Original Article

Prevalence and Associated Clinical Parameters of a Hyperglycemic Emergency among Type 2 Diabetic Patients: A Nationwide Cross-Sectional Study in Thailand

Jitjira Chaiyarit PhD[1], Thongchai Pratipanawatr MD[2]

[1] Faculty of Public Health, Khon Kaen University, Khon Kaen, Thailand
[2] Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

Background: A hyperglycemic emergency is a major acute complication among diabetics with high morbidity and hospital admission. In Thailand, the impact of hyperglycemic emergency has received scant attention.

Objective: The objectives of the current study were to explore the prevalence of hyperglycemic emergency and to identify the association between clinical parameters and hyperglycemic emergency among patients with type 2 diabetes in Thailand.

Materials and Methods: The present study was a cross-sectional study and utilized data from the national evaluation of care among type 2 diabetes and hypertension attending in hospitals of Ministry of Public Health and Bangkok Metropolitan Administration of Thailand (DMHT project) that was conducted between 2012 and 2015. Included were 255,133 registered diabetics. Multi-level, mixed-effects, logistic regression analysis was performed to determine the potential clinical parameters associated with a hyperglycemic emergency.

Results: Among the 121,527 type 2 diabetics included, the overall prevalence of hyperglycemic emergency was 3.51% (95% CI: 3.41 to 3.61). The increased risk of hyperglycemic emergency was significantly associated with (a) a lower BMI (adjusted OR 1.88; 95% CI: 1.58 to 2.24), (b) a higher HbA1c, (c) anti-hyperglycemic agents particularly taking insulin (adjusted $OR_{insulin}$ 5.35; 95% CI: 4.42 to 6.48), (d) poor kidney function (adjusted $OR_{stage\ 3}$ 1.38; 95% CI: 1.26 to 1.52 and adjusted $OR_{stage\ 4\text{-}5}$ 1.38; 95% CI: 1.18 to 1.60), (e) albuminuria (adjusted OR 1.23; 95% CI: 1.12 to 1.34), (f) previous cerebrovascular disease (adjusted OR 1.52; 95% CI: 1.20 to 1.92), (g) previous coronary disease (adjusted OR 1.36; 95% CI: 1.13 to 2.24), and (h) previous congestive heart failure (adjusted OR 1.70; 95% CI: 1.29 to 2.24).

Conclusion: According to results, these factors; a lower BMI, a higher HbA1c, anti-hyperglycemic agents, poor kidney function, albuminuria, previous cerebrovascular disease, coronary disease, and congestive heart failure found to be independently associated with risk of hyperglycemic emergency. Therefore, this information will inform clinical decision-making with respect to appropriate care and monitoring of diabetics.

Keywords: Clinical parameters, Hyperglycemic emergency, Type 2 diabetes

J Med Assoc Thai 2018; 101 [Suppl. 7]: S23-S29
Website: http://www.jmatonline.com

A hyperglycemic emergency diabetic ketoacidosis or hyperosmolar non-ketotic hyperglycemic syndrome due to poor management of diabetes can result in a potentially life-threatening condition[1]. It is, moreover, one of the reasons for hospital admission and causes of death among diabetics.

Global reports indicate a high admission rate (6.2% to 18.0%[2-4]) and a high mortality rate (11.3% to 17.7%[2-4]) related to the condition. In Thailand, few studies have investigated admission rates and mortality with respect to hyperglycemic emergencies: the 5-year hospitalization rate for hyperglycemic emergency is 7.5%[5], and the in-hospital mortality ranges between 8.4% and 12.2%[5,6].

Correspondence to:
Pratipanawatr T. Department of Medicine Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.
Phone: +66-43-363664
E-mail: thongcha@kku.ac.th

How to cite this article: Chaiyarit J, Pratipanawatr T. Prevalence and Associated Clinical Parameters of a Hyperglycemic Emergency Among Type 2 Diabetic Patients: A Nationwide Cross-Sectional Study in Thailand. J Med Assoc Thai 2018;101;Suppl.7: S23-S29.

There is, therefore, little documentation of hyperglycemic emergency, except that older age and uncontrolled diabetes are associated with an increased risk of death[7–9] while sex is not consistently associated with risk[4]. In Thailand, only one nationwide study reported that a hyperglycemic emergency was a cause of death among diabetics[10]. There has, thus, been no study addressing the prevalence of, and clinical parameters associated with, a hyperglycemic emergency among type 2 diabetics. The aims of the current study were to explore the prevalence of, and investigate the clinical parameters associated with, hyperglycemic emergency among type 2 diabetic patients in Thailand.

