Indonesia Cohort of IO HAT Study to Evaluate Diabetes Management, Control, and Complications in Retrospective and Prospective Periods Among Insulin-Treated Patients with Type 1 and Type 2 Diabetes

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ABSTRAK

Latar belakang: *hipoglikemia merupakan efek samping utama dari terapi insulin pada pasien diabetes melitus. Penelitian ini dilakukan untuk mengevaluasi kejadian hipoglikemia pada pasien diabetes melitus tipe 1 (T1DM) atau diabetes melitus tipe 2 (T2DM) yang diobati dengan insulin pada kohort Indonesia.* ***Metode:*** *penelitian kohort Indonesia ini terdiri dari evaluasi retrospektif dan prospektif terhadap episode hipoglikemik, dengan menggunakan International Operations Hypoglycemia Assessment Tool (IO HAT) pada 374 pasien diabetes Indonesia (T1DM; n=17 dan T2DM; n=357). Pasien berusia ≥18 tahun dan diobati dengan insulin selama >12 bulan dipilih untuk penelitian ini (ClinicalTrials.gov nomor: NCT02306681).* ***Hasil:*** *sebanyak 374 pasien disertakan untuk studi ini dan menyelesaikan self assessment questionnaire 1 (SAQ1). Semua pasien T1DM (17 [100%]) dan 347 pasien T2DM (97,2%) menyelesaikan SAQ2. Hampir semua pasien dalam 4 minggu periode prospektif melaporkan setidaknya satu kejadian hipoglikemi (T1DM 100%, T2DM 99,4%) dan tingkat kejadian hipoglikemia adalah 67,5 kejadian per pasien-tahun (PPY) dan 25,7 kejadian PPY masing-masing untuk pasien T1DM dan T2DM. Diantara pasien dengan T1DM dan T2DM, 5,9% dan 36,4%, masing-masing, tidak mengetahui apa hipoglikemia pada awal penelitian. Tercatat proporsi yang tinggi dari pasien memiliki kesadaran yang buruk akan kejadian hipoglikemi (82,4% dan 62,7%, masing-masing).* ***Kesimpulan:*** *secara keseluruhan, proporsi yang tinggi dari pasien yang melaporkan kejadian hipoglikemi pada periode prospektif mengindikasikan kurang pelaporan selama periode retrospektif karena bias ingatan (recall bias). Oleh karena itu dibutuhkan program pendidikan pasien untuk meningkatkan kesadaran akan hipoglikemia dari pasien diabetes di Indonesia.*

Kata kunci: *alat penaksir hipoglikemia operasi internasional, hipoglikemia, pasien dengan diabetes yang diobati dengan insulin, observasional, Indonesia.*

ABSTRACT

Background: *hypoglycemia is a major adverse event of insulin therapy for diabetes mellitus patients. The study was conducted to evaluate the incidence of hypoglycemia among insulin treated patients with type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) in the Indonesian cohort.* ***Methods:*** *this Indonesian cohort study consisted of retrospective and prospective evaluation of hypoglycemic episodes, using International Operations Hypoglycemia Assessment Tool (IO HAT) in 374 patients with diabetes (T1DM; n=17 or T2DM; n=357). The patients of ≥18 years of age and treated with insulin for >12 months were selected for this study (ClinicalTrials.gov number: NCT02306681).* ***Results:*** *a total of 374 patients were enrolled in this study and completed SAQ1. All patients with T1DM (17 [100%]), and 347 (97.2%) patients with T2DM completed SAQ2. Almost all the patients in the 4-week prospective period reported at least one hypoglycemic event (T1DM 100%, T2DM 99.4%) and the incidence rate of any hypoglycemia was 67.5 events per patient-year (PPY) and 25.7 events PPY for T1DM and T2DM patients, respectively. Among patients with T1DM and T2DM, 5.9% and 36.4%, respectively, did not know what hypoglycemia was at baseline, also high proportion of patients had impaired hypoglycemic awareness in the study (82.4% and 62.7%, respectively).* ***Conclusion:*** *overall, high proportion of patients reported hypoglycemic events in the prospective period indicating under reporting during the retrospective period due to recall bias. Therefore, there is a need for patient education program to improve the awareness of hypoglycemia in diabetes patient in Indonesia.*

Keywords: *international operations hypoglycemia assessment tool, hypoglycemia, insulin-treated patients with diabetes, observational, Indonesia.*

INTRODUCTION

In developing countries, increased urbanization, along with sedentary lifestyle and modified diet are the major contributors to increased prevalence of diabetes.[1,2] By the year 2040, the cases of diabetes in Indonesia are expected to increase to 16.2 million, compared to 10 million cases in 2015.[3]

Insulin therapy is the standard treatment option for Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM) patients due to progressive nature of disease.[4,5] Hypoglycemia is a major adverse event with insulin therapy. Symptoms of hypoglycemia range from unpleasant experience to life-threatening events; leading to patient fear and ultimately causing reduced compliance or even refusal of insulin treatment and also prevents health-care professionals from switching to insulin treatment or modifying the insulin dose whenever required.[6-11] In a study conducted to assess the barrier of insulin treatment, 80% of the family physicians reported that insulin treatment is not commenced due to fear of hypoglycemia.[10] Apart from impacting diabetes management, hypoglycemia also increases economic burden by impacting work productivity, interfering with daily functioning of patients, increasing health care utilization, increasing mortality risk, and severe hypoglycemia increases risk of cardiovascular adverse events and death.[7,12,13]

