

## Risk Factors of Severe Hypoglycemia in Type 2 Diabetic Patients at District Hospital, Wiang Pa Pao Chiang Rai, Thailand

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### Abstract:

**Background:** The incidence of hypoglycemia in diabetic patients in District Hospital Wiang Pa Pao, Chiang Rai increases every year. Hypoglycemia is very common in the emergency room, which potentially causes morbidity and mortality in these patients. Hypoglycemia causes limitation in the treatment of diabetes and subsequent glucose control. Therefore, this research attempted to identify the main factors associated with this hypoglycemic syndrome of type 2 diabetic patients in Wiang Pa Pao district, Chiang Rai province. It is anticipated that this information can be used to plan for treatment and prevention.

**Objective:** The objective of this study is to identify the main factors associated with hypoglycemic episodes in type 2 diabetic patients receiving health care at Wiang Pa Pao hospital, Chiang Rai during 2018 - 2020.

**Methods:** The design is a case control study in type 2 diabetic patients who received treatment at Wiang Pa Pao Hospital, Chiang Rai during 2018 - 2020. The number of cases and controls were 59 and 236 respectively. Data collection was obtained from the patient hospital information system including gender, occupation, weight, height, age, body mass index (BMI), HbA1c, eGFR, total cholesterol, diabetic medications, and comorbid diseases. Analytical statistics used in this study was univariable logistic regression described in odd ratio and statistical significance P-value < 0.05.

**Results:** This study found that the factors associated with hypoglycemic syndrome in type 2 diabetic patients were BMI, HbA1C level and type of diabetic medications. In BMI of 18.5 - 22.9 kg/m<sup>2</sup>, patients had a risk of developing hypoglycemia more than patients who had BMI 23 kg/m<sup>2</sup> (P-value 0.02, OR 2.51). In BMI below 18.5 kg/m<sup>2</sup>, patients had a risk of developing hypoglycemia more than patients who had BMI 23 kg/m<sup>2</sup> (P-value < 0.0001,

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OR 7.14). This research also found that for the HbA1C 10.1% - 13% there was a risk for hypoglycemic episodes more than HbA1C 4 % - 7% (P-value 0.02, OR 2.14). Finally, this research found that the patients who used insulin treatment had a higher chance of developing hypoglycemic episodes compared to the patients who used oral anti-diabetic drugs alone (P-value < 0.0001, OR 27.26) and patients who used both oral anti-diabetic agents and insulin, had a higher risk of developing hypoglycemic syndrome more than patients who used oral medications alone. (P-value < 0.0001, OR 3.95).

**Conclusion:** The study found that the level of HbA1c had an association with hypoglycemia in type 2 diabetic patients. The higher initial HbA1c level, the greater the chance of having the hypoglycemic episode. Additionally, patients who had low body mass index were at increased risk of hypoglycemia. The type of anti-diabetic medications also had an effect. Patients who used only insulin injection and patients who used combination of insulin and oral agents, had a higher risk of hypoglycemia than patients who used oral medication alone.

**Keywords:** Severe hypoglycemia, Type 2 Diabetes Mellitus

## Introduction

Type 2 diabetes presents an important public health burden worldwide including Thailand. The number of people with diabetes in adults aged 20 years and over in Thailand will increase from 1,017,000 in 2000 to 1,923,000 in 2025.<sup>1</sup> Also, the incidence of hypoglycemia in type 2 diabetes increases every year. Approximately, 51 percent of hypoglycemic patients in western pacific region will increase from 2019-2045.<sup>2</sup> In 2017, Thailand was rated in fourth place of having large number of hypoglycemia in its region.<sup>3</sup> This issue become a problem of the country that need to be investigated. From the existing data, the incidence of hypoglycemia in diabetic patients who received healthcare in Wiang Pa Pao District Hospitals had been increasing dramatically since 2018. It is very commonly found in the emergency room, which potentially causes morbidity and mortality in these patients. The previous study found that factors related to hypoglycemia in type 2 diabetic patients including already known chronic complications of diabetes and glipizide uses<sup>4</sup> resulting in hospitalization

and morbidity including accident, myocardial infarction, cardiac arrhythmia, seizure and coma.<sup>5</sup> Therefore, the research team attempted to identify the main factors associated with hypoglycemic episodes in type 2 diabetic patients in Wiang Pa Pao district, Chiang Rai province during 2018-2020. It is hoped that this information can be used to plan for the treatment and prevention regime.