Materials and Methods

Setting and subjects

A nationwide, cross-sectional, hospital-based study was designed to evaluate the status of standard care among type 2 diabetics visiting the hospitals of the Ministry of Public Health and the Bangkok Metropolitan Administration (DMHT project) between 2012 and 2015. Representative samples were collected using a stratified cluster, proportional sampling technique. The diabetics were treated at the hospital not less than 12 months and they provided informed consent before participation in the study. The study was approved by the Khon Kaen University Ethics Committee for Human Research, Thailand.

Criteria for inclusion and exclusion

We excluded patients who (a) were under 35 years of age, (b) were diagnosed for diabetes before the age of 35, and (c) had no report of their hospitalized hyperglycemic emergency. Thus, we included only patients >35 years of age with a complete report of a hyperglycemic emergency.

Baseline measurements and definition

The registry data were retrospectively reviewed from medical records and registered on a case record form. This included demographic data (sex, age, duration of diabetes, body mass index [BMI], glycosylated hemoglobin [HbA1c], estimated Glome rular Filtration Rate [eGFR], and history of smoking), medication treatment (anti-hyperglycemic agents, Angiotensin-converting enzyme inhibitors [ACEI] or Angiotensin Receptor Blockers [ARBs], and anti-platelet agents), and comorbidities verified by physician's report (hypertension, cerebrovascular disease, coronary disease, atrial fibrillation, congestive heart failure, peripheral arterial disease, and albuminuria).

HbA1c, serum creatinine, urine albumin test, urine exam (microalbuminuria, macroproteinuria, and albumin/creatinine ratio) were determined by the laboratory at each hospital using standard methods within 12 months.

The eGFR was measured using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula and categorized by the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative [NKF-KDOQI] guideline[11] that as stage 1 to 2 (eGFR >60 mL/minute/1.73 m^2), stage 3 (eGFR 30 to 59 mL/minute/1.73 m^2), and stage 4 to 5 (eGFR <30 mL/minute/1.73 m^2).

History of smoking was categorized as: current smoker (those still smoke), ex-smoker (those who had stopped smoking), and non-smoker (those who had never smoked).

Anti-hyperglycemic agents were classified as biguanides and/or diet, sulphonylureas-based (SU-based), non-sulphonylureas-based (non-SU based), only insulin, insulin and oral hypoglycemic agents.

Anti-platelet agent was classified as received or never received aspirin/clopidogrel.

Cerebrovascular disease verified by physician report included cerebrovascular accident, ischemic stroke, hemorrhagic stroke, unspecified stroke, cerebral infarction, cerebral hemorrhage, and transient ischemic attack.

Coronary disease also verified by physician's report included angina pectoris, myocardial infarction, and coronary revascularization.

Albuminuria was defined as a positive urine dipstick test, a positive microalbuminuria dipstick, or an albumin/creatinine ratio >30 mg/g, or urine albumin >20 mg/L, >2 mg/dL, >20 mg %, >0.02 g/L, >0.002 g/dL, >30 mg/g, or ≥30 mg/24 h were categorized by the Kidney Disease: Improving Global Outcomes [KDIGO] Clinical Practice Guideline[12], based on a laboratory examination.

Outcome events

A hyperglycemic emergency was defined as severe hyperglycemia (i.e., blood glucose ≥250 mg/dL) requiring hospitalization confirmed in the medical record.

Statistical analysis

Demographic characteristics were presented as means ± SD for the continuous data and count and

percentage for the categorical data. The proportions of studied variables were compared using the Chi-squared test or Fishers' exact test. Comparisons of continuous variables were made using the t-test or Mann-Whitney U-test. Prevalence was reported as a percentage with its 95% confidence interval [95% CI].

A multilevel mixed-effect logistic regression model was used to analyze the concurrent effect of clinical parameters on hyperglycemic emergency by adjusting for any potential hospital clustering effect and presented as odds ratios with its respective 95% CI.

A *p*-value of <0.05 was considered significant. Statistical analyses were performed using STATA version 13.0 (StataCorp, TX).

Results

Baseline characteristics of patients

Of the 121,527 type 2 diabetic patients; 4,264 had a hyperglycemic emergency. The prevalence of hyperglycemic emergency was 3.51% (95% CI: 3.41 to 3.61).

The characteristics of these two groups are summarized in Table 1. A higher HbA1c level in patients experiencing a hyperglycemic emergency was greater than those not having an emergency (9.49±2.60 and 7.93±2.00, respectively). The patients experiencing a hyperglycemic emergency had a longer duration of diabetes and a lower BMI than those who did not.