DiabCare Asia study published in 2008 highlighted that despite the availability of clinical practice guidelines in the region, large number of T2DM patients (68%) still have poor glycemic control.[14] Treatment guidelines in Indonesia have emphasized on the need for patient education, diabetes management during Ramadan, and also stressed on regular blood glucose monitoring in patients who are at high risk of developing hypoglycemia.[15,16] However, awareness-to-adherence model study conducted in Indonesia has shown that in spite of high awareness of guidelines among physicians, adherence to these guidelines is really low mainly due to inability to access guidelines, physicians' attitude, and belief toward the guidelines.[17] This further worsens the case as there is not much awareness regarding insulin-associated hypoglycemia among patients. This shows that data on hypoglycemic rates and its impact on economic and social life of patients is lacking in the region. There is an unmet need for such studies and increased patient education program in the region due to perceived risk of

hypoglycemia.

The International Operations Hypoglycemia Assessment Tool (IO HAT) study was a non-interventional, real-world, observational 6-month retrospective and 4-week prospective study of self-reported hypoglycemic events in 7289 patients with insulin-treated T1DM and T2DM from nine countries.[18] The aim of the present study was to evaluate the hypoglycemic rates in insulin-treated Indonesian patients with T1DM and T2DM. In addition, impact of hypoglycemia on work/study and healthcare, patients' response and patients' knowledge of hypoglycemia were also studied.

METHODS

The IO HAT study was a retrospective and prospective observational study to evaluate hypoglycemic episodes using a two-part self-assessment questionnaire (SAQ1 and SAQ2) and patient diary (PD) (**Figure 1**). The current study concentrates on the results from Indonesian cohort of IO HAT study where insulin-treated T1DM and T2DM patients were recruited at 23 sites between 18 December 2014 and 04 April 2015 (for further details, please refer the Study Center Details at the end of this manuscript). The study was conducted in accordance with the guidelines for Good Pharmacoepidemiology Practices (2007), Declaration of Helsinki (2004), the International Conference on Harmonization Guidelines for Good Clinical Practice (1996), and the study protocol and the assessments were approved by country-specific regulatory and ethical agencies.[19,20] The study material was translated to local language and the data obtained was back transferred to English for analysis purpose.

Study Population

Male or female patients of ≥18 years of age with T1DM or T2DM, treated with insulin (e.g. pre-mixed, short-acting, and/or long-acting) for >12 months and who had given informed consent were eligible for this study. Non-ambulatory, illiterate patients with language barrier in understanding the questionnaire were excluded from this study. Patients were recruited randomly into the study via consecutive sampling during routine clinical visit with their healthcare provider in Indonesia.

Study Objective

Primary objective was to determine the percentage of patients experiencing at least one hypoglycemic episode during the 4-week prospective observational period.

The secondary objectives were to determine

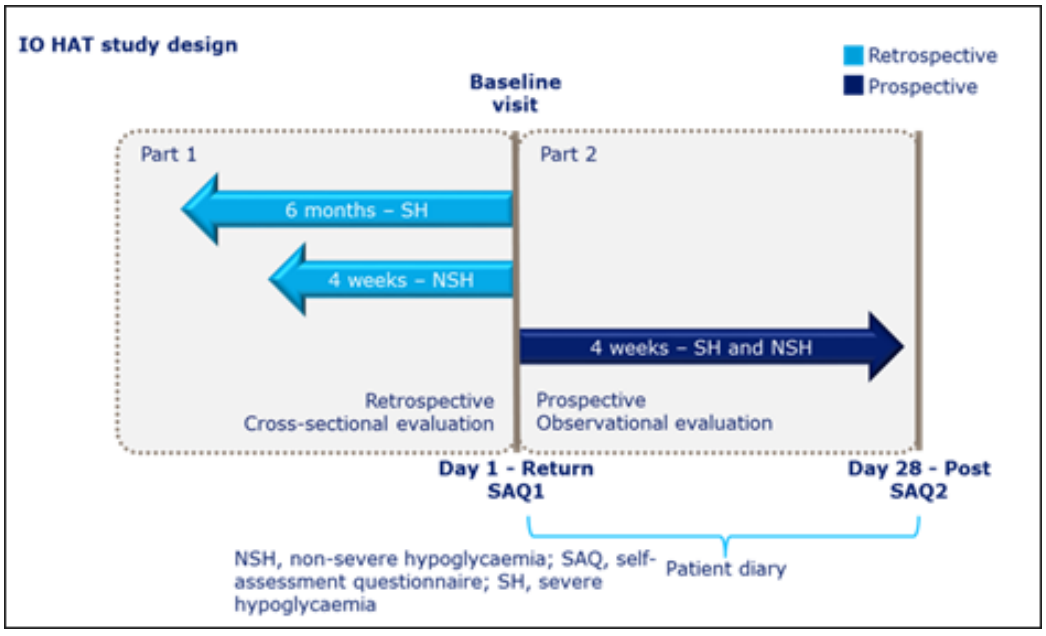


Figure 1. IO HAT study design

the difference in incidence of various types of hypoglycemic episodes (e.g. any, nocturnal, and severe) between the 4-week retrospective period (or 6-month retrospective period for severe hypoglycemia) and 4-week prospective period, relationship between incidence of hypoglycemia and insulin regimen, patient knowledge of hypoglycemia, proportion of patients with hypoglycemic unawareness, fear of hypoglycemia, patients' response to hypoglycemia, and impact of hypoglycemia on work/study.