## Material and method

The study design is retrospective case control. Cases were type 2 diabetic patients who had a hypoglycemic episode. Controls were type 2 diabetic patients who never had a hypoglycemic episode.

The statistical parameters included age, body mass index, diabetic medication, HbA1c level, cholesterol level and comorbid diseases. Analytical statistics used in this study was univariable logistic regression described in odd ratio and statistical significance, P-value < 0.05.

## Population and sample

Type 2 diabetic patients aged over

15 years old who received treatment care at Wiang Pa Pao Hospital, Chiang Rai during 2018 - 2020. This hospital is a community hospital with 90 beds, and there are 3 internists with 10 - 15 interns which most of them are family medicine practitioner. Patient information was retrieved from the electronic hospital database and the research team received a permission to access an information from hospital director. Only first episode of hypoglycemia at emergency room was analyzed.

### **Inclusion criteria**

Type 2 diabetic patients who had severe hypoglycemic episode according to Whipple's triad and for those who had multiple hypoglycemic episodes, the researcher select only the first one.

### **Exclusion criteria**

Exclusion criteria are including incomplete patient information retrieved from the hospital data system which only from first episode of hypoglycemia at emergency room, patient who had hypoglycemic episode during admission from other medical illness such as sepsis, tumor, hormonal deficiency. Also, patient with pregnancy or critical ill such as shock, coma, and immunocompromised patients such as cancer, bedridden and HIV infection and patients who had underlying diseases including liver diseases, endocrine diseases and chronic kidney diseases are excluded from the study.

The research protocol was approved by the research ethical committee of Mae Fah Luang University.

### **Sample size**

The total type 2 diabetic patient visits in 2018 - 2020 were 3,874. After divided into 2 groups based on hypoglycemic episode, the first group was patients who had a hypoglycemic episode of 674. After

exclusion, the number of cases that were suitable for the study were 59. The second group was the patient who never had a hypoglycemic episode 2,873 visits. After simple random sampling, the number of controls were 236. Data collection was obtained from the patient information system of Wiang Pa Pao Hospital which were divided into 2 parts: Part 1, geographic data including gender, age, occupation, weight, height, body mass index, eGFR, HbA1c and total cholesterol and Part 2, study factors including age, occupation, body mass index, HbA1c, total cholesterol, co-morbid diseases and diabetic medications.

### **Statistical analysis**

The data was analyzed by STATA version 16. Categorical variables were presented in form of frequency and percentage. Continuous variables were presented in mean and standard deviation. Using univariable logistic regression to analyzed the relationship of each factor and hypoglycemic episodes, described in odd ratio and statistical significance P-value < 0.05.

### **Result**

The number of cases was 59 and 37.29% were male and 62.71% were female. Majority of occupation was farmer (52.54%). The average body weight and height were  $53.33 \pm 10.71$  kg and  $155.56 \pm 6.57$  cm. The average body mass index of the case was  $22.10 \pm 4.61$  kg/m<sup>2</sup> which was lower than that of the control ( $24.90 \pm 4.53$  kg/m<sup>2</sup>). On glycemic control, the average level of HbA1c of the case was higher than that of the control without statistical significance (10.32 mg% and 9.49 mg%). And for the kidney function, the eGFR of the case and control was not different ( $87.23$  mL/min/ $1.73$  m<sup>2</sup> and  $92.47$  mL/min/ $1.73$  m<sup>2</sup>) (Table 1).

For analysis of association of the risk factors including age, body mass index, HbA1c level, total cholesterol, diabetic medications and comorbid diseases with hypoglycemic episodes by using univariable logistic regression, this study found that patients with BMI of 18.5-22.9 kg/m<sup>2</sup> had risk of developing hypoglycemia more than

patients who had BMI 23 kg/m<sup>2</sup> (P-value 0.02, OR 2.51). In BMI < 18.5 kg/m<sup>2</sup>, patients had a risk of developing hypoglycemia more than patients who had BMI 23 kg/m<sup>2</sup> (P-value < 0.0001, OR 7.14). On the patients with HbA1C of 10.1% to 13% there was a risk for hypoglycemic episodes more than patients who had HbA1c of 4% to 7%