Frequency of medication treatment

The differences in medication treatment are presented in Table 2. The proportion of patients taking insulin experiencing a hyperglycemic emergency was greater than those who did not. The proportion receiving anti-platelet agents among patients experiencing a hyperglycemic emergency was greater than those did not. Likewise, the proportion of those taking ACEI or ARBs experiencing a hyperglycemic emergency was lower than those who did not.

Table 1. Baseline characteristics of diabetic patients stratified according to hospitalization

Characteristic	No hyperglycemic emergency (n = 117,263)	Hyperglycemic emergency (n = 4,264)	*p*-value
Female, n (%)	80,489 (68.64)	2,967 (69.58)	0.192
Age ≥65 years, n (%)	43,504 (37.10)	1,523 (35.72)	0.066
Mean (SD)	61.56 (10.59)	60.65 (1047)	
Diabetes duration >5 years, n (%)	64,293 (57.87)	2,644 (65.53)	<0.001
Mean (SD)	7.27 (4.76)	8.17 (5.24)	
BMI (kg/m^2), n (%)	(n = 112,055)	(n = 4,094)	<0.001
<18.50	3,890 (3.47)	311 (7.60)	
18.50 to 22.99	28,583 (25.51)	1,208 (29.51)	
≥23.00	79,582 (71.02)	2,575 (62.90)	
Mean (SD)	25.58 (4.50)	24.72 (4.66)	
HbA1c, n (%)	(n = 92,391)	(n = 3,026)	<0.001
<7.00%	33,157 (35.89)	493 (16.29)	
7.00% to 7.99%	21,572 (23.35)	473 (15.63)	
8.00% to 8.99%	14,481 (15.67)	463 (15.30)	
9.00% to 9.99%	9,433 (10.21)	423 (13.98)	
≥10.00%	13,748 (14.88)	1,174 (38.80)	
Mean (SD)	7.93 (2.00)	9.49 (2.60)	
eGFR (mL/minute/1.73 m^2), n (%)	(n = 106,758)	(n = 3,906)	<0.001
Stage 1 to 2	65,450 (61.31)	1,883 (48.21)	
Stage 3	33,941 (31.79)	1,489 (38.12)	
Stage 4 to 5	7,367 (6.90)	543 (13.67)	
Mean (SD)	68.53 (25.90)	61.31 (27.78)	
History of smoking, n (%)	(n = 116,833)	(n = 4,253)	0.136
Non-smoker	102,821 (88.01)	3,707 (87.16)	
Current smoker	4,797 (4.11)	199 (4.68)	
Ex-smoker	9,215 (7.89)	347 (8.16)	

Frequency of comorbidity

The summary of comorbidities among diabetic patients is shown in Table 3. A greater proportion of patients experiencing a hyperglycemic emergency had several comorbidities compared to patients not experiencing a hyperglycemic emergency.

Clinical parameters associated with hospitalization among Thai diabetes patients

A backward elimination, multilevel mixed-effect logistic regression model was used to adjust for any potential hospital clustering effect. The result of the final, multivariable analysis, revealed the following factors were significantly associated with hyperglycemic emergency: :duration of diabetes, BMI, kidney function, HbA1c, anti-hyperglycemic agents, receiving ACEI or ARBs, and having a previous history of cerebrovascular disease, coronary disease, congestive heart failure and albuminuria (Table 4).

The analyses showed that the respective corresponding odds of patients treated with insulin only or treated with insulin combined with OHAs was 5.35 and 4.36 compared to those treated with biguanides (and/or diet) (adjusted $OR_{only\ insulin}$ 5.35, 95% CI: 4.42 to 6.48, and adjusted $OR_{insulin\ with\ OHAs}$ 4.36, 95% CI: 3.62 to 5.25, respectively). Similarly, patients treated with SU-based and Non-SU-based also had an increased risk of admission (1.77 (adjusted OR 1.77, 95% CI: 1.49 to 2.11) vs. 2.54 (adjusted OR 2.54, 95% CI: 1.28 to 5.07, respectively).