Hypoglycemic Assessments

Severe hypoglycemia is an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions (as per American Diabetes Association [ADA] definition).[21] Non-severe hypoglycemia is an episode managed by the patient alone. Any hypoglycemia is the sum of severe hypoglycemia and non-severe hypoglycemia. Nocturnal hypoglycemia is hypoglycemia occurring between midnight and 06:00 hours.

The incidence of hypoglycemia was captured in the SAQ1 and SAQ2 and in the PD. Part 1 was used to record baseline demographic, treatment information, patient information, hypoglycemic unawareness, history of severe hypoglycemia over the last 6 months and any and nocturnal hypoglycemia over the last 4 weeks. Part 2 was used to evaluate the occurrence of all types hypoglycemia over 4 weeks after baseline and the effect of hypoglycemia on productivity and healthcare utilization. To assist patients recall and as a reminder to complete SAQ2, patients were provided with a PD to capture hypoglycemic episodes.

Patient knowledge of hypoglycemia was evaluated by checking if the patient's definition of hypoglycemia was consistent with ADA hypoglycemia definition, and if there was awareness regarding hypoglycemia before reading the instructions provided in informed consent.[22] Hypoglycemic unawareness was assessed using SAQ, according to response to question: 'Do you have symptoms when you have a low blood sugar?', if 'Yes' denoted normal awareness, 'usually' denoted impaired awareness, and 'occasionally' and 'never' denoted severely impaired awareness.[22] Fear of hypoglycemia was reported on a scale of 0 to 10 by the patients, where '0' indicated 'not afraid at all' and '10' indicated 'absolutely terrified'.

Data Analysis

The primary endpoint was the percentage of patients who experienced at least one episode of hypoglycemia calculated together with the 95% confidence interval (CI). For secondary endpoints, the incidence rate (IR) of various type of hypoglycemia was calculated as the number of events per patient year (PPY) together with the 95% CI, computed as total number of events divided by total follow-up time in patient years. The incidence rate was reported by diabetes type (T1DM, T2DM) and insulin regimen used.

All statistical tests were two-sided and regarded as exploratory, with statistical significance of $p < 0.05$. There were no adjustments for multiple comparisons. Continuous and categorical data was reported using descriptive statistics (as percentage of patients).

RESULTS

A total of 374 patients were enrolled in this study and completed SAQ1; of which 17 patients were with T1DM and 357 patients were with T2DM. All patients with T1DM (17 [100%]) and 347 (97.2%) patients with T2DM completed SAQ2 and PD. The demographic and baseline characteristics were comparable between T1DM and T2DM patients, with few exceptions (**Table 1**).

Incidence of Hypoglycemia

Any hypoglycemia. During the 4-week prospective period, 100% (95%CI: 80.5%, 100.0%) patients reported hypoglycemic events in TIDM group and 99.4% (95%CI: 97.9%, 99.9%) patients reported hypoglycemic events in T2DM group. While during the retrospective period, 52.9% (95% CI: 27.8%, 77.0%) patients reported hypoglycemic events in T1DM group and 39.5% (95% CI: 34.4%, 44.8%) patients reported hypoglycemic events in T2DM group. In patients with T1DM, the IR of any hypoglycemia increased significantly from the retrospective period to prospective period (33.0 events PPY [95%CI: 23.9%, 44.4%] to 67.5 events PPY

Table 1. Baseline characteristics of patients in Indonesian cohort

Variables	T1DM (n=17)	T2DM (n=357)
Age (years)	31.8 (13.9)	57.9 (10.1)
Male/female (%)	41.2/58.8	45.9/54.1
Duration of diabetes (years)	11.5 (9.3)	11.2 (7.7)
Duration of insulin use (years)	8.7 (9.6)	4.0 (3.4)
BMI (kg/m^2)	22.4 (3.3)	26.2 (4.3)
HbA1c (mmol/mol)	73.8 (23.4)	71.5 (22.0)
HbA1c (%)	8.9 (2.1)	8.7 (2.0)
FBG (mmol/l)	8.6 (4.2)	9.2 (3.9)
PPG (mmol/l)	9.9 (4.4)	11.3 (4.3)
Oral anti-diabetic medications [n (%)][a]		
- Alpha-glucosidase inhibitors	0	51 (14.3)
- Metformin	2 (11.8)	96 (26.9)
- Bile acid sequestrant	0	3 (0.8)
- Dipeptydyl peptidase IV	0	46 (12.9)
- Glucagaon-Like Peptide-1	0	1 (0.3)
- Suphonylurea	1 (5.9)	32 (9.0)
- Thiazoledinediones/ Glitazones	0	2 (0.6)
- None	15 (88.2)	194 (54.3)
- Missing	0	0
Insulin regimen [n (%)][a]		
- Short-acting insulin	0	21 (5.9)
- Long-acting insulin	0	60 (16.8)
- Pre-mix	4 (23.5)	107 (30.0)
- Both short and long acting	13 (76.5)	164 (45.9)
- Both short acting and pre-mix	0	1 (0.3)
- Both long acting and pre-mix	0	4 (1.1)
Symptoms of diabetes-related complications, %		
- Tremor	100	86.3
- Sweating	82.4	69.2
- Weakness	88.2	68.1
- Hunger	82.4	66.7
- Yellow vision	82.4	62.5

Data are mean (SD) unless otherwise stated.
[a] Percentages based on number of patients with evaluable data.
BMI, Body mass index; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; N, total number of subjects participating; PPG, postprandial glucose; SD, standard deviation; SGLT2, Sodium-glucose co-transporter-2; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

[95%CI: 54.2%, 83.2%], respectively; p=0.015) (**Figure 2 [a]**). Similarly, a significant increase in incidence rate of any hypoglycemia was observed for T2DM patients from retrospective period to prospective period (11.2 events PPY [95%CI: 9.96%, 12.51%] to 25.7 events PPY [95%CI: 23.8%, 27.7%], respectively; p<0.001) (**Figure 2 [b]**).