**Table 1** Demographic data of hypoglycemic patients and control group.

Geographic data	number (percentage)		P-value
	Diabetic patients with hypoglycemia (59)	Diabetic patients without hypoglycemia (236)	
Gender			
- Male	22 (37.29)	88 (37.29)	
- Female	37 (62.71)	148 (62.71)	
Occupation			
- Government officer	1 (1.69)	5 (2.12)	0.40
- Farmer	31 (52.54)	117 (49.58)	0.40
- Shopkeeper	2 (3.39)	22 (9.32)	0.40
- General employee	16 (27.12)	63 (26.69)	0.00
- Monk	1 (1.69)	0 (0)	0.49
- Elderly	8 (13.56)	14 (5.93)	0.28
- Housewife	0 (0)	12 (5.08)	
Weight (kg)			
- Mean ± SD	53.33 ± 10.71	63.20 ± 19.21	< 0.001
- Median	52 (34.6 - 88)	61 (33 - 274.9)	
Height (cm)			
- Mean ± SD	155.56 ± 6.57	157.91 ± 7.97	< 0.001
- Median	155 (140 - 168)	156 (138 - 185)	
Body mass index (kg/m <sup>2</sup> )			
- Mean ± SD	22.10 ± 4.61	24.90 ± 4.53	< 0.001
- Median	21.33 (14.45 - 39.11)	24.27 (14.66 - 42.97)	
Hemoglobin A1C (mg%)			
- Mean ± SD	10.32 ± 2.68	9.49 ± 9.01	0.23
- Median	9.8 (5.2 - 14)	8.2 (5.4 - 14)	
eGFR (mL/min/1.73 m <sup>2</sup> )			
- Mean ± SD	87.23 ± 19.03	92.47 ± 16.93	0.98
- Median	88.78 (60.05 - 137.47)	93.8 (60 - 172.8)	

(P-value 0.02, OR 2.14). In addition, insulin used patients had a higher chance of developing hypoglycemic episodes compared to the patients who used oral anti-diabetic medications (P-value < 0.0001, OR 27.26) and the patients who used both

oral anti-diabetic drugs and insulin, had a higher risk of developing hypoglycemic episodes more than the patients who used oral anti-diabetic drugs alone (P-value < 0.0001, OR 3.95) as shown in Table 2

**Table 2** Factors related with hypoglycemia

Risk factor	Number (Percentage)		OR	95% CI for OR		P-value
	Diabetic with hypoglycemia	Diabetic without hypoglycemia		Lower	Upper	
1. Age (year)						
- 21-50	11 (18.64)	49 (20.76)	1			
- 51-60	20 (33.90)	77 (36.63)	1.14	0.51	2.62	0.73
- 61-70	18 (30.51)	84 (35.59)	0.95	0.41	2.19	0.91
- 71-90	10 (16.95)	26 (11.02)	1.71	0.64	4.56	0.28
2. Body mass index (kg/m <sup>2</sup> )						
- ≥ 23	21 (35.60)	150 (63.56)	1			
- 18.5-22.9	26 (44.07)	74 (31.36)	2.51	1.32	4.75	0.02*
- < 18.5	12 (20.34)	12 (20.34)	7.14	2.84	17.95	0.0001*
3. Hemoglobin A1C (mg%)						
- 4-7	12 (20.34)	55 (23.30)	1			
- 7.1-10	19 (32.20)	132 (55.93)	0.66	0.30	1.45	0.30
- 10.1-13	20 (33.90)	35 (14.83)	2.26	1.14	6.02	0.02*
- > 13	8 (13.56)	14 (5.93)	2.62	0.90	7.63	0.08
4. Total Cholesterol (mg/dL)						
- < 200	41 (69.50)	154 (65.25)	1			
- 200 – 239	15 (25.42)	61 (25.85)	0.97	0.50	1.88	0.92
- ≥ 240	3 (5.08)	21 (8.90)	0.54	0.15	1.91	0.34
5. Types of anti-diabetic drugs						
- Oral anti-diabetic drug	22 (37.29)	171 (72.46)	1			
- Insulin	11 (18.64)	3 (1.27)	27.26	7.07	105.02	0.0001*
- Combined insulin and oral anti-diabetic drugs	25 (42.37)	47 (19.91)	3.95	2.06	7.59	0.0001*

**Table 2** Factors related with hypoglycemia (continued)

Risk factor	Number (Percentage)		OR	95% CI for OR		P-value
	Diabetic with hypoglycemia	Diabetic without hypoglycemia		Lower	Upper	
- Sulfonylurea group	21 (35.59)	116 (49.15)	1			
- Other group of oral anti-diabetic drug	38 (64.41)	120 (50.85)	1.75	0.97	3.16	0.06
6. Comorbid diseases						
- DM related diseases**	24 (40.68)	99 (41.95)	0.95	0.86	0.53	1.69
- DM related Complications***	6 (10.17)	19 (8.05)	1.29	0.06	0.49	3.40
- Others	3 (5.08)	3 (1.27)	4.24	0.08	0.83	21.56