Patients with mild kidney impairment (i.e., a eGFR between 30 to 59 mL/minute/1.73 m^2) had a 38% increased a risk of hyperglycemic emergency. By comparison, patients with moderate and severe kidney

Table 2. Characteristics of medication treatment divided by hospitalization

Medication treatment	No hyperglycemic emergency (n = 117,263)	Hyperglycemic emergency (n = 4,264)	*p*-value
Anti-hyperglycemic agents, n (%)			<0.001
Biguanides (and/or diet)	25,112 (21.42)	326 (7.65)	
SU-based	67,206 (57.31)	1,754 (41.14)	
Non-SU-based	616 (0.53)	12 (0.28)	
Only insulin	10,565 (9.01)	1,114 (26.13)	
Insulin and OHA	13,764 (11.74)	1,058 (24.81)	
ACEI or ARBs, n (%)	(n = 116,141)	(n = 4,169)	<0.001
Not receiving	66,061 (56.88)	2,732 (65.53)	
Receiving	50,080 (43.12)	1,437 (34.47)	
Anti-platelet agents, n (%)	(n = 116,501)	(n = 4,248)	<0.001
Not receiving	47,885 (41.10)	1,556 (36.63)	
Receiving	68,616 (58.90)	2,692 (63.37)	

* OHA = Oral hypoglycemic agents

Table 3. Comorbidities among diabetic patients by type of hospitalization

Comorbidity	No hyperglycemic emergency (n = 117,263)	Hyperglycemic emergency (n = 4,264)	*p*-value
Hypertension, n (%)	95,469 (81.41)	3,192 (74.86)	<0.001
Cerebrovascular disease, n (%)	2,744 (2.34)	133 (3.12)	0.001
Coronary disease, n (%)	4,877 (4.16)	246 (5.77)	<0.001
Atrial fibrillation, n (%)	850 (0.72)	40 (0.94)	0.109
Congestive heart failure, n (%)	1,500 (1.28)	108 (2.53)	<0.001
Peripheral arterial disease, n (%)	480 (0.41)	31 (0.73)	0.002
Albuminuria, n (%)	59,219 (53.90)	2,416 (63.46)	<0.001

Table 4. Crude and adjusted odd ratio of parameters associated with hyperglycemic emergency and 95% confidence interval

Parameters	Crude OR OR (95% CI)	Adjusted OR OR (95% CI)
DM duration: >5 years	1.38 (1.30 to 1.48)	0.86 (0.79 to 0.94)
Body mass index: BMI (kg/m^2)		
<18.50	1.89 (1.66 to 2.15)	1.88 (1.58 to 2.24)
18.50 to 22.99	1	1
≥23.00	0.77 (0.71 to 0.82)	0.76 (0.69 to 0.84)
HbA1c (%)		
<7.00	1	1
7.00 to 7.99	1.47 (1.30 to 1.67)	1.47 (1.27 to 1.71)
8.00 to 8.99	2.15 (1.89 to 2.44)	1.87 (1.61 to 2.17)
9.00 to 9.99	3.02 (2.64 to 3.44)	2.48 (2.12 to 2.89)
≥10.00	5.74 (5.16 to 6.39)	4.00 (3.52 to 4.56)
Anti-hyperglycemic agents		
Biguanides (and/or diet)	1	1
SU based	2.01 (1.78 to 2.64)	1.77 (1.49 to 2.11)
Non-SU based	1.50 (0.84 to 2.68)	2.54 (1.28 to 5.07)
Only insulin	8.12 (7.16 to 9.20)	5.35 (4.42 to 6.48)
Insulin and OHA	5.92 (5.22 to 6.72)	4.36 (3.62 to 5.25)
ACEI or ARB	0.69 (0.65 to 0.74)	0.81 (0.74 to 0.88)
eGFR (mL/minute/1.73 m^2)		
Stage 1 to 2	1	1
Stage 3	1.52 (1.42 to 1.63)	1.38 (1.26 to 1.52)
Stage 4 to 5	2.51 (2.28 to 2.78)	1.38 (1.18 to 1.60)
Albuminuria	1.49 (1.39 to 1.59)	1.23 (1.12 to 1.34)
History of cerebrovascular disease	1.34 (1.13 to 1.60)	1.52 (1.20 to 1.92)
History of coronary disease	1.41 (1.24 to 1.61)	1.36 (1.13 to 1.63)
History of congestive heart failure	2.01 (1.65 to 2.44)	1.70 (1.29 to 2.24)

impairment (i.e., eGFR <30 mL/minute/1.73m^2) had a 37% increased a risk of hyperglycemic emergency.

A previous history of cerebrovascular disease increased a risk of admission by 52% (adjusted OR 1.52, 95% CI: 1.20 to 1.90), with increased to 36% (adjusted OR 1.36, 95% CI: 1.13 to 1.63) in those had a previous history of coronary disease, and increased to 70% (adjusted OR 1.70, 95% CI: 1.29 to 2.24) in patients with a previous history of congestive heart failure.