Nocturnal hypoglycemia. During the 4-week prospective period, 29.4% (95%CI: 10.3%, 56.0%) patients reported hypoglycemic events in TIDM group and 15.3% (95%CI: 11.7%, 19.6%) patients reported hypoglycemic events in T2DM group. While during the retrospective period, 47.1% (95%CI: 23.0%, 72.2%) patients reported hypoglycemic events in T1DM group and 13.4% (95%CI: 10.1%, 17.4%) patients reported hypoglycemic events in T2DM group. The IR of hypoglycemia was higher in retrospective period compared to prospective period in T1DM patients, while the IRs were comparable in both the periods in T2DM patients (**Figure 2 [a] and [b]**).

Severe hypoglycemia. The proportion of T1DM patients with severe hypoglycemia was higher in the retrospective period (70.6%; [95%CI: 44.0%, 89.7%]) than in the prospective period (47.1%; [95%CI: 23.0%, 72.2%]); while the IRs increased from the retrospective period (3.6 events PPY; [95%CI: 2.4%, 5.2%]) to the prospective period (7.7 events PPY; [95%CI: 3.7%, 14.1%]) (**Figure 2 [a]**). In T2DM group, the proportion of patients with severe hypoglycemia was higher in prospective period (75.1%; [95%CI: 70.2%, 79.6%]) than in the retrospective period (59.0%; [95%CI: 53.7%, 64.1%]). The IRs also increased significantly from retrospective period to prospective period (2.7 events PPY [95%CI: 2.4%, 2.9%] to 13.0 events PPY [95%CI: 11.7%, 14.5%], respectively; p-value<0.001) (**Figure 2 [b]**).

Rates of Hypoglycemia by Insulin Regimen

In T1DM patient group, the estimated IRs of any hypoglycemic events in the retrospective and prospective periods were highest in patients using short-acting insulin plus long-acting insulin regimen (**Figure 3 [a]**). The IRs of any hypoglycemic events in T2DM patients were almost comparable with no differences among

different treatment regimens (**Figure 3 [b]**).

The IR of nocturnal hypoglycemia in patients with T1DM was highest in the retrospective period and prospective period in patients using short-acting insulin plus long-acting insulin regimen (14.1 events PPY and 9.0 events PPY, respectively) (**Figure 3[c]**). Similar to any hypoglycemia, the IR of nocturnal hypoglycemic events in T2DM patients was almost comparable with no differences among different treatment regimens.

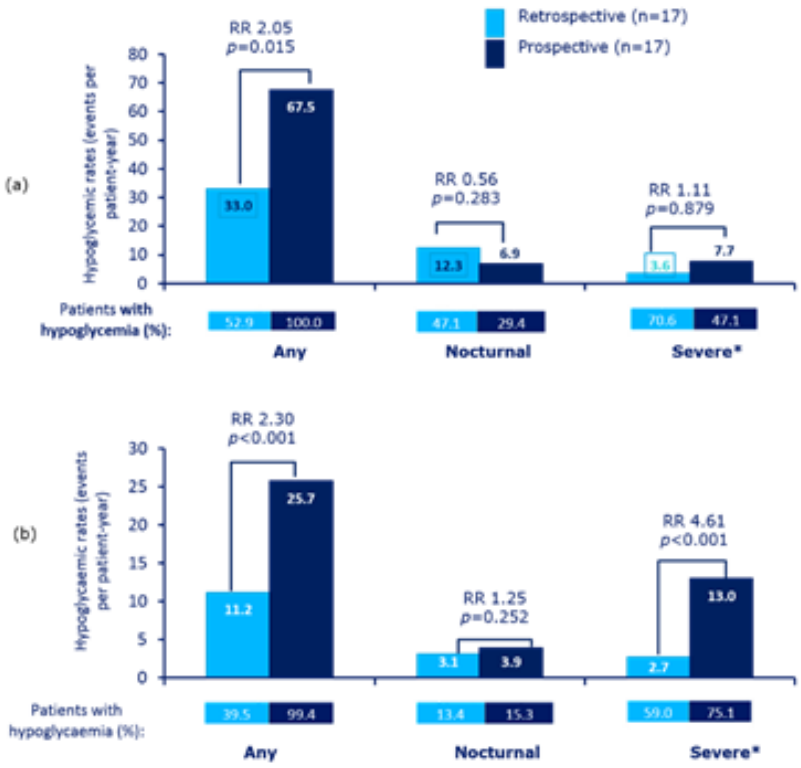
Patient Perspective on Hypoglycemia

At baseline, more patients with T1DM (94.1%) than with T2DM (63.6%) knew about hypoglycemia before providing the definition in SAQ1 (**Figure 4**).

Among the patients who used blood glucose monitoring to determine hypoglycemia, majority of patients (94.1%T1DM and 77.6% of T2DM) provided consistent values of blood glucose measurements as per the standard definitions of hypoglycemia (≤3.9 mmol/L or ≤70 mg/dL). Patient perspectives, including hypoglycemic awareness, fear of hypoglycemia, and response to hypoglycemia are described in **Table 2**.