\*P-value < 0.05

\*\* DM related diseases : hypertension, dyslipidemia

\*\*\* DM related complications : heart failure, peripheral arterial disease, DKA (diabetic ketoacidosis), HHS (hyperosmolar hyperglycemic state)

## Discussion

Hypoglycemia is a preventable event that is commonly found in diabetic patients. In 2018 - 2020, there were 3,874 visits of type 2 diabetic patients in Wiang Pa Pao district and had 674 hypoglycemic events. Preventing hypoglycemia could help to reduce expense, morbidity and mortality. This study is a retrospective case - control that identifies the main factors associated with hypoglycemic episodes in type 2 diabetic patients at Wiang Pa Pao hospital during 2018-2020. The number of cases and controls are 59 and 236 respectively. The study factors are including age, body mass index, HbA1c, cholesterol level, anti-diabetic medications and comorbid diseases.

The research found that age was not associated with hypoglycemic events in type 2 diabetic patients which corresponded to the study from Chanakarn Chaitanakul<sup>3</sup>.

However, body mass index was statistically associated with hypoglycemic episodes. In BMI of 18.5-22.9 kg/m<sup>2</sup>, patients had a risk of developing hypoglycemia more than patients who have BMI 23 kg/m<sup>2</sup> (P-value 0.02, OR 2.51). In BMI < 18.5 kg/m<sup>2</sup>, patients also had a risk of developing hypoglycemia more than patients who had BMI 23 kg/m<sup>2</sup> (P-value < 0.0001, OR 7.14). This result was opposite to the study from Chanakarn Chaitanakul that body mass index was not associated with hypoglycemia. In patient with low BMI, the capacity of insulin secretion was decrease then the body was used to the low level of insulin secretion. So, when the patient received the treatment with insulin, the body will loss glycemic balance and resulted in hypoglycemia. As for the HbA1C parameter, the result found that for the HbA1C of 10.1% - 13% there was a risk



for hypoglycemic episodes more than the patients with HbA1c of 4% - 7% (P-value 0.02, OR 2.14). This result was different from the study of Thuanjai Poosakaew<sup>4</sup>, because of time collecting of HbA1c. One study shows that the patient with uncontrolled diabetes might experience hypoglycemic symptoms when blood glucose values were in normal range and might have blunted hypoglycemic awareness.<sup>6</sup> The researcher also found that total cholesterol level was not associated with hypoglycemia which opposite to the study from Thuanjai Poosakaew<sup>4</sup> because the different in categorized range of cholesterol level. Using insulin had a higher chance of developing hypoglycemic episodes compared to oral anti-diabetic medication. (P-value < 0.0001, OR 27.26) and the patients who used both oral anti-diabetic drugs and insulin, had a higher risk of developing hypoglycemic episode more than oral anti-diabetic drugs alone. (P-value < 0.0001, OR 3.95). Finally, comorbid diseases were not associated with hypoglycemia.

Because this is a case control study which received the information from electronic hospital database system, the researcher could not study other risk factors those were not recorded in the system. For example, the researcher could not evaluate the compliance of using anti-diabetic drugs, the educational level of patients and the duration of diabetes. Although those factors might be associated with hypoglycemic episode. Another limitation of this study is the number of cases which less than the calculated sample size.

## Conclusion

This case control study found that factor associated with hypoglycemia in type 2 diabetic patients who received treatment at Wiang Pa Pao district hospital were level of HbA1c, body mass index and types of anti-diabetic medications. The

higher initial HbA1c level, the greater the chance of having hypoglycemic episodes. Additionally, patients who had low body mass index were at increased risk of hypoglycemia. The type of diabetic medications also had an effect. Patients who used only insulin injection and patients who used combination of insulin and oral agents, had a higher risk of hypoglycemia than patients who used oral medication alone.

Finally, this research was created for studying the risk factor that associated with hypoglycemia in type 2 diabetic patient of Wiang Pa Pao hospital. The result is helpful for creating plan to prevent the hypoglycemic episode. It can reduce the cost of treatment and can help produce better quality of life for diabetic patient of the community.

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### Conflict of Interest

The authors declare no potential conflict of interest in this study.

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