR: odd ratio; CI 95: confidence interval 95 %; ; χ2: bivariate chi-square analysis; *$p < 0.05$; [a]variable include in multivariate analysis; SU: sulfonylurea; DPP4-I: dipeptidyl peptidase-4 Inhibitor; AGI: alpha glucosidase inhibitor; SGLT2-I: sodium glucose co-transporter 2 inhibitor; DM: diabetes mellitus; CKD: chronic kidney diseases; CVD: cardiovascular diseases; DMDF: diabetes mellitus diabetic foot; uncontrolled blood glucose: HbA1C >7%, fasting >126mg, prandial & random >200mg/dL; controlled blood glucose: HbA1C <7%, fasting <126 mg/dL, prandial & random <200mg/dL; BMI: body mass index; HU: hypoglycemic unawareness

Table 3: Step-wise multivariate logistic regression analysis

Variable include in multivariate analysis		**HU cases (n=32)**	**Non-HU control (n=100)**	*P-value* **crude**	*OR (CI 95 %)* **crude**	*P-value* **adjusted**	*OR (CI 95 %)* **adjusted**
Insulin User	Yes (n %)	26(81.3)	33(33.0)	0.001*	8.80*	0.007*	6.15*
	No (n %)	6(18.8)	67(67.0)		(3.30-23.46)		(1.65-22.86)
Metformin user	Yes (n %)	12(37.5)	60(60.0)	0.026*	0.40*	0.173	0.369
	No (n %)	20(62.5)	40(40.0)		(0.18-0.91)		(0.88-1.55)
CKD	Yes (n %)	13(40.6)	10(10.0)	0.001*	6.16*	0.016*	6.56*
	No (n %)	19(59.4)	90(90.0)		(2.35-16.11)		(1.41-30.39)
Neuropathy DM	Yes (n %)	25(78.1)	31(31.0)	0.001*	7.95*	0.001*	24.61*
	No (n %)	7(21.9)	69(69.0)		(3.12-20.33)		(5.17-117.11)
CVD	Yes (n %)	29(90.6)	54(54.0)	0.001*	8.24*	0.805	0.748
	No (n %)	3(9.4)	46(46.0)		(2.35-28.80)		(0.10-7.48)
Hypertension	Yes (n %)	26(81.3)	41(41.0)	0.001*	6.24*	0.048*	3.76*
	No (n %)	6(18.8)	59(59.0)		(2.36-16.50)		(1.01-13.96)
Dyslipidemia	Yes (n %)	13(40.6)	11(11.0)	0.001*	5.54*	0.008*	6.44*
	No (n %)	19(59.4)	89(89.0)		(2.16-14.22)		(1.62-25.71)
DM Duration (years)	≥5 (n %)	31(96.9)	63(63.0)	0.001*	18.21*	0.104	7.01
	<5 (n %)	1(3.1)	37(37.0)		(2.39-138.94)		(0.67-73.13)

Note: n: number; OR: odd ratio; CI 95: confidence interval 95 %; *$p < 0.05$; CKD: chronic kidney diseases; DM: diabetes mellitus; CVD: cardiovascular diseases; HU: hypoglycemia unawareness

It has been reported to be associated with HU due to decreased insulin excretion following renal failure. Prolonged insulin half-life and unadjusted frequency and dose will increase the risk of patients with hypoglycemia. Several studies have directly associated CKD with hypoglycemic effects. This suggests that high intensity of recurrent hypoglycemia is a secondary outcome of HU [1,2,11,17]. Diabetic neuropathy was identified as the comorbidity with the highest risk. Affected patients were 24.6 times more susceptible to developing HU compared to control group. Chronic hyperglycemia leads to nervous system disorder, which disrupts neuronal communication. This process includes the release of classical neurotransmitters, such as gamma-aminobutyric acid (GABA), a potent inhibitory neurotransmitter. Damage to the nervous system impairs neuronal sensitivity, causing significant increase in ventromedial hypothalamus (VMH) GABA concentrations that fail to decrease appropriately during subsequent hypoglycemia. This dysfunction is correlated with reduced glucagon and epinephrine responses [9,15,16,18].

In this study, hypertension and dyslipidemia were discovered to be associated with HU, presenting 3.8 and 6.4 times the risk, respectively, compared to control group. These comorbidities were not directly related to HU but were potential predictors of future effects in T2DM patients. Dyslipidemia is associated with hypertension by several mechanisms. Atherosclerosis resulting from lipid abnormalities causes structural changes in large arteries, thereby reducing elasticity. Furthermore, endothelial dysfunction due to dyslipidemia decreases nitric oxide production, release, and activity, leading to abnormal vasomotor function and hypertension [14,17]. Chronic dyslipidemia and hypertension have an impact on homeostasis disorders such as decreased ATP-sensitive K+ (KATP) channels, opioid system disorders in hypoglycemic counter-regulation, and decreased adrenergic receptors' activity, all of which contribute to weakened counter-regulatory responses in subsequent episodes of HU [3,10,11]. Results of this study provide evidence for managing significant risk factors associated with HU. Since all identified risk factors were modifiable, effective cooperation between health workers, patients, and caregivers is essential to ensure patient safety.

Study limitations

This study has several limitations, including predictors being measured based on medical records in a multicenter setting. The rare prevalence of HU in type 2 DM patients also results in a lack of data on case groups that may be analyzed. Also, the possible time-varying effects of the predictors were not reported. Another limitation was that patients with T2DM were enrolled in three centers in Bali Province, Indonesia. Therefore, the results may not be generalized to other Southeast Asian populations because of different genetic backgrounds and healthcare systems.

CONCLUSION

This study shows that insulin users, comorbid CKD, DM neuropathy, hypertension, and dyslipidemia are modifiable risk factors associated with HU.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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