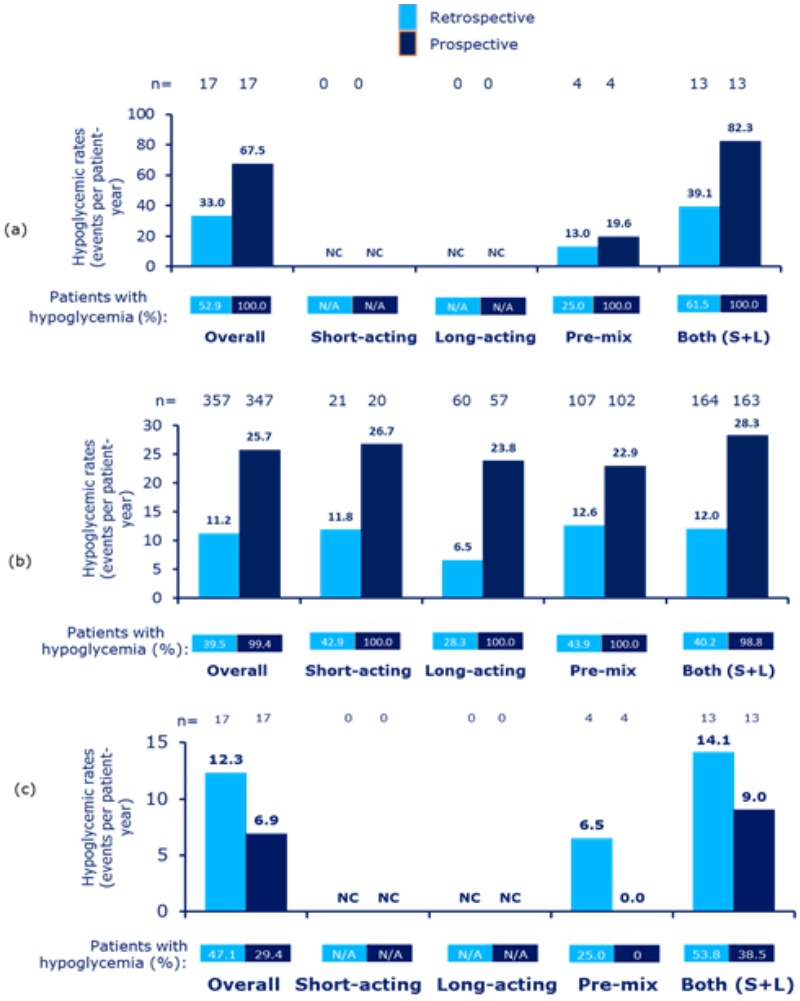
Most of the patients (82.4% and 67.2% patients with T1DM and T2DM, respectively) had impaired hypoglycemia awareness. Both T1DM and T2DM patients experienced similar severity of fear; with a mean (SD) score of 5.1 (3.17) and 4.1 (2.99), respectively.

Overall, the proportion of patients who took actions was greater in T1DM than T2DM group in both retrospective and prospective periods (**Table 2**). The proportion of T1DM and T2DM patients who increased calorie intake was greater in retrospective period (76.5% and 27.5%, respectively) than in prospective period (52.9% and 21.6%, respectively). Similar results were observed for actions such as avoiding physical exercise and requiring any form of medical assistance.



'Any' and 'Nocturnal' based on 4-week period for both retrospective and prospective analyses. *Retrospective data based on 6-month period and prospective data based on 4-week period. RR, rate ratio; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Figure 2. Incidence of hypoglycemia rates in (a) T1DM and (b) T2DM patients.



Data based on 4-week period for both retrospective and prospective analyses for any hypoglycemia. Retrospective data based on 6-month period and prospective data based on 4-week period for Nocturnal hypoglycemia. S+L, short-acting and long-acting insulin; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Figure 3. Rates of hypoglycemia by insulin regimen: (a) Any hypoglycemic events (T1DM), (b) Any hypoglycemic events (T2DM), and (c) Nocturnal hypoglycemic events (T1DM).

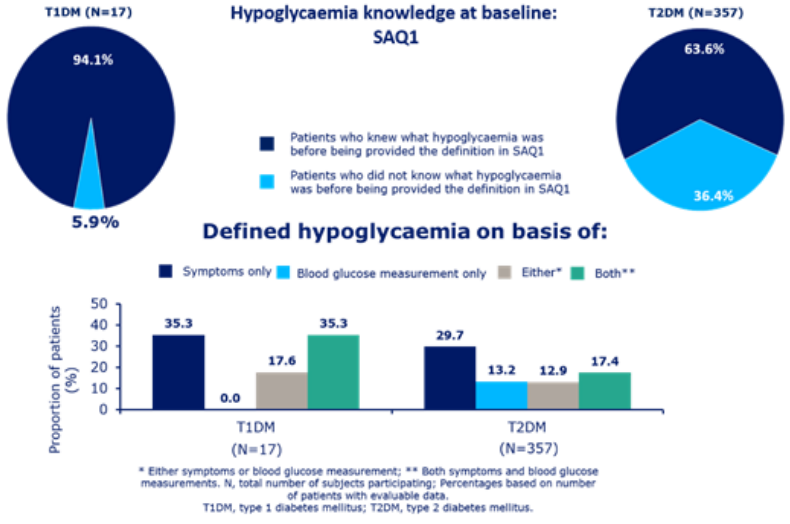


Figure 4. Patient perspective on hypoglycemia.