Discussion

The current nationwide study included 121,527 patients and revealed a prevalence of hospitalization for hyperglycemic emergency of 3.51%. An increased risk of hyperglycemic emergency was associated with a lower BMI, a high HbA1c, poor kidney function, treating with anti-hyperglycemic agents, and history of cerebrovascular disease, coronary disease, congestive heart failure, and/or albuminuria. Meanwhile, a higher BMI and taking ACEI or ARBs were associated with a lower hospitalization for a hyperglycemic emergency.

The authors found that patients who were underweight had an increased risk of admission for a hyperglycemic emergency. By contrast, overweight patients had a decreased risk of admission. It should be noted that insulin deficiency trends to present in underweight rather than overweight persons. Consistent with a retrospective study [13], being underweight is an independent predictor for patients hospitalized with hyperglycemia.

The current findings confirm that patients, who cannot control diabetes, have an increased risk of a hyperglycemic emergency. The current study also revealed that a higher HbA1c level increased the risk of admission for a hyperglycemic emergency by almost 4-fold. The finding is supported in previous studies in which poor glycemic control was strongly associated with hospitalization for a hyperglycemic emergency[14,15].

The current study found that patients treated with insulin had a significantly increased risk of hyperglycemic emergency; possibly, these patients

require insulin therapy due to the progression of beta cell failure in advanced disease. Consistent with previous reports, severe diabetes was associated with both beta cell dysfunction and decreased beta-cell mass, both of which require insulin replacement therapy[16-18].

To the authors' knowledge, patients treated with anti-hypertensive agent have a lower hospitalization rate for hyperglycemic emergencies. Indeed, ACEI or ARBs therapy is known to enhance insulin sensitivity as shown by a meta-analysis of randomized clinical trials[19].

The present findings underscore the micro- and macro-vascular complications associated with a hyperglycemic emergency. Patients who had myocardial infarction, congestive heart failure, and coronary disease had a 30% to 70% increased risk of a hyperglycemic emergency, which is consistent with previous studies[2,20,21]. The risk of a hyperglycemic emergency increased by about 20% when the eGFR value decreased and the patient had albuminuria. As with previous findings, if renal function declines, it is a cause of increased insulin resistance. Thus, patients with kidney disease with poor control of their diabetes, had an increased risk for a hyperglycemic emergency[22,23].

The current study had a few limitations. The database had only discharge records and it was not linked with other databases such as vital statistics. Consequently, the authors could not investigate the incidence rate of hyperglycemic emergency and were limited to mortality rates. There was, moreover, no record of lifestyle or dietary variables so their effect on the prevalence of hyperglycemic emergency could not be studied. Despite these limitations, the current study was a large nationwide, multicenter study of hospitalized hyperglycemic emergency among type 2 diabetes: the first of its kind in Thailand. Importantly, we also considered potential the clustering effect of hospital size.

Conclusion

The present study revealed that patients who cannot control diabetes had a higher risk of hospitalization for a hyperglycemic emergency than patients with good diabetic control, and those taking insulin or oral hypoglycemia agents, being underweight, having impaired renal function, and having comorbidities were associated with an increased risk of a hyperglycemic emergency. To prevent hyperglycemic emergency, the patient should be monitored in order to provide appropriate, timely care, especially for poor control of diabetes and for those with comorbidities.

What is already known on this topic?

In Thailand, the previous studies reported that there were high admission rate and for mortality for hyperglycemic emergency. The increased significant associated factors with death in hyperglycemic emergency were serum sodium level on admission, infection, myocardial infection, severe pneumonia, gram-negative septicemia, massive UGIH, and severe acute pancreatitis.

What this study adds?

This is a nationwide, cross-sectional, hospital-based study demonstrated the current situation on hyperglycemic emergency among Thai type 2 diabetes. This study reported the prevalence of hyperglycemic emergency among type 2 diabetic patients in Thailand and this also revealed the clinical parameters (a) patients health status; BMI, HbA1c, having impaired renal function, and having comorbidities (b) medical treatment; anti-hyperglycemic agent and ACEI/ARBs were associated with an increased risk of a hospitalized hyperglycemic emergency among type 2 diabetic patients.

Acknowledgements

The authors thank a collaborative clinical study supported by the Thailand National Health Security Office [NHSO] and the Thailand Medical Research Network [MedResNet] granted the dataset which was archived at the web site http://www.damus.in.th maintained by MedResNet.

We also thank (a) Thailand Research Fund (number IRG 5780016) for supporting (b) the Research Group for Prevention and Control of Diabetes Mellitus in the Northeast of Thailand for many excellent suggestions and (c) Mr. Bryan Roderick Hamman for assistance with the English-language presentation of the manuscript.

Potential conflicts of interest

The authors declare no conflict of interest.

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