Table 2. Patient perspectives on hypoglycemia

Variables	T1DM (N=17)		T2DM (N=357)	
Knew what hypoglycemia was at baseline before SAQ1 [n/N total (%)][a]	16/17 (94.1)		225/354 (63.6)	
Hypoglycemia awareness (%)				
- Normal	17.6		13.7	
- Impaired	82.4		67.2	
- Severely impaired	0		13.7	
Fear of hypoglycemia (scale of 0 to 10; %)[a]				
- 0 = no fear	5.9		14.6	
- 1	11.8		9.0	
- 2	5.9		9.8	
- 3	5.9		14.8	
- 4	11.8		9.0	
- 5	23.5		14.0	
- 6	5.9		5.9	
- 7	5.9		7.6	
- 8	5.9		5.6	
- 9	0		2.2	
- 10 = absolutely terrified	17.6		7.6	
Impact of hypoglycemic events on the medical system (%)[a]	Retrospective (n=17)	Prospective (n=17)	Retrospective (n=308)	Prospective (n=345)
- Events requiring hospital admission	11.8	0	6.2	0.6
- Attended additional clinical appointments	0	5.9	1.9	1.7
- Made additional telephone contacts	0	11.8	2.9	2.9
Patient response to hypoglycemia (%)[a]				
- Consulted their doctor/nurse	52.9	58.8	34.7	21.0
- Required any form of medical assistance	64.7	58.8	38.9	21.3
- Increased calorie intake	76.5	52.9	27.5	21.6
- Avoided physical exercise	35.3	41.2	14.6	9.5
- Reduced insulin dose	29.4	35.3	18.2	12.4
- Skipped insulin injections	17.6	11.8	6.4	7.5
Increased blood glucose monitoring	29.4	52.9	17.9	14.1

N, total number of subjects participating; n, number of subjects who responded to the set of questions; a Percentages based on number of patients with evaluable data. SAQ1, self-assessment questionnaire part 1; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus

Impact of Hypoglycemic Events on Work and Study

Overall the proportion of patients with T1DM and T2DM, who had taken leave from work, arrived late to work, or left early from work due to hypoglycemic events was lesser in prospective period than in retrospective period.

In retrospective period, 9 of 17 T1DM patients and 107 of 357 T2DM patients were either studying or were part-time or full-time employee. Out of those, three (33.3%) T1DM patients had taken leave from work and left early from work or study in each category and two (22.2%) arrived late for work or study. In the prospective period, one (11.1%) T1DM patient arrived late and left early from work or study in each category. In T2DM patient group, ten (9.3%), nine (8.4%), and eight (7.5%) patients had taken leave, left early, and arrived late to work or study respectively, in the retrospective period, while five (4.9%) had taken leave and three (2.9%) each had left early and arrived late to work or study, in the prospective period.

Impact of Hypoglycemic Events on the Medical System

In T1DM patient group, 11.8% of patients required hospital admission in the retrospective period, while in the prospective period. None of the T1DM patients required hospital admission due to hypoglycemic events, while 11.8% of patients made additional telephone contacts and 5.9% of patients took additional clinical appointments. In T2DM patient group, similar proportion of patients made additional telephone contacts (2.9% in both) and took additional clinical appointments (1.9% and 1.7%) in both retrospective period and prospective period respectively. The proportion of patients who required hospital admission was higher in retrospective period compared to prospective period (6.2% vs 0.6%, respectively).

DISCUSSION

This study describes results from Indonesia cohort of the multicenter, international, 6 month retrospective and 4-week prospective study using a two-part SAQ to investigate the prevalence of hypoglycemia in insulin-treated adults with T1DM or T2DM. This is the first patient-reported observational study to assess hypoglycemia in Indonesia.

Almost all the patients in the prospective period reported at least one hypoglycemic event (T1DM: 100%, T2DM: 99.4%). The lesser proportion of patients reporting hypoglycemia in the retrospective period could be attributed to patient recall bias as SAQs were used to record data; in prospective period, PDs were additionally used to improve recall. In contrast, the proportion of patients reporting nocturnal hypoglycemia was either comparable or more in the retrospective period than in the prospective period. This could have been possible as the patients had clear definition of nocturnal hypoglycemia in the prospective period and hence reported only those events which occurred during this period. Moreover, the PDs which were used to record events in prospective period can be difficult to fill at night probably resulting in under-reporting of nocturnal hypoglycemia.

In addition, impact of nocturnal hypoglycemia may have resulted in increased reporting of nocturnal hypoglycemia in the retrospective period when patients were asked to recall. The incidence of any hypoglycemia was significantly higher in the prospective period compared to retrospective period in both T1DM and T2DM patients (T1DM: 33.0 vs. 67.5 events PPY, $p=0.015$; T2DM: 11.2 vs. 25.7 PPY, $p<0.001$). The higher incidence in the prospective period may be due to the fact that SAQs and PDs acted as a learning tool and reinforce patients' knowledge resulting in increased hypoglycemic awareness.

Similarly, severe hypoglycemia was also reported with higher proportion in the prospective period compared to the retrospective period for T2DM patients. In this case, recall bias was more pronounced as retrospective data was based on 6 month period in contrast to 4 week period for any or nocturnal hypoglycemia.

Overall, the incidence of any hypoglycemia (11.2 to 67.5 events PPY) and severe hypoglycemia (7.7 to 13.0 events PPY) in this sub-study was found to be higher than the previously reported studies.[23,24] A systematic review and meta-analysis study by Edridge et al[23] had reported that IR of mild hypoglycemia was 19 events per patient year and IR of severe hypoglycemia was just 0.80 events per patient year in T2DM patients. An observational study in United States where hypoglycemic events were identified by claim showed that the overall incidence of hypoglycemia was just 3.46/100 patient years.[24] The incidence of severe hypoglycemia in Hypos-1 study in T1DM patients was found to be 0.49 events/patient years.[25] There are no previous clinical trials or observational studies in this region to compare the results of this sub-analysis. Nevertheless, higher IRs of hypoglycemia in this region emphasize on the need for patient education and regular blood glucose monitoring in diabetic patients with insulin therapy. The guidelines on proper diabetes management should be made available to all healthcare professionals in the region and should focus on use of insulin regimens and newer treatment options which have low risk of hypoglycemia.[26-28] In T1DM patients, the IRs of any and nocturnal hypoglycemia were highest in patients receiving short- plus long-acting

insulin regimens during the retrospective and prospective periods, while in T2DM the IRs of hypoglycemia were independent of the type of insulin regimen used and were in general higher in the prospective period than in the retrospective period.

In general, 35% of patients did not know what hypoglycemia was at baseline. Only 29.9% and 18.2% of the overall patients defined hypoglycemia by symptoms only and by both symptoms and blood glucose measurements, respectively. Majority of the patients reported occasional symptoms of hypoglycemia during low blood glucose measurements indicating impaired hypoglycemia awareness. This indicates the need of patient education on the importance of blood glucose monitoring, risks associated with hypoglycemia and symptoms of hypoglycemia to create awareness in the region.

Hypoglycemia has an impact on quality of life (QoL) such as work and study and also impacts healthcare utilization. The impact of hypoglycemia on the work life was lesser in the prospective period than in retrospective period. This suggests that study tools (SAQ and PDs) may have played some role in hypoglycemia management in this period and therefore improving QoL of patients'. A study by Pranoto et al[29] which were conducted to assess the safety of insulin when administered by primary health care providers in Indonesia concluded that there were minimal hypoglycemic events noted with early initiation of insulin therapy and all of them were mild without requiring hospital admission. Self-monitoring of blood glucose examination done in the study indicated that by creating awareness for use of insulin therapy among healthcare, providers will help in proper management of diabetic patients in the region.

CONCLUSION

The high incidence of hypoglycemia in almost all patients reporting events during the prospective period may indicate under-reporting of hypoglycemia during the retrospective period due to recall bias. The influence of patient education during the study leading to increased hypoglycemia knowledge and therefore higher reporting during the prospective period was also one of the contributing factors. The successful management of diabetes is to achieve targeted glycemic control, while minimizing patient risk of hypoglycemia through appropriate monitoring and creating sufficient awareness about hypoglycemia. There is an unmet need for better education including the importance of self-monitoring of blood glucose, creating sufficient awareness by minimizing the fear of hypoglycemia, and need for newer treatment options with low risk of hypoglycemic profile.

STUDY CENTRES DETAILS

Sahid Sahirman Memorial Hospital, Jakarta (1 investigator, 9 study subjects); Fatmawati Hospital, Jakarta (1 investigator, 57 study subjects); Mitra Keluarga Hospital, Bekasi (1 investigator, 50 study subjects); Jakarta Medical Center Hospital, Jakarta (1 investigator, 10 study subjects); Gatot Soebroto Hospital, Jakarta (1 investigator, 20 study subjects); Siloam Hospital, Surabaya (1 investigator, 30 study subjects); Ulin Hospital, Banjarmasin (2 investigators, 30 study subjects); Ratu Zalecha Hospital, Banjarmasin (1 investigator, 7 study subjects); Sanglah Hospital, Denpasar (3 investigators, 16 study subjects); M. Djamil Hospital, Padang (2 investigators, 22 study subjects); Hasan Sadikin Hospital, Bandung (3 investigators, 33 study subjects); Saiful Anwar Hospital, Malang (3 investigators, 45 study subjects); R.D. Kandou Hospital, Manado (3 investigators, 45 study subjects).

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COMPETING INTERESTS

All authors had provided their inputs into the data interpretation and preparation of the final manuscript for publication, met the ICMJE criteria for authorship, and had approved the final article for submission. The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported;

that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

Roy Panusunan Sibarani - Sahid Sahirman Memorial Hospital, Jakarta, Ida Ayu Made Kshanti - Fatmawati Hospital, Jakarta, Olly Renaldy - Mitra Keluarga Hospital, Bekasi, Susie Setyowati - Gatot Soebroto Hospital, Jakarta, Soebagijo Adi - Siloam Hospital, Surabaya, Agus Yuwono - Ulin Hospital, Banjarmasin, Nanang Miftah Fajari - Ratu Zalecha Hospital, Banjarmasin, Rizqi Rifani - Ulin Hospital, Banjarmasin, Ketut Suastika - Sanglah Hospital, Denpasar, I Made Pande Dwipayana - Sanglah Hospital, Denpasar, Asman Manaf - M. Djamil Hospital, Padang, Eva Decroli - M. Djamil Hospital, Padang, Hikmat Permana - Hasan Sadikin Hospital, Bandung, Ervita Ritonga - Dr. Hasan Sadikin Hospital, Bandung, Octo Indradjaja - Hasan Sadikin Hospital, Bandung, Laksmi Sasiarini - Saiful Anwar Hospital, Malang, Rulli Rosandi - Saiful Anwar Hospital, Malang, Yuanita Langi - R.D. Kandou Hospital, Manado, and Karel Pandelaki - R.D. Kandou Hospital, Manado were the other principal investigators and investigators at their respective study sites.

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REFERENCES

1. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract. 2010;87(1):4–14.
2. Hu FB. Globalization of diabetes: the role of diet, lifestyle, and genes. Diabetes Care. 2011;34(6):1249–57.
3. International Diabetes Federation. IDF Diabetes Atlas, 7th edn. Brussels, Belgium: IDF; 2015.
4. Abiola D, Sathyapalan T, Hepburn D. Management of type 1 and type 2 diabetes requiring insulin. Prescriber 2016. 2016;27(9):50-7.
5. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of diabetes. Diabetes Care. 2015;38(1):140–9.
6. Leiter LA, Boras D, Woo VC. Dosing irregularities and self-treated hypoglycemia in type 2 diabetes: results from the Canadian cohort of an international survey of patients and healthcare professionals. Can J Diabetes. 2014;38(1):38–44.
7. Kunt T, Snoek FJ. Barriers to insulin initiation and intensification and how to overcome them. Int J Clin Pract Suppl. 2009;63(164):6–10.
8. Brod M, Christensen T, Thomsen TL, et al. The impact of non-severe hypoglycemic events on work productivity and diabetes management. Value Health. 2011;14(5):665–71.
9. Workgroup on Hypoglycemia American Diabetes Association. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care. 2005;28(5):1245–9.
10. Nakar S, Yitzhaki G, Rosenberg R, et al. Transition to insulin in Type 2 diabetes: family physicians' misconception of patients' fears contributes to existing barriers. J Diabetes Complications. 2007;21(4):220–6.
11. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. J Clin Endocrinol Metab. 2013;98(5):1845-59.
12. McEwan P, Larsen Thorsted B, Wolden M, et al. Healthcare resource implications of hypoglycemia-related hospital admissions and inpatient hypoglycemia: retrospective record-linked cohort studies in England. BMJ Open Diabetes Res Care. 2015;3(1): e000057. doi: 10.1136/bmjdrc-2014-000057

13. Moheet A, Seaquist ER. Hypoglycemia as a driver of cardiovascular risk in diabetes. Curr Atheroscler Rep. 2013;15(9):351.
14. Soewondo P, Soegondo S, Suastika K, et al. The DiabCare Asia 2008 study – Outcomes on control and complications of type 2 diabetic patients in Indonesia. Med J Indones 2010;19(4):235–44.
15. Goh S, Hussein Z, Rudijanto A. Review of insulin-associated hypoglycemia and its impact on the management of diabetes in South East Asian countries. Journal of diabetes investigation. doi: 10.1111/jdi.12647/pdf.
16. Soeatmadji DW, Rosandi R, Sasiarini L. Indonesian guideline of type-2 DM management during Ramadan, 2015.
17. Widyahening IS, Yolanda van der Graaf, Soewondo P, et al. Awareness, agreement, adoption and adherence to type 2 diabetes mellitus guidelines: a survey of Indonesian primary care physicians. BMC Fam Pract. 2014;15:72. doi:10.1186/1471-2296-15-72
18. Emral R, Pathan F, Cortes C, et al. Self-reported hypoglycemia in insulin-treated patients with diabetes: Results from an international survey of 7289 patients from nine countries. Diabetes Res Clin Pract. 2017; doi: http://dx.doi.org/10.1016/j.diabres.2017.07.031.
19. International Society for Pharmacoepidemiology (ISPE); Guidelines for Good Pharmacoepidemiology Practices (GPP).Initially issued: 1996. Revision 2, April, 2007.
20. World Medical Association (WMA) Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. 64th WMA General Assembly, Brazil, October 2013.
21. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care. 2005;28(5):1245-9.
22. Pedersen-Bjergaard U, Pramming S, Thorsteinsson B. Recall of severe hypoglycaemia and self-estimated state of awareness in type 1 diabetes. Diabetes Metab Res Rev. 2003;19:232-40.
23. Edridge CL, Dunkley AJ, Bodicoat DH, et al. Prevalence and incidence of hypoglycaemia in 532,542 people with type 2 diabetes on oral therapies and insulin: A systematic review and meta-analysis of population based studies. PLoS One. 2015;10(6):e0126427.
24. Curkendall SM, Zhang B, Oh KS, et al. Incidence and cost of hypoglycemia among patients with type 2 diabetes in the United States: Analysis of a health insurance database. JCOM. 2011;18(10):455-62.
25. Giorda CB, Ozzello A, Gentile S, et al. Incidence and risk factors for severe and symptomatic hypoglycemia in type 1 diabetes. Results of the HYPOS-1 study. Acta Diabetol. 2015;52(5):845-53.
26. Kalra S, Mukherjee JJ, Venkataraman S, et al. Hypoglycemia: The neglected complication. Indian J Endocrinol Metab. 2013;17:819-34.
27. Martin Gilmour of the Diabetic Hypoglycemia Editorial Team. Diabetes Treatment Review: Reducing the risk of hypoglycemia with basal insulin analogues. Diabetic Hypoglycemia. 2008;1(1):15-6.
28. Eliaschewitz FG, Barreto T. Concepts and clinical use of ultra-long basal insulin. Diabetol Met Syndr. 2016;8:2. DOI: 10.1186/s13098-015-0117-1.
29. Pranoto A, Novida H, Prajitno JH, et al. Safety and efficacy in early insulin initiation as comprehensive therapy for patients with type 2 diabetes in primary health care centers. Acta Med Indones. 2015;47(2):104-10.